PHARMACOLOGY OF BPSD (BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA)

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PHARMACOLOGY OF BPSD (BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA)

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EDITORIAL
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Editorial: Pharmacology of BPSD (Behavioral and Psychological Symptoms of Dementia)

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Editorial on the Research Topic

Pharmacology of BPSD (Behavioral and Psychological Symptoms of Dementia)

This Research Topic started out on a sombre note. Despite being common in older adults and affecting even some young people, awareness is limited about neuropsychiatric symptoms (NPS) in dementia, the so-called BPSD, even among health professionals, and only a few drugs registered for them. Around 2018, several pharmaceutical companies stopped or downsized neuroscience research divisions oriented toward Alzheimer's disease (AD), some of which had drug candidates of potential interest for BPSD. Antipsychotics had fallen out of favor in many locations, as there were reports of elevated mortality that restricted their use. Nonpharmacological treatments usually mandated by law or guidelines were often given limited resources; there was limited agreement about the optimal nonpharmacological treatment and scarce research on them. To address this situation, this Research Topic has involved multiple disciplines ranging from clinics to basic research. The idea is to move away from an abstract view of BPSD toward a detailed understanding and optimized therapeutic interventions. This Research Topic presents 31 papers (one is this Editorial and one is a correction); 139 authors contributed to these.

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ANTIPSYCHOTICS, OLD AND NEW

The contributions by Calsolaro et al. and Magierski et al. start out by listing the symptoms counted as BPSD and notice that they may occur at any stage of dementia, the typical time profile depending on the type of dementia. The authors go on to present the more conventional drug treatments for BPSD such as dopamine receptor antagonists and move on to newer drugs. The contribution by Magierski et al. also includes a section on nonpharmacological treatments. The review by Yunusa and El Helou deals with the single antipsychotic, risperidone, approved for BPSD (one component of it, aggression) in many countries. It brings up statistically significant effectiveness of this antipsychotic against BPSD in some situations and lists side-effects and regulatory differences among countries. Ohno et al. point out that antipsychotic drugs can have extrapyramidal side effects, including Parkinsonian symptoms, also when used in elderly with dementia. These authors discuss drug choice and combination strategies, as cholinesterase inhibitors and antidepressants that are 5-HT reuptake inhibitors may potentiate EPS whereas NMDA receptor antagonist memantine and adrenergic and 5-HT receptor antagonist mirtazapine reduce EPS. These authors go into some detail on modulation of EPS by 5-HT receptor subtypes. The contribution by Yunusa et al. highlights

encouraging preliminary results on a newer antipsychotic, pimavanserin, for the treatment of dementia-related psychosis (already FDA-approved in U.S. for Parkinson-related psychosis), the first antipsychotic with little antagonism of adrenergic, dopaminergic, histaminergic and muscarinic receptors, but significant interactions with 5-HT receptors.

NEW LOOKS AT TRADITIONAL MEDICINES

Looking back in time but also into the future, the papers by Park et al. and Fu et al. deal with herbal medicines that have traditionally been, and still are, given to old people for i.a. cognitive and depressive symptoms. Both explore how these (and potentially other traditional drugs) can be researched using modern methods and formulations improved. Interestingly, both drugs described have statistically significant effects in some of the assays used. The systematic review by Fu et al. of a medicine traditionally used in the old people found an improvement in preclinical scores for cognitive functioning and mood. Possible mechanisms for Kaixinsan (KXS) were found to be antioxidant, anti-inflammatory and antiapoptotic activity, neuroprotection and synapse protection. suggesting that KXS might be considered for depressive symptoms in dementia acting through multiple mechanisms. The study of PSM-04, derived from a natural medicine, by Park et al. addresses mechanisms of another drug that is traditionally used in elderly with cognitive or depressive problems, addressing its mechanisms. In preclinical models, PSM-04 had significant neuroprotective effects against neurotoxicity induced by L-glutamate or oligomeric Aβ and decreased oxidative stress induced by H_2O_2. The drug also reduced cognitive impairment and decreased amyloid deposition in a mouse model. This paper points to the interesting possibility that the mood improvement by PSM-04 (and related drugs) may be mediated (in part) by reduction in amyloid deposits. Both Park et al. and Fu et al. mention neuroprotection and reduction in oxidative stress, suggesting mechanisms that may be common to both KXS and PSM-04 and to both cognitive and depressive symptoms.

ADVANCES IN METHODOLOGY AND IT

The contribution of Lin and Lane deals specifically with glutamate-related mechanisms. It starts from memantine, the NMDA receptor antagonist used in AD, and notices evidence that both under- and overactivity can be detrimental, and suggest that "precision medicine," specifically tailoring treatment to each patient using NMDA-related biomarkers, can be helpful. Somewhat less high-tech, but possibly important technology development is the blood concentration measurements of AChE inhibitors (AChE-I) by Ortner et al. AChE-I are used for the treatment of cognitive symptoms of dementia but also BPSD. Ortner et al. find that serum concentrations below the recommended range in about two thirds of the patients and suggest that therapeutic drug monitoring might help to identify the cause of poor clinical response of cognition and behavioral and psychological symptoms in patients. This could be especially relevant to BPSD, as there is some evidence that relatively higher doses of AChE-I might be needed for BPSD than for cognitive impairments. IT is the main theme of two contributions, Piau et al. and Husebo et al. The contribution by Piau et al. focuses on digital biomarkers and points to an unmet need to monitor nature, frequency, severity, impact, progression, and response to treatment of BPSDs after the initial assessment. to reevaluate therapeutic strategies more quickly and, in some cases, to treat earlier, when symptoms are still amenable to therapeutic solutions or even prevention. These authors suggest digital biomarkers are monitoring more than diagnostic tools. In addition to the implications for clinical care, several ways to use digital biomarkers for more effective pharmaceutical research are suggested. Husebo et al. find that technology can often pick up behaviors of BPSD such as sleep disturbances, agitation and wandering, and may be well accepted. These authors also propose a framework for sustainable ethical innovation in healthcare technology. Advancements in methodology of a different kind, i.e., design of clinical trials, are proposed in Hulshof et al. This study indicates that resources have been wasted in clinical trials of antipsychotics for neuropsychiatric symptoms of dementia, because sample sizes were either too small or unnecessarily large. The article suggests ways to improve clinical trials in the BPSD area both during study design and when findings are later reported. Interesting methodology developments in the use of animal models are dealt with in the contributions by Torres-Lista et al. and Pifferi et al. A string of publications from the first-mentioned lab shows that BPSD can be modeled in mice. In their mouse model, the benefits of risperidone were limited, both at cognitive and BPSD-like level, and there was early and long-lasting mortality risk. Since mortality from an antipsychotic is reproduced in this mouse model, it might be possible to address antipsychotic toxicity using this animal model. A fresh approach to BPSD may be the one of Pifferi et al. Here, it is suggested that the gray mouse lemur, a primate, is a more translatable animal model of dementia and BPSD. Interestingly, effectiveness of approved cognitive enhancers such as acetylcholinesterase inhibitors or N-methyl-D-aspartate antagonists is demonstrated in sleep–deprived animals. Knowledge of similarities between age-related symptoms in the lemur with BPSD in humans might help understand and treat BPSD.

FOCUS ON DEPRESSIVE AND OTHER SPECIFIC SYMPTOMS

Several contributions deal with the depressive symptoms that commonly co-exist with or precede cognitive impairments in dementia disorders, and with the related but distinct problem of apathy in dementia. The contribution by Cassano et al. begins by noticing that the question if depression is a prodromal symptom preceding cognitive deficits or an

independent risk factor for AD is still unclear, although a connection between depressive disorders and AD is widely recognized. Moreover, there is growing evidence reporting that conventional antidepressants are not effective in depression associated with AD and, therefore, there is an urgent need to understand the neurobiological mechanism underlying the resistance to the antidepressants. The paper by Linnemann and Lang explores possible mechanistic relationships between late-life depression and dementia, both of which are common in old age and often occur together. The fact that depression often comes with cognitive impairment and dementia often presents with depressive symptoms is a challenge. However, more than six several pathophysiological substrates are proposed to explain the link between late-life depression and dementia. The Systematic Review of Wiels et al. suggests that depressive symptoms and dementia have common risk factors, that depressive symptoms being a prodromal symptom of dementia and/or depression being a risk factor for dementia. To the editors, it seems that all these causal relationships may be operating at the same time. Since clinical diagnostic criteria were usually used, not biomarkers, different pathophysiologies might be operative in different patients. The contributions on apathy by Bogdan et al. and Theleritis et al. point out the lack of drive in many patients with dementia. They notice that apathy in dementia may have separate pathways from depression and points to several possible targets for drug treatment in apathy, although approved agents for apathy are still missing. The authors suggest early treatment is important, as apathy may have a negative impact on the disease progression. They suggest that optimizing treatment duration and samples sizes may improve future clinical trials. Besides Bogdan et al., Gottesman and Stern deal with the question of BPSD and rate of cognitive decline. They make the interesting point that BPSD is positively correlated with the rate of decline in AD and suggest that the presentation and course of AD is highly heterogenous with BPSD contributing to heterogeneity. The HIDA axis is almost the antithesis of depressive symptoms: Hyperactivity–Impulsivity–Irritiability–Disinhibition–Aggression–Agitation. Keszycki et al. argue that some symptoms in the HIDA axis do not respond adequately to nonpharmacological treatments, necessitating adjunct pharmacological intervention.

MECHANISMS OF BPSD AND POSSIBLE CONNECTIONS WITH OTHER DISORDERS

Ng et al. sort the diverse symptoms of BPSD into subsyndromes and notice that they may arrive early in AD, even before the onset of cognitive impairment. They point to metabolic dysfunction in specific brain areas and networks in the different BPSD. They find that neuropsychiatric symptoms are associated with poorer outcomes in cognition and function and discuss opportunities of intervention. The study by Liu et al. addresses whether anticholinergic activity of drugs is associated with risk of dementia and BPSD. Drugs with anticholinergic activity are strongly suspected to increase risk of dementia. However, this study found limited evidence for such relationships; nevertheless, with high anticholinergic burden the relationship became apparent. Thus, there is still limited consensus connecting dementia with anticholinergic activity; however, toward the end of their paper, these authors give suggestions to design more definitive studies in the future. Some aids for drug review in dementia discommend tricyclic antidepressants due to their anticholinergic effects (Religa et al., 2021, in press). Nevertheless, Hessmann et al., in their contribution, found that patients being diagnosed with dementia frequently are prescribed tricyclic antidepressants. In many locations, the tricyclics would be deprescribed during regular medication reviews. However, considering the contribution of Liu et al. suggesting limited increase in dementia risk by a modest exposure to anticholinergic drugs, and since tricyclics are sometimes prescribed after nonresponse to other antidepressants, could this prescription be warranted in some instances? Disorders of the urinary system are common in geriatric patients with dementia. Many such patients have reduced kidney function, although the only sign of it may be abnormal markers such as creatinine. The contribution of Simões e Silva et al. explores the connection between chronic kidney disease and neuropsychiatric disorders, among which depression is common. There is some evidence for increased cerebrovascular disease from uremic toxins, but the authors find evidence for bidirectional cross-talk between brain and kidney through mechanisms including inflammatory cytokines and the renin-angiotensin system. There is evidence for involvement of the kynurenine pathway, an alternative pathway of tyrosine metabolism, in neuropsychiatric symptoms as well as AD progression and neurodegeneration. In some tissues with AD-type changes, overactivity of the kynurenine pathway has been demonstrated, which is likely to increase levels of certain neurotoxic metabolites. Against this background, Fertan et al. tested a whether a novel inhibitor of this pathway could improve cognitive and behavioral changes in a mouse model of AD. DWG-1036 showed improvements in in memory and behavior in several but not all assays used. Could the kynurenine pathway be one that connects BPSD and memory loss? The contribution of Tarasov et al. is relevant because of a recent surge in publications implicating a role of astrocytes in AD and other neurodegeneration (Verkhratsky et al., 2019). They review evidence for alterations of astrocytes also in schizophrenia in which their role may be neuroinflamation and an indirect influence on dopamine neurons *via* NMDA receptors. A state of hyperactive dopamine projections in the mesolimbic system and reduced dopamine projections in the mesocortical system in schizophrenia is mentioned. Could it be that dopamine-related mechanisms of Tarasov et al. be a cause of hypometabolism in frontal cortical areas in AD with psychosis reviewed in the contribution by Ng et al.? Autism and BPSD are seldom considered together, but the contribution by Eissa et al. compares these two conditions side by side. They identify some commonalities in symptoms and mechanistic roles of inflammation, histamine, amyloid precursor protein (APP) and changes in white matter. The experimental study of Scuteri et al. points to the possibility that BPSD can be a manifestation of pain, a common co-morbidity that these patients can have difficulty to express. It was found that formalin-induced behavioral pattern in older mice was different and suggests a possible animal model of pain in the elderly.

FINAL NOTES

Finalizing this Research Topic, we are now optimistic. A few trends can be discerned: Antipsychotics, even those that are strong blockers of dopamine receptors, have not been written off from treatment of BPSD. Side effects of antipsychotics may at times be effectively dealt with, as described here. New antipsychotics with different receptor binding profile may have a better benefit to risk ratio. Improvements in methodology such as IT, biomarkers, drug concentration measurements and study design will optimize the use of existing drugs and speed discovery of new drugs. Traditional medicines are still of interest, and new technologies may make them more effective and useful.

The new disease classification ICD-11, being introduced internationally, associates dementias with a specific nervous system disease process and, if needed, BPSD or a specific symptom of BPSD (World Health Organization, 2018). The present Research Topic outlines many mechanistic pathways, containing potential drug targets, for BPSD but also cognitive impairments and CNS disease processes. Candidate drugs against AD are often divided in three groups (Cummings et al., 2020), the larger "disease-modifying" group, and the groups whose purpose is cognitive enhancement or controlling neuropsychiatric symptoms. However, it has been noticed that some agents may belong to more than one group (Cummings et al., 2020), and several drugs and mechanisms mentioned in this Research Topic can reasonably be placed in more than one group. Several of the contributions touch upon possibly overlapping neural/mechanistic pathways with comorbidities (pain, urinary system disorders). Bladder dysfunction, for which drugs with anticholinergic activity are often prescribed, may be an integrated part of neurodegenerative disorders or a consequence of treatment prescribed (Winge, 2015). Perhaps altered behavior patterns during micturition might be considered a specific Behavioral and Psychological Symptom of Dementia? The evidence that BPSD are associated with quickened cognitive decline is of clear interest to pharmacologists, primarily because some drugs used in BPSD might quicken cognitive decline (see Gottesman and Stern). However, an interesting possibility is that optimized treatment of BPSD could reduce cognitive decline, as there is very recent evidence that that the abovementioned antipsychotic pimavanserin might be disease-modifying in AD (Yuede et al., 2021) as well as effective against neuropsychiatric symptoms. Park et al. presents evidence for an anti-amyloid effect of a natural medicine used i.a. for depressive symptoms in the elderly, which might be an indication that amyloid contributes to such symptoms. **Figure 1** tries to place mechanisms mentioned in this Research Topic in the context of the multiple clinical manifestations of the dementias.

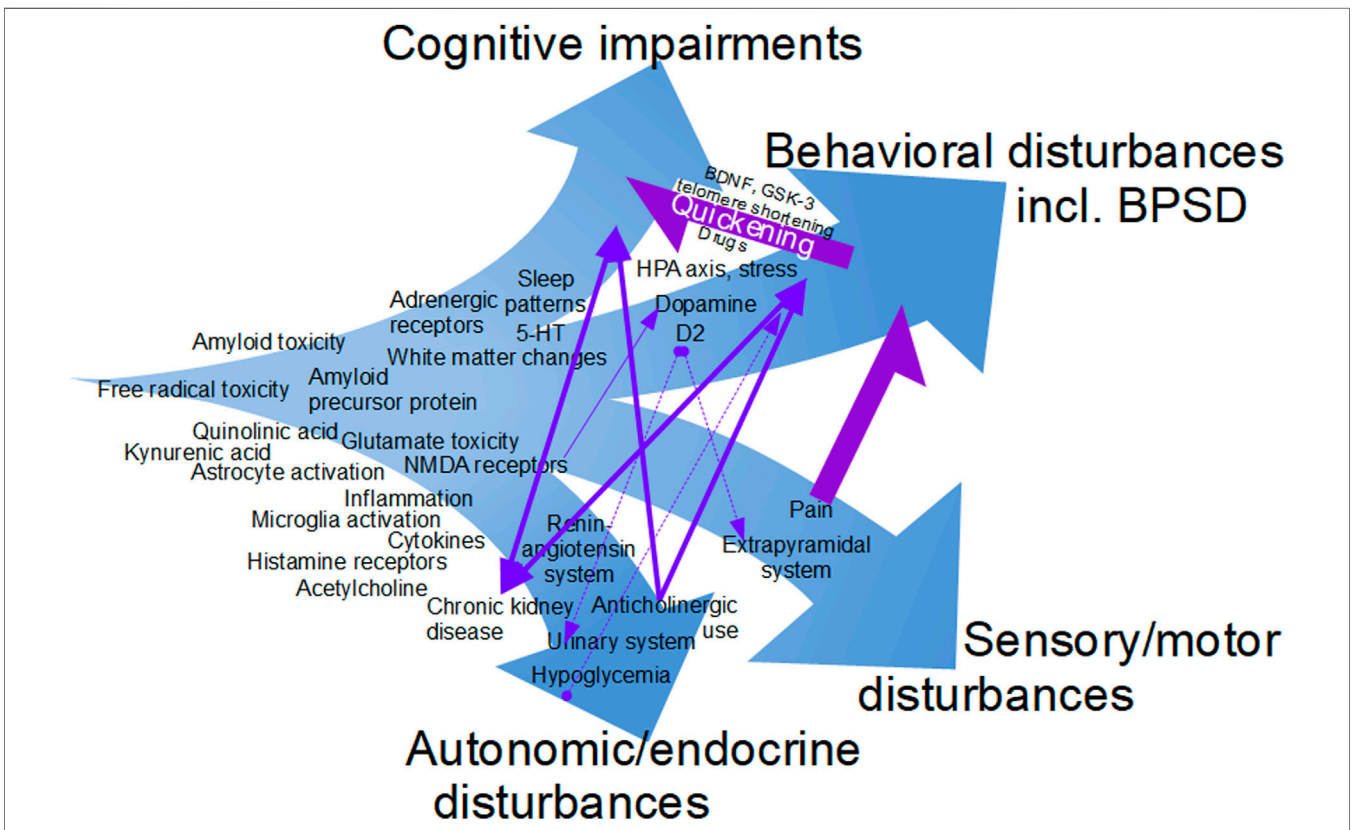

FIGURE 1 | The multiple facets of the dementias, as gleaned from the contributions to this Research Topic. Relationships among cognitive impairments, behavioral problems and co-morbidities such as pain and disorders of the urinary system. This figure is work in progress, as this version is not a complete summary of all mechanisms mentioned in the contributions or all suggestions received from the authors.

We feel that the multidisciplinary approach taken in this Research Topic has been successful and will quicken progress in the BPSD treatment. *For natural reasons, many therapies described here are of an experimental nature, so always check with law and local rules and guidelines before making clinical decisions.*

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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The Protective Effects of PSM-04 Against Beta Amyloid-Induced Neurotoxicity in Primary Cortical Neurons and an Animal Model of Alzheimer's Disease

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Polygala tenuifolia Willdenow is a herb known for its therapeutic effects in insomnia, depression, disorientation, and memory impairment. In Alzheimer's disease (AD) animal model, there has been no report on the effects of memory and cognitive impairment. PSM-04, an extract from the root of *P. tenuifolia* Willdenow, was developed with improved bioabsorption. The present study aimed to investigate the neuroprotective effects of PSM-04 on AD and reveal the possible molecular mechanism. The neuroprotective effect of PSM-04 in primary cortical neurons treated with L-glutamate, oligomeric Aβ, or H_2O_2. PSM-04 exhibited significant neuroprotective effects against neurotoxicity induced by L-glutamate or oligomeric Aβ was studied. PSM-04 exhibited significant neuroprotective effects against neurotoxicity induced by L-glutamate or oligomeric Aβ. Oxidative stress induced by ROS was monitored using the DCF-DA assay, and apoptosis was assessed using the TUNEL assay in primary cortical neurons treated with H_2O_2 or oligomeric Aβ. PSM-04 also decreased oxidative stress induced by H_2O_2 and apoptotic cell death induced by oligomeric Aβ. We evaluated the therapeutic effect of PSM-04 in 5xFAD (Tg) mice, an animal model for AD. PSM-04 was orally administered to 4-month-old 5xFAD mice for 2 months. To confirm the degree of cognitive impairment, a novel object recognition task was performed. The treatment with PSM-04 significantly alleviated cognitive impairments in Tg mice. In addition, amyloid plaques and gliosis decreased significantly in the brains of PSM-04-administered Tg mice compared with Tg-vehicle mice. Furthermore, the administration of PSM-04 increased the superoxide dismutase-2 (SOD-2) protein level in hippocampal brain tissues. Our results indicated that PSM-04 showed therapeutic effects by alleviating cognitive impairment and decreasing amyloid plaque deposition in Tg mice. Therefore, PSM-04 was considered as a potential pharmacological agent for neuroprotective effects in neurodegenerative diseases, including AD.

Keywords: Alzheimer's disease, *Polygala tenuifolia* Willdenow, PSM-04, neuroprotection, 5xFAD mice

INTRODUCTION

Alzheimer's disease (AD) is the most common neurodegenerative disease and constitutes approximately two-thirds of all cases of dementia (Reitz et al., 2011). AD is pathologically characterized by amyloid plaque deposition, intracellular neurofibrillary tangles, and cognitive function impairment (Tanzi and Bertram, 2005). Clinical features of AD include memory loss, altered memory, and cognitive impairment (Burns and Iliffe, 2009). The costs of caring for patients with AD are increasing annually, which imposes tremendous financial and social burden on the community and patients' families. Clinically prescribed medicines alleviate symptoms of AD but cannot provide a fundamental treatment (Tan et al., 2014). During the last decade, all phase III clinical trials of promising candidate drugs, such as solanezumab and verubecestat, have failed due to no cognitive improvement and adverse effects.

In recent times, researches have been conducted to search for novel active extracts or components derived from various natural products which can be used for the treatment of brain diseases (Howes et al., 2003; Houghton and Howes, 2005). These natural products have proven effective with low side effects (Bent, 2008). *Polygala tenuifolia* Willdenow is one of the main components of Kai-Xin-San (KXS), a well-known traditional Chinese herbal decoction, which has been widely used to treat mental depression and memory loss in China (Yan et al., 2015). The roots of *P. tenuifolia* Willdenow, a natural oriental plant, have been used for memory improvement and for the treatment of insomnia, amnesia, depression, and palpitations with anxiety (Liu et al., 2010). BT-11 was extracted from the dried root of *P. tenuifolia* Willdenow by ethanol distillation (Park et al., 2002). Previous studies showed that BT-11 has neuroprotective effects as it improved scopolamine- and stress-induced amnesia in rats (Park et al., 2002; Shin et al., 2009b). BT-11 reportedly enhances cognitive functions, including memory, in the elderly (Lee et al., 2009; Shin et al., 2009a). Recently, *BT-11* is reportedly non-genotoxic at the appropriate dose (Shin et al., 2015). We have developed new *P. tenuifolia* Willdenow extract, PSM-04, for improving bioabsorption by removing stearic acid from BT-11.

In the present study, we investigated the neuroprotective effect of PSM-04 against neurotoxicity induced by L-glutamate, oligomeric Aβ, or H_2O_2 in primary cortical neurons. We also checked the improvement of cognitive dysfunction and pathological changes in 5xFAD transgenic mice, an animal model for AD.

MATERIALS AND METHODS

Chemicals and Antibodies

PSM-04 was provided by Braintropia (Korea) for research purposes. BDNF was purchased from Peprotech (United States). Donepezil, 6E10 antibody, hexafluoroisopropanol (HFP), and vitamin E were purchased from Sigma Aldrich (St. Louis, MO, United States). Anti-BDNF antibody was purchased from Abcam (Cambridge, United Kingdom), and anti-Mn-SOD antibody was purchased from Merck Millipore (Darmstadt, Germany).

Rat Primary Cortical Neuron Culture

Pregnant Sprague–Dawley (SD) rats were purchased from Koatech (Korea). The cerebral cortex was dissected from an embryonic day 17 (E17) SD rat embryo and dissociated with a trypsin solution. The isolated cells (3×10^3 cells) were plated on a 12-mm coverslip or a 96-well plate coated with poly-L-lysine (Sigma, United States). Primary cortical neurons were grown in Neurobasal medium supplemented with 2% B27, 2-mM L-glutamine, and 1% penicillin–streptomycin–amphotericin B mixture (Gibco BRL). Cultured media were changed every 2–3 days. Cortical neurons were cultured in a 5% CO_2 humidified incubator at 37°C for 14–15 days. The *in vitro* experimental scheme is shown in **Figure 1A**. This study was performed in agreement with the principles of the Basel Declaration and recommendations of the Institutional Animal Care and Use Committee of the Lee Gil Ya Cancer and Diabetes Institute, Gachon University. The protocol was approved by the Institutional Animal Care and Use Committee of the Lee Gil Ya Cancer and Diabetes Institute, Gachon University (LCDI-2016-0061).

Oligomeric Aβ Preparation

An oligomeric form of the $A\beta_{1-42}$ peptide was prepared as described previously (Dahlgren et al., 2002). Vials containing 1 mg of the $A\beta_{1-42}$-HFP film were allowed to thaw at room temperature for 10 min. Then, $A\beta_{1-42}$ was dissolved in HFP at a concentration of 1 mmol/L. The HFP was removed under vacuum, and $A\beta_{1-42}$ peptide film was stored at −20°C. The $A\beta_{1-42}$ peptide film was dissolved in DMSO (Dochefa, Netherlands), and the peptide was then kept at −20°C in aliquots until use. For supporting oligomeric conditions, F-12 medium was added to the $A\beta_{1-42}$ peptide and was incubated at 4°C for 24 h to oligomerize.

Cell Viability Assay

To measure the metabolic activity of viable cells, WST-1 (Roche, Switzerland) or CCK-8 (Dojindo, Japan) assay was performed according to the manufacturer's instructions. Primary cortical neurons were plated at a density of 3×10^3 cells/well in the 96-well plate. Next, 1 μg/mL PSM-04 or medium was added into the media for pretreatment of primary cortical neurons (DIV 7-8) 12 h before treatment with 20 μM of the oligomeric form of $A\beta_{1-42}$ or F12 medium. Thereafter, 200 ng/mL BDNF was used as positive control. Then, WST-1 or CCK-8 reagent was added to each well, and primary cortical neurons were additionally incubated at 37°C in 5% CO_2 for 2 h. The absorbance of control or treated samples was measured using a multi-label plate reader (PerkinElmer, VICTOR X4) at OD of 450 nm.

Measurement of ROS Generation

Cellular ROS formation was evaluated in primary cortical neurons using the DCF-DA assay kit (Abcam, United States) or DCF-DA compound (Sigma, United States). Briefly, primary

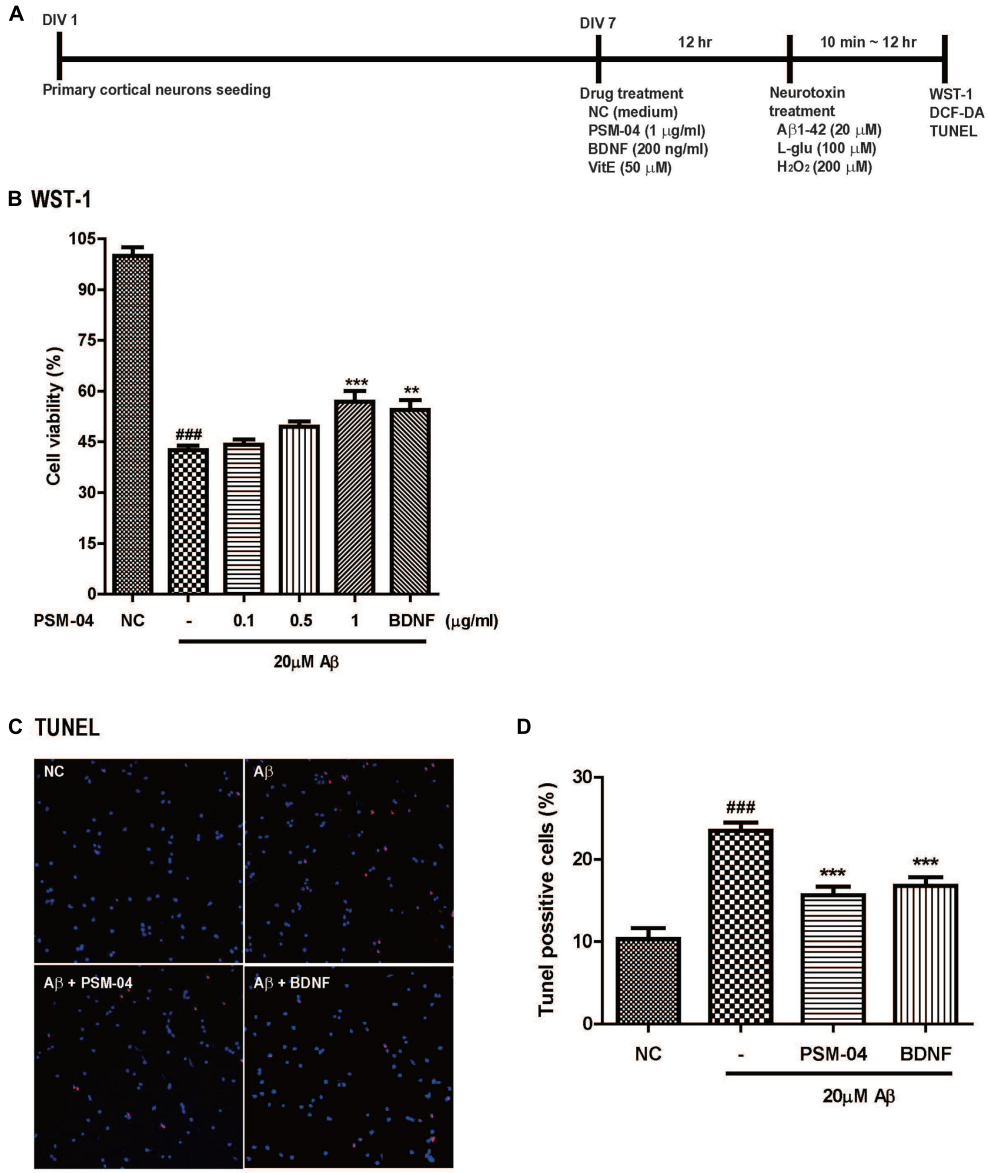

FIGURE 1 | PSM-04 reduced the apoptotic cell death induced by oligomeric Aβ. **(A)** A schematic diagram of the *in vitro* experimental plan is shown. **(B–D)** Primary cortical neurons were pretreated with PSM-04 (0.1, 0.5, or 1 μg/mL) for 12 h and then treated with 20 μM of Aβ for 12 h. **(B)** Cell viability was determined by using WST-1 assay. All data are given as means ± standard error of the mean (SEM), and each experiment was repeated five times (n = 4–6 wells per group, N = 5). **(C)** The apoptotic cell death in primary cortical neurons was visualized by TUNEL staining (red) and counterstaining with DAPI (blue); consequently, 1-μg/mL PSM-04 or 200-ng/mL BDNF reduced the apoptotic cell death induced by 20 μM of Aβ. **(D)** The population of TUNEL-positive cells (red) is shown as a percentage compared to the total cell number. All data are given as means ± SEM and each experiment was repeated five times (n = 3 wells per group, N = 5). The statistical analyses were performed by one-way ANOVA followed by the Newman–Keuls *post hoc* test $^{###}p < 0.001$ vs. control (NC). $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$ vs. Aβ only.

cortical neurons were plated at a density of 3×10^3 cells/well in 96-well optical black plates. PSM-04 was added into the medium for the pretreatment of primary cortical neurons (DIV8) for 12 h. The cultured medium was removed and replaced with 5-μM DCF-DA-treated Hank's balanced salt solution (HBSS) for 20 min in the dark at 37°C. Then, cortical neurons were treated with 20-μM H_2O_2 and incubated for 10 min. BDNF (200 ng/mL) was used as positive control. The fluorescence was detected using a multi-label plate reader with excitation wavelength of 485 nm and emission wavelength of 535 nm.

Measurement of Apoptotic Cell Death With the TUNEL Assay

The terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining kit was purchased from Roche (Switzerland). Apoptotic cell death was measured using the TUNEL assay following the manufacturer's protocol. Briefly,

primary cortical neurons were plated on prepared 12-mm coverslips, and 1-μg/mL PSM-04 was added into the media for the pretreatment of primary cortical neurons (DIV7) at 12 h before treatment with 20-μM $A\beta_{1-42}$ or medium. BDNF (200 ng/mL) was used as positive control. Continually, primary cortical neurons were fixed with 4% paraformaldehyde in 4% sucrose and were then permeabilized for 2 min on ice. Primary cortical neurons were treated with the TUNEL reaction mixture and incubated for 60 min at 37°C. The nucleus was counterstained with DAPI. The nuclei were stained with DAPI and identified as a control. At the end of this procedure, coverslips were mounted on a slide glass and visualized by confocal microscopy (Olympus Laser scanning microscope, Japan). TUNEL-positive cells were counted by Image J.

Animals and PSM-04 Treatment

5xFAD transgenic (Tg) mice expressing five human APP and PS1 genes [three in APP (Swedish mutation: K670N, M671L; Florida mutation: I716V; London mutation: V717I) and two in PS1 (M146L, L286V)] were donated by Seoul National University and maintained by crossing hemizygous transgenic mice with B6SJL F1 mice. A 12L:12D photoperiod was provided, and the temperature and humidity of the breeding room were automatically maintained at 22°C ± 2°C and 50 ± 10%, respectively. Food and water were provided *ad libitum* during the acclimation period to the polycarbonate cage.

PSM-04 or vehicle (saline) was orally administered to 4-month-old Tg or WT mice for 2 months, followed by the experimental scheme in **Figure 3A**. Each experimental group comprised 6–10 male mice per the following group: *vehicle*-treated *wild-type mice* (WT-v, $n = 10$); 5-mg/kg PSM-04-treated *wild-type mice* (WT-PP-5, $n = 10$); *vehicle*-treated Tg *mice* (Tg-v, $n = 8$); 5-mg/kg PSM-04-treated Tg *mice* (Tg-PP-5, $n = 8$); 10-mg/kg PSM-04-treated Tg *mice* (Tg-PP-10, $n = 8$); and donepezil-treated Tg *mice* (Tg-DP, $n = 6$) (**Figure 3A**). This study was performed in agreement with the principles of the Basel Declaration and recommendations of the Institutional Animal Care and Use Committee of the Lee Gil Ya Cancer and Diabetes Institute, Gachon University. The protocol was approved by the Institutional Animal Care and Use Committee of the Lee Gil Ya Cancer and Diabetes Institute, Gachon University (LCDI-2015-0025).

Novel Objective Recognition Task

We conducted Novel objective recognition (NOR) task with the six groups of Tg mice to assess the changes in cognition and memory. NOR task was performed as described previously (Leger et al., 2013). The setup comprised a black-walled square box measuring 40 × 40 × 40 cm^3. On the first day, mice were placed in the middle of the open-field box and allowed to adapt for 30 min. Next day, two same objects were placed in the box, and mice were habituated for 30 min. Last day, one object was changed to a novel object, and the exploration time of novel or familiar object was recorded for 5 min using the EthoVision XT 9 system (Noldus Information Technology, Wageningen, Netherlands). The following parameters were measured: the total exploration time, frequency, objective recognition time, and the memory index. The memory index is calculated by the exploration time for each object divided by the total exploration time.

Immunohistochemistry

The mice were anesthetized with Zoletil and Rompun mixture (1 mg/g, ip) and euthanized by transcardial perfused with saline. Brain hemisphere tissues were fixed in 4% paraformaldehyde at 4°C for 24 h and were then dehydrated and paraffin-embedded. Paraffin-embedded tissues were cut at 4-μm thickness from the hippocampal region using a microtome (Thermo Electron Corporation, United States). Serial sections were placed on a slide glass. The brain slides were placed in a 60°C incubator for 1 h, rinsed with xylene for deparaffinization, and washed by ethanol series for dehydration. The brain slides were retrieved by treatment with 0.01-M citric acid (pH 6.0) for 10 min at 60°C and washed with 0.5% Triton X-100 in Tris-buffered solution. The slides were incubated with primary antibody (6E10) overnight at 4°C in Tris-buffered solution. For DAB staining, the tissue slide was incubated with liquid DAB substrate chromogen (DAKO, Japan) for 10 min at room temperature. The slides were washed with PBS and coverslipped with mounting solution. Extracellular Aβ load was evaluated in the cortex and the dentate gyrus of the hippocampus using a Zeiss AxioImager Z1 microscope equipped with Axiocam HRC camera and the Image J software (V1.4.3.67, NIH, United States). Serial images of 40 × or 100 × magnification were captured on an average of 2–3 sections per animal. The Aβ plaque load in the same brain region of the same size was measured with blind count and presented as numbers in the area.

Western Blotting

For Western blot, brain tissues were lysed with RIPA buffer containing a cocktail of protease inhibitors (Roche Science, Mannheim, Germany) and a cocktail of phosphatase inhibitors (Sigma Aldrich). Protein was loaded on 8%–12% SDS–PAGE gel and transferred onto a PVDF membrane (Merck). Then, membranes were incubated in 6% skim milk for 1 h at room temperature. The primary antibody (SOD2 or β-actin) was incubated overnight at 4°C. After washing with TBS-T, membranes were incubated with the proper secondary antibody for 1 h at room temperature. The membranes were detected using the Pico EPD Western blot detection kit (ELPIS-Biotech, South Korea). The immunoblots were imaged using BLUE detection medical X-ray film (AGFA, Mortsel, Belgium). Quantification of blots was analyzed using the Image J software.

Statistical Analysis

Statistical analysis was performed using the one-way analysis of variance (ANOVA) followed by the Newman–Keuls *post hoc* test. All data were expressed as mean ± standard error of the mean (SEM) value. The difference was considered statistically significant for $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$. All calculations were performed using SPSS 23 (IBM, United States) or GraphPad Prism software (GraphPad Software Inc.).

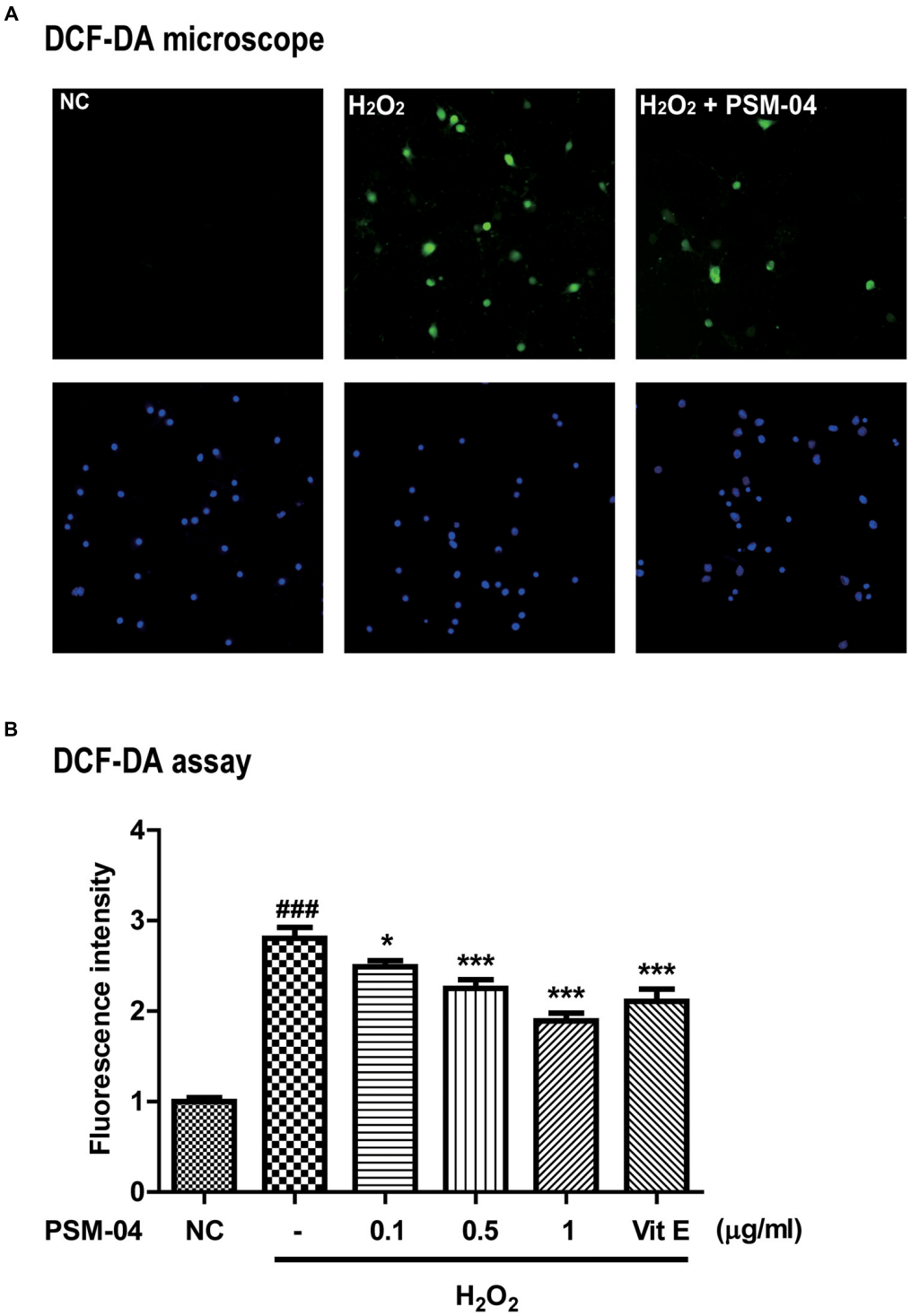

FIGURE 2 | PSM-04 reduced the ROS generated by H_2O_2. Primary cortical neurons were treated with PSM-04 (0.1, 0.5, and 1 μg/mL) at 12 h before 200-μM H_2O_2 treatment. ROS production was determined by the DCF-DA assay. **(A)** Primary cortical neurons were stained with DCF-DA (green), counterstained with DAPI (blue), and visualized via fluorescence microscopy. It was seen that 1-μg/mL PSM-04 reduced the number of oxidative stress-induced cells by 200-μM H_2O_2 treatment. **(B)** The quantification of DCF-DA fluorescence was shown as a ratio versus the control. PSM-04 or vitamin E significantly reduced the fluorescence intensity (ROS production) induced by 200-μM H_2O_2 treatment. All data are given as means ± SEM, and each experiment was repeated five times (n = 4–6 wells per group, N = 5). The statistical analyses were performed by one-way ANOVA followed by the Newman–Keuls *post hoc* test. $^{###}p < 0.001$ vs. control (NC). $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$ vs. H_2O_2 only.

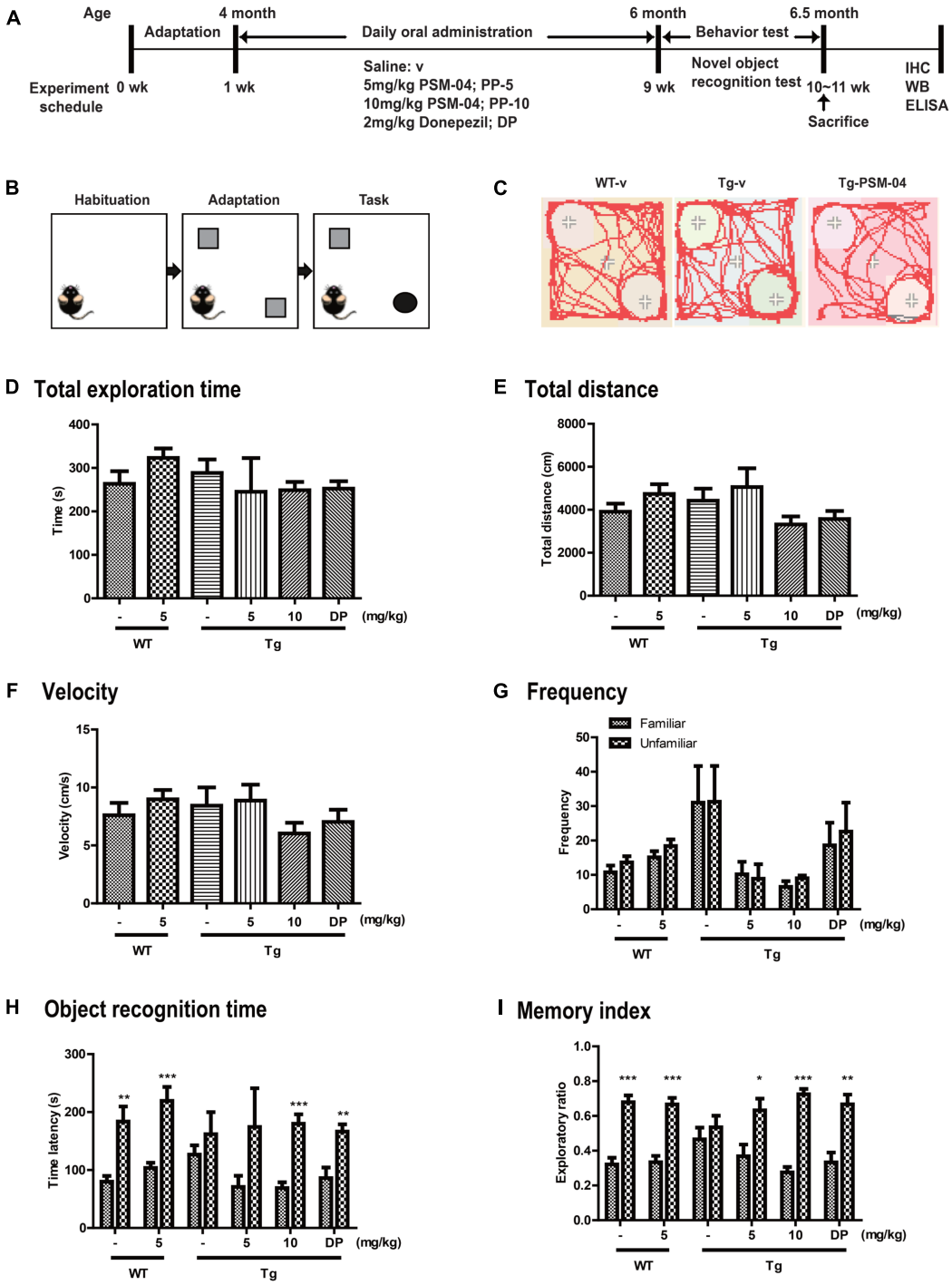

FIGURE 3 | PSM-04 alleviated cognitive impairment in 5xFAD mice. **(A)** A schematic diagram of the *in vivo* experimental plan is shown. **(B)** The design of a novel object recognition (NOR) task is shown; in the habituation phase (30 min duration), mice were adapted to the open-field box. In the adaptation phase, the mice were exposed to two same objects. On the last day, one object was changed to a novel object and recorded for 10 min. **(C)** Representative track sheets showed alteration in locomotion and exploratory behavior in the NOR task (distance traveled to familiar vs. unfamiliar object). **(D–I)** Graphs represent total exploration time **(D)**, total distances **(E)**, velocity **(F)**, frequency **(G)**, objective recognition time **(H)**, and the memory index **(I)**. The statistical analyses were performed by one-way ANOVA, and data are presented as means ± SEM. $*p < 0.05$, $**p < 0.01$, and $***p < 0.001$. Vehicle-treated WT mice (WT-v, $n = 8$); 5-mg/kg PSM-04-treated WT mice (WT-PP-5, $n = 10$); vehicle-treated Tg mice (Tg-v, $n = 7$); 5-mg/kg PSM-04-treated Tg mice (Tg-PP-5, $n = 6$); 10-mg/kg PSM-04-treated Tg mice (Tg-PP-10, $n = 6$); donepezil-treated Tg mice (Tg-DP, $n = 5$).

RESULTS

PSM-04 Did Not Induce Cytotoxicity in Primary Cortical Neurons

We first checked whether PSM-04 causes cytotoxicity in primary cortical neurons or not. To measure the cytotoxicity of PSM-04, we treated primary cortical neurons with various concentrations of PSM-04 (0.1, 0.5, 1, and 5 μg/mL) for 24 h and then evaluated the cell viabilities by a WST-1 assay. The treatment of PSM-04 did not induce cytotoxic events (**Supplementary Figure S1A**).

Neuroprotective Effect of PSM-04 Against the Excitotoxicity Induced by L-Glutamate Treatment

We studied the neuroprotective effects of PSM-04 against the neurotoxicity induced by L-glutamate. Glutamate plays an important role in neurotransmission in the brain, but it causes cell death if it is present in excess (Amor et al., 2010), leading to neurodegenerative diseases, such as AD. To measure the excitotoxic effects of L-glutamate, we evaluated cell viability by performing the CCK-8 assay after treatment of L-glutamate at various concentrations in primary cortical neurons for 2 h. Based on this result, we treated primary cortical neurons with 100-μM L-glutamate for 2 h after they were treated with 1-μg/mL PSM-04 or 200-ng/mL BDNF for 12 h. Then, we performed the CCK-8 assay (**Supplementary Figure S2A**) and TUNEL staining (**Supplementary Figure S2B**) to evaluate apoptotic cell death. The cell viability of the L-glutamate-treated cell decreased compared to that of the control (36.01 ± 1.62%) (**Supplementary Figure S2A**). PSM-04 rescued L-glutamate -induced cell death in a dose-dependent manner and showed a protective effect at 0.5 and 1 μg/mL (41.57 ± 1.47%, $p < 0.001$ and 42.88 ± 1.30%, $p < 0.001$, respectively) significantly; BDNF treatment also increased cell viability (48.99 ± 1.95%, $p < 0.001$) (**Supplementary Figure S2A**). In **Supplementary Figure S2C**, the 100-μM L-glutamate treatment (32.82% ± 1.26%) increased apoptosis compared with the control (16.64% ± 1.19%). Primary cortical neurons pre-treated with PSM-04 or BDNF showed that apoptotic cell death was reduced (20.2 ± 1.19%, $p < 0.001$; 20.13 ± 1.26%, $p < 0.001$) compared with the L-glutamate -only treatment (**Supplementary Figure S2C**).

Protective Effect of PSM-04 on the Neurotoxicity Induced by Oligomeric $A\beta_{1-42}$

We checked the neuroprotective effects of PSM-04 against oligomeric $A\beta_{1-42}$ peptide-induced neurotoxicity. Oligomeric $A\beta_{1-42}$ peptides (Aβ) play a pathological role in neurodegenerative diseases in AD (Neves et al., 2008). After pretreatment with various concentrations of PSM-04 (0.1, 0.5, 1, and 5 μg/mL) for 12 h, 20 μM of Aβ was treated for 12 h, and the WST-1 assay was performed to confirm cell viability. In this condition, the cell viability of the Aβ-treated cell decreased compared to that of the control (42.63 ± 1.28%) (**Figure 1B**). PSM-04 rescued Aβ-induced cell death in a dose-dependent manner and showed a protective effect at 1 μg/mL (56.87 ± 3.24%, $p < 0.001$) significantly; BDNF treatment also increased cell viability (54.49 ± 2.93%, $p < 0.001$) (**Figure 1B**).

Next, TUNEL staining was performed to confirm that apoptotic cell death was reduced by PSM-04. Primary cortical neurons were treated with 1 μg/mL of PSM-04 for 12 h, and then, were treated with 20 μM of Aβ for 12 h. The apoptotic cell death was visualized by TUNEL staining (red) and counterstaining with DAPI (blue) (**Figure 1C** and **Supplementary Figure 3**). Primary cortical neurons pre-treated with PSM-04 showed that apoptotic cell death induced by Aβ was reduced (15.83 ± 1.22%, $p < 0.001$) compared to that observed with Aβ-only treatment (23.2 ± 1.18%); further, BDNF treatment also reduced apoptotic cell death (16.53 ± 1.35%, $p < 0.001$) (**Figure 1D**).

Neuroprotective Effect of PSM-04 on the ROS Generation Induced by H_2O_2

We studied the neuroprotective effects of PSM-04 on the oxidative stress induced by H_2O_2. H_2O_2 induces oxidative stress through ROS production in neurodegenerative diseases (Uttara et al., 2009).

We checked that PSM-04 reduced the intracellular ROS produced by H_2O_2 treatment in primary cortical neurons. To measure the ROS induced by H_2O_2, we treated primary cortical neurons with various concentrations of H_2O_2 for 10 min and evaluated the ROS level by the DCF-DA assay. H_2O_2 treatment increased ROS levels in a dose-dependent manner (**Supplementary Figure S1B**). Subsequently, we treated primary cortical neurons with 200-μM H_2O_2 for 10 min after pretreatment with 0.1, 0.5, and 1-μg/mL PSM-04 for 12 h. In DCF-DA staining, enhanced oxidative stress was observed in primary cortical neurons treated with H_2O_2 via fluorescence microscopy (**Figure 2A**). The fluorescence intensity was expressed as a ratio to the untreated control (NC) group. Primary cortical neurons pretreated with PSM-04 (H_2O_2 + 0.1 μg/mL PSM-04, 2.49 ± 0.08, $p < 0.05$; H_2O_2 + 0.5-μg/mL PSM-04, 2.22 ± 0.12, $p < 0.001$; H_2O_2 + 1-μg/mL PSM-04, 1.80 ± 0.09, $p < 0.001$) showed reduced ROS generation compared to H_2O_2-only treatment (2.90 ± 0.14). In this result, H_2O_2-induced ROS production was significantly reduced by PSM-04 (**Figure 2B**).

These results indicated that PSM-04 increased cell viability and reduced apoptosis and ROS generation.

PSM-04 Alleviated Cognitive Impairment in 5xFAD Mice

From the *in vitro* studies, PSM-04 reduced the neurotoxicity induced by L-glutamate or oligomeric $A\beta_{1-42}$. PSM-04 also reduced the oxidative stress induced by H_2O_2. Here, we investigated whether PSM-04 is therapeutically effective in 5xFAD mice. Currently, a biomarker for AD is unknown (Blennow et al., 2015). Thus, patients with AD usually visit the hospital when they have mild cognitive impairment. In 5xFAD mice, memory deficits are detected from 4–6 months of age (Zeng et al., 2015). Therefore, we administered PSM-04 4 months-old 5xFAD mice. We treated 5xFAD mice with 5 or 10 mg/kg of PSM-04 or 2 mg/kg of donepezil (dissolved in 0.3% CMC) by oral administration daily for 2 months. To

investigate the alleviation of cognitive impairment, we performed a novel objective recognition (NOR) task. As shown in the schematic diagram of the NOR task (**Figures 3B,C**), we checked the time spent in object recognition; WT-v showed significantly longer time spent exploring the unfamiliar object (familiar, 79.85 ± 10.08 s; unfamiliar, 183.62 ± 26.02 s, $p < 0.01$), whereas Tg-v showed comparable time spent exploring familiar and unfamiliar objects (familiar, 126.54 ± 16.07 s; unfamiliar, 161.96 ± 37.85 s) (**Figure 3H**). The Tg mice treated with 5-mg/kg or 10-mg/kg PSM-04 exhibited significantly longer time spent exploring the unfamiliar object (5-mg/kg PSM-04: familiar, 70.9 ± 19.34 s; unfamiliar, 174.43 ± 66.68 s, and 10 mg/kg PSM-04 familiar, 68.99 ± 9.86 s; unfamiliar, 179.83 ± 16.27 s, $p < 0.001$) (**Figure 3H**). The memory index also increased in Tg mice treated with 5-mg/kg (familiar, 0.37 ± 0.07 s; unfamiliar, 0.63 ± 0.07 s, $p < 0.05$) or 10 mg/kg PSM-04 (familiar, 0.28 ± 0.03 s; unfamiliar, 0.72 ± 0.03 s, $p < 0.001$) compared with those treated with the vehicle (**Figure 3I**). There was no difference in total exploration time, speed, total distance, and frequency (**Figures 3D–G**). In this result, PSM-04 alleviated cognitive impairment in 5xFAD mice.

PSM-04 Reduced Amyloid Plaques in the Hippocampus but Not in the Cortex

Amyloid deposition is known to occur in 5xFAD mice at 1.5 months (Oakley et al., 2006). To investigate deposition of amyloid plaques in the hippocampus and cortex, immunohistochemistry was performed using 6E10 antibody (**Figure 4A**). Although WT mice showed no amyloid plaques, amyloid plaques were observed in Tg-vehicle mice in most regions of the brain (25 ± 3.02 n) (**Figure 4B**). In the dentate gyrus, the number of amyloid plaques was significantly reduced in the Tg-5-mg/kg (16.58 ± 2.58 n, $p < 0.05$) or Tg-10-mg/kg PSM-04-treated mice (16.50 ± 3.24 n, $p < 0.05$) (**Figure 4B**). Compared with Tg-vehicle mice (5.35 ± 0.91 n), amyloid plaque load was also reduced in the Tg-5-mg/kg (3.18 ± 0.89 n, $p < 0.05$) or Tg-10-mg/kg PSM-04-treated mice (2.73 ± 0.23 n, $p < 0.05$) in the dentate gyrus (**Figure 4D**). However, in the cortex, amyloid plaques were not significantly reduced in the Tg-5-mg/kg or Tg-10 mg/kg PSM-04-treated mice (**Figures 4C,E**).

These results indicated that PSM-04 reduced amyloid plaques in the dentate gyrus of the hippocampus but not of the cortex.

PSM-04 Reduced Gliosis in the Dentate Gyrus

In 5xFAD mice, gliosis was detected at 6 months of age (Girard et al., 2014). To investigate whether gliosis was present in the dentate gyrus and it was reduced by PSM-04, we performed immunohistochemistry using GFAP antibody (**Supplementary Figure S4**). The number of GFAP-positive cells were increased in Tg mice (1.99 ± 0.26, $p < 0.05$) compared to WT mice (1 ± 0.10). Conversely, 5 mg/kg (1.06 ± 0.20, $p < 0.05$) or 10 mg/kg (1.01 ± 0.24, $p < 0.05$) of PSM-04 treatment reduced the number of GFAP-positive cells.

PSM-04 Increased the Expression of SOD-2 and BDNF in the Brain of 5xFAD Mice

Next, we tried to reveal the possible molecular mechanism under the neuroprotective effects of PSM-04 on AD. In a previous study, the overexpression of superoxide dismutase (SOD-2) reduced hippocampal superoxide and prevented memory impairment in 5xFAD mice (Massaad et al., 2009) and brain-derived neurotrophic factor (BDNF) signaling was shown to exert neuroprotective effects against Aβ peptide toxicity *in vivo* and *in vitro* (Arancibia et al., 2008). Therefore, the effect of PSM-04 treatment on the expression of SOD-2 and BDNF protein in the hippocampus of Tg mice was investigated. The expression levels of SOD-2 were decreased in Tg mice ($P < 0.05$) compared to WT mice and PSM-04 significantly increased SOD-2 protein level compared to Tg-vehicle mice (**Figures 5A,B**). In addition, mature.BDNF (mat.BDNF)/pro-BDNF ratio also was decreased in Tg mice ($P < 0.05$) compared to WT mice (**Supplementary Figures S5A,B**). While PSM-04 rescued SOD-2 protein level in Tg mice, PSM-04 slightly increased the mat.BDNF/proBDNF ratio, but not significant (**Supplementary Figures 5A,B**).

DISCUSSION

PSM-04, the root extract of *P. tenuifolia* Willdenow with improved bioabsorption, has been investigated for its neuroprotective effects in *in vitro* and *in vivo* models of Alzheimer's disease. *In vitro* studies showed that PSM-04 dose-dependently reduced not only L-glutamate- or oligomeric Aβ-induced apoptosis but also H_2O_2-induced oxidative stress in primary cortical neurons. *In vivo* study suggested that the oral administration of PSM-04 prevented cognitive impairments and reduced amyloid plaques and gliosis in 5xFAD (Tg) mice brains. Furthermore, the administration of PSM-04 increased superoxide dismutase-2 (SOD-2) protein level in the hippocampus. It was concluded that PSM-04 could be considered for the treatment of neurodegenerative diseases, including AD.

In chronic neurodegenerative diseases, including Parkinson's disease, Huntington disease, and AD, neuronal loss induced by neurotoxin is one of the important characteristics. Particularly, AD is characterized by the deposition of Aβ in the brain, which results in the neurotoxicity (Suh and Checler, 2002). In addition, oxidative stress is also an important factor in the pathogenesis of neurodegenerative diseases, including AD (Butterfield et al., 2001). Several studies have implicated oxidative stress in Aβ-induced neurotoxicity (Apelt et al., 2004; Mohmmad Abdul et al., 2006). Further, Aβ increases the levels of hydrogen peroxide and lipid peroxides (Behl et al., 1994). In addition, the intracellular accumulation of ROS may contribute to memory dysfunction and cognitive impairment in AD (Vitte et al., 2004). Therefore, Aβ induced neurotoxicity by oxidative stress, resulting in neuronal loss and cognitive dysfunction.

Several animal and human studies have reported that the extract of *P. tenuifolia* Willdenow reduces neurotoxicity and improves cognitive impairment (Park et al., 2002; Lee et al., 2009;

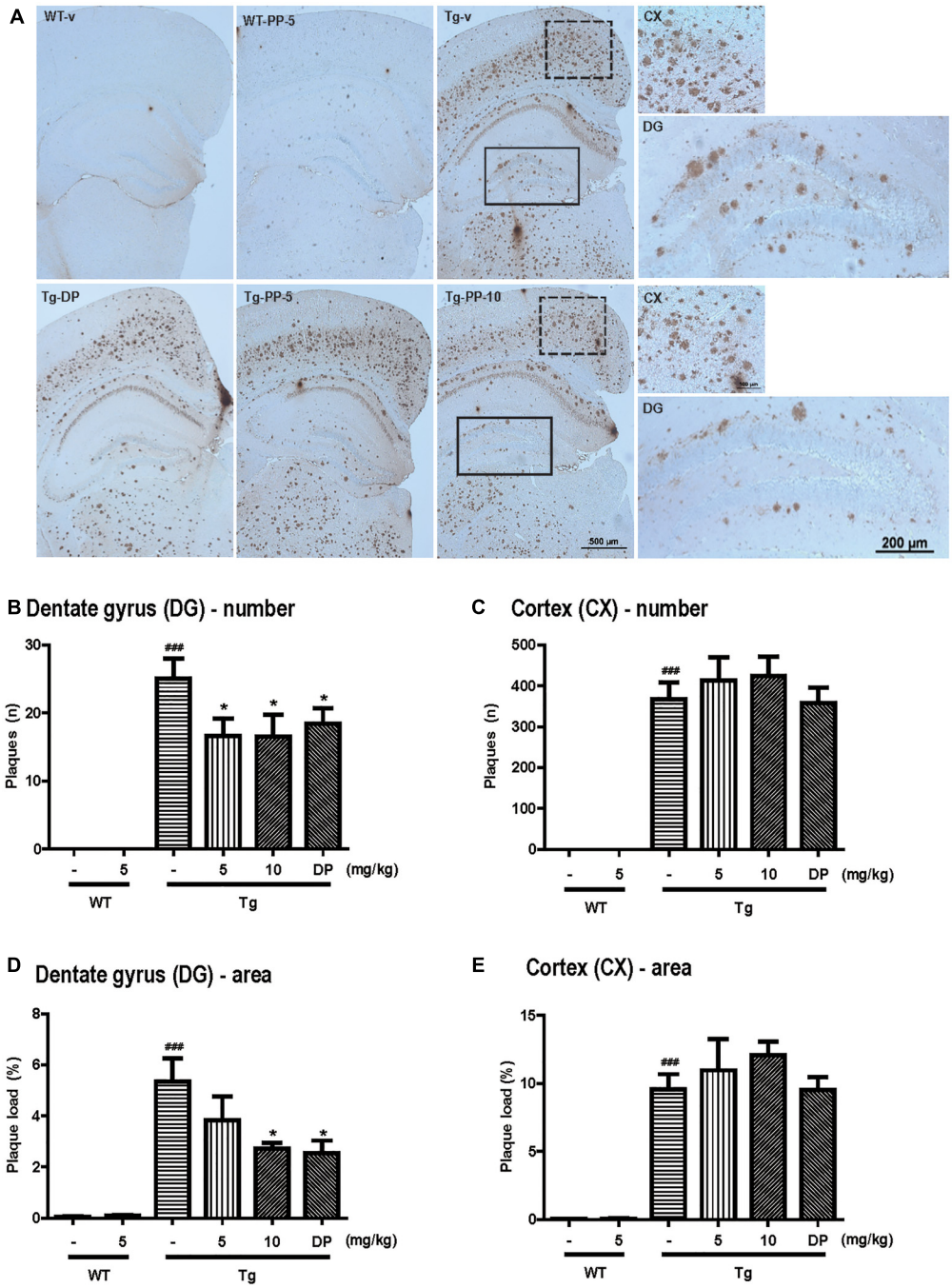

FIGURE 4 | PSM-04 reduced amyloid plaques in the brains of 5xFAD mice. **(A)** Immunohistochemistry using a 6E10 antibody to stain amyloid plaques in the brains. Amyloid plaques were calculated as plaque counts **(B,C)** and plaque area **(D,E)** in the dentate gyrus **(B,D)** and the cortex **(C,E)**. In the dentate gyrus, amyloid plaque counts **(B)** and plaque area **(D)** significantly reduced in PSM-04-treated Tg brains compared with the non-treated Tg brains. However, there was no change in the plaque count **(C)** and plaque area **(E)** in the cortexes of PSM-04-treated Tg brains and non-treated Tg brains. The statistical analyses were performed by one-way ANOVA, and data are presented as the means ± SEM. $^{###}$ $p < 0.001$ vs. WT-v; $^{*}p < 0.05$ vs. Tg-v. WT-v ($n = 8$); WT-PP-5 ($n = 9$); Tg-v ($n = 7$); Tg-PP-5 ($n = 6$); Tg-PP-10 ($n = 6$); and Tg-DP ($n = 5$).

Shin et al., 2009a; Liu et al., 2010). However, these studies used a "depression-like behavior" mice model or "scopolamine-induced amnesia" rat model, neither of which is an Alzheimer's disease animal model.

In this study, we showed that PSM-04 itself did not induce cytotoxicity at concentrations of 0.1–5 μg/mL in primary cortical neurons but it rather reduced apoptosis from excessive L-glutamate-induced neurotoxicity

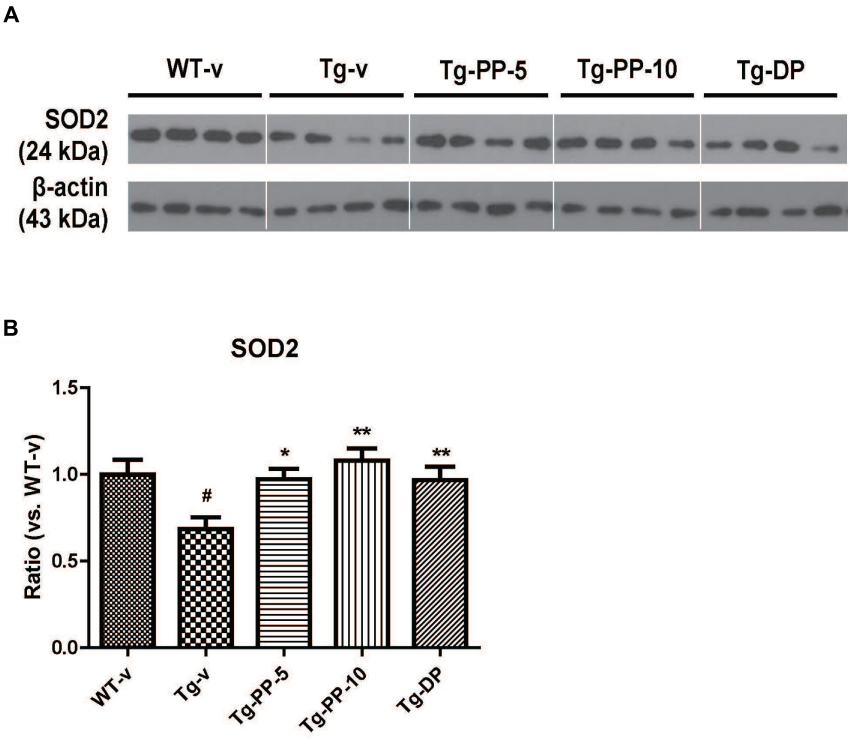

FIGURE 5 | PSM-04 increased the expression of SOD-2 in the brain of 5xFAD mice. Representative Western blot demonstrating protein expression levels of SOD-2 in the hippocampus of each group. **(A)** Representative blot showing that SOD-2 protein levels increased in the hippocampal tissue lysates of PSM-04-treated Tg mice compared with those of the non-treated Tg mice. **(B)** The relative SOD-2 protein levels were shown as a ratio versus to the control (Tg-v). The statistical analyses were performed by one-way ANOVA, and data are presented as the means ± SEM. $^{\#}p < 0.05$ vs. WT-v. $^{*}p < 0.01$ and $^{**}p < 0.01$ vs. Tg-v. WT-v ($n = 8$); WT-PP-5 ($n = 9$); Tg-v ($n = 7$); Tg-PP-5 ($n = 6$); Tg-PP-10 ($n = 6$); Tg-DP ($n = 5$).

(**Supplementary Figure S2A**). Because Aβ induces free radical oxidative stress and neurotoxicity in AD brain (Butterfield, 2002; Suh and Checler, 2002), we investigated whether PSM-04 has neuroprotective effects against oxidative stress induced by oligomeric Aβ in primary cortical neurons. We found that oligomeric Aβ-induced neurotoxicity was reduced by PSM-04 treatment in primary cortical neurons (**Figure 1B**) and that PSM-04 also reduced ROS generation induced by H_2O_2 (**Figure 2**). These results show that PSM-04 has neuroprotective effects against neurotoxicity induced by glutamate, oligomeric Aβ, or oxidative stress in primary cortical neurons. Next, we evaluated the *in vivo* therapeutic effects of PSM-04 in 5xFAD mice. At first, the NOR task was performed by the 6-month-old 5xFAD mice after 2-months of daily oral administration of PSM-04. The NOR test is a highly validated test for assessing recognition memory and is now among the most commonly used behavioral tests for mice (Leger et al., 2013). Tg-PSM-04 groups showed increased cognition of the novel object compared with the Tg-vehicle group. Regarding pathological changes, the Tg-PSM-04 mice showed reduced amyloid plaques and fewer GFAP-positive glial cells compared with Tg-vehicle mice. Next, we tried to determine the exact mechanism through which PSM-04 alleviated cognitive impairment and reduced amyloid plaques and gliosis in the dentate gyrus of the hippocampus region in the brain. Symptoms of AD in humans not only include memory loss but also neuropsychiatric, behavioral, and psychological symptoms of dementia (BPSD) (Lalonde et al., 2012). Although BPSD is very common in dementia, no pharmacological therapy or medication has yet been developed because of the lack of efficacy and safety (Huang et al., 2012). Recent researches show that BPSD occurs in the animal model of AD as well (Lalonde et al., 2012; Pfeffer et al., 2018) and is related with the dysfunction of NMDA neurotransmission (Huang et al., 2012) and Aβ-induced neurotoxicity (Tamano et al., 2016). Furthermore, studies on the antidepressant-like effect of *P. tenuifolia* Willdenow have been increasing in recent times (Shin et al., 2014; Zhu et al., 2017). Therefore, the neuroprotective effect of PSM-04 may alleviate BPSD in the 5xFAD mice; however, to establish this, the BPSD-like behavior in the 5xFAD mice needs to be further studied to investigate the possibility of PSM-04 treatment in BPSD.

We have looked at the proteins that can be involved with the neuroprotective effects of PSM-04, such as SOD and BDNF. SOD-2, known as manganese-dependent superoxide dismutase (MnSOD), is an enzyme that removes mitochondrial ROS and consequently prevents cell death (Pias et al., 2003). In AD, the interaction of ROS and AD is supported by clinical findings that revealed an upregulation of antioxidant enzymes, such as SOD-2 (De Leo et al., 1998). In addition, SOD-2 plays an anti-apoptotic role against oxidative stress (Becuwe et al., 2014). Further, the

overexpression of SOD-2 protein prevents memory impairment in AD model mice (Massaad et al., 2009). In our result, SOD-2 protein levels increased in the hippocampal tissue lysates of PSM-04-treated Tg mice compared with the non-treated Tg mice. This result, including *in vitro* results, suggests that PSM-04 exerts neuroprotective effects by removing ROS and modulating the expression of ROS regulatory proteins such as SOD-2.

BDNF is a neurotrophin essential for long-term synaptic plasticity and memory formation as well as in synaptogenesis (Cunha et al., 2010). Dysregulation of BDNF signaling is involved in several neurodegenerative diseases, including AD (Schindowski et al., 2008). BDNF protein is formed from the cleavage of a 35-kDa proBDNF protein and is secreted as the 15-kDa mature BDNF (mat.BDNF) (Lessmann et al., 2003). Protease mediated conversion of proBDNF to mBDNF is considered to be an important mechanism contributing to activation-dependent synaptic competition in the central nervous system (CNS) (Lu et al., 2005). In our result, while mat.BDNF/pro-BDNF ratio was decreased in Tg mice, PSM-04 did not significantly rescue the mat.BDNF/proBDNF ratio (**Supplementary Figure 5**). These results suggest PSM-04 could relate with not processing mechanism of BDNF but another pathway.

Taken together, due to its ability to enhance neuroprotective effects by reducing apoptosis and ROS production, PSM-04 can be a potential pharmacological agent for treating neurodegenerative diseases, particularly in the treatment of Alzheimer's disease.

AUTHOR CONTRIBUTIONS

K-AC and Y-HS supervised the project and designed the experiments. HP carried out the experiments, analyzed data, and wrote the manuscript. SK guided mouse behavior test. EN assisted in analyzing the data. All authors performed data quantification, discussed the results, and commented on the manuscript.

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SUPPLEMENTARY MATERIAL

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FIGURE S1 | PSM-04 did not induce cytotoxicity and H_2O_2 treatment increased ROS production in primary cortical neurons. **(A)** Primary cortical neurons were treated with PSM-04 (0.1, 0.5, 1, and 5 μg/mL) for 12 h, and cell viability was then measured using the WST-1 assay. PSM-04 was not found to affect cytotoxicity in primary cortical neurons (n = 7∼10 wells per group, N = 5). **(B)** Primary cortical neurons were treated with various concentrations (50, 100, 200, or 400 μM) of H_2O_2 for 10 min. In the DCF-DA assay, fluorescence intensity was significantly increased in a dose-dependent manner, indicating that ROS production was increased by H_2O_2 treatment (n = 2 wells per group, N = 3). The statistical analyses were performed by T-test, and data are presented as the means ± SEM. $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$ vs. control.

FIGURE S2 | PSM-04 reduced cytotoxicity induced by L-glutamate in primary cortical neurons. The primary cortical neurons were treated with L-glutamate for 2 h, and then, cell viability was measured using the WST-1 assay and TUNEL staining. **(A)** Cell viability was the reduced by L-glutamate (L-glu) treatment in a dose-dependent manner (n = 4∼6 wells per group, N = 5). **(B–C)** The apoptotic cell death in primary cortical neurons treated with 100-μM L-glu for 2 h was visualized via TUNEL staining. **(B)** It was seen that 1-μg/mL PSM-04 or 200-ng/mL BDNF reduced the apoptotic cell death induced by 100-μM L-glu. **(C)** TUNEL-positive cells were counted and analyzed (n = 3 wells per group, N = 5). The statistical analyses were performed by T-test, and data are presented as the means ± SEM. $^{\#}p < 0.05$ vs. control (NC). $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$ vs. L-glutamate only.

FIGURE S3 | PSM-04 reduced cytotoxicity induced by Aβ in primary cortical neurons. TUNEL staining was performed using the primary cortical neurons treated with PSM-04 for 12 h before being treated with 20-μM Aβ for 2 h. The apoptotic cell death was visualized in red fluorescence, and the nuclei were counterstained with DAPI.

FIGURE S4 | PSM-04 reduced gliosis in the dentate gyrus. **(A)** Immunohistochemistry using a GFAP antibody to stain astrocyte in the cortex and dentate gyrus. **(B)** The number of GFAP-positive cells per area were counted in the dentate gyrus. The statistical analyses were performed by one-way ANOVA, and data are presented as the means ± SEM. $^{\#}p < 0.05$ vs. WT-v; $^{*}p < 0.05$ vs. Tg-v. WT-v (n = 8); WT-PP-5 (n = 9); Tg-v (n = 7); Tg-PP-5 (n = 6); Tg-PP-10 (n = 6); Tg-DP (n = 5).

FIGURE S5 | PSM-04 slightly increased the ratio of mat.BDNF to proBDNF in the brain of 5xFAD mice. **(A)** Representative Western blot demonstrating protein expression levels of proBDNF and mat.BDNF in the hippocampus of each group. **(B)** The ratio of mat.BDNF to proBDNF normalized to the WT group. In the hippocampal lysates of PSM-04 treated Tg mice, the ratio of mat.BDNF / proBDNF slightly increased compared to the hippocampal lysates of Tg-v mice, but it was not significant. The statistical analyses were performed by one-way ANOVA, and data are presented as the means ± SEM. $^{\#\#}p < 0.01$ vs. WT-v. WT-v (n = 8); WT-PP-5 (n = 9); Tg-v (n = 7); Tg-PP-5 (n = 6); Tg-PP-10 (n = 6); Tg-DP (n = 5).

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REVIEW
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The Role of N-Methyl-D-Aspartate Receptor Neurotransmission and Precision Medicine in Behavioral and Psychological Symptoms of Dementia

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While the world's population is aging, the prevalence of dementia and the associated behavioral and psychological symptoms of dementia (BPSD) rises rapidly. BPSD are associated with worsening of cognitive function and poorer prognosis. No pharmacological treatment has been approved to be beneficial for BPSD to date. Dysfunction of the N-methyl-D-aspartate receptor (NMDAR)-related neurotransmission leads to cognitive impairment and behavioral changes, both of which are core symptoms of BPSD. Memantine, an NMDAR partial antagonist, is used to treat moderate to severe Alzheimer's disease (AD). On the other hand, a D-amino acid oxidase inhibitor improved early-phase AD. Whether to enhance or to attenuate the NMDAR may depend on the phases of dementia. It will be valuable to develop biomarkers indicating the activity of NMDAR, particularly in BPSD. In addition, recent reports suggest that gender difference exists in the treatment of dementia. Selecting subpopulations of patients with BPSD who are prone to improvement with treatment would be important. We reviewed literatures regarding the treatment of BPSD, focusing on the NMDAR-related modulation and precision medicine. Future studies examining the NMDAR modulators with the aid of potential biomarkers to tailor the treatment for individualized patients with BPSD are warranted.

Keywords: behavioral and psychological symptoms of dementia, Alzheimer's disease, N-methyl-D-aspartate receptor, precision medicine, gender difference

INTRODUCTION

Dementia is a severe neurodegenerative disorder, affecting 1.5% of the population at the age of 65, and >20% at the age of 85 (Ritchie and Kildea, 1995). The morbidity and mortality of dementia are high. For elderly people aged between 65 and 85 years, the prevalence rate of dementia doubles every 5 years (Fratiglioni et al., 1999). About 24.3 million people worldwide were diagnosed with dementia in 2005 (Ferri et al., 2005). In 2010, 35 million people had dementia worldwide (Brodaty et al., 2011). The population of people with dementia is estimated to be

65 million by 2030 and 113 million by 2050 (Brodaty et al., 2011). The prevalence rate has been rising fast in the rapid-aging society (Prince et al., 2016).

The etiology of dementia remains unclear. Its increasing prevalence rate contributes to both a health and social problem, resulting in heavy caregiver burdens and economic impacts to the societies (2012 Alzheimer's Disease Facts and Figures, 2012). Age and female gender are two major risk factors for Alzheimer's disease (AD), which is the main cause of dementia; two-thirds of elderly people with AD are women. Even regarding the difference in longevity, studies suggest that women are still at a higher risk (Prince et al., 2016). Precision medicine approaches have advanced our understanding of the development and treatment of AD dementia. However, gender has not yet been adequately addressed by many of these approaches. More attention to gender differences will improve outcomes for people with dementia (Nebel et al., 2018). Previous research on NMDAR function has focused on cognition, particularly learning and memory. The current article focuses on mood or other psychological symptoms rather than memory.

BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA IS COMMON AND DETRIMENTAL IN DEMENTED PATIENTS

One of the most troublesome domains of treating dementia is the behavioral and psychological symptoms of dementia (BPSD). The term "BPSD" was first described in late 1980s, and was then defined as "a term used to describe a heterogeneous range of psychological reactions, psychiatric symptoms, and behaviors occurring in people with dementia of any etiology" in the 1996 International Psychogeriatric Association (IPA) consensus conference (Finkel, 2003). BPSD can be classified into four domains: (1) disorders of thought content, including delusions, suspiciousness, etc. (Burns et al., 1990a); (2) disorders of perception, including misidentification syndromes, hallucinations, etc. (Burns et al., 1990b); (3) disorders of mood, including elevated mood, anxiety, depression, etc. (Burns et al., 1990c); and (4) disorders of behavior, including agitation, aggression, wandering, binge-eating, hyperorality, sexual disinhibition, urinary incontinence, etc. (Burns et al., 1990d).

BPSD is common among patients with dementia. Sixty-four percent of dementia patients revealed BPSD at initial evaluation (Devanand et al., 1997) and 90% of them had BPSD over the whole dementia course (Steinberg et al., 2008). In Taiwan, the prevalence rate of all types of BPSD in patients with AD is around 20–60%, varying with different symptoms (Fuh, 2006). About 30–60% patients with AD have delusion, 21–26% hallucination, 35–76% anxiety, 22–50% depression, and 26–61% sleep abnormalities (Fuh, 2006).

The manifestations of BPSD vary with different types and stages of dementia. Mood symptoms are usually more common while psychotic symptoms are less common in vascular dementia (VaD) (O'Brien, 2003). In Eastern Asia, patients with AD had a high incidence of anxiety/phobia (61.2%) and people with VaD had more paranoid and delusional ideation (71.9%) and affective disturbance (46.9%) (Chiu et al., 2006). Depression is more commonly observed in early stages of dementia while psychosis occurs more often in later stages (Paulsen et al., 2000; Savva et al., 2009). Furthermore, the severity of BPSD is often associated with the stage of dementia (Thompson et al., 2010). It is believed that BPSD without adequate treatment leads to poorer prognosis of dementia (Bourgeois et al., 1996; Shah and Allen, 1999; Brodaty et al., 2003; Huang et al., 2012).

NO CURRENT MEDICATION IS APPROVED BY FOOD AND DRUG ADMINISTRATION FOR TREATING BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

Despite the high prevalence rate of BPSD and its hazards in patients with dementia, there has not yet been medication that is effective and approved for the treatment of BPSD by the Food and Drug Administration (FDA) (Sink et al., 2005). The efficacy of antipsychotics for the treatment of BPSD is scanty (Schneider et al., 2006). In addition, there is safety concern for antipsychotics use in BPSD (Lee et al., 2004; Schneider et al., 2005). Furthermore, atypical antipsychotics may worsen the cognitive decline in patients with AD (Vigen et al., 2011), implying that antipsychotics may not be the best remedy for BPSD.

The efficacy of acetylcholinesterase inhibitors (AChEIs), which are the current main medication for AD, for treating BPSD is controversial (Huang et al., 2012).

N-METHYL-D-ASPARTATE RECEPTOR AND THE PATHOGENESIS OF DEMENTIA AND BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

N-methyl-D-aspartate receptors (NMDARs) exert multiple activities including two opposite ones: neurotoxicity and neurotrophic effects. Both NMDAR hypofunction and excitotoxicity are implicated in neurodegeneration. NMDAR activation is critical for synaptic plasticity, learning, and memory (Takehara et al., 2004; Zhao et al., 2005; Nakazawa et al., 2006; Gardoni et al., 2009). Attenuation of NMDAR neurotransmission can result in loss of neuronal plasticity and cognitive deficits (Collingridge and Bliss, 1995; Hawasli et al., 2007). Moreover, hypo-NMDAR function induced by NMDAR antagonists is neurotoxic, accounting for deterioration and brain atrophy (Olney and Farber, 1995).

NMDAR plays a vital role in the pathogenesis of AD. Compared with healthy controls, individuals with AD have fewer NMDARs in the frontal cortex and hippocampus (Procter et al., 1989), lower CSF concentrations of excitatory amino

acids (Martinez et al., 1993), lower serum levels of D-serine (Hashimoto et al., 2004), and reduced D-aspartate uptake (Lowe et al., 1990). In a mouse model of AD, expression of surface NMDARs decreases in neurons (Snyder et al., 2005). Amyloid-β peptide (Aβ), which is the pathological hallmark for AD, can impair NMDAR signal transduction and synaptic function (Shankar et al., 2007; Yamin, 2009; Cisse et al., 2011). Apolipoprotein E4, an amyloid binding protein isoform related to the AD risk, also decreases NMDAR functions in patients with AD (Chen et al., 2010). Loss of presenilins reduces NMDAR-mediated responses and synaptic levels of NMDAR subunits, thereby affecting both short- and long-term plasticity in AD pathogenesis (Pimplikar et al., 2010).

N-METHYL-D-ASPARTATE RECEPTOR INHIBITING AGENTS

Memantine, an NMDAR partial antagonist and a drug for treating moderate-to-severe AD, had conflicting data in the treatment of neuropsychiatric symptoms in dementia from randomized controlled trials (Reisberg et al., 2003; Tariot et al., 2004; Sink et al., 2005). In subsequent individual studies and pooled analyses (Gauthier et al., 2005, 2008; Wilcock et al., 2008), memantine had some benefits in the treatment of irritability/liability, agitation/aggression, and psychosis in patients with AD, but stronger evidence from randomized controlled trials for BPSD is still lacking (Ballard et al., 2009). Lately, memantine's effect for BPSD has been found to be boosted by combination of citalopram, an antidepressant (Zhou et al., 2019). Of note, an initial reason for the use of memantine to treat AD is the hypothesis that activity of the NMDAR could be a mechanism for cell death (Foster et al., 2017). Thus, a potential fear is that enhancing NMDAR function would adversely affect the trajectory of dementia. This may be true for a subclass of dementia. On the other hand, another hypothesis (Foster et al., 2017) also indicates that NMDAR hypofunction is more detrimental to the progression of AD and that the use of memantine as a treatment may be more detrimental, producing cognitive impairments.

Inhibition of NMDAR function by NMDAR antagonists, such as ketamine or phencyclidine, produces psychotic/behavioral symptoms or relevant physiological reactions (Oranje et al., 2002; Carlen et al., 2012; Lin et al., 2012). However, the NMDAR antagonist ketamine has been shown to exhibit antidepressant effects (Duman, 2018). Since depression is one of the BPSD symptoms, whether ketamine and its derivatives, as rapid-acting antidepressants, are beneficial for BPSD treatment deserves further studies (Steenblock, 2018).

NMDAR dysfunction is also involved in ischemic stroke and vascular dementia. Although some studies revealed serum glutamate elevation in acute phase of ischemia stroke (Gusev et al., 2000; Marcoli et al., 2004), this increment of glutamate was only found 10–30 min after ischemic injury (Benveniste et al., 1984). Similarly, NMDAR hyperfunction occurs very briefly after brain injury; soon after the acute glutamate elevation, profound NMDAR hypofunction ensues and lasts for >7 days (Biegon et al., 2004). In fact, trials using NMDAR antagonists in the treatment of stroke have failed (Ikonomidou and Turski, 2002).

N-METHYL-D-ASPARTATE RECEPTOR ENHANCING AGENTS

Enhancing NMDA neurotransmission can improve memory and behavior symptoms of both dementia and schizophrenia (Goussakov et al., 2010; Lane et al., 2013). Clinical characteristics of BPSD, such as hallucinations, delusions, disorganized speech, and disturbing behavior, resemble positive symptoms of schizophrenia. Social withdrawal, apathy, alogia, and avolition, which resemble negative symptoms in schizophrenia, and behavior, sleep, or affective problems, are also frequently seen in patients with schizophrenia.

Augmentation through the NMDA-glycine site, a co-agonist site, is preferred to avoid the excitotoxicity (Coyle and Puttfarcken, 1993; Collingridge et al., 2013; Hackos and Hanson, 2017; Yao and Zhou, 2017; Hsu et al., 2018). Clinically, D-cycloserine, a partial agonist of the NMDA-glycine site, can improve cognitive functions of demented patients (Schwartz et al., 1996; Tsai et al., 1999). There are also several studies that suggest no benefit of D-cycloserine in AD patients (Randolph et al., 1994; Fakouhi et al., 1995; Tsai et al., 1998). Several possible reasons may explain the discrepancies; the lack of effect may be due to the dose or symptoms examined. Alternatively, the effects of D-cycloserine may depend on the stage of dementia. Since D-cycloserine appears to have benefits in improving cognition (Kalisch et al., 2009; Onur et al., 2010; Kuriyama et al., 2011a,b; Feld et al., 2013), it may have differential effects on mood and learning depending on the stage of dementia.

Since D-serine is more potent than D-cycloserine and glycine as the glycine co-agonist site of the NMDAR (Heresco-Levy, 2005; Lin et al., 2012), one method to enhance NMDAR function is to inhibit activity of D-amino acid oxidase (DAAO), which is responsible for degrading D-serine and D-alanine (Fukui and Miyake, 1992; Vanoni et al., 1997). One of the candidates of DAAO inhibitors is benzoic acid and its salt, sodium benzoate. They can inhibit DAAO activity and thereby raise synaptic concentrations of D-serine both *in vitro* and in animal studies (Van den Berghe-Snorek and Stankovich, 1985).

Several clinical trials have shown the potential of NMDAR-enhancing agents [for example, sarcosine (a glycine transporter I inhibitor) and sodium benzoate] in alleviating psychotic symptoms of schizophrenia (Lane et al., 2005, 2006, 2008, 2010, 2013; Lin et al., 2018b), in treating major depressive disorder (Huang et al., 2013), in decreasing oppositional defiant disorder symptoms of attention deficit hyperactivity disorder (Tzang et al., 2016), and in reducing neuropsychiatric symptoms of Parkinson's disease with dementia (Tsai et al., 2014).

In a 6-week, randomized, double-blind, placebo-controlled trial in patients with schizophrenia (<65 year old), sodium benzoate (1 g/day) adjunctive therapy was significantly better than placebo in reducing positive and negative symptoms

and in improving Global Assessment of Functioning, and revealed favorable safety (Lane et al., 2013). The effect size of sodium benzoate treatment for Positive and Negative Syndrome Rating Scale (PANSS) total score from baseline to endpoint was 1.26, much higher than effect size (0.51) of sarcosine adjuvant therapy for the PANSS total score in chronic schizophrenia patients (Tsai et al., 2004). It is noteworthy that sodium benzoate treatment was significantly better than placebo in improving cognitive functions, such as processing speed and visual memory (Lane et al., 2013). In another clinical trial on mild cognitive impairment or mild AD, a total of 60 patients were randomized into sodium benzoate or placebo group. The patients also tolerated sodium benzoate 250–1,500 mg/day well without evident side effects. Interestingly, the patients taking sodium benzoate improved more in Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and other cognitive assessments than placebo (Lin et al., 2014).

Of note, a single nucleotide polymorphism (rs2153674) in the G72 (D-amino acid oxidase activator, DAOA, responsible for metabolism of D-serine) gene is associated with the occurrence of psychotic symptoms in patients with AD (Di Maria et al., 2009). In addition, affinity of the glycine recognition sites of NMDARs was related with the anxiety tone, one domain of BPSD, in patients with AD (Tsang et al., 2008). Therefore, it is possible that NMDAR-enhancing agents, which have been demonstrated to be effective in treating schizophrenia, depression, and other psychiatric symptoms, could also be used in the treatment of BPSD.

Moreover, stimulation of NMDARs 24 and 48 h after brain injury could attenuate neurological deficits and improve cognitive performance, implying that NMDAR function is crucial for neural repair in subacute or chronic stroke (Biegon et al., 2004). The aforementioned studies suggest the potential use of DAAO inhibitors for the treatment of BPSD.

GENDER DIFFERENCE IN N-METHYL-D-ASPARTATE RECEPTOR FUNCTION

Age and female gender are two major risk factors for AD; two-thirds of elderly people with AD are women. Even regarding the difference in longevity, studies suggest that women are still at a higher risk (Prince et al., 2016). However, gender has not yet been adequately addressed by many of these approaches. More attention to gender differences will improve outcomes for demented people (Nebel et al., 2018).

A previous study showed that female rats were much more susceptible to NMDAR modulation than males (Honack and Loscher, 1993). Another study found that the average density of NMDAR currents was 2.8-fold larger in dorsal root ganglia of female rats than that of male rats, and that addition of 17-ß-estradiol (E2) increased NMDAR currents by 55% in female neurons, but only 19% in male, indicating sex differences in the activity and estrogen modulation of NMDAR (McRoberts et al., 2007). Further, estrogen also plays a role in NMDAR function during aging (Vedder et al., 2014; Bean et al., 2015). E2 treatment can enhance the long-term potentiation (LTP) magnitude at CA3-CA1 synapses, NMDAR/AMPAR ratio, GluN2B-mediated NMDAR current, hippocampal CA1 dendritic spine density, and novel object recognition (NOR), a task that requires hippocampal NMDARs, in female rats during a critical period between 9 and 15 months, but not at 19 months post-ovariectomy (OVX) (Smith et al., 2010; Vedder et al., 2014).

Sex hormones were found to modulate hippocampal NMDAR expression in mice (McCarthny et al., 2018), and interact with circulating antioxidants in human blood (Bellanti et al., 2013). Noteworthily, benzoic acid ester of estrone, a precursor of estradiol, has prolonged duration of action (Labhart, 2012), suggesting that benzoate may interact with female sex hormone (Lemini et al., 1997).

Whether benzoate can improve cognitive function and the behavioral symptoms in patients with BPSD in a gender-specific manner deserves investigation. Further study is needed to verify the possible mediating roles of sex hormones in benzoate effect for dementia and its associated BPSD.

HUNTING FOR PERIPHERAL BIOLOGICAL MARKERS OF DEMENTIA

At present, the diagnosis of dementia mainly relies on clinical manifestation. There was no satisfactory laboratory test from the peripheral approach for the diagnosis of dementia. There have been lots of postmortem brain studies in fields of AD and related neurodegenerative disorders (Chen et al., 2001; Stewart et al., 2001). It was highly concerning that RNA expressions might be affected by many factors (e.g., coma. hypoxia) under postmortem condition (Tomita et al., 2004). A peripheral measurable marker is needed, to enable a simple, more rapid, and more accurate diagnosis and monitoring (Ilani et al., 2001; Lin et al., 2017a).

It is proposed that white blood cells and lymphocytes may serve as neural probes since there are similarities of signal transduction and receptor expression between peripheral blood cells and neurons/glia (Gladkevich et al., 2004). A blood-derived sample will be a more feasible alternative to brain tissue biopsy if the gene expressions are synchronized in both (Tsuang et al., 2005). For example, Hye et al. reported that glycogen synthase kinase-3 was increased in both AD and mild cognitive impairment patients (Hye et al., 2005). However, some molecules would be not suitable for serving as biomarkers, due to the large overlap between patient and control groups.

POTENTIAL PERIPHERAL PREDICTORS FOR TREATMENT RESPONSE OF N-METHYL-D-ASPARTATE RECEPTOR ENHANCERS

Precision medicine approaches have advanced our understanding of the development and treatment of dementia. Many genes

which lie in different pathways were found to be associated with susceptibility of dementia and/or psychosis. Genes on the pathways, which are associated with the metabolism of D-amino acids, glycine and glutamate, may be able to regulate the NMDAR function.

D-Amino Acids Metabolism

D-amino acid oxidase activator (DAOA, or named G72) protein regulates DAAO activity (Goldberg et al., 2006), enhances metabolism of D-serine and D-alanine, and can attenuate NMDAR neurotransmission. D-serine is generated from L-serine by serine racemase (SRR) (Wolosker et al., 1999) and degraded by DAAO (Nagata, 1992). Over the past few years, more than 30 studies have demonstrated the association of DAAO and G72 with schizophrenia (Boks et al., 2007). Diminished D-serine along with elevation in L-serine also suggests the dysfunction of SRR activity (Hashimoto et al., 2003). DAAO is implicated in oxidative stress (Stegman et al., 1998; Lu et al., 2012). Studies indicated that the DAAO level in peripheral blood increased with the severity of cognitive deficits in the elderly (Lin et al., 2017b) and decreased after 6-week treatment of sodium benzoate (a DAAO inhibitor) in patients with schizophrenia (Lin et al., 2018a). It is hypothesized that G72, DAAO, and SRR, which regulate the metabolism of the main co-agonist of the NMDAR, D-serine, are associated with dementia and its BPSD.

Glycine Metabolism

Glycine, a co-agonist of the NMDAR, is abundant throughout the brain and serves as a major inhibitory neurotransmitter in the hindbrain. Serine hydroxymethyltransferase (SHMT) is the enzyme which cleaves serine into glycine (Cossins et al., 1976). The activity of SHMT was significantly lower in psychotic individuals than in nonpsychotic ones (Waziri et al., 1985). Phosphoserine aminotransferase (PSAT) enzyme accounts for the serine biosynthesis (Pestka and Delwiche, 1981). Patients with PSAT deficiency manifest a broad spectrum of neuropsychiatric symptoms clinically (Hart et al., 2007). Glycine C-acetyltransferase, also known as GCAT, acts in concert with L-threonine 3-dehydrogenase (TDH) in the degradation of threonine to form glycine (McGilvray and Morris, 1969). Aminomethyltransferase (AMT) is an enzyme that catabolizes the creation of methylenetetrahydrofolate. It is part of the glycine decarboxylase complex.

Glutamate Metabolism

Glutamate is the most abundant amino acid neurotransmitter in the mammalian brain. Glutamatergic neurotransmission has drawn attention for its role in the pathophysiology of many mental illnesses (Lin et al., 2012). The extracellular concentration of glutamate is regulated by the action of transporter proteins, which include glial high-affinity glutamate transporter, member 3 (SLC1A3) (Kanai and Hediger, 2004) and neutral amino acid transporter (ASCT1) (Weiss et al., 2005). Glutamate receptor, metabotropic 3 (GRM3) (Carter, 2007) and glutamate receptor, ionotropic, kainate 1 (GluR5) (Wisden and Seeburg, 1993) are among the genes related to the glutamatergic neurotransmission systems. Glutamate decarboxylase 1 (GAD1), encoding the 67-kDa isoform of glutamate decarboxylase, is the key enzyme for GABA biosynthesis and is expressed at altered levels in postmortem brain of subjects diagnosed with schizophrenia and related psychotic disorders (Straub et al., 2007).

Increased oxidative stress also contributes to aging processes and neurodegenerative diseases (Gallagher et al., 1996; Serrano and Klann, 2004; Butterfield and Halliwell, 2019), while free radicals damage cells and tissues (Harman, 1956). Antioxidants may help to prevent and reverse cognitive deficits induced by free radicals (Guerrero et al., 1999; Bickford et al., 2000; Tardiolo et al., 2018). Studies indicate a link among age-related NMDAR dysfunction, oxidative stress, and senescence and related cognitive decline (Guidi et al., 2015; Kumar, 2015).

SUMMARY

BPSD appears the hardest-to-treat domain of dementia. Non-pharmacological approaches are the mainstream treatment; however, psychotropics are still needed for a substantial portion of patients. While second-generation antipsychotics have been widely used for the treatment for BPSD, their adverse effects generally offset the benefits. To date, no pharmacological approach has been approved for the treatment of BPSD.

Lately, NMDAR activating strategies, such as DAAO inhibition, have been demonstrated to benefit early-phase dementia as well as psychotic disorders such as schizophrenia. Whether such a novel medical route can also improve BPSD (or a fraction of it, with the aid of molecular precision medicine) deserves studies.

Since BPSD is difficult to treat, it is important to identify subpopulations that tend to respond to certain treatments. Recent studies suggest that the NMDAR expression may be different between female and male species. Genes involved in the pathways associated with the regulation of NMDAR might be altered in BPSD, and have potential to be developed as biomarkers for detecting dementia and predicting the treatment response.

In summary, the review addressed the NMDAR-related modulation and precision medicine in BPSD. Future studies examining the NMDAR modulators with the aid of potential biomarkers to tailor the treatment for individualized patients with BPSD will advance the treatment of BPSD.

AUTHOR CONTRIBUTIONS

C-HL and H-YL determined the outline, reviewed the literature, and wrote and approved the manuscript.

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frontiers in Pharmacology

BRIEF RESEARCH REPORT
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Claims Data Analysis on the Dispensing of Tricyclic Antidepressants Among Patients With Dementia in Germany

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Objective: A restrictive use of tricyclic antidepressants (TCA) in patients with dementia (PwD) is recommended due to the hazard of anticholinergic side effects. We evaluated the frequency of TCA dispensing in PwD over a period of 1 year and the use of TCA before and after the incident diagnosis of dementia.

Methods: This analysis was based on administrative data from a German statutory health insurance for a period of 2 years. Totally, 20,357 patients with an incident diagnosis of dementia in 2014 were included. We evaluated the dispensing of TCA in 2015. Subgroup analyses were conducted to evaluate associations between the incident diagnosis of dementia and modifications in TCA dispensing.

Results: In 2015, 1,125 dementia patients (5.5%) were treated with TCA and 31% were medicated with TCA in all four quarters of 2015. Most dispensings were conducted by general practitioners (67.9%). On average, patients received 3.7 ± 2.6 dispensings per year. Amitriptyline (56.3%), doxepin (26.8%), and trimipramine (16.8%) were dispensed most often. Subgroup analyses revealed that the dispensing of TCA remained mainly unchanged following the incident diagnosis.

Conclusion: A relevant number of PwD were treated with TCA. To maintain the patients' safety, an improved implementation of guidelines for the pharmaceutical treatment of PwD in healthcare institutions might be required. Since 68% of the patients suffered from depression, future studies should further evaluate the indications for TCA.

Keywords: antidepressants, tricyclic, claims data, dementia, pharmacotherapy

INTRODUCTION

Patients with dementia (PwD) frequently experience comorbid psychiatric disorders like depression, anxiety, and sleep disturbances (Enache et al., 2011; Mortamais et al., 2018). Randomized controlled trials suggest that antidepressants can be effective in treating depression in PwD, although the evidence is inconclusive and there is no evidence of superior efficacy of any particular antidepressant

(Dudas et al., 2018). Certain antidepressants can also be used for symptoms like sleep disturbances, anxiety, and restlessness (McCurry et al., 2005). However, the German guideline for the treatment of PwD does not contain specific pharmacological recommendations for the treatment of comorbid sleep disorders or anxiety in PwD (Deuschl and Maier, 2016).

From a neurochemical perspective, the bioavailability of several neurotransmitters is diminished in PwD. This is especially apparent in Alzheimer's disease (AD), where the reduced availability of acetylcholine and consequent dysfunctions of the cholinergic system are considered essential factors in the occurrence of typical AD symptoms (Pinto et al., 2011). Unfortunately, anticholinergic side effects are often seen in patients using tricyclic antidepressants (TCAs), leading to an increased risk of further cognitive decline, tachycardia, epileptic seizures, delirium, and urinary retention (Patel et al., 2017). TCAs might also increase the risk of impaired coordination and fall due to their sedative effects (O'Neil et al., 2018). Current guidelines therefore recommend a restrictive use of TCA in PwD (Deuschl and Maier).

Previous studies have examined the dispensing of antidepressant drugs using either primary databases or claims data (Arbus et al., 2010; Majic et al., 2010; Rapp et al., 2010; Wetzels et al., 2011; Martinez et al., 2013; Taipale et al., 2014; Giebel et al., 2015; Laitinen et al., 2015; Booker et al., 2016; Breining et al., 2016; David et al., 2016; Jacob et al., 2017; Jobski et al., 2017; Puranen et al., 2017). However, the specific dispensing of TCAs have not yet been analyzed using claims data of the German healthcare system. This information about TCA dispensing behavior would be important for health care providers regarding patients' safety and guideline-adherent pharmacotherapy (Holt et al., 2010).

The aim of our study was therefore to evaluate the frequency of TCA dispensing over a period of 1 year. In particular, this analysis illustrates how often TCAs were dispensed to PwD over a period of 12 months by evaluating the number of quarters in 2015 with at least one TCA dispensing per patient. Second, we included PwD who were diagnosed with dementia for the first time in the previous year (2014), which allowed us to detect modifications of TCA dispensing during those 12 months after the incident diagnosis of dementia. We hypothesized that physicians avoid dispensing TCAs after a dementia diagnosis owing to their adherence to current guidelines. To the best of our knowledge, this is the first evaluation using claims data to analyze the dispensing of TCAs for PwD in Germany.

PATIENTS AND METHODS

For this observational cohort study, we used anonymized claims data from the years 2014 and 2015, provided by a large German statutory health insurance fund (Allgemeine Ortskrankenkasse Niedersachsen, AOK). The local research ethics committee at the University Medical Center Goettingen, Germany, confirmed that the project is exempt from the requirement of a regular review by the committee because all data were anonymized.

We included patients who were diagnosed with dementia for the first time in 2014, based on diagnostic criteria of the International Classification of Diseases (ICD-10-GM codes F00.0, F00.1, F00.2, F00.9, F01.0, F01.1, F01.2, F01.3, F01.8, F01.9, F02.0, F02.3, F03, G30.0, G30.1, G30.8, G30.9, G31.0, G31.82) (International Classification of Diseases, 2018). To be eligible, patients had i) to be ≥65 years at the beginning of 2014, ii) to be continuously insured in 2014 and 2015, and iii) no diagnosis of dementia in the year before the new diagnosis. To confirm a subsequent diagnosis of dementia in the dataset, dementia had to be encoded again at least once (inpatient main or secondary diagnosis) or twice in two different quarters (confirmed outpatient diagnosis) over a period of 12 months after the first codification (Lange et al., 2015). TCAs were identified in the claims data according to the Anatomical Therapeutic Chemical Classification.

We evaluated the frequency of TCA dispensing in 2015 according to the prescription dates. For this 12-month observation period, we examined the total number of patients treated with at least one TCA dispensing. Additionally, we evaluated for how many quarters of 2015 (one, two, three, or all four quarters) a TCA dispensing was registered for each patient and which specialist dispensed the TCA. Furthermore, the dispensing of TCAs before and after the diagnosis of dementia was analyzed. Patients who were first diagnosed with dementia either in the third or the fourth quarter of 2014 were selected, and the dispensing of TCAs was evaluated two quarters before and four quarters after the incident diagnosis. A detailed description of the methods applied is given in a recently published study (Hessmann et al., 2018).

This study aimed at descriptively analyzing dementia patients' treatment with TCAs. Data are presented as total numbers of cases and percentages or as means with standard deviations (*SD*), median, minimum, and maximum. All statistical analyses were conducted with Microsoft Office Excel 2010 (Microsoft Corporation, Redmond, USA) and SPSS Version 24.0 (IBM SPSS Statistics, Armonk, USA). Significance was defined as $\alpha = 0.05$, and the normal distribution was assessed with the Kolmogorov–Smirnov test before conducting bivariate analyses. Friedman tests and Cochran's *Q* tests were used to examine whether TCA dispensing differs before and after diagnosis of dementia.

RESULTS

The study sample was derived from a cohort of 23,232 persons who were registered as incident PwD for the year 2014 in claims data of the AOK Niedersachsen. We excluded 2,875 patients who were below 65 years of age at the beginning of 2014 and/or who were not constantly insured during 2014 and 2015. The remaining 1,125 participants (5.5%) had at least one TCA dispensing in 2015 (77.4% females, $n = 871$) and were 80.5 ± 6.9 years (*median* = 80.0). The majority (75.6%, $n = 851$) had already received a TCA in 2014, while for 24.4%, the first TCA dispensing was encoded in 2015. Depressive syndromes (monophasic or recurrent) were encoded for 764 patients (67.9%) in our cohort. As shown in **Figure 1A**, patients were most often treated with amitriptyline (56.3%, $n = 633$), doxepin (26.8%, $n = 302$), and trimipramine (16.8%, $n = 189$).

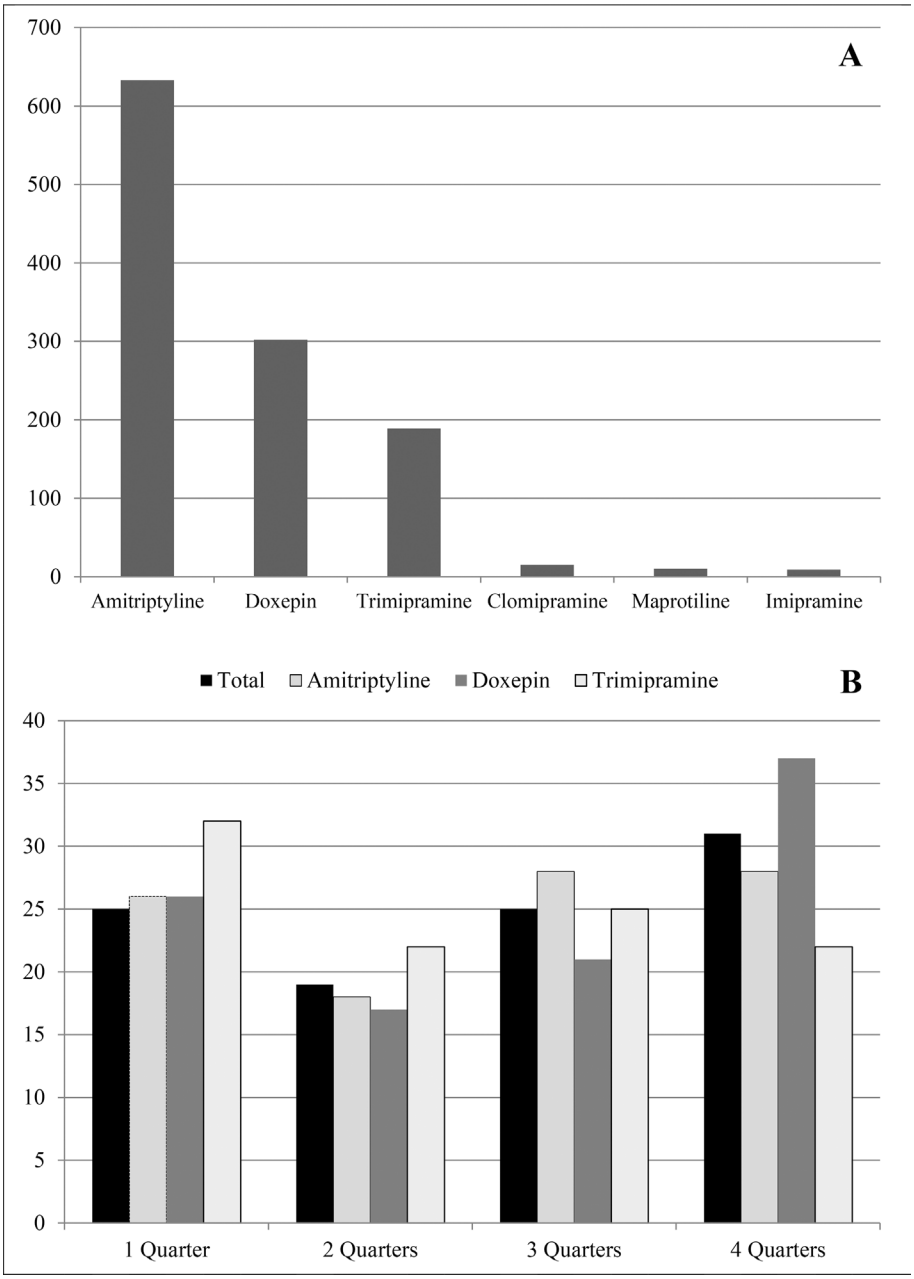

FIGURE 1 | Total number of patients with at least one dispensing of tricyclic antidepressants (TCA) in 2015 **(A)** and frequency (%) of TCA dispensing in 2015 **(B)**.

In 2015, patients had 3.7 ± 2.6 (*median* = 3.0) dispensings of TCA on average, with an average of 4.0 ± 3.2 (*median* = 3.0) dispensings for doxepin, while patients with amitriptyline received 3.5 ± 2.3 (*median* = 3.0) and those with trimipramine received 3.0 ± 2.0 (*median* = 3.0) dispensings. Of the total 4,914 TCA dispensings in 2015, most dispensings were made by general practitioners (n = 3,336, 67.9%), while specialists in internal medicine were responsible for 822 (16.7%) dispensings, and psychiatrists and neurologists for 660 (13.4%).

Next, we examined the number of quarters in 2015 with at least one TCA dispensing per patient (**Figure 1B**). Totally, 31.0% (n = 349) of the patients received a dispensing in all four quarters, while 24.9% (n = 281) patients received a TCA in one or three quarters, and 19.0% (n = 214) had dispensings in two quarters. Most patients treated with trimipramine (32.1%, n = 61) received dispensings in only one quarter, while doxepin was dispensed over all four quarters for the majority (37.1%, n = 112). However, dispensings in two quarters were less often seen, especially in the case of amitriptyline (18.0%, n = 114).

Finally, we evaluated whether the dispensing of TCAs was associated with the incident diagnosis of dementia. We conducted subgroup analyses in those patients with an

incident diagnosis in the third or fourth quarter of 2014 who were already treated with TCAs over a period of two quarters prior to the incident diagnosis (30.1%, n = 339). Specifically, TCA dispensings among the selected patients were evaluated for two quarters before and four quarters after the incident dementia diagnosis. The number of patients receiving TCAs diminished following the incident diagnosis, although this was not significant, and no differences in the dispensing frequencies of TCAs were seen. A distinguished analysis of the dispensing of each substance also showed no trend towards a diminished dispensing of TCAs, except for doxepin (**Table 1**). However, after adjusting for multiple testing differences in the dispensing of doxepin did not remain significant.

DISCUSSION

In addition to earlier studies exploring the use of antidepressant drugs among PwD in general (Martinez et al., 2013; Taipale et al., 2014; David et al., 2016; Jacob et al., 2017), this paper specifically focuses on the dispensing of TCA in PwD based on German healthcare claims data. In our study cohort, 5.5% of those patients who were diagnosed with dementia for the first time in 2014 were treated with TCA, while about one third of TCA users did not have a diagnosis of depression. According to international guidelines, TCA should be avoided in PwD due to the risk of anticholinergic side effects (Deuschl and Maier). Therefore, the results of our study underline the importance of a well-considered pharmaceutical treatment of PwD. Additionally, the appropriate implementation of guidelines for the treatment of PwD in healthcare institutions should be further evaluated.

Generally, the use of different databases (primary *vs*. claims data), the included types of dementia, and divergent sample sizes complicate comparisons with earlier studies. Nevertheless, earlier studies in Germany reported antidepressant dispensing rates of about 19 to 47% in PwD (Majic et al., 2010; Giebel et al., 2015). These findings are comparable with European studies determining utility rates of antidepressants of 13 to 40% (Laitinen et al., 2015; Breining et al., 2016). However, the use of TCA was not explicitly evaluated in the majority of earlier studies. Therefore, further studies on the use of TCA would be relevant to assess whether a dispensing rate of 5.5% in PwD is comparable to other samples. In case, further studies report that considerably lower dispensing rates would be highly important to evaluate reasons for a lower use of TCA. Implementing methods to diminish the use of TCA could contribute to the patients' safety and guideline-adherent treatment.

In our study, TCAs were dispensed most often by general practitioners. This contradicts other studies which showed that PwD who were seen by specialists (psychiatrists or neurologists) had a considerably higher chance of being treated with antidepressants in general (Rapp et al., 2010; Hessmann et al., 2018).

In Germany, claims data do not contain details on indications for the dispensing of certain substances. Our data therefore do not allow for direct conclusions about the appropriateness of TCA dispensing regarding different indications such as depression, anxiety disorders, sleep disturbances, or chronic pain syndrome, but it can provide clues on potentially inappropriate use of TCAs. In a prospective study, Wetzels et al. reported that more than 60% of PwD living in nursing homes received antidepressants over a period of 2 years, although depressive symptoms were not observed for many of these patients during clinical examination (Wetzels et al., 2011). However, some authors also suggest that antidepressants may be under-used in PwD. Giebel et al. showed that less than half of all PwD with clinically relevant depression received antidepressant drugs (Giebel et al., 2015).

The specific indications for TCA in PwD should be evaluated in future studies to understand the medical background of the dispensing. For this purpose, the attending physicians should be directly involved, e.g., using standardized questionnaires or qualitative interviews. Nevertheless, the relatively high number of PwD with a comorbid depression of about 67% might be the most likely reason for the dispensing of TCAs. Furthermore, the

TABLE 1 | Dispensing of tricyclic antidepressants (TCA) over two quarters before and four quarters after the diagnosis of dementia in Q3 or Q4 of 2014 (n = 339).

	Two quarters before Dx	One quarter before Dx	Quarter of Dx	One quarter after Dx	Two quarters after Dx	Three quarters after Dx	*p* value
TCA total (*n*, %)	271 (79.9)	275 (81.1)	266 (78.5)	264 (77.9)	259 (76.4)	254 (74.9)	$p = 0.305$
Mean ± SD	1.50 ± 0.89	1.42 ± 0.75	1.54 ± 0.85	1.44 ± 0.87	1.43 ± 0.80	1.37 ± 0.72	$p = 0.090$
Median (range)	1 (1–7)	1 (1–7)	1 (1–7)	1 (1–8)	1 (1–7)	1 (1–7)	
Amitriptyline (*n*, %)	150 (44.2)	150 (44.2)	152 (44.8)	151 (44.5)	153 (45.1)	147 (43.4)	$p = 0.981$
Mean ± SD	1.43 ± 0.79	1.46 ± 0.72	1.46 ± 0.75	1.40 ± 0.73	1.34 ± 0.64	1.29 ± 0.62	$p = 0.178$
Median (range)	1 (1–5)	1 (1–4)	1 (1–4)	1 (1–5)	1 (1–4)	1 (1–4)	
Doxepin (*n*, %)	84 (24.8)	75 (22.1)	70 (20.6)	72 (21.2)	61 (18.0)	62 (18.3)	$p = 0.016$
Mean ± SD	1.53 ± 0.97	1.45 ± 0.91	1.63 ± 1.07	1.56 ± 1.16	1.62 ± 1.14	1.50 ± 0.90	$p = 0.585$
Median (range)	1 (1–7)	1 (1–7)	1 (1–7)	1 (1–8)	1 (1–7)	1 (1–7)	
Trimipramine (*n*, %)	40 (11.8)	41 (12.1)	37 (10.9)	34 (10.0)	38 (11.2)	38 (11.2)	$p = 0.667$
Mean ± SD	1.48 ± 0.59	1.22 ± 0.53	1.46 ± 0.73	1.26 ± 0.57	1.37 ± 0.59	1.32 ± 0.62	$p = 0.257$
Median (range)	1 (1–3)	1 (1–3)	1 (1–3)	1 (1–3)	1 (1–3)	1 (1–3)	

TCA total (n, %), Number of patients with at least one dispensing of TCAs in the respective quarter; Mean ± SD, Average number of TCA dispensings in the respective quarter; Median (Range), Median number of TCA dispensings in the respective quarter; Quarter of Dx, Quarter 3 or 4 in 2014 when dementia was diagnosed; SD, standard deviation; p-value according to Friedman-tests and Cochran's Q-tests.

frequency of dispensing varied between the different TCAs. For example, trimipramine was dispensed in only one quarter during the study period by majority. This might be associated with the common use of trimipramine for sleeping disorders which do not necessarily have to be treated permanently.

LIMITATIONS

Although the effective study sample consisted of more than 20,000 patients, our data do not cover the dispensing of TCAs for the entire German population of PwD. Another limitation concerns the diagnostic codes in claims data which are encoded. In particular, only those medical conditions fulfilling the diagnostic criteria according to the ICD-10-GM (e.g., major depression) are registered by the attending physicians. In contrast, disorders not fulfilling these criteria are usually not encoded. This is especially important for the evaluation of indications for TCAs, which are also dispensed as symptomatic treatment for certain psychiatric disturbances (e.g., sleep disorders, anxiety). Therefore, drawing conclusions about the appropriateness of a TCA dispensing based on claims data is generally limited and additional clinical information is required. In addition, more detailed analyses on the number of dispensings as well as the defined daily doses in each quarter are planned on the basis of these claims data.

AUTHOR CONTRIBUTIONS

PH, JZ, JS, SE, and BK contributed to the study design, the data analysis, and the writing of the manuscript. JV, MA-H, CW-M, and JW contributed to the data interpretation and critically reviewed the manuscript.

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REVIEW
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Neuropsychiatric Disorders in Chronic Kidney Disease

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Neuropsychiatric conditions including depression, anxiety disorders, and cognitive impairment are prevalent in patients with chronic kidney disease (CKD). These conditions often make worse the quality of life and also lead to longer hospitalizations and higher mortality. Over the past decades, some hypotheses have tried to explain the connection between CKD and neuropsychiatric disorders. The most common hypothesis is based on the occurrence of cerebrovascular disease and accumulated uremic toxins in adult patients with CKD. However, the lack of a direct association between known vascular risk factors (e.g., diabetes and hypertension) with CKD-related cognitive deficits suggests that other mechanisms may also play a role in the pathophysiology shared by renal and neuropsychiatric diseases. This hypothesis is corroborated by the occurrence of neuropsychiatric comorbidities in pediatric patients with CKD preceding vascular damage, and the inconsistent findings on neuroprotective effects of antihypertensives. The aim of this narrative review was to summarize clinical evidence and potential mechanisms that links CKD and brain disorders, specifically in regard to cognitive impairment, anxiety, and depression.

Keywords: chronic kidney disease, neuropsychiatric disorders, cognition, cerebrovascular disease, anxiety, depression

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INTRODUCTION

Several studies support the association between decreased renal function and cognitive impairement (Kurella et al., 2006; Yaffe et al., 2010; Kurella Tamura et al., 2011; Da Silva et al., 2014). For a decrease of 15 ml/min/1.73 m^2 in glomerular filtration rate (GFR), there is an estimated decline in cognitive function similar to that of a 3-year aging (Buchman et al., 2009). Accordingly, chronic kidney disease (CKD) is an established independent risk factor for cognitive decline (Etgen et al., 2012). Psychiatric disorders are also very common in patients with CKD (Kimmel et al., 1998; Cohen et al., 2007; De Sousa, 2008; Stasiak et al., 2014). Hospitalizations due to psychiatric disorders (particularly depression, anxiety, and substance abuse) are 1.5 to 3 times more common among patients with CKD than individuals with other chronic diseases (Kimmel et al., 1998). In addition, cognitive impairment and psychiatric disorders can be leading factors of poor quality of life in CKD patients (Radic et al., 2010; Moreira et al., 2015).

Cognitive impairment has been associated with the stage of CKD, being particularly high—up to 60%—in patients undergoing hemodialysis (Murray et al., 2006; Kurella Tamura et al., 2011).

The mechanisms underlying this cognitive impairment are not completely elucidated. Direct effects of uremic toxins can cause cognitive decline. However, the cognitive impairment persists despite adequate dialysis prescription, thus concluding that other factors may contribute to brain dysfunction (Radic et al., 2010). Cerebral hemodynamics dysfunction may also play a role in the pathogenesis of cognitive impairment in CKD (Skinner et al., 2005). Old age, depression, and white matter injury have also been linked to both cognitive impairment and changes in cerebral vasomotor reactivity (Da Matta et al., 2014).

Depression is the most frequently reported psychiatric condition in CKD patients, especially in those at end-stage renal disease (ESRD) (Palmer et al., 2013). The prevalence of depression among patients with CKD can be as high as 100%, depending on the diagnosis criteria and the studied population. The prevalence of depression and the risk of hospitalization due to psychiatric disturbances are higher in patients on dialysis in comparison with pre-dialysis and post-transplant patients (Palmer et al., 2013).

The neuropsychiatric manifestations in CKD patients impose unique diagnostic and therapeutic challenges. In this scenario, the aim of this narrative review was to summarize clinical evidence and potential mechanisms that links CKD and brain disorders, specifically regarding cognitive impairment, anxiety, and depression.

BRAIN-RENAL AXIS: AN EVOLVING CONCEPT

Accumulating evidence has shown high prevalence of neuropsychiatric disorders, mainly cognitive decline, depression, and anxiety in CKD patients (Bugnicourt et al., 2013; Miranda et al., 2017). Indeed, the CKD-related neuropsychiatric conditions have been independently associated with poor clinical outcomes, including decrease in health-related quality of life, longer hospitalization, and higher risk for mortality (Lee et al., 2013).

A rationale for neuropsychiatric disorders secondary to kidney damage, known as the "vascular theory," relies on the hemodynamic similarities between the brain and the kidneys (Mogi and Horiuchi, 2011). Similar anatomical and functional regulations of the microvasculature in renal and brain tissues may account for susceptibility of both organs to vascular damage and to traditional cardiovascular risk factors, including aging, obesity, diabetes, hypertension, dyslipidemia, and smoking (Toyoda and Ninomiya, 2014; Lau et al., 2017). Importantly, CKD have been regarded as a nontraditional risk factor for stroke, sleep apnea, chronic inflammation, and malnutrition (Bang et al., 2015).

Because of the vascular and hemodynamic similarities between the brain and the kidneys, it is reasonable to speculate that the microvascular damage in the kidney mirrors that in the brain. In this regard, not only CKD has been recognized as a risk factor for stroke and vascular dementia, but also it can be associated with subclinical cerebrovascular diseases. Accordingly, reduced kidney function has been independently associated with worse microstructural integrity of brain white matter, as evaluated by diffusion tensor imaging (DTI) magnetic resonance imaging (MRI) (Sedaghat et al., 2015). Also, albuminuria has been associated with larger white matter volume and decreased estimated GFR with higher cerebral blood flow in nondiabetic hypertensive adults (Tamura et al., 2016). Although subclinical cerebrovascular damage in CKD can be easily detected by MRI, this is not performed routinely in clinical practice. In addition, studies about this issue are still scarce. It is important to understand the mechanisms shared by renal impairment and brain dysfunction in order to minimize the risk for future neuropsychiatric conditions due to CKD.

Despite the known association between renal damage and neuropsychiatric conditions, direct evidence linking CKD to brain damage is still missing (Lu et al., 2015). Moreover, the vascular theory is not able to fully explain CKD-related central nervous system (CNS) dysfunction, as indicated by: (i) lack of direct association between known vascular risk factors, such as diabetes and hypertension and cognitive deficits secondary to CKD; (ii) occurrence of neuropsychiatric disorders in pediatric patients with CKD preceding vascular damage; (iii) inconsistent findings regarding potential neuroprotective effects of antihypertensive drugs against cognitive decline in CKD (Seliger et al., 2004; Duron and Hanon, 2010; Moreira et al., 2015). In this context, alternative hypotheses have proposed additional mechanisms in the kidney–brain communication, including inflammation, oxidative stress, and renin–angiotensin system (RAS) (Miranda et al., 2017). It is worth highlighting that the cross-talk between brain and kidney seems to be bidirectional since CNS conditions, like migraine and traumatic brain injury, are also independent risk factors for CKD (Weng et al., 2017; Wu et al., 2017).

Inflammation is a common feature in brain and kidney lesions, being quite reasonable to assume that inflammatory mediators may facilitate the kidney–brain cross-talk. The well-recognized role of cytokines in mediating peripheral and CNS communication reinforces this hypothesis (Lu et al., 2015). For instance, patients with CKD undergoing hemodialysis exhibit elevated serum concentrations of the chemokine MCP-1/CCL2, a protein chemoattractant for monocytes. Multiple logistic regression analysis revealed that MCP-1/CCL2 levels were significantly associated with the presence of silent cerebral infarction in this population (Uchida et al., 2012). A serum proteomic profile consisting of the inflammatory mediators IL-10 and C-reactive protein exhibited 93% accuracy in predicting mild cognitive impairment secondary to CKD (Szerlip et al., 2015).

Pre-clinical studies have also shown the involvement of inflammatory cytokines in CKD-related brain dysfunction. Increased levels of interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF) were associated with oxidative DNA damage in brain cells of rats submitted to subtotal nephrectomy (Hirotsu et al., 2011). Accordingly, increased expression of NF-κB and TNF in the hippocampus and frontal cortex were associated with aversive memory and attention impairments in subtotal nephrectomized rats at 4 months after 5/6 renal mass removal (Degaspari et al., 2015).

Oxidative stress has been associated with both brain and kidney dysfunctions. The administration of antioxidant drugs

significantly prevents cognitive and behavioral alterations in experimental models of CKD, indicating a potential role for oxidative stress in the interactions between kidney and brain (Deng et al., 2001; Fujisaki et al., 2014). A significant increase of nitrotyrosine—a reactive and cytotoxic product generated by the interaction of nitric oxide (NO) and reactive oxygen species (ROS)—has been found in the brain cortex of nephrectomized rats at 6 weeks after 5/6 nephrectomy. Importantly, a protective effect was obtained with the administration of a potent antioxidant, lazaroid. This antioxidant was able to normalize the plasma levels of the lipid peroxidation product and malondialdehyde and to decrease the concentration of nitrotyrosine in the cerebral cortex of nephrectomized rats (Deng et al., 2001). The administration of tempol, another antioxidant compound, prevented spatial working memory impairment in a murine model of CKD. The protective effect of tempol was associated with inhibition of oxidative DNA damage in the hippocampus independently of renal function improvement (Fujisaki et al., 2014). More recently, in an experimental study with CKD induced by 4 weeks of adenine-rich diet, animals developed depressive-like behavior, locomotor alterations, and cognitive decline. In parallel with these behavioral and cognitive changes, animals also had decreased catalase and increased superoxide dismutase activities, elevated lipid peroxidation, and enhanced NOS-active neurons and dysfunction of mitochondrial complexes in key areas like striatum, substantia nigra, cortex, and hippocampus (Mazumder et al., 2019). Altogether, these experimental studies support the involvement of oxidative stress in neuropsychiatric disorders secondary to CKD.

The potential role of the RAS in kidney–brain crosstalk has also been investigated. The treatment with both ACE inhibitors and AT_1 receptor antagonists exerted neuroprotective effects against the development of neurodegenerative diseases, besides exerting renoprotection (Kaur et al., 2015; Villapol and Saavedra, 2015). O'Caoimh et al. (2014) reported that patients with Alzheimer's disease receiving ACE inhibitors have a reduced rate of functional decline. ACE inhibitors also exerted neuroprotective actions in a rat model of Parkinson's disease (Lopez-Real et al., 2005). Treatment with captopril reduced oxidative stress and protected dopaminergic neurons in a 6-hydroxydopamine rat model of Parkinson's disease (Lopez-Real et al., 2005). Similar results were obtained with the administration of AT_1 receptor antagonists in patients and in experimental models of Alzheimer's disease, Parkinson's disease, stroke, traumatic brain injury, and spinal cord injury (Villapol and Saavedra, 2015). Our research group has investigated the profile of RAS molecules in the blood and/or cerebrospinal fluid (CSF) of patients with different neuropsychiatric conditions, including Parkinson's disease (Rocha et al., 2016), Alzheimer's disease (Rocha et al., 2018), and schizophrenia (Mohite et al., 2018). In patients with Parkinson's disease, lower circulating levels of angiotensin II (Ang II) and Ang-(1–7) were associated with increased severity of depressive symptoms (Rocha et al., 2016). Patients with Alzheimer's disease had decreased levels of ACE when compared with controls, and there was a significant positive correlation between ACE and amyloid-β_{42} concentrations in the CSF of patients (Rocha et al., 2018). Patients with schizophrenia exhibited reduced circulating levels of ACE in comparison to controls (Mohite et al., 2018).

The treatment with ACE inhibitors and AT1 receptor antagonists also exerted neuroprotection in experimental models of ESRD. 6 weeks after 5/6 nephrectomy, rats treated with the ACE inhibitor captopril decreased oxidative stress, ROS–NO interaction, and tyrosine nitration production in the cerebral cortex (Deng et al., 2001). Also, mice submitted to 5/6 nephrectomy and treated for 8 weeks with 0.5 mg/kg/day of telmisartan, an AT1 receptor blocker, improved spatial memory impairment as measured by the radial arm water maze test. The prevention of cognitive decline was associated with reduction in brain oxidative DNA damage and lipid peroxidation, supporting the hypothesis that increased action of Ang II in the CNS may underlie CKD-associated neuropsychiatric disorders (Haruyama et al., 2014).

Based on the counter-regulatory role played by the RAS axis formed by the enzyme ACE2, angiotensin-(1–7) (Ang-[1–7]), and the Mas receptor, usually opposing the actions of the ACE–Ang II–AT_1 axis, it is expected that treatment with Ang-(1–7) and/or ACE2 activators might also lead to neuroprotection. Wang et al., 2016 showed that mice with genetic deletion of ACE2 displayed impaired cognition probably due to reduced levels of BDNF mRNA and protein in the hippocampus and increased oxidative stress. Additionally, intracerebroventricular infusion of Ang-(1–7) improves cognitive and memory decline in an experimental model of Alzheimer's disease (Uekawa et al., 2016). Intracerebroventricular infusion of Ang-(1–7) was also able to reverse anxiety- and depression-like behaviors of hypertensive transgenic (mRen2) rats with RAS overactivity (Almeida-Santos et al., 2016). However, only few studies evaluated the ACE2-Ang-(1–7)-Mas receptor axis in neuropsychiatric disorders. Future studies are warranted to clarify the mechanisms and brain areas mediating the neuroprotective effects of ACE2-Ang-(1–7)-Mas receptor axis. It also remains to be investigated the RAS axes in cognitive impairment, anxiety, and depression related to CKD.

Figure 1 shows factors linking CKD and neuropsychiatric disorders.

COGNITIVE IMPAIRMENT IN CKD

Cognitive impairment is defined by the decline in one or more cognitive domains, as perceived by the individual or a reliable informant and/or observed and documented by a clinician. There must be a clear decline from a previously higher cognitive level, and the impairment must not be better explained by another psychiatric condition or delirium.

Dementia (or major neurocognitive disorder) is diagnosed when the cognitive impairment is severe enough to interfere with independence in everyday activities (Americanpsychiatricassociation, 2013; Hugo and Ganguli, 2014). The number of people living with dementia increases exponentially with increasing age. In 2010, the number of people living with dementia worldwide has been estimated to be 35.6 million. By 2050, this number is expected to reach 115.4 million people. Dementia is an important cause of death,

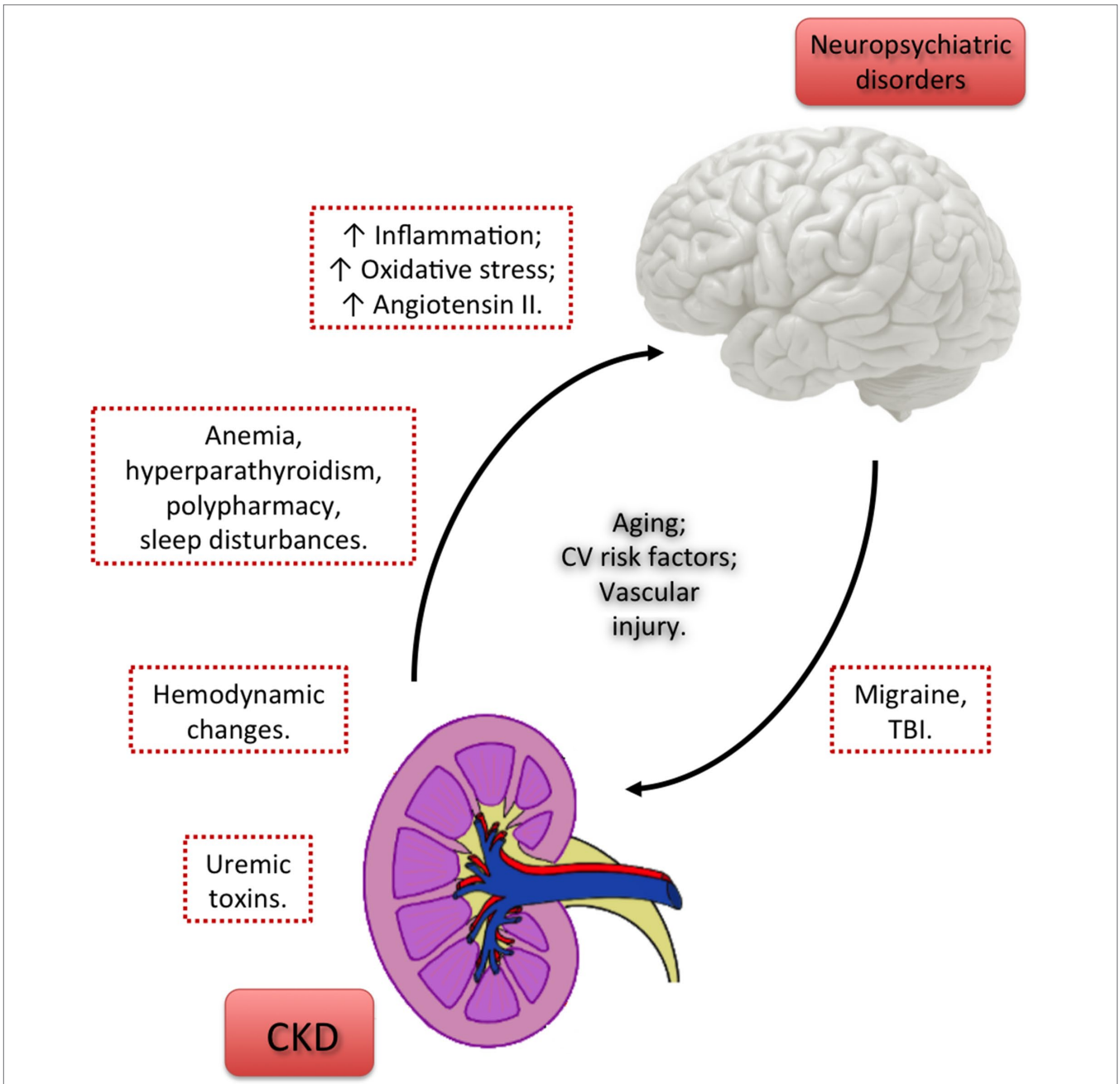

FIGURE 1 | Factors linking chronic kidney disease and neuropsychiatric disorders. Uremic toxins released as a result of CKD directly contribute to brain damage and the consequent cognitive decline and psychiatric disorders. However, the persistence of neuropsychiatric conditions despite adequate dialysis prescription points out that other factors may probably contribute to brain dysfunction. Hemodynamic changes, anemia, hyperparathyroidism, polypharmacy, and sleep disturbances due to CKD may represent a link between CKD and neuropsychiatric disorders. Other factors, shared by kidney and brain tissue injuries, as the increase in the levels of inflammatory molecules, reactive oxygen species and Angiotensin II may also contribute to kidney-to-brain interactions and, consequently, to neuropsychiatric comorbidities in CKD patients. The cross-talk between brain and kidney seems to be bidirectional, since central nervous system diseases, like migraine and TBI, are independent risk factors for CKD. Aging, CV risk factors, and vascular injury represent risk factors shared by CKD and neuropsychiatric disorders, notably cognitive impairment.
CKD, chronic kidney disease; CV, cardiovascular; TBI, traumatic brain injury.

hospitalizations, skilled nursing facility admissions, and home health care burden (Hugo and Ganguli, 2014). The global annual costs of US$818 billion associated with dementia are expected to increase significantly in the near future (Shah et al., 2016).

The main risk factors for cognitive impairment and dementia are increasing age, lower educational level, cardiovascular disease, stroke, head injury, lifestyle habits such as smoking and heavy alcohol consumption, and psychiatric disorders notably

late-life depression and anxiety (Hugo and Ganguli, 2014). The identification of risk factors and the understanding of the impact and interactions of non-modifiable (e.g., sex, genetics, age) and modifiable risk factors (e.g., educational level, habits) for dementia have been identified as one of the research priorities to reduce the global burden of dementia (Shah et al., 2016). Addressing the modifiable risk factors for cognitive impairment and dementia would significantly benefit millions of patients, their families, and society.

CKD is an independent risk factor for cognitive impairment and dementia (Etgen et al., 2012). The prevalence of cognitive impairment in individuals with kidney failure has been reported to be around 30 to 60% (Madero et al., 2008). Cognitive dysfunction can potentially affect the CKD patients' ability to make decisions and to understand the complex treatment, including fluid and dietary restrictions (Dahbour et al., 2009; Sorensen et al., 2012). Additionally, patients with cognitive impairment present an increased risk of hospitalization, mortality, and poor quality of life (O'lone et al., 2016).

The association between CKD and cognitive impairment can be explained by several factors. First, patients with CKD have a higher prevalence of cerebrovascular disease and cardiovascular risk factors than the general population. Traditional vascular risk factors, i.e., hypertension, hypercholesterolemia, diabetes mellitus, smoking, and cardiovascular disease, are strongly associated with CKD, cerebrovascular disease, and dementia. Second, nontraditional vascular risk factors such as hyperhomocysteinemia, hemostatic abnormalities, and hypercoagulable states are frequently detected in CKD patients and have been associated with cognitive impairment. Third, increased oxidative stress and inflammation due to CKD are also associated with cognitive impairment and dementia. Finally, nonvascular risk factors such as anemia, hyperparathyroidism, polypharmacy, sleep disorders, and depression may represent an additional link between CKD and cognitive decline (Madero et al., 2008). Furthermore, dialysis patients undergo hypoxemia, large fluid and osmolar shifts, fluctuating uremic toxin titers, and a proinflammatory state. All these factors can potentially affect cognitive function. In fact, patients under hemodialysis have worse cognitive performance when compared to the general population, particularly in the orientation, attention, and executive function domains (O'lone et al., 2016).

A recent study indicated that for every 10ml decrease in the estimated GFR below 60 ml/min/1.73m^2, there is an 11% increase in the risk of cognitive impairment (Tian et al., 2019). A meta-analysis of cross-sectional and longitudinal studies comprising 54,779 participants corroborated these findings. Not only the study concluded that CKD is significantly associated with cognitive decline, but this association was independent of the CKD stage and was stronger in the group with moderate-to-severe CKD compared with mild-to-moderate CKD (Etgen et al., 2012).

There are several studies investigating cognitive performance across the CKD spectrum, i.e., pre-dialysis CKD patients, patients on renal replacement therapy (hemodialysis or peritoneal dialysis), and transplant recipients for a systematic review, see (Vanderlinden et al., 2019). A recent meta-analysis found that ESRD patients submitted to different modalities of renal replacement therapy have distinct cognitive deficits. Both pre-dialysis and patients on hemodialysis exhibited worse global cognition performance in comparison with non-CKD controls, as demonstrated by the significantly lower scores on the Mini-Mental State Examination. Also, patients on peritoneal dialysis or hemodialysis had worse attention/working memory performance, as evaluated by the Trail Making Test-A, than non-CKD controls (Vanderlinden et al., 2019).

Hemodialysis and peritoneal dialysis are equivalent in terms of survival (Yeates et al., 2012), and both dialysis modalities are associated with high prevalence (60–70%) of moderate to severe cognitive impairment (Kalirao et al., 2011). However, studies have reported better cognitive outcomes in patients on peritoneal dialysis compared with patients on hemodialysis (Tilki et al., 2004). In uremic patients, although the hemodialysis was able to restore a normal cognitive function, this effect was observed only transiently in the post-dialytic phase. Differently, peritoneal dialysis preserved cognitive function steadily close to normal (Buoncristiani et al., 1993). In addition, peritoneal dialysis has been reported to be more effective than hemodialysis in reversing uremic encephalopathy (Wolcott et al., 1988), and the risk of dementia for patients who started on peritoneal dialysis is lower compared with those who started on hemodialysis (Wolfgram et al., 2015). These results were confirmed by a recent systematic review and meta-analysis, which concluded that peritoneal dialysis is better in preserving the cognitive functions and is associated with a lower risk of dementia in comparison with hemodialysis (Tian et al., 2019).

Taken together, patients with CKD exhibit worse cognitive performance than the general population. The clinical phenotype and severity of cognitive impairment may depend on the renal replacement therapy, with peritoneal dialysis showing better outcomes than hemodialysis. There are potentially biased studies that did not control for educational level and other confounding variables, besides a high heterogeneity of results, mainly due to the large variety of tests used to assess cognition. Cognitive deficits in specific domains must be better investigated and considered for disease management. Accordingly, larger studies with more careful design, including comprehensive neuropsychological and behavioral phenotyping, are needed to draw more definite conclusions. Noteworthy, aging is a common risk factor for both cognitive impairment and CKD (Bowe et al., 2018). Given that the incidence of CKD is increasing, particularly in the elderly, recognizing and understanding cognitive dysfunction in CKD patients have become a research priority as well.

It is worth mentioning that the relationship between cognitive impairment and reduced renal function seems to be bidirectional. For instance, a case-control study has shown that people with Alzheimer's disease have greater renal impairment than controls, even after adjustment for age, diastolic blood pressure, apolipoprotein E (APOE) ε4 genotype and education level (Kerr et al., 2009). Also, the reduced renal function can worsen clinical symptoms in patients with cognitive impairment. For instance, it has been reported that psychotic symptoms are associated with poorer renal function in people with mild cognitive impairment and Alzheimer's disease (Kunschmann et al., 2017).

DEPRESSION AND ANXIETY IN CKD

Psychiatric conditions, especially depression and anxiety, are commonly found in CKD patients. Psychiatric disorders in CKD population have been associated with significant decline in overall quality of life, rapid progression to ESRD, as well as higher risk of hospitalization and death (Hedayati et al., 2010; Cukor et al., 2012; Tsai et al., 2012; Chiang et al., 2015).

Depression

Depression is highly prevalent in patients with CKD. A systematic review and meta-analysis that analyzed 216 studies involving 55,982 patients with CKD or ESRD showed a prevalence of 26.5% of depressive symptoms in CKD patients when evaluated by screening questionnaires, and of 21.4% of clinically significant depression when evaluated by clinical interview (Palmer et al., 2013). The prevalence of depression in CKD patients is three to four times higher compared with the general population and two to three times higher compared to other chronic diseases including diabetes, coronary artery disease, and chronic obstructive pulmonary disease (Waraich et al., 2004; Katon, 2011; Pratt and Brody, 2014). Accordingly, the rate of antidepressant prescription is nearly 1.5 times higher in CKD patients than in the general population (Iwagami et al., 2017).

Demographic, socioeconomic, and clinical risk factors including younger age, female sex, Black race, Hispanic ethnicity, lower education, lower family income, unemployment, hypertension, smoking status, and diabetes have been associated with depression secondary to CKD (Kop et al., 2011; Fischer et al., 2012; Tsai et al., 2012). Based on the fact that these risk factors seem to be more frequently in CKD patients compared with the general population, they may explain, at least in part, the higher prevalence of depressive symptoms in the CKD population (Nicholas et al., 2015). CKD also influences the emotional state of the patients due to of several stressors, including adjustments to a strict dietary and fluid restriction, and occurrence of pain and fatigue (Kimmel, 2002; Davison and Jhangri, 2010).

It has been reported that depression in CKD might be related with poor clinical outcomes, which include hospitalization, kidney function decline, progression to ESRD, and mortality (Hedayati et al., 2010; Tsai et al., 2012; Chiang et al., 2015). A prospective study with a mean follow-up of 2 years evaluated the association of depression and renal function decline in 568 patients with CKD. Individuals with depressive symptoms (160 subjects) presented a faster decline in estimated GFR and were 1.7 times more likely to progress to ESRD or death than those without depression (Tsai et al., 2012). Decline in GFR was also reported in CKD patients with elevated depression scores in the Beck Depression Inventory (BDI) in a 6-month follow-up study. Notably, depressive symptoms were associated with adverse psychosocial outcomes such as poor quality of life, inferior social support, and worse community integration (Cukor et al., 2012). A negative correlation was found between quality of life measures and depression, as measured by the Hospital Anxiety and Depression Scale in pre-dialysis CKD patients. This finding reinforces the concept that detection and adequate treatment of depressive symptoms might improve the quality of life of these patients (Lee et al., 2013). A cross-sectional study with 152 CKD patients reported a prevalence of depressive symptoms in 27% of the subjects who were starting renal replacement therapy by hemodialysis or peritoneal dialysis. Depressive symptoms affected both physical and emotional components of quality of life as measured by the Kidney Disease Quality of Life Short Form (Rebollo Rubio et al., 2017). Similar findings were reported in a cross-sectional study with 335 ESRD patients on hemodialysis (Li et al., 2016). Poor quality of life and lower resilience were also associated with depression in pediatric (age range from 9 to 18 years) patients at stages 1 to 4 of CKD (Moreira et al., 2015).

Depression is an independent risk factor for hospitalization and death in both patients receiving dialysis or at pre-dialysis stages of CKD (stages 1–4) (Lopes et al., 2002; Hedayati et al., 2005; Hedayati et al., 2008; Hedayati et al., 2010). In 1-year follow-up study with 267 CKD patients at stages 2–5 not under dialysis, major depression was observed in 56 (21%) patients and, at the end of 1 year, the diagnosis of depression at baseline independently predicted progression to dialysis and hospitalization. The poor outcomes in CKD patients with depressive symptoms were not related with the presence of comorbidities or kidney disease severity (Hedayati et al., 2010). A more recent cohort study followed pre-dialysis CKD patients for 3 years to investigate whether depression is an independent risk factor for initiation of dialysis and for mortality. A total of 262 CKD patients was enrolled in the study, with 56 (21.4%) presenting clinically meaningful depressive symptoms at baseline. In line with the previous report (Hedayati et al., 2010), the presence of depressive symptoms at baseline independently predicted the risk of initiation of dialysis and mortality (Chiang et al., 2015). Another prospective study showed that patients with more depressive symptoms at baseline had higher risk of hospitalization and death due to cardiovascular complications (Fischer et al., 2011).

The presence of depression at the time of dialysis onset is also an independent predictor of lower survival rates, greater frequency of dialysis withdrawal, higher risk of hospitalization, and longer hospitalization (Chilcot et al., 2011; Lacson et al., 2012; Lacson et al., 2014). A longitudinal study investigated for 2 years the occurrence of depressive symptoms and frailty in 771 patients on dialysis and whether these conditions were independently associated with mortality. At baseline, 13.1% of individuals presented depressive symptoms based on the Center for Epidemiologic Studies Depression scale, 21.8% had frailty, and 10.0% met criteria for both. After 2 years of follow-up, 26.6% of CKD patients had frailty, and 12.7% exhibited depressive symptoms, and depressive symptoms and frailty were independent predictors of mortality (Sy et al., 2019).

Despite its high prevalence and significant clinical and socioeconomic burden, depression seems to be undertreated in patients with CKD. A large cross-sectional involving 1,099 adults with CKD stages 3 to 4 who had depressive symptoms as defined by the score of 11 or higher in the BDI revealed that only 31% of the patients reported the prescription of antidepressants (Fischer et al., 2012). The low prescription rate of antidepressants among

the CKD population may rely on the fact that these drugs are highly protein-bound and metabolized by the liver, making them unlikely to be removed by dialysis, raising medical concerns with their prescription (Hedayati et al., 2012). The first-line antidepressants for CKD patients are the selective serotonin re-uptake inhibitors. However, few studies have investigated the safety and efficacy of these medications in CKD patients, and most of them had significant limitations including small sample sizes, lack of control group, and selection and drop-out bias (Nagler et al., 2012; Palmer et al., 2016). Treatment of CKD-related depressive symptoms must also include non-pharmacological strategies like psychotherapy (e.g., cognitive-behavioral therapy), exercise training programs, and social support (Symister and Friend, 2003; Duarte et al., 2009; Ouzouni et al., 2009; Kouidi et al., 2010). A randomized trial with 85 patients on hemodialysis and presenting with depressive symptoms obtained a significant improvement in the BDI score following 12-week sessions of cognitive-behavioral therapy (Duarte et al., 2009). Exercise training programs can reduce depressive symptoms in dialysis patients, but the improvement depends on at least 6 months of intervention (Ouzouni et al., 2009; Kouidi et al., 2010). Whether CKD patients with pre-existing depression would benefit from physical activity intervention still deserves investigation, as these individuals may lack the motivation to engage in exercise programs. Finally, social support is also a promising strategy to decrease depressive symptoms, specifically by increasing optimism and self-esteem (Symister and Friend, 2003). Although non-pharmacological approaches play a definite role for the management of CKD-related depression, several factors including lack of patients willingness to follow recommendations and limited availability of those non-pharmacological strategies in CKD clinics or dialysis centers hamper their integration in the clinical practice (Green et al., 2012; Weisbord et al., 2013; Hedayati et al., 2016). In this regard, a clinical trial was recently conducted in patients receiving hemodialysis in order to assess: (i) the effect of an engagement interview on patients' willingness to accept treatment for depression and (ii) the efficacy of cognitive-behavioral therapy in comparison with sertraline for treating depression. The engagement interview did not affect patients' acceptance of treatment for depression (which was 64–66%). Both cognitive-behavioral therapy and sertraline improved depressive symptoms and other secondary outcomes such as energy/vitality and sleep quality. The outcome scores were modestly better for the sertraline group, which also presented more frequent adverse events in comparison with the cognitive-behavioral therapy group (Mehrotra et al., 2019).

Anxiety

Anxiety is also a common psychiatric condition in patients with CKD, although this condition has been substantially lesser studied than depression. A longitudinal study conducted with 50 CKD patients on hemodialysis revealed symptoms of anxiety in 45.7% of them, as assessed by the Hospital Anxiety and Depression Scale (HADS). After 16 months of follow-up, a significant portion of these CKD patients (30%) remained with anxiety symptoms (Cukor et al., 2008). A 3-year follow-up study showed that 31 among 100 patients with pre-dialysis CKD exhibited anxiety symptoms evaluated by the Beck Anxiety Inventory (Loosman et al., 2015).

High prevalence of anxiety in CKD population has been reported in cross-sectional studies as well. In a study involving 208 pre-dialysis CKD patients, the frequency of anxiety, as assessed by the HADS, was found to be 24.8% in patients at CKD stage 3, 29.9% in patients at stage 4, and 34.3% in patients at stage 5 (Lee et al., 2013). No significant differences were detected in the frequency of anxiety symptoms according to CKD stages (Lee et al., 2013). In a cross-sectional study including 155 patients undergoing hemodialysis for at least 6 months, anxiety symptoms evaluated by Beck Anxiety Inventory were found in 53%, being moderate to severe symptoms in 28% of patients (Feroze et al., 2012). The frequency of anxiety symptoms was not influenced by the method of renal replacement therapy. Similar scores were obtained in BAI and HADS for 128 patients on hemodialysis in comparison with 27 on peritoneal dialysis (Stasiak et al., 2014). Additionally, comparable frequencies of anxiety symptoms were also found in CKD patients before (21.6% of a total of 101 individuals) and after kidney transplantation (25% of a total of 151 patients), as assessed by the HADS (Muller et al., 2015). A more recent study conducted with 152 CKD patients starting renal replacement therapy identified anxiety symptoms in 26.6% of the patients. Taken together, these studies showed that anxiety symptoms are at least two times higher in CKD patients in comparison to general population (Kessler et al., 2005; Feroze et al., 2012).

Anxiety symptoms may be associated with poor clinical and psychological outcomes like poor health–related quality of life, hospitalization, and mortality. Regarding the health-related quality of life, prospective and cross-sectional studies have shown lower scores of quality of life related to the stage of CKD. In these studies, the Kidney Disease Quality of Life questionnaire and the Medical Outcomes Survey 36-item Short Form (SF-36) were employed to evaluate the health-related quality of life in CKD patients, and the most pronounced impairments were in physical function and physical scales (Molsted et al., 2007; Mujais et al., 2009; Pagels et al., 2012; Lee et al., 2013; Li et al., 2016). Anxiety symptoms were independently associated with impairment in physical and emotional components of health-related quality of life in pre-dialysis CKD patients at the start of dialysis and in patients under hemodialysis (Lee et al., 2013; Kang et al., 2015; Rebollo Rubio et al., 2017). It is worth noticing that lower scores for health-related quality of life domains have been associated with higher risks for ESRD and for all-cause mortality in CKD patients (Tsai et al., 2010). Anxiety symptoms also seem to be an independent risk factor for hospitalization and mortality amongst CKD patients. A 3-year prospective cohort study including 100 pre-dialysis CKD patients showed that anxiety symptoms were associated with adverse clinical outcomes such as death, initiation of dialysis, or hospitalization (Loosman et al., 2015). A recent prospective cohort study showed that anxiety symptoms were independently associated with increased risk for mortality and days of hospitalization (Schouten et al., 2019).

Few studies have investigated therapeutic strategies for CKD-associated anxiety symptoms. Although benzodiazepines are

often prescribed for the treatment of acute episodes of anxiety, their use should be avoided due to high rates of side effects, including drowsiness, risk of falls, and abuse liability (Cohen et al., 2004; Yeh et al., 2014). As for CKD-related depression, the first-line pharmacological strategy recommended to treat anxiety disorders in CKD patients is the selective serotonin re-uptake inhibitors (Bandelow et al., 2012). A recent study showed that a brief cognitive-behavioral intervention consisting of positive self-reinforcement, deep breathing, muscle relaxation, and cognitive restructuring decreased anxiety and depressive symptoms and improved quality of life after 4-week follow-up compared with the baseline scores. This study was conducted in ESRD patients on hemodialysis (Lerma et al., 2017). The benefits of cognitive-behavioral intervention and other non-pharmacological strategies for early stages of CKD still need to be evaluated.

CONCLUDING REMARKS

The interactions between kidney and brain are complex and multifaceted, thus justifying the significant neuropsychiatric comorbidity observed in patients with CKD. Cognitive impairment, highly prevalent in CKD patients, may be linked, but not exclusively, to common susceptibility of brain and kidney tissues to vascular injury. Depression and anxiety, also frequently diagnosed in all stages of CKD, cannot be explained by neuronal dysfunction related to uremic state or vascular injury. Alongside psychosocial factors, other pathological mechanisms, shared by both kidney and brain tissue injuries, as inflammatory mediators, ROS and components of the RAS might contribute to cerebrorenal interactions and, consequently, to neuropsychiatric comorbidities in CKD patients.

A direct link between CKD and brain damage is still elusive. Understanding the pathophysiology of these interactions between chronic renal impairment and brain dysfunction is pivotal to prevent and/or minimize the occurrence and impact of cognitive impairment, depression, and anxiety in CKD patients.

AUTHOR CONTRIBUTIONS

ACSS and ALT proposed the topics and made general supervision. NPR and ASM searched for articles and wrote the first draft of the review. All authors revised the manuscript and approved the final version.

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REVIEW
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Antipsychotic Treatment of Behavioral and Psychological Symptoms of Dementia (BPSD): Management of Extrapyramidal Side Effects

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Antipsychotic drugs are often used for the treatment of behavioral and psychological symptoms of dementia (BPSD), especially psychosis and behavioral disturbances (e.g., aggression and agitation). They are prescribed alone or in conjunction with anti-dementia (e.g., anti-Alzheimer's disease drugs) and other psychotropic drugs (e.g., antidepressants). However, antipsychotic drugs frequently produce serious extrapyramidal side effects (EPS) including Parkinsonian symptoms (e.g., bradykinesia, akinesia, tremor, and muscle rigidity). Therefore, appropriate drug choice and combination strategy are important in the treatment of BPSD. Among anti-Alzheimer's disease drugs, cholinesterase inhibitors (ChEIs, e.g., donepezil and galantamine) have a propensity to potentiate EPS associated with antipsychotic treatment in a synergistic manner. In contrast, the NMDA receptor antagonist memantine reduces antipsychotic-induced EPS. Antidepressant drugs, which inhibit 5-HT reuptake into the nerve terminals, also synergistically augment antipsychotic-induced EPS, while mirtazapine (α_2, 5-HT_2 and 5-HT_3 antagonist) reduces the EPS induction. Importantly, previous studies showed that multiple 5-HT receptors play crucial roles in modulating EPS associated with antipsychotic treatment. Specifically, activation of 5-HT_{1A} receptors or blockade of 5-HT_2, 5-HT_3 and 5-HT_6 receptors can alleviate EPS induction both by antipsychotics alone and by combined antipsychotic treatments with ChEIs or 5-HT reuptake inhibitors. In this article, we review antipsychotic use in treating BPSD and discuss the favorable drug selection in terms of the management of antipsychotic-induced EPS.

Keywords: behavioral and psychological symptoms of dementia (BPSD), extrapyramidal side effects (EPS), antipsychotics, anti-Alzheimer's disease drugs, antidepressants, 5-HT receptors

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INTRODUCTION

Dementia is a neurodegenerative brain disorder with diverse clinical symptoms including cognitive impairment (e.g., memory loss and learning deficits) and non-cognitive disorders (e.g., behavioral and psychological deficits). Nearly 50 million patients worldwide develop dementia and this population is expected to exceed 130 million in 2050 (Prince et al., 2015; Jin and Liu, 2019). The global cost associated with dementia was about 1,000 billion dollars in 2015, and this continues to increase rapidly. There are numerous causes of dementia including Alzheimer's disease, cerebrovascular diseases,

Parkinson's disease, Lewy body disease, and mixed types, among which Alzheimer's disease is the most frequent (Lee et al., 2004; Prince et al., 2015; Sturm et al., 2018).

Behavioral and psychological symptoms of dementia (BPSD) occur in the majority (up to 90%) of dementia patients, and this causes significant distress to both patients and caretakers (O'Donnell et al., 1992; O'Brien, 2003; Rosdinom et al., 2013). BPSD includes behavioral excitement (e.g., agitation and aggression), mood disorders (e.g., apathy, depression and anxiety), psychosis (e.g., hallucinations and delusions) and other symptoms (e.g., eating disturbances and sleep disorders) (**Figure 1**). Although the prevalence of BPSD varies among reported studies, hallucinations occur in 15–50% of patients with dementia, delusions in 10–75% and behavioral disturbances (e.g., agitation and aggression) in about 50%, while affective symptoms are less common (van der Linde et al., 2014; Devshi et al., 2015). To treat BPSD, non-pharmacological interventions such as cognitive stimulation training, exercise, music therapy, light therapy and aromatherapy are recommended as first-line treatments. Nonetheless, pharmacological treatments with antipsychotics and other psychotropic drugs are necessary to treat BPSD (Brimelow et al., 2019; Jin and Liu, 2019; Kales et al., 2019) (**Figure 1**). Specifically, antipsychotic drugs are the first choice to reduce psychosis and behavioral disturbances despite their frequent side effects (Lee et al., 2004; Trifirò et al., 2009; Brimelow et al., 2019; Sturm et al., 2018).

It is well known that antipsychotic drugs commonly cause serious extrapyramidal side effects (EPS) (e.g., bradykinesia, muscle rigidity, tremor, and akathisia) by blocking dopamine D_2 receptors in the striatum (Remington and Kapur, 1999; Kapur and Remington, 2001; Ohno et al., 2013; Ohno et al., 2015; Ohno, 2019). Antipsychotic-induced EPS often leads to suboptimal treatment of BPSD or treatment discontinuation. In addition, recent studies showed that cholinesterase inhibitors (ChEIs), licensed drugs for cognitive impairment due to Alzheimer's disease, potentiate EPS induction with antipsychotic treatments (Shimizu et al., 2015). It is therefore important to understand the mechanism underlying antipsychotics-induced EPS and antipsychotic drug interactions with other medications in the treatment of BPSD.

In this article, we review the pharmacological features of antipsychotic drugs, especially those related to EPS, and discuss the proper usage and selection of antipsychotics in treating BPSD in terms of EPS management.

ANTIPSYCHOTIC USE IN BPSD TREATMENT

Antipsychotic drugs are used to treat BPSD with a prescription rate of about 20–50% (Lee et al., 2004; Brimelow et al., 2019; Sturm et al., 2018). The target symptoms of antipsychotic drugs include agitation, aggression, psychosis, and inappropriate behaviors (**Figure 1**). None of the antipsychotics, except for haloperidol and risperidone in several countries, are approved to treat BPSD; therefore, these drugs are generally prescribed as off-label. Nonetheless, antipsychotic

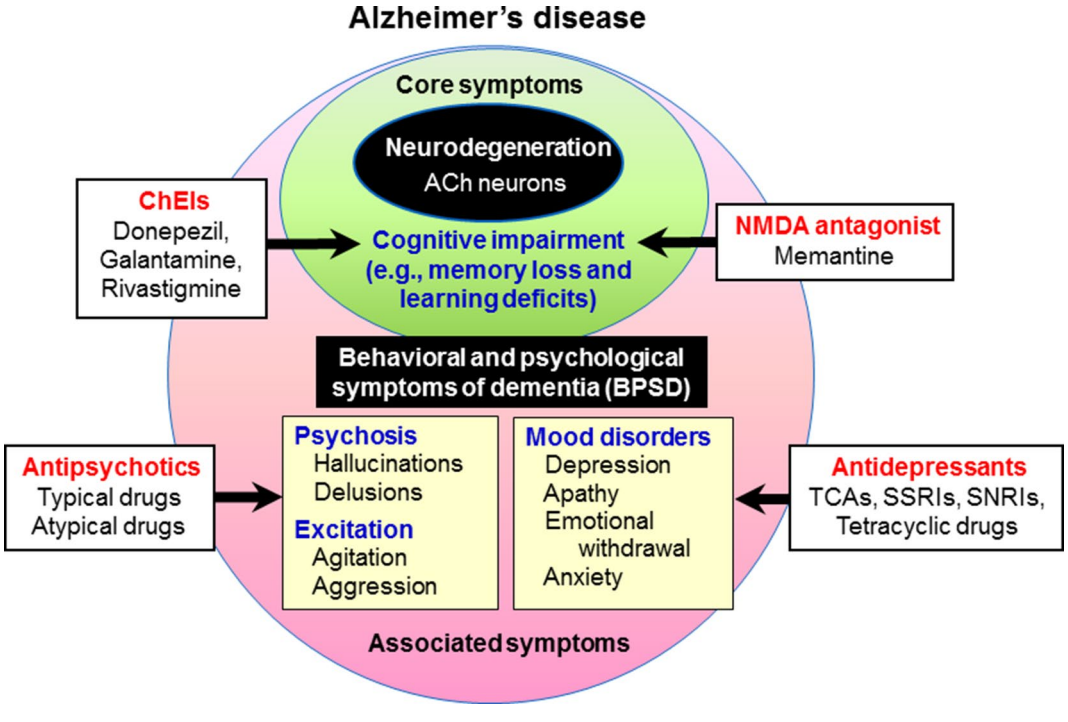

FIGURE 1 | Behavioral and psychological symptoms of dementia (BPSD) in Alzheimer's disease. Patients with dementia show not only core symptoms of dementia (e.g., memory loss and learning deficits), but also various associated symptoms including BPSD (e.g., psychosis, behavioral excitation, and mood disorders). Cognitive impairment in Alzheimer's disease is usually treated with cognitive enhancers such as the cholinesterase inhibitors (ChEIs, e.g., donepezil, galantamine, and rivastigmine) and the NMDA antagonist (e.g., memantine). In the treatment of BPSD, antipsychotic drugs are used for psychosis and behavioral disturbances, and antidepressants for depressive mood.

drugs are reported to produce significantly better improvements than placebos in treating BPSD (Lee et al., 2004; Brimelow et al., 2019; Sturm et al., 2018).

Antipsychotic drugs commonly possess dopamine D_2 blocking actions. It is known that D_2 receptor blockade by antipsychotics in the cortico-limbic regions (e.g., nucleus accumbens) contributes to antipsychotic activities, which alleviates psychosis (e.g., hallucinations and delusions) and behavioral excitation (e.g., agitation, aggression and hyperactivity) (**Figure 2**). However, it should be noted that all antipsychotic drugs frequently cause extrapyramidal motor disorders due to the striatal D_2 receptor blockade, which disrupts the effective treatment of BPSD.

Antipsychotic drugs are generally classified into two groups, typical and atypical (Ohno et al., 1997; Ohno et al., 2012). Typical antipsychotics are the classic standard drugs and frequently cause severe EPS. Based on their chemical structures, they are grouped into several classes, phenothiazines (e.g., chlorpromazine and fluphenazine), butyrophenones (e.g., haloperidol and spiperone), benzamides (e.g., sulpiride and tiapride), and others. On the other hand, atypical antipsychotics were developed as second generation, and are generally less potent than typical ones in inducing EPS (**Figures 2** and **3**). These include the serotonin and dopamine antagonists (SDAs) with potent blocking action for 5-HT_2 receptors, the multiple-acting receptor targeted antipsychotics (MARTAs) and the dopamine D_2 partial agonists (Ohno et al., 2012). Besides reduced EPS, these drugs were originally expected be superior to typical antipsychotics in terms of their efficacy to treat negative symptoms (e.g., apathy and emotional withdrawal) (**Figure 2**). However, comprehensive clinical studies including the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and European First-Episode Schizophrenia Trial (EUFEST), revealed no clear advantages of atypical over typical drugs in terms of efficacy (Lieberman et al., 2005; Keefe et al., 2007; Davidson et al., 2009). Nonetheless, due to the reduced side effect profile, atypical antipsychotics are widely used as a first line drug in BPSD treatment as well as schizophrenia treatment.

ANTIPSYCHOTIC-INDUCED EPS

Clinical Symptoms

Major EPS symptoms associated with antipsychotic treatment of BPSD include Parkinsonian symptoms, akathisia, and dystonia. Tardive dyskinesia (repeated abnormal involuntary movements) is another antipsychotic-induced EPS, but is rare during the relatively short-term BPSD treatment as it is a chronic side effect associated with long-term antipsychotic treatment and usually appears upon the cessation of treatment.

Parkinsonian Symptoms

Antipsychotic-induced Parkinsonian symptoms are involuntary movement disorders including bradykinesia, tremor and muscle rigidity (Samii et al., 2004; Haddad and Dursun, 2008; Ohno et al., 2015). Parkinsonian symptoms usually occur in a few weeks after starting the antipsychotic treatment. Bradykinesia refers to reduced motor activity and slowing movements, which leads to akinesia in more severe cases. Tremor is an involuntary, rhythmic muscle contraction and relaxation (oscillation or twitching movements), affecting the hands, feet and head especially during resting state. In addition, affected patients often exhibit a stooped posture with increased muscle tone (rigidity) and a slow gait without arm swing.

Akathisia

Patients with akathisia suffer from restlessness and repetitive movements of the legs and feet (Keefe et al., 2007; Haddad and Dursun, 2008). As a result, they cannot keep sitting and

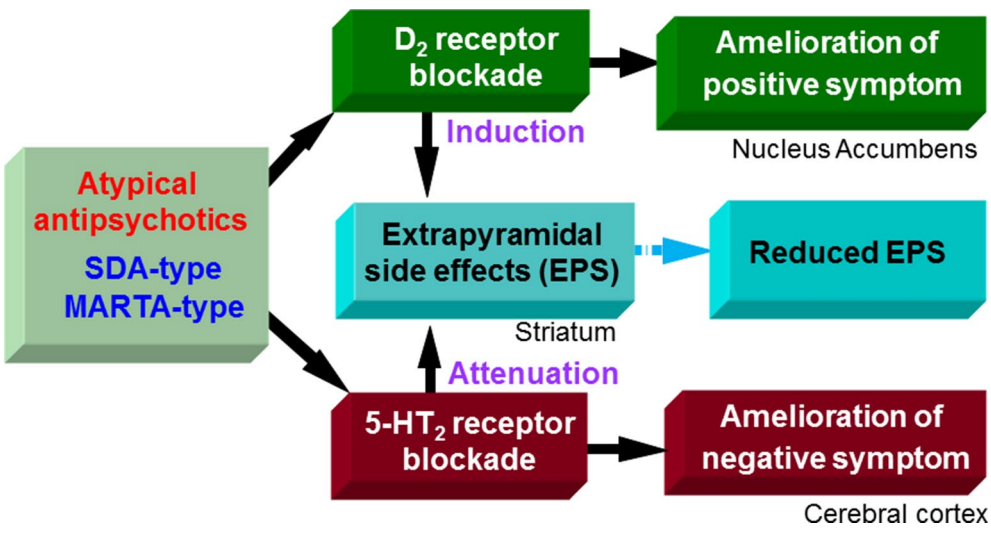

FIGURE 2 | Pharmacological actions of atypical antipsychotics. Likely typical antipsychotic drugs, D_2 blocking actions of serotonin and dopamine antagonists (SDA)-type and multiple-acting receptor targeted antipsychotics (MARTA)-type antipsychotics ameliorate positive symptoms (e.g., hallucination, delusions, and excitation) in schizophrenia, but induce extrapyramidal side effects (EPS). On the other hand, SDA-type and MARTA-type antipsychotics show higher 5-HT_2 than D_2 binding affinities and possess potent 5-HT_2 antagonistic actions. The 5-HT_2 blocking activities of SDA-type antipsychotics ameliorate negative symptoms (e.g., apathy and social withdrawal) in schizophrenia and can reduce EPS. Thereby, overall EPS liability of SDA-type antipsychotics is lower than typical antipsychotics (D_2 antagonists).

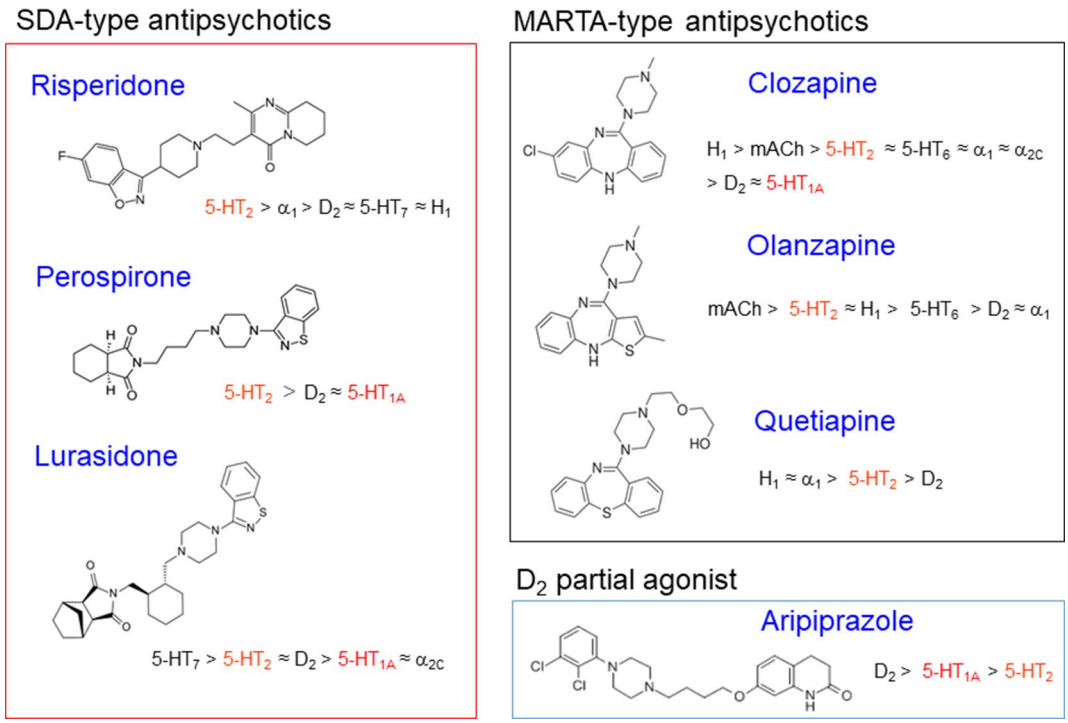

FIGURE 3 | Classification and characteristics of atypical antipsychotic drugs. Figure shows chemical structures of atypical antipsychotics with their receptor binding profiles (affinities). Most atypical antipsychotics possess potent 5-HT_2 blocking actions and act as serotonin and dopamine antagonists (SDAs). Among SDAs, clozapine derivatives (e.g., olanzapine and quetiapine) show various actions on other receptors than D_2 and 5-HT_2 receptors, including histamine H_1, adrenergic α_1, and muscarinic blocking actions. Thereby, they are sometimes called as multi-acting receptor-targeted antipsychotics (MARTAs) and differentiated from SDAs (e.g., risperidone, perospirone, and lurasidone). Although aripiprazole possess moderate 5-HT_2 blocking activities, it primarily acts as a dopamine D_2 partial agonist. Furthermore, several atypical antipsychotics have own characteristics such as 5-HT_{1A} partial agonistic actions for perospirone, lurasidone and aripiprazole, 5-HT_6 blocking actions for olanzapine and quetiapine, and 5-HT_3 blocking actions for olanzapine.

frequently shift their body position. Akathisia usually appears soon after starting antipsychotics or after increasing the dose.

Dystonia

Dystonia causes sustained muscle contraction, often leading to postural distortion (Haddad and Dursun, 2008). Dystonia often attacks the neck muscles, tongue, trunk, and limbs. Acute dystonia usually appears in the first week after starting or increasing the dose of antipsychotics.

Neural Mechanism of EPS Induction

It is well known that antipsychotic-induced EPS are caused by the blockade of dopamine D_2 receptors in the striatum (caudate-putamen) (Ohno et al., 1997; Ohno et al., 2013; Ohno et al., 2015; Ohno, 2019) (**Figure 4**). The GABAergic medium spiny neurons in the striatum receive excitatory glutamatergic inputs from the cerebral cortex and acetylcholinergic inputs from striatal interneurons. The medium spiny neurons also receive inhibitory dopaminergic inputs from the substantia nigra pars compacta (SNc) and express a high density of D_2 receptors (Ohno et al., 2015). In addition, the dopaminergic neurons from the SNc also negatively regulate activities of the acetylcholinergic interneuron *via* D_2 receptors. Most antipsychotic drugs commonly act as dopamine D_2 receptor antagonists and activate the medium spiny neurons and acetylcholinergic interneurons in the striatum, eliciting various EPS symptoms (Ohno et al., 2013) (**Figure 4**).

To reduce EPS, a series of atypical antipsychotics, that show potent 5-HT_2 blocking activities have been developed in the last three decades (Ohno et al., 1997; Ohno et al., 2012) (**Figures 2** and **3**). These agents include risperidone, perospirone, olanzapine, quetiapine, lurasidone, and paliperidone, and they commonly exhibit higher 5-HT_2 than D_2 affinities. Since olanzapine and quetiapine also show high affinities for other multi-receptors (e.g., histamine H_1, adrenergic α_1, and muscarinic acetylcholine (mACh) receptors), these drugs are sometimes called as MARTAs and distinguished from SDAs.

It is well documented that blockade of 5-HT_2 receptors attenuates antipsychotic-induced EPS associated with the striatal D_2 receptor blockade (**Figure 2**). 5-HT_2 receptors are located on nerve terminals and cell bodies of dopaminergic neurons in the striatum and the SNc, respectively, and inhibit dopaminergic neuron activities (Ohno et al., 1997; Ohno et al., 2012; Ohno et al., 2013). It is therefore proposed that blockade of 5-HT_2 receptors relieves 5-HT_2 receptor-mediated inhibition of dopamine release in the striatum and of dopamine neuron firing in the SNc, which leads to alleviation of EPS (**Figure 5**) (Remington and Kapur, 1999; Kapur and Remington, 2001). In fact, blockade of 5-HT_2 receptors can reverse various responses of striatal neurons to

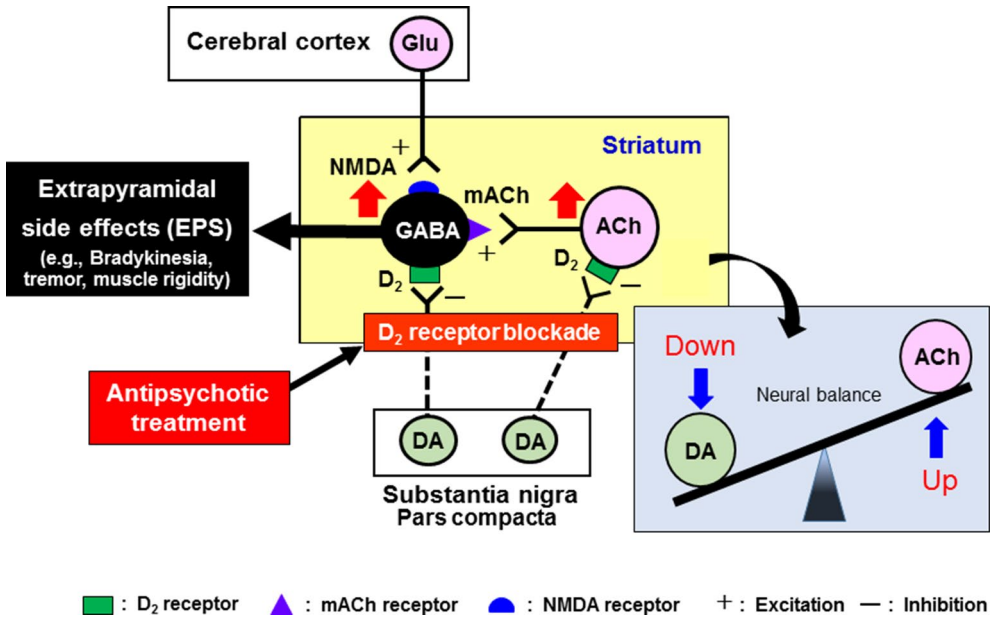

FIGURE 4 | Pathophysiological mechanisms underlying the induction of extrapyramidal side effects (EPS) with antipsychotic treatments. Antipsychotic drugs commonly exert dopamine D_2 blocking actions in the striatum, which relieves the striatal neurons (GABA-containing medium spiny neurons and acetylcholine (ACh)-containing interneurons) from negative regulation by the nigrostriatal dopaminergic neurons. Thus, overall activation of striatal medium spiny neurons by antipsychotics evokes EPS (e.g., bradykinesia, tremor, and muscle rigidity). Antipsychotic-induced EPS can be alleviated by anti-muscarinic drugs (e.g., trihexyphenidyl and biperidene), which reverses the imbalance between dopamine and ACh neuron activities in the striatum. However, due to the side effects, these agents are not recommended for the elderly patients.

antipsychotics (D_2 receptor blockade), such as the enhancement of acetylcholine (ACh) release, the increase in metabolic turnover rate of dopamine and the induction of Fos protein expression, in the striatum Ohno et al., 1997; Ohno et al., 2013).

SEROTONERGIC MODULATION OF ANTIPSYCHOTIC-INDUCED EPS

As described previously, the serotonergic nervous system plays an important role in modulating EPS induction. Specifically, antipsychotic-induced EPS is augmented by stimulation of 5-HT_2 receptors and attenuated by 5-HT_2 receptor blockade. Besides 5-HT_2 receptors, several 5-HT receptor subtypes, including 5-HT_{1A}, 5-HT_3 and 5-HT_6 receptors, are involved in regulation of EPS induction associated with antipsychotic treatment (Ohno et al., 2013; Ohno et al., 2015).

5-HT_{1A} receptors function as both presynaptic autoreceptors and postsynaptic receptors, which inhibits neural activities *via* activating G-protein-gated inwardly rectifying K^+ channels (Baumgarten and Grozdanovic, 1995; Barnes and Sharp, 1999; Shimizu et al., 2013a; Shimizu et al., 2013b; Ohno, 2019). Activation of 5-HT_{1A} receptors is known to reduce antipsychotic-induced EPS and motor disorders in animal models of Parkinson's disease (Neal-Beliveau et al., 1993; Wadenberg et al., 1999; Mignon and Wolf, 2002; Ohno et al., 2008a; Ohno et al., 2008b; Ohno et al., 2009; Shimizu et al., 2010). Our previous studies showed that selective 5-HT_{1A} agonists (e.g., 8-OH-DPAT) ameliorated haloperidol-induced EPS (e.g., bradykinesia and catalepsy) and reversed the striatal Fos protein expression by the haloperidol treatment (Ohno et al., 2008a; Ohno et al., 2008b; Ohno et al., 2009). In addition, the anti-EPS action of 5-HT_{1A} agonists persisted against the denervation of 5-HT neurons with *p*-chlorophenylalanine treatment, illustrating that postsynaptic 5-HT_{1A} receptors are responsible for EPS reduction (Neal-Beliveau et al., 1993; Mignon and Wolf, 2002; Ohno et al., 2008a; Ohno et al., 2008b) Furthermore, microinjection of 5-HT_{1A} agonists into the striatum or the cerebral cortex (i.e., motor cortex) also attenuated extrapyramidal disorders (Shimizu et al., 2010). Therefore, it is likely that activation of 5-HT_{1A} receptors reduces antipsychotic-induced EPS by inhibiting neural activity in the striatum and motor cortex (**Figure 5**). Nonetheless, several studies suggest that presynaptic 5-HT_{1A} autoreceptors are also involved to reduce EPS (Wadenberg et al., 1999; Mombereau et al., 2017).

5-HT_3 receptors function as cation (Na^+, K^+, and Ca^{2+})-permeable ion channels and excite target neurons (Barnes and Sharp, 1999; Ohno, 2019). Several studies demonstrated that blockade of 5-HT_3 receptors reduced haloperidol-induced EPS (e.g., catalepsy and bradykinesia) (Silva et al., 1995; Ohno et al., 2011; Tatara et al., 2012) (**Figure 5**). Clinical studies also showed that the selective 5-HT_3 antagonist, ondansetron, reduced the incidence and severity of antipsychotic-induced EPS in the schizophrenia treatment (Zhang et al., 2006; Akhondzadeh et al., 2009).

5-HT_6 receptors are highly expressed in the basal ganglia (e.g., striatum), as well as the limbic (e.g., olfactory tubercles and hippocampus) and cortical regions (Barnes and Sharp, 1999; Ohno, 2019). We previously showed that the selective 5-HT_6 antagonist, SB-258585, alleviated haloperidol-induced bradykinesia and catalepsy (Ohno et al., 2011; Tatara et al., 2012). In addition,

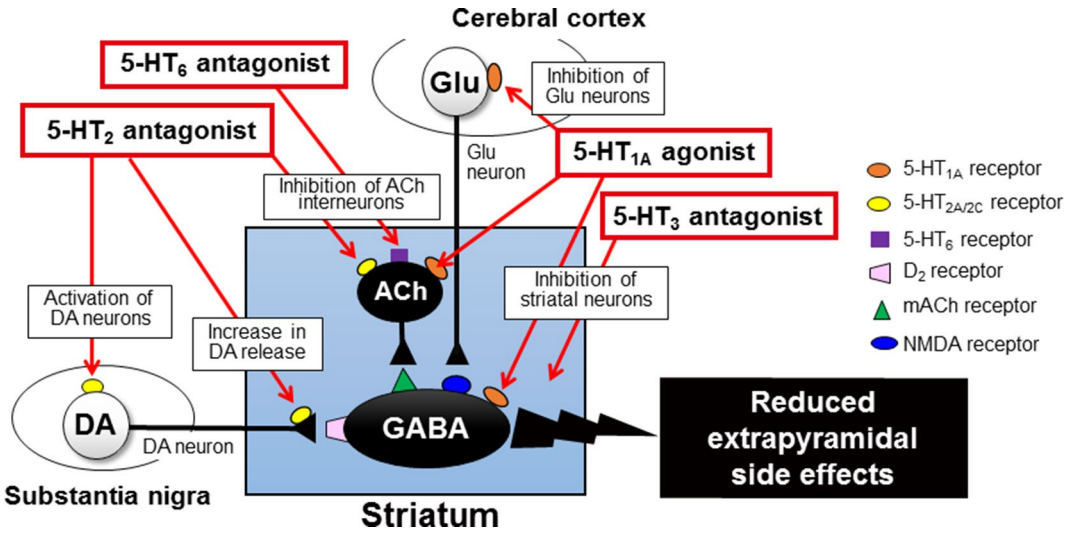

FIGURE 5 | Mechanisms underlying serotonergic modulation of antipsychotic-induced extrapyramidal side effects (EPS). Activation of 5-HT_{1A} receptors, especially postsynaptic 5-HT_{1A} receptors in the striatum and cerebral cortex, alleviates antipsychotic-induced EPS. Blockade of 5-HT_2 receptors on nigral dopamine neurons and their nerve terminals in the striatum can relieve the negative serotonergic regulation and thereby can increase the dopaminergic activities, which contributes to EPS reduction. Similarly, blockade of 5-HT_3 and 5-HT_6 receptors attenuates antipsychotic-induced EPS possibly *via* acting in the striatum. This figure is quoted and arranged from Biol. Pharm. Bull. 36, 1396, 2013.

EPS induction was also reduced by microinjection of SB-258585 into the striatum, implying that blockade of the striatal 5-HT_6 receptors is at least partly involved in alleviating EPS. Since 5-HT_6 receptors positively regulate the neural activities of the striatal ACh interneurons (Bonsi et al., 2007), it is conceivable that 5-HT_6 antagonists reduce antipsychotic-induced EPS by inhibiting them (**Figure 5**).

Regarding other 5-HT receptor subtypes, neither 5-HT_4 (GR-125487), 5-HT_{5a} (SB-699551), nor 5-HT_7 (SB-269970) antagonists affected antipsychotic-induced EPS (Ohno et al., 2011). Therefore, the modulatory roles of these 5-HT receptors in modulating EPS appear to be minimal.

EFFECTS OF ANTI-ALZHEIMER'S DISEASE DRUGS ON ANTIPSYCHOTIC-INDUCED EPS

Alzheimer's disease is the major component of elderly dementia. Since Alzheimer's disease accompanies the loss of ACh neurons (Fibiger, 1991; Silva et al., 2014), several ChEIs such as donepezil, galantamine, and rivastigmine, which can increase the ACh level by inhibiting cholinesterase, are widely used to treat the cognitive impairment in Alzheimer's disease. In addition, an NMDA receptor antagonist, memantine, is also used to alleviate the cognitive impairment. These anti-Alzheimer's disease drugs are often prescribed in combination with antipsychotic drugs which can reduce BPSD (Salamone et al., 2001; Kozman et al., 2006), giving greater efficacy than monotherapy (Schmitt et al., 2004).

Although information on the drug interactions between antipsychotic and anti-Alzheimer's disease drugs is limited, our previous study revealed that they markedly potentiated antipsychotic-induced EPS induction (Shimizu et al., 2015). Specifically, donepezil and galantamine rarely induce EPS signs when taken alone; however, they markedly potentiated bradykinesia induction by low dose of haloperidol in a dose-dependent and synergistic manner (**Figure 6**). In addition, the bradykinesia potentiation by galantamine was significantly reversed by a 5-HT_{1A} agonist (8-OH-DPAT), a 5-HT_2 antagonist (ritanserin) and a 5-HT_6 antagonist (SB-258585) (Shimizu et al., 2015). These findings indicate that caution is needed in the combined usage of antipsychotics and ChEIs in BPSD treatment. Furthermore, antipsychotics that can stimulate 5-HT_{1A} receptors or antagonize 5-HT_2 and 5-HT_6 receptors appear favorable as an adjunctive therapy for BPSD. Interestingly, in contrast to ChEIs, memantine, which antagonizes NMDA receptors, attenuated antipsychotic-induced EPS (**Figure 6**). Therefore, it seems likely that memantine is more favorable than ChEIs in the combined therapy of BPSD with antipsychotics.

Precise mechanisms underlying the synergistic potentiation of EPS by ChEIs is still unknown. However, the action of antipsychotics on cholinergic interneurons in the striatum seems to be involved since the firing of striatal cholinergic interneurons is negatively regulated by dopaminergic neurons and is reportedly facilitated by antipsychotics, increasing the ACh release (Damsma et al., 1990; DeBoer and Abercrombie, 1996). Therefore, ChEIs may augment the induction of EPS more potently in the presence of antipsychotics than their monotherapy.

EFFECTS OF ANTIDEPRESSANT DRUGS ON ANTIPSYCHOTIC-INDUCED EPS

Antidepressant drugs, as well as antipsychotic drugs, are often used to treat BPSD, especially the mood disorders such as apathy, depression and emotional withdrawal (Lee et al., 2004; Trifirò et al., 2009; Brimelow et al., 2019; Sturm et al., 2018; Jin and Liu, 2019;

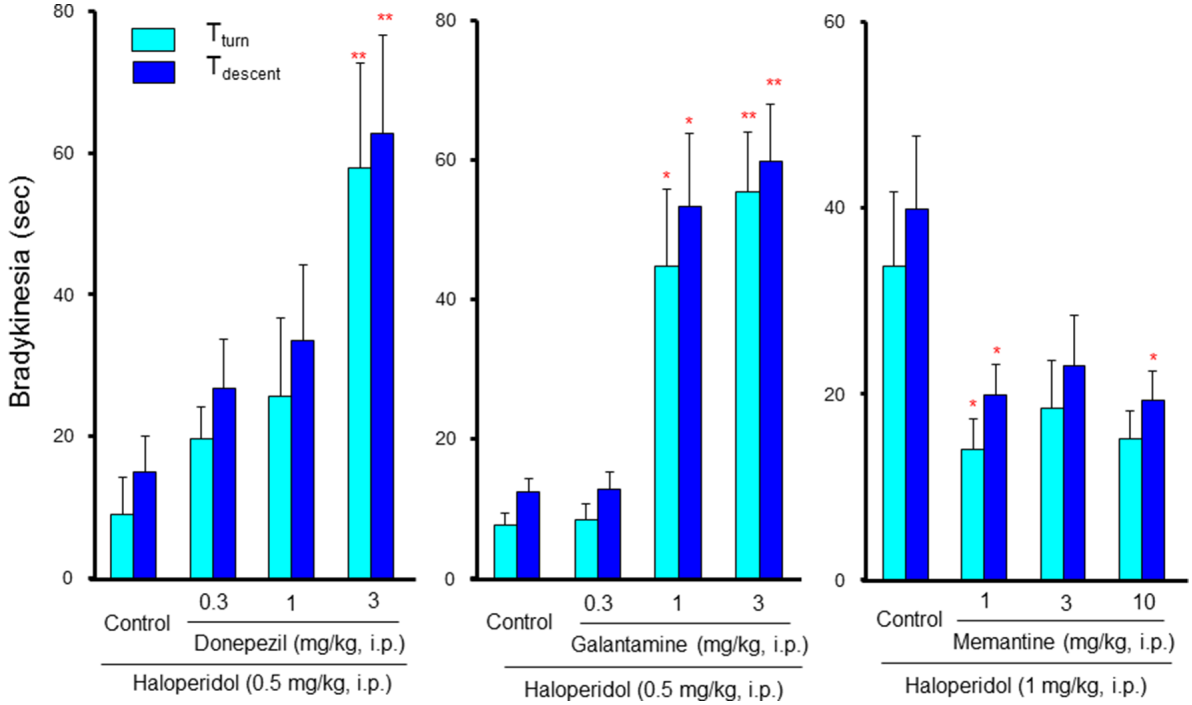

FIGURE 6 | Interactions between anti-Alzheimer's disease drugs and antipsychotics in induction of extrapyramidal side effects (EPS). Bradykinesia was estimated by the pole test, where mice were placed head-upward at the top of a pole (45 cm in height) and the time for mice to rotate downward (T_{turn}) and to descend to the floor ($T_{descent}$) was measured (Ohno et al., 2008a). Bradykinesia was evaluated as the prolongation of T_{turn} or $T_{descent}$ Values. Although low dose (0.5 mg/kg) of haloperidol showed marginal effects in the pole test, combined treatment with cholinesterase inhibitors, donepezil, and galantamine, markedly potentiated haloperidol-induced bradykinesia in a synergistic manner. By contrast, the NMDA antagonist, memantine, significantly reduced bradykinesia induced by a high dose (1 mg/kg) of haloperidol. *P<0.05, **P,0.01; Significantly different from the control values. This figure is partly quoted and arranged from J. Pharmacol. Sci. 127, 439, 2015.

Kales et al., 2019) (**Figure 6**). The majority of antidepressant drugs commonly inhibit neural reuptake of 5-HT and/or noradrenaline, and increase the synaptic levels of 5-HT and/or noradrenaline (Ohno, 2019). These drugs are generally classified as tricyclic antidepressants (TCAs) (e.g., nortriptyline, clomipramine, and imipramine), selective serotonin reuptake inhibitors (SSRIs) (e.g., fluoxetine, sertraline, and paroxetine) and serotonin noradrenaline reuptake inhibitors (SNRIs) (e.g., milnacipran, duloxetine, and venlafaxine). In addition, tetracyclic antidepressant drugs (e.g., mirtazapine and mianserin), which block adrenergic α2, 5-HT_2 and 5-HT_3 receptors without affecting 5-HT or noradrenaline transporters (Wood et al., 1993; Anttila and Leininen, 2001; Wikström et al., 2002; Fernández et al., 2005; Gillman, 2006), are also used to treat BPSD (**Figure 1**). These agents enhance noradrenaline and 5-HT release by inhibiting α2 autoreceptors on adrenergic nerve terminals and α2 heteroreceptors on serotonergic nerve terminals, respectively.

Neither SSRIs nor TCAs induced EPS by themselves; however, they markedly potentiated antipsychotic-induced bradykinesia and catalepsy in a dose-dependent manner (Tatara et al., 2012; Shimizu et al., 2013a; Shimizu et al., 2013b) (**Figure 7**). Clinical studies also showed that antidepressants worsen extrapyramidal motor disorders (Gill et al., 1997; Govoni et al., 2001; DeBattista and DeBattista, 2010). Therefore, caution should be taken in the combined usage of antidepressants with antipsychotics in BPSD treatment even though antidepressants do not cause EPS by themselves. Since both SSRIs and TCAs commonly enhance serotonergic activity, these agents potentiate antipsychotic-induced EPS probably by stimulating 5-HT_2, 5-HT_3 and 5-HT_6 receptors. In addition, although the synergistic mechanism in potentiating EPS remains uncertain, antipsychotic-induced activation of striatal cholinergic interneurons may be involved since 5-HT excites the cholinergic neurons *via* 5-HT_{2C} and 5-HT_6 receptors (Bonsi et al., 2007). In fact, blockade of 5-HT_2 receptors by ritanserin, 5-HT_3 receptors by ondansetron (5-HT_3 antagonist), and 5-HT_6 receptors by SB-258585 (5-HT_6 antagonist), significantly attenuated the EPS augmentation by SSRIs (Tatara et al., 2012). In addition, stimulation of postsynaptic 5-HT_{1A} receptors by 8-HO-DPAT also alleviated SSRIs-induced EPS augmentation (Shimizu et al., 2013a; Shimizu et al., 2013b). This implies that antipsychotics which possess 5-HT_{1A} stimulating actions or 5-HT_2, 5-HT_3, and 5-HT_6 blocking actions, could be useful as adjunctive therapies for BPSD.

In contrast to SSRIs and TCAs, tetracyclic antidepressants (mirtazapine and mianserin) did not augment, but rather attenuated antipsychotic-induced EPS (Tatara et al., 2012) (**Figure 7**). Thus, it seems likely that tetracyclic antidepressants are superior to SSRIs or TCAs in modulating EPS in combined treatment of BPSD with antipsychotics. Since the blockade of α_2 receptors reportedly reduced antipsychotic-induced EPS (Imaki et al., 2009), EPS reduction by tetracyclic antidepressants is probably due to the α2 blocking action in addition to their 5-HT_2 and 5-HT_3 blocking activities.

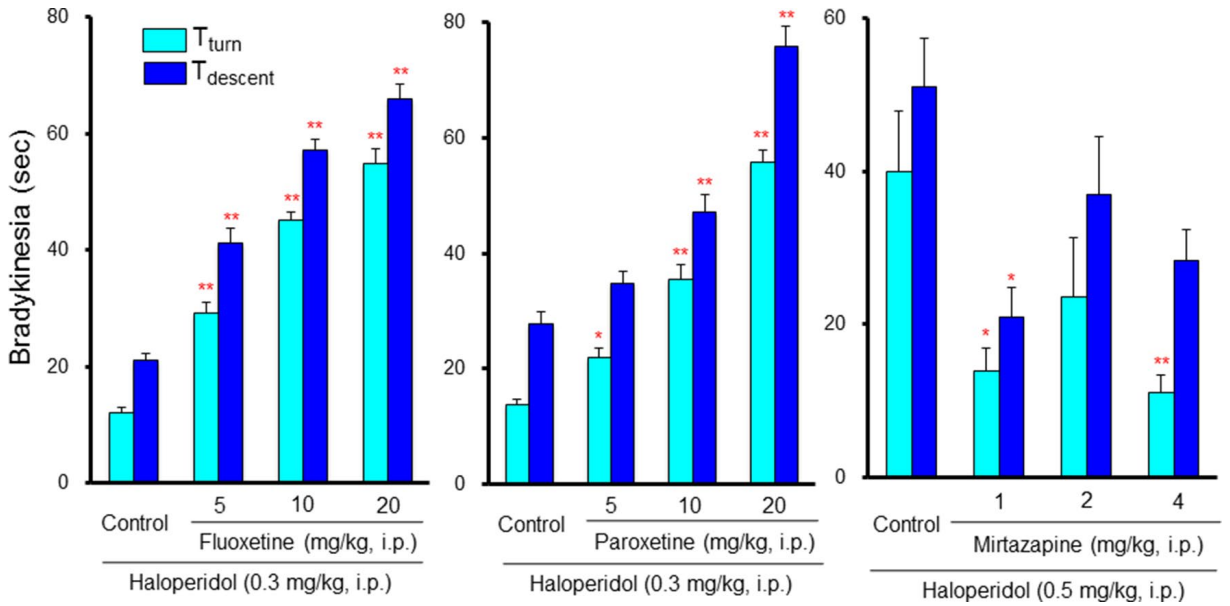

FIGURE 7 | Interactions between antidepressants and antipsychotics in induction of extrapyramidal side effects (EPS). Bradykinesia was estimated by the pole test as described in **Figure 6** legend. Although low dose (0.3 mg/kg) of haloperidol showed only weak effects in the pole test, combined treatment with selective serotonin reuptake inhibitors, fluoxetine and paroxetine, markedly potentiated haloperidol-induced bradykinesia in a synergistic manner. By contrast, the tetracyclic antidepressant mirtazapine, which possesses α_2, 5-HT_2 and 5-HT_3 antagonistic actions, reduced bradykinesia induced by a moderate dose (0.5 mg/kg) of haloperidol. *P<0.05, **P,0.01; Significantly different from the control values. This figure is quoted and arranged from Prog. Neuro-Psychopharmacol. Biol. Psychiatry 38, 252, 2012.

DRUG SELECTION IN BPSD TREATMENT

We reviewed antipsychotic use in BPSD treatment focusing on EPS, the most frequent side effects associated with the striatal D_2 receptor blockade. Antipsychotic-induced EPS significantly disrupts activities of daily life and impairs the quality of life in the elderly patients with dementia. Therefore, information on the mechanisms and the drug interactions in modulating EPS induction are necessary to achieve proper pharmacotherapy of BPSD. In this regard, we should be very careful not only about EPS liability of antipsychotics by itself, but also about the interaction of antipsychotics with anti-Alzheimer's disease drugs and antidepressant drugs.

Atypical antipsychotics (e.g., SDAs, MARTAs, and D_2 partial agonists) are now the first line drug to treat psychosis and inappropriate behaviors (e.g., agitation and aggression) in patients with dementia. But, we should pay more attention to individual pharmacological characteristics of the atypical drug, especially their interactions with 5-HT receptor subtypes. Although most SDAs or MARTAs commonly possess high affinities to 5-HT_2 receptors, many atypical antipsychotics shows a differential binding profile each other, interacting with various monoamine receptors (Farah, 2005). In fact, olanzapine additionally show high affinities for 5-HT_3 and 5-HT_6 receptors and acts as antagonist (Bymaster et al., 2001). In addition to 5-HT_2 receptors, the SDA antagonist lurasidone also binds to 5-HT_{1A} receptors and acts as a partial agonist (Ishibashi et al., 2010). Furthermore, the dopamine D_2 partial agonist aripiprazole also binds to 5-HT_{1A} and 5-HT_2 receptors, and acts as a partial agonist and an antagonist, respectively (Stark et al., 2007). Since the actions of these agents with 5-HT receptor subtypes can reduce EPS caused by combined treatment of antipsychotics with anti-Alzheimer's disease drugs and antidepressants, they could be a favorable BPSD treatment in terms of EPS management.

Among anti-Alzheimer's disease drugs, the NMDA antagonist memantine appears superior to ChEIs in the combined BPSD therapy with antipsychotics as it attenuates antipsychotic-induced EPS. Likewise, the tetracyclic antidepressants (mirtazapine and mianserin) are recommended for combined use with antipsychotics to treat BPSD. Unlike 5-HT reuptake inhibitors (e.g., SSRIs, SNRI, and TCAs), these agents do not augment EPS induction, but alleviate antipsychotic-induced EPS, which is possibly by blocking α_2, 5-HT_2 and 5-HT_3 receptors (Imaki et al., 2009; Ohno et al., 2011).

CLOSING REMARKS

This article provides information on the safe usage of antipsychotics in adjunctive therapy for BPSD in patients with dementia. The crucial roles of 5-HT receptors, especially 5-HT_{1A}, 5-HT_2, 5-HT_3, and 5-HT_6 receptors, in modulating antipsychotic-induced EPS were revealed. Although antipsychotic drugs are effective for psychosis, agitation, excitation, and abnormal behaviors, we should be very careful about drug selection

in the combined use of antipsychotics with anti-Alzheimer's disease drugs or antidepressants. Specifically, ChEIs and 5-HT reuptake inhibitors (SSRIs, SNRI, and TCAs) markedly potentiate antipsychotic-induced EPS in a synergistic manner. In contrast, the NMDA antagonist (memantine) or the tetracyclic antidepressants (mirtazapine and mianserin) seem to be more suitable for adjunctive therapy of cognitive impairment and mood disorders of BPSD, respectively. Furthermore, antipsychotics which have 5-HT_{1A} agonistic actions or 5-HT_2, 5-HT_3, and 5-HT_6 antagonistic actions appear to be useful for adjunctive BPSD treatment.

AUTHOR CONTRIBUTIONS

YO drafted the initial manuscript. All authors (YO, NK, SS) improved, contributed to and agreed on the final version of the manuscript.

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REVIEW
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Behavioral and Psychiatric Symptoms of Dementia and Rate of Decline in Alzheimer's Disease

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Alzheimer's disease causes both cognitive and non-cognitive symptoms. There is increasing evidence that the presentation and course of Alzheimer's disease is highly heterogenous. This heterogeneity presents challenges to patients, their families, and clinicians due to the difficulty in prognosticating future symptoms and functional impairment. Behavioral and psychiatric symptoms are emerging as a significant contributor to this clinical heterogeneity. These symptoms have been linked to multiple areas of neurodegeneration, which may suggest that they are representative of network-wide dysfunction in the brain. However, current diagnostic criteria for Alzheimer's disease focus exclusively on the cognitive aspects of disease. Behavioral and psychiatric symptoms have been found in multiple studies to be related to disease severity and to contribute to disease progression over time. A better understanding of how behavioral and psychiatric symptoms relate to cognitive aspects of Alzheimer's disease would help to refine the models of disease and hopefully lead to improved ability to develop therapeutic options for this devastating disease.

Keywords: Alzheimer's disease, behavioral and psychiatric symptoms, cognitive decline, functional decline, predictors of decline

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INTRODUCTION

Dementia is characterized by a decline in cognitive function when compared with others with similar age and education. It is an important cause of morbidity and mortality, especially in the elderly.

In 1906, Alois Alzheimer reported a case of a woman with prominent and progressive psychiatric symptoms and memory disturbance, who he followed for 5 years until her death (Maurer et al., 1997). Alzheimer's disease is the most common cause of cognitive impairment, and its prevalence increases with age (Erkkinen et al., 2018). However, the rapidity of decline in this first patient has generally not been considered the usual course of the disease. In fact, there is significant heterogeneity in the rates and manners in which patients progress through the stages of Alzheimer's disease (Mayeux et al., 1985).

Part of this heterogeneity is the presence of behavioral and psychiatric symptoms (BPSD). These symptoms affect over 80% of patients with AD over the course of disease, however their presentations are highly variable both between patients and over an individual's disease course (Garre-Olmo et al., 2010a). Psychiatric symptoms can be present at all stages of disease, however specific symptoms are more common at different stages of disease. Although all symptoms worsen with disease severity,

certain symptoms such as delusions, agitation, and apathy tend to become much more prevalent (Lyketsos et al., 2002).

The prevalence of psychiatric symptoms early in the course of dementia has become increasingly recognized. Mild behavioral impairment is a recently defined diagnostic construct that has been used to describe the presence of these symptoms, even in the absence clear cognitive change (Ismail et al., 2016).

Management of psychiatric symptoms is an important component of caring for these patients. Behavioral symptoms are a significant source of caregiver stress (Van Den Wijngaart et al., 2007) and contribute to the financial burden of caring for these patients (Murman et al., 2002; Schnaider Beeri et al., 2002; Herrmann N et al., 2006). These symptoms also contribute to earlier nursing home placement (Yaffe et al., 2002). A better understanding of BPSD and how they relate to neurodegenerative disease and its progression is important to patients, their families, and clinicians.

BPSD have been associated with overall clinical deterioration (Stella F et al., 2016), and there is evidence that patients with severe symptoms have identifiable neuroanatomical changes (Poulin et al., 2017). Delusions and hallucinations have been associated with atrophy within the neural networks that regulate complex behaviors (Rafii MS et al., 2014).

The ability to prognosticate clinical course is extremely important for clinicians as well as patients and their families. In addition, from a public health perspective, it is important to be able to predict costs and the health care resources needed to care for patients with AD as the population ages, as well as for identifying appropriate clinical targets for disease-modifying therapies. The trajectory of progression is not necessarily linear (Samtani et al., 2012) and is quite heterogeneous both between individuals and over the course of one case (Mayeux et al., 1985). To that end, several studies have tried to find ways of predicting clinical progression of disease. Although there are few FDA-approved treatments for BPSD at this time, the ability to predict disease course is highly valuable in its own right.

Although significant amounts of research have been devoted to a better understanding of the "negative" BPSD—namely, depression and anxiety—comparatively less has been devoted to "positive" symptoms, such as hallucinations and delusions. This review will discuss three major clusters of positive BPSD: hallucinations, delusions, and aggression/agitation. It will explore the underlying neural bases for these clusters of symptoms and discuss how these symptoms affect the rates of cognitive and functional decline in patients. A selection of the papers referenced are summarized in **Table 1**.

HALLUCINATIONS

Epidemiology/Neurobiology

The reported prevalence of hallucinations in Alzheimer's disease is wide ranging, with some estimates from 12% to 33% (Leroi et al., 2003; Wilson et al., 2006; Scarmeas et al., 2005). Unlike dementia with Lewy bodies, where visual hallucinations are a core clinical feature (McKeith et al., 2017), the hallucinations of Alzheimer's disease can be visual, auditory (Wilson et al., 2006), olfactory, or rarely, tactile (Devanand et al., 1992). Hallucinations in Alzheimer's disease have been associated with lower education, non-Caucasian ethnicity, and worse severity of disease (Bassiony et al., 2000; Wilson et al., 2006).

Efforts to identify the anatomy underlying visual hallucinations have yielded variable results. Hallucinations have been associated with occipital atrophy (Holroyd et al., 2000) and hypoperfusion in left dorsolateral prefrontal, left medial temporal, and right parietal cortices (Lopez et al., 2001). One study found that atrophy in the right supramarginal gyrus predicted worsened hallucinations over 3 years (Donovan et al., 2014). It would be intuitive to propose that more global network dysfunction underlies the relationship between hallucinations and cognitive decline. However, there have been few formal studies assessing this network. The right anterior insula has been proposed as the "core region" for hallucinations, in part, due to its role in integrating external sensory input with the internal milieu (Blanc et al., 2014).

Deficiency in acetylcholine from the basal forebrain underlies attentional and arousal deficits in Alzheimer's disease and other neurodegenerative diseases (Pepeu et al., 2013). Accordingly, acetylcholinerase inhibitors have long been a mainstay in the treatment of Alzheimer's disease. It has been proposed that a form of cholinergic deficiency syndrome, which is characterized by restlessness, memory disturbances, and visual hallucinations, and was initially described as an iatrogenic syndrome from anticholinergic treatment, may exist in a more chronic form in neurodegenerative diseases (Lemstra et al., 2003). Although this proposal suggested that cholinergic deficiency syndrome is more specific to dementia with Lewy bodies, the symptoms of the syndrome are often present in patients with Alzheimer's disease as well. An EEG study of patients with Alzheimer's disease or dementia with Lewy bodies found that patients with hallucinations and Alzheimer's disease had similar slowing of EEG activity as those with hallucinations and dementia with Lewy bodies, suggestive of cholinergic loss in both populations (Dauwan et al., 2018).

The effect of hallucinations on cognition has been associated with genetic predispositions. A large study using 900 autopsy-confirmed cases of AD from the National Alzheimer's Coordinating Center (NACC) data to study the effect of psychosis and *APO* ε4 on cognition found that hallucinations were significantly associated with worse cognition, and that the presence of *APO* ε4 attenuated this relationship (Qian W et al., 2018). Interestingly, the presence of *APO* ε4 was also significantly associated with more Lewy body pathology in this study.

Additionally, hallucinations have been associated with sleep disturbances. It has been hypothesized that this is due to dysregulation of the neurotransmitter systems involved in sleep (Sinforiani et al., 2007). Hallucinations tend to be more likely to occur during sleep or during sleep–wake phase transitional phases (i.e. falling asleep and waking up) (Sinforiani et al., 2007). Intuitively, this supports an association between the sleep–wake cycle and the presence of hallucinations.

Contribution to Rates of Decline

Hallucinations are associated with more severe cognitive impairment (Wadsworth et al., 2012), are persistent (Holtzer

et al., 2003), and may increase in incidence over time (Vilalta-Franch et al., 2013). There have been several studies both in community-based and clinic-based cohorts that assessed the relationship between hallucinations and the rate of decline. They have largely shown that the presence of hallucinations at baseline is associated with more rapid decline. Wilson et al. (2006) followed patients for an average of 2.2 years in the Rush Alzheimer's Disease Center and community-dwelling adults and found that in addition to being related to poorer performance on cognitive screening (average MMSE of 10.7 for patients with hallucinations versus 14.1 for those without), patients demonstrated more rapid cognitive decline if they had hallucinations at baseline. Patients with hallucinations also had increased risk of mortality by the end of the study (RR, 1.55). Similarly, Connors et al. (2018) demonstrated that patients in memory clinics in Australia with hallucinations had worsened dementia severity, lower cognition and function, and greater caregiver burden over a 3-year period. Similar results have been found by several other studies (Forstl et al., 1993; Vilalta-Franch et al., 2013; Tchalla et al., 2018).

A limitation of any longitudinal study of hallucinations is that symptoms fluctuate over time (Devanand, 1999). Therefore, extended follow-up would be beneficial and contribute to improved robustness of the analysis. Hallikeinen et al. (2018a) analyzed data from the ALSOVA study, a cohort of patients with very mild and mild AD (CDR 0.5-1 at baseline) in Finland, using generalized estimated equations (GEE), and did not find evidence that hallucinations predicted disease severity over 5 years. However, using linear mixed models, they did find that hallucinations were significantly associated with Alzheimer's disease severity over time.

In contrast, Scarmeas et al. (2005) analyzed data from participants in the Predictors 1 and Predictors 2 cohorts, which are longitudinal studies of patients diagnosed with probable Alzheimer's disease in multiple centers in the United States and Europe (Stern et al., 1993; Scarmeas et al., 2004), for an average of 4.5 years, and up to 14 years, and using Cox analysis looked at the risk of reaching specified functional and cognitive endpoints. They found that the presence of hallucinations was associated with increased risk of cognitive (RR, 1.62) and functional (RR, 2.25) decline, institutionalization (RR, 1.60), and death (RR, 1.49). It is possible that part of the difference in results may be related to the use of different statistical measures.

An additional limitation of studying the role of hallucinations in Alzheimer's disease is that it is often difficult to determine whether there is comorbid dementia with Lewy bodies (DLB). One large study found evidence of Lewy Body pathology in the brains of 60.7% of a cohort of clinically diagnosed Alzheimer's disease. When NIA-RI criteria, which require AD pathology to make the diagnosis (The National Institute on Aging, and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease, 1997), were applied, Lewy bodies were found in 56.8% of the cohort (Hamilton, 2000). Furthermore, it can be clinically challenging to discriminate between the two conditions. Chung et al. found that pathology-confirmed AD did have distinct clinical phenotypes when co-occurring with Lewy body pathology (Chung et al., 2015). In contrast, Roudil et al. found that there were no significant clinical differences in many clinical and neuropsychological aspects between pathology-confirmed AD with Lewy bodies (either confined to the amygdala or more widespread in the cortex) and without, including the presence of hallucinations (Roudil et al., 2018), although this was a much smaller study and used a cohort that may have been worse cognitively.

AGGRESSION/AGITATION

Epidemiology/Neurobiology

Agitation and aggression are common in Alzheimer's disease, with one large study of electronic health records estimating the prevalence of agitation as over 50% in mild cases (Halpern et al., 2019), as measured in a large study of electronic health records. It may be among the most significant contributors to longitudinal caregiver stress, possibly due to undermining a caregiver's sense of security (Hallikainen et al., 2018b). However, there are fewer studies of agitation and aggression compared with other BPSD (Victoroff et al., 2018). One study of pathologically confirmed AD with intermediate or high pathology load found that patients with agitation and aggression tend to do worse on cognitive testing and are worse functionally (Sennik et al., 2017). It is a significant symptom from a public health perspective due to its association with higher healthcare costs through increased institutionalization (Costa et al., 2018) as well as "informal costs," such as caregiver time (Rattinger et al., 2019).

Like hallucinations, the presence of agitation has been correlated with multiple anatomic locations. Agitation has been correlated with increased neurofibrillary tangle burden in the orbitofrontal and anterior cingulate cortices (Tekin et al., 2001). Supporting this is an anatomical study using ADNI data which found that the presence of worsening agitation and aggression was associated with greater atrophy in frontal, insular, amygdala, cingulate, and hippocampal regions of interest in patients with mild cognitive impairment and AD dementia over 2 years (Trzepacz et al., 2013). It has also been suggested that right frontal lobe dysfunction may be predominant (Lopez et al., 2001). Functional imaging studies have similarly suggested that agitation is associated with lower metabolism in frontal and temporal regions (Sultzer et al., 1995). Interestingly, Ehrenberg et al. (Ehrenberg et al., 2018) found that agitation was associated with neurofibrillary tangle pathology at Braak stages I to IV but not at levels V to VI, suggesting that subcortical pathology may be an important contributor as well.

Aggression has been linked to increased amyloid burden. Transgenic mice expressing a human APP mutation have been shown to be significantly more aggressive than non-transgenic littermates, even early on the course of disease (Alexander et al., 2011). In humans, a large study found that the presence of agitation/aggression was directly correlated to high burden of amyloid pathology in a cohort of pathologically confirmed AD (Sennik et al., 2017), and that other clinical diagnoses were attributed to patients with agitation/aggression, including dementia with Lewy Bodies and frontotemporal dementia. In this cohort, phosphorylated TDP-43 deposits were more common in male patients with agitation, indicating the difficulty in diagnosing patients appropriately when behavioral disturbances are present.

In a cohort of pathologically confirmed Alzheimer's disease, the presence of a higher overall score on the Cohen-Mansfield Agitation Inventory (Cohen-Mansfield, 1986), a scale specifically for agitation and aggression in the elderly, was significantly associated with decreased levels of 5-HIAA in the hippocampus. In this cohort, the presence of physically nonaggressive behavior (which may still be distressing to the patient and caregiver) was significantly associated with increased dopamine catabolism in the cerebellum (Vermeiren et al., 2014). An autopsy-based study of individuals with a clinical diagnosis of Alzheimer's disease showed that aggression was a significant predictor of decreased cholinergic innervation on autopsy, and overactivity was the best predictor of decreased serotonergic innervation (Garcia-Alloza et al., 2005).

Association With Rates of Decline

Agitation, alone and in combination with other BPSD, has been associated with disease severity over time, but inconsistently with disease progression. There are few studies that assess agitation as an isolated factor. Haupt and Kurz (Haupt and Kurz, 1993), in a small clinic-based study, found that aggression was one factor that predicted institutionalization over 1 year. Similarly, Peters et al. (2015) in the Cache County Dementia Progression Study, found that agitation/aggression was a significant predictor of the risks of both of severe dementia (defined as CDR $\geq$ 2 or MMSE $\leq$ 10) and death (HR 2.946, 1.942 respectively) in a Cox proportional hazards model, although the baseline status of participants in that cohort is unclear. Further, Lopez et al. (1999) in their study of the effects of psychiatric symptoms and psychiatric medications on disease progression found that the presence of either aggression or agitation was independently associated with a significantly increased risk of shorter time to significant functional impairment (RR, 2.35, 2.26, respectively) while controlling for age, education, sex, and baseline cognitive and functional status.

In contrast, Barnes and colleagues, using data from the Chicago Health and Aging Project, a longitudinal population-based study, found that hostility was both associated with worse cognition at baseline in both non-Hispanic whites and African Americans but not with cognitive decline over 4.4 years, in a mixed-effects regression model (Barnes et al., 2009). Zahodne et al. studied data from the Predictors 1 cohort and found that agitation/aggression at baseline were not correlated with cognition at baseline, functional decline, or cognitive decline in a latent growth curve model over 6 years. However, change over time in agitation/aggression did account for a small amount of the variability in cognitive decline over time (Zahodne et al., 2015). Similarly, in the ALSOVA study, agitation at the time of diagnosis did not predict disease progression but was significantly associated with severity of disease over 5 years (Hallikainen et al., 2018a).

Of note, Hallikainen et al. found that, along with agitation and aggression, aberrant motor behavior tended to track with disease severity and was a predictor of disease progression (Hallikainen et al., 2018a). Aberrant motor behaviors are sometimes, (Aalten et al., 2003; van der Linde et al., 2014) but not always, (Garre-Olmo et al., 2010b) clustered together with agitation in studies that have looked for grouping of neuropsychiatric symptoms out of the neuropsychiatric inventory (NPI) by methods such as factor analysis and latent class analysis.

DELUSIONS

Epidemiology/Neurobiology

Delusions are a well-recognized symptom of Alzheimer's disease although Holtzer et al. found that they may worsen initially and then become less prevalent over time (Holtzer et al., 2003), which can make estimating its prevalence difficult. Delusions tend to be considered either "persecutory" or related to misidentification phenomena, such as Capgras syndrome or phantom boarder syndrome. The presence of delusions tends to be combined with the presence of hallucinations to create the construct of psychosis. Although psychosis certainly encompasses both of these symptoms, delusions may be representative of different neural circuits than hallucinations. Clinically as well, it is worthwhile considering the two symptoms separately. There are many circumstances where visual and auditory hallucinations may occur in the absence of fixed beliefs on the part of the patient believing that they are true, and delusions can occur in the absence of hallucinations. Interestingly, delusions may have a different impact on patients' functioning than hallucinations or agitation. Bertrand and colleagues (Bertrand et al., 2017) found that patients with mild to moderate AD who had delusions had a decreased ability to express treatment choice preference, potentially impacting their ability to consent to medical care. In contrast, patients with hallucinations, agitation/aggression, and several other BPSD did not have weaknesses in decision-making abilities.

Structurally, the presence of delusions has been associated with decreased gray matter density in the right inferior frontal gyrus and inferior parietal lobule, as well as the left inferior and medial frontal gyri and claustrum in patients with mild AD (Bruen et al., 2008). Interestingly, Fischer and colleagues compared MRI scans in patients with MCI before and after the onset of delusions (generally within the span of 6 months), and found significant differences in gray matter morphology in 14 locations, including the bilateral insulae, the cerebellum, the right thalamus and posterior cingulate gyrus, and the left precuneus, left superior temporal gyrus, and parahippocampal gyrus (Fischer et al., 2016). During that time, some patients had converted from MCI to mild AD, and the mean cognition had worsened as well. The presence of delusions has also been associated with abnormalities in the integrity of white matter in the left parietooccipital region and the corpus callosum (Nakaaki et al., 2013), as well as advanced neurofibrillary tangle pathology (Ehrenberg et al., 2018).

Association With Rates of Decline

Delusions are often studied in conjunction with hallucinations. Their presence is often associated with poorer performance on cognitive testing cross-sectionally (Jeste et al., 1992) as well as faster decline longitudinally. Connors et al, in the PRIME study

in Australia, found that the presence of delusions alone was associated with worse cognition, function, and dementia severity, as well as increased caregiver burden, over 3 years using a linear mixed model. Delusions also predicted institutionalization, but not mortality (Connors et al., 2018). Similarly, Scarmeas et al. found in the Predictors cohort that delusions were associated with increased risk for cognitive (RR, 1.50) and functional (RR, 1.41) decline as well as institutionalization (RR, 1.60) and mortality (RR, 1.49) (Scarmeas et al., 2005).

Interestingly, D'Onofrio and colleagues, in a single-center study, found that delusions were associated with a trend toward significantly longer disease duration in patients with mild to moderate AD (D'Onofrio et al., 2016). Further, Wilson et al. studied the effects of hallucinations and delusions over 4 years and found that delusions were not associated with the rate of cognitive decline (Wilson et al., 2000). There are few studies that separate delusions from hallucinations in longitudinal studies; however, the evidence regarding the effect of delusions on the rate of cognitive decline seems to be less conclusive. Additional studies would be useful in better understanding the effect of the presence of delusions.

USING BPSD TO INFORM MODELS OF DISEASE

The clinical diagnosis of probable Alzheimer's disease requires the presence of worsening cognition in either an amnestic or nonamnestic pattern (McKhann et al., 2011). Noncognitive symptoms are not considered in these diagnostic criteria; however, BPSD are a prevalent aspect of disease. Although the time point of disease during which these symptoms initially manifest varies, they persist over time and increase with worsening of disease. These symptoms may be more challenging for families to address than cognitive symptoms and represent a public health concern due to the increased morbidity, mortality, and associated healthcare costs. The areas of the brain which correlate to these symptoms are likely affected due to the spread of pathology across neural networks, and it remains unclear why these behavioral areas become affected early in some patients. The genetic and environmental contributors to the presence and timing of these symptoms have yet to be elucidated. The variable results in attempting to identify specific brain regions associated with specific symptoms suggests that the presence of BPSD may be reflective of network-wide dysfunctions. Indeed, the presence of hyperactivity, which includes agitation, has been linked to changes in the anterior salience network, which is important in generating appropriate responses to the external environment, in resting-state functional MRI (Balthazar et al., 2014). It is worth considering whether the presence of these symptoms should be considered as important in diagnosing Alzheimer's disease as are cognitive changes. Due to the extensive heterogeneity in Alzheimer's disease, different models of disease prediction may need to be developed. In fact, Razlighi et al, in developing and validating a longitudinal Grade of Membership (L-GoM) model to predict time to institutionalization, full-time care, and death in the Predictors 1 and 2 cohorts, included the presence of BPSD, such as psychosis and wandering (Razlighi et al., 2014). Further studies are needed to better understand these issues, so that ultimately effective symptomatic treatments can be developed.

Additionally, the relationship between neuropathological changes and BPSD is likely affected by outside factors. Casanova et al, in their review of clinicopathological correlates of BPSD, note that neuroleptics may increase the risk for cerebrovascular events in patients with dementia which may itself increase the risk for certain BPSD (namely, depression and apathy) and also worsen cognitive decline (Casanova et al., 2011). Neuroleptics and other antipsychotics may also have an impact on disease presentation and progression; these medications may reduce symptoms of BPSD, although a consensus of geriatric mental health experts noted that the evidence is limited and inconsistent with regard to agitation and aggression (Salzman et al., 2008). However, Lopez et al. (1999) found that antipsychotics were associated with increased functional decline, and hypothesized that this effect could be related to sedation or extrapyramidal effects. Nonpharmacologic therapies such as music, bright light, and pet therapy have also been noted to be possibly effective in reducing symptoms of BPSD, although such therapies are often part of a broader care program (Forlenza et al., 2017; Doody et al., 2001) and can be difficult to isolate for purposes of a trial. Many, but not all, studies looking at the effect of BPSD on disease progression take pharmacologic therapy into account; however, we were unable to find studies that accounted for nonpharmacologic approaches. If the use of nonpharmacologic therapies can be strengthened with additional clinical trials, this will need to be taken into account in future studies of BPSD as well.

Furthermore, the use of cholinesterase inhibitors and memantine may confound these effects as well; in the Predictors 2 cohort, cholinesterase inhibitors were associated with delayed functional decline, and memantine was associated with delayed time to death when controlled for several patient characteristics, including the presence of psychiatric symptoms (Zhu et al., 2013). Although this does not confer causality, it implies that current standard of care treatment for Alzheimer's disease may affect the influence of BPSD on dementia severity.

An additional factor not usually accounted for is the role of social support or family involvement in care, whose relative absence has been associated with increased depression in the elderly (Sonnenberg et al., 2013). In contrast, Chan et al. found that those with a child or child-in-law as the caregiver were more likely to be reported as having psychopathy, although it is not clear whether this was due to a difference in prevalence of the symptoms or a difference in likelihood of reporting them (Chan et al., 2003). It is plausible that the presence of a more extensive social support network and family presence could help to alleviate distress caused by symptoms, such as hallucinations and perhaps mitigate the effect of these symptoms on functioning and cognitive decline. Further studies would be useful in clarifying this effect.

An important limitation in many studies has been the lack of pathologic confirmation of diagnosis. BPSD are present in many neurodegenerative diseases, such as Lewy body disease and frontotemporal dementia. Clinically, these entities can be

TABLE 1 | Select papers studying BPSD and effect on decline in AD.

Author, Year	Symptom	Sample Characteristics	Analysis Modality	Findings
Wilson et al. (2006)	Hallucinations Delusional thinking Misperceptions	Rush ADRC and older adult day care centers (mean 2.2 yrs follow up) n = 568 with clinical diagnosis of AD mean 11.7 yrs education; 70.1% white; 69.2% women 478 in analysis	Linear mixed effects model for composite score of global cognition Cox proportional hazards for mortality	Psychosis at baseline: 29.6% hallucinations, 27.3% delusional thinking, 25.5% misperceptions + hallucinations and misperceptions: ↓ cognition at baseline LMM: Hallucinations: ↑ rate of decline linearly (0.20 unit/yr) and nonlinearly (0.03 unit/yr); nonlinear decline was affected by level of education Delusions: ↑ rate of decline linearly (0.08 unit/yr) Misperceptions: ↑ rate of decline linearly (0.07 unit/yr) Together: only hallucinations was associated with more rapid decline Cox: + hallucinations: 60% more likely to die; maintained when adjusting for global cognition at baseline (RR = 1.56; 95% CI 1.16-2.09); stronger in those with higher education No association for delusions/misperceptions
Connors et al. (2018)	Hallucinations Delusions	PRIME study in Australia (clinic-based, 3 yrs follow up) n = 445 with mild dementia (mean CDR-sb 5.5) 33.7% with post-secondary education; 50.1% women Psychosis at baseline: 13.5% delusions; 5.8% hallucinations; 5.4% both 34.3% without psychosis at baseline developed over 3 years	Linear mixed models for cognition, function, overall neuropsych symptoms, caregiver burden Cox proportional hazards for mortality and institutionalization	+ psychosis at baseline: ↑ CDR-sb, ↓ cognition, ↓ function, ↑ NPI, ↑ caregiver burden LMM: +delusions: ↑ disease severity (1.2 units), ↓ cognition (0.8 units), ↓ function (2.6 units), ↑ NPI (6.5 units), ↑ caregiver burden (7.8 units) + hallucinations: ↑ disease severity (0.9 units), ↓ cognition (1.0 units), ↓ function (2.7 units), ↑ NPI (4.8 units), ↑ caregiver burden (5.7 units) + both were even worse Cox: Delusions +/- hallucinations (not hallucinations alone) predicted institutionalization (HR for delusions alone 2.35 95% CI 1.48, 3.73; HR for both 4.26, 95% CI 2.31, 7.86) Neither predicted mortality
Scarmeas et al. (2005)	Hallucinations Delusions	Predictors 1&2 in USA and Europe (clinic-based, mean 4.5 yrs follow up) n = 456 with mild AD Mean MMSE 21; mean 13 yrs education; 59% women	Cox proportional hazards	Psychosis at baseline: 34% delusions, 32% hallucinations 70% developed delusions during follow up +delusions: ↑ risk of cognitive decline (RR 1.91, 95% CI 1.41-2.60), functional decline (RR 1.90, 95% CI 1.41-2.54), and institutionalization (RR 1.63, 95% CI 1.26-2.12) +hallucinations: ↑ risk of cognitive decline (RR 2.08, 95% CI 1.41-3.07), functional decline (RR 2.55, 95% CI 1.80-3.62), institutionalization (RR 1.94, 95% CI 1.40-2.70), and death (RR 1.52, 95% CI 1.08-2.15)
Hallikainen et al. (2018a)	All domains from NPI	ALSOVA cohort in Finland (clinic-based, 5 years follow up) n = 236 with very mild or mild AD (CDR 0.5-1) mean education 7.58 yrs, 51.27% female	Generalized estimating equations for disease progression Linear mixed effects model for AD severity	At baseline: 22.9% delusions, 14.8% hallucinations, 28.8% agitation By year 5: 39.7% delusions, 28.8% hallucinations, 31.5% agitation Baseline predictors of AD progression: delusions ($p = 0.001$), agitation ($p = 0.010$), aberrant motor behavior ($p = 0.015$), euphoria ($p < 0.001$) BPSD associated with AD severity over time: delusions, hallucinations, agitation, depression, anxiety, apathy, irritability, sleep disturbances, aberrant motor behavior, appetite disturbances
Barnes et al. (2009)	Hostility	Chicago Health and Aging project (population-based study, mean, 4.4 years follow-up) n = 4913 mean education 12.1 yrs, 62.2% women, 29.6% white	Mixed-effects regression model	Hostility associated with lower cognition at baseline (-0.028 units cognition for each 1 unit increase in hostility) No association between hostility and cognitive decline, including when adjusting for race and lifetime socioeconomic status

(*Continued*)

TABLE 1 | Continued

Author, Year	Symptom	Sample Characteristics	Analysis Modality	Findings
Zahodne et al. (2015)	Agitation Aggression Psychosis Depression	Predictors 1 in USA (clinic-based, 6 years follow up) n = 517 mean education 13.72 yrs, 93.2% white, 56.9% women	Latent growth curve modeling	+psychosis explained 5.3% of variance in initial cognitive impairment, 7.3% of variance in cognitive decline, 17% of variance in initial dependency, and 2.4% of variance in trajectory of dependency +agitation/aggression not related to cognitive decline or changes in dependency but 6% of variance in cognitive decline and ~3% variance in changes in dependency were related to change in agitation/aggression, +depression explained 1.6% of variance in cognitive decline and 8.6% of variance in initial dependency
Haupt and Kurz (1993)	Delusions Angry outbursts Agitation Aggression Depression	Outpatients with mild-moderate AD in Germany over 12 months n = 66 (44 at home, 22 in institution)	Stepwise discriminant function analysis	Those admitted to nursing homes more likely to have aggressive behavior ($p = 0.03$) and had worse cognitive impairment ($p = 0.04$) Variables that contributed most to discrimination between the 2 groups: incontinence, caregiver wish to give care to someone else, cognitive decline, age, aggression, angry outbursts, depression
Peters et al. (2015)	Psychosis Agitation Aggression Affective Apathy	Incident AD from Cache County Dementia Progression Study in USA (community-based) n = 335	Kaplan-Meier plots Cox proportional hazards	50.9% with at least one neuropsychiatric symptom Predictive of progression to severe dementia: psychosis (HR = 2.007), agitation/aggression (HR = 2.946), agitation/aggression (HR = 2.946) Predictive of progression to death: psychosis (HR = 1.537), affective (HR = 1.510), agitation/aggression (HR = 1.942), at least one mild NPS (HR = 1.448), at least one NPS (HR = 1.951)
Lopez et al. (1999)	Aggression Agitation Wandering Insomnia Psychosis Depression Medication	Patients with probable AD at University of Pittsburgh (study-based, mean follow up 4.16 yrs) n = 179	Proportional hazard models	Psychosis significantly associated with decreased functional ability (RR = 2.02) and institutionalization (RR = 2.10) Adjusted for baseline age, education, MMSE, BDRS, significant associations with decreased functional ability (BDRS≥15): MMSE < 19 (RR = 4.08), psychosis (RR = 2.73), agitation (RR = 2.26), aggression (RR = 2.35), antipsychotics (RR = 1.98); psychosis associated with increased risk of institutionalization (RR = 2.11)
D'Onofrio et al. (2016)	Delusions	Patients with AD at an AD evaluation unit in Italy n = 380 mean education 5.24 yrs, 64.4% women	Comparison of means: Welch 2-sample t-test or ANOVA Wilcoxon rank sum test	Those with delusions were older, had later age of onset, worse cognitive impairment and dementia stage, more depression, higher risk of malnutrition and bedsores ($p < 0.0001$ for all) Those with delusions had higher NPI scores for depression ($p = 0.007$), hallucinations, agitation/aggression, apathy, irritability/lability, aberrant motor activity, sleep disturbances, and eating disorders ($p < 0.0001$ for all)
Wilson et al. (2000)	Hallucinations Delusions	Rush ADC n = 410 men education 12.0 yrs, 85.1% white, 66.8% female, mean MMSE 18.7	Random effects regression models	At baseline: +hallucinations 41.0%, +delusions 54.7% +hallucinations associated with lower cognition by 0.33 units +hallucinations: ↑ rate of cognitive decline (0.69 units/yr vs 0.47 units/yr without) +hallucinations at any point: ↑ cognitive decline (0.61 units/yr vs 0.39 units/yr without) +delusions associated with lower cognition +delusions not associated with rate of decline

difficult to distinguish from each other, particularly early in the course of disease. As an example, the frontal variant of Alzheimer's disease may be misdiagnosed as frontotemporal dementia—one clinic-based study found that nearly 40% of cases diagnosed clinically as frontotemporal dementia were changed to a diagnosis of Alzheimer's disease based on PET scan results (Ossenkoppele et al., 2013). Similarly, an autopsy series of Lewy body disease, Alzheimer's disease, and AD with amygdala-predominant Lewy bodies found that the presence of visual hallucinations did not distinguish between the groups, although they tended to occur earlier in Lewy body disease. The underlying pathologies of Alzheimer's disease and Lewy body disease frequently coexist (Hamilton, 2000), which can make it difficult to ascertain clinically which pathology is causing the symptoms.

Additionally, there is no standard method for estimating baseline effects on downstream events. Statistical methods that are commonly used are Cox proportional hazards, latent growth

curve modeling, and generalized estimating equations. Each model has its strengths; however, it can be difficult to directly compare results obtained from different methods, leading to additional difficulty in using baseline characteristics to predict effects over time.

In the clinical setting, the presence of early hallucinations and agitation may direct the clinician's diagnostic approach away from the possibility of underlying Alzheimer's pathology. Current diagnostic criteria for other neurodegenerative disorders encourage this approach; however, this may be an incomplete understanding. It may be more useful to view the presence of BPSD in the setting of other cognitive changes as a relatively nonspecific symptom of underlying neural network dysfunction. Biomarker-based diagnosis in the form of imaging, as well as CSF and serum diagnostics, is likely to be increasingly important in refining clinical diagnostic criteria.

CONCLUSION

The ability to prognosticate is critically important for patients and their families. The balance of the evidence suggests that early presence of positive BPSD may predict faster progression of disease. This does not account for the effect of negative BPSD (namely, depression and apathy, which likely also contribute to progression of disease). Although the etiology underlying this effect is not well understood, it is likely a complex combination of genetic predisposition and comorbid neuropathology. Cohort studies that followed patients with early dementia have been vitally important in elucidating this effect, although few studies have followed patients for long enough to capture the variability over a long disease course. Additional long-term studies are needed to ensure the generalizability of these effects.

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Impact of Chronic Risperidone Use on Behavior and Survival of 3xTg-AD Mice Model of Alzheimer's Disease and Mice With Normal Aging

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Psychosis and/or aggression are common problems in dementia, and when severe or persistent, cause considerable patient distress and disability, caregiver stress, and early institutionalization. In 2005, the Food and Drug Administration (FDA) determined that atypical antipsychotics were associated with a significantly greater mortality risk compared to placebo, which prompted the addition of an FDA black-box warning. The American College of Neuropsychopharmacology (ACNP) White Paper, 2008, reviewed this issue and made clinical and research recommendations regarding the use of antipsychotics in dementia patients with psychosis and/or agitation. Increased mortality risk has also been described in cerebrovascular adverse events in elderly users of antipsychotics. In the present work, at the translational level, we used male 3xTg-AD mice (PS1M146V, APPSwe, tauP301L) at advanced stages of the disease reported to have worse survival than females, to study the behavioral effects of a low chronic dose of risperidone (0.1 mg/kg, s.c., 90 days, from 13 to 16 months of age) and its impact on long-term survival, as compared to mice with normal aging. Animals were behaviorally assessed for cognitive and BPSD (behavioral and psychological symptoms of dementia)-like symptoms in naturalistic and experimental conditions (open-field test, T-maze, social interaction, Morris water maze, and marble test) before and after treatment. Weight, basal glucose levels, and IPGTT (i.p. glucose tolerance test) were also recorded. Neophobia in the corner test was used for behavioral monitoring. Survival curves were recorded throughout the experiment until natural death. The benefits of risperidone were limited, both at cognitive and BPSD-like level, and mostly restricted to burying, agitation/vibrating tail, and other social behaviors. However, the work warns about a clear early mortality risk window during the treatment and long-lasting impact on survival. Reduced life expectancy and life span were observed in the 3xTg-AD mice, but total lifespan (36 months) recorded in C57BL/6 × 129Sv counterparts with normal aging was also truncated to 28 months in those with treatment. Sarcopenia at time of death was found in all groups, but was more severe in wild-type animals treated with risperidone. Therefore, the 3xTg-AD mice and

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their non-transgenic counterparts can be useful to delimitate critical time windows and for studying the physio-pathogenic factors and underlying causal events involved in this topic of considerable public health significance.

Keywords: comorbidities, antipsychotics, risk factors, mortality, aging, memory, neuropsychiatric symptoms, social behavior

INTRODUCTION

Behavioral changes and neuropsychiatric symptoms (NPS), also known as "behavioral and psychological symptoms of dementia (BPSD)," may occasionally signal the onset of Alzheimer's disease (AD) (Reisberg et al., 1987). They are present in 90% of patients as the disease progresses in a neurodegenerative process which is faster and more severe in males in spite of similar incidence of AD among sexes or women showing higher incidence with increasing age (Lapane et al., 2001; Pike, 2017; Rezanni et al., 2019). The prevalence of delusions in patients with AD is between 9% and 63% and that of hallucinations is between 4% and 41%; the rate of aggression is between 11% and 46% and agitation has an even higher prevalence rate among 20–80% (Jeste et al., 2008). Most of these symptoms diminish the quality of life of the patients and, particularly, the psychosis is associated with a rapid cognitive deterioration (reviewed by Cummings, 2000 and Kalman et al., 2008). The cognitive decline characteristic of dementia is also associated with an increase in social vulnerability in humans that sometimes leads to death (Andrew and Rockwood, 2010). Therefore, these neuropsychiatric symptoms present diverse clinical implications in patients, as is the specific case of psychosis, agitation, and aggression, which increase the burden of disease, also resulting a strong cause of distress among the familiar and professional caregivers (Tan et al., 2005).

During the last two decades, the most recent atypical antipsychotic drugs that have been approved by the Food and Drug Administration of the US Department of Health and Human Services (US FDA) are risperidone in 1993, olanzapine in 1996, quetiapine in 1997, ziprasidone in 2001, and aripiprazole in 2002. These atypical antipsychotics have replaced the first-generation antipsychotics such as haloperidol and thioridazine (Schneider et al., 2005 and Jeste et al., 2008). Atypical antipsychotics are used as the first line of pharmacological approach for the treatment of neuropsychiatric symptoms in AD (Ballard et al., 2009). In the present work, we focused on risperidone, one of the most used atypical antipsychotics and co-administered with different types of drugs. At the pharmacological level, risperidone is a selective monoaminergic antagonist, which has a high affinity with serotonergic receptors 5-HT_2 and dopaminergic D_2 and binds also to α_1 adrenergic receptors and with lower affinity to histaminergic H_1 and α_2 adrenergic receptors. It has been approved by the FDA for the treatment of schizophrenia (positive and negative symptoms), bipolar disorders, and autism. It is also used in dementia, depression, obsessive-compulsive disorders, personality disorders, and attention deficit hyperactivity disorder (Katz et al., 2007; Shekelle et al., 2007 and Rodriguez-Antona et al., 2009). This drug has a moderate but significant effect on short-term treatment (> 6–12 weeks) for aggression but is limited in long-term therapy, whereas for agitation symptoms, the results are not well established. In addition, there's an increase in the concerns about adverse outcomes with these treatments, including strokes and death (Ballard et al., 2009).

In April 2005, the FDA issued the following warning for all atypical antipsychotics based on their evaluations: "The FDA informed health professionals and the public about the increased risk of mortality in elderly patients who received atypical antipsychotic drugs for the treatment of dementia-related psychosis. Analyses of 17 placebo-controlled trials involving 5,377 elderly patients with conduct disorders associated with dementia revealed a risk of death in patients treated with the drug between 1.6 and 1.7 times that observed in patients treated with placebo. The mortality rate in the drug-treated patients was approximately 4.5% compared to a rate of approximately 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be cardiovascular (for example, heart failure, sudden death) or infectious (pneumonia)". Based on this analysis, the FDA requested manufacturers of the atypical antipsychotic drugs to include information about this risk in the package leaflet of the drug (Jeste et al., 2008). These alerts brought a diversity of opinions in the scientific community. Some authors considered the warnings about atypical antipsychotics as alarming and potentially harmful for patients with dementia, while others were concerned that there was no clear evidence to support a greater benefit in relation to atypical antipsychotics compared to conventional antipsychotics (Trifiro et al., 2009). In a previous work at our UVaMiD neurology unit, we studied the mortality risk in AD patients at advanced ages of the disease who received risperidone therapy, but we could not find any relationship to metabolic syndrome nor history of heart disease (Vilalta-Franch et al., 2008).

This diversity of opinions can be observed in studies of circadian cycle disorders where patients with dementia after a 12-week treatment at a dose of 1.49 mg/day of risperidone reported improvements in total sleep hours, waking hours in bed, insomnia, and other variables related to sleep (Durán et al., 2005). Other studies have indicated that in elderly patients with dementia low doses of risperidone 0.5 and 1 mg were well tolerated and were associated with reductions in BPSD, in particular, agitation, aggression, irritability, delusions, sleep disturbances, anxiety, and phobias. Despite efficacy in the reduction of various adverse symptoms, risperidone and olanzapine should not be used routinely for the treatment of aggression and psychosis in patients with dementia (Onor et al., 2007). Other studies have indicated that risperidone and olanzapine increase the risk of mortality in elderly patients with dementia with an increased risk of the latter over the former (Vilalta-Franch et al., 2008). Also, mortality risks are increased with high doses of atypical antipsychotics and the

causes of mortality are cerebrovascular accidents, respiratory diseases, and circulatory disorders (Huybrechts et al., 2012) compared with people who received placebo (Trifiro et al., 2009). Cerebrovascular risks (CVA) are especially observed during the first weeks of treatment; this risk decreases with time and normalizes after 3 months of treatment (Kleijer et al., 2009). Currently, atypical antipsychotics continue to be used under strict supervision and monitoring in some hospitals and/or geriatrics for the BPSD. This is even though older people are more sensitive to their side effects than young and middle-aged adults, in part by the interaction of changes caused by age and pharmacological sensitivity to antipsychotic treatments (Salzman et al., 2008).

Due to the variety of results and the ethical impossibility of conducting new clinical studies in humans, it is important to model the pharmacological responses of antipsychotics in animal models of the disease and to study their effects in the BPSD. At the translational level, the triple transgenic mouse for AD hosts human transgenes PS1/M146V, APPswe, and tau P301L (Oddo et al., 2003a). These rodents uniquely mimic various symptoms of the disease in a temporal and neuroanatomical pattern similar to that observed in humans (Belfiore et al., 2019). The onset of symptoms has been established between 4 and 6 months of age and involves electrophysiological deficits (in LTP, long term potentiation and fEPSP, field excitatory postsynaptic potential) at the hippocampal level, learning and memory problems, cholinergic deficiencies, and emotional disturbances. However, at these ages, the brains of the animals only show presence of intraneuronal immunoreactivity of Aβ (Kitazawa et al., 2005; Giménez-Llort et al., 2007; Oddo et al., 2003a; Oddo et al., 2003b). After 12 months of age, the neuropathological profile finds its parallelism with the advanced stages of the disease in humans, with the characteristic deposits of Aβ and neurofibrillary tangles of tau protein (Oddo et al., 2003a; Oddo et al., 2003b). We have previously shown increased mortality in male 3xTg-AD mice as compared to females, ranging from 33% (Giménez-Llort et al., 2008) to 100% at 15 months of age (García-Mesa et al., 2012) and its relation to impaired neuroimmunoendocrine system (Giménez-Llort et al., 2014). The increased impact of AD (faster, more severe) of male sex has recently also been reported in the human patient (Pike, 2017; Rezanni et al., 2019).

The present study aims to model in 3xTg-AD mice the vulnerability that leads to an increase in mortality observed in patients with AD chronically treated with atypical antipsychotics such as risperidone. Before we can address this modeling, we defined the starting phenotype of the subject of study. To this end, the animals were evaluated in a battery of tests for measuring exploratory activity, anxiety, learning and memory, burying of objects, and social behavior. An assessment of the basal state of glucose and the tolerance response to it when administered intraperitoneally was also made.

MATERIALS AND METHODS

Animals

Homozygous triple-transgenic 3xTg-AD mice harboring human $PS1/_{M146V}$, APP_{Swe}, and tau_{P301L} transgenes were genetically engineered at the University of California Irvine, as previously described (Oddo et al., 2003b). Briefly, two independent transgenes (encoding human APPSwe and human tauP301L, both under control of the mouse Thy1.2 regulatory element) were co-injected into single-cell embryos harvested from homozygous mutant PS1M146V knock-in (PS1KI) mice. The PS1 knock-in mice were originally generated as a hybrid C57BL/6 x 129Sv.

Forty-six 12-month-old 3xTg-AD mice (n = 23) and C57BL/6 x 129Sv (n = 23) wildtype mice (from now, referred as non-transgenic mice, NTg) from litters of a breeding program established in our laboratory at the Medical Psychology Unit, Universitat Autònoma de Barcelona, were used in this study. All the animals were housed three to four per cage and maintained (Makrolon, 35 × 35 × 25 cm) under standard laboratory conditions (12 h light/dark, cycle starting at 8:00h, food and water available *ad libitum,* 22 ± 2ºC, 50–60% humidity). The circadian activity was recorded during one whole light/dark (LD) period, and the rest of the tests from 9:00h to 13:00h.

This study was carried out in accordance with the recommendations of ARRIVE guidelines developed by the NC3Rs (Kilkenny et al., 2010) and the Spanish legislation on "Protection of Animals Used for Experimental and Other Scientific Purposes" and the European Communities Council Directive (2010/63/EU) on this subject. The protocol CEEAH 2481/DMAH 8700 entitled "Risk factors and preventive/therapeutical strategies in Alzheimer's disease: studies in triple-transgenic 3xTg-AD mice" was approved by Departament de Medi Ambient i Habitatge, Generalitat de Catalunya.

Experimental Design and Risperidone Treatment

A longitudinal study divided into successive phases including a "before–after treatment" design was performed. The study started at 12 months of age; that in the 3xTg-AD mice has been extensively reported mimicking neuropathological hallmarks of the disease (Belfiore et al., 2019) and that in the NTg mice (C57BL/6 x 129Sv genetic background) corresponds to middle age. The sample of NTg mice was segregated into two groups according to the activity levels exhibited in the corner test (CT) for neophobia and the open-field (OF) test, to be used as controls that will be treated with saline (NTg mice with low motor activity) or risperidone (NTg mice with high motor activity), respectively.

Risperidone was used at a dose of 0.1 mg/kg equivalent to that administered in patients with AD and used in most experimental work performed in rodents (Bruins Slot et al., 2005). The chronic administration, subcutaneous for 3 months from 13 to 16 months of age, rotated three injection sites (the neck and the two flanks).

First, we characterized the basal phenotype (*phase 1*, weeks 1–6, phenotype "before treatment"; animals at 12 months of age). As in the case of geriatric patients, the treatment regimen was initiated with a lower dose of 0.05 mg/kg (*phase 2*, low dose and follow-up tests, week 7; animals at 13 months of age). After 7 days, the final dose of 0.1 mg/kg was started and behavioral effects assessed (*phase 3*, treatment and behavioral effects

"after treatment", weeks 8–16; animals until 15 months of age). Thereafter, treatment followed without behavior and completed the total period of 3 months of subcutaneous treatment (*phase 4,* only treatment, until 16 months of age). From that moment and until the end of their days, the variables of weight and survival were recorded continuously with a weekly or daily cadence, respectively (*phase 5*, from 16 to 36 months of age).

Four experimental groups were studied and are plotted in the before/after graphs of the figures as follows: NTg mice (s) (NTg mice that will receive or have received saline, $n = 12$), NTg mice (r) (NTg mice that will receive or have received risperidone, $n = 11$), 3xTg-AD mice (s) (3xTg-AD mice that will receive or have received saline, $n = 12$), and 3xTg-AD (r) (3xTg-AD mice that will receive or have received risperidone, $n = 11$).

Behavioral Assessments

Behavioral assessment consisted in a battery of naturalistic and experimental conditions (Giménez-Llort et al., 2007). Neophobia in the CT was used for behavioral monitoring through the treatment.

Corner Test (CT)

Animals were individually placed in the center of a clean standard home cage, filled with wood shave bedding. Number of corners visited were recorded during 30 s (Belzung and Le Pape, 1994). Latency to realize the first rearing, and the number of rearings were also registered (Giménez-Llort et al., 2007).

Open Field Test (OF)

Immediately after the CT, mice were placed in the center of an open field (homemade woodwork, white box, 50 × 50 × 20 cm) and observed for 5 min (Hall and Ballachey, 1932). The ethogram, described by the temporal profile of the following sequence of behavioral events, was recorded: duration of freezing behavior, latency to leave the central square and that of entering the peripheral ring, as well as latency and total duration of self-grooming behavior. Horizontal (crossings of 10 × 10 cm squares) and vertical (rearings with a wall support) locomotor activities were also measured. Bizarre behaviors observed in this test were also measured according to the previous reported criterion (Baeta-Corral and Giménez-Llort, 2014). During the tests, defecation boli and urination were also recorded as measures of individual differences in emotionality (Hall, 1934).

T-Maze (TM)

Working memory was assessed by means of a spontaneous alternation task (Douglas, 1966) in a black TM. The apparatus consisted of a woodwork, three arms of 30 × 5 × 20 cm connected by a 5 × 5 × 20 cm intersection. The animal was placed inside the "vertical" arm of the maze with its head facing the end wall, and it was allowed to explore the maze during a maximum of 3 min. Freezing behavior (latency to move), the latency to reach the intersection, the total time invested to explore the three arms of the maze, and the number of errors (revisiting an arm) were recorded. Defecation boli and urination were also noted.

Social Interaction Test (SIT)

Behavioral signatures of social dysfunction in 3xTg-AD mice were assessed by means of the SIT (File and Hyde, 1978) as recently described (Torres-Lista and Giménez-Llort, 2019). A dyad of two unfamiliar mice of the same genotype and sex were introduced in a standard home cage and video recorded for 5 min. Behaviors were classified into social (social investigation, aggression, vibrant tail) and non-social (exploring, digging, self-grooming) interactions. We also scored the total number of episodes and their total duration.

Morris Water Maze (MWM)

A 5-day place learning task for short- and long-term spatial reference memory (four trial sessions per day, with trials spaced 30 min apart) was followed 2 h 30 min later by a probe trial (removal of the platform) for short-term memory in the MWM (Morris, 1981; Morris, 1984). Mice were trained to locate a hidden platform (7-cm diameter, 1 cm below the water surface) in a circular pool for mice (Intex Recreation Corp., Long Beach, CA, United States; 91-cm diameter, 40-cm height, 25°C opaque water), located in a completely black painted 6-m^2 test room. Mice that failed to find the platform within 60 s were placed on it for 10 s, the same period as was allowed for the successful animals. White geometric figures, one hung on each wall of the room, were used as external visual clues. Behavior was evaluated by direct observation and analysis of videotape-recorded images. Variables of time (escape latency) and quadrant preference and entries were analyzed in all the trials of the tasks. The escape latency was readily measured with a stopwatch by an observer unaware of the animal's genotype and confirmed during the subsequent video-tracking analysis. In the probe trial, the time spent and number of entries in each of the four quadrants were also measured retrospectively by means of the automated video-tracking analysis.

Marble Burying Test (MB)

The procedure for MB was adopted with minor modifications from that originally described by Broekkamp et al. (1986). Mice were placed individually in a standard home cage containing six glass marbles (1 × 1 × 1 cm) evenly spaced making a triangle (three rows of three, two, and one marble per row only in the left area of the cage) on a 5-cm-thick layer of sawdust. The mice were left in the cage with marbles for a 30-min period after which the test was terminated by removing the mice and counting the number of marbles: intact (untouched), rotated or at least half buried by sawdust, and buried (completely hidden) as previously described (Torres-Lista et al., 2015)

Body Weight (BW) and Basal Glucose Levels (G)

Throughout the experimental process, evaluation of weight and survival was continuously monitored until the natural end of the life of the animals. The blood samples were taken from an incision made at the tip of the tail.

Survival Curve

The survival curves were obtained with the percentage of animals that were maintained throughout the experimental procedure.

Statistics

Statistical analysis were performed using SPSS 17.0 software. The results are expressed as means ± SEM or percentage. A 2×2 factorial design with multivariate general lineal model analysis evaluated genotype (G) and treatment (T) effects, followed by *post hoc* Tukey B test. In the Morris water maze, the factor 'day (D)' was included when appropiate. Student's *t*-test was used to compare two independent groups. The comparisons for related samples were made with the paired *t*-test. Survival curve was analyzed with Kaplan-Meier test. The correlations between survival and the different variables studied were evaluated with the Pearson's correlation. In all the tests, $P < 0.05$ was considered statistically significant.

Results

We confirmed that the sample of 3xTg-AD mice studied exhibited cognitive deficits in the MWM, mimicking the cognitive hallmark of AD. However, only data of animals that could be included in the "before–after" analysis were considered (animals dying in phases 1, 2, and 3 were excluded). Statistics of genotype effects for the different behavioral tests and variables studied in 3xTg-AD and NTg mice at 12 months of age (week 1, basal, but without the segregation for the treatment they will receive) are cited in the text and depicted in **Supplementary Table 1**. Behavioral correlates with lifespan in animals treated with saline or risperidone are also indicated. **Figures 1–12** depict the effects of chronic risperidone on these behaviors, weight, and survival curves of animals. Finally, **Table 1** details the behavioral correlates with lifespan in male NTg and 3xTg-AD mice chronically treated with saline or risperidone.

Corner Test (CT)

Increased neophobia exhibited by 3xTg-AD mice before the treatment, as shown by reduced number of corners and rearings and increased latency of rearing, was not ameliorated by risperidone (**Figure 1**). The repeated CT allowed to observe a reduction of the number of corners through the treatment as compared to basal levels, in all groups [**Figure 1A**, NTg (s), $t = 3.015$, gl 11, $P < 0.05$; NTg (r), $t = 8.517$, gl 10, $P < 0.001$; 3xTg-AD(s), $t = 2{,}620$, gl 11, $P < 0.05$; 3xTg-AD(r), $t = 2.776$, gl 10, $P < 0.05$]. Likewise, a decrease in vertical activity was observed in NTg (r) mice ($t = 2.637$, gl 10, $P < 0.05$) and 3xTg-AD (s) mice ($t = 2.327$, gl 11, $P < 0.05$) (**Figure 1C**). When the four groups were compared, genotype effects were still shown in the "number of corners visited" in weeks 11 [$F(1,43) = 6.623$, $P < 0.05$] and 12 [$F(1,43) = 15{,}503$, $P < 0.001$]. The latency of rearing was more sensitive to the genotype effect as it was observed from weeks 9 to 12 [all $F(1,43) < 14{,}450$, $P < 0.001$] and showed a treatment effect in week 9 [$F(1,43) = 4.495$, $P < 0.05$] and interaction "genotype × treatment" in week 10 [$F(1,43) = 7.151$, $P < 0.05$] (**Figure 1B**). In the variable "number of rearings," genotype effect was observed from weeks 8 to 12, with all the [$F(1,43) < 25.961$, $P < 0.001$] and interaction effect genotype × treatment in week 10 [$F(1,43) = 5.975$, $P < 0.05$] (**Figure 1C**).

Open Field Test (OF)

The delayed ethogram (sequence of behavioral events), the reduced horizontal and vertical activities, and the increased emotionality behavior (urination) exhibited in the OF described an increased anxious-like profile in the 3xTg-AD mice. After treatment, genotype and treatment effects were found as detailed in **Figure 2**. In the NTg mice treated with saline, the latencies of "first movement" (freezing behavior) ($t = 2.353$, gl 11, $P < 0.05$) and "grooming" ($t = 2.935$, gl 11, $P < 0.05$) were delayed as compared before treatment (**Figures 2A, B**). In addition, there was a decrease in the "total distance traveled" ($t = 4.674$, gl 11, $P < 0.01$) (**Figure 2E**). In contrast, the sequence of behaviors ["first movement", "leaving the center," "entering into the periphery," all $t(10) < 14{,}317$, $P < 0.001$; "grooming," $t = 3{,}681$, gl 10, $P < 0.01$] was faster in those receiving risperidone. A decrease in the "total number of rearings" ($t = 2.948$, gl 10, $P < 0.05$) was observed (**Figure 2D**). In the 3xTg-AD mice treated with saline and risperidone, the "latency to enter the periphery" was advanced in time ($t = 3.236$, gl 11, $P < 0.01$ and $t = 4.071$, gl 10, $P < 0.01$, respectively). Likewise, 3xTg-AD (r) mice showed a decrease in the horizontal activity "distance traveled" ($t = 4.104$, gl 10, $P < 0.01$) (**Figure 2E**) and in the vertical activity "total number of rearings" ($t = 2.512$, gl 10, $P < 0.05$) indicating differences between the untreated phase and the treatment phase at 0.1 mg/kg (**Figure 2D**). When the four groups of treated animals were compared with each other, a genotype effect [$F(1,43) = 20.950$, $P < 0.001$], treatment effect [$F(1,43) = 6.802$, $P < 0.05$], and interaction effect "genotype × treatment" [$F(1,43) = 13.161$, $P < 0.01$] was detected in the variable "total distance traveled." This was due to the fact that the NTg (r) mice performed greater horizontal exploratory activity with respect to the group of NTg (s) mice, while the 3xTg-AD (r) mice performed less horizontal activity with respect to the 3xTg-AD mice (s) (**Figure 2E**). In addition, in the variables of vertical activity, it was observed that the "latency of the first rearing" showed treatment effect [$F(1,43) = 4.376$, $P < 0.05$]. Similarly, the "total number of rearings" indicated genotype effect [$F(1,43) = 16.431$, $P < 0.001$], treatment [$F(1,43) = 5.594$, $P < 0.001$], and interaction "genotype × treatment" [$F(1,43) = 4.410$, $P < 0.05$] (**Figures 2C, D**). The variable "grooming latency" showed genotype effect [$F(1,43) = 26.950$, $P < 0.001$] because time was delayed in 3xTg-AD mice relative to the other two NTg groups. Regarding the variable "total number of grooming," a "treatment × genotype" interaction effect was observed [$F(1,43) = 8.718$, $P < 0.01$] due to a decrease in behavior in the groups of 3xTg-AD mice with respect to the other two NTg groups. In the "urine," a genotype effect was observed [$F(1,43) = 11.133$, $P < 0.01$] due to higher incidence of urine in the 3xTg-AD groups with respect to the NTg groups (**Figure 2F**).

T-Maze (TM)

Behavioral patterns exhibited in the TM differing between genotypes were referred to emotionality behavior (urination), which was increased in the 3xTg-AD mice. As shown in

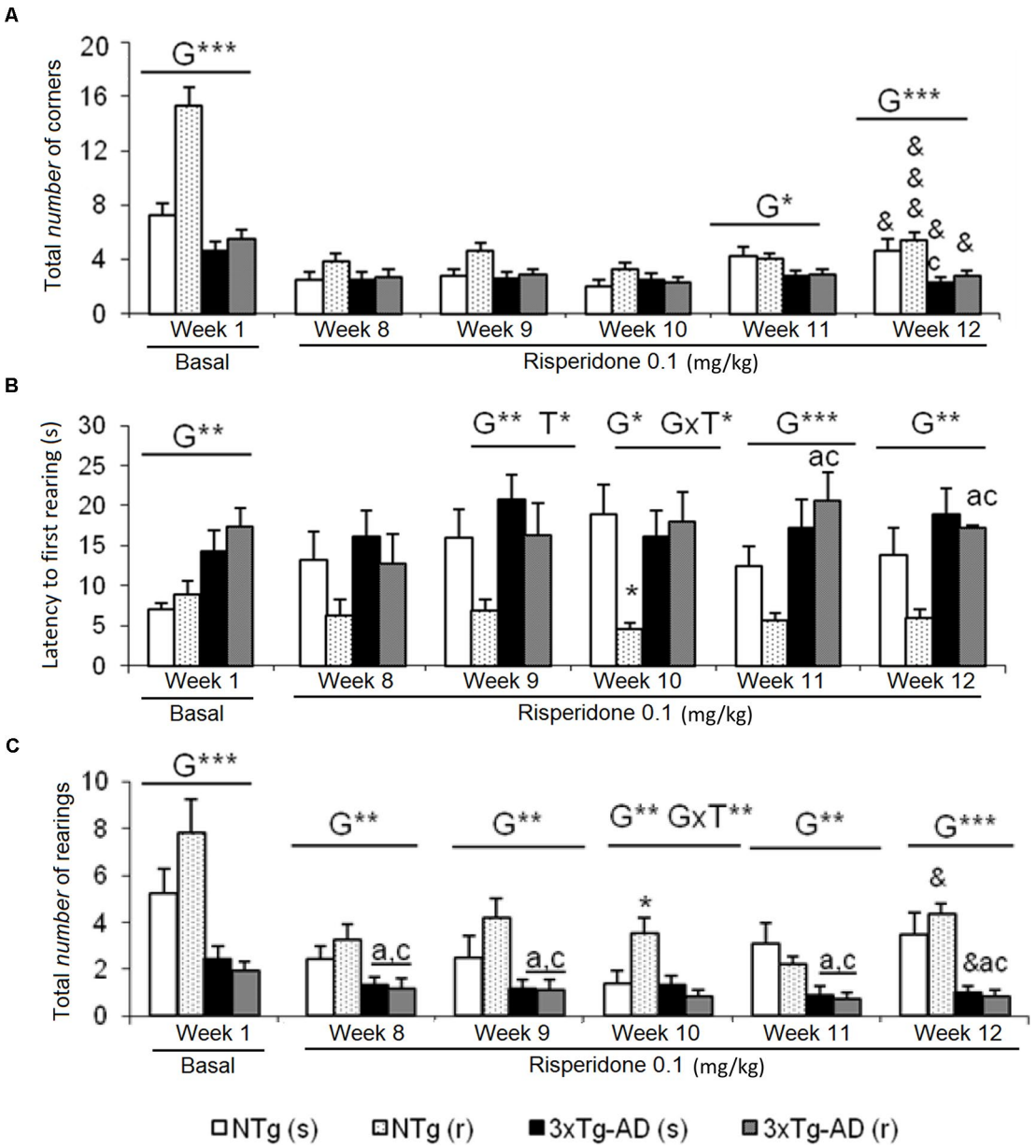

FIGURE 1 | Effects of chronic risperidone assessed in the corner test. Results in the corner test before (basal) and through different weeks of treatment. **(A)** Number of corners, **(B)** latency of first rearing, and **(C)** number of rearings. ANOVA 2×2, genotype effect (G), genotype × treatment interaction (G×T), ***$p < 0.001$, **$p < 0.01$, and *$p < 0.05$. *Post hoc* Tukey B test *$p < 0.05$ *vs*. all other experimental groups; $^{a}p < 0.05$ *vs*. different genotype but the same treatment; and $^{c}p < 0.05$ *vs*. different genotype and different treatment. *t -test* for paired data, treatment effect: treatment with a dose of 0.1 mg/kg *vs*. no treatment, $^{\&\&\&}p < 0.001$ and $^{\&}p < 0.05$.

Figure 3, before–after differences were only shown in the groups of 3xTg-AD mice. Animals treated with saline showed an increase in the number of defecation boli (t = -4.486, gl 11, P < 0.01), while the 3xTg-AD (r) group needed longer "time to complete the maze" (t = -2.578, gl 10, P < 0.05). When the four groups of animals were compared with each other, the "latency to cross the intersection" indicated genotype effects [F(1,43) = 5.668, P < 0.05] due to a delay in the 3xTg-AD mice with respect to the two groups of NTg mice. The genotype effect was also evidenced in the variable "exploratory activity" [F(1,43) = 4.496, P < 0.05] because the groups of 3xTg-AD mice performed a greater number of episodes with respect to the two NTg groups. "Genotype × treatment" interaction effects were shown in the "number of fecal boli" [F(1,43) = 4.930, P < 0.05] and "total number of urine" [F(1,43) = 11.381, P < 0.01].

Social Interaction Test (SIT)

In this test, exhibition of social (**Figure 4**) and non-social (**Figure 5**) behaviors were analyzed. "Face/body contact,"

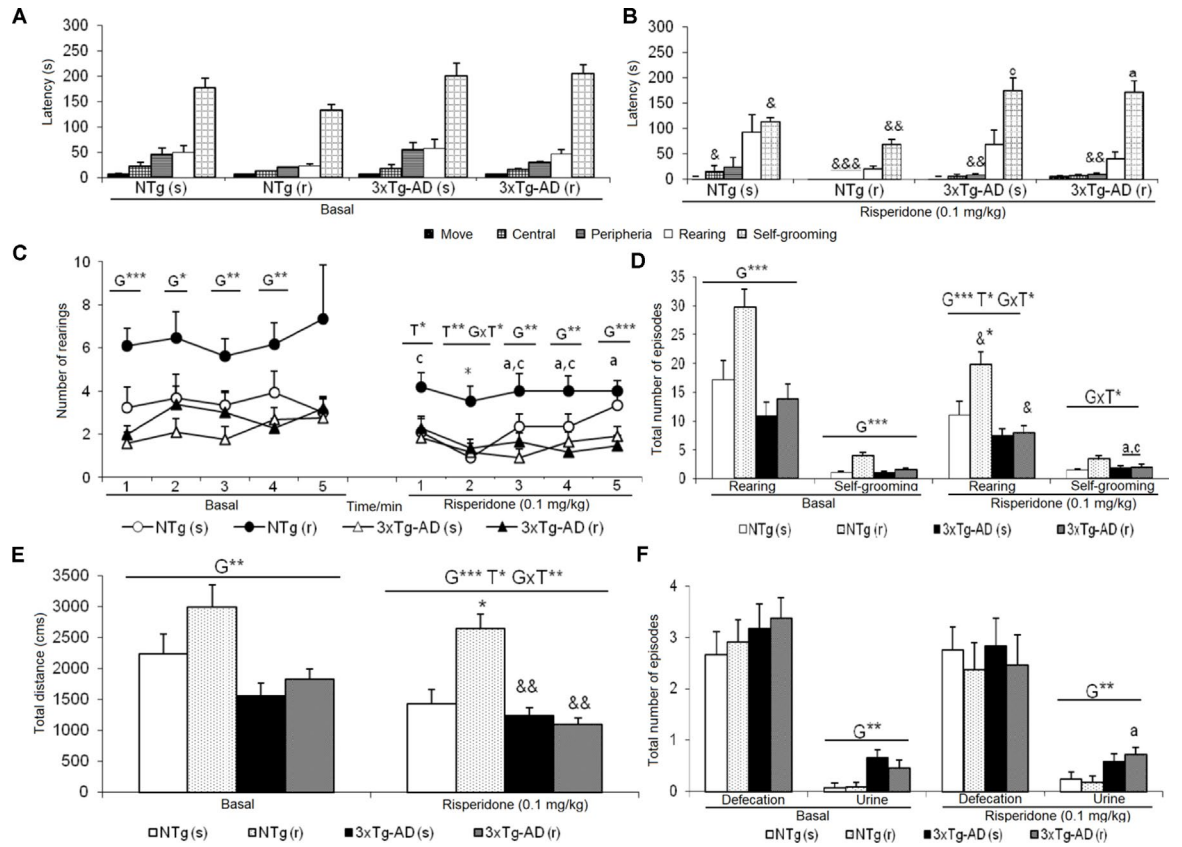

FIGURE 2 | Effects of chronic risperidone assessed in the open field test. Results in the open field test before (basal) and during treatment. **(A)** Latencies before treatment; **(B)** latencies after treatment; **(C)** number of rearings; **(D)** total number of episodes of rearing and self-grooming; **(E)** total distance covered; **(F)** total number of episodes of defecation and urine. ANOVA 2×2, genotype effect (G), treatment (T) and genotype × treatment interaction (G×T), $^{***}p < 0.001$, $^{**}p < 0.01$, and $^{*}p < 0.05$. *Post hoc* Tukey B test $^{a}p < 0.05$ *vs*. different genotype but the same treatment and $^{c}p < 0.05$ *vs*. different genotype and different treatment. Effect *t*-test for paired data, treatment effect: treatment with a dose of 0.1 mg/kg *vs*. before treatment $^{\&\&\&}p < 0.001$, $^{\&\&}p < 0.01$, and $^{\&}p < 0.05$.

"anogenital contact," "vibrant tail," and "aggressive contact" presented distinct latencies of appearance and number of episodes depending on the genotype and were modified by treatment. Before treatment, reduced body/face interaction, horizontal and vertical exploratory behaviors but increased vibrating tail and digging were phenotypic characteristics of 3xTg-AD mice (**Figure 4B**). After treatment, in NTg (s) mice, the face/body contact behavior showed a decrease in the "total number of episodes" (t = 2.217, gl 11, P < 0.05) (**Figure 4C**). In the NTg (r) mice, it was observed that the "face/body" latency was delayed in time (t = 3.006, gl 10, P < 0.05) and the "vibrant tail" latency was advanced (t = 3.738, gl 10, P < 0.01) (**Figure 4A**). In addition, there was a decrease in the contact time "face/body" (t = 4.107, gl 10, P < 0.01) and "anogenital" (t = 3.546, gl 10, P < 0.01) and an increase in "vibrant tail" (t = -4.282, gl 10, P < 0.01) (**Figure 4B**). Likewise, there was a decrease in the number of episodes in "face/body" (t = 5.255, gl 10, P < 0.001), "anogenital" (t = 3.975, gl 10, P <0.01) and an increase in "vibrant tail" (t = -4.282, gl 10, P <0.01) (**Figure 4C**). The mice 3xTg-AD (s) presented a decrease in the duration "anogenital contact" (t = 2.520, gl 11, P < 0.05) (**Figure 4B**) and number of episodes of the "vibrant tail" behavior (t = 2.480, gl 11, P <0.05) (**Figure 4C**). The 3xTg-AD (r) mice showed statistical differences in the appearance of the "face/body contact" behavior (advancement, t = 2.754, gl 10, P < 0.05) and "vibrant tail" (delay, t = -4.643, gl 10, P < 0.01) (**Figure 4A**). These differences were also reflected in the duration and in the number of episodes, since the animals spent more time in the "face/body contact" behavior (t = 2.443, gl 10, P < 0.05) and it increased the number of episodes "face/body" and decreased the number of "vibrant tail" (t = 2.372, gl 10, P < 0.05) (**Figures 4B, C**). When comparing the four groups with each other, the variable "face/body contact latency" showed a "genotype × treatment" interaction effect [F(1,43) = 8.4428, P < 0.01], which was also evidenced in the variable total number of episodes of "face/body contact" [F(1.43) = 9.199, P < 0.01] (**Figures 4A, B**).

In the "latency of anogenital contact," genotype effects were observed [F(1,43) = 0.818, P < 0.01) with a delay in the groups of 3xTg-AD mice as compared to the other two NTg groups (**Figure 4A**). Conversely, "total anogenital contact time" showed genotype [F(1,43) = 6.766, P < 0.05], treatment [F(1,43) = 5.855, P < 0.05], and interaction "genotype × treatment" [F(1,43) = 4.535, P < 0.05] effects (**Figure 4B**). The genotype effect was also

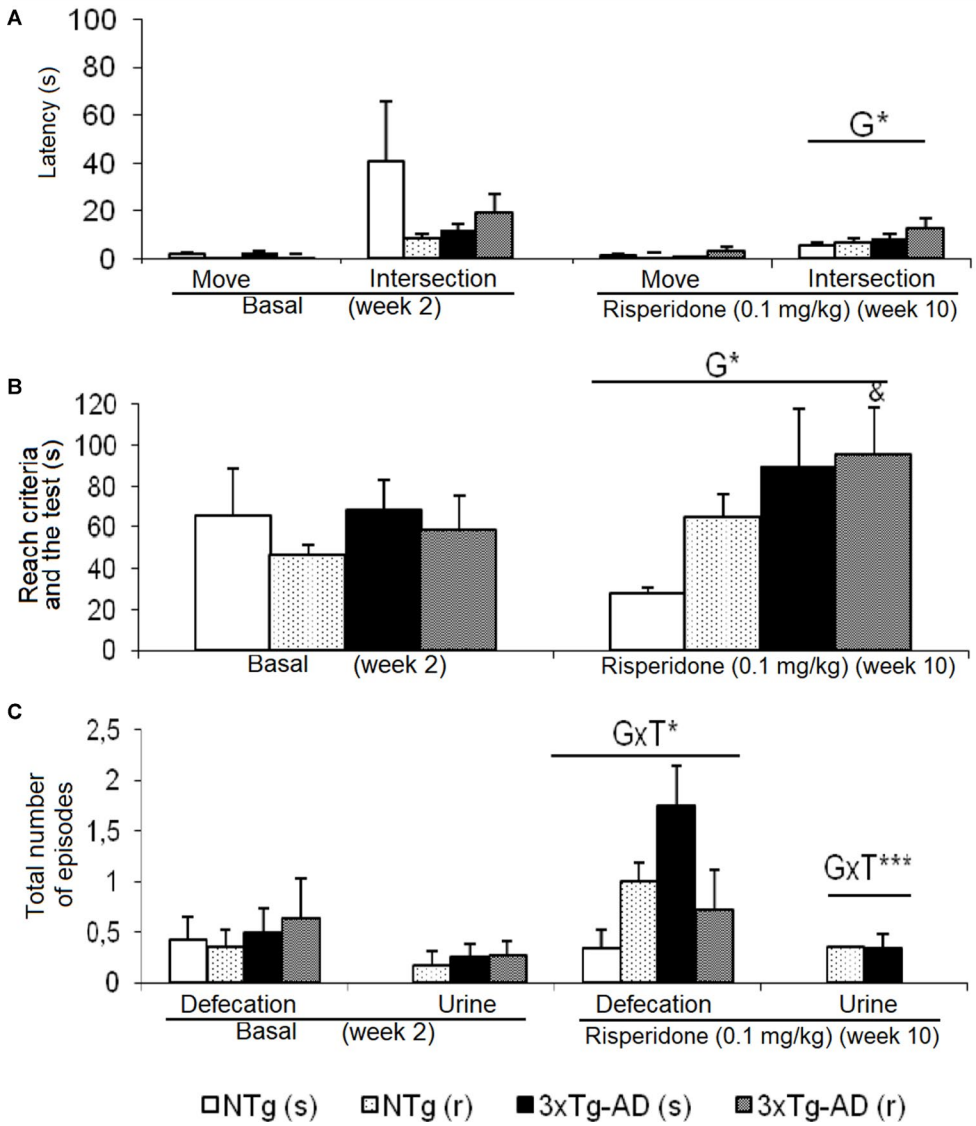

FIGURE 3 | Effects of chronic risperidone assessed in the T-Maze before (basal) and during the treatment. **(A)** Latencies (s), **(B)** time to complete the maze (s), and **(C)** total number of defecations and urine. ANOVA 2×2, genotype effect (G), genotype × treatment (GxT), ***$p < 0.001$ and *$p < 0.05$. *Post hoc* Tukey B test $^{a}p < 0.05$ *vs*. different genotype but the same treatment and $^{c}p < 0.05$ *vs*. different genotype and different treatment. *t*-Test effect for paired data, treatment effect: treatment with a dose of 0.1 mg/kg vs. no treatment, $^{\&}p < 0.05$.

evidenced in the total number of "anogenital contact" episodes [F(1,43) = 9.264, P < 0.01], treatment [F(1,43) = 7.509, P < 0.01], and interaction [F(1,43) = 5.017, P < 0.05] (**Figure 4C**). This was due to the fact that the NTg (s) mice had greater contact duration and number of episodes with respect to the other three experimental groups. In the "tail vibration latency," "genotype × treatment" interaction effect was observed [F(1,43) = 5.396, P < 0.05] (**Figure 4A**). Likewise, the variable "total time" presented genotype effect [F(1,43) = 7.836, P < 0.01] as well as the variable "number of episodes" [F(1,43) = 6.949, P < 0.05] because groups of 3xTg-AD mice invested more time and presented an increase of episodes with respect to the other two NTg groups (**Figures 4B, C**). In the aggressive contact component, no significant differences were observed in any of the three variables studied for this behavior (**Figures 4A, B, C**).

Figures 5A and B illustrate the pattern of non-social behaviors before and after the treatment. In the NTg mice, changes were only observed in those animals treated with the antipsychotic, with a reduced number of rearings (t = 5.519, gl 10, P < 0.001) and visited corners (t = 2.679, gl 10, P < 0.001) as compared to basal levels (**Figure 5B**). In the 3xTg-AD (s) mice, the "latency of rearing" was delayed in time (t = 2.205, gl 11, P < 0.05) resulting in a decrease of the "number of rearings" (t = 3.116, gl 11, P < 0.01). This was also evidenced in the 3xTg-AD (r) mice where the "latency of rearing" was delayed in time (t = -2.323, gl 10, P < 0.05), the "number of rearings" decreased (t = 5.723, gl 10, P < 0.001) and

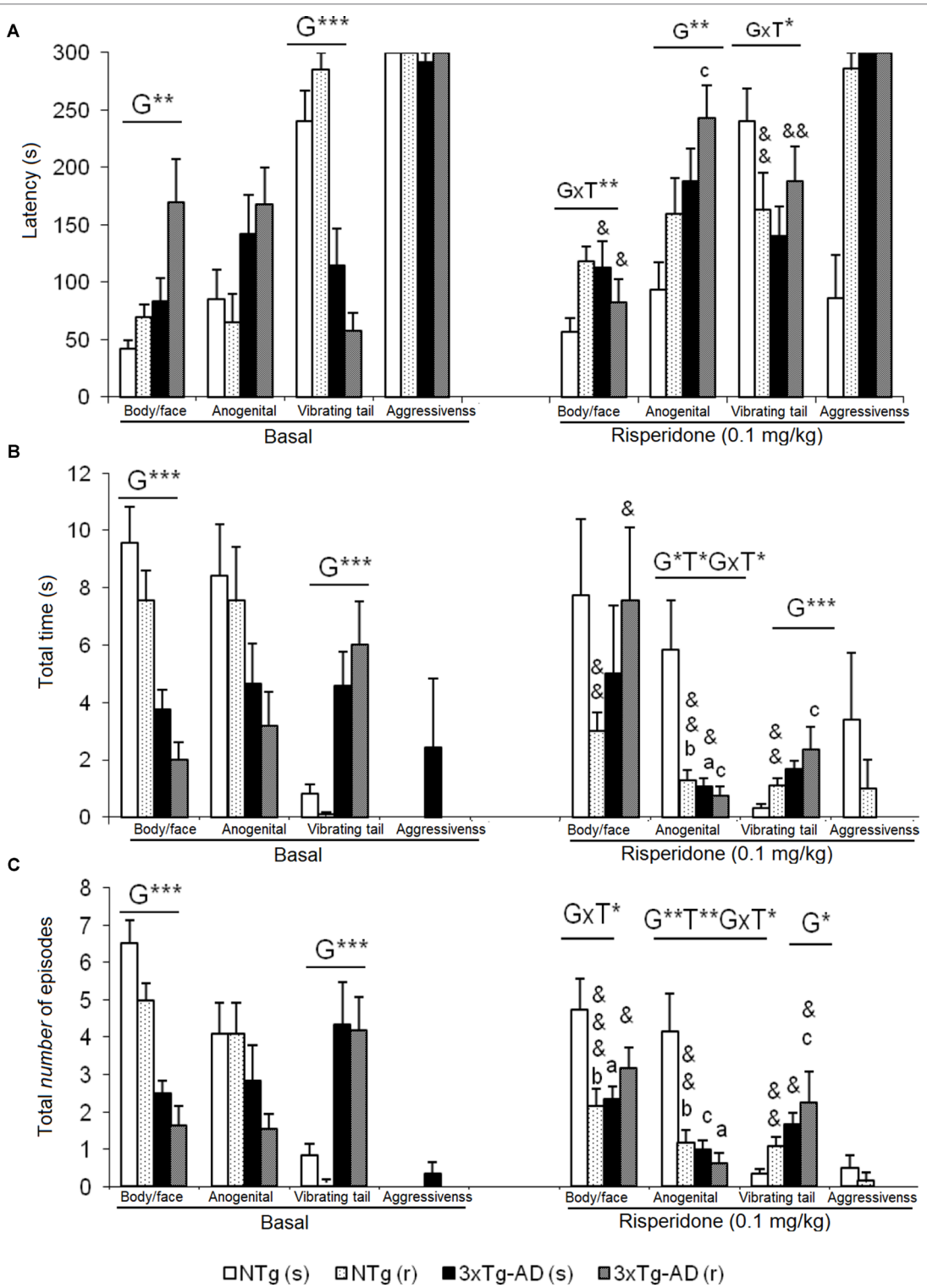

FIGURE 4 | Effects of chronic risperidone in the social behaviors assessed in the social interaction test before (basal) and during the treatment. **(A)** Latencies (s). ANOVA 2×2, genotype effect (G), genotype × treatment interaction (G×T), $^{**}p < 0.01$ and $^{*}p < 0.05$. *Post hoc* Tukey B test $^{*}p < 0.05$. *vs.* all other experimental groups; $^{a}p < 0.05$ *vs.* different genotype but the same treatment and $^{c}p < 0.05$ vs. different genotype and different treatment. *t*-test effect for paired data, treatment effect (T): treatment with a dose of 0.1 mg/kg *vs.* no treatment, $^{\&\&}p < 0.01$ and $^{\&}p < 0.05$. **(B)** Total time and **(C)** total number of episodes. ANOVA 2×2, genotype effect (G) treatment effect (T) and genotype × treatment interaction effect (G×T), $^{***}p<0.001$ $^{**}p < 0.01$ and $^{*}p < 0.05$. *Post hoc* Tukey B test $^{*}p < 0.05$. *vs*. all other experimental groups; at $p < 0.05$ *vs*. different genotype but the same treatment; $^{b}p < 0.05$ *vs.* different treatment but the same genotype and $^{c}p < 0.05$ *vs*. different genotype and different treatment. *t*-test effect for paired data, treatment effect: treatment with a dose of 0.1 mg/kg *vs*. no treatment, $^{\&\&\&}p < 0.001$, $^{\&\&}p < 0.01$, and $^{\&}p < 0.05$.

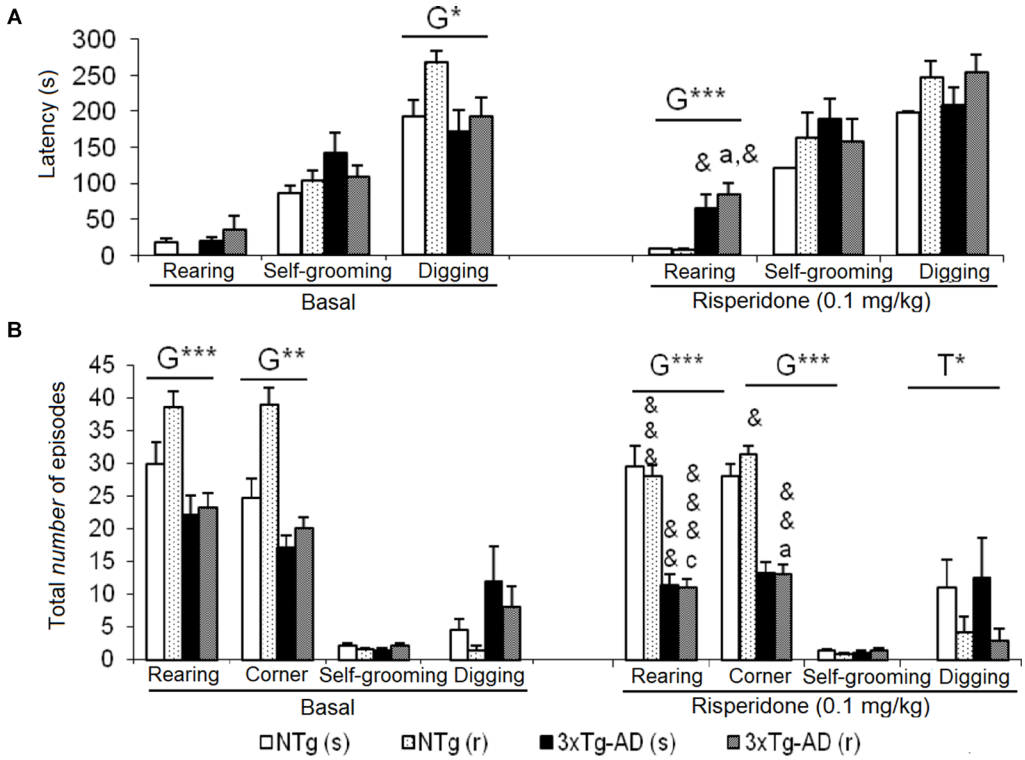

FIGURE 5 | Effects of chronic risperidone in the non-social behaviors assessed in the social interaction test before (basal) and during the treatment. **(A)** Latencies (s) and **(B)** total number. ANOVA 2×2, genotype effect (G), treatment (T), ***$p < 0.001$ and *$p < 0.05$. *Post hoc* Tukey B test $^{a}p < 0.05$ *vs.* different genotype but the same treatment and $^{c}p < 0.05$ *vs.* different genotype and different treatment. Effect *t*-test for paired data, treatment effect: treatment with a dose of 0.1 mg/kg *vs.* untreated $^{\&\&\&}p < 0.001$, $^{\&\&}p < 0.01$, and $^{\&}p < 0.05$.

also the "number of visited corners" reduced (t = 3.264, gl 10, P < 0.01) (**Figures 5A, B**). When comparing the four experimental groups with each other, these results were noted as genotype effect in the "latency of the first rearing" [F(1,43) = 24,813, P < 0.001], "total number of rearings" [F(1,43) = 67.857, P < 0.001], and "total number of corners" [F(1,43) = 89.604, P < 0.001] due to the reduced activity of 3xTg-AD mice with respect to the two groups of NTg mice. The treatment effect was observed only in the duration of the burying, which was reduced by risperidone [F(1,43) = 4.185, P < 0.05] in both genotypes. No effects of the genotype or treatment were observed in the "grooming" variable.

Morris Water Maze (MWM)

Figure 6 depicts the before and after trial-by-trial (**Figures 6A, B**) and day-by-day (**Figure 6C**) place learning task acquisition curves as well as the platform preference shown in the probe trial to assess memory after treatments (**Figure 6D**). The trial-by-trial performance before treatment indicated that on each day, except for day 3, there was an effect of the "trial" [day 1, F(3,144) = 9.914, P < 0.001; day 2, F(3,144) = 4.082, P < 0.01; day 4, F(3,144) = 7.242, P < 0.001; day 5, F(3,144) = 4.934, P < 0.01]. However, this basal performance in the 3xTg-AD mice resulted in a worse day-by-day acquisition curve with higher latencies as compared to NTg mice, on days 3, 4, and 5. After treatment, statistical significant differences were only shown on day 1, with a "trial × genotype" [F(3,144) = 2.664, P < 0.05] and "trial × genotype × treatment" [F(3,144) = 3.766, P < 0.05] effects. No differences in the acquisition curves were found among the four treated groups. When performance on this first day after treatment was compared to the last performance before treatment, only NTg (s) mice showed worsen performance (t = -2.239, gl 11, P < 0.05). As compared with their respective acquisition curves before treatment, all groups of mice were faster finding the platform in this re-test. NTg (s) showed statistical differences on days 1, 2, and 5 (all t > 2.484, gl 11, P < 0.05), NTg (r) on days 1 and 2 (both t > 1.866, gl 10, P < 0.01), 3xTg-AD (s) from days 1 to 4 (all t > 1.950, gl 11, P < 0.01), and 3xTg-AD (r) on all the days (all t > 2.096, gl 11, P < 0.01).

The second paradigm consisted of the *removal* of the platform. Before treatments, NTg groups showed the highest number of entries in the trained quadrant, where the platform was previously located, with respect to the other quadrants [NTg (s), F(3,47) = 13.48, P < 0.001; NTg (r), F(3,43) = 9.62, P < 0.001]. The number of entries in the trained platform was significantly lower in the 3xTg-AD groups. The detailed analysis showed that preference was also shown for the right quadrant [3xTg-AD (s), F(3,47) = 8.80, P < 0.001; 3xTg-AD (r), F(3,43) = 8.14, P < 0.001] indicating lower focused search strategies in these mice. After treatment, the NTg (s) mice showed an increase in the

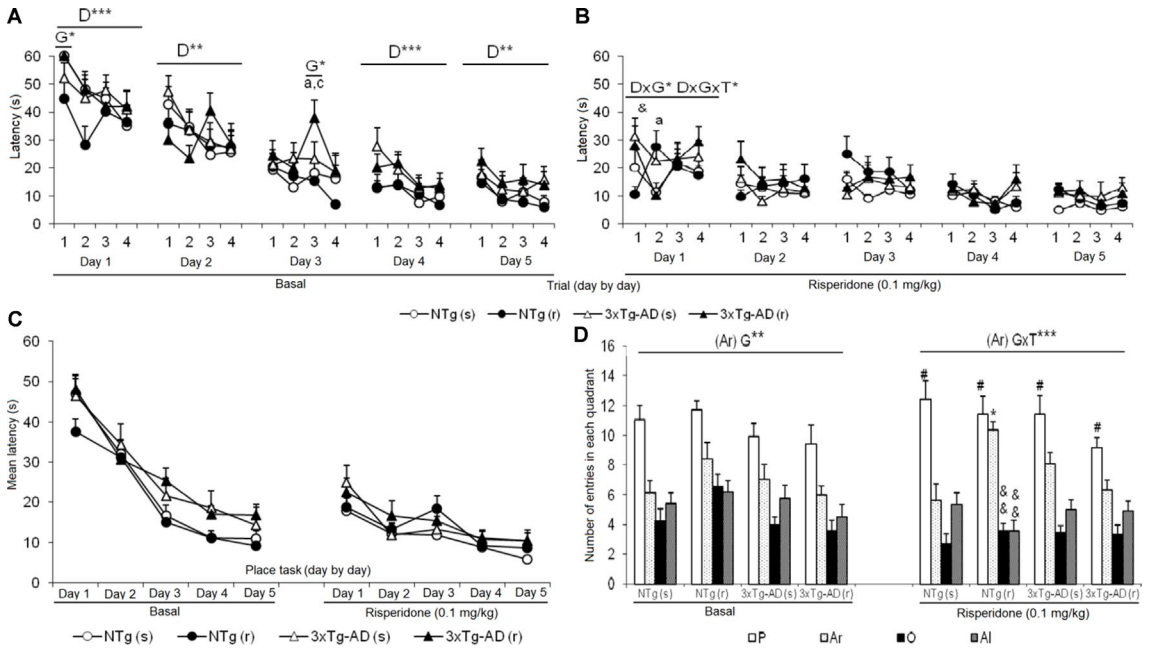

FIGURE 6 | Effects of chronic risperidone in the Morris water maze before (basal) and during the treatment genotype effect (G). Latencies (s) evolution before **(A)** and after **(B)** the treatment, evolution of learning and memory, trial by trial for each of the 5 days. Repeated measures ANOVA, 2×2×5, day effect (D), day × genotype effect (DxG), and interaction effect (D×G×T), $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$. *Post hoc* Tukey B test $^{a}p < 0.05$ vs. different genotype but the same treatment and $^{c}p < 0.05$ *vs*. different genotype and different treatment. *t*-Test for paired data, treatment effect: trial 1 of day 1 with treatment *vs.* trial 4 of day 5 without treatment, $^{\&}p < 0.05$. **(C)** Latency (s), evolution of learning and memory day by day. Repeated measures ANOVA 2×2×5, ns and *post- hoc* Tukey B test, ns **(D)** total number of entries in the quadrant: platform (P), right (Ar), opposite (O), and left (Al). ANOVA 2×2, genotype × treatment interaction effect (G×T), $^{***}p < 0.001$. *t*-Test for paired data, treatment effect: treatment with a dose of 0.1 mg/kg vs no treatment, $^{\&\&}p < 0.01$ and $^{\&}p < 0.05$. ANOVA and *post hoc* Tukey B test interaction of the three levels #p < 0.001.

number of entries in the "trained quadrant" with respect to the other quadrants [F(3,47) = 18.91, P < 0.001]. In contrast, in the other treated groups, an increase in entries was observed in both the quadrant of the platform and the right quadrant [NTg (r), F(3,43) = 31.18, P < 0.001; 3xTg-AD (s), F(3,47) = 18.91, P < 0.001; 3xTg-AD (r) [F(3,43) = 15.27, P < 0.001]. Thus, the variable "number of entries in the right quadrant" indicated "genotype × treatment" interaction effect [F(1,43) = 19.401, P < 0.001]. As compared to their respective performances before treatment, statistical differences were only found in the NTg (r) mice, as a decrease in the number of entries in the opposite (t = 3.203, gl 10, P < 0.01) and left (t = 3.909, gl 10, P < 0.01) quadrant.

Marble Burying Test (MB)

As illustrated in **Figure 7**, before treatment, 3xTg-AD mice showed an increased pattern of interaction with marbles, with a higher number of marbles that changed position and were buried than NTg counterparts. After treatment NTg (s) mice the "intact" marbles were the least frequent compared to the marbles that changed position and were buried [F(2,35) = 19.51, P < 0.001]. Oppositely, in NTg (r) mice, an increase in the number of marbles "intact" and a decrease in "buried" marbles [F(2,32) = 13.05, P < 0.001] was observed. In the two groups of treated 3xTg-AD mice, no significant changes were observed between the three levels of interaction with marbles. In each group, before and after comparisons indicated differences: NTg (s) mice, in the marble number variables "intact" (t = 5.348, gl 11, P < 0.001) and "buried" (t = -3.824, gl 11, P < 0.001) because after the treatment, there was a decrease in the number of intact marbles and an increase in the number of marbles buried. In the 3xTg-AD (s) mice, an increase in the number of "changed position" marble was observed (*t* = -2.601, gl 11, P < 0.05) and a decrease in "buried" marble (*t* = 3.348, gl 11, P < 0.01). In the groups of animals treated with risperidone NTg (r) and 3xTg-AD (r), no changes were observed. Treatment effects were shown in the "number of intact marble" [F(1,43) = 7.802, P < 0.01] as an increase in its number in the groups treated with risperidone compared to those treated with saline. Conversely, the "number of buried marbles" also indicated treatment effect [F(1,43) = 8.573, P < 0.01] with a reduction as compared to those treated with saline, although this decrease is only significant in the case of NTg (r) animals. Furthermore, in this variable, the interaction effect "genotype × treatment" was observed [F(1,43) = 6.114, P < 0.05] due to a decrease in the number of marbles buried in the NTg (r) mice and an increase in the 3xTg-AD (r) mice.

Baseline State of Blood Glucose

Basal state of glucose levels before treatment did not differ between 3xTg-AD and NTg mice (**Figure 8**). However, after treatment, NTg (r) mice showed a marked decrease (t = 7.611, gl 11, P < 0.001). This led to a "genotype × treatment" effect [F(1,43) = 9.441, P < 0.01].

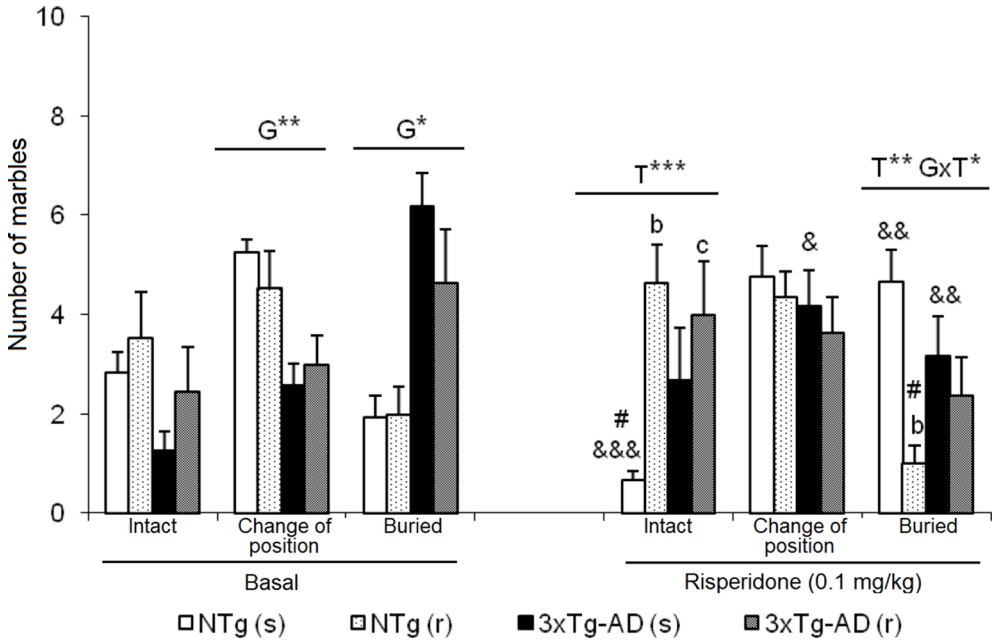

FIGURE 7 | Effects of chronic risperidone in the marble burying test before (basal) and during the treatment. Number of marbles. *t*-Test for paired data, treatment effect: treatment with a dose of 0.1 mg/kg vs no treatment, $^{\&\&\&}p < 0.001$, $^{\&\&}p < 0.01$, and $^{\&}p < 0.05$. ANOVA and *post hoc* Tukey B test interaction of the three levels $^{\#}p < 0.001$. ANOVA 2×2, (T), treatment effect and (G×T), genotype × treatment interaction, $^{***}p < 0.001$, $^{**}p < 0.01$, and $^{*}p < 0.05$. *Post hoc* Tukey B test $^{b}p < 0.05$ vs. different treatment but the same genotype and $^{c}p < 0.05$ vs. different genotype and different treatment.

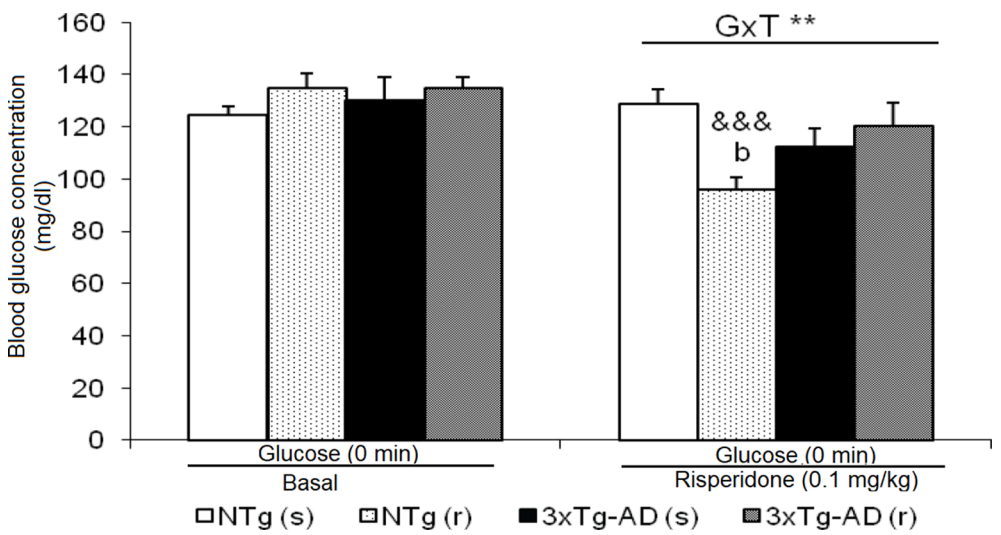

FIGURE 8 | Effects of chronic risperidone in basal state of glucose before and during the treatment. *t*-Test for paired data, treatment effect: treatment with a dose of 0.1 mg/kg vs no treatment, $^{\&\&\&}p < 0.001$. ANOVA 2×2, interaction effect genotype × treatment (G×T), $^{**}p < 0.01$. *Post hoc* Tukey B test $^{b}p < 0.05$ vs. different treatment but the same genotype.

Weight

The body weight (BW) of animals was monitored throughout the experimental procedures (**Figure 9**). At the beginning of the experiments, weight of 3xTg-AD mice was higher than that of controls (t = -2.213, gl 50, P < 0.05), but differences were attenuated through the experiments. Statistical significance was lost in week 6, just before treatment started (NTg mice, t = 4.035, gl 23, P < 0.01; 3xTg-AD mice, t = 6.234, gl 27, P < 0.001). During the first week of treatment (risperidone, 0.05 mg/kg), all the groups lost weight [NTg (r) mice, t = 2.965, gl 10, P < 0.05; 3xTg-AD (s), t = 2.718, gl 11, P < 0.05; 3xTg-AD (r), t = 4.633, gl 10, P < 0.01] except NTg mice treated with saline. At 10 weeks

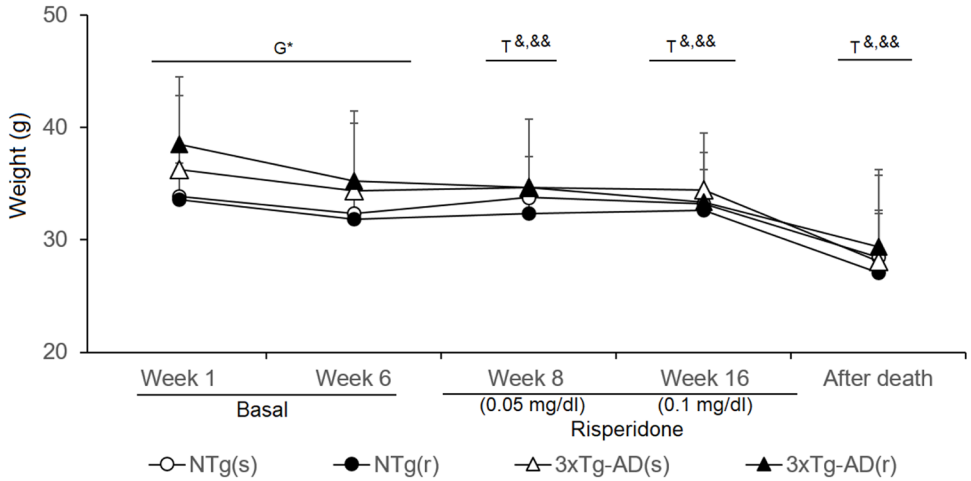

FIGURE 9 | Effects of chronic risperidone in the body weights of the animals before (basal), during the treatment, and immediately after death Phase 1 Basal. Student's *t*-test; $^{*}p < 0.05$. Phase 2. Start of treatment with risperidone at a dose of 0.05 mg/kg. Weights. *t*-Test for paired data, treatment effect: treatment with a dose of 0. 05 mg/kg vs untreated, $^{\&\&}p < 0.01$ $^{\&}p < 0.05$ for Phase 3. Treatment with risperidone at a dose of 0.1 mg/kg. *t*-Test for paired data, treatment effect: treatment with a dose of 0. 1 ml/kg vs untreated $^{\&\&}p < 0.01$ $^{\&}p < 0.05$ Phase 4. Immediately after death vs. the weights at the beginning of the longitudinal study. *t*-Test for paired data $^{\&\&}p < 0.01$, and $^{\&}p < 0.05$.

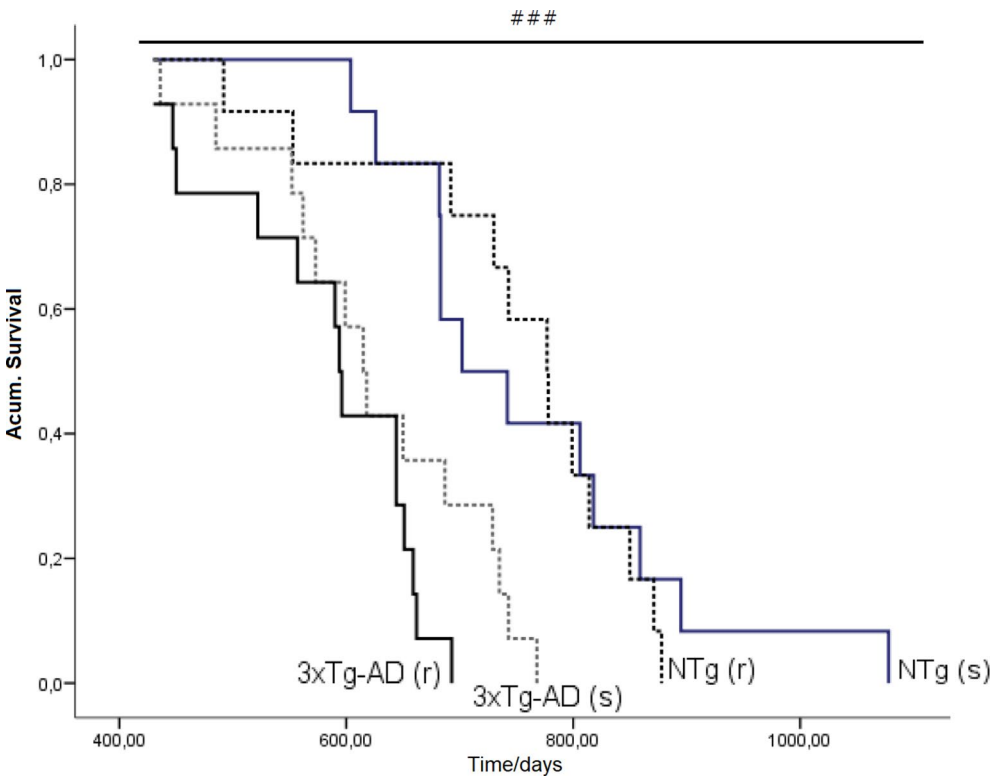

FIGURE 10 | Effects of chronic risperidone in the total mean survival. Mean ± SEM. Survival curves based on the age of the animals (in days). Each line represents the cumulative survival of the animals of each experimental group [NTg (s) and 3xTg-AD (s)] Log-rank test $p < 0.001$. Survival curve based on the age of the animals (in days). Each line represents the cumulative survival of the animals of each experimental group [NTg (s), NTg (r), 3xTg-AD (s) and 3xTg-AD (r)]. Log-rank-test $^{###}p < 0.001$.

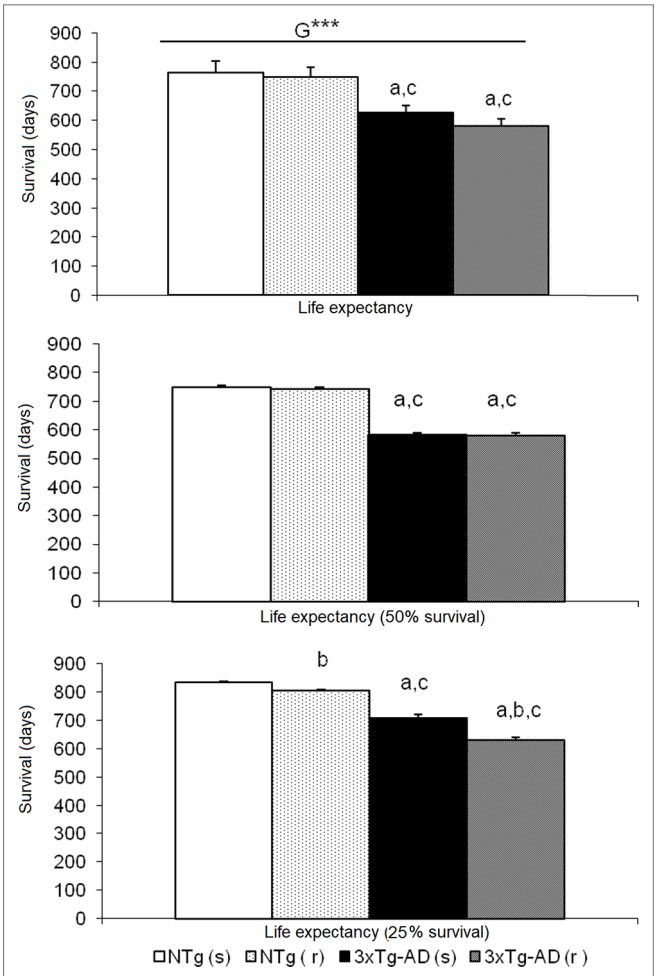

FIGURE 11 | Effects of chronic risperidone in the total mean survival. Mean ± SEM. ANOVA and *post hoc* Tukey B test ***p<0.001, [a]*p* < 0.05 vs. same treatment but different genotype, [b]*p* < 0.05 vs. different treatment but the same genotype and [c]*p* < 0.05 vs. different treatment different genotype.

of treatment (risperidone, 0.1 mg/kg), the loss of weight was only observable in the 3xTg-AD mice [3xTg-AD (s), $t = 2.312$, gl 11, P < 0.05; 3xTg-AD (r), $t = 3.478$, gl 11, P < 0.01]. The four experimental groups showed reduced "weight immediately after death" as compared to before treatment [NTg (s), $t = 2.209$, gl 11, P < 0.05; NTg (r), $t = 5.382$, gl 10, $P < 0.0$ 01; 3xTg-AD (s), $t = 5.721$, gl 11, P < 0.001; 3xTg-AD (r), $t = 3.937$, gl 10, P < 0.01]. When the four groups of animals were compared with each other, no differences were found among them at either of both time points.

Survival Curve

Figure 10 illustrates the survival curves and lifespan, which differed among the groups: NTg (s): 1.078 days (36 months), NTg (r): 874 days (28 months), 3xTg-AD (s): 768 days (24 months), 3xTg-AD (r): 660 days (22 months), with a genotype effect in mean lifespan. Lifespan was reduced by AD genotype [F(1,48) = 24.812, P < 0.001] but also by risperidone treatment (shortened 2 months in 3xTg-AD but in 8 months in NTg mice). Survival curves showed that until 14 months of age, all groups exhibited 100% survival. Thereafter, only NTg (s) mice maintained its survival intact until 19 months, that is, 5 months longer than the other groups. When comparing the four groups, their mean survival at 15 months of age showed a genotype [F(1,45) = 4.968, P < 0.05] and "genotype × treatment" [F(1,45) = 4.968, P < 0.05] interaction effects. Thus, although onset of mortality window was 15 months for NTg (r), 3xTg-AD (s), and 3xTg-AD (r), the different slopes in their survival curves indicated different severity levels: NTg (r), survival of 91.61%, 3xTg-AD (s), survival of 85.71%, 3xTg-AD (r), 78.48% (**Figure 11).** Average life expectancy (50% survival) differed among the four groups [F(3,28) = 262.25, P < 0.001]. In NTg mice, the average life expectancy was 24 months, whereas in the two groups of 3xTg-AD mice, it was 18 months. Likewise, when 25% of the survival was analyzed, statistically significant differences with respect to the group of NTg (s) mice [F(3,12) = 137.41, P < 0.001] were found. The Kaplan-Meier test showed significant differences between 3xTg-AD (s) and NTg (s) (Log rank = 7.218, gl 1, P < 0.01) and also among the four experimental groups (Log rank = 22.833, gl 1, *P* < 0.001).

Table 1 summarizes the meaningful correlation analysis of lifespan with the behavioral phenotype before and after treatment with risperidone for each one of the four experimental groups, while **Figure 12** illustrates the correlations with the whole sample of 46 animals. As shown, in most tests, freezing behavior and activity to complete the task were strongly (P < 0.01) correlated with lifespan in NTg (s). In the NTg (r), it was mostly related to the elicitation of emotionality (grooming), vertical exploratory activity (rearing), and agonistic behaviors (body face, inversely with vibrating tail). Poorest behavioral correlates were found in 3xTg-AD mice, where survival was inversely correlated to a poor marble burying, scarce and slow exploratory activity, and presence of vibrating tail. Survival in 3xTg-AD (r) was negatively correlated with delay in the elicitation of vertical exploratory activity and number of groomings. Correlation with cognitive task was only shown in NTg(s), while the tests and/or variables with predictive value in the whole sample were those related to the BPSD-like phenotype.

DISCUSSION

The main objective of the present work was to model in 3xTg-AD mice the increased mortality risk induced by the chronic administration of the atypical antipsychotic risperidone shown in patients with AD. This is the first study that considers this objective despite the imperative need to have an animal modeling this vulnerability, an issue that cannot be addressed in clinical studies.

Experimental design. First, the battery of behavioral tests allowed us to confirm the AD phenotype of the animals (Giménez-Llort et al., 2007). Thus, we verified the existence of cognitive and BPSD-like behaviors in this initial sample of middle-aged 3xTg-AD mice, an age that has extensively been described to mimic advanced neuropathological stages of the disease

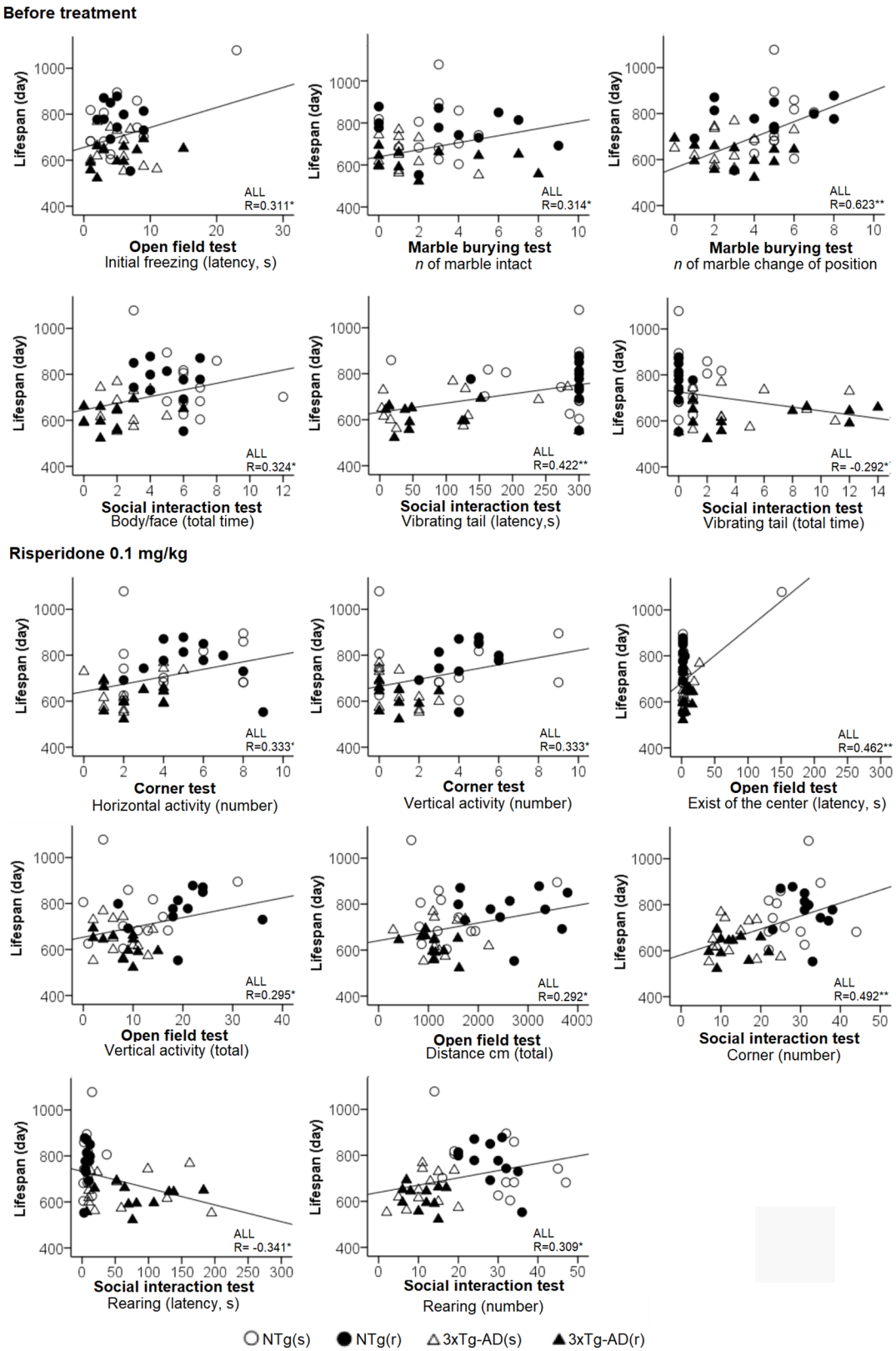

FIGURE 12 | Behavioral correlates for lifespan considering all the sample of animals. Pearson's correlations between behavioral variables and lifespan: $^{*}p < 0.05$, $^{**}p < 0.01$.

TABLE 1 | Behavioral correlates with lifespan in male NTg and 3xTg-AD mice chronically treated with saline or risperidone.

Behavioral test and variable	**Lifespan (days)**			
	NTg(s)	**NTg(r)**	**3xTg-AD(s)**	**3xTg-AD(r)**
Before treatment.				
Corner Test				
Vertical activity (latency, s)	0.684*	*n.s.*	*n.s.*	*n.s.*
Vertical activity (number)	-0.614*	*n.s.*	*n.s.*	*n.s.*
Open field test				
Initial movement (latency of freezing, s)	0.715**	*n.s.*	*n.s.*	*n.s.*
Exist of the center (latency, s)	0.63**	*n.s.*	*n.s.*	*n.s.*
Vertical activity (latency, s)	*n.s.*	*n.s.*	*n.s.*	-0.606*
Self-grooming (latency, s)	*n.s.*	*n.s.*	*n.s.*	*n.s.*
Vertical activity (3 min)	*n.s.*	*n.s.*	*n.s.*	*n.s.*
Vertical activity (5 min)	*n.s.*	*n.s.*	*n.s.*	*n.s.*
Self-grooming (number)		*n.s.*	*n.s.*	-0.657*
T-maze test				
Initial movement (latency of freezing, s)	0.721**	*n.s.*	*n.s.*	*n.s.*
Complete the test (total time, s)	0.751**	*n.s.*	*n.s.*	*n.s.*
Social Interaction Test				
Non-social interactions	*n.s.*			
Self-grooming (latency, s)	*n.s.*	-0.716**	*n.s.*	*n.s.*
Marble interaction test				
Intact (number of marbles)	*n.s.*	*n.s.*	-0.707**	*n.s.*
Morris water maze				
Day 4 (mean latency, s)	0.684*	*n.s.*	*n.s.*	*n.s.*
After treatment.				
Corner Test				
Vertical activity (latency, s)	*n.s.*	*n.s.*	0.633**	*n.s.*
Vertical activity (number)	*n.s.*	0.594*	-0.734**	*n.s.*
Open field test				
Initial movement (latency of freezing, s)	0.724**	*n.s.*	*n.s.*	*n.s.*
Exist of the center (latency, s)	0.734**	*n.s.*	*n.s.*	*n.s.*
Entrance to the periphery (latency, s)	0.713**	*n.s.*	*n.s.*	*n.s.*
T-maze test				
Initial movement (latency of freezing, s)	*n.s.*	*n.s.*	-0.687**	*n.s.*
Complete the test (total time, s)	*n.s.*	-0.653*	*n.s.*	*n.s.*
Social Interaction Test				
Social interactions				
Body/face (latency, s)	*n.s.*	-0.599*	*n.s.*	*n.s.*
Vibrating tail (latency, s)	*n.s.*	0.611*	*n.s.*	*n.s.*
Vibrating tail (total time)	*n.s.*	-0.611*	*n.s.*	*n.s.*
Vibrating tail (total no. of episodes)	*n.s.*	0.611*	*n.s.*	*n.s.*

*Pearson's correlations, *P < 0.05, **P < 0.01. n.s., non significant.*

(Belfiore et al., 2019). Here it is important to note that although the cognitive deficits in the MWM were confirmed, the inclusion criteria in the "before–after treatment" analysis excluded the animals that died during the period of behavioral assessments. In AD, treatments with atypical antipsychotics are effective in controlling anger, agitation, aggression, and symptoms more typical of the psychotic spectrum such as hallucinations, paranoia, and delusions, while cognitive symptoms, quality of life, and attention do not improve with these treatments (Kalman et al., 2008). In view of the pharmacological action of the antipsychotic treatment, it is therefore interesting to note that the animals before treatment had cognitive deficits but also an increase in the stereotyped behavior of marble burying (usually used to assess the efficacy of antipsychotics) and alterations in social behavior (also modifiable with antipsychotics). Once the phenotype was verified, we evaluated the response of 3xTg-AD mice to chronic treatment with risperidone as compared to the effects exerted on age-matched NTg mice but also as compared to their own phenotype before treatment. Risperidone was used at a dose of 0.1 mg/kg equivalent to those administered in patients with AD and used in most experimental work performed in rodents. As in the case of geriatric patients, the treatment regimen was initiated with a lower dose of 0.05 mg/kg.

In the longitudinal study, the baseline characterization was performed at 12 months of age and the administration of the treatment started at 13 months, which in both cases corresponds to advanced neuropathological stages of the disease. The number of animals used (n = 12–14 for each group) was adequate for behavioral studies according to the guidelines on the use of genetically mutated animals and taking into account that at the middle age, the individual variability increases due to age. However, for the study of long-term survival curves, it would have been advisable to use a much greater number, between 40 and 50 animals. This and other works of the literature are limited

experimentally to use a reduced number of animals by the difficulty of obtaining the experimental subjects.

Corner test. In the modeling of the behavioral effects induced by the atypical antipsychotic risperidone, the behavior of neophobia was evaluated by the CT. At the beginning of the treatment, the 3xTg-AD mice showed a greater behavioral inhibition when confronting novelty, presenting higher levels of neophobia with respect to the NTg mice, in the three variables of the test. Although this response was independent of treatment, it was observed that in NTg (r) mice, the dose of 0.05 mg/kg of risperidone induced a significant increase in vertical activity with respect to the other three experimental groups. In the following week (week 8, dose of 0.1 mg/kg), an attenuation of the differences between genotypes was observed, now only detectable in the rearing variable. In fact, in general, during the rest of the weeks, vertical behavior was the most sensitive to indicate the effects of the factors studied. Repeatedly, the predominant factor was genotype, corroborating the neophobia described in our laboratory in 3xTg-AD mice (Giménez-Llort et al., 2006; Giménez-Llort et al., 2007; Giménez-Llort et al., 2008 and Giménez-Llort et al., 2010), and in a few cases, treatment effect was observed. Therefore, chronic treatment with risperidone did not modify the neophobic response of the 3xTg-AD mice, and if any effect had, it was sporadically in NTg animals.

Open-field test. In agreement with the increased neophobia in the CT, in the OF to assess exploratory activity and anxiety, AD genotype differences were also observed with reduction of vertical and horizontal activity, temporal delay of the grooming behavior, and increased presence of urine. This predominant effect of the genotype factor corroborates the results obtained in the open field in the pretreatment phase and the CTs. Both the corner and open-field tests converged to show the emotional and anxious-like profile of 3xTg-AD mice, in agreement with our previous studies describing the appearance of these behaviors (Giménez-Llort et al., 2007; Giménez-Llort et al., 2008; Giménez-Llort et al., 2010; Giménez-Llort et al., 2018; García-Mesa et al., 2011; García-Mesa et al., 2012) since the early stages to advanced stages of the disease (Giménez-Llort et al., 2006).

The activity variables, both horizontal and vertical, also showed treatment effect *per se* and their effects were influenced by the interaction with the genotype. Thus, most of the effects of risperidone were observed again in NTg (r) animals as an increase with respect to the other three experimental groups. This seems to be a pattern similar to that observed in the CT, but in both horizontal and vertical vectors of locomotor activity, with the NTg (r) group being different from all the others.

When comparing the data at the longitudinal level, it can be seen that in the treatment phase, there is an attenuation of all the responses that could be due to the simple fact of the repetition of the test. Also, it could be attributed to the repeated manipulation or handling of animals. In both cases, these are some of the limitations inherent to the use of behavioral batteries and are enhanced in longitudinal studies and chronic treatments. These limitations are difficult to avoid but can be mitigated by reducing the number of tests and the use of tests with variables with convergent validity, as we have done in our study, and the selection of guidelines for oral administration or subcutaneous pumps.

Risperidone enhanced the behavioral differences but did so differently depending on the genotype. Although the differences between the two groups of NTg animals before the use of drugs may be potentiating this contrast of NTg (r) mice, we have verified that this group, but not the one that would be treated with saline, is the one that shows the most standard values described for the NTg male animals of our colonies. Therefore, in any case, the results of NTg mice treated with saline are downward biased.

About the effect of risperidone, studies with other mouse models for other pathologies, such as the ICR mouse, have found that a low dose of risperidone (0.01 mg/kg, i.p.) decreases the freezing or freezing behavior, and at high doses (0.04 mg/kg, i.p.), spontaneous motor activity is reduced. However, when co-administered with other drugs, it loses effectiveness in its anxiolytic effect (Miyamoto et al., 2004). In male ddY mice of 5 weeks of age, risperidone at a dose of 0.1 mg/kg inhibits methamphetamine-induced hyperlocomotion and at several other doses attenuates that induced by MK-801 through blockade of the 5-HT2A/2C receptor (Uchida et al., 2009). In BTBR mice at doses of 0.125 and 0.25 mg/kg i.p., risperidone decreases exploratory activity (total distance traveled) in the OF (Silverman et al., 2010). The data confirm the dopaminergic action of the drug modulating motor and motivational functions (Rinaldi et al., 2007) and exerting anxiolytic properties.

On the other hand, the literature also suggests that atypical antipsychotics such as risperidone could be useful in attenuating stereotyped behaviors and not just locomotor activity. In the open field, grooming behavior also showed genotype and genotype interaction effects by treatment. Grooming is an activity of daily life linked to hygiene of animals but is also part of copying with stress strategies, and can be developed as a stereotyped behavior that gives and looks easily modified in anxious situations (Kalueff and Tuohimaa, 2004a, Kalueff and Tuohimaa, 2004b). Furthermore, the grooming is used experimentally as a tool to measure behavioral stimulation of D1 receptors (Rimondini et al., 1998) so that risperidone, as regards its antagonist action D1, could induce a decrease in this behavior. In this respect, in the 3xTg-AD mice, it was observed that the grooming behavior appeared later in time with respect to its NTg control, thus corroborating the genotypic differences in the anxious-like profile of these animals described in our laboratory (Giménez-Llort et al., 2006). In these previous studies with old male and female 3xTg-AD mice, the grooming behavior appears later than in the NTg mice and, in turn, aging reduces the duration (Giménez-Llort et al., 2008). Regarding the effect of the treatment, the effects of interaction with the genotype are due to a more frequent grooming behavior in the NTg (r) group of mice, although this selective difference replicates the existing one before treatment. In fact, work on strains of standard mice such as Swiss albino mice indicates that risperidone, at doses of 0.1 and 0.2 mg/kg, decreases the number of grooming (De Oliveira et al., 2008). Similarly, in the BTBR mouse model for autism, they have also observed that at doses of 0.125 and 0.25 mg/kg i.p. they reduce grooming by 40% to 50% with respect to their control, although the reduction in behavior can be confused with levels of sedation (Silverman et al., 2010).

Social interaction test. The SIT was found the most complete and sensitive tests to evaluate the deficits of social behavior among 3xTg-AD mice in comparison with those observed among NTg mice of the same age and sex (Torres-Lista and Giménez-Llort, 2019). Here, in the basal characterization before treatment, we replicated the results but, this time, evaluated within a behavioral battery. The 3xTg-AD mice showed results similar to those of the NTg animals in the most common social interaction behavior such as body-face contact. However, the genotype effects indicated less anogenital contact, greater vibrant tail, and absence of aggressiveness in groups of 3xTg-AD mice with respect to what was observed among NTg mice. Besides, the effect of chronic treatment with risperidone was evaluated in these behaviors since atypical antipsychotics are often chosen to treat BPSD symptoms, such as psychosis, aggression, and agitation. Risperidone exerted effects decreasing the anogenital behavior and in the case of the 3xTg-AD mice, it significantly corrected the preponderance of the vibrant behavior recently described as a characteristic of the social interaction pattern of female 3xTg-AD mice (Torres-Lista and Giménez-Llort, 2019). The effects of risperidone interacted with genotype in several variables of social behaviors studied, in such a way that the effects were more intense in the NTg genotype where risperidone decreased social behaviors, bringing them to levels equivalent to those 3xTg-AD groups.

Among the non-social behaviors that appear interspersed during the development of social interactions, the effects of the genotype were observed as a decrease in the horizontal and vertical exploratory activity in the groups of 3xTg-AD mice with respect to the NTg groups. In fact, the behavior of vibrant tail is associated with an immobility of the animal, so that the highest levels of this behavior in the 3xTg-AD mice justify that the exploratory activity, which usually is already lower in these animals, be significantly reduced.

The effects of risperidone were observed only in the variable number of burials, where the drug decreased this behavior, considered mimicking psychotic type stereotypies or obsessive-compulsive type anxiety. The improvement in this variable in both genotypes and the improvement also of the behavior of vibrant tail in the 3xTg-AD mice suggest that risperidone mainly exerted an antipsychotic/anxiolytic management effect, modifying the features of the anxious trait and/or anxious states, in both genotypes, respectively.

While the effects of atypical antipsychotics in exploratory activity and emotionality are discussed by the scientific community as mainly due to their dopaminergic actions, it is considered that the treatment with risperidone could modify the pattern of the social behavior thanks to its profile as a 5-HT2 antagonist, since these serotonergic receptors have been implicated in social interaction behavior (File and Seth, 2003). In a comparative study in APP/London mice, treatment with risperidone decreased its aggressive behavior and did so consistently to that exerted by 8-OH-DPAT and buspirone, two serotonergic agonists (Moechars et al., 1998). In other models for AD, such as the APP23 mice, treatment with risperidone also attenuates the aggressive behavior of animals (Vloeberghs et al., 2008) whereas in psychosis models, the deterioration of social interaction induced by PCP can be improved with anticholinesterase galantamine (0.3 mg/kg) and with 0.1 mg/kg of risperidone (Wang et al., 2007). Risperidone also corrects the aggression induced by social isolation in male ddY mice (Uchida et al., 2009) and the attack behavior in male albino mice, although it is not exempt from side effects at the level of motor behavior (Rodríguez-Arias et al., 1998). In our animal model, we observed spontaneous increase aggressiveness in 3xTg-AD mice[1]. However, in this study, the presence of this behavior in mice was very low or nonexistent, since it is spontaneous aggressiveness and not induced/enhanced by isolation (animals start from a daily social condition). Even so, the aggressiveness observed in the NTg (s) mice is corrected in the group treated with risperidone NTg (r). In the case of 3xTg-AD mice, it is likely that[1] the behavior of "vibrant tail" acts as a dissipating mechanism that temporarily attenuates the response of directed aggressiveness, with no "aggressiveness" observed.

T-maze. The spontaneous alternation in the TM is a paradigm mostly used to evaluate working memory, which also includes aspects such as exploratory activity and emotionality/anxiety. It is a test based on the possibility that the rodent chooses one of the arms arranged in a T-shape. Many brain areas, such as the hippocampus, septum, prefrontal cortex, and the basal forebrain, as well as several neurotransmitters, such as dopamine and norepinephrine, are involved in the implicit working memory involved in the performance of the test (Zhang et al., 2004; Deacon and Rawlins, 2006). Variables such as latency to cross the intersection of the maze allow, in addition, to assess the copying with stress strategies of animals, this being a variable that correlates with a worse neuroimmunoendocrine function, indicators of accelerated aging in mice, and premature death (Guayerbas et al., 2001). In our study, no differences were observed in the number of execution errors, but the efficiency to complete the different phases of the test was diminished in 3xTg-AD mice and slightly affected by risperidone. Thus, in phase 2 of the study, the genotype effects were observed in the emotionality as an increase in the presence of urine with respect to the NTg groups. Later, in phase 3, the variable latency to intersection and time to complete the maze denoted the deficiencies of the 3xTg-AD.

The effects of the treatment were only observed in phase 2, in which the groups treated with risperidone at the dose of 0.05 mg/kg needed more time to complete the exploration of the maze with respect to the groups that received saline. In addition, in the 3xTg-AD (r) mice, the time to complete the maze was also higher compared to that needed before treatment. The effects of the interaction between genotype and treatment were observed in phase 3 at the emotional level in both bowel movements and urine.

In our previous studies, we have observed that the latency to cross the intersection is a variable that reflects changes and subsequent deficiencies in the stress management strategies of animals and is related to the deterioration of the homeostasis of the neuroimmunoendocrine system, due to the age itself and, above all, in the presence of transgenes (Giménez-Llort et al., 2010; Giménez-Llort et al., 2012). In 6-month-old female 3xTg-AD mice, these changes are reflected as a greater speed to

[1]Ramírez-Boix, P., and Giménez-Llort, L. (submitted). Modeling BPSD in rodents: relevance of spontaneous aggressiveness and chronic mild social stress.

reach the intersection of the TM with respect to the controls in a typical flight behavior, while at later ages, the strategy fight-or-flight chosen to combat the acute stressful situation is the petrifaction (Giménez-Llort et al., 2010, Giménez-Llort et al., 2012). These observations agree with those of the reference laboratory that described this functional relationship in a longitudinal study with female OF-1 Swiss mice. Thus, De la Fuente's laboratory showed that the animals that spend more time in the TM show high levels of emotionality/anxiety and have a less competent immune system with respect to those that explore more quickly. In addition, the animals that showed lower performance in the TM showed a reduction in survival compared to those that obtained better results (Guayerbas et al., 2001).

The decrease of spontaneous alternation in the TM has also been observed in other transgenic models of AD such as Tg2576 (Lalonde et al., 2003) and APP/PS1 (Tempier et al., 2013) mice, in animal models for schizophrenia as STOP-null mice (Delotterie et al., 2010), or pharmacological models by selective blockade of dopamine D1 and D2 receptors in the pre-limbic region of the prefrontal cortex (Rinaldi et al., 2007). The effects of antipsychotics differ depending on the model, the drug, and the duration of treatment. Thus, in APP/PS1 mice, the chronic treatment with Quetiapine for 7 and/or 10 months normalized the anxiety-like behavior observed in the maze, minimized memory deterioration, and decreased Aβ plaques in the brain. In the STOP-null mice, treatment with risperidone only induced a trend to reduce the spontaneous alternation in the Y-maze (Delotterie et al., 2010). Other work in the radial maze has shown beneficial effects of olanzapine and clozapine on the memory impairment of male BALB/c mice, although they were not exempt from some extrapyramidal effects (Mutlu et al., 2012).

Together with the CT and the open field, the results in the TM provided new data to confirm the emotional/anxious-like profile of the 3xTg-AD mice and their worse capacity to cope with stress; however, it did not show problems in working memory as measured by spontaneous alternation. The chronic treatment with risperidone, in any case, worsened this AD-profile and the exploratory efficiency of NTg animals, probably due to the extrapyramidal effects. Still, being an atypical antipsychotic and administered in a low dose regime, it is considered that these side effects are much lower than in other classic antipsychotics.

Morris water maze. To evaluate short- and long-term spatial reference learning and memory, the MWM was used (Morris, 1981; Morris, 1984). All groups showed the same acquisition curve in either the "trial-by-trial" or the "day-by-day" analysis for short-term and long-term learning and memory, respectively. Likewise, in the probe trial with removal of the platform, all the groups distinguished the quadrant of the platform with respect to the other quadrants, although the risperidone treatment decreased the selective search of the platform incorporating one of the adjacent quadrants in the preference. The preference of this adjacent area indicates less focused goal-directed swimming strategies (Baeta-Corral and Giménez-Llort, 2015). The interaction between genotype and treatment in the preferences of the two adjacent quadrants indicated that the effects of risperidone affect the two genotypes differently, although in general these and the other data do not indicate deficiencies *per se* but rather changes in search strategies. Thus, as in the case of working memory, risperidone did not affect the results decisively since the animals continued to distinguish what had been the position of the platform. It should also be noted that the parity in the results of this test is surely conditioned by the fact of the previous knowledge of the paradigms since the genotype differences that were observed in the first experience in the water maze no longer exist among the saline groups. The latencies to reach the platform in the first trials were very low, equivalent to the third day of testing before treatment, supporting this interpretation. Here, it is important to remind that the analysis is based on a "before–after design" on censured data, that is, excluding the animals that died during phases 1, 2, and 3. Since the performance of the initial sample of animals was in agreement with the cognitive deficits described in this animal model at 12 months of age, the present results in the before–after analysis suggest a mortality bias, with exclusion of animals with worse life prognostic as determinant to the deficits in the overall group performance. Also, this suggests that the effects of risperidone illustrated here were those exerted in the "less worse" animals, as those that died during the behavioral assessments were excluded.

In some cases, in this mouse model, it has also been observed that the treatments, according to their pharmacological actions, selectively affect different aspects of the learning and memory process. This is the case of the study with 10-month-old 3xTg-AD mice in both sexes, where it was found that the chronic treatment of 5 months with paroxetine improved the deficit of the space navigation in both males and females, without affecting the speed of swimming or the distance traveled, which suggests a conservation of cognitive functions (Nelson et al., 2007). Likewise, studies with 12-month-old female 3xTg-AD mice treated with melatonin found that the treatment improved learning retention from platform position (García-Mesa et al., 2012). In APP/PS1 mice treated with quetiapine, the continuous administration of 4 to 7 months of the antipsychotic decreased the number of plaques of Aβ in the cortex and in the hippocampus of the animals and reduced memory loss, also attenuating the anxiety-like behavior (He et al., 2009). On the other hand, it has been described that olanzapine does not affect the processes of acquisition, consolidation, or recovery in the MWM test (Hou et al., 2006). However, the same work shows that clozapine and haloperidol appeared to affect the acquisition process and consolidation and induced a deterioration in spatial learning (Hou et al., 2006).

In fact, the effects of antipsychotics on learning and memory in processes that occur properly with psychosis are controversial, since there are studies in rats that have indicated that the classic antipsychotic haloperidol and the atypical antipsychotic risperidone, at certain doses, affect cognitive processes (Didriksen et al., 2007), while clozapine and sertindole were effective in the treatment of psychosis without producing detrimental effects on cognition (Mutlu et al., 2012). It is more than probable that these discrepancies in the pharmacological actions are due to the differences they present in the profile of pharmacological selectivity by different neurotransmission systems such as dopamine and serotonin. In this respect, risperidone is classified as a "qualitatively atypical" antipsychotic agent with a relatively low

incidence of extrapyramidal effects when given at low doses that have a serotonergic antagonist action higher than dopaminergic.

Marble burying test. The burial test for marbles, which is used for the detection of new antidepressants, anxiolytics, and antipsychotics (Njung'e and Handley, 1991; Bruins Slot et al., 2005 and Kaurav et al., 2012), was found sensitive to detect alterations in the 3xTg-AD mice (Torres-Lista et al., 2015). The response patterns were clearly different, since the level of interaction of the NTg mice with the marbles results in half of the objects being changed of position, while the other two quarters remained intact or have been buried. In the 3xTg-AD mice, the burying behavior is enhanced so that more than half of the objects appear buried at the end of the test, a quarter changed position, and only the remaining 10% remained intact.

The marble burying behavior of marbles was studied again to evaluate the effect of the antipsychotic. However, it is interesting to observe previously, in the results of the groups treated with saline, that the behavioral pattern described above for one and another genotype has been significantly modified by the protocol of chronic manipulation. In the NTg mice, the interaction with the objects increased, enhancing the burying of the marbles, which are now quantitatively equivalent to the marbles that changed position. In contrast, in 3xTg-AD mice, chronic saline treatment reduced the interaction with the objects, significantly decreasing the number of marbles buried in favor of the marbles that changed position. Taken together, these effects reduce genotype differences.

When all the factors are evaluated together, the observation of the absence of genotype effect is ratified. Risperidone increased the number of marbles intact and decreased the number of marbles buried with respect to the groups administered with saline, so, in general, risperidone reduced the interaction with objects. These results corroborate those observed in the burying/digging behavior during the SITs. Converging, differences were also found between genotypes with greater burying behavior in the 3xTg-AD mice, the genotype differences disappeared when studied during the treatment, and risperidone decreased burying behavior in the two groups. Although the burying/digging behavior that is evaluated during the SIT is not a behavior with respect to any object, the behavior is similar to that which is measured, in a more directed way, in the marble burying test.

Investigations with other mouse models such as male ICR treated with risperidone at a dose of 1 mg/kg, p.o. have observed that risperidone treatment is effective in reducing the number of buried marbles, although it also reduces locomotor activity (Matsushita et al., 2005). This effect is also shown in male BTBR mice (Gould et al., 2011) and in NIH Swiss male mice (Li et al., 2006). Likewise, in male NMRI mice, risperidone, at a dose of 0.16–0.63 mg/kg, significantly reduces marble behavior and locomotor activity, suggesting that the antagonist action of the drug 5-HT2A receptor may contribute to the effectiveness of the burying of marbles and having anxiolytic effect (Bruins Slot et al., 2005). According to these results, it can be said that risperidone, at a low dose without cataleptic effect, can effectively reduce the number of buried marbles (Bardin et al., 2006).

Glucose levels. Antipsychotic drugs can cause a variety of metabolic problems such as weight gain, hyperglycemia, lipid abnormalities, and development of type 2 diabetes. Given these serious health risks, FDA requested that antipsychotics of second generation such as clozapine, olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole should be labeled to indicate that they increase the risk of developing diabetes (Cope et al., 2009 and Savoy et al., 2010). In the case of increased vulnerability to higher mortality risk in AD induced by atypical antipsychotics, the metabolic syndrome has been hypothesized initially as one of the possible risk factors. Antipsychotics bind with high affinity to a wide variety of neurotransmitter and transporter receptors that could be involved in various metabolic effects; however, the underlying mechanisms are not entirely clear.

In the basal study, we evaluated baseline fasting glucose levels as well as ip glucose tolerance test (IPGTT) and we repeated the measurement of basal glucose levels, this time without fasting, after chronic treatment with risperidone. The glucose tolerance test was ignored because it also involves fasting in animals added to the normal fast in the light phase and the consequent loss of weight that, at these ages, could affect the survival curves of the animals.

As in the basal characterization phase, no genotype differences were observed during the treatment phase but genotype × treatment interaction effects. These effects resulted, however, from a significant decrease in glucose levels in the NTg (r) mice compared to those in the NTg (s) animals or when the glycemic values of the NTg (r) were compared longitudinally with those obtained before treatment. The results also agree with studies carried out in our laboratory with 3xTg-AD animals at 6 months of age in which we observed, in both sexes, that the basal levels of plasma glucose with and without fasting are normal, with the homeostasis of glucose being the one that is compromised in 3xTg-AD mice, although with aging, the genotype differences are lost (Giménez-Llort et al., 2010). Studies in male C57BL/6 mice administered with risperidone showed a slight increase in blood glucose levels, but only at a low dose of the drug (Dwyer and Donohoe, 2003), while other more recent studies, with males FVB/N mice, observed a significant reduction of plasma glucose (-30%) through the induction of insulin release (Savoy et al., 2010).

Body weight curves. The results on weight in patients with AD treated with antipsychotics are somewhat contradictory since there are studies that indicate that the administration of risperidone, olanzapine, or quetiapine at low doses is not associated with weight gain (Rondanelli et al., 2006). However, other research indicates that the use of olanzapine and quetiapine significantly increases weight in women and modifies cholesterol levels (Zheng et al., 2009). At the experimental level, weight measurements are a good indicator of the health status of the animal. In addition, in this study, we can evaluate the possible effect of chronic treatment with risperidone in this variable, in addition to the fact that weight is required to administer the correct dose of treatment.

For these reasons, it was decided to make a longitudinal follow-up of the weight from the beginning of the experimental process to the end of the mice's life. According to our own data, higher BW was found in the 3xTg-AD mice (Giménez-Llort et al., 2007), and as they advanced in age, these differences were attenuated. Risperidone produced a weight loss only in 3xTg-AD

mice, while groups of NTg mice maintained their BW. In the final stages of the animal's life, an acute weight loss was observed and this, immediately after the death, was found to be diminished in the four experimental groups, although the process of cachexia and the dehydration intrinsic to the death process make the data to lose accuracy. Previous studies with 6-month-old 3xTg-AD mice (males and females) have observed a decrease in the weight curve only in the group of females in potentially stressful situations (Giménez-Llort et al., 2010). This could be because they are more sensitive to repeated handling or the exposure of behavioral tests; however, it cannot be stated to what extent weight loss can be associated with emotional reactivity.

Several studies suggest that weight reduction may be associated with decreased activity but depending on the doses administered. Some authors have shown a relationship of the neuroleptic effects of olanzapine, ziprasidone, and risperidone with the decrease in food intake, the reduction of body mass, and motor activity since these changes are only present in wild-type mice but not in D2R knockout mice (Yoon et al., 2010). However, treatment with risperidone 4 mg/kg p.o. in female C57BL/6J mice of 12 weeks of age induces an increase in food consumption, the corresponding weight gain, an increase in body temperature during the light phase, and a reduction in the activity during the dark phase (Cope et al., 2009).

Life expectancy and survival. Treatment with atypical antipsychotics may double the risk of mortality in elderly patients with dementia, although this risk is similar to or even lower than antipsychotics. The increase in risk is faster in antipsychotic treatment and does not seem to be related either to the dose or to the type of substance (Vilalta-Franch et al., 2008). Recent studies have indicated that patients with dementia and prescription antipsychotics such as thioridazine, chlorpromazine, haloperidol, trifluoperazine, and risperidone to treat neuropsychiatric symptoms increased the long term risk. The most pronounced difference will be between 24 and 36 months after the start of treatment (Ballard et al., 2009; Kales et al., 2012). In addition, on other mental pathologies such as bipolar disorder in the elderly patient, risperidone has a higher incidence of mortality associated as compared to quetiapine (Bhalerao et al., 2012).

Our longitudinal study replicates the increased mortality described in male 3xTg-AD mice as compared to age-matched NTg mice by our laboratory (Giménez-Llort et al., 2008) and demonstrates that this animal can model the vulnerability to increased mortality risk associated with risperidone in the human patients. Thus, the group of NTg (s) mice maintained their survival intact until 19 months of age, while the start of mortality was during 15 months of age for the groups of NTg (r), 3xTg-AD (s), and 3xTg-AD (r). In previous studies with 15-month-old males 3xTg-AD and NTg mice, the increase in mortality, evaluated from 6 to 15 months of age, was 40%. In the present study, at the same age, the percentage was 15% since survival was recorded from 12 months and, therefore, mortalities that occurred earlier (i.e., from 6 months of age) were not counted (Giménez-Llort et al., 2008). Increased mortality in 10–20-month-old male 3xTg-AD mice as compared to B6129F2 wild-type controls has also been found by other laboratories and shown to be accompanied by elevated frailty scores (Kane et al., 2018).

The total life expectancy, the mean life expectancy, and the life expectancy with a lifespan of 25% showed the predominant effects of the genotype, but also the effect of risperidone in the range of ages below. Therefore, although the survival curves in the mice treated with risperidone and saline showed similar slopes in the four experimental groups, the initial vulnerability and from the mean life expectancy determined important changes in the maximum survival recorded. In NTg mice, this maximum was reduced by 8 months with the risperidone treatment (from 36 to 28 months), and in groups of 3xTg-AD mice, the maximum survival was reduced by 2 months (from 24 to 22 months). The data suggest, in addition, that risperidone exerted deleterious effects in NTg animals that equaled them in vulnerability to animals with 3xTg-AD genotype. This deleterious effect of risperidone in NTg animals was mainly observable between 15 and 17 months of age, although it reappeared in the age ranges corresponding to their half-life expectancy (24 and 25 months, respectively) and the difference persisted until the end of the curve.

The behavioral correlates for survival pointed out variables and tests related to the BPSD-like phenotype, in agreement with the neuroimmunoendocrine hypothesis (Giménez-Llort et al., 2014) pointing at sex-specific neuroimmunoendocrine aging in 3xTg-AD mice and its relation with longevity (Giménez-Llort et al., 2008). The crosstalk refers to the oxi-inflamaging theory developed in PAM and NPAM mice where the divergence of the speed of the aging process (premature in PAM and normal in NPAM) was correlated with immune function, oxidative stress, and worse/better copying with stress strategies in the TM (Guayerbas et al., 2001). While neophobia and worse long-term memory were found to be correlated with reduced survival in female NTg and 3xTg-AD mice (Torres-Lista et al., 2017), it was surprising that memory variables did not correlate with survival in the present work, probably due to the mortality bias, as discussed above. Thus, this was probably because the impairment was less pronounced in the current male sample, as correlation was only found with the level of optimization of the performance (day 4) in the water maze. Interestingly, the effects of risperidone on social behaviors in the NTg mice were the ones to correlate with survival, with faster body/face interaction and delayed elicitation of vibrating tail being correlated with longer longevity of NTg (r) animals, but also when the whole sample of animals was considered. This is important to note, since, to our knowledge, it is the first time that social behavior is being related to lifespan.

Risperidone is mainly metabolized in the liver (Mannens et al., 1993 and Zhou et al., 2006) by the enzyme cytochrome P-450 2D6 (CYP2D6), which has more than 20 genetic polymorphisms (Leysen et al., 1988; Mannens et al., 1993 and Matsubara et al., 2007). Whether biological aspects related to the individual variability in drug metabolism either by polymorphisms or by hepatomegaly (Marchese et al., 2014) explain the increased mortality risk remains to be elucidated.

In summary, in this longitudinal study, the effects of the chronic administration of risperidone on cognition and BPSD-like (motor, NPS, emotional, and social) symptoms were evaluated in male 3xTg-AD and NTg mice, as well as the short- and long-term impact on their survival. It was observed that the factors "genotype," "treatment," and "genotype ×

treatment" interaction effects were present in most of the behaviors studied, such as decreased neophobia, and improved the development of exploratory activity in the open field in NTg mice but had a weak effect on these variables in the 3xTg-AD mice model. Risperidone was effective in reducing the number of marbles buried in the groups of mice that received antipsychotics with respect to the groups that were given saline. The study replicated, in 3xTg-AD mice, the increased mortality risk associated to risperidone observed at a clinical level in humans. Thus, despite the fact that risperidone allowed to modify the alterations shown by the 3xTg-AD mice in their interaction with congeners (social behavior) or environment (burying behavior of marbles), it exerted negative effects by reducing the vertical and horizontal exploratory activity in the tests. What is more relevant, chronic treatment with risperidone severely compromised the life expectancy of the animals already since the beginning of treatment as shown by early mortality windows. The impact of this mortality on the analysis of "before–after treatment" effects on the censured data is relevant to note since it further suggests that the reported effects are those exerted in the "less worse" animals, that is, those that are able to survive during the period of behavioral assessment. In the same way, risperidone exerted especially severe effects in the old NTg animals, also modeling, at the experimental level, the window of early vulnerability described for the adverse effects of cerebrovascular risk in the elderly treated with atypical antipsychotics. The results support the awareness on the use of risperidone and the associated increased risk of mortality in AD, which suggests the relevance of the dosage (dose and treatment period) and that this treatment has to be used in short-term schedules to address the symptoms that cause morbidity and pain in the patient and to diminish the potential of self-hurt. The decision to use atypical antipsychotics should be based on the patient's medical history and both the benefit and the risk of treatment. At the translational level, the 3xTg-AD mice model and their NTg counterparts can be useful to delimitate critical time windows and for studying the physio-pathogenic factors and underlying causal events involved in this topic of considerable public health significance.

DATA AVAILABILITY

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

The animal study was reviewed and approved by the protocol CEEAH 2481/ DMAH 8700 entitled "Risk factors and preventive/ therapeutical strategies in Alzheimer's disease: studies in triple-transgenic 3xTg-AD mice" and was approved by Departament de Medi Ambient i Habitatge, Generalitat de Catalunya.

AUTHOR CONTRIBUTIONS

Development of the concept and study design: LG-L. Financial resources: LG-L and SL-P. Treatment: LG-L and VT-L. Behavioral studies and data collection: VT-L. Data analysis: VT-L. Data interpretation: VT-L and LG-L. Scientific discussions: VT-L, SL-P, LG-L. Drafting manuscript: VT-L and LG-L. Critical revision of manuscript: VT-L, SL-P, LG-L. Approving final version of manuscript: VT-L, SL-P and LG-L.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2019.01061/full#supplementary-material

TABLE S1 | Genotype effects in the behavioral phenotype before treatment. Statistics: Student t-test, 3xTg-AD vs. NTg (n=46), *p<.05, **p<.01, ***p<0.001.

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Effects of the Novel IDO Inhibitor DWG-1036 on the Behavior of Male and Female 3xTg-AD Mice

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The kynurenine pathway metabolizes tryptophan into nicotinamide adenine dinucleotide, producing a number of intermediary metabolites, including 3-hydroxy kynurenine and quinolinic acid, which are involved in the neurodegenerative mechanisms that underlie Alzheimer's disease (AD). Indolamine 2,3-dioxygenase (IDO), the first and rate-limiting enzyme of this pathway, is increased in AD, and it has been hypothesized that blocking this enzyme may slow the progression of AD. In this study, we treated male and female 3xTg-AD and wild-type mice with the novel IDO inhibitor DWG-1036 (80 mg/kg) or vehicle (distilled water) from 2 to 6 months of age and then tested them in a battery of behavioral tests that measured spatial learning and memory (Barnes maze), working memory (trace fear conditioning), motor coordination and learning (rotarod), anxiety (elevated plus maze), and depression (tail suspension test). The 3xTg-AD mice treated with DWG-1036 showed better memory in the trace fear conditioning task and significant improvements in learning but poorer spatial memory in the Barnes maze. DWG-1036 treatment also ameliorated the behaviors associated with increased anxiety in the elevated plus maze and depression-like behaviors in the tail suspension test in 3xTg-AD mice. However, the effects of DWG-1036 treatment on the behavioral tasks were variable, and sex differences were apparent. In addition, high doses of DWG-1036 resulted in reduced body weight, particularly in females. Taken together, our results suggest that the kynurenine pathway is a promising target for treating AD, but more work is needed to determine the effective compounds, examine sex differences, and understand the side effects of the compounds.

Keywords: Alzheimer's disease, kynurenine pathway, quinolinic acid, behavior, mouse models, novel therapeutic

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INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that results in synaptic dysfunction and cerebral atrophy (Marcello et al., 2012; Pini et al., 2016). Behavioral consequences of AD include memory loss and dementia, accompanied by motor deficits and mood disorders, such as anxiety and depression (Lyketsos et al., 2011; Albers et al., 2015; Scheltens et al., 2016). Although the exact causes of AD are unknown, amyloid beta (Aβ) plaques and neurofibrillary tangles of tau protein have been identified as the neuropathological hallmarks of the disease (Glenner and Wong 1984; Stelzmann et al., 1995; Chong et al., 2018). The amyloid cascade hypothesis postulates that

increased $A\beta_{42}$ in the brain initiates a cascade of neurological deficits that cause the cognitive and behavioral symptoms associated with AD (Hardy and Allsop, 1991; Selkoe, 1991; Selkoe and Hardy, 2016). Oxidative stress, immune deficiencies, and glial dysfunction may also contribute to the progression of AD (Gella and Durany, 2009; Zhao et al., 2013; Heppner et al., 2015; Jain et al., 2015). However, the relationship between these proposed disease mechanisms, their temporal pattern of development, and their contributions to specific neurobehavioral deficits remain unclear.

Treatments for AD have focused on preventing the loss of acetylcholine and glutamate neurotransmitter functions (Francis, 2005; Kandimalla and Reddy, 2017). The cholinergic theory is based on the early degeneration of forebrain cholinergic neurons in AD patients, resulting in decreased acetylcholine levels at synapses (Francis et al., 1999). Drugs such as donepezil and galantamine function as cholinesterase inhibitors to decrease acetylcholine breakdown (Birks, 2006). Memantine targets glutamatergic transmission by blocking NMDA receptors to decrease excitotoxicity (Molinuevo et al., 2005; Olivares et al., 2012). Other neurotransmitter systems such as dopamine (Martorana and Koch, 2014; Nobili et al., 2017) and serotonin (Li et al., 2017; Vakalopoulos, 2017) may be involved in the progression of AD. There is also growing evidence that tryptophan is involved in the pathogenesis of AD independently of its role as the serotonin precursor.

Tryptophan is involved in neurotransmission, immune function, and kynurenine synthesis (Moffett and Namboodiri, 2003; Ruddick et al., 2006), and 95% of the tryptophan in the body is metabolized through the kynurenine pathway (KP; Soliman et al., 2010). As shown in **Figure 1**, a cascade of enzymes converts tryptophan to nicotinamide adenine dinucleotide (NAD). Although the activity of the KP is necessary for tryptophan homeostasis, immune system regulation, and NAD synthesis, overactivity of the KP is associated with neurodegenerative disorders, including Parkinson's disease (Havelund et al., 2017), Huntington's disease (Mazarei and Leavitt, 2015), multiple sclerosis (Rejdak et al., 2002), amyotrophic lateral sclerosis (Guillemin et al., 2005b), and AD (Widner et al., 2000; Bonda et al., 2010; Gulaj et al., 2010; Campbell et al., 2014; Maddison and Giorgini, 2015). Research on the relationship between the KP and neurodegenerative diseases has focused on the neuroactive metabolites of tryptophan catabolism (Schwarcz and Stone, 2017). Of these, 3-hydroxy kynurenine (3-HK) and quinolinic acid (QA) are neurotoxic, whereas kynurenic acid (KA) and picolinic acid (PA) are protective (Urenjak and Obrenovitch, 2000; Lovelace et al., 2017).

Indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO) are the first and rate-limiting enzymes of the KP (Munn et al., 1998; Moon et al., 2015) and are responsible for metabolizing tryptophan into N-formyl-kynurenine, which is broken down to form 3-HK and QA, the two neurotoxic metabolites of the KP (Chen and Guillemin, 2010). 3-HK increases oxidative stress (Mackay et al., 2006), which can exacerbate neurodegeneration and contribute to AD pathogenesis (Zhao et al., 2013; Wang et al., 2014). QA, which is only synthesized by microglia in the brain, is an N-methyl-D-aspartate (NMDA) agonist that can increase excitotoxicity (de Carvalho et al., 1996; Guillemin, 2012). Because QA is also involved in tau phosphorylation (Crowley et al., 1992; Rahman et al., 2009), it could increase neuronal and synaptic dysfunction (Dubal, 2018; Tracy and Gan, 2018). The neuroprotective properties of KA are caused by its function as an antagonist at NMDA receptors (Albuquerque and Schwarcz, 2013), hence it can decrease the excitotoxicity caused by QA. KA is also an antagonist at alpha-7 ($\alpha 7$) nicotinic receptors, reducing the endocytosis of $A\beta_{42}$ (Nagele et al., 2002; Hernandez and Dineley, 2012). However, significantly less KA is produced relative to 3-HK and QA (Moroni et al., 2007). PA has protective effects because it enhances immune function (Grant et al., 2009).

IDO gene expression is stimulated by interferon gamma (INF-ɣ, Taylor and Feng, 1991; Jurgens et al., 2009) and by $A\beta_{42}$ (Guillemin et al., 2003). IDO levels are increased in the hippocampus of AD patients (Guillemin et al., 2005a), and INF-ɣ and IDO levels are increased in the cerebrum of female triple transgenic mice (3xTg-AD), a commonly used model of AD (Fertan et al., 2019a). Thus, overactivity of IDO in the KP may integrate the various mechanisms involved in the pathogenesis of AD, leading to neuronal loss and behavioral deficits. These include increases in $A\beta_{42}$ levels, tau phosphorylation, immune dysfunction, and oxidative stress. On the other hand, the role of TDO in AD pathogenesis is unclear. Unlike the universal expression profile of IDO, TDO is mostly found in the liver (Dale et al., 2000), yet it has been measured in the frontal cortex of individuals with schizophrenia (Miller et al., 2004) and mouse brains at different levels during development (Kanai et al., 2009). Unlike IDO, TDO has not been shown to be regulated by inflammatory cytokines or Aβ42; however, the expression levels are increased by glucocorticoids (Green et al., 1975; Nakamura et al., 1987). Wu et al. (2013) showed significantly elevated levels of TDO in the cerebellum, but not cerebrum, of 3xTg-AD mice and hippocampi of humans with AD. Because 3-HK is increased in the serum (Schwarz et al., 2013) and QA is increased in the hippocampus of AD patients (Guillemin et al., 2005a) as well as 3xTg-AD mice (Fertan et al., 2019a), the KP may be a worthy target for AD treatment (**Figure 1**). There is evidence that reducing KP activity can ameliorate some of the symptoms of AD in animal models (Vamos et al., 2009; Zwilling et al., 2011; Yu et al., 2014; Deora et al., 2017).

In the current study, we tested the ability of a novel inhibitor of IDO and TDO (DWG-1036) to reverse the behavioral deficits seen in the 3xTg-AD mice. These mice were engineered by injecting APP_{Swe} and tau_{P301L} transgenes into single-cell embryos of homozygous $PS1_{M146V}$ knock-in mice, causing an increase in $A\beta_{42}$ and tau phosphorylation (Oddo et al., 2003b). Interneuronal amyloid aggregation in the frontal cortex and the hippocampus starts around 2 months of age in these mice, and plaque accumulation accompanied by neuroinflammation is observed at 6 months of age, with tau tangles at 12 months of age (Oddo et al., 2003a; Belfiore et al., 2019). Working memory deficits in the 3xTg-AD mice in the eight-arm radial maze have been shown at 2 months of age (Stevens and Brown, 2015), and spatial memory deficits in the Barnes maze have been shown at 6 months of age (Stover et al., 2015a, Stover et al., 2015b). Increased anxiety and depression-like behaviors have also been shown

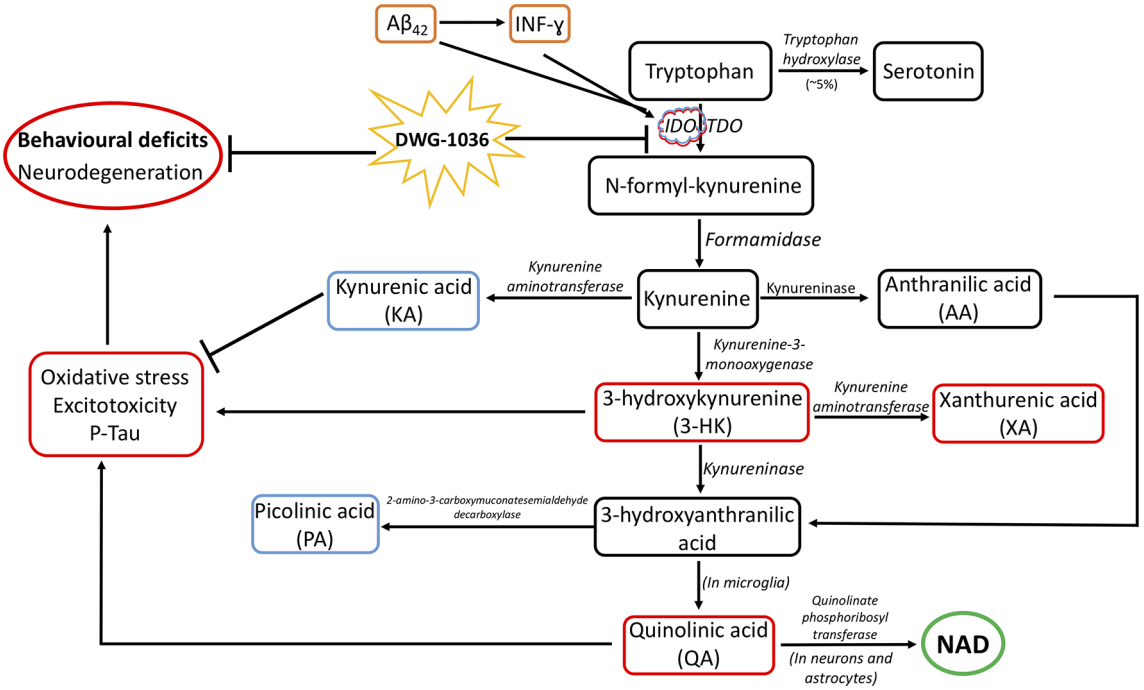

FIGURE 1 | The kynurenine pathway (KP) and its suggested role in Alzheimer's disease (AD) pathogenesis. Although 5% of tryptophan is converted to serotonin by tryptophan hydroxylase, the remainder gets metabolized by the KP. Indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO) are the rate-limiting enzymes of the KP, which metabolize tryptophan to N-formyl-kynurenine, which is further metabolized into kynurenine, 3-hydroxykynurenine (3-HK), 3-hydroxyanthranilic acid, quinolinic acid (QA), and eventually, nicotinamide adenine dinucleotide (NAD). Kynurenine is converted to anthranilic acid and kynurenic acid, which is neuroprotective. 3-Hydroxykynurenine is neurotoxic and can be converted to xanthurenic acid. 3-Hydroxyanthranilic acid is converted to picolinic acid, which is neuroprotective, whereas QA is neurotoxic (Chen and Guillemin, 2010; Schwarcz and Stone, 2017). The involvement of the KP in AD pathogenesis is caused by the elevation of IDO by amyloid beta 42 ($A\beta_{42}$) and interferon gamma (INF-γ), resulting in neurodegeneration and the cognitive and behavioral deficits shown in AD. It is proposed that the IDO inhibitor DWG-1036 will act to reduce the neurobehavioral deficits seen in AD. RED = neurodegenerative processes; BLUE = neuroprotective processes.

in the 3xTg-AD mice by 7 months of age (Romano et al., 2014; Zhang et al., 2016; Nie et al., 2017). However, these mice show better motor performance on the rotarod than wild-type (WT) controls (Stover et al., 2015a; Garvock-de Montbrun et al., 2019). In this study, male and female 3xTg-AD and WT mice were treated with DWG-1036 from 2 to 6 months of age and then tested in a behavioral test battery that measured spatial learning and memory, working memory, motor coordination and learning, anxiety, and depression. We hypothesized that DWG-1036 would decrease or reverse the behavioral deficits observed in the 3xTg-AD mice.

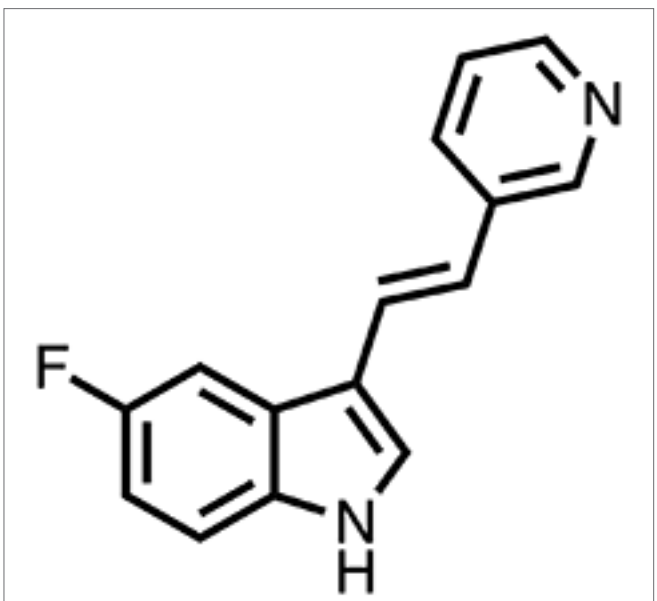

FIGURE 2 | The molecular structure of DWG-1036. The chemical formula of the compound is $C_{15}H_{11}FN_2$, and the molecular weight is 238.265 g/mol.

METHODS

DWG-1036 Synthesis and Pharmacokinetics

DWG-1036 ($C_{15}H_{11}FN_2$) is a synthetic IDO inhibitor **(Figure 2)**, developed by Dr. Donald F. Weaver's group at the Krembil Research Institute in Toronto, Canada, using the following procedure: A 500 mL round-bottom flask was charged with the 3-pyridylacetic acid (HCl salt, 13.7 g, 78 mmol), then anhydrous 1,4-dioxane (200 mL) was added. Triethylamine (28 mL, 200 mmol) was added

dropwise at room temperature, and the mixture was stirred for 30 min. 5-Fluoroindole-3-carboxaldehyde (10.9 g, 66.8 mmol) was then added, followed by piperidine (14.5 mL, 147 mmol). The reaction mixture was heated at 110°C for 18 h. The reaction mixture was cooled to room temperature, and an additional aliquot of 3-pyridyl-acetic acid (HCl salt, 2.32 g, 13.4 mmol) and piperidine (1.3 mL, 13.4 mmol) was added. The reaction mixture was heated at 110°C for an additional 18 h. The reaction mixture was cooled to room temperature and then partitioned between aqueous ammonium chloride (100 mL) and ethyl acetate (200 mL). The organic fraction was separated and then washed with brine (50 mL) and dried with anhydrous Na_2SO_4. After filtration, silica gel was added, and the solution was concentrated *in vacuo*. Automated flash column chromatography (100:0 to 1:1 hexanes:ethyl acetate gradient) afforded 12.5 g of the desired product. The free base was suspended in water (1 mL per 20 mg of compound); 5% aqueous HCl was added slowly until most of the suspended material had dissolved. The reaction mixture was filtered and then concentrated *via* lyophilization to provide 11.3 g of the desired product as a bright yellow solid (HCl salt, 62% yield). HPLC purity analysis was carried out using a Waters 1525EF Binary pump system equipped with a dual wavelength absorbance detector (254 nm, 280 nm) and a manual injector. The stationary phase consisted of a Silicycle Silia Chrom SB C18 column (250 × 4.6 mm), and the mobile phase used water (0.1% trifluoroacetic acid) and acetonitrile (0.1% trifluoroacetic acid) at the following gradient system, eluting at 1 mL/min: 80% H_2O/20% CH_3CN for 1 min, then a linear ramp to 5% H_2O/95% CH_3CN over 7 min, hold at 5% H_2O/95% CH_3CN for 4 min, and then return to a linear ramp to 80% H_2O/20% CH_3CN for 3 min.

The IC_{50} value for IDO was determined to be 80 μM using the enzymatic *in vitro* assay of Takikawa et al. (1988) and 7 μM in a cell-based assay. The IC_{50} value of DWG-1036 for TDO was determined as 9.7 μM. As measured in pilot studies (data not shown), DWG-1036 was detectable (μ = 59, 198 ng/mL) in the brain of the WT (B6129SF2/J) mice 15 min after administration *via* oral gavage and reached the highest levels (μ = 69,753) in 30 min. The half-life of DWG-1036 was calculated as 1.24 h, the area under the curve (AUC) from 0 to last measured point (AUC0–last) was 138,652 ng.h/mL. The AUC for 0 to infinity was (AUC0-∞) 138,760 ng.h/mL, and the mean residence time (MRT) was 1.79 h.

DWG-1036 Tolerability Testing

To determine any side effects or dose by genotype interactions of DWG-1036, a tolerability study was performed prior to treatment and behavioral testing. Eight wild-type and two 3xTg-AD mice at 2 months of age were treated with distilled water (vehicle) or 30, 60, or 80 mg/kg of DWG-1036 once a day or with 80 mg/kg of DWG-1036 twice a day for 25 days. Body weights of the mice were recorded every day before treatment and compared with a generalized linear mixed model regression analysis. All of the procedures and experimental techniques used in the tolerability study were approved by the Dalhousie University Council of Animal Ethics (16-016).

There were significant differences in body weight between treatment groups over days as the models including the effect of treatment type ($AIC_{Treatment}$ = 728.64, LH = 18.625, $p < 0.005$), day (AIC_{Day} = 734.10, LH = 66.079, $p < 0.005$), and the treatment by day interaction ($AIC_{Treatment:Day}$ = 757.57, LH = 226.85, $p < 0.005$) differed significantly from the null model (AIC_{Null} = 716.02). Although the weights of the mice receiving the vehicle increased over the 25-day period, mice receiving 30 or 60 mg/kg of DWG-1036 did not gain weight. Mice receiving 80 mg/kg showed weight loss over the treatment period, and the mice receiving 80 mg/kg twice a day had to be removed from the study by day 15 because of excessive weight loss **(Figure 3)**. Based on these results, it was decided to use a dose of 80 mg/kg DWG-1036 once a day in the experiment.

Subjects

The study began with 41 3xTg-AD (23 female/18 male) and 52 B6129SF2/J wild-type control mice (30 female/22 male). Because of removal from the study for excessive weight loss, 34 3xTg-AD (19 female/15 male) and 37 B6129SF2/J wild-type control mice (16 female/21 male) completed behavioral testing **(Table 1).** All of the mice were born in-house from breeding pairs originally purchased from Jackson Laboratories in Bar Harbor, Maine (JAX stock: 34830). After weaning, the mice were housed in same sex groups of two to four in translucent polyethylene cages (13 × 30 × 15 cm) with wire food hoppers and micro-isolator filter lids in a climate-controlled (20 ± 2°C) vivarium on a reversed 12:12 h light/dark cycle with lights off at 10:00 am. The mice were fed Purina Laboratory Rodent Chow #5001 (Agribrand Purina, Strathroy, Ontario, Canada) and tap water *ad libitum*. A black polyethylene tube (4 cm diameter, 7.5 cm length) was placed in the cages for environmental enrichment. Cages were cleaned once a week. All of the procedures and experimental techniques used in this study were approved by the Dalhousie University Council of Animal Ethics (16-017).

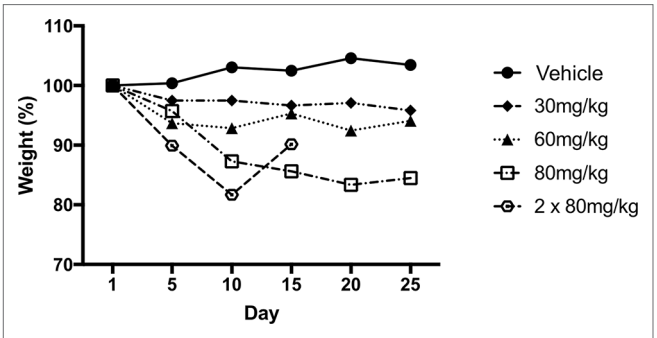

FIGURE 3 | Change in body weight (%) of mice over 25 days of receiving vehicle or 30, 60, or 80 mg/kg DWG-1036 once a day or 2 × 80 mg/kg each day. Body weights on day 1 were normalized to 100%.

TABLE 1 | Sample sizes for each group of mice.

B6129SF2/J (Wild type)		3xTg-AD	
DWG-1036	**Vehicle**	**DWG-1036**	**Vehicle**
11/11 males 5/19 females	11/11 males 10/11 females	8/10 males 11/15 females	7/8 males 8/8 females

The first number in each box represents the number of mice used in the behavioral tests. The second number indicates the starting sample sizes for each group. Due to excessive weight loss, some mice were removed from the study at different times during the treatment period.

Treatment

Treatment with DWG-1036 or vehicle (distilled water) started at 2 months of age and continued until the end of behavioral testing. Once a day (around 5 pm, which was at least an hour after behavior testing during that period), mice were weighed and then given a dose of 80 mg/kg DWG-1036 with an injection volume of 0.01 ml/g by oral gavage using 1-ml syringes and 22-gauge gavage needles covered with a flavored (pomegranate and strawberry) edible lubricant (Sliquid Swirl®). If a mouse lost more than 2 grams in weight in a 24-h period, no treatment was applied. Mice not receiving treatment for 5 days in a row or 10 days in total were removed from the study.

Behavioral Tests

Behavioral testing started when the mice were 6 months of age, and tests were given in the order listed below. Tests were conducted between 10.00 am and 4.00 pm each day in a specific test room. The experimenter was blind to the genotype and treatment condition of each mouse during behavioral testing.

Elevated Plus Maze

Mice were carried to a dark room, separated from the test room, in their home cages, with the water bottle removed. Then individual mice were carried to the elevated plus maze (EPM) in a clean plastic container while their cage mates remained in the holding room with *ad libitum* food and water. The EPM consisted of a plus-shaped maze with two open arms (30 × 5 cm) with a 4-mm lip to prevent the mouse from slipping off and two closed arms (30 × 5 cm) with transparent Plexiglas walls (15 cm high) located across from each other. The arms were connected by a center square (5 × 5 cm). The floor of the maze was black Plexiglas, and the walls of the closed arms were clear. Testing was completed in a room (2 × 5 m) illuminated by two 60-watt white light bulbs. Each mouse was tested on one 5-min trial, and between mice, the maze was cleaned with Sparkleen® solution. At the beginning of the trial, the mice were placed in the center square. A camera 2.1 m above the maze recorded the movement of the mice throughout the trial. The time in the open and closed arms and the distance traveled were analyzed with a computerized tracking system (EthoVision®, Noldus, Wageningen, The Netherlands). The frequency of freezing (remaining completely immobile except for respiration) bouts was recorded using a computerized tracking system (Limelight®, Actimetrics Inc., Wilmette, IL). According to O'Leary et al. (2013), the total distance traveled in the EPM is a measure of locomotion, whereas frequency of entering the closed arms and freezing are measures of anxiety.

Rotarod

The AccuRotor accelerating rotarod (Accuscan Instruments Inc., Columbus, Ohio), consisted of a 44-cm-long acrylic rod with a diameter of 3 cm, covered with rubber to provide better gripping. The rod was separated into four 11-cm sections by circular Plexiglas dividers (15 cm high), allowing four mice to be tested concurrently. There were separate holding chambers 39 cm beneath each section of the rod. The latency to fall from the rod was measured with electronic timers, which automatically stopped when the mouse touched the surface of the holding chamber. The rotarod was located in a 112 × 260 cm room, lit by a single 60-watt red light. Mice were gently held by their tails and placed on the floor of the holding chamber. Once all four mice were in the rotarod, they were placed on the rod, facing the opposite direction of the rotation as well as the experimenter. The maximum length of each trial was 360 s, and during the trial, the rod gradually accelerated from 0 to 48 rotations per min. After the last mouse fell from the rod, a 1-min break was given before starting the next trial. Mice completed six trials on the rotarod per day for 5 consecutive days. The rotarod was cleaned with soap and water after each group of mice completed a daily test session of six trials. The time to fall from the rotarod is a measure of motor coordination and learning (O'Leary et al., 2018).

Barnes Maze

The Barnes maze (BM) was a white polyethylene platform (122 cm diameter) elevated 48.4 cm from the floor with 16 holes (4.45 cm diameter) equally spaced around the perimeter 1.3 cm from the edge (O'Leary and Brown, 2012). Four of the holes (4, 8, 12, and 16) were capable of having a black plastic escape box beneath them. A buzzer (0–37.2 kHz, 89 dB) and two 150-watt flood lamps placed 155 cm above the maze were used as aversive stimuli. A polyvinyl-chloride tube (8 cm diameter, 12.5 cm height) was used to hold the mouse in the center of the maze until the trial began. A camera was mounted 1.7 m above the maze to record the trials. Mice were tested in groups of three to five, and each mouse in the group was assigned a specific escape hole location. There were five phases in the test procedure: habituation, acquisition training, acquisition probe, reversal training, and reversal probe (O'Leary and Brown, 2013). During the habituation phase, mice were placed in a 2-L glass beaker, which was inverted over the assigned escape hole. The mice were then free to explore the escape hole, escape box, and the adjacent area for 2 min. The acquisition training phase consisted of two trials per day for 15 days. On each trial, mice were placed in the center tube and after an interval of 5–10 s, the tube was lifted, and the buzzer was turned on. The mice were given 300 s to locate the escape hole, and if they did not enter the escape box within this time, they were led to the escape hole with a plastic cup that was used to transport the mice. The maze was cleaned between trials with Sparkleen® solution to prevent odor cues from developing around the escape holes. The measures of learning (latency to enter the escape hole, distance traveled, and average speed) were analyzed for each trial using Ethovision® (Noldus, Wageningen, The Netherlands). The number of errors (when a mouse dips its head into a hole that is not the escape hole) and correct head dips were recorded by the experimenter. Repeated head dips into the same hole were recorded as one head dip. The maze was rotated 90° between each group, and all escape holes and the escape box were cleaned to prevent the use of extraneous cues.

The day after acquisition training was completed, the mice were given a 5-min memory probe trial with the buzzer turned off. During this trial, the escape box was removed, and the maze was rotated 45° so that a non-escape hole was in the correct escape hole location. For analysis of spatial memory, the maze was divided into 16 pie-shaped zones, and the number of entries and time spent in each zone were recorded. The mice were then

given a 5-day reversal training phase with the escape hole moved to the opposite side of the maze followed by a reversal probe trial using the same procedure as during the acquisition probe trial. Measures of learning and memory were analyzed for the reversal test.

Tail Suspension Test

The tail suspension test (Med Associates, St. Albans, VT, USA) consisted of a box (32 × 33 × 33 cm) that was open on one side to allow an observer to view the subjects and for video recording. An aluminum strip (11.5 × 2.2 × 0.15 cm) was suspended vertically from a strain gauge within the enclosure, which the mouse was attached to by its tail with duct tape. After their weights were recorded, individual mice were placed on an upside-down cage located under the aluminum strip, and their tails were gently attached to the strip. Then the cage was slowly removed to allow the mice to hang from the strip by its tail. Mice were observed for immobility for one 6-min trial, which was recorded with a video camera. Testing was done in a quiet room lit by two 60-watt white light bulbs. At the end of the trial, the empty cage was placed under the mouse so it could stand on four feet without any pressure on the tail. Then the duct tape was removed to free the tail, and the mouse was carried back to its home cage. During the trial, frequency of immobility (lack of escape attempts) was analyzed as a measure of depression-like behavior (Can et al., 2012).

Trace Fear Conditioning

Trace fear conditioning and testing took place in two identical MED Associates Inc. (St. Albans, VT) fear conditioning chambers. The front, top, and back of the chamber were transparent Plexiglas, and the other two remaining were stainless steel. The floor of the chamber consisted of 36 3.2-mm stainless steel rods that were capable of delivering an electric shock. A speaker was attached to one of the stainless steel walls, and a video camera was mounted in front of one of the Plexiglas walls to record the behavior of the mouse. The procedure consisted of a training and test phase, which took place on 2 consecutive days. During the training phase, mice were placed in the chamber, and their levels of baseline freezing were recorded for 774 s. During this time, five 80-dB tone cues lasting 15 s were presented with 130-s intervals. Each tone cue was followed by a 1-s 0.7-mA foot shock, delivered 30 s after the tone. Thirty seconds after the last shock, the mice were removed from the chamber and returned to their home cage, and the chamber was cleaned with Sparkleen® solution.

In the working memory test phase, mice were placed in the second chamber, a modified version of the chamber used during training, for 265 s. Black Plexiglas was placed over the floor of the chamber to cover the steel rods, the inside walls of the testing chamber were covered with black and white striped plastic, and a novel lemon odor was introduced into the chamber. The mice were then placed in this modified chamber, and their freezing time was recorded for 2 min, followed by a 15-s-long 80-dB tone identical to the one presented during training. After the tone, the duration of freezing was recorded for another 130 s as a measure of working memory (Gilmartin and Helmstetter, 2010; Raybuck and Lattal, 2014).

Statistical Analyses

Analysis of variance (ANOVA), generalized linear mixed model regressions, and chi-square tests were used to analyze the data. To deal with unequal sample sizes, a Type 2 calculation of sums of squares was used. Differences between individual groups were determined using 95% confidence intervals and indicated in the graphs using asterisks. "R: The R Project Statistical Computing®" version 3.5.2 (2018-12-20) - "Eggshell Igloo" was used for all of the statistical analyses, and the graphs were generated in "Graph Pad Prism VII®" using group means and standard errors (SEM). Data from each test were first analyzed for the existence of a sex difference. If there was a significant sex difference, the data were analyzed separately for each sex. If there was no significant sex difference, data were analyzed by pooling the sexes. Based on this criterion, sex differences were found in the Barnes maze probe trial total distance, freezing duration in trace fear conditioning, latency to fall from the rotarod, and freezing frequency in the elevated plus maze.

RESULTS

Mice Removed From the Study

Over the 4-month treatment period, 22 mice were removed from the study for showing significant weight loss **(Table 1)**. The removal rate differed significantly between the groups ($\chi^2(7) = 37.62$, $p < 0.001$). Only two mice receiving the vehicle lost weight during the treatment period, whereas 20 mice receiving DWG-1036 lost weight, 18 of which were female. Thus, there was a sex difference in the side effects of the treatment.

Elevated Plus Maze

Locomotion

The 3xTg-AD mice traveled a less distance on the EPM than WT mice ($F(1, 67) = 17.469$, $p < 0.001$), but there were no main effects of treatment ($F(1, 67) = 1.679$, $p > 0.05$) nor any significant interactions (all $p > 0.05$, **Figure 4A)**.

Open Arm Entry

The 3xTg-AD mice visited the open arms more than the WT mice ($F(1, 63) = 5.214$, $p < 0.05$), and this was decreased by DWG-1036 treatment, but not significantly ($F(1, 63) = 3.058$, $p = 0.09$). Overall, DWG-1036-treated mice visited the open arms less than the controls ($F(1, 63) = 6.614$, $p < 0.05$). There was also a significant genotype by sex interaction ($F(1, 63) = 9.063$, $p < 0.01$) because the female 3xTg-AD mice had lower frequencies of open arm entry than the female WT mice; however, the male 3xTg-AD mice had higher frequencies compared to the male WT mice **(Figure 4B).**

Freezing Frequency

For the male mice, there were no main effects of genotype ($F(1,34) = 2.584$, $p = 0.12$) or treatment condition ($F(1,34) = 0.266$, $p = 0.61$), but there was a genotype by treatment interaction ($F(1, 34) = 6.030$, $p < 0.05$), as the freezing frequency was decreased in 3xTg-AD mice treated with DWG-1036 and increased in the WT controls **(Figure 4C)**.

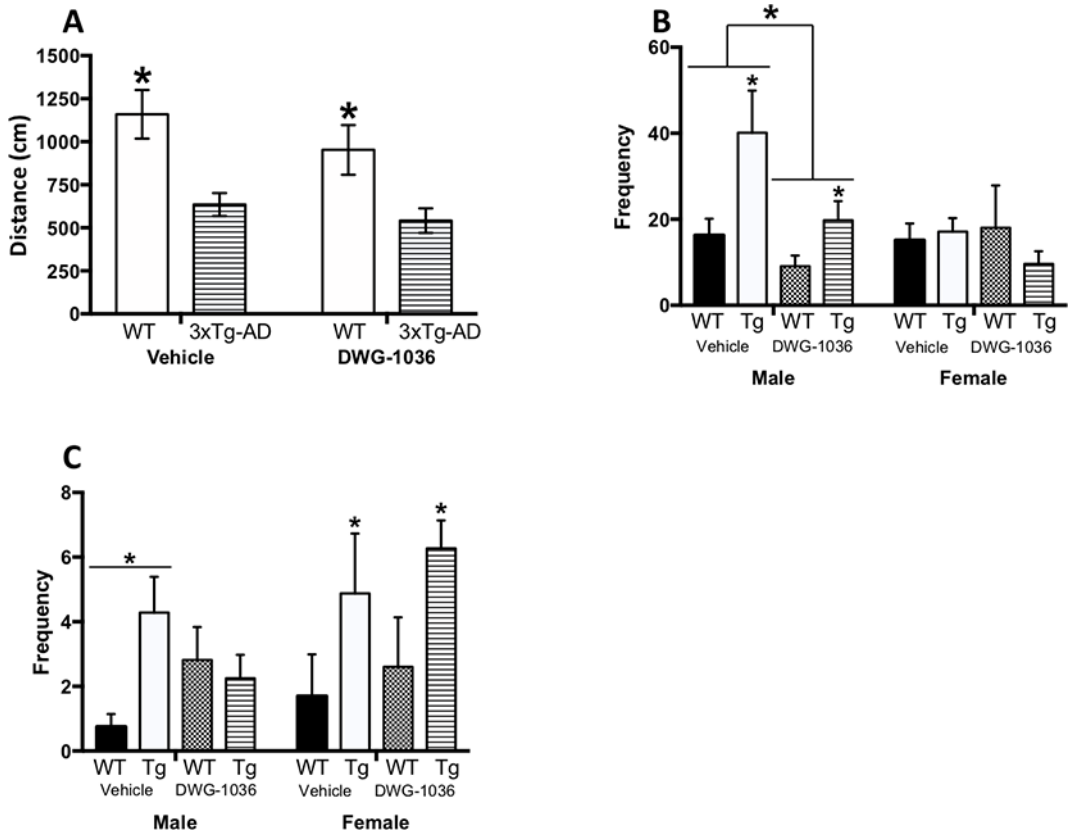

FIGURE 4 | Performance of male and female wild-type (WT) and 3xTg-AD mice given vehicle or DWG-1036 on the elevated plus maze. **(A)** Mean (±SEM) distance (in centimeters) traveled by the mice, a measure of locomotor behavior. **(B)** Mean (+SEM) frequency of visiting the open arms, a measure of reduced anxiety. **(C)** Mean (+SEM) frequency of freezing behavior, a measure of anxiety. *'s are used to present individual group differences determined by 95% confidence intervals.

For the females, there was a genotype difference ($F(1,30) = 5.946$, $p < 0.05$) because the 3xTg-AD mice froze more frequently than the WT control mice, but there was no difference between the treatment conditions ($F(1,30) = 0.739$, $p = 0.40$, **Figure 4C**).

Rotarod

For the male mice, models including test day ($AIC_{Day} = 1632.7$, $LH = 39.95$, $p < 0.005$) and genotype by treatment by day interaction ($AIC_{Genotype:Treatment:Day} = 1609.7$, $LH = 12.06$, $p < 0.05$) differed significantly from the null model ($AIC_{null} = 1600.7$). Although all of the mice improved over the 5-day test period, the DWG-1036-treated male WT mice showed the greatest improvement (**Figure 5A**).

For the female mice, models including test day ($AIC_{Day} = 1759.1$, $LH = 49.26$, $p < 0.005$), genotype ($AIC_{Genotype} = 1722.2$, $LH = 6.35$, $p < 0.05$), and genotype by day interaction ($AIC_{Genotype:Day} = 1721.5$, $LH = 28.91$, $p < 0.005$) differed significantly from the null model ($AIC_{null} = 1717.8$). The 3xTg-AD females had longer latencies to fall from the rod compared to the WT mice, and they improved more over the 5-day period **(Figure 5B)**. There were no significant drug treatment effects or interactions

Barnes Maze

Acquisition Latency

Models including the effect of day ($AIC_{Day} = 25448$, $LH = 327.89$, $p < 0.005$), the genotype by day interaction ($AIC_{Genotype:Day} = 25151$, $LH = 44.614$, $p < 0.005$), and the genotype by treatment by day interaction ($AIC_{Genotype:Treatment:Day} = 25135$, $LH = 27.397$, $p < 0.05$) differed significantly from the null model ($AIC_{null} = 25148$). Overall, all mice reduced their latencies to find the escape hole over the 15-day period, and the 3xTg-AD mice treated with DWG-1036 showed a greater reduction than the other groups **(Figures 6A)**.

Acquisition Errors

Models including day ($AIC_{Day} = 14525$, $LH = 383.81$, $p < 0.005$), genotype ($AIC_{Genotype} = 14178$, $LH = 14.94$, $p < 0.005$), and a genotype by day interaction ($AIC_{Genotype:Day} = 14181$, $LH = 31.261$, $p = 0.005$) differed significantly from the null model ($AIC_{null} = 14169$). Although all mice decreased their number of errors over the 15-day period, the decrease was greater for the WT mice than the 3xTg-AD mice, and there was no significant effect of DWG-1036 **(Figures 6B)**.

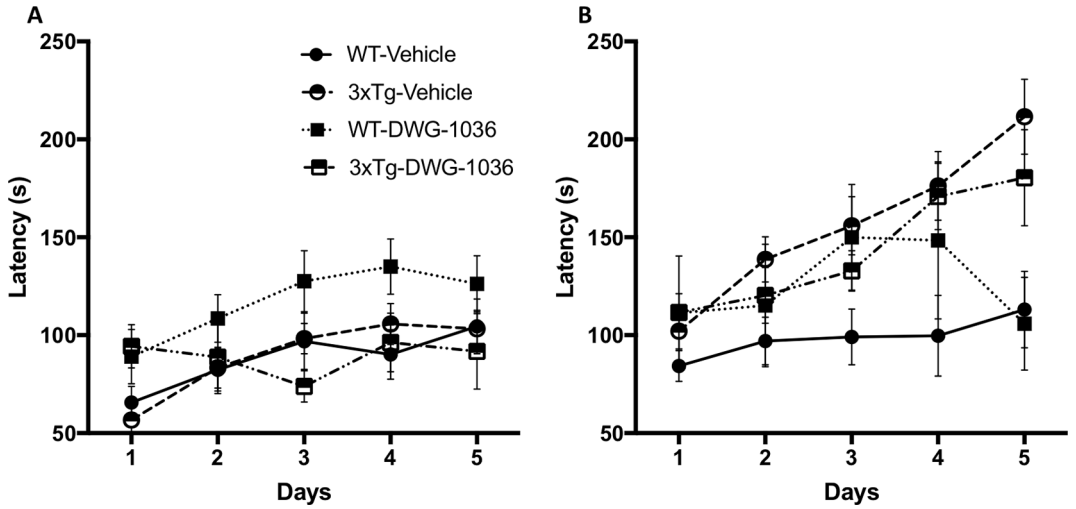

FIGURE 5 | Mean (± SEM) latency (in seconds) to fall from the rotarod on each of the days for **(A)** male and **(B)** female mice in each treatment group. The rotarod was used to measure motor learning and coordination.

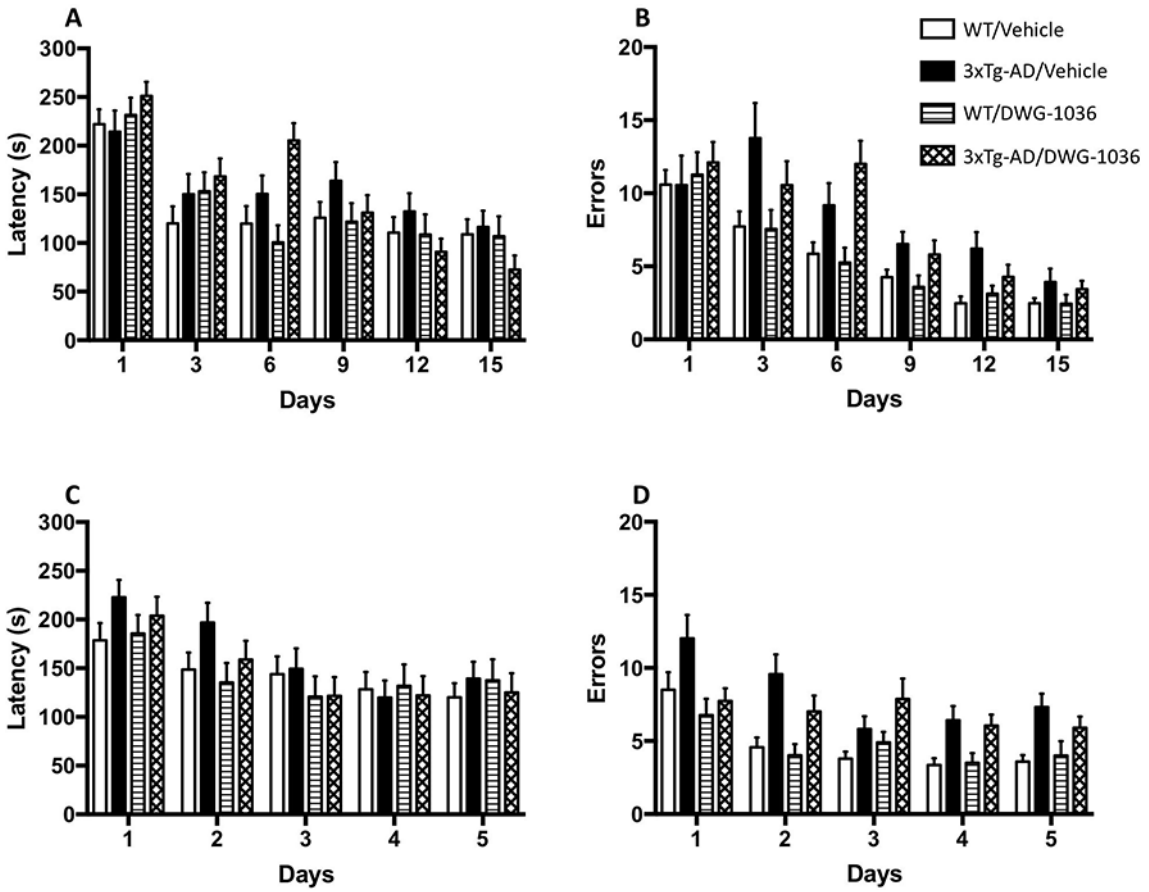

FIGURE 6 | Learning performance of mice in each group on the acquisition and reversal phases of the Barnes maze. Mean (+ SEM) latency (in seconds) for male and female 3xTg-AD and wild-type (WT) control mice to reach the goal box in the acquisition **(A)** and reversal **(C)** test days. Mean (+ SEM) frequency of errors for male and female 3xTg-AD and WT control mice to reach the goal box in the acquisition **(B)** and reversal **(D)** test days.

Reversal Latency

The models including day (AIC_{Day} = 8122.8, LH = 88.254, $p < 0.005$) and genotype by day interaction ($AIC_{Genotype:Day}$ = 8047.6, LH = 10.763, $p < 0.05$) differed from the null model significantly (AIC_{null} = 8042.6). Although all of the mice improved in the 5-day period, the 3xTg-AD mice improved more than the WT controls, but neither group showed a treatment effect **(Figures 6C)**.

Reversal Errors

The models including day (AIC_{Day} = 4317.1, LH = 52.719, $p < 0.005$), genotype ($AIC_{Genotype}$ = 4289.1, LH = 18.711, $p < 0.005$), and treatment by day interaction ($AIC_{Treatment:Day}$ = 4078.0, LH = 15.084, $p < 0.005$) differed significantly from the null model (AIC_{null} = 4272.4). Although all of the mice decreased their number of errors over the 5-day period, the WT mice made fewer errors than the 3xTg-AD mice. Moreover, the DWG-1036-treated mice improved less than the vehicle treated mice, regardless of genotype **(Figures 6D)**.

Acquisition Probe

For the frequency of visiting the correct hole, there were no main effects of genotype, treatment, or sex, nor any significant interactions (all $p > 0.05$, **Figure 7A**). For the time spent by the correct hole, the 3xTg-AD mice spent more time by the correct hole than the WT mice; however, the difference was not significant ($F(1, 66) = 2.921$, $p = 0.09$). On the other hand, the DWG-1036-treated mice spent significantly less time by the correct hole than the vehicle-treated mice ($F(1, 66) = 4.348$, $p < 0.05$, **Figures 7B**).

Reversal Probe

For the time spent by the correct hole and the number of times visiting the correct hole, there were no main effects of genotype, treatment, or sex, nor any significant interactions (all $p > 0.05$, **Figure 7C, D**).

Tail Suspension

Although the 3xTg-AD mice showed a higher immobility frequency compared to the WT mice, the difference was not statistically significant ($F(1, 62) = 3.774$, $p = 0.057$). However, there was a significant effect of treatment ($F(1, 62) = 6.360$, $p < 0.05$) because the vehicle-treated mice were immobile more frequently overall compared to the DWG-1036-treated mice. There was also a genotype by treatment interaction ($F(1, 62) = 7.011$, $p < 0.05$): the DWG-1036-treated 3xTg-AD mice stayed immobile less than the vehicle-treated 3xTg-AD mice, but there was no such difference for the WT mice (**Figure 8**).

Trace Fear Conditioning

The data for freeze duration were analyzed by calculating the difference between the duration of freezing before and after the sound cue and comparing these values between the groups. For the male mice, there were no main effects of genotype ($F(1,27) = 0.123$, $p = 0.73$) or treatment ($F(1,27) = 0.007$, $p = 0.93$), but there was a significant interaction between these factors ($F(1,27 = 4.820$, $p < 0.05$): although the DWG-1036-treated 3xTg-AD mice froze longer than the vehicle-treated 3xTg-AD mice, the opposite was the case for the WT control mice **(Figure 9A)**.

For the female mice, there was a significant effect of genotype ($F(1,26) = 4.950$, $p < 0.05$) because the WT mice froze longer than the 3xTg-AD mice. On the other hand, treatment condition had no effect ($F(1,26) = 0.700$, $p = 0.41$, **Figure 9B).**

DISCUSSION

The 3xTg-AD mouse model has deficits in spatial and working memory but shows improved motor coordination and motor learning compared to the WT mice. The 3xTg-AD mice also show increased anxiety and depression-like behaviors. The aim of this study was to determine if the novel IDO/TDO inhibitor DWG-1036 reversed these deficits.

Cognitive Function

In this experiment, cognitive function was measured in tests of spatial learning and memory (Barnes maze) and working memory (trace fear conditioning). Stover et al. (2015b) showed deficits in learning in the Barnes maze at 6 months of age in 3xTg-AD mice. Our results agree with their findings because the 3xTg-AD mice made more errors than WT mice in the reversal phase. However, in the acquisition phase, the greatest improvement was shown by the 3xTg-AD mice treated with DWG-1036. This suggests that the hippocampal damage seen in the 3xTg-AD mice (Oddo et al., 2003b) can be, up to a degree, halted or reversed by blocking the KP. The activity of the KP in the hippocampus has been studied in various ways. Increased IDO activity and quinolinic acid levels have been measured in hippocampi of AD patients (Guillemin et al., 2005a). Similarly, decreased KA to QA and KA to 3-HK ratios have been shown in the hippocampi of patients with depression (Savitz et al., 2015), which contributes to episodic memory deficits (Young et al., 2016). Moreover, xanthurenic acid, another KP metabolite, has been shown to reduce excitatory postsynaptic potentials (EPSPs) in mouse hippocampal slices (Neale et al., 2013). Increased microglia activation is negatively correlated with hippocampal volume of AD patients (Femminella et al., 2016). Because QA is only synthesized in microglia and is involved in excitotoxicity and neuronal loss, it may be at least partly responsible for the hippocampal shrinkage in AD. Indeed, NMDA receptor antagonists, such as memantine, which is commonly used in AD treatment (Kishi et al., 2017), reduce quinolinic acid-induced hippocampal damage (Keilhoff and Wolf, 1992). However, because IDO-induced KP activity increases quinolinic acid production, treatments reducing IDO may be more specific and selective at reducing NMDA-induced excitotoxicity.

Deficits in working memory function have been shown in the 3xTg-AD mice as early as 2 months of age (Stevens and Brown, 2015; Fertan et al., 2019b). In the trace fear conditioning test in this study, female 3xTg-AD mice showed working memory deficits compared to female WT mice, but these were not reversed by DWG-1036 treatment. On the other hand, male 3xTg-AD mice treated with DWG-1036 showed improvements in working memory compared to those receiving the vehicle, suggesting a sex difference in DWG-1036 action. Similar sex differences have been shown in rats because increased KP metabolites contributed to memory deficits in male rats, but no differences were found in females or gonadectomized

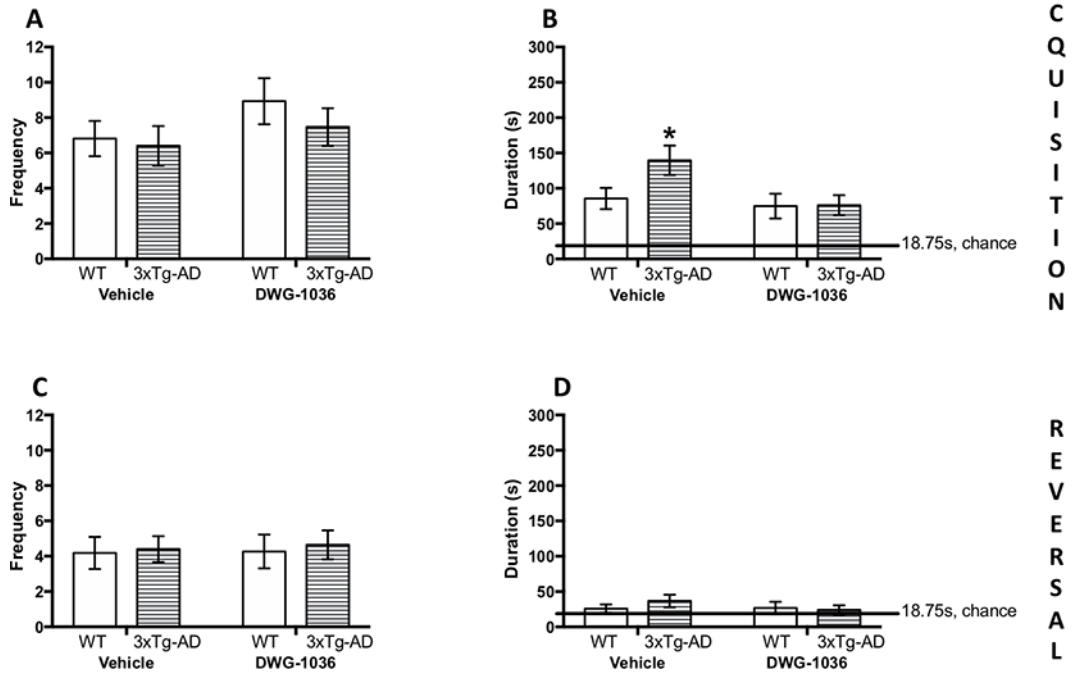

FIGURE 7 | Mean (±SEM) frequency of entering the correct sector (1/16 of the maze) in the acquisition **(A)** and reversal **(C)** memory probe trials in the Barnes maze. Mean (±SEM) time (in seconds) spent in the correct sector (1/16 of the maze) in the acquisition **(B)** and reversal **(D)** memory probe trials in the Barnes maze. *'s are used to present individual group differences determined by 95% confidence intervals.

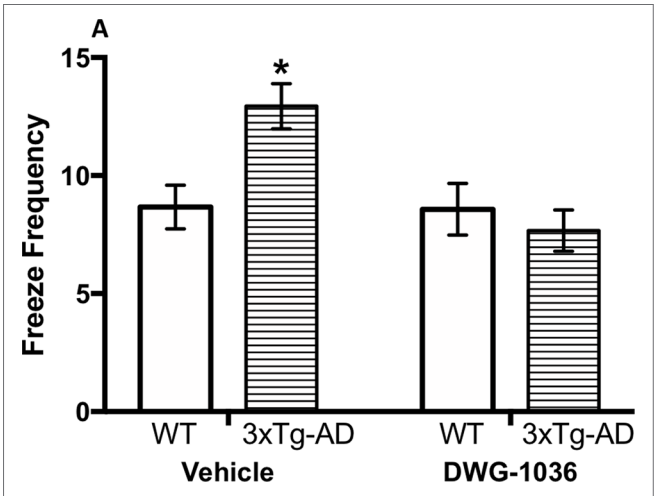

FIGURE 8 | Mean (± SEM) frequency of freezing in the tail suspension test in mice of each group, a measure of depression-like behavior. *'s are used to present individual group differences determined by 95% confidence intervals.

males (Baratta et al., 2018). Moreover, when injected in the striatum with quinolinic acid, male and ovariectomized female rats lost significant amounts of weight, whereas females with intact ovaries did not (Zubrycki et al., 1990). Together, these findings suggest that male and female gonadal hormones modulate the KP in different ways (de Bie et al., 2016). The brain areas involved in trace fear conditioning, such as the frontal cortex and the amygdala (Runyan et al., 2004; Gilmartin and Helmstetter, 2010; Song et al., 2015), are rich in sex hormone receptors (Cooke et al., 2003; Cushing et al., 2008; Zeidan et al., 2011), thus the differential genotype and treatment interactions between the male and female mice may be caused by sex hormone modulation of the KP.

Locomotion and Motor Performance

Although motor deficits have not been the major area of focus in AD (unlike other dementias, such as Parkinson's disease), they are one of the leading causes of death because AD patients often fall and break their bones or choke on their food because of the loss of the swallowing reflex (dysphagia). The 3xTg-AD mice show enhanced performance on the rotarod compared to the WT controls as early as 6 months of age (Stover et al., 2015a), and this continues into old age (Garvock-de Montbrun et al., 2019). Female mice also perform better than males; however, this is likely caused by the smaller body size of the female mice. We replicated these results in the present study because female mice performed better than males and female 3xTg-AD mice performed better than female WT mice. DWG-1036 did not have an effect on the performance of the 3xTg-AD mice. The Tau_{P301L} mutation that occurs in 3xTg-AD mice has been shown to improve motor performance on the rotarod at early ages (Morgan et al., 2008). Hence, the motor improvement of the 3xTg-AD mice may be unrelated to Aβ pathology and increased KP activity, which explains the lack of DWG-1036 treatment effect on the 3xTg-AD mice. On the other hand, DWG-1036 improved the motor performance of the WT mice, which may be caused by the increased tryptophan levels caused by KP

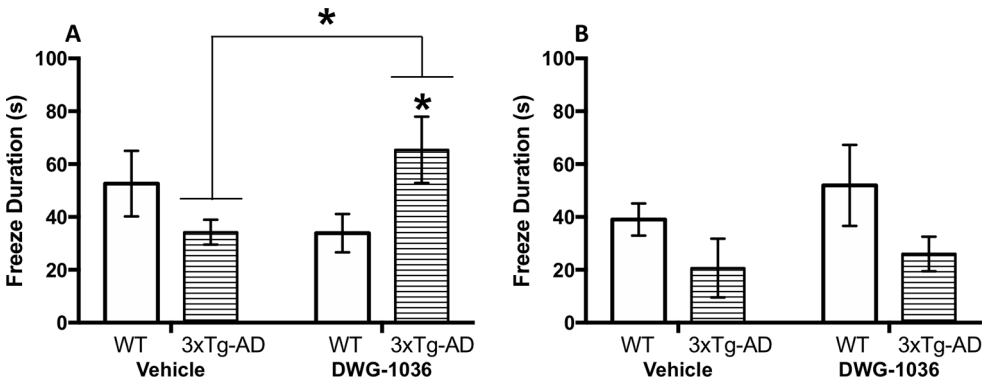

FIGURE 9 | Mean (± SEM) duration of freezing by **(A)** males and **(B)** females in the working memory test of the trace fear conditioning procedure. *'s are used to present individual group differences determined by 95% confidence intervals.

inhibition. This extra tryptophan can be converted into serotonin, and serotonergic antidepressant administration has been shown to improve performance of chronically stressed mice on the rotarod (Mizoguchi et al., 2002). Moreover, mice lacking the serotonin transporter (5-HTT) showed poor performance on the rotarod compared to the WT controls (Holmes et al., 2002).

Anxiety and Depression

Increased irritability, anxiety, and depression-like symptoms are commonly observed in AD patients. These mood disturbances have a significant negative impact on the life of AD patients and their caregivers. In our study, changes in anxiety levels were measured by open arm entrance and freezing frequency in the EPM, and depression-like symptoms were measured by immobility in the tail suspension task. Previous studies using the EPM showed elevated anxiety levels in the 3xTg-AD mice (Sterniczuk et al., 2010; Pietropaolo et al., 2014; Zhang et al., 2016). In our study 3xTg-AD mice spent more time in the open arms of the EPM, which may be interpreted as reduced anxiety. However, it is important to consider any confounding variables, especially because the 3xTg-AD mice spent more than 50% of the time in the open arms, which indicates a preference rather than exploratory behavior. Jawhar et al. (2012) showed a similar trend in the 5xFAD mice, another commonly used mouse model of AD (Oakley et al., 2006), and interpreted the increased time in the open arms as reduced anxiety. Conversely, Flanigan et al. (2014) showed that interneuronal loss in the barrel field was causing painful whisker stimulation in the 5xFAD mice, which caused an avoidance for the closed arms in the EPM. To the best of our knowledge, the whisker barrel field of the 3xTg-AD mice has not been studied, but GABAergic neuronal loss has been shown in a mouse model carrying the same mutations (Loreth et al., 2012). In addition, we have measured differences in whisker movements, such as lower mean angular positions and retraction speeds in 3xTg-AD mice compared to WT controls (Simanaviciute et al., in press). Thus, the increased time spent in the open arms may be caused by painful whisker stimulation in the closed arms, and therefore, it is important to study other anxiety-related behaviors in the EPM. For freezing behavior, a similar trend to the results in trace fear conditioning was observed: although freezing frequency was decreased in the male 3xTg-AD mice treated with DWG-1036, there was no such effect of treatment for the females, which once again suggest a sexually dimorphic effect of DWG-1036, which improves the symptoms of males but not females.

The tail suspension test was used as a measure of learned helplessness and depression-like behavior, which is seen in both humans with AD (Chi et al., 2014) and mouse models (Nyarko et al., 2019), including the 3xTg-AD mice, and have been linked to impaired monoamine transmission (Romano et al., 2014). In this study, 3xTg-AD mice treated with DWG-1036 froze less frequently than the 3xTg-AD mice that received the vehicle, whereas there were no differences between the treatment groups in WT mice. As discussed above, inhibiting IDO/TDO may increase the serotonin levels, compensating for the decrease caused by other AD mechanisms. IDO and KP activity has been studied in depression independent of AD as well: although kynurenine and KA were decreased in patients with depression, IDO and quinolinic acid levels were elevated (Wichers and Maes, 2004; Ogyu et al., 2018). Hence, our results suggest that DWG-1036, and other agents decreasing KP activity, may be successful at reducing depression-like symptoms.

DWG-1036 Side Effects

Although DWG-1036 treatment was successful at reversing or ameliorating some of the behavioral symptoms of AD, it also had some negative side effects. As shown by the tolerability study and throughout the treatment period, DWG-1036 caused weight loss, especially in the female mice, which may be a direct result of treatment or caused by other accompanying complications. Since IDO and TDO are the first and rate-limiting enzymes of the KP, DWG-1036 may cause excessive tryptophan accumulation or hypertryptophanemia (Ferreira et al., 2017). This may cause various disorders, such as excessive fatigue (Yamamoto et al., 2012), and if it occurs during development, intellectual disability, mood disorders, hypersexuality, and sensory deficits (Martin et al., 1995). Another possible outcome of decreasing KP activity is increased serotonin levels, which may cause serotonin syndrome-like symptoms in mice (Haberzettl et al., 2013). Moreover, serotonin is involved in feeding regulation (Magalhães et al., 2010), as serotonergic receptors 5-HT1B, 5-HT2C, and 5-HT6 mediate satiety (Voigt and Fink, 2015). This may also explain the weight loss observed in the mice

treated with higher doses of DWG-1036. Moreover, the weight loss affected female mice more than male mice in this study. This may be caused by sex differences in body weight prior to treatment. As the female mice had lower body weights compared to the male mice, equal amounts of weight loss resulted in a higher percentage of the body weight loss for the females. In addition, in a preclinical population of individuals with high neocortical AB levels, higher serum KP metabolite levels compared to healthy controls were shown in women but not men (Chatterjee et al., 2018). This may explain the protection of female TG mice from toxicity because KP activity is elevated in TG females, and thus DWG-1036 may be normalizing their levels without causing hypertryptophanemia.

CONCLUSIONS

After being treated with the novel IDO inhibitor DWG-1036 between 2 and 6 months of age, 3xTg-AD mice showed improvements in cognition as well as anxiety and depression-related behaviors. This shows the therapeutic potential of targeting the KP and tryptophan metabolism in AD. KP overactivity and metabolite-related neurotoxicity are downstream of increased Aβ, which potentially increases the window for therapeutic intervention: although treatments targeting KP would not decrease $A\beta_{42}$ accumulation, they would decrease neurodegeneration. Thus, neurobiological studies on KP-related interventions should focus on neurodegeneration instead of Aβ42 clearance. Indeed, reduced neurodegeneration upon TDO inhibition has been shown in animal models of AD, Parkinson's disease, and Huntington's disease (Breda et al., 2016). Similarly, inhibition of kynurenine 3-monooxygenase has been shown to reduce synaptic loss in the APPtg mouse model of AD (Zwilling et al., 2011).

However, inhibiting IDO/TDO may not be the ideal method to target the KP. The neuroactive metabolites of the KP have opposing roles in neurodegenerative diseases: although 3-HK and QA contribute to neurotoxicity, KA is neuroprotective (Tan et al., 2012). Therefore, targeting individual metabolites may be more beneficial for developing treatments for AD. Both 3-HK and KA are synthesized from kynurenine with the enzymes kynurenine-3-monooxygenase (KMO) and kynurenine aminotransferase (KAT), respectively (Wang et al., 2012; **Figure 1**), which makes these enzymes valuable targets of intervention (Han et al., 2010; Smith et al., 2016). Moreover, 3-HK gets further metabolized into 3-hydroxyanthranilic acid, which gets metabolized to QA in microglia with a non-enzymatic reaction. Finally, QA is converted to NAD by quinolinate phosphoribosyl transferase (QPRT) in neurons and astrocytes. Hence, a combination of compounds inhibiting the activity of KMO and enhancing KAT and QPRT might have better outcomes in decreasing the neurotoxicity in AD and ameliorating the behavioral deficits. Even though tryptophan metabolism *via* the KP seems to be involved in the progression of AD, there are many other mechanisms underlying AD, including cholinergic (dys)function, metabolic deficits, and environmental factors (Grant et al., 2002; Dziewczapolski et al., 2009; Lee et al., 2018). In addition, thioredoxin-interacting protein (TXNIP) is increased by $A\beta_{42}$ and increases oxidative stress, thereby increasing the progression of AD (Fertan et al., 2019a). Future studies should investigate the neurobiological mechanisms in which these factors contribute to AD and their interaction with each other and $A\beta_{42}$.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The animal study was reviewed and approved by Dalhousie University Council of Animal Ethics.

AUTHOR CONTRIBUTIONS

EF: Conception and design, collection and assembly of data, analysis and interpretation, final approval of manuscript. AW and RB: Conception and design, analysis and interpretation, final approval of manuscript. MB, PS, BK, ED-C: Design and production of DWG-1036, preliminary pharmacodynamic testing of DWG-1036. KS and DW: Design and production of DWG-1036, preliminary pharmacodynamic testing of DWG-1036, conception and design.

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REVIEW
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The Hyperactivity–Impulsivity–Irritiability–Disinhibition–Aggression–Agitation Domain in Alzheimer's Disease: Current Management and Future Directions

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Behavioral and psychological symptoms of dementia (BPSD) afflict the vast majority of patients with dementia, especially those with Alzheimer's disease (AD). In clinical settings, patients with BPSD most often do not present with just one symptom. Rather, clusters of symptoms commonly co-occur and can, thus, be grouped into behavioral domains that may ultimately be the result of disruptions in overarching neural circuits. One major BPSD domain routinely identified across patients with AD is the hyperactivity–impulsivity–irritiability–disinhibition–aggression–agitation (HIDA) domain. The HIDA domain represents one of the most difficult sets of symptoms to manage in AD and accounts for much of the burden for caregivers and hospital staff. Although many studies recommend non-pharmacological treatments for HIDA domain symptoms as first-line, they demonstrate little consensus as to what these treatments should be and are often difficult to implement clinically. Certain symptoms within the HIDA domain also do not respond adequately to these treatments, putting patients at risk and necessitating adjunct pharmacological intervention. In this review, we summarize the current literature regarding non-pharmacological and pharmacological interventions for the HIDA domain and provide suggestions for improving treatment. As epigenetic changes due to both aging and AD cause dysfunction in drug-targeted receptors, we propose that HIDA domain treatments could be enhanced by adjunct strategies that modify these epigenetic alterations and, thus, increase efficacy and reduce side effects. To improve the implementation of non-pharmacological approaches in clinical settings, we suggest that issues regarding inadequate resources and guidance for implementation should be addressed. Finally, we propose that increased monitoring of symptom and treatment progression *via* novel sensor technology and the "DICE" (describe, investigate, create, and evaluate) approach may enhance both pharmacological and non-pharmacological interventions for the HIDA domain.

Keywords: behavioral and psychological symptoms, dementia, Alzheimer's disease, non-pharmacological treatment, pharmacological intervention

INTRODUCTION

Though dementia encompasses an array of neurodegenerative conditions and is characterized by a progressive decline in cognitive functions and ability to execute activities of daily living (Prince et al., 2013), severe behavioral and psychological symptoms of dementia (BPSD) are nearly universal in these patients. For instance, in Alzheimer's disease (AD), which represents 60–80% of all dementias (Alzheimer's Association, 2016), over 90% of patients display BPSD, including depression, anxiety, apathy, agitation and aggression, disinhibition, delusions, hallucinations, irritability and emotional lability, euphoria, and aberrant motor, sleep, and eating behaviors (Kales et al., 2019). These symptoms may present before clinically significant memory decline and are correlated with a greater likelihood of conversion to AD from mild cognitive impairment (MCI) (Serra et al., 2010). Overall, BPSD are associated with decreased quality of life, increased cognitive and functional decline, greater likelihood of institutionalization, and heightened risk of mortality (Gilley et al., 2004; Scarmeas et al., 2005; Wilson et al., 2006; Gaugler et al., 2009; Rowe et al., 2009). Moreover, these symptoms are correlated with greater direct and indirect costs as well as higher caregiver burden (Clyburn et al., 2000; Allegri et al., 2006; Herrmann et al., 2006).

Given the high prevalence of BPSD in neurodegenerative patients, clinical instruments to aid in BPSD assessment are essential. To date, there are more than 80 instruments for measuring BPSD (van der Linde et al., 2014b). Patients in the earlier stages of dementia may answer some of these measures *via* self-report, but as cognitive decline progresses, it is more common for clinicians, caregivers, or informants to complete these instruments based on their observations of patients' BPSD (Conn and Thorpe, 2007). Of the measures available, the Neuropsychiatric Inventory (NPI) is most commonly used in both research and clinical settings (Conn and Thorpe, 2007; van der Linde et al., 2014b). The NPI provides information about the frequency and severity of patients' overall BPSD and subdomains of symptoms (e.g., agitation and aggression) as well as an indication of caregiver distress. While the NPI was designed to assess BPSD across various forms of dementia, the Behavioral Pathology in AD Rating Scale (BEHAVE-AD) was specifically developed to measure global BPSD in patients with AD (Jeon et al., 2011; van der Linde et al., 2014b). The BEHAVE-AD is the second most cited assessment of global BPSD in the literature, and it provides information about the severity of a patient's global and specific BPSD symptoms. Although measures of overall BPSD can provide insight into the presence and extent of specific symptoms, there are also numerous instruments designed to examine these in depth. Examples of symptom-specific measures include the Overt Aggression Scale (OAS) for irritability and aggression and the Cohen-Mansfield Agitation Inventory (CMAI) for agitation. Although these instruments were not originally created to assess these symptoms in patients with dementia, they are currently the most widely used instruments in the literature for measuring irritability, aggression, and agitation in the context of BPSD.

Clinical presentations of BPSD across patients vary widely due to baseline individual differences, dementia type, and severity of cognitive decline (Jeste et al., 2006; Petrovic et al., 2007; Azermai, 2015). Overall, however, BPSD tend to cluster into "domains," as certain symptoms show high frequencies of co-occurrence (Jeste et al., 2006; Azermai, 2015). Indeed, numerous researchers and clinicians conceptualize symptom domains for BPSD (Jeste et al., 2006; Azermai, 2015) and have suggested that there is a high likelihood of common underlying molecular and cellular pathologies for symptoms in each domain (Aalten et al., 2003; Jeste et al., 2006; Aalten et al., 2007; Aalten et al., 2008). One systematic analysis of 62 studies utilizing unbiased clustering approaches, such as principal component, factor, latent class, or cluster analysis, on behavioral data from participants with dementia routinely identified specific BPSD domains across studies, including affective domain, apathy domain, psychosis domain, euphoria domain, and hyperactivity–impulsivity–irritability–disinhibition–aggression–agitation (HIDA) domain (van der Linde et al., 2014a).

The HIDA domain, in particular, represents one of the most difficult sets of symptoms to manage in AD, accounts for much of the burden for caregivers and hospital staff, and represents an area of special concern regarding safety (Fuh et al., 2001; Rymer et al., 2002; Nguyen et al., 2008; Fauth and Gibbons, 2014). Aggression is correlated with an increased risk of self-injurious behavior (Gilley et al., 2004; de Jonghe-Rouleau et al., 2005). Impulsivity and impaired executive functioning are related to increased wandering and disorientation, which can in turn put patients at an increased risk for falls and mortality (Chiu et al., 2004). As a result of these risks and their impact on caregivers, patients with severe HIDA domain symptoms are more likely than those with other BPSD to be institutionalized and put in restraints (Matteson and Linton, 1996; Gilley et al., 2004). Further, a 2016 meta-analysis suggested these symptoms are common, revealing that individual symptoms within the HIDA domain occur at a prevalence rate of 17% to 40% in patients with AD (Fauth and Gibbons, 2014, Zhao et al., 2016). These symptoms are often more prevalent as patients can no longer be cared for at home, and rates of aggression and agitation may be as high as 60% in care facilities (Margallo-Lana et al., 2001).

In this review, we focus on the HIDA domain from the likely pathophysiology to symptom management, including non-pharmacological and pharmacological interventions. Regarding treatment for the HIDA domain, most studies have focused on reducing aggression and agitation, with no or very few studies focusing on the treatment of aberrant motor activity, irritability, impulsivity, or disinhibition directly. Therefore, this review summarizes current trends in treating agitation and aggression specifically, noting the non-pharmacological and pharmacological trends in management as well as future directions that may yield newer strategies for improved patient care.

PATHOPHYSIOLOGY OF THE HIDA DOMAIN

Though the specific molecular mechanisms that lead to HIDA domain symptoms are generally unknown, pathology and human imaging studies have provided some insight into this

domain's pathophysiology. At first, the HIDA domain may seem like a disparate set of aberrant motor dysfunctions and behavioral states, but these symptoms all represent a common deficit in the appropriate inhibition of one's actions. Mirroring this common deficit, very similar neurocircuitry is implicated for all of these symptoms, namely, loss of corticostriatal control and reduction in neurotransmission of far-reaching monoaminergic inputs that modulate this corticostriatal circuitry (Coccaro et al., 2011; Blair, 2016; Waltes et al., 2016; Dalley and Robbins, 2017). While specific investigation into the symptoms of the HIDA domain in AD has been limited, similar brain regions are usually implicated (Rosenberg et al., 2015).

More specifically, frontal cortical brain areas such as the orbitofrontal cortex, the ventromedial prefrontal cortex, and anterior cingulate cortex interact with the ventral and dorsal striatal nuclei, mediating inhibition of impulsive thoughts and motor responses, respectively (Coccaro et al., 2011; Whelan et al., 2012; Hoptman, 2015; Blair, 2016; Dalley and Robbins, 2017; Leclerc et al., 2018). In addition, areas like the amygdala, periaqueductal gray, anteroventral medial hypothalamus, lateral septum, ventral hippocampus, and medial preoptic nucleus promote impulses for certain behaviors (Coccaro et al., 2011; Hoptman, 2015; Blair, 2016; Dalley and Robbins, 2017; Leclerc et al., 2018). In terms of monoaminergic pathways, serotonin, norepinephrine, and dopamine are all implicated in these impulsive tendencies, and multiple genetic studies have implicated receptors and enzymes involved in these signaling pathways as influencing the presentation of these behaviors (Waltes et al., 2016). In AD, reductions in cholinergic and serotonergic markers have been reproducibly associated with agitation and aggression (Rosenberg et al., 2015). In terms of AD pathology, increased pS396 tau in Brodmann area 9 was associated with increased agitation and aggression (Guadagna et al., 2012), suggesting that increased phosphorylated tau in specific frontal cortical regions may lead to loss of inhibitory control over one's actions.

Interestingly, the brainstem monoaminergic nuclei—especially the serotonergic dorsal raphe nucleus and noradrenergic locus coeruleus—are some of the first to degenerate in AD, suggesting that loss of normal function in these regions may underlie some symptoms within the HIDA domain in the early stages of the disease (Parvizi et al., 2001; Lyness, 2003; Šimić et al., 2017). Some degeneration in the mesolimbic dopamine circuitry has also been described and may contribute to these symptoms (Lyness, 2003; Nobili et al., 2017; D'Amelio et al., 2018). Comparatively, later spread of pathology to frontal cortical areas may lead to more severe symptoms within the HIDA domain at later stages of AD, as spread of AD pathology tends to progress from the ventral to dorsal cortical areas (Braak and Braak, 1991; Šimić et al., 2017). Though speculative, these represent two complementary pathways of neurodegeneration that may underlie HIDA domain symptoms.

NON-PHARMACOLOGICAL TREATMENT APPROACHES

Dementia treatment guidelines assert that non-pharmacological approaches are first-line for mild or moderate HIDA domain symptoms that do not compromise the patient's immediate safety (American Geriatrics Society and American Association for Geriatric Psychiatry, 2003). Unlike drug treatments for BPSD, which tend to carry a high risk of side effects for elderly patients, the side effects for psychosocial interventions are minimal (Sink et al., 2005; Konovalov et al., 2008; Coupland et al., 2011; Brodaty and Arasaratnam, 2012). There are an extensive number of non-pharmacological interventions available that vary greatly in their effectiveness in terms of target symptoms (Livingston et al., 2005; Azermai et al., 2012; Azermai, 2015; Tible et al., 2017; Legere et al., 2018). This section will describe how treatments rooted in psychological theory can be tailored towards patients with dementia to ameliorate HIDA domain symptoms. Moreover, it will outline a number of sensory stimulation and bodily activation techniques that are independent of theoretical orientation yet can be implemented to treat the HIDA domain as well. For a succinct overview of the non-pharmacological interventions discussed in this section, refer to **Table 1**.

Person-Centered Interventions

Person-centered care focuses on techniques that value dementia patients as individuals, assess and meet personal needs, view the world from patients' perspectives, and facilitate positive relationships and communications (Brooker, 2003). Two randomized controlled trials (RCTs) exploring the effects of staff-training programs in person-centered care revealed that these programs resulted in significant reductions in patients' agitation and aggression (Sloane et al., 2004; Chenoweth et al., 2009). Another RCT in which care staff received training in person-centered care demonstrated that this approach significantly reduced the extent to which patients were prescribed antipsychotics, a common agent used to treat HIDA domain symptoms (Fossey et al., 2006). However, there was no difference between groups in scores on the CMAI or in instances of aggression. This suggests that person-centered approaches may have modest benefits in reducing the severity of agitation and aggression, likely prolonging or negating the use of pharmacological alternatives.

Within the umbrella of person-centered care techniques, various approaches and therapies have been studied individually for reducing HIDA domain symptoms. One of these approaches is needs-driven care in which assessing and addressing patients' needs is postulated to prevent agitation and aggression. In a needs-driven approach, care providers analyze the contexts in which disruptive behaviors occur to determine if these behaviors are an expression of patients' unmet needs and seek to address them. Thus, a number of RCTs have examined the effects of needs-driven approaches in ameliorating BPSD (Kovach et al., 2006; Cohen-Mansfield et al., 2007; Husebo et al., 2011; Cohen-Mansfield et al., 2012). Some RCTs have found that broadly addressing patients' unmet needs is associated with significant decreases in agitation during the intervention period (Cohen-Mansfield et al., 2007; Cohen-Mansfield et al., 2012). Studies examining the effects of addressing pain needs specifically have revealed mixed, short-term results in ameliorating general disruptive behaviors and symptoms of agitation (Kovach et al., 2006; Husebo et al., 2011). However, research has failed to demonstrate long-term, significant

TABLE 1 | Non-pharmacological interventions for BPSD.

Person-centered and Behavioral Interventions			
Intervention	**Definition**	**Studies**	**Efficacy**
Person-Centered Care	Valuing patients with dementia, assessing and meeting their individual needs, viewing the world from their perspective, and promoting positive relationships and communications (Brooker, 2003)	Sloane et al., 2004 Fossey et al., 2006 Chenoweth et al., 2009	- Training programs are generally effective for reducing agitation, aggression, and antipsychotic use
Needs-Driven Approaches	Analyzing the context of patients' BPSD to determine and address unmet needs (Cohen-Mansfield et al., 2007)	Kovach et al., 2006 Cohen-Mansfield et al., 2007 Husebo et al., 2011 Cohen-Mansfield et al., 2012	- Addressing patients' overall unmet needs leads to significant reductions in agitation during the intervention period - Attending to pain needs specifically has mixed short-term efficacy on agitation with no evidence for long-lasting benefits
Validation Therapy	Encouraging patients with dementia to express their feelings and legitimatizing these communications regardless of quality or content (Toseland et al., 1997)	Toseland et al., 1997 Deponte and Missan, 2007	- Only one study on HIDA domain symptoms - No evidence for a significant benefit over other psychotherapies nor translation to clinical outcomes
Reminiscence Therapy	Using prompts to stimulate memories that patients have intact, allowing them to re-experience and share these memories (Tadaka and Kanagawa, 2007)	van Diepen et al., 2002 Tadaka and Kanagawa, 2007 Van Bogaert et al., 2016 O'Shea et al., 2014	- No evidence for that this therapy produces significant reductions in HIDA domain behaviors
Reality Orientation Therapy	Repeating orienting information (e.g., time, location, date, or weather) over a prolonged period of time each day to patients (Wallis et al., 1983)	Hanley et al., 1981 Wallis et al., 1983 Baldelli et al., 1993 Onder et al., 2005	- No evidence for efficacy in reducing overall BPSD - RCTs have not examined HIDA domain behaviors specifically
Simulated Presence Therapy (Family Presence Therapy)	Presenting patients with audiotapes or videotapes of loved ones recounting pleasant, autobiographical memories to increase the familiarity of the environment (Woods and Ashley, 1995)	Camberg et al., 1999 Garland et al., 2007	- Mixed efficacy findings for ameliorating HIDA domain - No evidence for lasting effects
Behavior Management	Identifying problematic behaviors and modifying the environment in ways that discourage them while promoting positive behaviors (Gormley et al., 2001)	Suhr, 1999 Teri et al., 2000 Gormley et al., 2001 Weiner et al., 2002 Burgio et al., 2002 Huang et al., 2003	- Therapist-conducted behavioral management significantly reduces overall BPSD - Informal, caregiver-conduced behavioral management generally does not produce significant, long-term reductions in HIDA domain symptoms
Cognitive Behavioral Therapy (CBT)	Addressing maladaptive interactions between thoughts, emotions, and behaviors *via* therapeutic experiences and coping skills tailored towards patients with dementia (Spector et al., 2015)	Marriott et al., 2000 Akkerman, 2004 Kurz et al., 2012 Kwok et al., 2014 Spector et al., 2015	- Generally effective in decreasing overall BPSD and symptoms within the affective domain, such as depression - Some evidence for long-lasting effects - No RCTs conducted on the HIDA domain
Staff and Informal Caregiver Psychoeducation	Educating caregivers or staff about dementia and BPSD, including how to cope with and manage stressful situations and problematic behaviors (Livingston et al., 2005)	McCallion et al., 1999 Hébert et al., 2003 Hepburn et al., 2007 Deudon et al., 2009	- Effective in reducing caregiver burden, overall BPSD, and agitation
Sensory stimulation interventions			
Intervention	**Definition**	**Studies**	**Efficacy**
Aromatherapy	Eliciting olfactory stimulation *via* essential oils with or without therapeutic touch (Yoshiyama et al., 2015)	Smallwood et al., 2001 Ballard et al., 2002 Holmes et al., 2002 Snow et al., 2004 Lin et al., 2007 Burns et al., 2011 Fu et al., 2013 O'Connor et al., 2013	- Inconsistent effect on agitation across studies with a trend towards insignificant or absent benefits
Massage or Therapeutic Touch	Applying pressure with the hands to certain parts of a patient's body (e.g., hands or feet) using a slow, stroking motion (Suzuki et al., 2010)	Smallwood et al., 2001 Remington, 2002 Hicks-Moore and Robinson, 2008 Fu et al., 2013 Moyle et al., 2014	- Mixed findings regarding effect on agitation - No evidence for a significant benefit over other sensory stimulation approaches

(Continued)

TABLE 1 | Continued

Sensory Stimulation Interventions			
Intervention	**Definition**	**Studies**	**Efficacy**
Music Therapy	Listening or actively participating in music in a controlled therapeutic environment in order to accomplish treatment goals (Pedersen et al., 2017)	Remington, 2002 Garland et al., 2007 Raglio et al., 2008 Cooke et al., 2010 Sung et al., 2012 Sánchez et al., 2016b	- Most studies do not show a significant positive effect over other non-pharmacological approaches - Most studies do not provide evidence of long-term benefits
Light Therapy	Providing a source of artificial light for a period of time during the day or night	Ancoli-Israel et al., 2003 Dowling et al., 2007 Burns et al., 2009	- Ineffective in producing clinically significant reductions in agitation and hyperactivity in patients with dementia
Multisensory Stimulation Therapy/Snoezelen Therapy	Using various stimuli to activate multiple senses, facilitating patients' interaction with their environment in a non-directive way that requires few intellectual and physically demands (Sánchez et al., 2016a)	Robichaud et al., 1994 Baker et al., 2001 van Diepen et al., 2002 Baker et al., 2003 Baillon et al., 2004 Sánchez et al., 2016a	- Mixed findings on ability to significantly reduce agitation and aggression - No evidence for a significant benefit over other sensory stimulation approaches - Most studies do not support long-term efficacy
Physical Activity	Usually walking and/or muscle training (Tible et al., 2017)	Alessi et al., 1999 Cott et al., 2002 Rolland et al., 2007 Eggermont et al., 2010 Lowery et al., 2014	- Most evidence shows that physical activity does not have a positive, significant impact on nighttime restlessness, daytime activity, irritability, or overall BPSD
Therapeutic Activities	Engaging patients in meaningful activities such as playing games, completing puzzles, or reading	Baker et al., 2001 Buettner and Fitzsimmons, 2002 Fitzsimmons and Buettner, 2002 Kolanowski et al., 2011	- Mixed findings regarding efficacy for reducing agitation - No evidence for lasting benefits

BPSD, behavioral and psychological symptoms of dementia; HIDA, hyperactivity–impulsivity–irritability–disinhibition–aggression–agitation.

reductions in HIDA domain symptoms relative to usual care once needs-based interventions end (Husebo et al., 2011). Future studies should clarify which aspects and types of needs-driven care are most beneficial in ameliorating agitation and aggression in patients with dementia. Given that addressing unmet needs has generally delivered promising short-term results, future research should also focus on how to implement needs-driven approaches on a more continual basis to elicit long-term benefits (Cohen-Mansfield et al., 2007; Cohen-Mansfield et al., 2012; Husebo et al., 2011).

Promoting positive social interactions and meaningful relationships is also central to person-centered care. As dementia progressively compromises patients' communication abilities, attempts to communicate may manifest as agitated and aggressive behaviors (Ragneskog et al., 1998). Validation therapy purports that BPSD have latent causes and that communications from patients with dementia are meaningful regardless of aberrant content or expression (Dietch et al., 1989). Patients can become withdrawn or agitated when they feel disregarded; thus, therapists performing validation therapy practice empathy towards patients with dementia, encourage them to express their feelings, and legitimatize these communications (Feil, 1982; Dietch et al., 1989; Toseland et al., 1997). There have not been many high-quality RCTs of validation therapy, and only one RCT has examined the impact of validation therapy on HIDA domain symptoms (Toseland et al., 1997). In comparison with social contact or with usual care, this intervention led to significant decreases in nurses' ratings of patients' physical and verbal aggression. However, these differences did not translate to other clinical outcomes such as frequency of physical restraint use, psychotropic delivery, or time spent intervening due to difficult behavior. Validation therapy, therefore, has the potential to reduce the perceived severity of HIDA domain symptoms, but there is no evidence yet that this intervention translates to other clinical outcomes nor superior to other non-pharmacological approaches. Thus, this approach may benefit from additional research aimed at identifying how and why benefits in clinical ratings fail to transfer into tangible outcomes.

Reminiscence therapy is a second approach that aims to promote positive social interactions and communications with patients who have dementia. It involves stimulating old memories with prompts such as photographs or songs, emphasizing intact cognitive abilities, and encouraging patients to share their memories with others (Tadaka and Kanagawa, 2007). One small RCT demonstrated that both validation therapy and reminiscence therapy significantly reduced overall BPSD scores as measured by the NPI in patients compared with patients receiving no treatment (Deponte and Missan, 2007). Moreover, reminiscence therapy led to significantly improved cognitive functioning and performance of activities of daily living in this study than did validation therapy. However, in RCTs specifically focusing on the HIDA domain, reminiscence therapy has not produced significant reductions in these behaviors nor significant increases in life quality (van Diepen et al., 2002; Tadaka and Kanagawa, 2007; O'Shea et al., 2014; Van Bogaert et al., 2016).

One of the first psychological therapies that drew on person-centered approaches for dementia patients was reality orientation therapy (Bowlby, 1991; Spector et al., 2000), which involves repeating orienting information, such as the date or the weather, over a prolonged period of time each day (Wallis et al., 1983).

This approach aims to re-orient patients with dementia to their environments and to increase their engagement (Bowlby, 1991). The literature contends that reality orientation therapy should occur within a person-centered framework in which care providers facilitate positive, quality interactions with patients rather than simply providing information (Dietch et al., 1989). Likewise, case examples illustrate that reality orientation delivered mechanically may actually increase agitation and aggression in some patients with dementia (Dietch et al., 1989). RCTs utilizing reality orientation therapy have demonstrated mild, short-term cognitive improvements; however, they have not shown that it elicits a significant reduction in overall BPSD (Hanley et al., 1981; Wallis et al., 1983; Baldelli et al., 1993; Onder et al., 2005). Unfortunately, one frequent method of delivering reality orientation therapy utilizes a classroom approach (Bowlby, 1991), but patients who exhibit aggressive symptoms or wandering are often excluded due to concerns about managing disruptions in a classroom setting (O'Connell et al., 2007). Consequently, no studies have specifically examined the effects of reality orientation therapy on behaviors within the HIDA domain. In addition, despite the immediate popularity of reality orientation therapy following its creation in the mid-1960s, its use has decreased substantially in recent decades due to the formulation of other approaches (Spector et al., 2000).

Similar to reality orientation therapy, simulated presence therapy attempts to make the environment less foreign for patients with dementia. Simulated presence therapy—sometimes called family presence therapy—presents patients with audiotapes or videotapes of loved ones recounting pleasant, autobiographical memories (Woods and Ashley, 1995). As opposed to reminiscence therapy in which care providers use prompts to elicit memories and to facilitate communication, the goal of simulated presence therapy is to minimize distress by increasing the familiarity of the environment with the simulated presence of a family member. Some studies demonstrate significant yet short-lasting reductions in verbal and physical aggression during therapy sessions (Garland et al., 2007). However, other studies have failed to demonstrate similar reductions in patients' agitation (Camberg et al., 1999). Thus, research findings regarding simulated presence therapy have been mixed, and there is no evidence that this intervention leads to long-term benefits.

Behavioral Interventions

As described, person-centered care involves tailoring patients' environments and treatments to align them better with individual values, needs, and perspectives. By increasing patients' congruence with their surroundings, this approach aims to reduce BPSD by increasing patients' quality of life, promoting positive feelings and experiences, and facilitating healthy social interactions and relationships. In contrast, the goal of behavioral interventions is to identify specific, problematic stimuli or situations that may be eliciting disruptive behaviors from a patient with dementia. Moreover, therapists teach caregivers and dementia patients specific strategies for lessening the frequency of these disruptive behaviors. Behavioral interventions for BPSD most prominently include behavior management and cognitive behavioral therapy (CBT).

Behavioral management strategies presume that disruptive behaviors in patients with dementia are due to maladaptive interactions between patients and their environment as a result of AD (Gormley et al., 2001). Thus, behavioral management techniques aim to identify the contexts in which problematic behaviors occur and to modify the environment to decrease the likelihood of these behaviors. One RCT focusing on therapist-conducted behavior management demonstrated significant reductions in overall BPSD as assessed with the NPI (Suhr, 1999). Behavioral management RCTs targeting the HIDA domain generally involve teaching caregivers to employ corresponding strategies in more informal settings (Teri et al., 2000; Gormley et al., 2001; Burgio et al., 2002; Weiner et al., 2002; Huang et al., 2003). Two of these studies showed some significant benefits of informal behavior management on agitation symptoms; however, there was no evidence that this effect persisted beyond intervention completion, and the majority of studies did not elicit similar positive results. Given the success of professionally administered behavior management on global BPSD, future studies examining the effects of formal behavior management on the HIDA domain may produce more positive results.

While behavioral management techniques focus solely on adjusting a patient's environment to lessen the frequency of disruptive behaviors, CBT is more complex in that it teaches patients skills to address maladaptive interactions between their thoughts, emotions, and behaviors (Spector et al., 2015). Although CBT involves a learning component, there is evidence that some patients with dementia can acquire new skills with cognitive training despite impairment (Spector et al., 2003). Moreover, therapists can modify the content of the skills they teach and the methods they use to deliver them in ways that are compatible with the diminished cognitive function in dementia (Stanley et al., 2013). While several RCTs have shown that CBT can significantly decrease overall BPSD and lead to long-lasting reductions in affective domain symptoms, namely, depression (Marriott et al., 2000; Kwok et al., 2014; Spector et al., 2015), some research has not demonstrated that CBT has significant benefits on patients' behavioral disturbances (Kurz et al., 2012). Additionally, there have been no studies that have directly implicated its use for aggression or agitation. Therefore, research into the efficacy of CBT in treating HIDA domain symptoms is needed.

Caregiver and staff psychoeducation targeted towards BPSD goes beyond education in person-centered care or behavioral interventions in that it provides information about dementia and effective coping, communication, and behavioral management strategies (Livingston et al., 2005). Although studies have examined the sole effects of psychoeducation programs on BPSD, elements of this approach relate to both person-centered and behaviorally oriented interventions and can, thus, be used in combination with the other non-pharmacological strategies described above. RCTs have consistently demonstrated that dementia-related psychoeducation reduces BPSD and perceived caregiver burden (McCallion et al., 1999; Hébert et al., 2003; Hepburn et al., 2007). Moreover, staff education programs can significantly reduce agitation among nursing home residents with dementia (Deudon et al., 2009). Thus, on an institutional level, psychoeducation of caregivers and staff is one of the most effective ways to reduce HIDA domain symptoms.

Sensory Stimulation Interventions

Patients with dementia who are socially isolated, inactive, or bored demonstrate increased verbally disruptive behavior and excess motor activity (Cohen-Mansfield, 2000; Cohen-Mansfield et al., 2015). Thus, the goals of sensory stimulation techniques are to reduce these behaviors by increasing engagement and alertness (Strøm et al., 2016). These interventions can activate either a single sensory modality or multiple sensory modalities within a session. Approaches that use a sensory stimulation orientation include aromatherapy, massage, music therapy, light therapy, multisensory stimulation, physical activity, and therapeutic activities. Though head-to-head investigations of these techniques are sparse, and few if any of these techniques have been found to be beneficial in every study, certain approaches have more consistently demonstrated success in the literature than others.

For instance, studies of music therapy for agitation and aggression have shown mixed results. During music therapy, care providers utilize music in a controlled environment to facilitate the accomplishment of treatment goals (Pedersen et al., 2017). In the context of the HIDA domain, it is thought that music may reduce distress, promote quicker adaptation, and improve communication, thus reducing behaviors such as agitation and aggression that can arise when patients feel disoriented and frustrated in their attempts to communicate (Raglio et al., 2008). Active music therapy involves patients engaging in music activities such as singing or playing instruments, whereas passive music therapy involves patients listening to music. One RCT utilizing active music therapy showed that it significantly reduced dementia patients' aberrant motor behaviors, irritability, and agitation, and these effects remained a month after intervention completion (Raglio et al., 2008). However, most other RCTs have not found that active nor passive music therapy reduces HIDA domain symptoms to a greater degree than other non-pharmacological interventions or control conditions. (Remington, 2002; Garland et al., 2007; Cooke et al., 2010; Sung et al., 2012; Sánchez et al., 2016b). Moreover, these RCTs do not provide evidence that music therapy can produce long-lasting effects. Still, music therapy may be helpful for particularly responsive patients, especially if other techniques have failed.

Studying the effects of aromatherapy on agitation has also produced mixed results, though findings trend towards insignificant benefits (Ballard et al., 2002; Holmes et al., 2002; Snow et al., 2004; Lin et al., 2007; Burns et al., 2011; O'Connor et al., 2013). To explain the heterogeneity in these results, some researchers hypothesize that essential oil odors alone may not be beneficial for patients with severe dementia, as their olfaction is likely to be greatly impaired (Snow et al., 2004). Rather, these researchers suggest that the non-specific elements of aromatherapy, such as touch and human interaction, may drive the positive effects seen in some research (Burns et al., 2011). Despite this notion, RCTs examining the effects of massage on agitation have also been mixed. While some have demonstrated that massage in combination with aromatherapy can produce mild benefits on agitation (Smallwood et al., 2001), other RCTs have not managed to corroborate this finding (Fu et al., 2013). Additionally, some RCTs have shown that massage alone can significantly reduce agitation than can no treatment (Remington, 2002; Hicks-Moore and Robinson, 2008), though others have actually demonstrated an increase in agitation following massage (Moyle et al., 2014). Similarly, there is no evidence that massage exerts greater benefit than other sensory stimulation interventions (Hicks-Moore and Robinson, 2008; Moyle et al., 2014).

Bright light therapy has become increasingly used to treat hyperactive delirium, as circadian dysfunction has been found to greatly impact delirium severity. In turn, bright light therapy was found to improve functional status and sleep in patients with hyperactive, perioperative delirium, which occurs more commonly in patients with dementia compared with otherwise healthy elderly patients (Chong et al., 2013). Despite its benefits for delirium, non-delirious patients with dementia do not show a reduction in agitation or aberrant motor symptoms with bright light therapy (Ancoli-Israel et al., 2003; Burns et al., 2009; Dowling et al., 2007). Even in studies in which symptom reductions were observed, light therapy rarely outperformed care as usual or placebo, and caregiver-perceived improvements were not noted (Ancoli-Israel et al., 2003; Burns et al., 2009). Moreover, one study in which light therapy did lead to a statistically significant improvement in agitation and aberrant motor behavior stressed that this improvement was not large enough to be clinically meaningful (Dowling et al., 2007).

In contrast to sensory stimulation-oriented approaches that focus on activating one sensory system at a time, multisensory stimulation therapy—also known as Snoezelen therapy—utilizes a variety of stimuli to activate multiple senses simultaneously (Sánchez et al., 2016a). As described previously, agitation and aggression may arise in patients with dementia who can no longer communicate effectively and who feel socially isolated. Thus, multisensory stimulation therapy is thought to reduce these symptoms by facilitating patients' non-verbal interactions with their environment (Lykkeslet et al., 2014). Therapists conduct this intervention in a non-directive manner, promoting feelings of security in patients with dementia as they explore their environment in ways that require few intellectual and physical demands (Strøm et al., 2016; Sánchez et al., 2016a). Most RCTs comparing multisensory stimulation therapy with other approaches (e.g., individualized music sessions, reminiscence therapy, and structured activities) have demonstrated comparably significant reductions in agitation and aggression (Robichaud et al., 1994; Baker et al., 2001; Baker et al., 2003; Baillon et al., 2004; Sánchez et al., 2016a, Sánchez et al., 2016b), and similarly, these reductions rarely last beyond intervention completion (Baker et al., 2001; Baker et al., 2003; Sánchez et al., 2016a). Further, other RCTs have not demonstrated that multisensory stimulation therapy significantly reduces agitation or disruptive behavior (Robichaud et al., 1994; van Diepen et al., 2002). Thus, there is no evidence that multisensory stimulation therapy outperforms other sensory stimulation techniques that target one modality.

Although they do not specifically activate the senses, physical activity interventions targeting HIDA domain symptoms are very similar to sensory stimulation-oriented approaches in therapeutic philosophy. Physical activity programs for patients

with dementia often involve light aerobic exercise and/or strength training to increase kinesthesia (Tible et al., 2017). While RCTs examining the effects of exercise on overall BPSD have not found significant, objective benefits (Rolland et al., 2007; Lowery et al., 2014), one study observed that perceived caregiver burden was significantly lower for patients who participated in a physical activity program (Lowery et al., 2014). Still, research regarding the impact of exercise training on HIDA domain symptoms in particular has not revealed significant, positive findings for patients (Alessi et al., 1999; Cott et al., 2002; Eggermont et al., 2010), and corresponding studies have not demonstrated that physical activity significantly ameliorates patients' nighttime restlessness, daytime activity, or irritability.

Therapies that engage patients in meaningful activities such as playing games, completing puzzles, or reading aim to decrease agitation related to boredom and inactivity. One study in which dementia patients performed therapeutic activities revealed significant reductions in patients' overall BPSD than in controls; however, these effects did not persist beyond intervention completion (Baker et al., 2001). Within the HIDA domain specifically, RTCs utilizing therapeutic activities have shown inconsistent benefits towards ameliorating agitation in patients with dementia (Kolanowski et al., 2011).

Overall, there is inconclusive evidence for the immediate benefits of sensory stimulation approaches during intervention sessions, and there is little to no evidence that these approaches can lead to long-lasting reductions in HIDA domain symptoms. Some have conceptualized sensory stimulation interventions as a way to alleviate agitation and aggression due to boredom or a lack of sensory stimulation (Cohen-Mansfield, 2013). Thus, it is logical that any benefits observed during sensory stimulation sessions will remit once those sessions end. Research regarding sensory stimulation approaches within the context of a broader needs-based or person-centered framework may elicit more consistent, lasting results.

PHARMACOLOGICAL TREATMENT APPROACHES

As much of AD research has focused on mitigating cognitive decline, no drugs have been specifically designed to treat BPSD in AD. In fact, even among available medications, the FDA has yet to approve any of them for treatment of any BPSD in AD (Geda et al., 2013). Despite this lack of clear direction, clinicians routinely prescribe a number of common neuropsychiatric medications, especially for patients in long-term care facilities (Kirkham et al., 2017). Numerous professional societies—such as the American Psychiatric Association, the American Association for Geriatric Psychiatry, and the American Geriatrics Society—have suggested that non-pharmacological interventions are first-line therapy for BPSD, including HIDA domain symptoms (Kales et al., 2014; Reus et al., 2016; Lanctôt et al., 2017). Moreover, these organizations have recommended that pharmacological options should only be employed when a patient's behaviors are severe or when non-pharmacological options have been tried and failed. The appropriate medications for HIDA domain symptoms specifically is still a topic of debate, and almost all meta-analyses and organization guidelines suggest that these pharmaceuticals are of modest benefit (Ballard and Corbett, 2010; Kales et al., 2014).

Antipsychotics

The most commonly used class of drugs to treat HIDA domain symptoms are the atypical antipsychotics, with risperidone even being approved for this purpose in Europe, Canada, New Zealand, and Australia but not in the USA (Yunusa et al., 2019). Atypical antipsychotics share a common mechanism of action in reducing serotonin 2A receptor (5HT2A) activity, though they also provide some antagonism of other serotonergic receptors (5-HTRs) and the dopamine 2 receptor (D2R), similar to typical antipsychotics. Though risperidone is the best studied, other atypical antipsychotics may offer some benefits. For instance, a meta-analysis in 2011 concluded that there was high evidence to suggest that risperidone, aripiprazole, and olanzapine provide benefits for a total global outcome score of BPSD and HIDA domain symptoms specifically, including agitation and aggression (Maher et al., 2011). However, it was noted that the difference in total NPI scores was slightly below the threshold of minimum clinically significant change while the relative improvement was about 35%, just above the minimum clinically significant threshold (Maher et al., 2011). The extent to which changes in agitation and aggression specifically were clinically meaningful was not addressed. These results are largely in line with other meta-analyses of atypical antipsychotics for agitation and aggression in the context of dementia (Margallo-Lana et al., 2001; Passmore et al., 2008; Ballard and Corbett, 2010; Kongpakwattana et al., 2018).

Even though the modest benefit of atypical antipsychotics has been demonstrated across multiple studies, the adverse effects of these medications represent serious risks that often outweigh the benefit of their implementation. This was most notably highlighted by the CATIE trial, a 42-outpatient-site and 421-AD-patient trial, which concluded that the risks posed by atypical antipsychotics outweigh the modest benefits in treating agitation, aggression, and psychosis in AD (Schneider et al., 2006). Since this time, other trials have echoed this narrow risk–benefit trade-off (Passmore et al., 2008; Maher et al., 2011). The most concerning adverse event to atypical antipsychotics is the increased risk of death in elderly populations, estimated to have an odds ratio of 1.7 and a number needed to harm (NNH) of 87 (Maher et al., 2011). In addition, the best-studied drug, risperidone, confers a three-fold higher risk of stroke with an NNH of 53, an increased risk of extra-pyramidal side effects at an NNH of 20, and an increased risk of urinary tract symptoms at an NNH of 16–36 (Maher et al., 2011). These concerns for heightened adverse effects—especially risk of death—resulted in a black box warning from the FDA for all atypical antipsychotics in elderly patients, and similar warnings have been issued in Europe and Canada (Koenig et al., 2016). In addition, many programs have aimed to discourage the use of antipsychotics in the elderly, including Beers criteria, Screening Tool of Older Persons' Prescriptions (STOPP), Screening Tool to Alert Doctors to the Right Treatment (START), and Choosing Wisely (O'Mahony et al., 2015; Koenig et al., 2016; Kirkham et al., 2017;

Yunusa et al., 2019). A recent Cochrane Systematic Review suggests that withdrawal from these medications has little effect or no effect on overall BPSD, mortality, and cognitive function (Leeuwen et al., 2018). Further, this review purports that discontinuing atypical antipsychotics after prolonged exposure may actually decrease agitation in patients displaying mild behavioral disturbances. Overall, the general recommendation from these studies is that if atypical antipsychotics are needed due to severe HIDA domain symptoms, there should be discussion of their risks and benefits and consideration of tapering after 4 months of use (Reus et al., 2016).

While these medications have their place in treating HIDA domain symptoms, determining the relative efficacy and safety of one atypical antipsychotic versus another has been challenging. In a recent network meta-analysis (Yunusa et al., 2019), aripiprazole was suggested to be the most effective compared with risperidone, olanzapine, quetiapine, and placebo, while risperidone and placebo had the lowest risk of death. In contrast, aripiprazole and quetiapine were safer in terms of cerebrovascular accidents (CVAs) compared with the higher risk of CVAs when taking risperidone or olanzapine. Overall, the authors concluded that no atypical antipsychotic could be singled out as being definitively more efficacious based on current evidence.

Regarding typical antipsychotics, most notably haloperidol, results of their efficacy for treating HIDA domain symptoms are mixed (Suh et al., 2006; Kongpakwattana et al., 2018; Jin and Liu, 2019). However, their higher risk for extrapyramidal side effects and mortality make them a poor choice for treating elderly patients, and they generally are considered to be less prudent in ameliorating HIDA domain symptoms than atypical antipsychotics (Ballard and Corbett, 2010; Reus et al., 2016).

The newest antipsychotic to receive Food and Drug Administration (FDA) approval, pimavanserin, works slightly differently than previous atypical antipsychotics through selective 5HT2A inverse agonism (Kitten et al., 2018). While approved to treat psychosis in Parkinson's disease, the largest clinical trial of pimavanserin to treat AD-associated agitation and aggression showed no benefit of the drug at 6 to 12 weeks, though some secondary outcomes suggested modest benefit in treating irritability and emotional lability (Ballard et al., 2018).

Antidepressants

Though this class of drugs encompasses numerous agents that alter reuptake of various monoamines, the selective serotonin reuptake inhibitors (SSRIs) are most studied for HIDA domain symptoms. Interestingly, these drugs are notoriously poor for treating affective domain symptoms in AD (Sepehry et al., 2012; Farina et al., 2017), suggesting that their manifestation is unlikely to be similar to that in otherwise healthy, young patients. However, these drugs may be prescribed at rates of 25–42% in patients with dementia (Farina et al., 2017), either owing to their effectiveness in treating agitation and other HIDA domain symptoms or reflecting the limited toolbox that physicians have in treating affective domain symptoms.

Similar to atypical antipsychotics, antidepressants likely provide only a minimal benefit for patients with HIDA domain symptoms (Seitz et al., 2011; Wilkins and Forester, 2016; Farina et al., 2017). Arguably, the best evidence for the roles of SSRIs in the treatment of agitation comes from the CIT-AD trial (Porsteinsson et al., 2014) in which citalopram was shown to reduce agitation symptoms on the Neurobehavioral Rating Scale (NRBS-A), Clinical Global Impression of Change (CGIC), and CMAI over 9 weeks. However, enthusiasm for the use of citalopram to treat HIDA domain symptoms was tempered by the relatively high dose of this medication used in the study (30 mg). Recent FDA guidelines suggest that doses above 20 mg may be dangerous for patients over 60 years of age due to significant QT prolongation (Farina et al., 2017). In addition, the study suggested increased rates of anorexia, diarrhea, fever, and worsening cognition in patients taking citalopram (Porsteinsson et al., 2014), which need to be considered when determining the risk–benefit trade-off for this medication.

The effects of citalopram on reducing agitation in AD likely extend to other SSRIs, supported by a 2011 Cochrane Review (Seitz et al., 2011), suggesting that antidepressants were superior to placebo in treating agitation in dementia. However, while the review implied that citalopram and sertraline had the best evidence, it was unable to comment on the differences in efficacy between them or other antidepressants, and current evidence suggests that antidepressants are equivocal to atypical antipsychotics in terms of efficacy in reducing agitation (Seitz et al., 2011; Wilkins and Forester, 2016). Overall, the use of SSRIs to treat HIDA domain symptoms as an alternative to atypical antipsychotics is promising and may confer lower risks of mortality, stroke, and motor side effects.

There is little evidence for newer antidepressants that target individual 5-HTRs in treating HIDA domain symptoms. For instance, mirtazapine was associated with some benefits for reducing agitation in a 12-week prospective cohort study, but RCTs have yet to be completed (Cakir and Kulaksizoglu, 2008). Similarly, trazodone has shown modest benefits in some cohort studies, but RCTs have not reproduced these findings (Seitz et al., 2011; Farina et al., 2017).

Antiepileptic Drugs

The evidence for the use of antiepileptic drugs, compared with atypical antipsychotics and antidepressants, to treat HIDA domain symptoms remains scarce. The best evidence for antiepileptic drugs exists for valproic acid (VPA; also known as divalproex), for which a recent Cochrane Review of five RCTs suggested that the drug was probably ineffective for treating agitation in dementia (Baillon et al., 2018). Comparatively, a few very small RCTs (combined $n < 100$) implied a modest benefit of carbamazepine, though some trials showed no benefits (Gallagher and Herrmann, 2014). In addition, a meta-analysis supported the efficacy of carbamazepine for treating agitation in AD, but a 103-person RCT did not find a statistically significant benefit (Ballard et al., 2009)

Other antiepileptic drugs are much less well studied, usually having only case reports or small RCTs to support or discourage their use. For instance, gabapentin has a handful of case reports suggesting that it may be effective in treating agitation and aggression in dementia but has no prospective cohorts or RCTs (Supasitthumrong et al., 2019). Lamotrigine similarly has low-quality evidence from a retrospective chart review and open-label

clinical trial showing that it may reduce agitation in dementia (Ng et al., 2009; Suzuki and Gen, 2015). Results for levetiracetam are mixed across two open-label studies of its effect on agitation and manic-like symptoms in the context of BPSD (Weiner et al., 2005; Kyomen et al., 2007). A retrospective chart review of 15 patients suggested some benefits of topiramate for aggression in dementia (Fhager et al., 2003), and a small RCT of 48 patients suggested a similar benefit of topiramate to risperidone in reducing agitation (Mowla and Pani, 2010). Finally, a single RCT of oxcarbazepine, compared with placebo, did not find differences in agitation or aggression (Sommer et al., 2009). Overall, increased investigation of antiepileptic drugs is warranted, and use of them in patients with severe HIDA domain symptoms and resistance to atypical antipsychotics or antidepressants may be warranted in select clinical situations.

Cognitive Enhancers

Though cognitive decline in AD cannot currently be slowed or reversed, select drugs targeting cholinergic and glutamatergic pathways have been prescribed to ameliorate cognitive symptoms in this disease. The best-known drugs in this class are the acetylcholinesterase inhibitors and memantine, an NMDA antagonist. In general, acetylcholinesterase inhibitors are often used during the milder stages of AD, while memantine is often given as AD progresses to more moderate or severe stages. Because these drugs are often prescribed to patients with AD and other dementias, they are also well studied in terms of their effects on the HIDA domain, though often as secondary or exploratory analyses of larger trials.

Regarding acetylcholinesterase inhibitors, evidence for their efficacy in treating HIDA domain symptoms remains inconsistent. For instance, two meta-analyses have suggested that acetylcholinesterase inhibitors like donepezil may provide moderate benefits in reducing BPSD (Birks, 2006; Lockhart et al., 2011). However, an RCT of 272 patients did not find that donepezil reduced agitation or total NPI score (Howard et al., 2007). Finally, a systematic review of three acetylcholinesterase inhibitors suggested that only 3 out of the 14 included RCTs demonstrated a benefit of any acetylcholinesterase inhibitors on total NPI scores, agitation, or aggression, and the effect sizes were just at or below the minimum threshold for clinical significance (Rodda et al., 2009).

Results for memantine are similar. A recent Cochrane Review (McShane et al., 2019) suggested high-certainty evidence from 14 trials including 3,700 patients that memantine improves performance on the Clinical Global Ratings Scale (CGR), cognitive function, performance on the Severe Impairment Battery (SIB), and total NPI scores. However, the review concluded that while agitation occurred at a lower rate for patients treated with memantine, the drug provided no benefits when used to treat agitation specifically. Overall, the study suggested that although memantine was moderately effective in treating cognitive symptoms, it was unlikely to be an appropriate monotherapy for agitation. In conclusion, while acetylcholinesterase inhibitors and memantine may have small benefits on HIDA domain symptoms when used for their initial indications, it is unlikely they will provide much added benefits as monotherapy for HIDA domain symptoms.

Other Pharmacological Agents

Most other studied drugs to treat the HIDA domain symptoms have scant evidence to support their use, and even fewer have undergone testing in RCTs. However, there are a few promising candidates that deserve to be investigated in more detail.

One of these is dextromethorphan–quinidine (AVP-923), a combination drug acting on multiple receptors, including NMDA antagonism, σ1 receptor agonism, serotonin and norepinephrine reuptake inhibition, and nicotinic α3β4 receptor antagonism. In the USA and Europe, this drug has already been approved to treat pseudobulbar affect in amyotrophic lateral sclerosis (ALS). Excitingly, a recent RCT of 194 AD patients over 10 weeks (Cummings et al., 2015) demonstrated that AVP-923 improved aggression and agitation scores as measured by the NPI and was similarly effective at different stages during the disease. In addition, secondary analyses suggested that the drug effectively lowered irritability and emotional lability, aberrant motor behavior, and caregiver strain as measured by the NPI. In conjunction, a recent network meta-analysis suggested that risperidone and AVP-923 were the only two drugs to reach significance for treating dementia-related agitation (Kongpakwattana et al., 2018). Though longer-term follow-up is needed to evaluate the full potential of AVP-923, this drug may represent another tool for physicians to use in treating HIDA domain symptoms.

Drugs that target noradrenergic receptors are another set of medications that have been suggested for treating HIDA domain symptoms. For instance, prazosin, an α1 receptor blocker, successfully decreased agitation and aggression symptoms in 22 nursing home or community-dwelling adults with AD (Wang et al., 2009). In addition, there are a few scarce reports and one small trial of the beta-blockers propranolol and pindolol demonstrating that these drugs can significantly reduce dementia-related agitation (Peskind et al., 2005; Passmore et al., 2008). Further investigation of these drugs in larger RCTs would be helpful.

Cannabinoids have also been tried in the treatment of HIDA domain symptoms. Specifically, while two RCTs studying THC found no benefits of the compound in treating agitation or other BPSD symptoms as measured by the NPI, five trials of dronabinol demonstrated a reduction in agitation, motor activity, and total NPI score (Sherman et al., 2018). As cannabinoid research continues to progress, it will be interesting to see if these medications truly benefit patients with HIDA domain symptoms.

Lastly, the atypical anxiolytics tandospirone and buspirone, which block 5HT1A, have been suggested as potential treatments for the HIDA domain. Specifically, there have been a few case reports (Passmore et al., 2008) and one retrospective study (Santa Cruz et al., 2017) of buspirone that have implied its efficacy in reducing agitation and aggression in dementia. Similarly, an open-label study of 13 dementia patients treated with tandospirone suggested reduction in NPI scores corresponding to delusions, agitation, depression, anxiety, and irritability at 2 and 4 weeks after administration (Sato et al., 2007). As the side-effect profiles

of these drugs are particularly mild, RCTs with these drugs in treating HIDA domain symptoms would be beneficial.

Antipsychotics and Histone Deacetylase (HDAC) Inhibitors: a Novel Approach With Epigenetics

Though other approaches to reduce HIDA domain symptoms are being investigated, first-line pharmacotherapy for these symptoms is still likely to be atypical antipsychotics. However, the severity of adverse effects in elderly patients appropriately gives many physicians pause in prolonged prescribing of these medications. Biologically, both aging and AD are known to result in a number of epigenetic alterations, and within the central nervous system (CNS), many of these alterations lead to a more repressive transcriptional environment, reducing expression of key receptors that atypical antipsychotics target (Mastroeni et al., 2010; Zhang et al., 2012; Akbarian et al., 2013; Cacabelos and Torrellas, 2015; McClarty et al., 2018). As patients age, the efficacy of atypical antipsychotics decreases while the frequency and severity of adverse effects increase, effectively leading to lower doses of medications prescribed but also less benefit at those doses, thus narrowing the therapeutic window (Schneider et al., 2006; Passmore et al., 2008; Maher et al., 2011). We hypothesized that aging-related histone deacetylation at certain gene promoter regions decreases the expression and functioning of drug-targeted receptors, therefore limiting this window in elderly patients. This was corroborated by studies showing that elderly patients had reduced expression and occupancy of D2R and 5-HT2AR *via* positron emission tomography (PET) and single-photon emission computed tomography (SPECT) imaging (Antonini et al., 1993; Versijpt et al., 2003).

Our own preclinical studies in aged and young mice support our hypothesis. Specifically, we showed that during aging, certain lysine residues on histones 3 and 4 become hypoacetylated at the *Drd2* promoter, leading to reduced D2R expression and greater sensitivity to extrapyramidal side effects of haloperidol (Montalvo-Ortiz et al., 2017). Importantly, we also showed that HDAC inhibition *via* VPA or entinostat (MS-275) can reverse the repressive histone marks, increase D2R expression, and reverse the aging-related sensitivity to haloperidol (Montalvo-Ortiz et al., 2017). Additionally, we demonstrated that c-Fos expression in response to antipsychotics in the frontal cortex could be modified by these HDAC inhibitors, thus suggesting that the efficacy of antipsychotics could be impacted by histone modifications with aging (Montalvo-Ortiz et al., 2014). In non-aged mice, there is evidence that chronic administration of atypical antipsychotics leads to 5-HT2AR-mediated repression of histone modifications at the mGlu2 promoter (Kurita et al., 2012). Kurita and colleagues demonstrated that combined administration of the HDAC inhibitor vorinostat (suberoylanilide hydroxamic acid (SAHA)) with clozapine or risperidone rescued 5-HT2AR-mediated repression of histone modification at the mGlu2 promoter and attenuated schizophrenia-like behavior. Whether repressed histone modification at the mGlu2 promoter primarily affects the efficacy of atypical antipsychotics in aged mice has yet to be shown. However, this study provides evidence that general alterations in histone modification are likely at play.

Similar to healthy aging, AD is also associated with various epigenetic changes that are thought to exacerbate pathological processes while simultaneously repressing nonpathological processes, thus contributing to disease progression (Mastroeni et al., 2010; Zhang et al., 2012). Concordantly, imaging studies have demonstrated significant reductions in 5-HT2AR expression and binding in patients with various stages of AD than in age-matched controls (Versijpt et al., 2003; Hasselbalch et al., 2008; Marner et al., 2012). It is, therefore, likely that in patients with AD, the effects of epigenetic changes associated with aging are compounded by the disease process itself, significantly reducing the availability of receptors on which atypical antipsychotics act. As a result, HDAC inhibition may have a dual effect in reducing the adverse side effects of long-term atypical antipsychotics and improving other symptoms of AD pathogenesis.

A number of studies have already examined monotherapy with HDAC inhibition in various preclinical mouse models of AD, revealing that HDAC inhibitors can improve memory performance in these mice (Francis et al., 2009; Corbett et al., 2017; Cuadrado-Tejedor et al., 2017; Cao et al., 2018). Interestingly, HDAC inhibitors are also being explored in clinical trials as monotherapy for cognition in dementia (Teijido and Cacabelos, 2018). Studies regarding the efficacy of HDAC inhibition in the context of BPSD specifically are limited, however, and findings are, therefore, inconclusive. Some research indicates that HDAC inhibitors do not ameliorate anxiety-like behavior and hyperactivity in mouse models of AD (Cao et al., 2018), whereas other studies demonstrate reduced hyperactivity and apathy-like behavior (Zhang and Schluesener, 2013; Selenica et al., 2014; Cathomas et al., 2015). It is worth noting that these studies have only investigated the effects of HDAC inhibition alone. There have yet to be any studies in which HDAC inhibitors are used in combination with other treatments such as antipsychotics in the context of BPSD, which warrants future research. Though it is unclear if HDAC inhibitors may directly be prescribed to treat the HIDA domain or other BPSD, it is an intriguing hypothesis that the addition of these drugs to atypical antipsychotics may result in increased efficacy and reduced side effects. As reversal of the extrapyramidal side effects has been the focus of current studies, investigation into the effects of these compounds on antipsychotic-induced cerebrovascular dysfunction in aged mice or patients may be especially promising.

BEYOND AGITATION AND AGGRESSION

As evidenced in this review, most studies targeting the HIDA domain have mainly focused on agitation and aggression. Only a handful of quality trials have examined effects on patients' aberrant motor activity or irritability (Cott et al., 2002; Dowling et al., 2007; Raglio et al., 2008; Cummings et al., 2015; Ballard et al., 2018; Sherman et al., 2018), and additional studies are needed in order to determine which approaches are most efficacious in treating these symptoms. Within the HIDA domain, RCTs of interventions for impulsivity and

disinhibition are severely lacking. Similarly, there have been no RCTs assessing the efficacy of specific pharmacological or non-pharmacological approaches in treating these symptoms in AD (Tucker, 2010; Cipriani et al., 2016).

The discussion of treatment strategies to mitigate general disinhibition or impulsive behavior in AD patients within the literature is essentially nonexistent. Thus, current suggestions for treatment of these symptoms within this population are based on studies of these symptoms in other forms of dementia, such as frontotemporal dementia (FTD). One small, unblinded trial demonstrated that 67% of FTD patients with disinhibition who received SSRIs—namely, paroxetine, sertraline, and fluoxetine—experienced reductions in this symptom (Swartz et al., 1997). However, the authors did not report on the statistical significance of these reductions. Other small, open-label drug trials have demonstrated that treatment with SSRIs, such as citalopram and trazodone, can lead to significant reductions in disinhibition in patients with FTD (Lebert and Pasquier, 1999; Herrmann et al., 2012). Regarding potentially inefficacious pharmacotherapy for treating disinhibition, one study found that FTD patients treated with donepezil tended to demonstrate increased socially disinhibited behavior, such as inappropriate remarks or unusual interactions with strangers (Mendez et al., 2007). In the case of non-pharmacological interventions, the literature examining treatments for disinhibition and impulsivity in the context of dementia is even more scarce. However, case examples demonstrate that having patients with FTD engage in old hobbies or games may attenuate socially inappropriate, disinhibited behavior, potentially utilizing a similar mechanism as therapeutic activities that target agitation and aggression by reducing boredom and inactivity (Ikeda et al., 1995).

One common form of disinhibited behavior in AD is sexual disinhibition, defined as sexually oriented, verbal or physical acts that are inappropriate within the contexts that they are performed (Johnson et al., 2006). Regarding non-pharmacological methods to mitigate sexual disinhibition, the literature suggests redirecting behavior, expressing its inappropriateness, substituting staff who are less likely to trigger it, ignoring inappropriate and reinforcing appropriate behaviors, and providing patients with certain clothing that limits the likelihood of these behaviors (e.g., clothing that opens from the back; Kamel and Hajjar, 2003). In terms of pharmacotherapy, case studies and small, unblinded trials suggest that SSRIs—namely, citalopram—may have the potential to reduce sexual disinhibition in patients with dementia (Tosto et al., 2008). Case studies also suggest that the anticholinesterase inhibitor rivastigmine might be helpful for this symptom, whereas donepezil might increase sexual disinhibition (Alagiakrishnan et al., 2003; Lo Coco and Cannizzaro, 2010). Antiepileptics such as gabapentin and carbamazepine may ameliorate sexually disinhibited behavior in some patients with dementia (Miller, 2001; Alkhalil et al., 2004; Freymann et al., 2005). Regardless of these interventions' potential, substantial additional research is needed before reliable conclusions about efficacy and recommendations for the treatment of sexual disinhibition in dementia can be made.

CONCLUSIONS AND FUTURE DIRECTIONS

Summary of Effective and Promising Interventions for HIDA Domain Symptoms

Research findings suggest that the best non-pharmacological treatments for HIDA domain symptoms include training programs in person-centered care for staff and psychoeducation for staff and caregivers (McCallion et al., 1999; Hébert et al., 2003; Sloane et al., 2004; Fossey et al., 2006; Hepburn et al., 2007; Chenoweth et al., 2009; Deudon et al., 2009). Approaches that holistically assess and address patients' unmet needs have shown to have significant benefits during periods of intervention, warranting future studies of how to implement these approaches long-term on a continuous basis (Cohen-Mansfield et al., 2007; Cohen-Mansfield et al., 2012). Although studies have not specifically examined the benefits of CBT on HIDA domain symptoms, evidence for lasting reductions in overall BPSD and affective domain symptoms calls for additional research into the efficacy of CBT for agitation an aggression (Marriott et al., 2000; Akkerman, 2004; Kurz et al., 2012; Kwok et al., 2014; Spector et al., 2015). Unlike certain person-centered and behavioral interventions, sensory stimulation interventions either have mixed evidence or have been shown to be generally ineffective in ameliorating HIDA domain symptoms (Robichaud et al., 1994; Alessi et al., 1999; Baker et al., 2001; Smallwood et al., 2001; Buettner and Fitzsimmons, 2002; Fitzsimmons and Buettner, 2002; Ballard et al., 2002; Holmes et al., 2002; Cott et al., 2002; Remington, 2002; van Diepen et al., 2002; Ancoli-Israel et al., 2003; Baker et al., 2003; Baillon et al., 2004; Snow et al., 2004; Dowling et al., 2007; Garland et al., 2007; Lin et al., 2007; Rolland et al., 2007; Hicks-Moore and Robinson, 2008; Raglio et al., 2008; Burns et al., 2009; Cooke et al., 2010; Eggermont et al., 2010; Burns et al., 2011; Kolanowski et al., 2011; Sung et al., 2012; Fu et al., 2013; O'Connor et al., 2013; Lowery et al., 2014; Moyle et al., 2014; Sánchez et al., 2016a; Sánchez et al., 2016b). However, studying sensory stimulation in the context of person centered or needs driven may produce more beneficial results.

Regarding pharmacotherapy, atypical antipsychotics are most commonly prescribed to treat HIDA domain symptoms, but their long-term use in elderly patients is severely limited due to an increased risk of extrapyramidal side effects, stroke, and death (Margallo-Lana et al., 2001; Schneider et al., 2006; Passmore et al., 2008; Ballard and Corbett, 2010; Maher et al., 2011; Koenig et al., 2016; Kongpakwattana et al., 2018). Moreover, there is poor consensus as to which atypical antipsychotic is most efficacious (Yunusa et al., 2019). For antidepressants, SSRIs are the most common type prescribed for agitation and aggression in patients with dementia, but like atypical antipsychotics, they are only modestly effective in treating HIDA domain symptoms (Seitz et al., 2011; Porsteinsson et al., 2014; Wilkins and Forester, 2016; Farina et al., 2017). Still, it may be more beneficial to prescribe SSRIs than atypical antipsychotics in elderly patients because the risks of mortality, stroke, and extrapyramidal side effects are lower. However, whether the effects of these drugs are helpful for long-term control of HIDA domain symptoms is unclear. The evidence for other pharmacological approaches either does not support

their use, as is the case for VPA, or is in its infancy, as is the case for AVP-923 (Fhager et al., 2003; Weiner et al., 2005; Birks, 2006; Howard et al., 2007; Kyomen et al., 2007; Ballard et al., 2009; Ng et al., 2009; Rodda et al., 2009; Sommer et al., 2009; Mowla and Pani, 2010; Lockhart et al., 2011; Gallagher and Herrmann, 2014; Cummings et al., 2015; Suzuki and Gen, 2015; Baillon et al., 2018; Kongpakwattana et al., 2018; Sherman et al., 2018; McShane et al., 2019; Supasitthumrong et al., 2019). Overall, substantial improvement is needed to increase the efficacy and reduce the side effects of pharmacotherapies for HIDA domain symptoms.

Improving Treatment Implementation

Despite the fact that most professional geriatric medicine organizations recommend implementation of non-pharmacological therapies for BPSD first, medications are disproportionately favored to manage BPSD in clinical settings. One study revealed that in comparison with 71% of elderly nursing home residents who received pharmacotherapy, only 12% received non-pharmacological treatment (Molinari et al., 2010). Moreover, another study found that less than half of nursing home patients receiving antipsychotics had been prescribed in compliance with nursing home standards, and many were taking more than the maximum recommended dose or did not meet adequate symptom criteria for the prescription (Briesacher et al., 2005).

One reason for the disproportionately low use of non-pharmacological interventions for BPSD in real-world clinical settings is that properly assessing symptoms and implementing these treatments are time-consuming, and facilities often do not have adequate personnel (Kales et al., 2014). Similarly, research findings suggest that about half of nursing homes do not feel that they receive adequate psychiatric consultation, specifically in regard to non-pharmacological approaches (Reichman et al., 1998). It is also more difficult to get non-pharmacological interventions, compared with pharmacotherapy, reimbursed by insurance (Kales et al., 2014).

One of the most prominent reasons that non-pharmacological approaches are not implemented more frequently in clinical settings is the ambiguity that exists about which treatments to use and how to implement them. Methods are not standardized among non-pharmacological interventions of the same type, causing difficulty in interpreting results and in applying treatments in clinical practice (Leone et al., 2009). As a result, guidelines do not agree on their recommendations for specific psychosocial therapies and differ in respect to the quality of empirical support behind their guidance (Azermai et al., 2012). This leaves caregivers and clinicians with the burden of deciding which interventions are best. As there is no clear consensus on this, many physicians lack proper training in non-pharmacological approaches, BPSD assessment, and ways of choosing and communicating these interventions to caregivers (Kales et al., 2014).

To strengthen the consensus regarding non-pharmacological interventions, some researchers assert that evidence-based protocols and additional studies with greater methodological quality, particularly large RCTs, are necessary (Livingston et al., 2005; Kong et al., 2009; Vernooij-Dassen et al., 2010; Azermai, 2015; Scales et al., 2018). However, given that person-centered approaches tailored to individual patients appear to be the most efficacious, others have questioned the extent to which non-pharmacological approaches can be standardized and studied in large RCTs (Cohen-Mansfield, 2013).

To reconcile both of these perspectives and to integrate the implementation of both pharmacological and non-pharmacological interventions in practice, Kales and colleagues developed the describe, investigate, create, evaluate (DICE) approach (Kales et al., 2014). It involves detailed characterization of a patients' BPSD and the context in which they occur, exploration and identification of potential underlying causes for disruptive behaviors, collaboration with both caregivers and patients to develop and implement a treatment plan, and evaluation of the extent to which a treatment plan was carried out and was effective. Future research may utilize the DICE approach to conduct controlled trials that differentiate non-pharmacological strategies on their most efficacious attributes without sacrificing the individualized component of treatment. Additionally, the DICE approach's detailed symptom characterization and treatment evaluation may help to elucidate which patients will benefit most from certain pharmacotherapies.

To address concerns regarding inadequate resources in clinical settings for characterizing symptoms, implementing non-pharmacological interventions, and evaluating treatment responses, the literature suggests the use of environmental and wearable sensors (Bharucha et al., 2009; David et al., 2010; Kikhia et al., 2015). By continuously measuring patients' behavior, these sensors are capable of detecting changes from routine and of collecting much more data than is possible with a limited nursing home staff or a single caregiver (Kikhia et al., 2015). Regarding side effects to pharmacotherapies, wearable sensors that measure patients' vital signs and metabolic parameters could aid in early detection and intervention before the impact of these side effects becomes catastrophic (Bharucha et al., 2009). Although these methods are still being developed and are not yet widely used in clinical settings, research suggests that implementing them is feasible and well tolerated by patients with dementia. For instance, one study demonstrated that a nighttime monitoring system resulted in an 85% reduction in patients' likelihood to have a dangerous event (e.g., injury due to wandering) due to aberrant nighttime behavior (Rowe et al., 2009). Moreover, this intervention was so well tolerated by patients and their caregivers that all who received it opted to continue using it following the completion of the study. Other research has demonstrated that actigraphy—the use of a small, unobtrusive accelerometer to measure motor activity—is a feasible and inconspicuous method that can indirectly and objectively measure the timing and frequency of various BPSD, including agitation and aberrant motor activity (Volkers et al., 2003; Mahlberg et al., 2007; David et al., 2010; Mulin et al., 2011). Overall, ambient and wearable sensors represent a promising way to improve the implementation of both pharmacological and non-pharmacological interventions for BPSD.

Conclusion

Among various BPSD experienced by the majority of AD patients, HIDA domain symptoms are particularly tough to manage, causing great burden on caregivers and hospital staff and demonstrating an

area of special concern regarding safety (Fuh et al., 2001; Rymer et al., 2002; Nguyen et al., 2008; Fauth and Gibbons, 2014). Difficulty controlling HIDA domain symptoms is compounded by the fact that currently available non-pharmacological and pharmacological interventions are only moderately efficacious. Despite the extensive toolbox of non-pharmacological treatments available, limited resources and guidance have impeded the extent to which they are used in real-world clinical settings (Kales et al., 2014).

Regarding pharmacotherapy, agents that are currently available are either inefficacious or carry the risk for dangerous side effects that outweigh their benefits (Margallo-Lana et al., 2001; Schneider et al., 2006; Passmore et al., 2008; Ballard and Corbett, 2010; Maher et al., 2011; Koenig et al., 2016; Kongpakwattana et al., 2018). However, short-term use of these agents during periods of severe symptoms or psychosis may be necessary, and atypical antipsychotics and SSRIs currently have the best evidence. Newer approaches, including dextromethorphan–quinidine, cannabinoids, and HDAC inhibitors, are promising but will need more rigorous testing in RCTs before determining their use in these patients.

Future research utilizing the DICE approach to perform controlled trials on non-pharmacological interventions may be able to better differentiate non-pharmacological strategies on their most efficacious attributes while also providing individualized treatment (Kales et al., 2014). Moreover, future pharmacological studies that perform detailed symptom characterization and treatment evaluation *via* the DICE approach are more likely to reveal which patients will benefit most from certain pharmacotherapies. To further improve symptom characterization and treatment implementation in the real world, studies should also focus on bettering environmental and wearable sensors to make them more accessible to patients in clinical settings (Bharucha et al., 2009; David et al., 2010).

AUTHOR CONTRIBUTIONS

RK, DF, and HD decided upon the outline for this manuscript. RK and DF reviewed the literature extensively. All authors contributed to the writing and approval of this manuscript.

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MINI REVIEW
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Pharmacological Treatment of Depression in Alzheimer's Disease: A Challenging Task

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Besides the memory impairment, Alzheimer's disease (AD) is often complicated by neuropsychiatric symptoms also known as behavioral and psychological symptoms of dementia, which occur in one-third of patients at an early stage of the disease. Although the relationship between depressive disorders and AD is debated, the question if depression is a prodromal symptom preceding cognitive deficits or an independent risk factor for AD is still unclear. Moreover, there is growing evidence reporting that conventional antidepressants are not effective in depression associated with AD and, therefore, there is an urgent need to understand the neurobiological mechanism underlying the resistance to the antidepressants. Another important question that remains to be addressed is whether the antidepressant treatment is able to modulate the levels of amyloid-β peptide (Aβ), which is a key pathological hallmark in AD. The present review summarizes the present knowledge on the link between depression and AD with a focus on the resistance of antidepressant therapies in AD patients. Finally, we have briefly outlined the preclinical and clinical evidences behind the possible mechanisms by which antidepressants modulate Aβ pathology. To our opinion, understanding the cellular processes that regulate Aβ levels may provide greater insight into the disease pathogenesis and might be helpful in designing novel selective and effective therapy against depression in AD.

Keywords: Alzheimer's disease, depression, amyloid-β peptide, tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin

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INTRODUCTION

Alzheimer's disease (AD) is the most common type of dementia in western countries, corresponding to about 60% of the cases while vascular dementia is the second, with 20% of all the cases (Kalaria et al., 2008; Rizzi et al., 2014). According to World Alzheimer's report 2018, 50 million people worldwide are living with dementia, and this number is projected to increase to more than 150 million by 2050 (https://www.alz.co.uk/research/WorldAlzheimerReport2018).

Memory dysfunction is a symptomatic feature of AD, which is characterized pathologically by amyloid-β peptide (Aβ) deposition and neurofibrillary tangles (NFTs) (Querfurth and LaFerla, 2010; Tramutola et al., 2018; Sharma et al., 2019).

Besides the memory impairment, AD is often complicated by neuropsychiatric symptoms also known as behavioral and psychological symptoms of dementia (BPSD), which occur in one-third of patients at an early stage of the disease (Assal and Cummings, 2002). In particular, BPSD in AD patients include among others, hallucination, sleep disorder, depression and anxiety, appetite disorder, and hyperactivity (Aalten et al., 2007; Bellanti et al., 2017). This comorbidity complicates diagnosis, influences treatment strategies, outcomes and finally quality of life, and affects individuals and caregivers (Modrego, 2010).

Studies from clinical settings have suggested that the prevalence of a "major depressive episode" in AD patients is 20–25%, with other depressive syndromes, including minor depression affecting an additional 20–30% of patients (Pearlson et al., 1990; Assal and Cummings, 2002; Shim and Yang, 2006; Richard et al., 2013; Leong, 2014). AD patients with major depression show a greater and faster cognitive impairment compared to non-depressed patients (Milwain and Nagy, 2005) and, surprisingly, neuritic plaques and NFTs are more evident in the cerebral parenchyma of AD patients with comorbid depression than non-depressed AD patients (Rapp et al., 2008).

Although the link between depressive disorder and AD is debated, the question whether depression is a prodromal symptom or an independent risk factor for AD still remains unresolved. Moreover, there is growing evidence in the literature that conventional antidepressants are not effective in depression accompanied by AD (Pomara and Sidtis, 2007) and, therefore, there is an urgent need to understand the neurobiological mechanism underlying the resistance to the antidepressants.

Hence, we examined the possible link between depression and AD, and we focused on the resistance of antidepressant therapies in dementia. Subsequently, we explored probable mechanisms by which antidepressants modulate Aβ pathology. The latter evidence may be helpful in designing novel selective and effective therapy against depression in AD.

RELATIONSHIP BETWEEN DEPRESSION AND AD: PRODROMAL SYMPTOM OR RISK FACTOR?

To date, converging evidence suggests that depression may represent a risk factor for the development of AD (Steffens et al., 1997; Modrego and Ferrández, 2004; Bartolini et al., 2005; Ownby et al., 2006), mostly when depressive symptoms occur more than 10 years before the onset of AD (Speck et al., 1995). To this regard, a systematic meta-analysis study evaluated whether observed risk for developing AD was related to the interval between diagnosis of depression and AD (Ownby et al., 2006). The authors found that there was a positive correlation between this interval and the risk of developing AD, suggesting that, rather than a prodrome, depression can be considered as a risk factor for AD. This study reported that patients with a history of depression were more prone to be affected by AD later in life (Ownby et al., 2006).

Several hypotheses could be proposed for this interpretation and summarized in **Figure 1**. High cortisol levels or hypothalamic–pituitary–adrenal (HPA) axis dysregulation has been associated to depression symptoms and alteration of learning and memory (Swaab et al., 2005). Corticosteroid receptors are particularly abundant in the hippocampus, which is one of the main brain regions affected by AD pathology, and their excessive stimulation may be detrimental leading to neuronal death through an apoptotic mechanism (Sapolsky, 2000; Lee et al., 2002).

It has been demonstrated that pro-inflammatory cytokines play an important role in the expression of the clinical symptoms of depression in AD patients. In particular, tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-6 are increased during depression, as well as associated with cognitive impairment (Parissis et al., 2004; Suarez et al., 2004; Wuwongse et al., 2010).

Moreover, neurotrophic factors have a protective action against toxic agents, which may induce neurodegeneration. Chronic treatment with antidepressants up-regulate the expression of neurotrophic factors increasing hippocampal neurogenesis (Mattson, 2004).

The elevation of cortisol and pro-inflammatory cytokines, as well as the reduction of neurotrophic factors, may lead to alterations in the monoaminergic neurotransmitters, which are downregulated in either depression or AD (Reinikainen et al., 1990; Romano et al., 2014). To this regard, it has been demonstrated that depressed patients affected by AD show neuronal degeneration in locus coeruleus and raphe nuclei, both brain regions implicated in depression (Zubenko et al., 1990). Preclinical and clinical studies have demonstrated that reduced levels of brain serotonin (5-HT) and norepinephrine occur in depression, and antidepressants lead to an increase of both neurotransmitter activities in the brain (Chen and Skolnick, 2007). Yet, similar neurotransmitter alterations are also present in AD, as we have also demonstrated in an animal model of AD (Reinikainen et al., 1990; Romano et al., 2014).

Although many treatment options are available, several clinical trials suggest that antidepressants for the treatment of depression in AD patients appear ineffective (Pomara and Sidtis, 2007; Sepehry et al., 2012). To this regard, the results of the completed United States NIMH-funded, large-scale STAR*D effectiveness trial reported a remission rate of only 70% after 12 months with up to four treatment steps (Insel and Wang, 2009). In general, the tricyclic antidepressants (TCA) are less prescribed to AD patients with depression due to their serious cardiac and anticholinergic side effects (Raji and Brady, 2001; Banerjee et al., 2013), while the selective serotonin reuptake inhibitors (SSRIs) are the most prescribed drugs although evidence for their efficacy in this population is controversial (Nyth et al., 1992; Katona et al., 1998).

To date, no medication has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of depressive symptoms in AD. Some of the evidence found in geriatric population has demonstrated that antidepressant therapy can improve the depression after 4–6 weeks of treatment (Wilson et al., 2001). However, its efficacy and safety remain inconclusive in individuals with AD, and it can be a challenging task to evaluate the role and mechanisms of antidepressants in subjects with AD

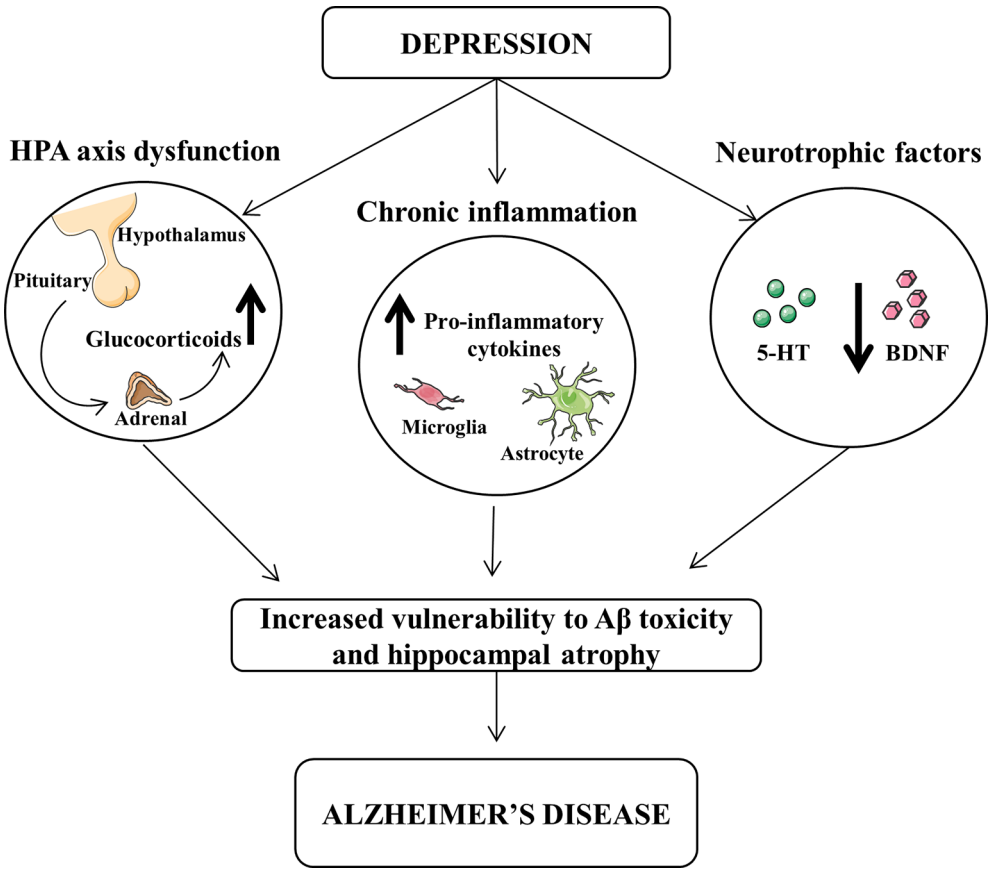

FIGURE 1 | Dysfunction of hypothalamic-pituitary-adrenal (HPA) and decrease of neurotrophic factors and chronic inflammation exert a central role in the pathophysiology of both depression and Alzheimer's disease (AD). The increased levels of glucocorticoids and pro-inflammatory cytokines, as well as the reduced levels of brain-derived neurotrophic factor (BDNF) and serotonin (5-HT) may lead to an increased vulnerability of β-amyloid toxicity and hippocampal atrophy, thus favoring the progression from depression to AD.

(Leong, 2014; Lozupone et al., 2018). Numerous mechanisms underlying resistance to antidepressants in patients with AD have been hypothesized (for review, see Lozupone et al., 2018). In upcoming future, for developing specific and effective therapy against depression in AD, studies investigating compounds targeting alternative signal transduction pathways are warranted.

ANTIDEPRESSANT TREATMENTS MODULATE Aβ LEVELS

Postmortem analyses of brain patients and studies on transgenic animal models have demonstrated that the major neuropathological hallmarks of AD are the extracellular deposits of Aβ plaques abundant mainly in the cortex and hippocampus (Oakley et al., 2006; Oddo et al., 2006; LaFerla et al., 2007; Cassano et al., 2011; Gatta et al., 2016). Moreover, numerous preclinical studies have firmly demonstrated that the accumulation of intracellular Aβ precedes extracellular plaque formation (Oakley et al., 2006; Oddo et al., 2006; LaFerla et al., 2007). Indeed, it has been demonstrated that intraneuronal Aβ levels decrease as extracellular plaques accumulate.

A number of pathogenic mechanisms triggering the neurodegenerative phenomena and leading to neuronal death have been described. Among them, a crucial role seems to be played by inflammation (Bronzuoli et al., 2018; Scuderi et al., 2018; Bronzuoli et al., 2019), oxidative damage (Reddy et al., 2009; Serviddio et al., 2011; Cassano et al., 2012; Cassano et al., 2016; Giudetti et al., 2018), iron deregulation (Adlard and Bush, 2006), and cholesterol metabolism (Stefani and Liguri, 2009; Barone et al., 2016). Therefore, novel therapeutical strategies aim to interfere with those pathogenic mechanisms at an early stage of the disease in order to stop/slow down the neurodegenerative process. For this reason, they have been termed "disease-modifying" drugs and should be administered to patients many years before the appearance of the first AD symptoms (Morris and Price, 2001). Consequently, if anti-Aβ therapies may be used for years or decades, then very safe compounds will likely be necessary. To this regard, SSRIs are good candidates for this purpose since their side effects are generally well tolerated, even with chronic use. In support to such hypothesis, it has been demonstrated that SSRIs reduce risk of AD in depressed individuals (Kessing et al., 2009). Therefore, individuals with a history of chronic use of antidepressant drug use may have reduced Aβ plaques and, as a result, a reduced risk of AD. Nevertheless, although this hypothesis

has been postulated, it is still matter of debate whether antidepressant treatment rises or declines the level of Aβ in the brain. To this purpose, many researchers have investigated whether the activation of 5-HT receptors can regulate Aβ metabolism. **Figure 2** and **Table 1** summarize the molecular mechanisms by which antidepressant drugs may induce a reduction of the Aβ levels.

Interestingly, in a preclinical study, it has been demonstrated that extracellular Aβ levels were decreased by 25% following the acute administration of several SSRI antidepressant drugs (fluoxetine, desvenlafaxine, and citalopram) and that chronic treatment with citalopram caused a 50% reduction Aβ plaques in the cortex and hippocampus of a mouse model of AD (Cirrito et al., 2011). In this study, authors demonstrated that SSRI can modulate APP processing through the activation of extracellular regulated kinase (ERK) pathway, which has been shown to suppress Aβ production *in vitro* and *in vivo* by increasing α-secretase cleavage of APP (Kim et al., 2006; Kojro et al., 2006). Once activated, ERK is able to phosphorylate specific effector proteins modulating a wide range of responses within the cytoplasm and the nucleus altering, in turn, the transcription of a wide range of genes (Kim et al., 2006; Kojro et

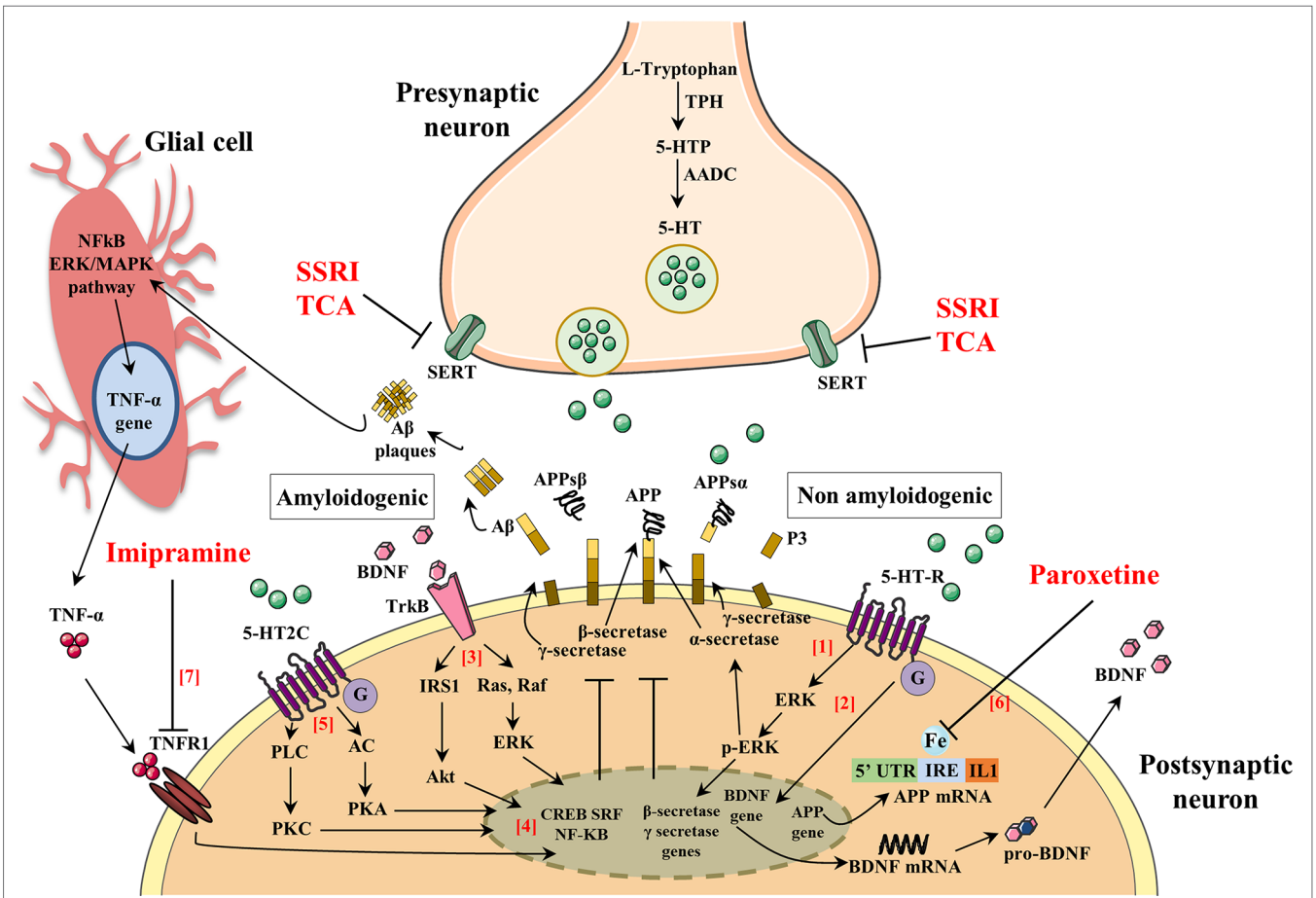

FIGURE 2 | The activation of serotonin receptors (5-HT-R) initiates a signaling cascade that leads to the activation of extracellular signal-regulated kinases (ERK). Once activated, p-ERK increases α-secretase activity and reduces β- and γ-secretase cleavage of APP (1). Brain-derived neurotrophic factor (BDNF) and serotonin (5-HT) regulate synaptic plasticity, neurogenesis, and neuronal survival. The activation of 5-HT-R stimulates the expression of BDNF, which in turn enhances the growth and survival of 5-HT neurons (2). BDNF binds to its high-affinity tyrosine receptor kinase B (TrkB) resulting in the recruitment of proteins that activate two different signal transduction cascades: (i) insulin receptor substrate-1 (IRS-1), phosphatidylinositol-3-kinase (PI-3K), and protein kinase B (Akt) and (ii) Ras, Raf, and extracellular signal regulated kinases (ERK) (3). BDNF signaling pathways activate one or more transcription factors that regulate the expression of genes encoding proteins. Such transcription factors include cAMP-response-element-binding protein (CREB), serum response factor (SRF), and nuclear factor kappa B (NF-kB) that exert an inhibitory action in the amyloidogenic pathways (4). 5-HT binds 5-HT-2C resulting in the recruitment of proteins that activate two different signal transduction cascades: (i) adenylate cyclase (AC), cAMP, and protein kinase A (PKA) and (ii) phospholipase C (PLC), diacylglycerol (DAG), and protein kinase C (PKC) (5). The 5-HT signaling pathway activates one or more transcription factors that regulate expression of genes encoding proteins (CREB, SRF, and NF-kB) leading to an inhibitory action in the amyloidogenic pathways (4). The 5'-untranslated region (5'UTR) of the APP mRNA is a key regulatory sequence that determines the amount of intracellular APP holoprotein present in brain-derived cells in response to interleukin-1 (IL-1) and iron (IRE). Paroxetine acts as an intracellular iron chelator to limit the translation of APP holoprotein guided by sequences of untranslated APP mRNA 5'UTR regions (6). Tumor necrosis factor α (TNF-α) signaling, through tumor necrosis factor receptor 1 (TNFR1), mainly results in activation of the transcription factors NF-kB and induces pro-inflammatory effects that exacerbate neuroinflammation and secondary neuronal damage. Imipramine blocks TNF-α/TNFR1 signaling and prevents the appearance of cognitive deficits in AD and Aβ formation (7).

TABLE 1 | Effect of antidepressant drugs on Aβ production.

PRECLINICAL STUDIES:

Antidepressant drugs	Subjects	Effects and mechanisms involved	References
Fluoxetine, desvenlafaxine, citalopram (SSRIs)	PS1APP transgenic mice	↓ Aβ levels ↓ Aβ plaques in the cortex and hippocampus ↓ ERK signaling ↑ α-Secretase activity	Cirrito et al., 2011
Paroxetine (SSRI)	3×TgAD mice	↓ Aβ levels ↓ APP production ↓ 5-HT reuptake ↑ BDNF expression	Nelson et al., 2007 Mattson, 2004
Paroxetine (SSRI)	TgCRND8 mice	↓ Aβ levels in the cortex ↓ APP holoprotein translation driven by APP mRNA 5′ untranslated region sequences	Tucker et al., 2005 and Tucker et al., 2006
Paroxetine (SSRI)	Neuroblastoma cells (SY5Y)	↓ APP holoprotein translation driven by APP mRNA 5′ untranslated region sequences	Morse et al., 2004
Imipramine (TCA)	Rat primary basal forebrain cultures	↑ APP secretion ↑ PKC level	Pákáski et al., 2005
Citalopram (SSRI)	Rat primary basal forebrain cultures	↑ APP secretion = PKC level	Pákáski et al., 2005
Imipramine (TCA)	Swiss mice after intracerebroventricular injection of $A\beta_{25-35}$	↓ Aβ levels in the frontal cortex ↓ TNF-α level	Chavant et al., 2010

HUMAN STUDIES:

Antidepressant drugs	Subjects	Effects	References
SSRI TCA Trazodone Venlafaxine (SNRI) Bupropion Mirtazapine (NaSSA)	Plasma of elderly depressed patients	= $A\beta_{42}$ levels ↓ $A\beta_{40}$ levels	Sun et al., 2007
Paroxetine (SSRI) Nortriptyline (TCA)	Plasma of elderly patients with late-life major depression	= $A\beta_{42}$ levels ↑ $A\beta_{42}/A\beta_{40}$ ratio	Pomara et al., 2006
Conventional antidepressants	Plasma of young patients affected by major depressive disorder	= Aβ levels ↑ $A\beta_{42}/A\beta_{40}$ ratio	Kita et al., 2009

SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; SNRI, serotonin–norepinephrine reuptake inhibitor; NASSA, noradrenaline and specific serotonergic antidepressant.

al., 2006). Therefore, authors showed that a reduction of Aβ levels in a mouse model of AD was obtained after both acute and chronic citalopram treatments through an increase of α-secretase activity (Cirrito et al., 2011). These and many other findings suggest that the activation of 5-HT receptors by SSRI may have an "upstream" role within the amyloid cascade that may modulate the proteases involved in Aβ production itself.

Moreover, SSRI treatment showed similar effect in a triple transgenic murine model of AD (3×Tg-AD), which harbors three mutant human genes (APPswe, PS1M146V, and tauP301L) and exhibited a depressive-like phenotype with deficits of monoaminergic neurotransmissions (Oddo et al., 2003; Nelson et al., 2007; Romano et al., 2014; Scuderi et al., 2018; Barone et al., 2019; Cassano et al., 2019). Nelson and colleagues reported that pre-symptomatic treatment with the antidepressant paroxetine reduces Aβ pathology in the hippocampus and improves cognitive performance in the 3×TgAD mice (Nelson et al., 2007). In particular, 5-month-old 3×Tg-AD mice were treated for 5 months with a dose of paroxetine that inhibits 5-HT reuptake and ameliorates behavioral deficits in mouse models of anxiety and depression (Cryan et al., 2004; Goeldner et al., 2005). Taking together these results and considering the safe profile of paroxetine after chronic treatment also in elderly patients, the authors suggested that paroxetine might be a valuable therapeutic option for depressed human subjects with early AD symptoms.

The beneficial effects of paroxetine seem to be mediated by the inhibition of 5-HT reuptake resulting in both enhanced serotonergic signaling and upregulation of brain-derived neurotrophic factor (BDNF) expression (Mattson, 2004). Preclinical and clinical studies have highlighted that there is a tight interplay between SSRI treatment and BDNF expression. In particular, results from animal studies have demonstrated that paroxetine elevates both 5-HT and BDNF in huntingtin mutant mice reducing the onset and progression of the disease (Duan et al., 2004), as well as BDNF expression was increased in both hippocampus and cortex after its chronic administration in rodents (Nibuya et al., 1995; Nibuya et al., 1996). Moreover, antidepressant effects were observed when BDNF was directly

injected into the rodent hippocampus (Siuciak et al., 1997; Shirayama et al., 2002). Furthermore, in human studies, it has been shown that (i) AD patients showed low levels of both 5-HT (Gottfries, 1990) and BDNF (Hock et al., 2000; Lee et al., 2005) in the hippocampus and cortex, and that (ii) antidepressants were able to increase also BDNF levels (Chen et al., 2001; Dwivedi et al., 2003).

Besides BDNF and 5-HT, antidepressant drugs may exert their effects also *via* different pathways. In fact, paroxetine seems to target APP gene expression through the 5'-untranslated region (5'UTR) of the precursor transcript suppressing translation of the APP protein (Morse et al., 2004; Tucker et al., 2005). The 5'UTR of the transcript encoding the APP (APP 5'UTR) is an important regulatory sequence that regulates the amount of intracellular APP holoprotein present in neuron cells in response to interleukin-1 (IL-1) (acute box-domain) (Rogers et al., 1999) and iron (Rogers et al., 2002). Within the 5'UTR of the APP transcript is present an Iron-responsive Element (IRE type II), which is a RNA stem loop that controls cellular iron homeostasis and is located immediately upstream of an IL-1 responsive acute box domain (Rogers et al., 2002). Therefore, the authors suggest that paroxetine may act as a chelator of intracellular iron to consequently limit APP holoprotein translation driven by APP mRNA 5'UTR sequences (Morse et al., 2004; Tucker et al., 2005). Treating 3-month-old TgCRND8 mice with paroxetine for 3 months, the authors found that paroxetine reduced the soluble and insoluble Aβ levels in the cortex of TgCRND8 transgenic mice (Tucker et al., 2005; Tucker et al., 2006). Moreover, Morse and colleagues have demonstrated that paroxetine significantly reduced the levels of APP in the neuroblastoma cells (SY5Y), whereas equivalent levels of APP-like protein 1 (APLP-1) were unchanged. As IRE sequences were absence in the 5'UTR of the APLP-1 transcript, paroxetine did not affect its levels (Morse et al., 2004).

Antidepressants seem to modulate also the expression of protein kinase C (PKC), which is a key signal transduction factor in the stimulation of APP secretion induced by the activation of 5-HT_{2C} receptors (Nitsch et al., 1996; Arjona et al., 2002). To this regard, Pákáski and colleagues investigated *in vitro* whether the TCA imipramine and the SSRI citalopram were able to modulate the PKC levels in rat primary basal forebrain cultures leading to an increased release of APP (Pákáski et al., 2005). The authors found that both imipramine and citalopram significantly increase the APP secretion (3.2- or 3.4-fold, respectively), although imipramine caused a more rapid and long-lasting APP secretion compared to citalopram. These results were accompanied by a consistent increase of PKC level after imipramine treatment while no significant effects were observed after citalopram treatment. This difference may be due to the different mechanism in monoamine uptake between antidepressants. In fact, after chronic treatment with SSRI fluoxetine, the activity of PKC was suppressed in the cortex and hippocampus of rodents (Mann et al., 1995), whereas while an increased PKC activity in rabbit and human platelets was reported after TCA administration (Morishita and Aoki, 2002). These results highlighted the primary role of antidepressants on the APP metabolism, although further investigations need to be performed in order to clarify the different profile between TCA and SSRI.

Preclinical and clinical evidences support a central role of inflammation in the pathogenesis of AD and depression (Tan et al., 1999; Dantzer et al., 2008). Human studies have demonstrated that the proinflammatory cytokines, TNF-α, and IL-1β are significantly increased in depressed subjects, as well as in the brain and plasma of AD patients (Dantzer et al., 2008). A crucial role of inflammation in the AD pathogenesis was further demonstrated by higher expression of tumor necrosis factor receptor 1 (TNFR1) in AD brain (Li et al., 2004). Moreover, the deletion of TNFR1 causes a reduction of both Aβ production and microglia activation as well as ameliorates the cognitive deficits in APP23 mice (He et al., 2007). TNF-α signaling through TNFR1 activates the transcription factors NF-κB and AP-1 and induces pro-inflammatory effects that further exacerbate neuroinflammation leading to neuronal death (Probert, 2015). Thus, the use of specific pharmacological agents that counteract TNF-α/TNFR1 signaling may be a promising therapeutic strategy to reduce the cognitive alterations and Aβ formation. To this regard, Chavant and colleagues investigated the effects of TCA imipramine on the TNF-α expression and APP metabolism using a model of $A\beta_{25-35}$ intracerebroventricular infusion in mice (Chavant et al., 2010). Previous reports have demonstrated that intracerebroventricular injection of $A\beta_{25-35}$ peptide induced alterations of spatial and working memory and enhanced the levels of APP and TNF-α in the frontal cortex and hippocampus of mice (Maurice et al., 1996; Lu et al., 2009). Chavant and colleagues found that imipramine prevented the $A\beta_{25-35}$-induced deficits of both long- and short-term memories and significantly reduced the intracellular Aβ immunoreactivity in the frontal cortex counteracting the TNF-α increase induced by the $A\beta_{25-35}$ intracerebroventricular injection (Chavant et al., 2010). Thus, these results support the claim that imipramine may be a potential candidate for the treatment of AD because of its intrinsic property to inhibit TNF-α. Overall, the preclinical studies showed a reduction of Aβ pathology after antidepressants treatment.

Differently, human studies did not show a clear-cut effect of antidepressants on Aβ metabolism. To this regard, Sun and colleagues reported that elderly depressed patients had lower plasma $A\beta_{42}$ levels than those without depression, and such difference was not modified after antidepressant treatment with SSRI, TCA, trazodone, and all others including venlafaxine, bupropion, and mirtazapine (Sun et al., 2007). Conversely, antidepressants were able to reduce the plasma $A\beta_{40}$ levels in depressed patients, although any significant difference was observed before treatment between subjects with depression and those without depression (Sun et al., 2007). Similarly, Pomara and colleagues confirmed that plasma $A\beta_{42}$ levels were not affected by either paroxetine or nortriptyline, although the authors reported for the first time an elevation in plasma $A\beta_{42}$ levels and the $A\beta_{42/40}$ ratio in elderly patients with late-life major depression (Pomara et al., 2006). Finally, Kita and colleagues reported that $A\beta_{42}$ was slightly increased also in young patients affected by major depressive disorder suggesting that $A\beta_{42}$ alteration may be detrimental even in young depressed population. Moreover, the latter study confirmed that the pharmacological treatment

with conventional antidepressants did not affect Aβ plasma concentrations (Kita et al., 2009).

Unfortunately, all data from clinical studies are quite mixed, and the results are difficult to interpret, due to different study methods, heterogeneous patient populations, variability in outcome measures, and concomitant treatments. Thus, more studies need to be done in order to establish whether AD patients with depression show increased or decreased plasma Aβ levels and whether these individuals may benefit from antidepressant treatments.

CONCLUSION

The present review provides evidence that depression is associated with an increased risk of AD, and although many treatment options are available, several clinical trials suggest that conventional antidepressants are ineffective for the treatment of depression in AD patients. Moreover, results from human investigations do not give a clear picture on whether antidepressants are able to clearly modulate the Aβ production and eventually slow down the accumulation of the $A\beta_{42}$ into the cerebral parenchyma. This calls for a critical analysis of the current trials on the efficacy of antidepressants, as a treatment option. In fact, although many studies have filled some of the gaps, conflicting and inconclusive results continue to represent a challenge for physicians. Moreover, depression in AD comorbidity represents a big challenge in term of correct identification and evaluation of symptoms, also because late-life depression occurs in a complex medical and psychosocial context. To this regard, the functional neuroimaging approach may contribute elucidating both the brain structure and function specifically affected in both pathologies.

This review pulls together evidence that justifies the therapeutical inefficacy of antidepressants in AD patients and promotes further research in order to design novel selective and effective therapy against depression in AD.

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All authors have contributed to the writing, design and preparation of figures. The senior authors TC and SG have carried out coordination of efforts.

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Information and Communication Technologies, a Promising Way to Support Pharmacotherapy for the Behavioral and Psychological Symptoms of Dementia

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Health care systems face an expansion in the number of older individuals with a high prevalence of neurodegenerative diseases and related behavioral and psychological symptoms of dementia (BPSDs). Health care providers are expected to develop innovative solutions to manage and follow up patients over time in the community. To date, we are unable to continuously and accurately monitor the nature, frequency, severity, impact, progression, and response to treatment of BPSDs after the initial assessment. Technology could address this need and provide more sensitive, less biased, and more ecologically valid measures. This could provide an opportunity to reevaluate therapeutic strategies more quickly and, in some cases, to treat earlier, when symptoms are still amenable to therapeutic solutions or even prevention. Several studies confirm the relationship between sensor-based data and cognition, mood, and behavior. Most scientific work on mental health and technologies supports digital biomarkers, not so much as diagnostic tools but rather as monitoring tools, an area where unmet needs are significant. In addition to the implications for clinical care, these real-time measurements could lead to the discovery of new early biomarkers in mental health. Many also consider digital biomarkers as a way to better understand disease processes and that they may contribute to more effective pharmaceutical research by (i) targeting the earliest stage, (ii) reducing sample size required, (iii) providing more objective measures of behaviors, (iv) allowing better monitoring of noncompliance, (v) and providing a better understanding of failures. Finally, communication technologies provide us with the opportunity to support and renew our clinical and research practices.

Keywords: remote follow-up, monitoring, digital biomarkers, behavioral and psychological symptoms of dementia, pharmacology, clinical trials, sensors, technology

CONTEXT: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOM TREATMENT IN CLINICAL CARE

Health care systems are facing a rapid increase in the number of older people with a high prevalence of neurodegenerative diseases and related behavioral and psychological symptoms of dementia (BPSDs) (Okura and Langa, 2011; Peters et al., 2015; World Alzheimer Report 2018, 2018). Behavioral and psychological symptoms of dementia are frequent, associated with faster disease progression and increased caregiver burden and health care costs (Schneider et al., 2006; Costa et al., 2018; Kales et al., 2019). Health care providers are expected to develop their ability to follow up patients at home after treatment is initiated and to adjust their treatments accordingly over time.

Apart from direct but episodic observation of behavior and mental states by the prescribing physician, the assessment of BPSDs is mainly based on reported information (by a professional or family caregiver). In addition to the information bias (Lyketsos, 2015), the episodic and evolving nature of BPSDs makes it difficult to reliably quantify their frequency and severity over time. Moreover, this assessment is often conducted in settings (health care settings) that can influence patients' behavior and thus distort conclusions (Krolak-Salmon et al., 2016). All these care-related issues are shared by pharmaceutical research. Beyond dropout rates and loss of follow-up, monitoring compliance with treatment plans and managing potential adverse drug reactions are major concerns. Researchers recommend and encourage the search for new monitoring outcomes, such as those based on new technologies (Soto et al., 2014; Soto et al., 2015; Sano et al., 2018). In addition, it is becoming increasingly difficult to ignore the importance of real-world data (McDonald et al., 2016), which lies between controlled clinical trials with highly selected participants and clinical care, for clinical research. Real-world data include all data not collected in the context of a randomized controlled trial (e.g., postmarketing drug safety), and technological advances could be a way to remotely collect and analyze this information.

Researchers and clinicians face the same difficulties in accurately monitoring symptom progression and response to treatment over time in real life setting (in the patient's own environment). They could benefit from complementary solutions allowing the remote collection of continuously updated and objectively measured data. Information and communication technologies (ICTs) could play a crucial role.

CURRENT TECHNOLOGICAL ADVANCES IN THE REMOTE ASSESSMENT AND MONITORING OF BPSDS

Beyond the potential organizational benefits (frequent and massive collection at lower cost), remote evaluation of personal data could provide more sensitive and ecologically valid measures (Wild et al., 2008). It is possible to passively collect data on a patient's behavior (e.g., sleep or motor activity) in his/her own environment or to collect information longitudinally *via* his/her caregiver through, for example, semiautomated questionnaires on a smartphone without the need to move the patient. This could limit the potential negative impact of the environment on the measure (Krolak-Salmon et al., 2016). Remote data collection could complement traditional care, providing potentially less biased and more in-depth information and nontraumatic care. Although some studies suggest the validity of computer-based tests (Wild et al., 2008; Rentz et al., 2013; Myers et al., 2016) and telemedicine (Ramos-Ríos et al., 2012; Martin-Khan et al., 2012) for cognitive evaluation, most initiatives do not exploit the potential of remote assessment at home and home-based studies generally focused on caregiver support (e. g., training and online support platform) (Boots et al., 2014).

However, research teams are increasingly interested in the possibilities of remote evaluation and monitoring of BPSDs (Mallo et al., 2018; Gibson and Gander, 2019; Gaugler et al., 2019; Nesbitt et al., 2019). The Mild Behavioral Disorder Checklist, administered remotely by telephone, is sensitive to the detection of mild behavioral disorders in people with Mild Cognitive Impairment (MCI) (Mallo et al., 2018) but is not designed for home monitoring. Recently, a randomized controlled pilot trial evaluated the effect of using WeCareAdvisor, an innovative online tool designed to enable caregivers to monitor and manage BPSDs in the home (Kales et al., 2018), with encouraging results. Megges et al. (2018) evaluated wearable global positioning system (GPS) devices for persons with dementia and their caregivers without being able to draw any conclusions in terms of effectiveness. Several other ongoing studies involve remote monitoring of BDSP at home using ICTs, suggesting that the field will evolve rapidly in this direction. In the ongoing FamTechCare study (Williams et al., 2018), caregivers create video recordings of difficult care situations, and a team of experts reviews the videos and proposes interventions. Wallack et al. (2018) are evaluating the value of the expertise provided remotely by a dementia treatment team through weekly Skype videoconferencing calls. Another team is currently conducting a trial (Malmgren Fänge et al., 2017) to send alerts (SMS and/or phone call) to the caregiver of a person with dementia if something unusual happens at home. The surveillance kit includes home-leaving sensors, smoke and water leak detectors, bed detectors, and automatic lights that monitor the person's behavior.

FUTURE DIRECTIONS FOR THE MANAGEMENT OF BPSDS IN THE PATIENT'S HOME: PERSONALIZED MEDICINE AND DIGITAL BIOMARKERS

Aside from technological products that directly provide therapy, such as the Food and Drug Administration–approved PARO biofeedback device, a "pet seal" robot that adjusts its responses based on patient behavior and has demonstrated clinical benefits in BPSDs (Mervin et al., 2018), digital technologies are positioned to play a central role in transforming our therapeutic approach through more effective monitoring.

Several authors consider them as a possible impetus for the implementation of a more personalized medicine, focused on the person rather than the disease (Insel, 2017; Antman and Loscalzo, 2016; Hird et al., 2016). This model of care would promote continuously updated and individualized treatment (Hood and Flores, 2012; Antman and Loscalzo, 2016). A recent consensus recommends this personalized approach as well as intensive home care based on new technologies for patients with dementia and their caregivers (Samus et al., 2018). A potential benefit is the opportunity to treat earlier, when symptoms can still be treated with existing nonpharmacological and pharmacological therapeutic solutions and to reassess treatments in a timely manner over time. Anticipation is extremely valuable in the management of BPSDs. New terms illustrating this technological reality are emerging in medical research: "digital biomarker" (Kramer et al., 2017; Califf, 2018), "electronic biomarker" (Faurholt-Jepsen et al., 2015), or "digital phenotyping" (Insel, 2017) (**Box 1**). These sensitive and continuous measures may even reveal subtle intraindividual changes or modified variability over time and may constitute new early biomarkers of mental health (Kaye, 2008; Dodge et al., 2014). Thus, these new biomarkers could detect mild or early BPSDs and then could be used to implement prevention strategies.

While the inability to track changes in cognition, mood, and behavior over time is a major challenge in care, technological innovations suggest possible improvements in this area (Insel, 2017; Seelye et al., 2018). Coupling ICT terminals (e.g., touchpads) with wearable or embedded connected sensors could allow objective, high-frequency data collection in patients' homes and would complement self-administered questionnaires (through an informant) and episodic clinical assessments (**Figure 1**). Advances in pervasive computing and high-dimensional data analysis have made this objective credible (Kaye et al., 2011; Lyons et al., 2015; Seelye et al., 2018). Several studies confirm the relationship between physiological parameters measured by sensors and cognitive, psychological, and behavioral outcomes. In a younger psychiatric population, data automatically generated using smartphones correlate with clinically rated symptoms in patients with bipolar disorder. According to Faurholt-Jepsen et al. (2015), such data could be used as an "electronic biomarker of illness activity." Features extracted from GPS and mobile phone use also provided behavioral markers that were strongly linked to depressive symptoms (Saeb et al., 2015). In the field of cognitive impairment, more and more publications support the feasibility of long-term remote monitoring of cognition using innovative technologies (Piau et al., 2019). From a research perspective, many consider digital biomarkers as the path to a better understanding of disease processes and therefore to potentially groundbreaking research hypothesis. They could also contribute to more effective pharmaceutical research (**Box 2**, Dodge et al., 2015; Dorsey et al., 2015; Torous et al., 2015; Leurent and Ehlers, 2015; Teipel et al., 2018).

From a much more concrete point of view and with regard to the choice of terminal, the desktop computer is the most widely proposed medium in the literature to communicate with family caregivers and in some cases collect sensor data. However, new interfaces seem more appropriate for home remote monitoring. Touchpads are commercially successful with the older population (Mobile fact sheet; Jenkins et al., 2016). Nevertheless, if we consider moving to a large-scale population-based evaluation, smartphones are the most mobile and ubiquitous device in the general population. They have the undeniable ability to reach a large population in a limited time (Dufau et al., 2011) and have also proven to be a feasible tool for the cognitive assessment of older people (Brouillette et al., 2013).

BOX 1 | Digital biomarker definition.

Objective, quantifiable, physiological, and/or behavioral data that are collected and measured by means of digital devices such as embedded environmental sensors, portables, wearables, implantables, or digestibles, and which opens up opportunities for the remote collection and processing of ecologically valid, real-life, continuous, long-term, health-related data.

CHALLENGES AND ILLUSIONS OF NEW TECHNOLOGIES

Technological tools, like any part of medical intervention, carry potential limitations, risks, and ethical concerns. Measurements based on passive sensors and remote questionnaires, while complementary to "traditional" data collection techniques, have their own unresolved limitations (e.g., algorithm reproducibility in different contexts). In addition, and apart from the regulatory issues related to clinical trials, which are discussed in detail elsewhere (Hird et al., 2016), pervasive computing raises serious privacy and security issues. The challenge of health data security is far from being solved despite the development of international health data security standards (Health Insurance Portability and Accountability Act security compliance, Personal Data Protection Regulation of European Union). Another concern, which is not specific to technology, is the ethical issue of monitoring a person with cognitive impairment without his/her conscious consent at all time (e.g., GPS monitoring of elopement behavior). However, just as chemical restrictions had to be considered in the light of available alternatives, i.e., physical restrictions, the negative side effects of technologies must be considered in the overall context of suboptimal treatment of BPSDs.

Of equal concern is the widespread dissemination of commercial applications or devices aimed at improving the health of older people. Even if privacy issues are set aside, it is not yet clear whether these solutions could provide a direct or indirect benefit. In the field of cognitive impairment, the obstacles to developing effective tools should not be underestimated. Potentially relevant and "simple" ideas are struggling to meet initial expectations. One example is the use of electronic pill dispensers or smartphone reminder apps. While attractive for their simplicity, they have not been found to improve compliance in a sustainable way (Hird et al., 2016). Incentive solutions such as prompting involve complex technical installations to provide a contextualized reminder to the user. Reminding people to take a medication at an

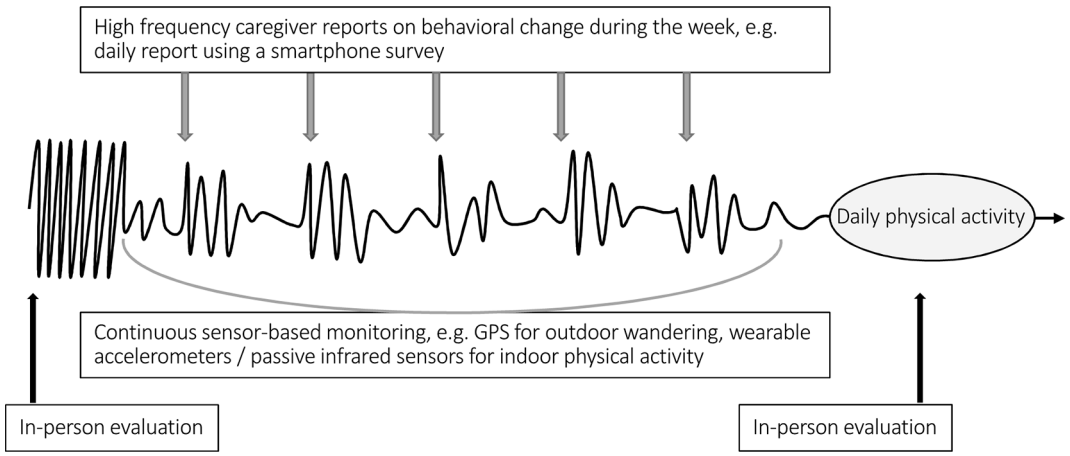

FIGURE 1 | Example of a drug prescription sequence and complementarity of clinical and technology-based assessment. In this example, an increase in night wandering was the reason for prescribing a psychotropic drug (we are not discussing the relevance of the prescription). The curve represents physical activity over time. We observe the restoration of a day-night rhythm in the following days (spontaneous or consecutive to treatment's effect). An increase in physical activity in the following nights or worrying inactivity during the day would, on the contrary, encourage a timely reassessment of the prescription. Information can be collected through caregiver input (e.g., semiautomated questionnaires on smartphones) and/or by sensors in addition to episodic clinical assessments.

BOX 2 | Information and Communication Technologies (ICT) and pharmaceutical research.

ICT could contribute to more effective pharmaceutical research in several ways by
(i) targeting the earliest stage of behavioral change;
(ii) reducing the sample size required (closer data points);
(iii) providing more objective measures of behavior (outcome measurement);
(iii) ensuring better monitoring of potential benefits and risks;
(iv) ensuring better follow-up of cases of noncompliance;
(v) allowing a better understanding of intervention failures;
(vi) providing a more in-depth understanding of disease processes;
(vii) allowing the development of innovative pathophysiological hypotheses; and
(viii) facilitating massive collection and processing of data (e.g., questionnaires).

inappropriate time or place (e.g., in a car without water) will have a negative impact on the expected benefits. In addition, the incentive solutions ignore the conscious and voluntary aspect of nonadherence to drugs (Hird et al., 2016). Finally, while ICTs have the potential for real-time monitoring, most field studies have used retrospective data analysis, and this possibility has been relatively unexplored (Piau et al., 2019).

Another point to consider is the potential consequences of implementing these technologies in real life situations for the current health care organization (e.g., information overload). The first step in the large-scale clinical use of ICTs is to clarify their exact place and role in the clinical care pathway. Digital measurements require extensive data processing before they can be translated into clinical information relevant to health stakeholders. While we know why this monitoring is relevant, it is not yet clear who will receive the information and when, in what form, for what type of action, and, finally, who will pay for it. To date, the feasibility of integrating such a solution into complex and multidisciplinary clinical care networks is still unknown. Community-based studies can first be implemented on a large scale before the health care system is ready for change. However, replication in different settings will remain an important issue.

Finally, one of the major obstacles to the deployment of ICTs in the field is the technical literacy and acceptance of caregivers and therefore their ability to act as an intermediate "field worker" to provide information at a distance. The caregiver is often an older person who also has health problems. Nevertheless, given the growth in ICT adoption, it can be expected that this type of organization will be easier to generalize in the coming years (Mobile fact sheet) with the new generations to come. To overcome the limitations of technical literacy, it is also possible to consider only the basic functions of a smartphone (e.g., text messaging) or to involve a third party (e.g., home technical assistance). Another limitation is the acceptability of sensor-based measurements in a population living with cognitive impairment and anosognosia. The very low compliance rate (32%) of wearable activity trackers in a younger population (52 years old on average) evaluated in the very short term is anything but encouraging (van der Meij et al., 2018; Piau and Wild, 2019). The literature supports a better acceptability of embedded sensors for monitoring daily life, although they pose their own problems (e.g., difficulties in following two people in the same house) (Piau et al., 2019). If wearable sensors are still an option (Farina et al., 2019), it seems clear that, regardless of the ethical implications, total unobtrusiveness would be desirable (e.g., patch device).

CONCLUSION

Behavioral and psychological symptoms of dementias challenge the traditional assessment of medical outcomes in clinical care and clinical trials. Self-evaluation is mostly unfeasible

because of underlying dementia, and the evolving nature of the symptoms biases the heteroevaluation. Remote description at high frequency by caregivers and continuous monitoring by sensors can provide additional information. Most recent or ongoing scientific work on mental health and technologies supports digital biomarkers, not so much as diagnostic tools but rather as monitoring tools, an area where unmet needs are significant. Follow-up is (or should be) an integral part of therapy, especially in complex geriatric situations. However, interpreting sensors raw data is not straightforward. The measuring devices must be validated: we must ensure that the measurement is reliable and reproducible and that we interpret the results correctly. Information and communication technology–derived data could also improve BPSD knowledge and treatment procedures. Potentially innovative molecules could be tested in an environmentally friendly setting, and their effectiveness, as well as their side effects, could be characterized more easily and quickly.

AUTHOR CONTRIBUTIONS

AP, PR, and MM: drafting of the manuscript; FN: critical revision of the manuscript for important intellectual content.

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Unmet Needs in Pharmacological Treatment of Apathy in Alzheimer's Disease: A Systematic Review

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Background: Apathy is one of the most prevalent neuropsychiatric symptoms encountered in Alzheimer's disease (AD) and may be an early sign in the development of dementia persisting over the disease course. It has been associated with poor disease outcome, impaired daily functioning, and significant caregiver distress. Early diagnosis and timely treatment of apathy in AD are of great importance. However, approved agents for apathy are still missing.

Methods: Within this context, we conducted an extensive electronic search in the databases included in the National Library of Medicine, PsychInfo, and Google Scholar for studies that have investigated the effect of pharmacological treatments in apathy in AD. There were no limitations regarding study design and all care settings were considered for inclusion. Structured measures for level of evidence and study quality were employed to evaluate the results.

Results: A total of 1,607 records were identified; 1,483 records remained after the removal of duplicates and were screened; 166 full-text articles were selected and assessed for eligibility and a remaining 90 unique studies and relevant reviews were included in the qualitative synthesis. Acetylcholinesterase inhibitors, gingko biloba, and methylphenidate were found to be successful in reducing apathy in patients with AD. Methodological heterogeneity in the studies and the small amount of studies where apathy was the primary outcome are limiting factors to assess for group effects.

Conclusions: Pharmacological treatment of apathy in AD is an underexplored field. Standardized and systematic efforts are needed to establish a possible treatment benefit. Elucidating the pathophysiology of apathy and its components or subtypes will inform disease models and mechanistic drug studies that can quantify a benefit from specific agents for specific AD groups.

Keywords: apathy, pharmacological, treatment, dementia, Alzheimer's disease

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INTRODUCTION

Applying the neuropsychiatric inventory (NPI), Mega et al. (1996) found that 88% of patients with Alzheimer's disease (AD) had neuropsychiatric symptoms, of which apathy was the most frequent, reported to occur in 27% to 72% of patients (Cummings, 1997; Benoit et al., 1999; Lyketsos et al., 2000; Lyketsos et al., 2002; Lyketsos et al., 2011). Apathy has been defined as the absence

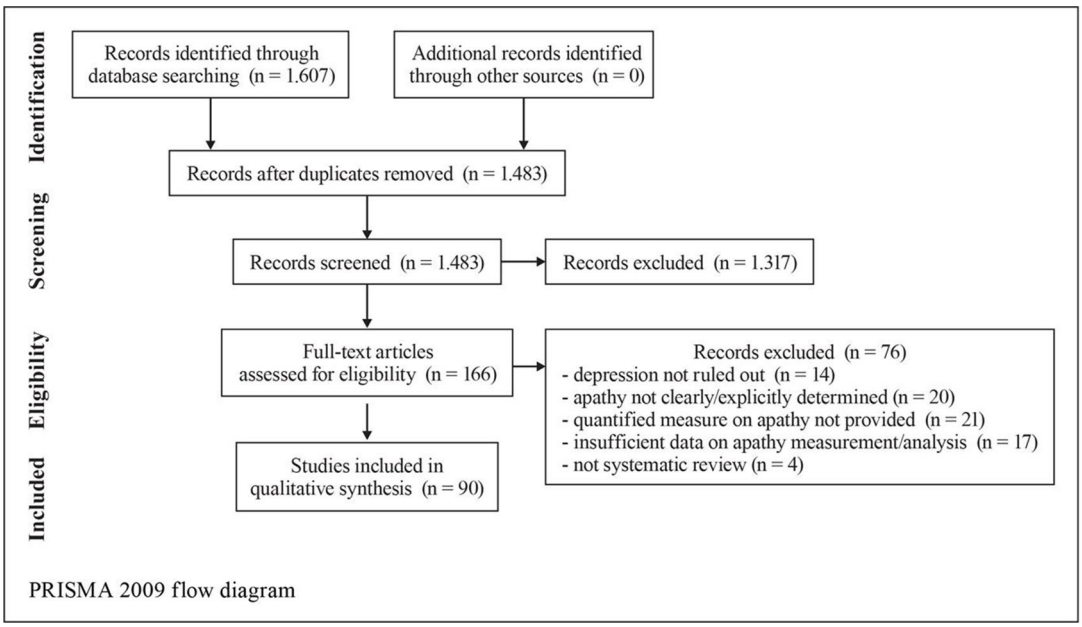

FIGURE 1 | PRISMA 2009 flow diagram.

or lack of feeling, emotion, interest, concern, or motivation not attributable to a decreased level of consciousness, cognitive impairment, or emotional distress (Marin, 1990). Starkstein et al. (2001) proposed the following core features of apathy: diminished motivation, diminished initiative and interest, and blunting of emotions. Recently, proposed diagnostic criteria (Robert et al., 2018) define "apathy" as a quantitative reduction of goal-directed activity that persists for at least 4 weeks, affects at least two of the three apathy dimensions (behavior/cognition, emotion, social interaction), is not fully explained by effects of a substance or major changes in the patient's environment, and is accompanied by identifiable functional impairments (Mulin et al., 2011). In patients with apathy, the capacity of the frontal cortex to select, initiate, maintain, and shift programs of action is undermined (Levy and Dubois, 2006). In dementia, Lyketsos et al. (2004) proposed that apathy is an aspect of executive dysfunction syndrome and is probably caused by damage to frontal–subcortical brain circuits. Indeed, apathy is correlated with neuronal loss, higher tangle counts, white matter hyperintensities, and hypoperfusion in regions involved in frontal–subcortical networks (Theleritis et al., 2014; Le Heron et al., 2018). Apathy frequently complicates the course and management of dementia and is prevalent in patients even with milder forms of cognitive impairment in clinic- (Drijgers et al., 2011) and community-based (Lyketsos et al., 2002; Clarke et al., 2010) samples. Onyike et al. (2007) proposed that apathy is an early sign of cognitive decline. Consequently, apathy has been associated with reduced daily functioning, functional disability, self-neglect, behaviors evoking embarrassment, caregiver distress, and poor outcome (Landes et al., 2001; Politis et al., 2004). Within this context, early diagnosis and effective treatment of apathetic patients with AD are of great importance. Although apathy is a prevalent neuropsychiatric syndrome, no specific treatment for apathy in AD has been approved. Clinical apathy implying motor, cognitive, affective, and behavioral symptoms suggests a benefit may systematically arise from different or close related or broad treatment classes and interestingly when combinations among them are tested.

METHODS

Inclusion and exclusion criteria: We searched for studies on pharmacological treatment of apathy in AD. We unrestrictedly included group studies, with patients diagnosed with AD using clinical criteria and structured tools treated with pharmacological agents in controlled and uncontrolled designs and an outcome measure on apathy is reported. Other neuropsychiatric manifestations and concomitant psychoactive medications were allowed. Other neurological conditions and dementias other than AD, drug abuse, and severe systematic or malignant conditions were exclusion criteria. Relevant reviews were also considered for inclusion. Reports on single cases were excluded.

Search strategy and study selection: The most current search was conducted on March 31, 2019. Building upon our previous review (Theleritis et al., 2017) we adopted the same search method in order to identify pharmacological studies relevant to the treatment of apathy in AD, from an extensive electronic search from the databases included in the National Library of Medicine for "apathy and dementia," as well as PsychInfo and Google Scholar. Further articles for inclusion were identified by searching the references of retrieved articles and by checking the Cochrane library. The following search terms were also

used: apathy, abulia, amotivation, or passivity, dementia, Alzheimer* disease, treatment, management, pharmacological, drug, donepezil, galantamine, rivastigmine, memantine, atypical antipsychotic, risperidone, olanzapine, amisulpride, antidepressants, conventional antipsychotics, stimulant, psychostimulant, methylphenidate, modafinil, anticonvulsants, and antiparkinsonic drugs. Articles that involved patients with dementia other than AD or that did not report a specific outcome measure of apathy were excluded. Three authors have gone through all the abstracts; when there was disagreement between the three authors, the issue was resolved by a consensus meeting with the last author. For pharmacological treatment of apathy, there were no limitations regarding study design, and thus, the review included meta-analyses, randomized controlled trials (RCTs), and open-label studies. All selected articles were read in full, and their level of evidence and outcome were assessed by all the authors. All care settings were considered for inclusion. We did not search for unpublished studies. The studies retained for inclusion were classified by their level of evidence following the system of the Medicine OCfE-b (2009). Grades of recommendation were also scored with this classification (**Table 1**). All RCTs were further evaluated with the use of the PEDro rating scale (Maher et al., 2003). It comprises 11 items as follows: participant eligibility criteria and source specified, random allocation of participants to interventions, allocation concealed, intervention groups similar at baseline regarding key outcome measures and important prognostic indicators, blinded subjects, blinded therapists who administered the intervention, blinded assessors who measured at least 1 key outcome, dropouts (attrition bias), intention to treat analysis, reported between group statistical comparisons, and reported measures of variability. Each item was evaluated (items 2–11) and added to give a total score. Trials were then qualitatively described according to PEDro scores as follows: a score of 7 or greater was "high" quality, a score of 5 or 6 was "moderate" quality, and a score of 4 or less was "poor" quality (Harvey et al., 2002).

TABLE 1 | Levels of evidence and grades of recommendation of OCEBM[a].

Level	Explanation
Levels of evidence	
1.	One or more RCTs (or systematic review of trials) of sufficient size to ensure a low risk of false-positive or false-negative results (narrow confidence interval).
2.	Good quality cohort studies or low-quality RCT (eg, too small, <80% follow-up).
3.	Case–control studies, including systematic reviews of case–control studies.
4.	Case series and poor quality cohort and case–control studies.
5.	Expert opinion without explicit critical appraisal or based on physiology, bench research, or "first principles."
Grades/strengths of recommendations	
A.	Consistent level 1 studies.
B.	Consistent level 2 or 3 studies or extrapolations from level 1 studies.
C.	Level 4 studies or extrapolations from level 2 or 3 studies.
D.	Level 5 evidence or troublingly inconsistent or inconclusive studies of any label.

OCEBM, Oxford Centre for Evidence-Based Medicine; RCTs, randomized controlled trials.

[a]*Summarized from Medicine OCfE-b, (2009).*

RESULTS—REVIEW OF PHARMACOLOGICAL TREATMENTS

A search using the keywords "apathy" and "dementia" yielded 1,607 results (**Figure 1**). When AD was chosen instead of dementia, results were limited to 877. The combination of keywords "apathy" AND "Alzheimer* disease" AND "treatment" yielded 420 results; of apathy AND Alzheimer* disease AND "pharmacological treatment" 166 results. In the final review, 60 pharmacological studies, 4 pooled data analyses on donepezil (N = 490), galantamine (N = 2033), mematine (N = 2311), and metrifonate (N = 672), respectively, and two meta-analyses (N = 6384 and N = 4867, respectively) were considered. The majority of the studies were of high quality according to PEDro scores and relatively high level of OCEBM evidence (**Table 3**). However, effect sizes were small and multiple heterogeneity exists. Description of the results is following (see also **Table 1**).

Donepezil

Sixteen studies (seven RCTs and nine open-label studies) were found to assess the efficacy of donepezil in the treatment of apathy in AD (**Tables 2** and **3**). Apathy was assessed in 12 studies using the NPI, in one with the Top Symptoms (TOPS) checklist and the NPI, in one with consortium to establish a registry for Alzheimer's disease (CERAD) Behavior Rating Scale for Dementia (BRSD), and in two with the Apathy Evaluation Scale (AES). All studies except two demonstrated at least some benefit in apathy scores after treatment with donepezil.

Randomized controlled trials: Tariot et al. (2001) in a 24-week RCT with 208 patients, did not find a significant difference in apathy NPI scores between donepezil-treated and placebo groups. Feldman et al. (2001) conducted a 24-week RCT in 290 patients. A retrospective sub-analysis (Gauthier et al., 2002) of individuals' NPI items from this study (Feldman et al., 2001) has shown significant differences in NPI scores for apathy, following treatment with donepezil versus placebo. A subsequent sub-analysis (Feldman et al., 2005) of the same RCT (Feldman et al., 2001) in 145 patients with severe AD also found a significant improvement in NPI apathy score with donepezil. In the Clinician's Interview-Based Impression of Change with caregiver input (CIBICþ) scale, patient and caregiver input on clinical, mental/cognitive, behavior, and functioning areas was received and rated on a seven-category scale (three categories for worsening, one for no change, and three for improvement) to make a composite change rater estimation. In a study by Holmes et al. (2004), 134 patients were treated openly with donepezil for 12 weeks, then they were randomized (60:40) to either placebo or 10 mg donepezil daily for another 12 weeks. Significant improvement in NPI apathy scores was observed after treatment. In a 24-week multicenter RCT by Seltzer et al. (2004), the efficacy of donepezil was assessed in 153 patients. On the AS, the donepezil-treated group tended to score higher versus placebo, but no significant difference was detected, probably because patients had only mild apathy at baseline. Cummings et al. (2006a) have conducted a secondary analysis of a three-phase study involving donepezil and sertraline. Factor analysis of the baseline NPI-12 data

TABLE 2 | Randomized, Placebo-Controlled Trials of Pharmacological agents for apathy in Alzheimer's disease.

Trial	N (ADG/C)	Intervention	Treatment duration (weeks)	Apathy scale (primary)	Outcome*	Comments
Donepezil						
Tariot et al. (2001)	208 (103/105)	Donepezil (up to 10 mg/day)	24	NPI (NPI)	NEGATIVE	- Long term care setting. AD with CVD included. - Similar rates and severities of AEs except of weight loss, abdominal pain, nausea, tremor, peripheral edema, myasthenia, back pain, stupor (twice the frequency in ≥ 5% of the AD group receiving donepezil).
Feldman et al. (2001) (Donepezil MSAD Study Investigators Group)	290 (144/146)	Donepezil (up to 10 mg/day)	24	NPI (CIBIC+)	POSITIVE only in the psychoactive-free patient subgroup	- sMMSE: 5-18. - Differences reported for NPI total scores. - Similar overall AEs except diarrhea, headache, arthralgia, vomiting (twice the frequency in ≥ 5% of the AD group receiving donepezil).
Gauthier et al. (2002)	290 (144/146)	Donepezil (up to 10 mg/day)	24	NPI (CIBIC+)	POSITIVE	- Sub analysis of Feldman et al. (2001). - Differences reported for NPI total scores. - Not significantly preventive in symptom-free patients at baseline.
Feldman et al. (2005)	290 (144/146)	Donepezil (up to 10 mg/day)	24	NPI (CIBIC+)	POSITIVE	- Subgroup analysis of the Feldman et al. (2001) study. - sMMSE: 5-12.
Holmes et al. (2004)	96 (41/55)	Donepezil (10 mg/day)	12	NPI (NPI)	POSITIVE NPI-total (NEGATIVE in the Observed Case Analysis)	- 12-week open label followed by a 12-week RCT. - Mean MMSE at randomization: 20.8 AD vs 21.1 NC. - Safety rates not reported.
Seltzer et al. (2004)	153 (96/57)	Donepezil (up to 10 mg/day)	24	AES (mADAS-cog)	NEGATIVE	- Mean MMSE: 24.2.- Similar safety rates between groups.
Cummings et al. (2006a)	120	Donepezil (10 mg/day)	20	NPI (NPI)	POSITIVE	- Post hoc analysis on the Donepezil+ placebo data from a 12-week RCT on Donepezil + Sertraline or Placebo and 8-weeks open label administration. - Relatively severe psychopathology (NPI: 30.5) in drug-free patients at baseline. - Safety outcomes not reported.
Winblad et al. (2001) (Donepezil Nordic Study Group)	286 (142/144)	Donepezil (up to 10 mg/day)	52 (1 year)	NPI (Gottfries-Bråne-Steen scale)	NEGATIVE	- MMSE: 10-26 - At least one serious adverse event in the Donepezil vs Placebo group: 25 % - 14 %. vertigo, asthenia, syncope (twice the frequency in ≥ 5% of the AD group receiving donepezil) - Relatively high dropout rates
Galantamine						
Tariot et al. (2000)	978 (692/286)	Up to 24 mg/day	20	NPI (ADAS-cog, CIBIC+)	POSITIVE	-Mean MMSE: 18. - Significant effects with 24mg. - Similar safety rates between groups. - Small dose-related weight loss effect in the galantamine group.

(Continued)

TABLE 2 | Continued

Trial	N (ADG/C)	Intervention	Treatment duration (weeks)	Apathy scale (primary)	Outcome*	Comments
Rockwood et al. (2001)	386 (261/125)	Up to 32 mg/day	12	NPI (ADAS-cog, CIBIC+)	NEGATIVE	- Mean MMSE: 19.7. - At least 13-fold higher discontinuation rates due to AEs in the treatment group. Nausea, dizziness, vomiting, anorexia, somnolence, abdominal pain, agitation occurred in ≥ 5% more often with galantamine than with placebo (serious AEs in 8 % and 6 % respectively).
Erkinjutti et al. (2002)	592 (396/196)	24 mg/day	24	NPI (ADAS-cog, CIBIC+)	POSITIVE (not enough powered to detect individual NPI items differences)	- MMSE: 10-25. - VaD patients also included (N = 188). - Discontinuation rates due to AEs were 19.7 and 8.2 for patients and controls respectively.
Cummings et al. (2004)	978 (692/286)	Up to 24 mg/day	21	NPI (NPI)	POSITIVE (NEGATIVE for apathy)	- Data analysis from Tariot et al. (2000). - Relatively low NPI baseline scores. - No adjustment for ADAS-cog and CIBIC+ scores for drug-placebo differences as these scales were not the primary outcome measures in this analysis. - Significant drug-placebo differences revealed for 16 and 24 mg/day. - Significantly less new apathy symptoms in psychopathology -free patients at baseline assigned to galantamine.
Memantine						
Pantev et al. (1993)	60	Up to 30 mg/day	4	Sandoz Clinical Assessment-Geriatric scale (SCAG), NOSIE	POSITIVE	
Winblad and Poritis (1999)	166 (82/84) 151 treated per protocol	10 mg/day	12	CGI-C, (Behavioral Rating Scale for Geriatric Patients - BGP)	POSITIVE	- Mean MMSE: 6.3. - 49 % AD 51 % VaD. - Similar rates of AEs and death reported. In all AEs cases a causal relationship to the trial medication was rated as 'unlikely' by the investigators. - Non-specific apathy measure.
Cummings et al. (2006b)	404 (201/203) (200/200)	20mg/day	24	12-item NPI (SIB, modified ADCS-ADL)	NEGATIVE	- Mean MMSE: 10. - Post-hoc exploratory analysis of a secondary outcome. - Concomitant Donepezil. - Treatment discontinuation for memantine vs placebo were 15 (7.4 %) vs 25 (12.4 %), respectively. Confusion and headache occurred in ≥ 5, in the memantine group and at least twice as much than in the placebo group.
Ginkgo Biloba						
Scripnikov et al. (2007)	400	240mg	22	NPI (SKT)	POSITIVE	- SKT 9-23 and NPI ≥ 5. - Possible AD with CVD and VaD also included. - Safe and well tolerated, with lower numbers of adverse events and serious adverse events in the active treatment group vs. placebo group (specifically, headache and dizziness).
Bachinskaya et al. (2011)	404 (202/202)	240 mg	24	NPI (NPI)	POSITIVE	- Mild-to-moderate dementia. NPI ≥ 5 and at least one item ≥ 3. AD with or without CVD, VD also included.

(Continued)

TABLE 2 | Continued

Trial	N (ADG/C)	Intervention	Treatment duration (weeks)	Apathy scale (primary)	Outcome*	Comments
Ihl et al. (2011)	410 (206/204)	240 mg	24	NPI (NPI)	POSITIVE	- Mild-to-moderate dementia. NPI ≥ 5 and at least one item ≥ 3. AD with or without CVD, VD also included. Safe and well tolerated, with a lower number of adverse events in the active treatment group vs. placebo group (specifically, dizziness and tinnitus).
Methylphenidate						
Hermann et al. (2008)	13	10mg/day	5	AES (AES)	POSITIVE	- All participants were stabilized on an AChEI for at least 3 months. - A significantly greater proportion of patients had ≥ 1 AE with methylphenidate compared with placebo (3 vs 1; $\chi 2 = 4.33$, P = 0.038) including delusions, agitation, anger, irritability, and insomnia, which resolved upon drug discontinuation. - Dose reduced in one patient due to irregular heartbeat.
Rosenberg et al. (2013)	60 (29/31)	20mg/day	6	AES/NPI (AES)	NEGATIVE (AES) POSITIVE (total NPI)	- Trends toward significance for greater anxiety [OR = 2.7, 95% CI(0.9, 7.8) P = .07], weight loss > 2% [OR = 3.7, 95%CI(0.9, 19.4) P = .06] in the methylphenidate-treated group, and more frequent arthralgia [OR = 0.3, 95%CI(0.1, 0.9; P = 0.03] in the placebo participants. - Four methylphenidate participants and two placebo participants discontinued due to hypertension, nervousness, nausea, anxiety, and insomnia, drop in hemoglobin respectively.
Padala et al. (2017)	60 (30/30)	9.5mg/day	12	AES-C, 3MS, MMSE, CGI-I, CGI-S, (AES-C)	POSITIVE	- Study in males. - Treatment effect over time was independent from baseline depression presence, severity as well as from antidepressant medication and AchEIs. - Higher systolic blood pressure observed in the methylphenidate group (median increase of 7mmHg, p < 0.001).
Modafinil						
Frakey et al. (2012)	22 (11/11)	Up to 200mg/day	8	Frontal Systems Behavior Scale	NEGATIVE	- Concomitant stable doses of an AchEI. - No safety reports.
Citalopram						
Porsteinsson et al. (2014)	186 (94/92)	Up to 30mg/day	9	NPI (NBRS-A, mADCS-CGI-C)	POSITIVE (total NPI score)	- Citalopram argued for cognitive dysfunction.

*Displayed are the RCTs reviewed after excluding the overlapping studies. *Outcome rated for statistically significant results at p < 0.05 favoring the specific treatment for apathy (positive) or not (negative). Abbreviations: AChEI(s) : acetylcholinesterase inhibitor(s); ADG/C: Active Drug Group/ Controls; IG/C: Intervention Group/Controls; (Primary): Primary Outcome measure for the study; AD: Alzheimer's Disease; VaD: Vascular dementia; AEs: adverse events; CVD: cerebrovascular disease; MMSE: Mini Mental State Examination; SIB: Severe Impairment Battery; ADCS-ADL: AD Cooperative Study-Activites of Daily Living inventory; DAIR: Dementia Apathy Interview and Rating; SKT: Short Cognitive Performance test; mADCS-CGI-C: modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change inventory; NBRS-A: Neurobehavioral Rating Scale; AES: Apathy Evaluation Scale; 3MS: Modified Mini Mental Examination; CGI-I: Clinical Global Impression scale-Improvement; CGI-S: Clinical Global Impression scale-Severity; AI: Apathy Inventory; MSS: Multi-sensory stimulation; BRS: Behavioral Rating Scale; BMD: Behavior and Mood Disturbance Scale, DCM: Dementia Care Mapping; CIBIC+:Clinician's Interview-Based Impression of Change with caregiver input; SCAG: Sandoz Clinical Assessment-Geriatric Scale; MOSES: Multidimensional Observation Scale for Elderly Subjects; NOSIE: Nurses Observation Scale for Inpatient Evaluation.*

TABLE 3 | Quality rating for the pharmacological/biological studies reviewed.

Pharmacological/ Biological therapies	PEDro	PEDro	PEDro	PEDro	PEDro	PEDro	PEDro	PEDro	PEDro	PEDro	PEDro	PEDro	OCEBM
	Random group allocation	Allocation concealed	Baseline group similarity	Blinding of all subjects	Blinding of all therapists	Blinding of all assessors of at least one key outcome	Less than 15% dropouts	Intention to treat analysis of at least one key outcome	Between group statistical comparisons reported for at least one key outcome	Point measurements and measurements of variability (range, interquartile range, variance, and SD) provided for at least one key outcome	Total 'yes' Score	Quality rate	OCEBM
Donepezil													
Cummings et al., 2006a (Donepezil+Sertraline)	Y	N	Y	Y	Y	Y	N	Y	Y	Y	8	high	A
Feldman et al., 2001	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	9	high	A
Tariot et al., 2001	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	9	high	A
Holmes et al., 2004	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	9	high	A
Seltzer et al., 2004	Y	N	N	Y	Y	Y	N	Y	N	N	5	moderate	A
Gauthier et al., 2002	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	9	high	A
Feldman et al., 2005	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	9	high	A
Winblad et al., 2001	Y	N	Y	Y	Y	Y	N	Y	N	N	6	moderate	B
Rea et al., 2015 (Donepezil+choline alphoscerate)	Y	Y	Y	Y	Y	Y	N	N	Y	Y	8	high	B
Galantamine													
Tariot et al., 2000	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	9	high	A
Rockwood et al., 2001	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	9	high	A
Erkinjuntti et al., 2002	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	9	high	A
Cummings et al., 2004	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	9	high	A
Memantine													
Winblad and Poritis, 1999	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	9	high	A
Cummings et al., 2006b	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	9	high	A
Zhou et al., 2019 (Memantine+Citalopram)	Y	N	Y	Y	N	N	Y	N	Y	Y	6	moderate	B
Methylphenidate													
Hermann et al., 2008	Y	N	N	Y	Y	Y	N	N	Y	Y	6	moderate	A
Rosenberg et al., 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	high	A
Padala et al., 2017	Y	Y	Y*	Y	Y	Y	Y	Y	Y	Y	10	high	A
Modafinil													
Frakey et al., 2012 Ginkgo Biloba	Y	N	Y	Y	Y	Y	Y	N	Y	Y	8	high	A
Scripnikov et al., 2007	N	N	Y	Y	Y	Y	N	N	Y	Y	7	high	A
Bachinskaya et al., 2011	Y	N	Y	Y	Y	Y	N	Y	Y	Y	8	high	A
Ihl et al., 2011	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	9	high	A
Tacrine													
Ahlin et al., 1991	Y	N	Y	Y	Y	Y	Y	N	Y	Y	8	high	A
Metrifonate													
Kaufer, 1998	Y	N	Y	Y	Y	Y	N	Y	Y	N	7	high	A
Dubois et al., 1999	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	9	high	A

*PEDro, PEDro Rating Scale; OCEBM, Levels of Evidence and Grades of Recommendation with Oxford Centre for Evidence-Based Medicine System. *Although groups differed significantly in terms of apathy severity (p = 0.024), activities of daily living (p = 0.006, p = 0.033) and Clinical Global Impression severity (p = 0.011) at baseline this is considered arising by chance with random allocation.*

revealed that a factor that comprised depression, anxiety, and apathy had a 27% reduction from baseline to final assessment (effect size = 0.39) in the 120 patients treated with donepezil. In an RCT by Rea et al. (2015) in patients with AD, the efficacy of cholinergic precursor choline alphoscerate and cholinesterase inhibitor donepezil versus donepezil alone on symptoms of apathy was investigated. Apathy severity was positively related to frontal assessment battery (FAB) scores (correlation: 0.404, P -.001). In these patients, namely those with normal FAB scores, the difference between the two treatments was statistically significant, while it was not significant in patients having a very low and mild FAB scores. Data were collected retrospectively, sample size was limited, and apathy was measured with NPI and was a secondary outcome of the association between the cholinesterase inhibitor donepezil and the cholinergic precursor choline alphoscerate in AD (ASCOMALVA).

Open-label studies: In an open-label retrospective study by Mega et al. (1999), behavioral improvement was seen in 35 patients, worsening in 24, and no change in 27 of the 86 participants treated with donepezil. Apathy NPI scores significantly improved for responders versus nonresponders. In an 18-month open-label study by Matthews et al. (2000), 80 patients participated. Apathy symptoms (assessed with NPI) reduced or cleared in 93% of patients treated with donepezil. In a 12-month open-label study by Weiner et al. (2000), 25 patients participated. Improvement in apathy symptoms (assessed with The CERAD BRSD) was found after treatment with donepezil. Barak et al. (2001) conducted a 24-week open-label study assessing the efficacy of donepezil in 10 patients. Apathy/indifference NPI score was reduced after 6-month treatment. In a 6-month open-label study by Paleacu et al. (2002), 28 patients participated. Mean apathy NPI score was improved after 6-month treatment. Tanaka et al. (2004), in a 12-week open-label study, assessed the efficacy of donepezil in 70 patients. After treatment, 21 patients showed a behavioral response, 42 showed no behavioral change, and 7 worsened. Apathy NPI score significantly improved among the responder group. Rockwood et al. (2007) in a multicenter, 6-month, open-label study, investigated the efficacy of donepezil in 101 patients. Apathy was assessed with the TOPS checklist and the NPI and was one of the two symptoms that benefited the most from treatment. Finally, Lopez et al. (2008) in a multicenter, 12-week, open-label study, assessed the efficacy of donepezil in 106 Hispanic patients. The NPI subdomain "apathy/indifference" showed statistically significant improvement. In a retrospective clinical cohort study (Okayama Memantine Study) by Matsuzono et al. (2015a), the clinical effects of combination therapy of donepezil plus memantine (n - 61) or galantamine plus memantine (n - 53) in patients with AD were investigated. The authors concluded that the combination therapy of galantamine plus memantine may be better for cognitive aspects of the older patients with AD, and donepezil plus memantine may be better for apathy in the older patients with AD. In a following retrospective clinical cohort study, Okayama Late Dementia Study, Matsuzono et al. (2015b) examined the effects of monotherapy donepezil (n - 55), galantamine (n - 222), rivastigmine (n - 63), or memantine (n - 33) in older patients with AD. Apathy scale scores were well preserved until 12 months for all four drugs.

Galantamine

Six studies (four RCTs and two open-label studies) were found to assess the efficacy of galantamine, an AChEI and nicotine modulator, in the treatment of apathy in AD. Apathy was assessed in five studies with NPI and in one with an 11-item behavior assessment scale. All studies except one demonstrated at least some clinical benefit in apathy scores after treatment.

Randomized controlled trials: Four RCTs were found to assess the efficacy of galantamine in the treatment of apathy in AD. Tariot et al. (2000) conducted a 5-month RCT to assess the efficacy of galantamine in 978 patients. Unlike the placebo group, the galantamine-treated groups did not show deterioration in behavioral symptoms, as indicated by NPI scores. Rockwood et al. (2001) conducted a 3-month, multicenter RCT in 386 patients. Behavioral symptoms as assessed by NPI did not change significantly neither in placebo nor in the galantamine-treated group. Moreover, significantly higher adverse events, such as nausea 13%, vomiting 6%, dizziness 5%, and anorexia 4%, occurred in the treatment group. In a multicenter 6-month RCT conducted by Erkinjuntti et al. (2002), the efficacy of galantamine was assessed in 457 patients. NPI apathy scores improved significantly from baseline in the galantamine-treated group versus placebo. Cummings et al. (2004) investigated the efficacy of galantamine with a 21-week, multicenter RCT in 978 patients. An observed case analysis of patients without specific behavioral symptoms at baseline revealed significantly less emergence of apathy in galantamine treated patients.

Open-label studies: Monsch et al. (2004) conducted a 3-month, open-label, multicenter study in Switzerland in which the effect of galantamine was assessed in 124 patients. A 27% reduction in NPI apathy score was observed after treatment. Brodaty et al. (2006) found that 6 months of galantamine treatment stabilized or improved apathy scores in many of the 345 participants.

Memantine

Six studies (four RCTs, one open-label study, and one post marketing surveillance study) were found to assess the efficacy of memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, in the treatment of apathy in AD. Apathy was assessed in three studies with NPI, one with Sandoz Clinical Assessment–Geriatric (SCAG) scale, one with the Nurses' Observation Scale for Inpatient Evaluation (NOSIE), and the last with Behavioral Rating Scale for geriatric patients (BGP) scale. One study had negative results, while the others demonstrated at least some benefit in apathy scores.

Randomized controlled trials: Pantev et al. (1993) conducted a 4-week RCT to assess the efficacy of memantine in 60 patients. After treatment, improvement in apathy scores (as evaluated by SCAG and NOSIE scales) was observed. Winblad and Poritis (1999) investigated the efficacy of memantine in 151 patients. Memantine-treated patients showed significant improvement in the hobbies/interest BGP subscale. Cummings et al. (2006b), in an exploratory analysis of a 24-week RCT, compared memantine treatment with placebo in 404 patients on stable donepezil treatment. Analyses of the 12 NPI domains revealed significant effects in favor of memantine on agitation/aggression, eating/appetite, and irritability but not on apathy. In a recent RCT by

Zhou et al. (2019), 80 patients with moderate AD randomly received memantine plus either citalopram (n = 40, study group) or placebo (n = 40, control group) in a 12week period. Apathy received NPI lower scores in participants who received memantine combined with citalopram vs. those before treatment.

Open-label studies: Schmidt et al. (2010) conducted a 16-week open label study to assess the efficacy of memantine in 53 patients. Improvement in the NPI apathy score (-11.3%) was observed after treatment. Postmarketing surveillance study: Clerici et al. (2012) in a postmarketing surveillance study of 399 memantine-treated patients, free of cholinergic medications, found that 49 patients showed improvement in the apathy scores.

Tacrine

Three studies (one RCT and two open-label studies) were identified that assess the efficacy of tacrine in reducing apathy in patients with AD. Apathy was assessed in two studies with NPI and in one with the NOSIE and the BGP scale. One study had negative results, while the others demonstrated at least some benefit in the apathy scores. Tacrine is not in use due to its serious adverse effect profile (hepatotoxicity).

Randomized controlled trials: In an RCT conducted by Ahlin et al. (1991), the efficacy of tacrine (75–150 mg/day) versus placebo was investigated in 15 patients over 9 weeks. No difference in "interest" on NOSIE scale was observed after treatment with tacrine.

Open-label studies: In two open-label trials (Kaufer et al., 1996; Kaufer et al., 1998), the efficacy of tacrine was assessed in 28 and 40 patients, respectively. In the first one (Kaufer et al., 1996), the improvement in NPI apathy score did not reach significance, while in the second one, apathy was significantly reduced (Kaufer et al., 1998).

Metrifonate

Randomized controlled trials: Two RCTs were found to assess the efficacy of metrifonate in the treatment of apathy in AD. Apathy was assessed in both studies with NPI. Both studies demonstrated benefit in apathy scores after metrifonate use. Metrifonate is not in use due to its serious adverse effect profile (respiratory paralysis and problems with neuromuscular transmission). In the 26-week RCT by Kaufer (1998), 393 patients participated. Statistically significant mean change difference was found in the NPI apathy score after treatment with metrifonate. In an RCT conducted by Dubois et al. (1999), 605 patients participated. Significant improvement in apathy was observed after treatment with metrifonate.

Rivastigmine

Open-label studies: Eight open-label studies were identified to assess the efficacy of rivastigmine in the treatment of apathy in AD. Apathy was assessed in five studies with NPI and in three studies with the abbreviated Clinician's Global Impression of Change (CGIc). All the studies demonstrated at least some benefit in apathy scores after treatment with rivastigmine. In a 6-month open-label study by Dartigues et al. (2002), 696 patients participated. Significant improvement was observed in the NPI apathy score after 12 weeks of treatment with rivastigmine but not after 6 months. Hatoum et al. (2005) conducted a prospective, multicenter, 52-week open-label study in 173 patients. The higher the daily dose of rivastigmine, the less likely were the patients to experience apathy. In a 12-week open-label study by Bullock et al. (2001) [first part of Cummings et al. (2005)], 173 patients participated. Improvements were noted in the mean NPI apathy score after treatment with rivastigmine. Cummings et al. (2005) conducted a prospective, 26-week, open-label study assessing the effects of rivastigmine (3–12 mg/day) in 173 nursing home residents. Significant improvement in NPI apathy scores was observed. In a prospective, multicenter 26-week open-label study (Aupperle et al., 2004; Edwards et al., 2005), extension to the 26-week study by Cummings et al. (2005), 72 patients participated. A 39.3% reduction in apathy symptoms from baseline was found (P = 0.008). Gauthier et al. (2006) conducted an observational open-label study in 2,633 patients. The effect of rivastigmine in apathy (assessed with CGIc) was reported to be clinically significant. In a study, Gauthier et al. (2007), in 2,119 patients, found that 62.6% of rivastigmine-treated patients experienced improvements in apathy. Finally, Gauthier et al. (2010) in an open-label, multicenter study assessed the efficacy of rivastigmine in 3,800 patients. The proportions of patients improving versus deteriorating at month 6 were 42.8% versus 7.2% for apathy.

Ginkgo Biloba

Randomized controlled trials: Three studies (three RCTs) were found to assess the efficacy of ginkgo biloba in the treatment of apathy in AD. Scripnikov et al. (2007), Bachinskaya et al. (2011), and Ihl et al. (2011) found significant improvement in NPI apathy scores after treatment with ginkgo biloba in 400, 404, and 410 patients, respectively.

Methylphenidate

Apathy seems to be related to some degree of dopaminergic neuronal loss; enhancing of dopaminergic transmission with methylphenidate may partially reverse the effects of apathy (Galynker et al., 1997; Hermann et al., 2008; Padala et al., 2010; Rosenberg et al., 2013; Lanctôt et al., 2014; Padala et al., 2017).

Five studies (three RCTs and two open-label studies) were found assessing the efficacy of methylphenidate in the treatment of apathy in AD. Apathy was measured in two studies with Apathy Evaluation Scale (AES), in one study with AES and NPI, in one study with the NOSIE, and in one study with the Scale for the Assessment of Negative Symptoms (SANS). All the studies demonstrated at least some benefit in apathy scores after treatment with methylphenidate; adverse events (delusions, irritability, etc.) were reported in some patients.

Randomized controlled trials: Hermann et al. (2008) in a 5-week crossover RCT, found that 13 apathetic patients demonstrated greater improvement after treatment with methylphenidate (P = 0.047). Two patients experienced serious adverse events (delusions, irritability, etc.), which resolved upon drug discontinuation. Rosenberg et al. (2013) in a 6-week RCT, assessed the efficacy of methylphenidate 20 mg/day in 60 apathetic patients and found that NPI apathy score improvement was significantly greater on methylphenidate versus placebo (P = 0.02); only 17 of completers had improved apathy scores (Lanctôt et al., 2014). Padala et al. (2017) in a12-week, RCT assessed the efficacy of methylphenidate in 60

community-dwelling veterans with mild AD; they found that AES-C apathy score improvement was significantly greater on methylphenidate versus placebo ($P < 0.001$).

Open-label studies: Galynker et al. (1997) conducted a pilot study in order to assess the efficacy of methylphenidate (5–20 mg/day) on negative symptoms in 27 patients. Significant improvement was observed in SANS from baseline. Two patients dropped out due to emergence of agitation and psychosis. Padala et al. (2010) in a 12-week study with 23 patients, observed significant improvement in AES apathy scores after treatment with methylphenidate.

Modafinil

Frakey et al. (2012) conducted an 8-week RCT in 23 patients being on a stable dose of an AChEI to estimate the efficacy of modafinil. Modafinil treatment did not result in significant additional reductions in the Frontal Systems Behavior Scale apathy scores. However, reductions in perceived apathetic symptomatology were correlated with reductions in reported caregiver burden.

Deanol

One open-label study assessed the effect of deanol (Ferris et al., 1977), a choline precursor, to treat apathy in 14 patients. The total score on the SCAG scale was lowered by the third week ($P < 0.01$), as a result of reduced depression, irritability, anxiety, and increased motivation initiative.

Antidepressants

Although often prescribed (Benoit et al., 2008), antidepressants do not significantly improve apathy in people with AD (Tariot et al., 1987; Nyth et al., 1992; Freedman et al., 1998; Pollock et al., 2002; Lyketsos et al., 2003; Siddique et al., 2009; Porsteinsson et al., 2014) with the exception of a recent RCT in which memantine and citalopram were combined (Zhou et al., 2019). In a RCT by Siddique et al. (2009) in which citalopram was prescribed for irritability, a large decrease in irritability of non-depressed patients was followed with a non-significant decrease in apathy. It is of interest that an increase in apathy was reported with the use of selective serotonin reuptake inhibitors (SSRIs) in depressed elderly patients (Wongpakaran et al., 2007). However, findings were not specific for patients with AD.

Atypical Antipsychotics

Atypical antipsychotics have shown favorable therapeutic response in apathetic patients with AD (Oberholzer et al., 1992; Negron and Reichman, 2000; De Deyn et al., 2004; Onor et al., 2007). However, extensive use of antipsychotics in dementia is not recommended since it is associated with serious adverse effects (Food and Drug Administration, 2005).

Conventional Antipsychotics

There are no studies using conventional antipsychotics to treat apathy specifically for patients with AD; these are mainly older studies in patients with various forms of dementia (Barton and Hurst, 1966; Birkett et al., 1972; Kirven and Montero, 1973; Cahn and Diesfeldt, 1973; Gotestam et al., 1981; Barnes et al., 1982; Petrie et al., 1982; Lovett et al., 1987; Pollock et al., 2002). Furthermore, conventional antipsychotics seem to carry greater risks for patients with AD in terms of extrapyramidal symptoms (EPS), cardiac arrhythmias, and overall mortality (Trifiro et al., 2009; Trifiro et al., 2014).

Other Psychotropic Compounds

In two studies, a calcium antagonist nimodepine (Ban et al., 1990; Pantoni et al., 1996) was used to treat apathy; these studies included patients with cognitive impairment and various forms of dementia. In one study, pentofylline (Bayer et al., 1996) was used to treat apathy in patients with multi-infarct dementia. For what concerns the use of anticonvulsants, two small studies, one RCT involving valproate in patients with senile dementia (Sival et al., 2002) and one open study involving gabapentin in patients with probable AD (Moretti et al., 2003), yielded negative results.

Evidence From *Post Hoc*, and Pooled Data Analyses

Metrifonate

Cummings et al. (2001) did a retrospective analysis on 672 patients, in which NPI data from two 26-week lasting RCTs (Morris et al., 1998; Raskind et al., 1999) were pooled together (**Table 4**). At 26 weeks, metrifonate-treated patients had significantly reduced apathy score versus placebo.

Donepezil

In a study by Waldemar et al. (2011) (**Table 4**), two RCTs (N = 490) were included (Feldman et al., 2001; Winblad et al., 2001). The authors proposed that donepezil may delay the onset of apathy in mild to moderate AD. However, both studies, although sharing design similarities, have used different effectiveness tools that do not specifically assess the clinical syndrome of apathy.

Galantamine

Herrmann et al. (2005) (**Table 4**) conducted a meta-analysis of three RCTs [Tariot et al., 2000; Rockwood et al., 2001; Data on file (Janssen-Ortho Inc)] in which the efficacy of galantamine was assessed in 2,033 patients. Patients treated with galantamine experienced a reduction in mean NPI apathy score from baseline; however, there was no significant difference between galantamine treated and placebo groups.

Memantine

Gauthier et al. (2005) analyzed the data of two RCTs (Reisberg et al., 2003; Cummings et al., 2006b) examining the efficacy of memantine in 656 patients. There was a trend for improvement in NPI apathy scores after treatment. Gauthier et al. (2008) (**Table 4**) conducted a pooled data analysis of six (24/28-week) RCTs including 2,311 patients (Reisberg et al., 2003; Tariot et al., 2004; Peskind et al., 2006; van Dyck et al., 2007; Bakchine and Loft, 2008; Porsteinsson et al., 2008). Apathy score did not differ significantly between memantine-treated and placebo groups.

DISCUSSION

Principal Findings

We attempted to systematically review apathy treatments in AD across pharmacological treatment modalities including combined

TABLE 4 | Meta-analyses, *post hoc* and pooled data analyses of agents reporting on apathy outcomes.

Study	N	Treatment	Duration considered (weeks)	Scale	Variable	Results/Effect size	Outcome	Comments
Waldemar et al. (2011)	490 (2 RCTs)	***Donepezil***						
		Feldman et al. (2001)	24	12-item NPI	First emergence of an apathy composite score (frequency x severity) ≥ 3.	Significant difference favoring donepezil (p = 0.01. Odds Ratio: 1.7)	Positive	- Female were significantly more in the donepezil group (p = 0.01) - Mild-to-moderate disease stage
		Winblad et al. (2001)	24	10-item NPI				
Herrmann et al. (2005)	2.033 (3 RCTs)	***Galantamine***						
		Rockwood et al. (2001)	12		A ≥30% change in apathy individual score considered as clinically relevant	-0.03[a]		p = 0.28
		Tariot et al. (2000)	20					
		Data on file (Janssen-Ortho Inc.)	24	NPI			Negative	
Gauthier et al. (2008)	2.311 (6 RCTs)	***Memantine***						
		Peskind et al. (2006)	24					
		Porsteinsson et al. (2008)	24. Patients were on stable dose of donepezil, rivastigmine, or galantamine		- Symptom improvement: lower apathy score than in baseline. - Symptom emergence: appearance of new apathy symptom while absent at baseline.		Negative	Mild to severe disease stages
		Bakchine and Loft (2008)	24	12-item NPI				
		van Dyck et al. (2007)	24					
		Tariot et al. (2004)	24. Patients were on stable dose of donepezil					
		Reisberg et al. (2003)	28					
Cummings et al. (2001)	672 (2 RCTs)	***Metrifonate***						
		Morris et al. (1998)	26		>30% reduction in the total NPI score	15% treatment benefit (P = 0.02)	Positive	- MMSE: 10-26
		Raskind et al. (1999)	26	NPI				- NPI was secondary outcome measure in both studies
Ruthirakuhan et al. (2018)	6384 (21 RCTs – four included for meta-analysis)	***Methylphenidate***						
		Hermann et al. (2008)	5	AES	Difference in the change in AES means (SD) scores from baseline to week 5	-2.31 (5.11), Wilcoxon Z = -2.00, P = 0.045	Positive	- Significant difference revealed for AES apathy but not for NPI-apathy - Apathy improvement with methylphenidate can be predicted on the basis of attentional response (i.e., increased inattention) to D-amph challenge - Tolerability concerns

(Continued)

TABLE 4 | Continued

Study	N	Treatment	Duration considered (weeks)	Scale	Variable	Results/Effect size	Outcome	Comments
		Rosenberg et al. (2013)	6	AES	Difference in the change in AES scores from baseline to week 6	–2.5 95%CI(–6.5, 1.6) $P = 0.23$	Negative	- Adequately powered study
		Padala et al. (2017)	12	AES-C	Score on the AES-C	-9.9, 95%CI(-13.6, -6.2) $p < 0.001$	Positive	- Higher apathy scores in the methylphenidate group at baseline
		Modafinil						
		Frakey et al. (2012)	8	FrSBe	Post-treatment score on the FrSBe	$F_{1,20} = 2.160$, $P = 0.157$, $\eta^2 = 0.097$	Negative	A placebo effect is hypothesized for significant decreases observed in both groups
Sepehry et al. (2017)	4864 (15 RCTs - eleven included for meta-analysis)	***Donepezil***						
		Gauthier et al. (2002)	24	NPI-apathy	Least squares means change from baseline score (±SE)	-2.58±0.69 ($p < 0.0001$ vs. placebo)	Positive	No significant differences in symptom emergence between groups
		Tariot et al. (2001)	24	NPI-NH	Drug-placebo differences in least squares means change from baseline scores		Negative	Primary outcome was the NPI total score
		Seltzer et al. (2004)	24	Shortened version of AES	Least squares means change from baseline scores		Negative	Apathy was secondary outcome
		Galantamine						
		Herrmann et al. (2005)	12, 20, 24	NPI	Mean changes in scores from baseline	-0.03[a]	Negative	- Post hoc analysis on pooled data from 3 multicenter, double blind RCTs (N = 2.033) differing in durations, doses, formulations of galantamine, and the dosing/titration schedules used. - Apathy was secondary outcome
		Memantine						
		Cummings et al. (2006b)	24	NPI	Least-squares means change from baseline on total NPI		Negative	- Apathy was secondary outcome
		Gauthier et al. (2008)	See above					
		Herrmann et al. (2013)	24	NPI	Change from baseline in NPI total scores	Baseline-to-week-24 difference in means 1.23, 95%CI(–1.75, 4.21) P = 0.42	Negative	- Efficacy based on observed cases analysis - NPI total score was primary outcome and Apathy item score secondary
		Araki et al. (2014)	24	NPI	Least squares means change from baseline score (±SE)	Significant difference observed between the groups ($p < 0.01$)	Positive	- Small Sample - Multiple testing corrected results - A relationship between NIRS measured hemodynamic group changes and apathy was not reported
		Modafinil						
		Frakey et al. (2012)	See above					
		Methylphenidate						
		Hermann et al. (2008)	See above					
		Rosenberg et al. (2013)						

[a]*Expressed as the Cohen's Δ (mean change on apathy score divided by the pooled within-group standard deviation).*

NPI, neuropsychiatric inventory; AES-C, Apathy Evaluation Scale – Clinician input; FrSBe, Frontal Systems Behavior Scale, AES, Apathy Evaluation scale; IFG, Inferior Frontal Gyrus; NIRS, Near Infrared Spectroscopy.

treatments. In many studies, apathy was not considered as the primary outcome measure (**Table 2**). Considering the amount of evidence, AChEIs may be the best available treatment choice for the pharmacological treatment of apathy. Reduced cholinergic tone has been argued for the presentation of apathy (Mega et al., 1997), and thus, AChEIs might prove helpful in this domain (Trinh et al., 2003; Cummings et al., 2008). Gingko biloba was also found to be effective (Scripnikov et al., 2007; Bachinskaya et al., 2011; Ihl et al., 2011). There was weaker evidence of efficacy for memantine; however, there are reports that memantine might be more effective in agitation and irritability (Cummings et al., 2008). Stimulants like methylphenidate alone or in combination with AChEIs have also been proven beneficial, and there is room for improvement in this category. Research groups might test hypotheses based on results from existing high-quality trials (Hermann et al., 2008; Rosenberg et al., 2013; Lanctôt et al., 2014). Atypical antipsychotics, on the other hand, cannot be used for long periods of time (Food and Drug Administration, 2005), while antidepressants (e.g., SSRIs, chlorophenylpiperazine, L-deprenyl) (Tariot et al., 1987; Nyth et al., 1992; Freedman et al., 1998; Pollock et al., 2002; Lyketsos et al., 2003; Siddique et al., 2009; Porsteinsson et al., 2014), with the exception of one study (Zhou et al., 2019), failed to improve patients' apathy significantly.

Strengths and Weaknesses

Appraisal of Methodological Quality of the Review

We reviewed a large body of evidence using flexible criteria to capture a more pragmatic picture on pharmacological treatment of apathy in AD. Although a certain amount of studies showed at least some benefit of various pharmacological interventions for apathetic symptoms, most of them reviewed were not designed to target apathy. In fact, the consistency of the widely used NPI-apathy item with more specific apathy scales, like AES, was reported to be problematic (Rosenberg et al., 2013). This, along with inconsistently reporting effect sizes and their parameters and the variety of psychometric tools used to assess apathy (sometimes involving scales not validated), would make a meta-analysis incomplete and/or misleading. Therefore, we evaluated the quality of the reported evidence using two published semiquantitative methods.

Several Limitations Apply to This Review

Any conclusions drawn rely on the quality of the included studies, while an unknown number of studies that involve combined treatments might have been excluded by the review design of older reviews. The studies included in this review were methodologically heterogeneous and conducted mainly with AChEIs, while those conducted with cognitive enhancers incorporated smaller sample sizes. Furthermore, age and gender may potentially have influenced the pharmacological effects (Matsuzono et al., 2015b). While not so prone to publication bias, as apathy was the secondary outcome in more cases, selective reporting cannot be excluded.

Relation to Other Reviews

There are only few reviews that specifically have focused on apathy outcomes in dementia and AD following the use of pharmacological interventions (Cummings et al., 2008; Drijgers et al., 2009; Berman et al., 2012; Theleritis et al., 2017). In their review, Drijgers et al. (2009) proposed that cholinesterase inhibitors and methylphenidate may be the best candidates for further study in the treatment of apathy in dementia. It is of interest that in a recent review by Sherman et al. (2018), the use of galantamine and risperidone was found to produce mild reductions of apathetic behaviors in patients with prodromal dementia.

The fact that in few studies apathy was the primary outcome measure led Ruthirakuhan et al. (2018) to define two objectives in their recent Cochrane systematic review on pharmacological interventions for apathy in AD, or mixed AD populations (**Table 2**). Objective 1 was the efficacy and safety, based on studies where clinically significant apathy (mean baseline NPI-apathy subscore > 3) was the primary outcome, and Objective 2 was the effect of pharmacotherapies for other primary outcomes and apathy was a secondary outcome. Four studies in mild-to-moderate AD, three on 20 mg methylphenidate (Hermann et al., 2008; Rosenberg et al., 2013; Padala et al., 2017) and one on modafinil (Frakey et al., 2012), were employed for Objective 1. Based on AES score in three studies, methylphenidate was found to improve apathy compared to placebo [mean difference (MD) = -4.99, 95%CI (-9.55, -0.43), P = 0.03, n = 145, 3 studies; heterogeneity: I^2 = 83%)]. A subgroup analysis by treatment duration (cutoff, 12 weeks) revealed significant differences between subgroups (greater apathy changes in administration longer than 12 weeks). However, the level of evidence in studies that have used the AES was rated as low (i.e., there is limited confidence for the closeness of the estimated effect to the true, and thus the true effect may be substantially different from the estimated effect). Contributing factors, as suggested by the authors, were imprecision due to a wide 95% CI and the inconsistency, due to heterogeneity, in the effects on apathy in the three methylphenidate studies. Based on NPI-apathy score in two studies, methylphenidate appeared not to have a significant effect on apathy [MD = -0.08, 95%CI (-3.85, 3.69), P = 0.97, n = 85, 2 studies; heterogeneity: I^2 = 84%]. This inconsistency was attributed by the authors to the type of scales and the smaller total number of participants included in the analysis with NPI. There were no significant differences in adverse events between subgroups [$Chi^2(1)$ = 0.03, P = 0.85; heterogeneity: I^2 = 0%]. Again, the low quality rated evidence substantially affects the certainty in these results. For Objective 2, six studies with AChEIs in AD patients and clinically nonsignificant apathy were included. AChEIs may slightly improve apathy compared to placebo, and this effect is not influenced by disease severity. On the other hand, discontinuation of AChEIs (1 study) revealed no significant improvement, antipsychotics (two studies) worsened apathy, discontinuation of antipsychotics (one study) revealed a slightly significant improvement, while there was uncertainty for what concerns antidepressants (two studies) due to very low evidence quality.

In a previous systematic review followed by meta-analysis (Sepehry et al., 2017) (**Table 2**), 15 RCTs were included of which 11 entered the meta-analysis. Studies on three drug classes were analyzed as passed the three-study-inclusion cutoff, namely, four on AChEIs (three on donepezil and one on galantamine), four on memantine, and three on stimulants (two

on methylphenidate and one on modafinil). In 9 of 11 studies, the NPI-apathy item was used to measure apathy, while AES (in a donepezil study) and Frontal Systems Behavior Scale (FrSBe) (in the modafinil study) were also used. No significant treatment effect was estimated for the cognitive enhancers [Hedges'g = -0.055, 95%CI (-0.322, 0.213), P = 0.687; heterogeneity: Q-value = 17.378, P = 0.001, I2 = 82.737], and small and nonsignificant effects were estimated for memantine [Hedges' g = 0.092, 95%CI (-0.134, 0.318), P = 0.423; heterogeneity: Q-value = 11.425, P = 0.010, I^2 = 73.742] and the stimulants [Hedges' g = -0.063, 95%CI (-1.067, 0.941), P = 0.903; heterogeneity: Q-value = 12.486; P = 0.002; I^2 = 83.982]. Besides the drugs' ineffectiveness, the lack of a significant drug effect was attributed, by the authors, to the variable disease state in the studies, the small sample size in the psychostimulant studies, the heterogeneity in the study design, as well as the review methodology (means aggregate was calculated from a small number of studies in each drug class, which does not allow to control for the above factors, while various studies had been excluded by the review design).

In the review by Harrison et al. (2016) on pharmacological trials targeting apathy in various dementia types, 24 studies (10 in AD, 6 in FTLD, 4 in dementia or probable dementia and MCI, 1 in PDD, 1 in LBD, and 2 in unspecified dementia) were included. Studies from the last 3 years were included for review, and the authors conclude that the evidence is not convincing. However, benefits from AChEIs and memantine seen in earlier studies did not appear in more recent studies. A model of therapies is proposed that act in a synergistic manner, as well as stepped approaches starting from psychosocial interventions. In the review by Ruthirakuhan et al. (2018), methylphenidate was found to demonstrate a benefit for apathy and slightly improve cognition and functional performance in people with AD.

Implications

Strengths and Weaknesses of the Evidence Included in the Review

A wide range of agents are included in this review. It appears that combined treatments (Chapman et al., 2004; Niu et al., 2010; Zhou et al., 2019) might be of greater benefit compared with monotherapies, and future studies should address this research topic more rigorously. Variable sensitivity of apathy scales may confound results and their interpretation.

Direction and Magnitude of Effects Observed in the Included Studies

Although a number of compounds proved beneficial, effect sizes were small. When symptoms resist and interfere with significant life domains, AChEIs and methylphenidate seem to be the first pharmacological choice, followed by gingko biloba. Only effect sizes provided from previous meta-analyses are reported.

Practical Implications for Clinicians and Policy Makers.

Implications for Practice

Poorer results in treating apathy in AD, from the concomitant use of psychoactive medication, may be indicative of greater disease severity. Furthermore, ethical constraints apply when testing drugs for apathy in AD (e.g., the concomitant use of AChEIs). Last but not least, drugs may be acting differently depending on doses, age, type, and stage of neurodegeneration and probably the different apathy syndromes.

Implications for Research

Apathy is understudied and a work in progress as social interaction was incorporated in the recently updated diagnostic criteria for apathy (Robert et al., 2018). Indeed, psycho-social factors are well recognized and described in motivation research and goal-directed behavior (e.g., Deci, 1971). Studies should set up their design so that they facilitate symptom expression and engagement (individualized treatments, environmental and cultural considerations, preferences, psycho-education, etc.). Currently, the lack of standard and widely accepted tools concerning apathy differentially adds to studies' heterogeneity and influences outcomes and their appraisal. It is worth mentioning that in a systematic review by Radakovic et al. (2015), among the highest quality apathy scales in AD were the DAIR and the AES–Clinical version, while in a review by Clarke et al. (2011), the most psychometrically robust measures for assessing apathy across any disease population appeared to be the AES and the apathy subscale of the NPI; while for patients with AD, the DAIR was found to be the most reliable and valid apathy measure. Moreover, the Lille Apathy Rating Scale (LARS, Sockeel et al., 2006) has been shown to assess emotional, cognitive, and behavioral aspects of apathy independently of depression, with high concurrent validity in relation to AES global scores and with reference to expert clinician categorization of syndrome severity.

Due to heterogeneity of the sample populations and the syndromic nature of apathy, its symptoms rather form clusters within different NPI symptoms, which are consistent across studies defining potential subsyndromes (Canevelli et al., 2013). In this context, recommendations on the design of clinical trials on apathy have recently been published (Cummings et al., 2015). Problematic allocation concealment and non-double-blind design may positively bias an effect by 41% and 17%, respectively (Schulz et al., 1995). Endorsement of CONsolidated Standards of Reporting Trials statement could substantially confer to completeness of the trials while quantification strategies in general are of great need. Clinical trials implementing combination strategies are of particular interest. Furthermore, different incident neuropsychiatric symptom profiles in relation to different vascular pathology (small vs. large vessel cerebrovascular disease) can inform and guide relevant studies (Staekenborg et al., 2010). It would also be interesting to investigate health outcomes and further individual implications by treatments administered for longer periods against the cost.

CONCLUSION

We argue for informed treatments that are frequently combinations of therapeutic interventions administered

in well-characterized patient groups based on rigorously designed RCTs with intervention outcomes assessed in long terms. It is, thus, fundamental to determine quantified markers and models of apathy (behavioral, social, imaging, computational, etc.) (Theleritis et al., 2014) after developing, validating, and standardizing diagnostics, interventions, and measures to effectively target apathy, while reconciling existing paradigms of specific apathy models and clinical research (Chong et al., 2016; Chong and Husain, 2016). Kales et al. (2014, 2015), for example, proposed that the "Describe, Investigate, Create, Evaluate" approach may enable clinicians to choose optimal treatment plans for the management of neuropsychiatric symptoms by considering conjointly the role of specific nonpharmacological, medical, and pharmacological treatment (Lanctôt et al., 2017; Theleritis et al., 2017; Theleritis et al., 2018). Concerning the measures for apathy, validation of the tools by the different apathy components may be of particular interest (Nobis and Husain, 2018). Incorporation of the "social interaction" term in the recent revision of diagnostic criteria for apathy (Robert et al., 2018) may aid developing more complete models and more effective treatments for apathy. Moreover, lifestyle modifications and context interventions, including exercise, leisure activities, cognitive stimulation, and social activities, might be effective for the prevention of apathy and MCI progression (Rosenberg and Lyketsos, 2008). All the above along with the accumulated neurobiological evidence (e.g., neuroimaging) and the emerging models (e.g., behavioral, computational) for apathy will help to identify target populations most likely responding to specific treatments.

AUTHOR CONTRIBUTIONS

All three authors have gone through all the abstracts; when there was disagreement between the 3 authors, the issue was resolved by a consensus meeting with the last author. The first two authors have written the review under the supervision of the last author.

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REVIEW
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Strengths and Weaknesses of the Gray Mouse Lemur (*Microcebus murinus*) as a Model for the Behavioral and Psychological Symptoms and Neuropsychiatric Symptoms of Dementia

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To face the load of the prevalence of Alzheimer's disease in the aging population, there is an urgent need to develop more translatable animal models with similarities to humans in both the symptomatology and physiopathology of dementia. Due to their close evolutionary similarity to humans, non-human primates (NHPs) are of primary interest. Of the NHPs, to date, the gray mouse lemur (*Microcebus murinus*) has shown promising evidence of its translatability to humans. The present review reports the known advantages and limitations of using this species at all levels of investigation in the context of neuropsychiatric conditions. In this easily bred Malagasy primate with a relatively short life span (approximately 12 years), age-related cognitive decline, amyloid angiopathy, and risk factors (i.e., glucoregulatory imbalance) are congruent with those observed in humans. More specifically, analogous behavioral and psychological symptoms and neuropsychiatric symptoms of dementia (BPSD/NPS) to those in humans can be found in the aging mouse lemur. Aged mouse lemurs show typical age-related alterations of locomotor activity daily rhythms such as decreased rhythm amplitude, increased fragmentation, and increased activity during the resting-sleeping phase of the day and desynchronization with the light-dark cycle. In addition, sleep deprivation successfully induces cognitive deficits in adult mouse lemurs, and the effectiveness of approved cognitive enhancers such as acetylcholinesterase inhibitors or N-methyl-D-aspartate antagonists is demonstrated in sleep–deprived animals. This result supports the translational potential of this animal model, especially for unraveling the mechanisms underlying dementia and for developing novel therapeutics to prevent age-associated cognitive decline. In conclusion, actual knowledge of BPSD/NPS-like symptoms of age-related cognitive deficits in the gray mouse lemur and the recent demonstration of the similarity of these symptoms with those seen in humans offer promising new ways of investigating both the prevention and treatment of pathological aging.

Keywords: *Microcebus*, primate model, aging, Alzheimer's disease, cognition, circadian rhythms

INTRODUCTION

Common laboratory model organisms—yeast, nematodes (*Caenorhabditis elegans*), fruit flies (*Drosophila melanogaster*), and mice—have helped scientists substantially advance our understanding of neuropsychiatric diseases (Götz and Ittner, 2008; Nestler and Hyman, 2010). However, the limits of such models are particularly pronounced in this field of research. Many of the human symptoms leading to psychiatric diagnoses (e.g., hallucinations, delusions, sadness, guilt) cannot be convincingly reproduced in the common animal models cited above. When reasonable correlates do exist, such as in rodents (e.g., abnormal social behavior, motivation, working memory, emotion, and executive function), the correspondence still remains limited. Moreover, determining how symptoms in a rodent correspond to a recognized human neuropsychiatric disorder is not trivial. According to the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (American Psychiatric Association, 2013), "most diagnoses are based on phenomenology, i.e., on symptoms, signs, and the course of the illness" rather than validated tests. Thus, it is of primary importance to take advantage of the extreme similarity between non-human primates (NHPs) and humans. Indeed, the anatomical and functional organization of NHP brains is homologous to the human brain (i.e., the existence of specialized motor, perceptual, and cognitive abilities not found in rodents) (Borra and Luppino, 2019). Therefore, neuropsychiatric disorders can be better replicated in NHPs than in rodents. However, the use of NHP species, as essential as it appears to be for neuropsychiatric research, has also been a caveat. Increased ethical pressure to regulate the use of animals for scientific purposes is especially strong in the case of primates. In addition to ethical issues, the high cost of breeding, the relatively long life spans, the large body size, and social system constraints are limiting factors that need to be taken into account. Therefore, the use of a smaller-sized NHP species such as mouse lemurs (*Microcebus murinus*) to model age-associated cognitive disorders and neuropsychiatric conditions, as reviewed herein, would be a good compromise. The gray mouse lemur belongs to the Strepsirhini suborder and to the Cheirogaleidae family, composed of small, omnivorous primates. As primates, they have the closest phylogenetic distance to humans, much closer than that of rodents (about mid-distance between mouse and human) (Ezran et al., 2017). These primates are nocturnal, arboreal solitary foragers that sleep in groups during the daytime. In the wild, during the 6 months of the hot rainy season, which is characterized by a long photoperiod, elevated temperatures, and abundant food resources, the mouse lemur exhibits a high level of activity and has a high metabolic rate during the dark phase. It corresponds to the mating season. Conversely, the 6 months of the cooler dry season are characterized by harsh conditions in terms of food resources and temperatures. At the onset of the dry season (photoperiod shorter than 12 h), the mouse lemur metabolism slows down, leading to an increase in fat deposits and the occurrence of pronounced daily phases of hypometabolism (Schmid and Speakman, 2000; Génin and Perret, 2003). These physiological changes are highly dependent on the photoperiod (Perret and Aujard, 2001; Génin and Perret, 2003). In captivity, gray mouse lemurs can live up to 13 years (Pifferi et al., 2019), while their lifespan in the wild is significantly shorter (Lutermann et al., 2006). In this study by Lutermann et al., no animals older than 6 years old were observed. In addition, due to their relatively small body size (head-body length of approximately 15 cm) and low body mass (60–80 g), mouse lemurs can be easily bred and kept in captivity at low costs. This species, thus, would be a good compromise between practical breeding methods and physiological and phylogenetic proximity to humans. In addition, this species offers a natural biological heterogeneity and spontaneous occurrence of pathologies, especially age-related neurodegenerative diseases. Thus, even though some limitations need to be considered, this species is considered an emerging model organism for biology, behavior, and health studies (Ezran et al., 2017; Roberts, 2019), particularly in the context of aging (Bons et al., 2006; Austad and Fischer, 2011; Finch and Austad, 2012; Laurijssens et al., 2013).

POTENTIAL MARKERS OF BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA IN GRAY MOUSE LEMURS OF ALL AGES

Cognition and Sensory–Motor Functions

The mouse lemur is a primate that has been extensively studied in relation to cognitive function and its evolution during aging (Languille et al., 2012b). Cognitive functions have been mainly studied in young and adult, male mouse lemurs and studies covered the following major cognitive domains: recognition, spatial or working memories, stimulus reward associative learning, and set-shifting performances. Such cognitive tasks rely on brain function and sensory–motor functions. Age-related effects on the sensory functions of mouse lemurs have been studied in this context and as markers of aging.

The overall pattern of cognitive performance throughout aging reflects changes similar, in many aspects, to those that occur in human aging. This similarity is not found in most rodents, whose memory function does not match that of humans (Deacon, 2014). One specific rodent species, *Octodon degus*, has more similarities with humans and can provide benefits in aging studies (Tarragon et al., 2013; Hurley et al., 2018). In most tasks, the acquisition of the rule is not impacted by aging (Picq, 1998; Picq and Dhenain, 1998), and cognitive processes involved in simple stimulus-reward association performances are preserved during aging (Joly et al., 2006; Picq, 2007). In tasks influenced by anxiety, aged mouse lemurs actually performed better than young ones (Picq, 1993; Némoz-Bertholet and Aujard, 2003; Languille et al., 2015) (see Anxiety Section for details). In contrast, retention capacity or new object memory expresses deficits with aging (Picq, 1998; Picq and Dhenain, 1998; Picq et al., 2015). In fact, the ability to form simple stimulus-reward associations is mainly preserved with aging, while working memory and the ability to shift strategies are impaired in most aged mouse lemurs. Interestingly, in some tasks such as those testing reference spatial memory, spatial and object recognition

memory, and the capacity to use flexibly acquired information (generalization and spatial rule-guided discrimination tasks), impairment is only observed in a subset of aged mouse lemurs. In some cases, even very old animals perform as well as young ones, while some middle-aged animals show drastic cognitive deficits. This high interindividual variability mimics, to some extent, the pattern of cognitive aging described in humans (Salthouse, 2017; Barter and Foster, 2018). It allowed to clearly distinguish good from bad performers in cognitive tasks (Languille et al., 2015). This variability is a fruitful background for exploring discriminant cognitive markers of behavioral and psychological symptoms of dementia (BPSD), and it also brings possibilities to search for physiological and neural correlates of normal vs pathological aging. Due to the relatively long life span of mouse lemurs compared to rodents, interindividual variability during middle age allows the implementation of various protocols for studying the aging process and risk factors for neurodegenerative pathologies. Recent attempts have been made to link cognitive function with fitness in wild mouse lemurs, showing that cognitive performance can be used to explain evolutionary trajectories and that the ecology of a species is highly relevant for understanding the consequences of individual differences in cognitive abilities (Huebner et al., 2018). Some personality traits have been linked to some life history traits, such as body weight at birth, showing that some behavioral variations can account for gene dispersal models and, thus, selection (Thomas et al., 2016). Finally, recent evidence of a correlation between glucose homeostasis impairment and cognitive deficits in middle-aged mouse lemurs reinforces the potential role of metabolic function as a risk factor for pathological aging (Djelti et al., 2016), as is the case in humans (Geijselaers et al., 2015). This link represents an interesting opportunity for research on type-2 diabetes as a risk factor for neurodegenerative diseases, since mouse lemurs express age-related glucose metabolism disorder, among other systemic disorders, that resemble those observed in humans. Similar to humans, impaired fasting blood glucose in the mouse lemur was associated with cognitive impairment and cerebral atrophy in middle-aged animals (Djelti et al., 2016). This relationship is confirmed by the positive impact of caloric restriction or micronutrient supplementation on both cognition (at least during the first years of treatment) and glucoregulatory functions. In the mouse lemur, cognitive performance is enhanced during chronic caloric restriction or resveratrol supplementation, which is linked to lower glucose intolerance and insulin response (Dal-Pan et al., 2011).

In 2007, the incidence of cataracts in mouse lemurs was published (Beltran et al., 2007). This research revealed a relatively high incidence of bilateral, progressive cataracts in aged mouse lemurs, with some starting as early as middle age. This incidence rate is not far from that observed in humans (Klein and Klein, 2013). Since then, all animals involved in cognitive tasks requiring vision have been regularly checked for vision. Motor performance and equilibrium are of major interest for their impact on cognitive task performance and in the aging process. In mouse lemurs, physical activity and jumping reduced and motor performance on a rotarod is worse in aged animals (Némoz-Bertholet and Aujard, 2003; Némoz-Bertholet et al., 2004). Olfaction, which plays a major role in communication, reproductive physiology, and mating in this nocturnal species, shows a significant decline with age (Némoz-Bertholet et al., 2004; Cayetanot et al., 2005). This finding deserves more investigation with regard to aging, since olfaction is one of the earliest sensory deficits preceding the emergence of Alzheimer's disease (AD) (Murphy, 2019).

Anxiety

In humans, anxiety disorders have an early onset [half of all lifetime cases start by age 14 and three-fourths have begun by age 24, according to Kessler and colleagues (Kessler et al., 2005)]. Anxiety is a component of a variety of diseases and appears to be associated with accelerated aging (Perna et al., 2016). No conclusion about causality between anxiety and accelerated aging can be drawn, and in this context, animal models could be useful for deciphering the potential mechanisms of this association. Several studies have focused on anxiety-linked behavior in gray mouse lemurs using mainly rodent-like apparatuses adapted to the specificities of the species. In a 2010 study, Trouche and colleagues (Trouche et al., 2010) used a sequential choice task based on a three-panel runway and tested the age-related differences in a procedural memory task with or without visual cues. They observed significant anxiety-related behavioral differences between young and aged animals. Young adult lemurs showed more perseverative errors than aged animals, particularly in the presence of visual cues. According to the authors, the behavioral response of young adult lemurs was influenced by novelty-related anxiety that contributed to perseverative errors during their performance of the task. Conversely, aged lemurs showed fewer perseverative errors and rapid habituation to the three-panel runway maze but made more memory errors. Overall, these findings are in accordance with observations made in other anxiety-related situations, such as the open field test. In a study by Languille and colleagues (Languille et al., 2015), the latency to the first movement in the open field, a parameter recognized as a marker of anxiety (Dal-Pan et al., 2011; Royo et al., 2018), differed significantly with age. In this task (the open field test adapted for mouse lemurs, consisting of an empty squared box of 1 × 1 m), old animals started exploring earlier than middle-aged and young animals, confirming a decrease in novelty-related anxiety in old animals compared to young animals. Similar observations were made in the light-dark plus maze in the same study (Languille et al., 2015). Interestingly, in both studies, an effect of age on the individual variability in anxiety-related parameters is observed. In the three-panel runway task (Trouche et al., 2010), young animals exhibit higher interindividual variation than older animals, as also reported in the Languille study (Languille et al., 2015). This result could be due to i) a very systematic decrease in anxiety-related behavior in older animals (in the Languille and colleagues study, all tested aged animals systematically moved before 800 s had elapsed, while approximately 70% of young animals did not move before 1,800 s had elapsed, which is the duration limit of the test); or ii) a selection bias of old animals: it cannot be excluded that at old age, the surviving animals are those with lower levels of anxiety behavior, which could explain the difference between young and aged animals. In a more recent

study (Zablocki-Thomas et al., 2018) assessing the relationship between early life inputs such as low birth weight and personality traits at older ages, Zablocki-Thomas and colleagues confirmed the difference in anxiety behavior between young and aged mouse lemurs. They performed emergence tests during which they measured the latency for the animals to escape from a small wooden box and return to their home cage. The authors found an effect of birth weight on emergence latency: animals born with a lower birth weight had the fastest emergence. This result is consistent with previous observation in the open field test, in which mouse lemurs with lower birth weight also started exploring earlier (Thomas et al., 2016). It was thus proposed that low body weight newborns were exploring their environment earlier to avoid competition. This hypothesis is supported by the fact that individuals with a shorter emergence latency tend to have higher growth rates. In addition, the authors found that age had an impact on emergence latency, suggesting that adult personality can potentially change during life span. This idea is consistent with field experiments, using open field and novel object tests on wild mouse lemurs, demonstrating that personality was influenced by age (at least in males). In this study, the authors observed that older individuals were bolder and took more risks than younger ones (Dammhahn, 2012). The authors thus proposed that younger males were less prone to take risks because they had not yet reproduced. This theory also applies in laboratory conditions where competition for females is also high. Indeed, generally, only one dominant male (compared to groups of three males) usually engenders all the offspring (Andrès et al., 2003). These compelling data show that anxiety levels can impact a wide range of physiological and behavioral parameters in the mouse lemur. Interestingly, the existence of an age difference in the expression of anxiety between young and aged mouse lemurs is similar to the difference found in humans. Indeed, even if the prevalence of anxiety disorders over the lifespan is debated (Baxter et al., 2013; Miloyan et al., 2014), it seems clear that a difference in the expression of anxiety behaviors exists in aging humans (Wuthrich et al., 2015). Interestingly, a study focusing on age differences in mental disorders in ten different European countries (McDowell et al., 2014) reported a lower prevalence of mood and anxiety disorders in older adults than in young adults in western European countries. Such observations suggest that the mouse lemur is a promising model for studying anxiety disorders across the lifespan.

Chronobiological Markers of BPSD

Circadian rhythms refer to biological processes that display an endogenous oscillation of about 24 h. The impairment of the time-keeping system is believed to be at the origin of the age-related changes observed in biological rhythms (Bonaconsa et al., 2013). These alterations can directly involve the central circadian clock or associated physiological and behavioral processes, such as activity–rest or temperature rhythms. Studying the effects of age on circadian parameters is particularly pertinent in the gray mouse lemur, which exhibits a much longer life span than most common laboratory rodents and is less subject to social bias than humans and other social primates (Lavery, 2000; Austad and Fischer, 2011; Languille et al., 2012b; Hozer et al., 2019). In humans, aging is associated with changes in the amplitude and temporal organization of several daily rhythms (Hood and Amir, 2017). In elderly people, the alternation of sleep–wake rhythms is affected by the appearance of, and increase in, activity periods during the night resting phase and periods of sleep during the diurnal activity phase (Huang et al., 2011; Lieverse et al., 2011). This phenomenon, defined as rhythm fragmentation, is generally accompanied by mood disorders (depressive syndrome) that can be at least partially treated with light therapy (Lieverse et al., 2011). Lieverse and colleagues (Lieverse et al., 2011) demonstrated that such treatment in elderly individuals with depressive symptoms led to the partial restoration of sleep–wake rhythms and led to an amelioration of mood and sleep quality. Biological rhythms thus constitute a core element of the aging process in humans (Hood and Amir, 2017). Similar observations were made in mouse lemurs. This species is known to express highly marked biological rhythms and, thus, constitutes an adequate model to study this phenomenon. Similar to humans, rest-activity rhythms in lemurs become more fragmented with age, with a notable and significant increase in locomotor activity during the resting period leading to lower amplitudes and fragmentation of rhythms (Aujard et al., 2006). Even if similar observations have previously been made in humans (Hofman and Swaab, 2006), they do not explain whether these alterations are due to reduced sensitivity to light or to changes at the central level of the circadian clock. It has been observed a high incidence of ocular pathologies in more than 7 years old mouse lemurs, what suggests a decrease in light responsiveness through the filtering of short wavelengths (Beltran et al., 2007). It has been demonstrated that short wavelengths are efficient in the synchronization of daily rhythms in mouse lemurs (Gomez et al., 2012). In addition, the impact of aging on circadian rhythms in mouse lemur has been associated with immune system alterations. Plasma levels of interferon-γ [IFN-γ, a pro-inflammatory cytokine acting as an activator of glial cells and involved in the pathogenesis of numerous brain diseases (Blasko et al., 2004)] correlate with age-related impairments in circadian rhythms and survival. High levels of IFN-γ have been associated with shorter lifespan and free-running period, i.e., *tau* (*tau* being the period expressed by a biological system in the absence of environmental cues). In mouse lemur, IFN-γ plasma levels also correlate with impairments of locomotor activity and body temperature rhythms that are characteristic of aging (increased level of diurnal locomotor activity, advanced onset, and delayed occurrence of minimal body temperature) (Cayetanot et al., 2009).

In addition to circadian rhythm alterations, aging is also accompanied with several changes in sleep patterns. In humans, they include an augmentation of sleep fragmentation (more wake events during the resting period) leading to decreased total sleep time, sleep efficiency, and slow-wave sleep (Luca et al., 2015). Comparable observations were made in lemurs. At a young age, this species exhibits a fragmented sleep pattern, with numerous periods of active waking during the light resting period (Pifferi et al., 2012), which is more comparable to patterns seen in small mammals (Van Erum et al., 2019) than in humans. At an older age, alterations in sleep–wake rhythms consist in less activity

during the active phase and more wake episodes and duration during the resting phase accompanied by a reduction in slow-wave sleep (Hozer et al., 2019). Mouse lemurs also exhibit a phase advance, resulting in an earlier wake time when light turns on (Pifferi et al., 2012; Hozer et al., 2019). This is comparable to observations made in older humans (Duffy et al., 1998). Thus, mouse lemur can be considered as an appropriate model of age-related sleep rhythm disturbances. As an example, circadian rhythms disruptions in humans are often associated to bipolar disorder. Among potential treatments, lithium and light therapy could be useful for addressing circadian dysfunction in this disorder (Moreira and Geoffroy, 2016; Sarrazin et al., 2018), and our knowledge of the behavioral abilities of mouse lemurs could provide an appropriate model to test such interventions.

MOUSE LEMUR AS A MODEL OF AD

The Case of Sporadic AD

Since the seminal study by Bons et al. (1991) reporting that a fraction of aged mouse lemurs over 8 years old displayed dramatic atrophy in the neocortex, hippocampus, basal ganglia, hypothalamus, brainstem, and cerebellum that was associated with a conspicuous increase in the size of the cerebral ventricles, the presence of neuritic plaques, and neurofibrillary changes, many studies have tried to assess the relevance of the model for sporadic AD. In this species, age-associated cognitive impairment occurs in 10% of >7-year-old animals (Languille et al., 2012b), a prevalence similar to that observed in >65-year-old humans (Steenland et al., 2015; Niu et al., 2017). Age-related cerebral atrophy predicts cognitive deficits in mouse lemurs (Picq et al., 2012), while cognitive function is related to brain network atrophy in AD and type 2 diabetes patients and in healthy individuals (Buss et al., 2018). In lemurs, however, brain atrophy starts in the frontal cortex, then progresses to the temporal and/or parietal regions and then, finally, to the occipital cortex (Kraska et al., 2011), while in AD, medial temporal structures (i.e. entorhinal cortex, hippocampus, and parahippocampal gyrus) are predominantly involved early, followed by the spreading of the pathology into the lateral temporal, inferior parietal, and orbitofrontal regions (Rasero et al., 2017). Other biomarkers, such as cerebrospinal fluid amyloid β_{1-42} and β_{1-40} or total- and phosphorylated-Tau, have not been measured in mouse lemurs. Nevertheless, similar to humans, low plasma amyloid β_{1-40} levels are associated with the atrophy of several white matter and subcortical brain regions, while high plasma amyloid β_{1-40} levels are negatively correlated with the density of neurons accumulating amyloid β deposits (Roy et al., 2015; Gary et al., 2018). Interestingly, higher plasma amyloid β_{1-40} levels are observed in the winter season when animals display high numbers of torpor bouts, but seasonality has not been taken into account for plasma amyloid β levels in human subjects (see (Lue et al., 2017; Hanon et al., 2018), for instance). However, clinically significant associations between seasonality and cognition and neurobiological correlates have been reported in older human subjects independently of AD pathology (Lim et al., 2018). In terms of sensory deficits, hearing loss and central auditory dysfunction in humans are associated with a high risk of conversion to dementia 5 to 10 years later (Bakhos et al., 2015), but only mild presbycusis is observed in >7-year-old animals (Schopf et al., 2014). Fifty percent of such animals develop (Beltran et al., 2007) cataracts, while particular visual functions may be selectively impaired in subgroups of AD patients (Kusne et al., 2017). Olfactory disorders represent an early characteristic of the human disease (Velayudhan, 2015), and olfactory memory deficits are present in 25% of >7-year-old animals (Joly et al., 2006).

The neuropathological diagnosis of AD depends on the concomitant presence of senile plaques and neurofibrillary tangles (NFTs) (Hyman et al., 2012). The former is ranked according to Thal phases and the CERAD neuritic plaque scoring system which ranks the density of histochemically identified neuritic plaques in the regions of the neocortex and the latter according to Braak stages (from limbic regions to cortex). Approximately 20% of >5-year-old mouse lemurs develop such neurodegenerative signs. In such animals, diffuse amyloid deposits are often observed in the cerebral cortex and amygdala, but mature neuritic plaques are rather scarcely present (Petiet et al., 2012; Bertrand et al., 2013). Concerning NFTs, neocortical areas are frequently decorated with hyperphosphorylated Tau "NFT-like" structures, even in young mouse lemurs, whereas the subiculum and entorhinal cortex are only occasionally involved in > 8-year-old animals (Delacourte et al., 1995). The relative sparing of the hippocampus in mouse lemurs contrasts sharply with the high NFT load invariably present in this structure in human Alzheimer's brains (Braak and Braak, 1991). The presence of "NFT-like" phosphorylated Tau in young animals may be related to the fact that mouse lemurs are one of the few heterothermic primate species. Indeed, hibernators, such as Arctic ground squirrels and Syrian hamsters, show the reversible formation of highly phosphorylated and dephosphorylated states during hibernation bouts and arousals, respectively (Stieler et al., 2011). Another neuropathological feature frequently observed in Alzheimer's patient brains and, more generally, in older subjects is amyloid angiopathy. This condition is also recorded in 70% of >5-year-old animals (Bertrand et al., 2013). Unfortunately, data are missing concerning synaptic loss in the cortex of cognitively impaired mouse lemurs, a phenomenon that is frequently observed in patients (Finch and Austad, 2012). The progressive loss of limbic and neocortical cholinergic innervation (Hampel et al., 2018) and the dysfunction of somatostatin-positive interneurons associated with memory deficits have also not been clearly demonstrated (Dournaud et al., 1994). Nevertheless, the acetylcholinesterase inhibitor donepezil—and the N-methyl-D-aspartate antagonist memantine—prevent sleep deprivation (SD)–induced deficits in the retrieval of spatial memory both in young and aged mouse lemurs (Rahman et al., 2017) (see Sleep Deprivation to Induce Transient Cognitive Impairment Section for details). Anti-amyloid β immunotherapy induced an immune response, increased amyloid β_{1-40} plasma levels, and elicited microhemorrhages and iron deposits in the choroid plexus (Joseph-Mathurin et al., 2013). Concerning transcriptomics, a single study pinpointed 47 genes discriminating young animals from healthy old animals and "AD-like" animals, particularly genes involved in protein synthesis pathways (Abdel Rassoul et al., 2010),

while amyloid precursor protein (APP) metabolism, tau protein binding, lipid metabolism, insulin-like growth factor 1 signaling, and immune response genes are commonly reported in human patients (George et al., 2017; Wingo et al., 2019).

Finally, AD is a heterogeneous disease depending on environmental and genetic risk factors. Genome-wide association studies have now identified 25 different loci associated with the disease (Kunkle et al., 2019), the most important one being the apolipoprotein E4 allele (Genin et al., 2011). In the *M. murinus* genome, only one ancestral allele, closer to apolipoprotein E4, exists (Calenda et al., 1995), with only one nucleotide differing from the human sequence (Salazar et al., 2016). In addition, phylogenetic analysis of two other proteins involved in AD (presenilin 1 and tau) also exhibited higher homology between mouse lemur sequences and human sequences than to any natural rodent model (Salazar et al., 2016).

Experimental Transmissibility of AD-Like Pathology

If the expression of an AD-like pathology in the mouse lemur has been demonstrated (Bons et al., 2006), the relatively low number of animals that express the pathology (~10%) (Bons et al., 1991; Bons et al., 2006) supports the interest in developing a model of pathology induction (Gary et al., 2017). A recent program of the experimental transmission of AD-like pathology has been tested in adult mouse lemurs by Dhenain and colleagues (Gary et al., 2019). In this study, AD patient brain homogenates were microinjected into the brains of adult animals without clinical signs of pathology in the beginning of the study. These mouse lemurs were compared to animals injected with control brain homogenates. One year post-inoculation, animals that received AD brain homogenates exhibited significant cognitive impairments, electroencephalographic activity alterations, progressive cerebral atrophy (spreading far from the injection site), and neuronal loss in both the hippocampus and entorhinal cortex. These animals also displayed more β-amyloid depositions, as well as more hyperphosphorylated Tau "NFT-like" structures, than control-inoculated animals. In contrast to brain atrophy, β-amyloid and "NFT-like lesions were only present in regions close to the initial injection sites and were never detected in animals inoculated with control brain homogenates. This result demonstrates that inoculation with AD brain homogenates systematically induced pathognomonic signs that thoroughly mimicked an AD-like pathology in this primate. This result is of primary importance, since it makes the model available for future research projects on AD and will avoid the long-lasting process of detecting and selecting animals naturally exhibiting such pathology.

INTERVENTIONS MIMICKING BPSD/ STUDYING BPSD MARKERS

Anxiolytic Effects of Omega-3 Fatty Acids

As described above (Anxiety Section), the exploration of anxiety disorders in lemurs has shown interesting results and has suggested the decreased prevalence of anxiety during aging in this species. Interestingly, several intervention studies assessed the anxiolytic impact of nutritional interventions such as polyunsaturated fatty acid (PUFAs) of the omega-3 (ω3) series. The brain cell membranes of vertebrates, including primates, are highly concentrated in long-chain PUFAs of the ω3 and omega-6 (ω6) series. These PUFAs are mainly represented by docosahexaenoic acid [DHA, 22:6 (n-3)] and arachidonic acid [AA, 20:4 (n-6)] (Alessandri et al., 2004). The role of ω3 fatty acids has been extensively investigated through dietary deficiencies using rodents deprived of any source of ω3 fatty acids during the perinatal period. Such chronic deficiency leads to decreased brain DHA content and is accompanied by major consequences at the neurosensory level (learning, memory, anxiety, and vision). These impairments have been related to modifications in the neurotransmission processes (mainly monoaminergic neurotransmitters) (Chalon, 2006). Studies in rodents demonstrated that chronic ω3 PUFA deficiency increased in particular anxiety (Takeuchi et al., 2003; Fedorova and Salem, 2006), and more specifically when animals were in an anxiogenic situation (Fedorova and Salem, 2006). Harauma and Moriguchi (Harauma and Moriguchi, 2011) demonstrated that dietary ω3 PUFA deficiency in mice increases chronic mild stress-induced anxiety. In line with the above mentioned results, restauration of dietary ω3 PUFA levels in rodents previously fed and raised with an ω3 PUFA-deficient diet, led to a reduction of anxiety and restored control-like fatty acid content of most brain regions (Carrié et al., 2000; Takeuchi et al., 2003). In addition, Enslen and colleagues (Enslen et al., 1991) observed that the exploration of a novel environment was reduced in ω3-deficient rats, confirming the impact of dietary ω3 PUFA levels on anxiety in rats. Similar exploratory behavior was improved in mice receiving an ω3 PUFA supplement (Carrié et al., 2000), supporting the potential major role of ω3 PUFAs on anxiety. In humans, the relationship between ω3 PUFAs intake and anxiety disorders is unclear. Although several studies suggested a relationship between low intakes of long-chain ω3 PUFAs and a higher prevalence of anxiety with stronger symptoms (Natacci et al., 2018; Thesing et al., 2018), to our knowledge, only one study tested the anxiolytic effect of ω3 PUFAs in humans (Su et al., 2018), which concluded that ω3 PUFAs can contribute lower anxiety symptoms. Thus, more research is needed in this domain, and adapted NHP models could be of interest. In a series of studies in mouse lemur, we tested the impact of tuna oil supplementation [containing mainly long chain ω3 PUFAs, under the form of eicosapentaenoic acid (EPA) and DHA] on behavioral, cognitive, and locomotor performances. In a first study, we supplemented young adult animals with ω3 PUFAs for 5 months and demonstrated, for the first time in a NHP species, that ω3 PUFA supplementation lowered both spontaneous locomotor activity and anxiety and concomitantly improved cognitive performances (animals being less anxious in novel environments, they performed better in learning and memory tasks) (Vinot et al., 2011). This result was confirmed in a further study in which the supplementation of young adults lasted longer (12 months) (Pifferi et al., 2015). We reported that 12 months of ω3 PUFA supplementation reduced anxiety in the open field task and concomitantly increased the

success rate in a learning and memory task (mainly due to higher adherence to the task than control animals). These results were linked to better glucose transport to the brain (Pifferi et al., 2015). In a more recent study, supplementation in young adults lasted 21 months and showed a similar conclusion of reduced anxiety in various cognitive tasks, including the open field task (Royo et al., 2018). Interestingly, in addition to better glucose uptake to the brain, we were able to measure increased neurogenesis in associated cerebral regions (including the amygdala). Such a measurement is impossible to perform in humans, reinforcing a major point of interest for using NHPs to model human mental health disorders. In addition, since anxiety varies throughout aging, including in lemurs, in which it decreases with age (see Anxiety Section), we assessed the impact of 5 months of ω3 PUFA supplementation on behavioral parameters including exploratory activity, emotional status, and spatial memory in old animals (Languille et al., 2012a). Aged ω3 PUFA-supplemented animals exhibited no change in anxiety levels measured in the open field task, in contrast to young animals (Vinot et al., 2011; Pifferi et al., 2015; Royo et al., 2018), confirming the specificity of the anxiety response in aged animals in this species.

Sleep Deprivation to Induce Transient Cognitive Impairment

The development of novel therapeutics to prevent cognitive decline during mild cognitive impairment and AD is facing difficulties. There is a translational barrier between rodents and clinical results (Deguil et al., 2013; Laurijssens et al., 2013). The use of NHPs is recognized as being of major interest in this context (Austad and Fischer, 2011; Laurijssens et al., 2013). However, although age-related functional impairments (including cognitive decline) have been described in gray mouse lemurs and correlated well with cerebral atrophy, not all animals exhibit such alterations. For example, it has been observed that about half of aged mouse lemurs display a specific alteration in long-term memory retention but not in learning (both assessed during a visual discrimination task) (Picq et al., 2015). Although this finding adequately mimics the natural differences that also exist in the human population, it might be insufficient when a higher number of animals presenting deficits is required. In this context, strategies have been developed to increase the availability of animals presenting cognitive alterations, such as *via* brain inoculation with brain extract from AD patients (see Experimental Transmissibility of AD-Like Pathology). A far less invasive alternative is the use of SD to induce reversible transient cognitive impairment. SD is a recognized method to induce transient cognitive alteration and has been extensively used in rodents [for review, see (Colavito et al., 2013)]. Numerous studies reported that SD efficiently induces transient cognitive deficits comparable to those observed in patients with AD-like dementia. The cognitive challenge offered by SD has several benefits over other strategies. Its effects are temporary, it is easy to administer in a standardized fashion without specific equipment, it avoids the bias of pharmacological intervention for the lowering of cognitive functions (drug-induced deficits), and it is ethically well accepted, since it does not induce pain or long-term distress. SD, as a cognitive challenge, provides an interesting strategy to induce cognitive impairment and is promising in the context of testing cognition-enhancing drugs. SD in mouse lemurs was first tested in young animals (Rahman et al., 2013) in a spatial learning and memory retrieval task [using a circular platform task inspired by the Barnes maze in rodents (Rosenfeld and Ferguson, 2014)]. In this task, a learning session preceded a 24 h testing session (memory). This first set of experiments demonstrated that SD applied before learning did not affect cognitive performance, whereas when it was before memory testing, it increased the number of errors and the latency time before reaching the exit (Rahman et al., 2013). The disruptive effect of SD on spatial memory retrieval thus constitutes an interesting validated challenge in investigating the impact of new drugs during both normal and pathological aging. The experiment was repeated in aged animals with similar conclusions, but the effects on memory retrieval (impairment) were stronger in aged animals (Rahman et al., 2017). In the Rahman study, two symptomatic AD drugs were tested to verify the validity of the model. Both donepezil (an acetylcholinesterase inhibitor) and memantine (an N-methyl-D-aspartate antagonist), when administered 3 h before the memory session (during the last third of the SD period), prevented the deficits induced by SD in memory retrieval in both young and aged animals (Rahman et al., 2017). The effect was dose dependent (donepezil at 0.1 and 1 mg/kg was efficient, while memantine was efficient at 1 mg/kg and not at 0.1 mg/kg). These results suggest that both memantine and donepezil can be effective in sleep deprived mouse lemurs. It further supports the translational potential of mouse lemur but also demonstrates the utility of this model for further testing therapies in the context of AD and other neuropsychiatric diseases.

LIMITATIONS AND FUTURE CHALLENGES

Although the utility of the mouse lemur as a model of neuropsychiatric conditions has been clearly demonstrated, such a model also exhibits some limitations. From a biological point of view, gray mouse lemurs exhibit particularities that are rare in primates and almost absent in humans. In addition to being nocturnal (active during the dark period), mouse lemurs are a highly photoperiodic species with strongly marked seasonal phenotypes (Génin and Perret, 2003). Faced with specific environmental constraints (cold, caloric, and water restriction), they can enter in a facultative state of daily hypometabolism (Storey, 2015). These peculiarities distinguish this species from humans and must be taken into account when designing experiments. In addition, if the anatomical and functional organization of NHP brains is more homologous to the human brain than to the rodent brain, *strepsirrhine primates* share fewer common characteristics with humans than haplorhine primates. This difference is exemplified by a description of the organization of the sensory thalamus and visual midbrain. In (Saraf et al., 2019b), the authors observe that the "thalamic nuclei and their overall layout in mouse lemurs resemble those of other strepsirrhine primates, and, in size, likely resemble the nuclei of early primates, which were also small and nocturnal." The same group also observed that "mouse lemurs are likely to

have fewer cortical areas than most or all monkeys […] and their brains are expected to closely resemble those of early primates" (Saraf et al., 2019a). Conversely, a more recent study of the functional microarchitecture of the visual cortex in the mouse lemur demonstrates that orientation preference maps reveal a common design principle of the primate visual cortex. This finding illustrates that mouse lemurs could be considered as an intermediary model species between rodents and higher primates. In addition, in the context of a study in which we assessed the hypothesis that electroencephalography (EEG) markers of motor and locomotor activity in mouse lemur could reflect the typical movement-related desynchronization of alpha rhythms (8–12 Hz) in humans. We observed that mouse lemurs and humans could share basic neurophysiological mechanisms. The EEG markers used in these study could represent an interesting experimental model for translational basic and applied research in neurophysiology (Infarinato et al., 2015)

From a societal point of view, there is increased ethical pressure to regulate the use of animals for scientific purposes, which is especially strong in the case of primates (Bennett and Panicker, 2016; Official journal of the European Communities. Legislation. 2019). In this context, using mouse lemurs could be considered a limitation but also an alternative. Indeed, ethical pressure in primate research is mainly focused on great apes (Bennett and Panicker, 2016; Official journal of the European Communities. Legislation 2019), which share more common traits with humans. From a practical point of view, although raising mouse lemurs is less expensive than raising larger primates (Austad and Fischer, 2011), the current limited number of animals is another major weakness. Only a few mouse lemur facilities exist in the world, and all of these are located in western Europe and the United States. The largest colony in the world, located in Brunoy (France), comprises ~450 live animals. The other smaller colonies are located in Montpellier (France), Hanover (Germany), and Durham (USA). Some laboratory/facilities also host some adult mouse lemurs for research purposes but do not breed them (CEA Fontenay-Aux-Roses, France and U. Stanford, CA, USA). This very limited number of animals (not more than 1,000 live animals in 2019), with regards to the 1.9 million animals used for research in 2017 only in France, limits access to aged animals (with the median lifespan of the mouse lemur being approximately 5.5 years (Languille et al., 2012b), aged animals represent less than 50% of the live animals in captivity). Among these animals, only a fraction will exhibit the specific neuropsychiatric alterations/biomarkers of interest. Thus, it seems obvious that more facilities and higher budgets would be needed in the future for the proper development of the model as an effective alternate model for BPSD studies. It is noteworthy that some of the abovementioned facilities have developed expertise in nonlethal neuroimaging techniques such as magnetic resonance imaging (Nadkarni et al., 2018; Nadkarni et al., 2019) and positron emission tomography imaging (Pifferi et al., 2015), which allow longitudinal neuroanatomical and neurobiological investigations in this species and would be particularly relevant in the context of aging.

In addition to drastically increasing the number of animals available, another near future challenge in promoting the mouse lemur as a more efficient and appropriate BPSD model would be developing genetic tools in this species. The first genome assembly of the mouse lemur dates back to 2007 (Larsen et al., 2017). However, recent improvement in its genome assembly (Larsen et al., 2017) and the publication of the complete mitochondrial genome sequence (Lecompte et al., 2016) have paved the way for the development of genetic tools and studies and represent a major and mandatory resource for the future of biomedical research with this species.

AUTHOR CONTRIBUTIONS

FP, JE, and FA all contributed to the writing of the manuscript.

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MINI REVIEW
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Brain Metabolic Dysfunction in Early Neuropsychiatric Symptoms of Dementia

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Neuropsychiatric symptoms (NPS) including behavioral and psychiatric symptoms are common in the dementia stages of Alzheimer's disease (AD) and are associated with poorer outcomes in cognition, functional states, quality of life, and accelerated progression to severe dementia or death. NPS are also increasingly observed in the mild cognitive impairment stage of AD and may predict incipient dementia. As such, there is an emerging conceptual framework, which support NPS as early non-cognitive symptoms of dementia. [^{18}F]fluorodeoxyglucosepositron emission tomography is a technique that is sensitive in detecting resting metabolism associated with NPS in neuropsychiatric conditions, and there is a growing body of literature evaluating the role of NPS as early indicators of brain metabolic dysfunctions in AD. In this mini-review, we examine the frequency and associations of NPS with metabolic dysfunction in the AD continuum, including preclinical, prodromal, and dementia stages of AD. We will also present the validated neurobehavioral syndrome, mild behavioral impairment describes the later life emergence of sustained NPS as an at-risk state for incident cognitive decline and dementia, and an early presentation of neurodegenerative diseases in some. Lastly, we will discuss future directions in the field so as to better understand the neurobiological basis of NPS in the early stages of the AD continuum, and their role in predicting AD pathophysiological progression and incident dementia.

Keywords: neuropsychiatric symptoms, Alzheimer's disease, metabolic dysfunction, [^{18}F]fluorodeoxyglucose PET, mild behavioral impairment

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INTRODUCTION

Neuropsychiatric symptoms (NPS) are non-cognitive symptoms common in the Alzheimer's disease (AD) continuum (Lyketsos et al., 2011; Brodaty et al., 2015; Vik-Mo et al., 2018), associated with poorer cognitive, functional, and quality of life outcomes, and accelerated progression to severe dementia (Teng et al., 2007; Karttunen et al., 2011; Fischer et al., 2012; Peters et al., 2015). An emerging conceptual framework proposes NPS as early clinical manifestations in the preclinical and mild cognitive impairment (MCI) stages of AD, better predicting progression to dementia than those without NPS (Donovan et al., 2014; Geda et al., 2014; Burhanullah et al., 2019;Ruthirakuhan et al., 2019; Wise et al., 2019). Therefore, studies of NPS in the early stage of AD are paramount, given that insight into

the underlying neurobiology of early NPS may enable targeted interventions to improve clinical outcomes (Mortby et al., 2018a).

[^{18}F]fluorodeoxyglucose ([^{18}F]FDG) positron emission tomography (PET) measures cerebral glucose metabolic rate (CMRglc) changes and AD studies using [^{18}F]FDG PET have demonstrated correlations between CMRglc reduction in the parietotemporal, posterior cingulate (PCC), and medial temporal and/or frontal cortices and synaptic dysfunction (Jack et al., 2016). Progressive CMRglc reductions occur years prior to clinical symptoms in patients with pathologically verified AD (Mosconi et al., 2009) and the degree of CMRglc reduction relates to disease severity (Furst et al., 2012). Studies in depression (Kennedy et al., 2001) and schizophrenia also demonstrate regional cerebral metabolic dysfunction correlating with psychiatric symptoms. Therefore, [^{18}F]FDG PET constitutes a valuable neuroimaging modality to investigate the relationship between NPS and metabolic changes in early stages of AD.

In this mini-review, we will examine the associations of NPS and metabolic dysfunction in the AD continuum, including preclinical, prodromal, and dementia stages of AD. We will also discuss a recently proposed diagnostic construct, mild behavioral impairment (MBI), that determines the emergence of NPS in later-life as an early manifestation of neurodegenerative diseases.

FREQUENCY OF NEUROPSYCHIATRIC SYMPTOMS IN AD

NPS are commonly observed across the AD continuum. In two population-based studies, 61%–75% of demented participants exhibited one or more NPS in the past month, with apathy, depression, and agitation/aggression being most common (Lyketsos et al., 2000; Lyketsos et al., 2002). A systematic review and population studies also show that behavioral abnormalities are observed in 35%–75% of MCI patients, with depression, apathy, anxiety, and irritability being most common (Lyketsos et al., 2002; Apostolova and Cummings, 2008; Geda et al., 2008). Another systematic review and meta-analysis found the prevalence of depression in MCI to be 32%, but higher in clinical (40%) vs. community (25%) settings, emphasizing the clinical significance of NPS (Ismail et al., 2017b). In the Dominantly Inherited Alzheimer Network (DIAN), early behavioral changes such as depression, apathy, disinhibition, irritability, sleep changes, and agitation are also more common in mildly symptomatic familial AD mutation carriers relative to non-carriers (Ringman et al., 2015).

NPS in cognitively normal individuals predict subsequent cognitive decline (Burhanullah et al., 2019). In a prospective cohort study over a median of 5.0 years, baseline NPS in cognitively normal persons also increased the risk of incident MCI (Geda et al., 2014). However, in DIAN, depressive symptoms were less common in cognitively asymptomatic mutation carriers than in non-carriers and the odds of experiencing at least one behavioral symptom in asymptomatic carriers was lower than in non-carriers (Ringman et al., 2015).

METHODS

A PUBMED search was conducted using the keywords "FDG," "fluorodeoxyglucose," "PET," "positron emission tomography," "metabolism," "Alzheimer," "dementia," "mild cognitive impairment," "predementia," "neuropsychiatric," and "behavior" in January 2019. A total of 5243 English language articles were found. Fifty articles reporting on metabolic dysfunction in dementia and cognitive impairment were identified, of which 32 studies reporting on non-AD dementia were excluded. Of the remaining 18 articles, 1 was excluded as the diagnosis of AD could not be separated from other causes of dementia. The remaining 17 articles (12 in AD, 5 in MCI or preclinical AD) were discussed here.

METABOLIC DYSFUNCTION AND NPS

It has been proposed that NPS in AD may cluster into specific subsyndromes and share similar clinical trajectories (Aalten et al., 2007; Canevelli et al., 2013; Nowrangi et al., 2015; Ballarini et al., 2016). In a large European cohort of more than 2000 AD subjects, four subsyndromes were identified based on the Neuropsychiatric Inventory (NPI): apathy, affective, hyperactivity, and psychosis (Aalten et al., 2007). Currently, the neurobiological basis of neuropsychiatric subsyndromes, especially in the early stages of AD remained poorly understood, and each subsyndrome may have distinct underlying neuroanatomical and neurobiological correlates (Nowrangi et al., 2015; Ballarini et al., 2016).

In this section, we present and discuss the evidence for metabolic dysfunction in each neuropsychiatric subsyndrome across the AD continuum. Where data are available, we emphasize preclinical and prodromal stages of AD (**Tables 1** and **2**).

Apathetic Subsyndrome

The apathetic subsyndrome consists of apathy, eating abnormalities, and aberrant motor behavior. However, existing literature consist of [^{18}F]FDG PET studies either in the apathetic subsyndrome or apathy only. On the whole, there is correlation between apathy and hypometabolism in the orbitofrontal cortex (OFC) and cingulate cortex in dementia subjects; while in MCI, apathy appears to be correlated with an AD-specific pattern of hypometabolism in the PCC.

In a cohort of 53 AD patients with mean disease duration of 28.7 months and Mini-Mental State Examination (MMSE) score of 22.5, apathy was associated with hypometabolism in the left OFC (Holthoff et al., 2005). In 41 AD patients, hypometabolism in bilateral ACC and bilateral medial OFC were reported (Marshall et al., 2007). Ballarini et al. examined the associations between regional metabolism, functional connectivity and neuropsychiatric subsyndrome clusters in early onset AD (EOAD). In 51 EOAD subjects, 27 had NPS, of which apathetic subsyndrome was the most common (74%). Hypometabolism was found in bilateral middle orbitofrontal and middle frontal gyri of subjects with the apathetic subsyndrome (Ballarini et al., 2016).

There are fewer [^{18}F]FDG PET studies in prodromal AD. A small study of 24 MCI subjects showed no significant association between apathy and regional glucose metabolism (Marshall et al.,

TABLE 1 | Summary of metabolic dysfunction in AD dementia subjects with NPS by subsyndromes.

NPS Subsyndrome	Study	NPS	Dementia	Number of subjects	Number of subjects with NPS	Findings
Affective	Sultzer et al., 1995	Anxiety/ depression	AD (mean MMSE 18.6)	21	Not available	Parietal lobe hypometabolism*
	Hirono et al., 1998a	Depression	Mild to moderate AD	53	16 (35.9%)	Bilateral superior frontal and left anterior cingulate cortex (ACC) hypometabolism
	Holthoff et al., 2005	Depression	Mild to moderate AD	53	10 (18.9%)	Left superior frontal and prefrontal cortex hypometabolism
	Lee et al., 2006	Depression	Mild AD	12	6 (50%)	Right superior frontal gyrus hypometabolism
	Hashimoto et al., 2006	Anxiety	AD (mean MMSE 19.6)	41	19 (46.3%)	Left superior temporal gyrus, entorhinal cortex, and parahippocampal region hypometabolism
	Ballarini et al., 2016#	–	EOAD (mean MMSE 20.78)	27	17 (63%)	Bilateral ACC and superior frontal gyrus (extending to supplementary motor area) hypermetabolism
Apathetic	Holthoff et al., 2005	Apathy	Mild to moderate AD	53	17 (32.1%)	Bilateral orbitofrontal cortex (OFC) hypometabolism
	Marshall et al., 2007	Apathy	AD (mean MMSE 19.6)	41	14 (34.1%)	Bilateral ACC and medial OFC hypometabolism
	Ballarini et al., 2016#	–	EOAD (mean MMSE 20.78)	27	20 (74.1%)	Bilateral middle frontal gyri and OFC hypometabolism
Hyperactivity	Sultzer et al., 1995	Agitation/ disinhibition	AD (mean MMSE 18.6)	21	Not available	Temporal lobe hypometabolism*
	Ballarini et al., 2016#	–	EOAD (mean MMSE 20.78)	27	19 (70.4%)	Left insula, superior frontal, anterior cingulate gyrus, temporal pole, precentral gyrus, and right inferior frontal gyrus hypermetabolism
	Weissberger et al., 2017	Agitation	AD (mean MMSE 19.3)			Bilateral posterior cingulate, right middle temporal gyrus, and right frontal cortex hypometabolism
Psychotic	Sultzer et al., 1995	Psychosis	AD (mean MMSE 18.6)	21	Not available	Frontal lobe hypometabolism*
	Mentis et al., 1995	Delusions of misidentification	Mild to moderate AD	24	9 (37.5%)	Bilateral OFC and cingulate hypometabolism Bilateral sensory association cortex hypermetabolism
	Hirono et al., 1998b	Delusions	Mild to moderate AD	65	26 (40%)	Left medial occipital region Left inferior temporal gyrus hypermetabolism
	Sultzer et al., 2003	Delusions	AD (mean MMSE 16.5)	25	76%	Right superior dorsolateral and inferior frontal hypometabolism. Right lateral orbifrontal hypermetabolism.
	Sultzer et al., 2014	Delusions	AD (mean MMSE 19.3)	88	28 (31.8%)	Right lateral frontal, orbitofrontal, and bilateral temporal cortex hypometabolism

**Derived from mean [^{18}F] FDG-PET metabolism from right and left hemispheres.*

#NPI symptoms clustered into subsyndromes: affective (anxiety and depression); apathetic (apathy and eating and appetite changes); hyperactivity (agitation/ aggression, irritability, euphoria/elation, aberrant motor behavior, and disinhibition); psychotic (delusions, hallucinations and night-time sleep disturbances). Breakdown not available.

TABLE 2 | Metabolic dysfunction and NPS in preclinical AD and MCI subjects.

Studies	NPS	Number of subjects	Subjects with NPS	Findings
Marshall et al., 2013	Apathy	24 amnestic MCI	Not available	No significant association
Delrieu et al., 2014	Apathy	65 amnestic MCI	11 (16.9%)	Bilateral posterior cingulate (PCC) hypometabolism
Gatchel et al., 2017	Apathy	402 subjects: -203 amnestic MCI -104 cognitively normal -95 mild AD	73 (18.2%)	Bilateral PCC hypometabolism
Lee et al., 2010	Depression	36 amnestic MCI	18 (50%)	Right superior frontal gyrus hypometabolism
Brendel et al., 2015	Depression	209 Aß +ve MCI 165 Aß -ve MCI	65 (31.1%) 41 (24.8%)	Right superior frontal, left middle frontal and left fusiform gyri hypermetabolism in Aß +ve subjects

2013). A larger study of 65 MCI individuals from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database showed an AD-specific pattern of PCC hypometabolism in MCI subjects with apathy (Delrieu et al., 2014). This was corroborated by a subsequent ADNI study including 422 cognitively normal, MCI, and early dementia subjects, demonstrating correlation between PCC hypometabolism and higher apathy scores (Gatchel et al., 2017). Baseline hypometabolism of the supramarginal gyrus was also found to predict the increase of apathy over time (Gatchel et al., 2017).

In AD dementia, the association between apathy and hypometabolism in the OFC and anterior cingulate cortex (ACC) is consistent with their role in recognition of salient stimuli, reward-based decision-making, drive, and motivation (Holthoff et al., 2005; Wallis, 2007; Kouneiher et al., 2009). This is supported by a number of studies using other imaging modalities such as magnetic resonance imaging (MRI), diffusion tensor imaging and single-photon emission computed tomography (Stella et al., 2014). Indeed, the ACC has been recognized as a key node in the salience network (SN) (Seeley et al., 2007; Menon, 2015).

In MCI with apathy, the finding of PCC hypometabolism mirrors the early metabolic dysfunction characteristically seen in amnestic MCI subjects reflecting underlying AD pathology (Drzezga et al., 2003; Nestor et al., 2003). The reason for sparing of frontal lobe metabolism is less certain. Firstly, the degree of apathy may be below the threshold for detection of hypometabolism in the OFC and ACC (Delrieu et al., 2014). Secondly, the frontal and parietal regions are interconnected, and dysfunction in one or more parts of the network may give rise to apathy (Gatchel et al., 2017).

Affective Subsyndrome

The affective subsyndrome comprises anxiety—a "positive" symptom—and depression—a "negative" symptom. [^{18}F]FDG PET studies have shown metabolic dysfunction in the superior frontal and ACC of subjects with affective subsyndrome in various stages of dementia, though studies in MCI are lacking (Sultzer et al., 1995; Hirono et al., 1998a; Holthoff et al., 2005; Hashimoto et al., 2006; Lee et al., 2010; Brendel et al., 2015; Ballarini et al., 2016). Two studies examined anxiety and depressive symptoms together as a subsyndrome in moderate AD (Sultzer et al., 1995; Ballarini et al., 2016). An early study showed reduced metabolism in the parietal lobes of subjects with moderate AD with anxiety/depression (mean MMSE 18.6, mean disease duration of 4.2 years) (Sultzer et al., 1995). In 17 EOAD subjects with affective subsyndrome, increased metabolism in the superior frontal gyri and ACC was demonstrated (Ballarini et al., 2016). These findings reflect the important role of the ACC in the SN, which mediates the "top-down" selection of significant emotional and sensory stimuli, directing attention and influencing goal-directed behavior (Seeley et al., 2007). More specifically, the ACC is involved in response selection and conflict monitoring (Menon, 2015). Therefore, increase in nodal activity in the ACC may lead to aberrant emotional responses to salience, especially the "positive" symptom of anxiety (Zhou and Seeley, 2014).

Furthermore, in a cross-sectional study of cognitively normal persons aged ≥ 70 years from the Mayo Clinic Study of Aging, depressive and anxiety symptoms were associated with decreased [^{18}F]FDG PET uptake in AD-related regions (Krell-Roesch et al., 2016), suggesting that NPS may play an important role in addition to the current biomarker-based investigations in presymptomatic AD.

Depression as an individual symptom has been studied in MCI and mild AD, demonstrating an association with abnormal glucose metabolism predominantly in the frontal lobes. In earlier studies, depressive symptoms in AD correlated with hypometabolism especially in the superior frontal gyri (Hirono et al., 1998a; Holthoff et al., 2005; Lee et al., 2010). However, a recent [^{18}F]FDG PET study of 371 MCI ADNI subjects showed hypermetabolism in the right superior frontal, left middle frontal, and left fusiform gyri in amyloid-positive MCI subjects (Brendel et al., 2015), consistent with the aforementioned findings in EOAD subjects with the affective subsyndrome (Ballarini et al., 2016). These findings are concordant with those in non-demented subjects with late-life depression, where hypermetabolism in the superior frontal gyri is correlated with severity of depression (Smith et al., 2009). The role of the superior frontal gyri in depression, and its relation to amyloid pathology warrants further study.

Hyperactivity Subsyndrome

Data of metabolic dysfunction and hyperactivity subsyndrome (agitation/aggression, euphoria, disinhibition, and irritability) in AD is limited, especially in the preclinical or prodromal stages. Significant correlation between the agitation/disinhibition factor score of the Neurobehavioral Rating Scale (NRS) and hypometabolism in the frontal and temporal lobes in 21 AD subjects have been demonstrated (Sultzer et al., 1995). In an EOAD cohort with mean disease duration of 3.18 years and MMSE 20.7, hypermetabolism in the left insula, superior frontal gyrus, temporal pole and precentral gyrus, the ACC, and the right inferior frontal gyrus were found in 19 subjects with the hyperactivity subsyndrome (Ballarini et al., 2016). This contrasts with a recent study in 88 mild to moderate late-onset AD (LOAD) (mean age 78 years, disease duration 3.2 years, MMSE 19.3), which instead found hypometabolism in the right temporal and bilateral middle and posterior cingulate regions in subjects with agitation (Weissberger et al., 2017).

The association between hyperactivity and metabolic dysfunction in the ACC and insula is explained by their roles in the SN (Menon, 2015). In mild to moderate AD with hyperactivity, increased functional connectivity in the anterior SN was demonstrated (Balthazar et al., 2014). Studies using structural MRI in MCI and mild AD with agitation have shown greater atrophy in regions of the SN such as the ACC, insula, and amygdala (Bruen et al., 2008; Trzepacz et al., 2013). Taken together, the evidence suggests a link between neurodegeneration in AD, dysfunction in the SN, and the hyperactivity subsyndrome. The reason for the discordant findings in metabolic dysfunction in EOAD and LOAD with agitation, however, remains to be elucidated.

A recent study of preclinical sporadic AD with both amyloid and tau pathologies present showed that NPS, driven by irritability and sleep behavior domains, are linked to metabolic dysfunction within the limbic networks that are vulnerable to

AD. NPS also predict subsequent hypometabolism in the PCC. These findings suggest that NPS may represent an early clinical manifestation of AD pathophysiology (Ng et al., 2017).

Psychotic Subsyndrome

Studies on metabolic dysfunction in the psychotic subsyndrome (delusion, hallucinations, night time disturbances) are mostly in AD subjects with delusions. We are unable to find similar studies in preclinical AD or MCI, unsurprising given that these NPS are less reported in the early stages of AD (Apostolova and Cummings, 2008) and are often given psychiatric diagnoses (Fischer and Agüera-Ortiz, 2018).

Sultzer et al. first demonstrated hypometabolism in the frontal lobes in AD subjects with higher psychosis factor score on the NRS (Sultzer et al., 1995). Hirono et al. found increased left inferior temporal gyrus and decreased left medial occipital metabolism in 26 subjects with predominantly moderate-severe AD (Hirono et al., 1998b). Two subsequent studies, including a larger study of 88 subjects with mild to moderate AD, showed mainly right-lateralized findings, with hypometabolism in the right lateral, inferior and orbitofrontal cortices, as well as bilateral temporal lobes (L Sultzer et al., 2003; Sultzer et al., 2014). This is consistent with structural, perfusion, and metabolic imaging studies in AD subjects that implicate right hemispheric pathology—in particular the right frontal lobe—in the formation of delusions (Ismail et al., 2012). Right hemispheric dysfunction may cause impaired salience, self-monitoring, perceptual integration, and release of the left frontal lobe, resulting in overactivity of the default mode network (DMN) and a hyper-inferential state that predisposes to delusions (Ismail et al., 2012; Gurin and Blum, 2017).

Specific subtypes of delusions may also be associated with abnormal glucose metabolism in distinct regions of the brain. Delusional misidentification syndrome (DMS) in AD was associated with hypometabolism in bilateral paralimbic and left medial temporal regions as well as normalized hypermetabolism in the sensory association cortices (Mentis et al., 1995). This is consistent with a more recent voxel-based morphometry study showing reduced right hippocampal grey matter volume in five AD subjects with DMS, suggesting a role for medial temporal lobe dysfunction in DMS (Serra et al., 2010). Further studies clearly differentiating persecutory type and misidentification delusions are required to better understand the neurobiology of these symptoms (Ismail et al., 2011).

MILD BEHAVIORAL IMPAIRMENT

MBI is a validated neurobehavioral syndrome characterized by later life emergent and sustained NPS as an at-risk state for incident cognitive decline and dementia, and the index manifestation of dementia in some (Taragano et al., 2009; Ismail et al., 2016; Creese et al., 2019; Matsuoka et al., 2019). MBI, which may precede or co-exist with subjective cognitive decline (SCD) or MCI, represents a later-life change in behavior or personality in the domains of drive and motivation (apathy), affective regulation (mood/anxiety symptoms), impulse control (agitation, reward salience), social cognition (socially inappropriate behavior), and perception/thought content (psychotic symptoms) for ≥6 months. MBI reflects the neurobehavioral axis of pre-dementia risk states, which complements the neurocognitive axis identified by SCD and MCI. Both axes identify individuals who may have increased risk of developing dementia, and there may be a common genetic etiology for MBI and AD (Andrews et al., 2018). Importantly, MBI offers a systematic way to approach later life psychiatric symptomatology, in order to differentiate between late life psychiatric conditions for which the links to dementia are not clear (Panza et al., 2010), and later-life emergent NPS, for which the links to dementia are very clear and supported by an increasing evidence base (Rosenberg et al., 2013; Geda et al., 2014; Wise et al., 2019). A 5-year longitudinal study demonstrated this difference to be meaningful, with the MBI group having a significantly higher rate of incident dementia compared to the late-life psychiatric disorder group (Taragano et al., 2018). In many dementia clinical trials, some with NPS, especially more severe NPS, are excluded from studies. However, severity alone is insufficient to distinguish between a psychiatric condition and a potential manifestation of prodromal dementia. The age of onset and natural history of psychiatric symptomatology are the essential elements required to distinguish groups (Ismail et al., 2018). Three large observational cohorts (totaling 42,000 participants) with up to 28 years of follow-up demonstrated a link between later life emergence of psychiatric conditions, and dementia diagnosis, to be 5–11 years depending on the study, with authors of all studies suggesting that these later life psychiatric conditions may in fact have been prodromal dementia (Almeida et al., 2017; Singh-Manoux et al., 2017; Tapiainen et al., 2017)

Thus, the key to incorporation of MBI into dementia research lies in appropriate case ascertainment. In a recent study of cognitive neurology patients, MBI was present in 83.5% of MCI and 76.5% of SCD (Sheikh et al., 2018). However, MBI was diagnosed using the Neuropsychiatric Inventory Questionnaire (NPI-Q), which is a limitation, given that NPI-Q is originally designed for individuals with dementia, and has a 1-month reference range, thus not necessarily capturing the 6-month symptom duration requirement for MBI diagnosis. This short reference range can result in poor specificity, inappropriately capturing as cases with transient symptoms and reactive conditions, thus inflating frequencies. A similar analysis in a population sample of 1,377 participants with normal cognition, pre-MCI and MCI, found MBI prevalence to be 34.1% (Mortby et al., 2018b), which is also likely to be an inflated estimate. The Mild Behavioral Impairment Checklist (Ismail et al., 2017a) (MBI-C, available at http://www.MBItest.org) was thus developed, specifically as a MBI case ascertainment instrument, consistent with the new MBI criteria, and for and monitoring of MBI symptoms in pre-dementia populations. In a primary care validation study, MBI prevalence was 14.2% in MCI using a cutoff point of 6.5 and 5.8% in SCD using a cutoff of 8.5 (Mallo et al., 2018; Mallo et al., 2019). The lower and more specific prevalence estimates likely better reflects an enriched population for biomarker positivity (Lussier et al., 2019), with a greater risk for incident cognitive decline and dementia. Thus, MBI offers an advance in the approach to NPS in pre-dementia populations. Incorporating the MBI-C into case selection, which

is free and easy to administer, may better identify those at risk, and those with preclinical or prodromal illness of pre-dementia patients. This group may then be worked up for pre-dementia markers, increasing the efficiency of clinical trial recruitment, and decreasing the cost (Mortby et al., 2018a).

CONCLUSION AND FUTURE DIRECTIONS

In this mini-review, we found that the present [^{18}F]FDG PET studies are consistent with findings from functional connectivity studies that implicate dysfunctions in key regions of the SN and DMN in different subsyndromes of NPS in AD, further supporting NPS as early clinical manifestations of metabolic dysfunctions in regions susceptible to AD pathophysiology.

While the metabolic correlates of NPS are widely studied in AD dementia, studies on the predictive role of NPS in determining subsequent metabolic decline in preclinical AD remained limited. One possible reason could be the lack of a diagnostic tool designed to identify sustained NPS of later-life onset in non-demented persons as an early presentation of neurodegenerative disease. In this regard, the recently proposed MBI criteria enables the systematic study of NPS in cognitively normal individuals using a common language which is explicit with respect to cognitive status, and facilitating the differentiation between psychiatric disorders and NPS in preclinical and prodromal AD. Despite promising early findings, further research is needed to test the reliability and validity of the MBI criteria, to quantify the risk of late-onset NPS and incident dementia, and to validate the MBI-C in a wider population using different modes of administration and languages.

Recent longitudinal studies show that NPS are common in cognitively intact individuals and predict cognitive decline (Burhanullah et al., 2019; Wise et al., 2019). Therefore, individuals with MBI form an important clinical and research population for AD studies. Future research should combine [^{18}F]FDG PET with functional studies and AD biomarkers, such as amyloid and tau, and should focus on the association of MBI with AD-related neurodegeneration, functional changes, and metabolic dysfunction. This will provide insight into the neurobiological basis of NPS in early AD, elucidate the role of MBI in the early detection of incident AD dementia, and facilitate the incorporation of MBI in the selection of individuals at risk for AD dementia for observational and clinical trials, especially in centers lacking access to AD biomarkers. Ultimately, the use of MBI in clinical practice to identify individuals with early presentation of AD may provide a window of opportunity to provide early interventions may alter disease course, delay the onset of dementia, and improve functional and cognitive outcomes.

AUTHOR CONTRIBUTIONS

KN did the study concept and design, compose table, and manuscript draft. HC did the study concept and design, compose table, and manuscript draft. PR-N did the study concept and manuscript draft. NK did the study concept and manuscript draft. ZI did the critical review of manuscript. SG did the study concept and design and critical review of manuscript for intellectual content.

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The Use of Antipsychotic Drugs for Treating Behavioral Symptoms in Alzheimer's Disease

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According to the World Alzheimer's report, dementia was estimated to affect 50 million worldwide in 2018, number expected to increase to more than 150 million within 30 years. Alzheimer's disease is the most common type of dementia, accounting on its own for 2/3 of all dementia cases. The initial signs and symptoms of Alzheimer's disease relate to progressive cognitive decline, inexorably progressing until the loss of independence. Neuropsychiatric and behavioral symptoms may occur during the progression of the disease; around 20% of patients without any behavioral symptoms at the diagnosis will experience some of them within 2 years. Consequences are early institutionalization, lower quality of life, of both patients and carers, and more severe cognitive impairment. Treatment options for behavioral symptoms include pharmacological and non-pharmacological approaches. The latter are usually preferred, since antipsychotic therapy is not free from several, and often serious, adverse events. However, behavioral symptoms are not always controllable with non-pharmacological intervention. The psychotropic class of medication more frequently prescribed for behavioral symptoms are atypical antipsychotics; among them, risperidone is the only one licensed for the treatment of aggression, in Europe but not in the USA. On that regard, the use of antipsychotic drugs should be limited, due to the increased risk of mortality, stroke, hallucination, and higher risk of relapse after discontinuation. Some new agents are under evaluation, such as pimavanserin and lumateperone. In this review, we are evaluating the current available pharmacological options to treat behavioral symptoms as well as the forthcoming new agents.

Keywords: Alzheimer's disease, antipsychotic drugs, D2 receptors, 5-HT2A receptors, agitation, hallucinations

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INTRODUCTION

According to the World Alzheimer's Report 2018, 50 million people are living with dementia worldwide (A.s.D. International, 2018), and Alzheimer's disease (AD) accounts on its own for almost 2/3 of all dementia cases. AD is a devastating neurodegenerative disease characterised by progressive cognitive impairment, usually affecting, at the beginning, episodic memory. As the disease progresses, other cognitive domains become affected, leading to the loss of independence.

Behavioral and psychological symptoms in dementia (BPSD) are a group of behavior, mood, perception, or thought disturbances manifesting with anxiety, agitation, delusions and hallucination (Abraha et al., 2017). The incidence of perceptual abnormalities in patient with dementia is high; around 20% of subjects with no behavioral symptoms at the diagnosis will develop some of them within 2 years (Abraha et al., 2017). Experiencing BPSD leads to institutionalization, greater cognitive impairment, worse quality of life and carers' distress, increased mortality (Creese et al., 2018), prolonged in-hospital stay, and more difficult discharge (Davies et al., 2018). The features of the psychiatric symptoms in AD usually differ from the ones in other psychiatric disorders. Compared to schizophrenia, delusions in AD are simpler, mostly characterized by misbelief, distrust about family members, theft, and suspiciousness of abandon (De Deyn et al., 2013). Hallucinations in AD are usually visual (Lanctot et al., 2017), more rarely somatic and olfactory (El Haj et al., 2017). Agitation has been related to structural and functional impairment of emotional circuits, leading, for example, to increased perception of threat (Lanctot et al., 2017).

Unfortunately, the management of BPSD is complicated and challenging; the available licensed treatment is limited, the success of the therapy varies, and the spectrum of possible adverse events limits the choices (Lane et al., 2018). The preferred approach is the non-pharmacological one; however, despite multiple studies, there is not enough homogeneity in sample size, intervention adopted and follow-up period (Abraha et al., 2017). An evidence-based algorithm has recently been designed and proposed by multidisciplinary teams, to better manage behavioral symptoms and lead clinicians on the therapeutic choice (Davies et al., 2018).

In this review we evaluate the use of antipsychotic drugs in AD. The search was conducted in PubMed and Scopus, with keywords and search criteria as detailed in the **Supplementary Material**.

Antipsychotic Drugs

Antipsychotic drugs can be divided in two groups: typical and atypical, depending on their strength as antagonists to dopamine D2 receptors, higher for the typical ones, and to the 5-hydroxytryptamine-A (5-HT2A) receptors, characteristic of the atypical ones (Ballard and Howard, 2006). Among the typical antipsychotic category, haloperidol remains the most prescribed; several concerns have been raised because of their low safety profile. Sedation, extrapyramidal symptoms (EPS), orthostatic hypotension, and anticholinergic effects were concerning safety issues, mainly due to the strong and long-lasting binding of D2 receptors across the whole brain regions, together with several other receptors (De Deyn et al., 2013). Risperidone, olanzapine, and quetiapine are atypical neuroleptics. The binding to D2 receptors is more targeted to selected brain regions, related to the psychotic symptoms, sparing the ones linked to the motor symptoms; these are due to an antagonist action on 5-HT2A receptors as well, or to a shorter blockage of D2 receptors (De Deyn et al., 2013). The use of antipsychotic drugs to treat agitation tracks back to the 60s (Ballard et al., 2011); since then, due to increasing evidences of safety concerns, their prescription has been widely reduced (Ballard et al., 2011).

Atypical Antipsychotic Drugs

Risperidone is a dopamine, serotonin, and noradrenalin receptor antagonist (Davies et al., 2018), licensed for the treatment of maniac and mixed bipolar disorder episodes and is approved for short-term treatment of behavioral symptom in dementia in UK, but not in the US (Davies et al., 2018). Several clinical trials evaluated the efficacy of risperidone in the treatment for BPSD. A significant improvement in aggression, measured with the BEHAV-AD (Behavioural Pathology in Alzheimer's Disease) scale, was seen with risperidone at 1 and 2 mg, with better outcome on the higher dose (–1.50 [–2.05, –0.95] $p < 0.0001$), compared to placebo (Katz et al., 1999; Ballard and Howard, 2006). Some difference was also seen at the dose of 1 mg, compared to placebo, in treating psychosis (–0.14 [–0.25, –0.03] $p = 0.01$) (Katz et al., 1999; Ballard and Howard, 2006). The largest randomized controlled study (RCT) "Cognitive Effects of A typical Antipsychotic Medications in Patients with Alzheimer's Disease" (CATIE-AD) gave interesting results. A cohort of 421 patients with AD, followed up in an outpatient setting for psychosis or agitation/aggression, was randomized to receive placebo, risperidone, quetiapine, or olanzapine for 36 weeks, with cognitive assessment at baseline, 12, 24, and 36 weeks (Vigen et al., 2011). The risperidone or olanzapine groups showed greater cognitive decline in the cognitive summary score (sum of 18 cognitive tests), while the olanzapine one had a greater decline in the mini mental state examination (MMSE); the BPRS cognitive factor was worse in quetiapine group, compared to the placebo group (Vigen et al., 2011). The phase 1 outcomes of CATIE-AD showed that, compared to placebo, the group receiving risperidone had greater improvement in the Brief Psychiatric Rating Scale (BPRS) psychosis factor and in the Clinical Global Impression of Changes (CGI-C) (Sultzer et al., 2008). The groups receiving either risperidone or olanzapine had greater improvement in the Neuropsychiatric Inventory scale (NPI) and BPRS hostile suspiciousness factor (Sultzer et al., 2008). However, the final results of the study did not show any significant advantages in the improvement in the CGI-C scale; adverse event and discontinuation due to poor tolerability favoured placebo (Schneider et al., 2006). The multicentre Antipsychotic Discontinuation in Alzheimer's disease (ADAD) trial evaluated a cohort of 180 patients with AD and agitation or psychosis. The whole cohort received risperidone for 16 weeks, and then was randomized to proceed with risperidone for 32 weeks, receive risperidone for 16 weeks and placebo for further 16 weeks, or receive placebo for 32 weeks (Patel et al., 2017). The discontinuation of the drug led to increased risk of relapse during the randomization window, particularly for severe hallucinations at baseline (Patel et al., 2017). The dementia antipsychotic withdrawal trial (DART-AD) randomized patients with AD in care facilities to continue the current medication (thioridazine, chlorpromazine, haloperidol, trifluoperazine, or risperidone) or switch to placebo for 12 months (Ballard et al., 2009), with mortality rate as a primary outcome. Among the whole cohort,

the mortality was higher in the subject continuing the medication, compared to the placebo branch (Ballard et al., 2009).

Olanzapine is an atypical antipsychotic, licensed for the treatment of schizophrenia and bipolar disorder in adults. Studies have been conducted to evaluate the efficacy in controlling behavioral symptoms in dementia. De Deyn et al. conducted a large study with > 600 AD patients with delusions or hallucinations, randomized to receive either placebo or a fixed dose of olanzapine (1.0, 2.5, 5.0, or 7.5 mg/day) for 10 weeks. An improvement in the sum of delusion and hallucination scores of the NPI was seen in the group treated, from the 2.5 mg dose, with higher efficacy for the 7.5 mg dose (De Deyn et al., 2004). Another study compared the efficacy and tolerability of a flexible dose of olanzapine and risperidone vs. placebo in the NPI and Clinical Global Impression–Severity (CGI-S) of Psychosis scale. Improvement has been noticed in all the three groups, with a higher rate of adverse events and withdrawal in the risperidone and olanzapine group (Deberdt et al., 2005). In a multicentre, double-blinded and placebo-controlled trial, 206 older patients AD patients in nursing home, showing psychotic or behavioral symptoms, were randomized to receive olanzapine (5, 10, or 15 mg/die) or placebo. Significant improvement in the summed scores of agitation/aggression, delusion and hallucination items in the NPI-nursing home version (NPI-NH) was seen in patient treated with lower doses of olanzapine, while the higher dose did not differ from the placebo. Six weeks treatment with either placebo or three different doses of olanzapine favoured the use of lower doses in controlling behavioral symptoms, compared to placebo or 15mg/day. The treatment was well tolerated. Apart from somnolence and gait disturbances, commoner in the treatment group, no other potential side effects were seen compared to placebo (Street et al., 2000).

Aripiprazole is an atypical antipsychotic drug licensed for the treatment of schizophrenia in adults and adolescents, mania in bipolar disease in children, adolescents and adults, autism, major depression in adults. Due to the safer profile, a broader use has been done, including psychosis in older patients with dementia (De Deyn et al., 2013). A 10 weeks double blind, placebo-controlled and multicentre study randomized 208 AD patients with delusions or hallucination, to receive aripiprazole 2 mg/day, possibly titrated to higher dosages, or placebo. Significant improvement was seen in the CGI-S of illness, and in the mean CGI-improvements, in patients more severely affected. Significant improvement has also been demonstrated in the BPRS psychosis and BPRS core scores, but the overall conclusion was that the improvement was only modest over placebo (De Deyn et al., 2005). A double-blind, multicentre and placebo-controlled study assigned institutionalized AD patients with psychotic symptoms to aripiprazole (2, 5 or 10 mg/day) or placebo, for 10 weeks. Significant improvement in the NPI-NH psychosis, delusion, agitation/aggression, anxiety, and irritability subscales was seen in the 10 mg treatment group. Some improvement was also seen in the Cohen-Mansfield Agitation Inventory (CMAI) scores in the 5 and 10 mg group, and the mean CGI-S was better in the 10 mg group (Mintzer et al., 2007). The higher efficacy of 10 mg of aripiprazole in controlling behavioral symptoms has been confirmed in another multicentre, placebo-controlled trial on institutionalized AD patients (Streim et al., 2008).

Quetiapine is licensed for the treatment of schizophrenia and bipolar disorder in adults, prescribed off-label to treat post-traumatic stress disorder, anxiety, insomnia, and behavioral symptoms in dementia. Two different doses of quetiapine (100 or 200 mg/daily) vs. placebo tested in a cohort of AD patients showed greater improvement, at a dose of 200 mg, in the Positive and Negative Syndrome Scale (PANSS)-Excitement Component (EC) score, as well as in the CGI-C (observation analysed as Last Observation Carried Forward (LOCF): $p = 0.014$ and Observed cases (OC): $p = 0.002$). No advantages over placebo at lower dose (Zhong et al., 2007). Quetiapine did not show any benefit compared to placebo or other antipsychotic drugs in the CATIE-AD study (Vigen et al., 2011). Another RCT compared quetiapine, rivastigmine, and placebo over 26 weeks in institutionalized AD patients; the endpoint was the improvement in agitation, measured with the CMAI scale, and cognition (Ballard et al., 2005). Neither rivastigmine nor quetiapine showed significant benefit compared to placebo, and quetiapine was associated with worse cognitive decline (Ballard et al., 2005). **Table 1** summarizes the above-mentioned studies. Overall, a meta-analysis by Ma et al. pooling RCTs with different antipsychotics, demonstrated their higher efficacy as assessed with NPI, CGI-C, CGI-S, BPRS, and CMAI, compared to placebo (Ma et al., 2014).

Antipsychotics and Safety

Neuroleptic drugs have been related to several adverse event and safety issues. The increasing concerns about adverse events and tolerability led the FDA to include a warning, in the form of a "black box" in the atypical and typical antipsychotic labels, to limit the prescription (Dorsey et al., 2010). The warning has also been issued by the European Medicines Agency (EMA); the committee for Medicinal Products for Human Use recommended including a warning of increased risk of death for all conventional antipsychotics in the older patients with dementia. Among the most frequent and widely reported side effect of neuroleptic, drowsiness, tardive dyskinesia and parkinsonism have been reported (Ballard and Howard, 2006). Moreover, increased risk of venous thromboembolic events (VTE) has been demonstrated in patients treated with antipsychotics, both in general and older population (Jonsson et al., 2018). In a meta-analysis in 2006, Ballard *et al.* reported several side effects of neuroleptics; haloperidol, among the first generation ones, was associated with EPS and drowsiness (Ballard and Howard, 2006). A systematic review aiming to compare the rates of EPS with second generation antipsychotic drugs with the first-generation ones, confirmed a reduced incidence with the former, across different pathologies and age groups (Correll et al., 2004). Among atypical neuroleptics, risperidone showed increased EPS at the dose of 1 mg and 2 mg; dose-dependent increase in somnolence and peripheral

TABLE 1 | The table summarizes the studies on atypical antipsychotic drugs included in the review

Drug	Comparison groups, study design	Dose	Outcome	AE	Ref
Risperidone	Risperidone vs. Placebo, randomized double blind, placebo controlled	1 and 2 mg 0.5 mg	BEHAV-AD scale $p < 0.0001$ at 2 mg BEHAV-AD psychosis sub-scale $p = 0.01$ at 1 mg	Dose dependent: EPS Somnolence Mild peripheral oedema for 2mg > 1mg. EPS at 1 mg NS > than placebo	(Katz et al., 1999)
	Risperidone vs. placebo/ randomised controlled	Flexible dose	(-) BPRS	Reported elsewhere	(Vigen et al., 2011)
	Risperidone vs. Placebo, double blind, placebo controlled	Flexible dose	(+) BPRS psychosis factor ($p = 0.01$) and CGI ($p < 0.001$) (+) NPI total score ($p = < 0.001$) and BPRS suspiciousness factor ($p = 0.003$)	Higher withdrawn depression factor in Olanzapine group ($p = 0.03$)	(Sultzer et al., 2008)
	Risperidone or olanzapine vs. placebo, double blind, placebo controlled	0.5 mg or 2.5 mg	(+) NPI and CGI-S of Psychosis	Higher rate of EPS symptoms and increased prolactin levels compared to olanzapine or placebo	(Schneider et al., 2006)
Olanzapine	Olanzapine vs. placebo, double blind, placebo controlled	Flexible dose	(-) BPRS	Greater cognitive decline	(Vigen et al., 2011)
	Olanzapine vs. placebo, double blind, placebo controlled	Flexible dose	(+) NPI total score ($p = 0.007$) and BPRS suspiciousness factor ($p = 0.006$)	Higher withdrawn depression factor in Olanzapine group ($p = 0.03$)	(Sultzer et al., 2008)
	Olanzapine vs. placebo, double blind, placebo controlled	1mg, 2.5 mg, 5 mg or 7.5 mg	(+) NPI/NH Psychosis Total scores in all groups ($p < 0.001$). (+)NPI/NH Psychosis Total scores at 7.5 mg ($p = 0.008$) and CGI-C at 2.5 ($p = 0.030$).	Significant overall treatment-group differences in weight gain, Anorexia or and urinary incontinence. NS increase in EPS or total AE	(De Deyn et al., 2004)
	Olanzapine vs. placebo, multicentre double blind, placebo controlled	5mg, 10 mg or 15 mg	(+) Summed score of agitation/aggression, delusion and hallucination items in the NPI-NH with 5 or 10 mg ($p < 0.001$ and $p = 0.006$ respectively)	Higher somnolence and gait disturbances in the olanzapine group. NS difference in EPS or anticholinergic effects	(Street et al., 2000)
	Olanzapine or risperidone vs. placebo, double blind, placebo controlled	2.5 mg or 10 mg	(+) NPI CGI-S of Psychosis	Higher weight gain compared to risperidone or placebo, NS	(Schneider et al., 2006)
Aripiprazole	Aripiprazole vs. placeb, double blind, placebo controlled, multicentre	2 mg titrated according to tolerability to 5 mg, 10 mg or 15 mg	(+) in NPI psychosis subscale in treated and placebo group, NS (+)CGI-S, in patients more severely affected ($p = 0.035$). (+) BPRS psychosis ($p = 0.029$) and BPRS core scores ($p = 0.042$)	Higher urinary tract infections, somnolence and bronchitis. NS difference in EPS or weight gain	(De Deyn et al., 2005)
	Aripiprazole vs. placebo, double blind, placebo controlled, multicentre	2mg, 5mg or 10 mg	(+) in NPI-NH psychosis subscale ($p = 0.013$), CGI-S ($p = 0.030$), BPRS Core (0.007), CMAI ($p = 0.023$) and NPI-NH Psychosis response rate ($p = 0.019$) at 10 mg. (+) in BPRS and CMAI at 5 mg No efficacy at 2 mg	Cerebrovascular events increasing with dose.	(Mintzer et al., 2007)
	Aripiprazole vs. placebo, placebo controlled, multicentre	2 mg to be titrated to 5, 10 or 15 mg	NS in NPI-NH psychosis score ($p = 0.08$) or CGI-S ($p = 0.19$). Improvement in NPI-NH total score, BPRS, CMAI, Cornell Depression scale. (+) in CGI-S was seen in more severely affected patients	Higher somnolence in treatment group	(Streim et al., 2008)
Quetiapine	Quetiapine vs. placebo, double blind, fixed dose study	100 mg or 200 mg	(+) in PANNS-EC (OC $p = 0.014$) and CGI-C (OC $p = 0.002$) at 200 mg. No difference with placebo at 100 mg	Mortality numerically higher in the quetiapine group	(Zhong et al., 2007)

(Continued)

TABLE 1 | Continued

Drug	Comparison groups, study design	Dose	Outcome	AE	Ref
	Quetiapine vs. placebo, double blind, placebo controlled	Flexible dose	No benefit	Greater cognitive decline	(Vigen et al., 2011)
	Quetiapine vs. placebo, randomised, placebo controlled		No improvement in agitation inventory scores	Significantly greater cognitive decline	(Ballard et al., 2005)

BEHAV-AD, Behavioural Pathology in Alzheimer's Disease; BPRS, Brief Psychiatric Rating Scale; NPI, Neuropsychiatric Inventory; NPI/NH, nursing home version; CGI-S, Clinical Global Impression–Severity; CGI-C, Clinical Global Impression of Changes; CMAI, Cohen-Mansfield Agitation Inventor; PANNS-EC, Positive and Negative Syndrome Scale (PANSS)-Excitement Component (EC).

oedema was also seen in institutionalized AD patients (Katz et al., 1999). The higher incidence of EPS, somnolence, urinary tract infection (UTI), has been confirmed in two more recent studies, among nursing home residents with AD, vascular dementia or mixed (Mintzer et al., 2006). Gait disturbances and somnolence were also more common in patients treated with olanzapine compared to placebo (Street et al., 2000). Moreover, the impact on cardiovascular system is also a concern. In particular, elongation of the QT interval, torsade de pointes (TdP), and sudden cardiac death have a known relationship with antipsychotic drugs (Sicouri and Antzelevitch, 2018). A case control study on a population aged 65 years or above, undertaking antipsychotics at possible or conditional risk of TdP, demonstrated higher TdP risk for drugs classified as "known TdP risk, " with risk ranking of haloperidol > risperidone > olanzapine > quetiapine (Danielsson et al., 2016). The risk of VTE is estimated to be double, compared to the general population, especially within the first three months of therapy, and several mechanisms are potentially responsible for this association. The reduced physical activity of older patients seems to play a role and, risk increases when associating more than one neuroleptic (Oglodek et al., 2018). Patients receiving typical antipsychotics have been reported to have elevated levels of antiphospholipid antibodies (including anticoagulants and anticardiolipin antibodies), which are associated with an increased VTE risk. Moreover, atypical antipsychotics may cause metabolic syndrome, which is per se a VTE risk factor (Oglodek et al., 2018).

Increased incidence of cerebrovascular disease has been demonstrated in randomized controlled studies in older patients (Herrmann and Lanctot, 2005), although the matter is debated. A recent meta-analysis demonstrated a more than doubled risk of stroke in general population using antipsychotics, which although appears to be lower in population with dementia. No association was seen with myocardial infarction, although the heterogeneity of the available studies limits the strength of the conclusion (Zivkovic et al., 2019). The meta-analysis by Ma et al., together with the efficacy of the antipsychotic therapy, showed higher risk for adverse events, such EPS (OR 1.74), cerebrovascular events (OR 2.5), somnolence (OR 2.95), gait disturbances (OR 3.35), oedema (OR 1.8), UTI (OR 1.35), and death (OR 1.52) (Ma et al., 2014). A large meta-analysis was published in 2018, including more than 380,000 patients with dementia, including more than 80,000 using antipsychotics, and 359,235 patients without dementia (Ralph and Espinet, 2018). The results showed the HR (hazard ratio) for all-cause mortality in patients treated with antipsychotic drugs 1.9–2.19, with higher risk within the first 180 days, and dose related. The risk was similar in subjects with and without dementia (Ralph and Espinet, 2018).

Treating patients with dementia often means treating older patients, presenting with polypathology, polypharmacy, and different sensitivity to the effect of psychotropic drugs. For this reason, potential drug drug-drug interaction needs to be considered (Pasqualetti et al., 2015). Taken together, the need of new therapeutic options, with a safer profile, is urgently needed, to better address such a delicate problem like the management of older patients and often frail patients.

Different Approaches and New Options

Different pharmacological approaches for the treatment of behavioral symptoms have been evaluated.

Acetylcholinesterase inhibitors (AChEI) demonstrated a mild effect on BPSD, particularly on agitation, delusion, aggression, or hallucination (Masopust et al., 2018); more benefits have been seen in Lewy Body dementia-related hallucinations (Creese et al., 2018). A recent meta-analysis demonstrated the efficacy of memantine in controlling "positive" symptoms such as aggression, agitation, delusions, disinhibition, compared to control; it was also effective on hallucinations (Kishi et al., 2017). The combined use of AChEI +memantine has been evaluated in a meta-analysis by Matsunaga et al; the results showed a better outcome of the combined therapy compared to AChEI alone in both behavioral and functional scores, with also a positive trend in cognitive performance (Matsunaga et al., 2014). A further meta-analysis

confirmed the better outcome in terms of both cognitive and behavioral symptoms of the combined therapy (Chen et al., 2017).

Among selective serotonin uptake inhibitors, sertraline showed some efficacy in a cohort of patients with mild to moderate agitation; citalopram gave good results on agitation in the face, however, of possible QTc prolongation. (Davies et al., 2018). When compared to atypical antipsychotic, such as perphenazine, risperidone, or quetiapine, improvement in agitation has been seen, with less adverse event for the citalopram-treated group (Ahmed et al., 2019). Trazodone has been tested as well; reduction in agitation could be a consequence of sedation due to its histaminergic effect (Davies et al., 2018). Anticonvulsants, such as carbamazepine and gabapentin, showed some potential effects, however in case reports or small and not RCT trials (Creese et al., 2018; Davies et al., 2018).

An algorithm for the therapeutic approach to agitation and aggression in patients with AD or mixed dementia, revised by a multidisciplinary team, was recently proposed (Davies et al., 2018). The algorithm hypothesizes a sequential use of medication, basing on evidences, efficacy, safety and tolerability. Risperidone is the first step of treatment (Davies et al., 2018), followed by quetiapine or aripiprazole; titration and switching-drug time-point are also suggested. (Davies et al., 2018).

Atypical antipsychotic drugs, such as primavanserin, lumateperone, and brexpiprazole, are currently under evaluation. Primavanserin, approved for the treatment of hallucinations and delusions in Parkinson's disease, works reducing the baseline activity of 5HT2A receptors, which are upregulated in psychotic symptoms, mediating the effects of 5HT2C without antagonizing D2 receptors. A phase II, double blind, placebo-controlled study in UK showed significant improvement in the NPI-NH psychosis score in the treatment group compared to placebo, at 6 weeks of treatment (Ahmed et al., 2019). However, concerns were raised about the reliability of the results, due to the small effect, only observed at 6 weeks, and the potential safety issues (Schneider, 2018). Nonetheless, another double blind, placebo-controlled study is undergoing to evaluate its efficacy in preventing relapse of psychotic symptoms (Ahmed et al., 2019). A phase III double blind, placebo-controlled study in AD patients with clinically significant agitation, is currently undergoing with lumateperone, a first-in-class agent in development for schizophrenia that acts synergistically through serotonergic, dopaminergic and glutamatergic systems (Porsteinsson and Antonsdottir, 2017). Brexpiprazole, a novel serotonin-dopamine receptor modulator with partial agonist activity at serotonin$_{1A}$ and dopamine$_{2/3}$ receptors, has been approved for the treatment of schizophrenia and major depressive disorders (Porsteinsson and Antonsdottir, 2017). Two Phase III, randomized, double blind, placebo-controlled studies were conducted in AD patients with agitation; only one showed improvement in the CMAI scores. However, a further Phase III study is ongoing (Ahmed et al., 2019).

CONCLUSIONS

AD is a growing healthcare, social, and economic problem. The increased life expectancy with the consequent progressive population ageing lead to higher incidence and prevalence of age-related, chronic diseases, mirrored by the complexity of older patients. Despite the improved diagnostic approach to AD, no disease-modifying medications exist. Behavioral symptoms represent part of the complexity of dementia, and are related to worse cognitive outcome; their treatment is particularly challenging, especially when facing complex and frail patients. Nonetheless, non-pharmacological treatments have shown promising effects in reducing behavioral and psychological symptoms of dementia. Among the available treatments licensed for psychiatric diseases, only risperidone is approved in Europe for behavioral disorders in dementia; other antipsychotics are prescribed "off label." However, some trials are currently undergoing with new potential medications with safer profile.

AUTHOR CONTRIBUTIONS

VC, RA, and CO equally contributed to scientific literature research and analysis. VC wrote the manuscript. FM designed the study, analyzed the scientific literature, and revised the manuscript.

SUPPLEMENTARY MATERIAL

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SYSTEMATIC REVIEW
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Kaixinsan, a Well-Known Chinese Herbal Prescription, for Alzheimer's Disease and Depression: A Preclinical Systematic Review

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Alzheimer's disease (AD), the most common cause of dementia, is highly prevalent worldwide with no modifying therapy. Behavioral and psychological symptoms of dementia (BPSD) occur in most patients with AD, and depression is one of the most common AD-related BPSD. Kaixinsan (KXS) is an ancient Chinese herbal prescription widely used to treat dementia and forgetfulness. In this systematic review, we conducted a meta-analysis to assess preclinical evidence for the effects of KXS on cognitive impairment and depression. Thirty-eight articles involving 1,050 animals were included after searching from six databases from the inception up to June 2019. The primary outcome measures were behavioral outcome. Indicators of cognitive function in AD included escape latency, time spent on the target quadrant, and the number of target platform crossings in the Morris water maze (MWM) test. Indicators of depression included number of rearing events and total distance in the open-field test, duration of immobility in the forced swim test, and sucrose consumption or sucrose preference index in the sucrose preference test. The secondary outcomes were mechanisms of KXS for treatment of AD and depression. The results showed that KXS significantly reduced escape latency ($P < 0.01$), increased time spent in the target quadrant ($P < 0.01$), and increased the number of target platform crossings ($P < 0.01$) in the MWM test in AD models compared with control. The possible mechanisms for KXS-mediated improvements in cognitive function were antioxidant activity, anti-inflammatory activity, antiapoptotic activity, neuroprotection, and synapse protection. In addition, the results demonstrated that KXS significantly increased the number of rearing instances ($P < 0.01$) in the open-field test, decreased the duration of immobility ($P < 0.01$) in forced swim test, and increased sucrose consumption or sucrose preference index ($P < 0.01$) in the sucrose preference test in depression models compared with control. The mechanisms of KXS-mediated anti-depressive effects were HPA axis regulation, antioxidant activity, anti-inflammatory activity, synapse protection, and neuroprotection. The results of this study suggested that KXS can be used to effectively treat AD and depression through multiple mechanisms, extrapolating the therapeutic potential of KXS for treating AD-related BPSD.

Keywords: Kaixinsan, Alzheimer's disease, behavioral and psychological symptoms of dementia, depression, systematic review, meta-analysis

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INTRODUCTION

Alzheimer's disease (AD), a common progressive neurodegenerative disease with gradual onset (Karlawish et al., 2017), is the leading cause of dementia (Alzheimer's, 2016). There are currently 44 million patients with dementia worldwide, 50–75% of whom have AD (Lane et al., 2018). Approximately 5–7 million individuals are diagnosed with AD annually (Robinson et al., 2018). The cost of AD treatment and care has resulted in a considerable economic burden to families and society (Alzheimer's, 2016). Acetylcholinesterase inhibitors (Birks and Grimley Evans, 2015) and memantine (Porsteinsson et al., 2008) are used to provide symptom relief. However, disease-modifying treatments have not been developed (Lane et al., 2018).

It was estimated that ∼90% of patients with AD exhibit obvious behavioral and psychological symptoms of dementia (BPSD) (Chakraborty et al., 2019), a series of behaviors and neuropsychiatric symptoms such as depression, agitation, mood disorders, sleep disturbances, psychosis, apathy, aberrant motor activity, dysphoria, delusions, and hallucinations in patients with dementia (Dyer et al., 2018). What adds insults to injury, BPSD further seriously affect survival quality of AD patients, leading to huge social burden (Moore et al., 2001).

Among mass of clinical presentations of BPSD, depression is a major symptom that occurs in 54–64% of patients with dementia (Preuss et al., 2016). Because development of BPSD can be multifactorial, a single treatment does not exist for this constellation of symptoms (Preuss et al., 2016). Current major treatments for BPSD can be divided into non-pharmacological approaches such as music therapy, touch therapies or massage, and pharmacological approaches such as cognitive enhancers, antipsychotics, mood stabilizers, and antidepressants (Gitlin et al., 2001). However, non-pharmacological approaches are rarely used because of lack of provider training, professional staff, or equipment (Cohen-Mansfield et al., 2013). Pharmacological treatments are often associated with side effects and other health risks (Preuss et al., 2016). Thus, it is necessary to find a comprehensive treatment for both AD and BPSD.

Traditional Chinese medicine (TCM) formulae is a combination of various kinds of herbs, could express synergistic efficacies through multiple targets. For thousands of years, TCM has been playing an indispensable role in disease treatment (Zhang et al., 2013). Kaixinsan, a traditional Chinese herbal prescription, was first used to treat dementia and forgetfulness in *Prescriptions Worth a Thousand Pieces of Gold* (*BeijiQianjinYaofang*), written by Sun Si-Miao in the Tang dynasty (618–907 A.D.). Kaixinsan is comprised of four herbs, Ginseng Radix (*Panax ginseng* C. A. Mey.), Polygalae Radix (*Polygala tenuifolia* Wild.), Poria [*Poriacocos* (Schw.) Wolf], and Acori Tatarinowii Rhizoma (*Acorustatarinowii* Schott), in a 4:4:2:1 ratio. Previous clinical trials showed that KXS ameliorated clinical symptoms of patients with dementia (Liu Y. T. et al., 2015) and depression (Bao et al., 2011). Pharmacological studies indicated that KXS significantly improved cognitive function (Chu et al., 2016b) and reduced depressive-like behavior (Dou, 2017).

KXS is a traditional prescription used to treat dementia and forgetfulness for thousands of years in east Asia. However, the clinical trials of KXS specifically used in BPSD are still insufficient. Preclinical studies could illustrate possible mechanisms and provide evidence for clinical application. Although there are numerous preclinical experiments, there is no systematic review of KXS for AD or depression at present. A systematic review of preclinical studies is an ethical approach to synthesize preclinical evidence, may identify confounding factors across animal studies (Ritskes-Hoitinga et al., 2014). Thus, the present study was conducted focusing on animal experiments, with the goal of confirming that KXS might be effective to BPSD.

METHODS

Database and Literature Search Strategy

The following six databases were searched: Web of Science, PubMed, the Cochrane Library, Wanfang database, Chinese National Knowledge Infrastructure (CNKI), and VIP Journals Database from inception to June 2019. Studies reporting the use of KXS to treat cognitive impairment or depression in animals were identified. The search terms were as follows: 1. kaixin*; 2. kai xin; 3. OR/1-2.

Study Selection

Two investigators screened the titles and/or abstracts independently. The inclusion criteria were as follows: (1) animal studies that assessed the effectiveness of KXS for treatment of cognitive impairment and depression; (2) experimental group received KXS as a monotherapy at any dose; (3) comparator interventions were non-functional liquids (normal saline or distilled water) or positive drugs; (4) no restriction on animal species, sex, age, or weight. Exclusion criteria were as follows: (1) clinical articles, case reports, reviews, comments, abstracts, and *in vitro* studies; (2) *in vitro* models; (3) cognitive impairment induced by vascular dementia, Parkinson's disease, or alcohol. In the case of duplicate publications from one study, we chose the articles with the earliest publication dates or with the largest sample sizes.

Data Extraction

The following details were extracted by two independent investigators per our previous systematic review (Ma et al., 2018): (1) first author name and publication year; (2) animal information for each study including species, sex, number, and weight; (3) modeling approach of animal models and anesthetic used in the model; (4) characteristics of intervention, including timing of initial treatment, duration of treatment, method and dosage of treatment, and corresponding control group information; (5) outcome measures and corresponding p-values. For each comparison, the mean value and standard deviation were extracted from each treatment and control group in every study. In the case of studies where the data were only expressed graphically, we attempted to contact the authors for detailed data, or we calculated the data ourselves using Engauge Digitizer 10.11 software. The result of the highest dose was included when the treatment group received different doses of the target drug. The

data from the middle time point was selected when data were collected at multiple time points.

Quality Assessment

Assessment of methodological quality of the included articles was conducted by two independent investigators according to our previous study (Ma et al., 2018) with one minor change: aging models were considered appropriate. Every item was assigned one point, and the sum was used as the quality score. Divergences were addressed through discussion or consultation with the corresponding investigator.

Statistical Analysis

Data analysis was conducted using RevMan 5.3 software. All outcome measures were entered as continuous data. The combined overall effect sizes were estimated using standard mean differences (SMD). I^2 values were used to determine whether the studies used fixed effects models ($I^2 < 50\%$) or random effects models ($I^2 > 50\%$). The efficacy of KXS and its bioactive ingredients was estimated using SMD and 95% confidence intervals (CI). Publication bias was assessed using funnel plots. Subgroup analysis was used to identify potential confounding factors that may have resulted in heterogeneity of outcome measures. Sensitivity analysis was conducted by excluding one study at a time from all studies to confirm that the results were stable. Heterogeneity among individual studies was assessed using the I^2 statistic. Statistical significance was indicated by $p < 0.05$.

RESULTS

Study Inclusion

Our search produced 566 hits across six databases. One hundred ninety-six articles remained after excluding irrelevant articles and duplicates. One hundred nine manuscripts were removed after scanning the titles and abstracts because they were clinical articles, case reports, comments, reviews, or pharmaceutical experiments. After reading the full text of the remaining 87 articles, 49 were excluded because they were duplicate publications, not *in vivo* model, or KXS was administered in conjunction with other treatments. Finally, 38 eligible studies which involved 1,050 animals were selected (**Figure 1**), in which 17 studies used depression models and 21 studies used cognitive impairment models.

Characteristics of Included Studies

The characteristics of the 38 included studies are summarized in **Table 1**. The included articles were published between 1999 and 2019. Thirteen (34.2%) articles were published in English and 25 (65.8%) were published in Chinese. Twenty-one (55.3%) studies used rat models, of which 12 used Wistar rats and nine used Sprague-Dawley (SD) rats. The remaining 17 (44.7%) studies used mouse models, including ICR ($n = 6$), APP/PS1 ($n = 1$), C57BL/6J ($n = 1$), SAMP8 ($n = 3$), and Kunming mice ($n = 8$). Seventeen (44.7%) studies induced cognitive impairment using Alzheimer's disease (AD) models, and 5 (13.2%) induced cognitive impairment using an aging model. Seventeen (44.7%) studies induced depression using a chronic stress model. For anesthesia, 7 (18.4%) studies used pentobarbital, 2 (5.3%) studies used chloral hydrate, 17 (44.7%) studies did not use anesthesia, and 13 (34.2%) studies did not mention if anesthesia was used. For outcome measures, 9 (23.7%) studies evaluated escape latency in the MWM. Eight (21.1%) studies reported the number of target platform crossings in the MWM. Five (13.2%) studies reported time spent on the target quadrant in the MWM. In the open-field test, 9 (23.7%) studies presented the number of rearing events and 3 (7.9%) studies reported total distance. Thirteen (34.2%) studies evaluated sucrose consumption or sucrose preference index in the sucrose preference test. Six (15.8%) studies reported duration of immobility in the forced swim test. Superoxide dismutase (SOD) was evaluated in 7 (18.4%) studies, malondialdehyde (MDA) was evaluated in 5 (13.2%) studies, acetylcholine (Ach) was evaluated in 4 (10.5%) studies, acetylcholinesterase (AChE) was evaluated in 7 (18.4%) studies, norepinephrine (NE) was evaluated in 9 (23.7%) studies, dopamine (DA) was evaluated in 9 (23.7%) studies, and 5-hydroxytryptamine (5-HT) was evaluated in 10 (26.3%) studies.

Study Quality

Methodological quality scores ranged from 2/10 to 7/10, as shown in **Table 2**. The mean score was 4.24/10. One (2.6%) study received 7 points, 12 (31.6%) studies received 6 points, 3 (7.9%) studies received 5 points, 6 (15.8%) studies received 4 points, 11 (28.9%) studies received 3 points, and the remaining 5 (13.2%) studies received 2 points. Thirty-three (86.8%) studies included records that were published in peer-reviewed databases or journals, and 5 (13.2%) studies were masters or doctoral theses. Twenty-seven (71.1%) records mentioned control of room temperature. Thirty-seven (97.4%) studies randomly allocated animals to the treatment and control groups. One (2.6%) study used blinded procedures. No (0%) studies mentioned blind induction of the model, or calculations to determine sample size. Twenty-nine (76.3%) studies used anesthetics without significant intrinsic neuroprotective activity. Five (13.2%) studies used appropriate animal models. Eighteen (47.4%) studies complied with animal protection law. Eleven (28.9%) studies declared no potential conflicts of interests.

Effectiveness

As an indicator of cognitive function, 9 (23.7%) studies (Zhong, 2005; Zhou et al., 2008; Gao et al., 2010; Chu et al., 2016a,b; Li et al., 2016; Wang X. J. et al., 2017; Xu and Jiang, 2017; Xu et al., 2019) measured escape latency in the MWM. The pooled data showed that KXS significantly decreased escape latency in the MWM ($P < 0.00001$; SMD $= -1.19$, 95% CI [−1.65, −0.74]; Heterogeneity: $\chi 2 = 16.08$, df $= 8$ ($P = 0.04$); $I^2 = 50\%$, **Figure 2A**). Eight (21.1%) studies (Liu M. et al., 2012; Chu et al., 2016a,b; Li et al., 2016; Shi et al., 2017b; Wang X. J. et al., 2017; Xu and Jiang, 2017; Xu et al., 2019) reported the number of target platform crossings in the MWM as an indicator of cognitive function. The pooled data showed a significant difference between the KXS treatment groups and the control groups ($P < 0.00001$; SMD $= 1.24$, 95% CI [0.90, 1.59]; Heterogeneity: $\chi 2 = 5.45$, df $= 7$ ($P = 0.61$); $I^2 = 0\%$, **Figure 2B**). Five (13.2%) studies (Gao et al., 2010; Liu M. et al., 2012; Shi et al., 2017b; Xu and Jiang, 2017; Xu et al., 2019) reported the length

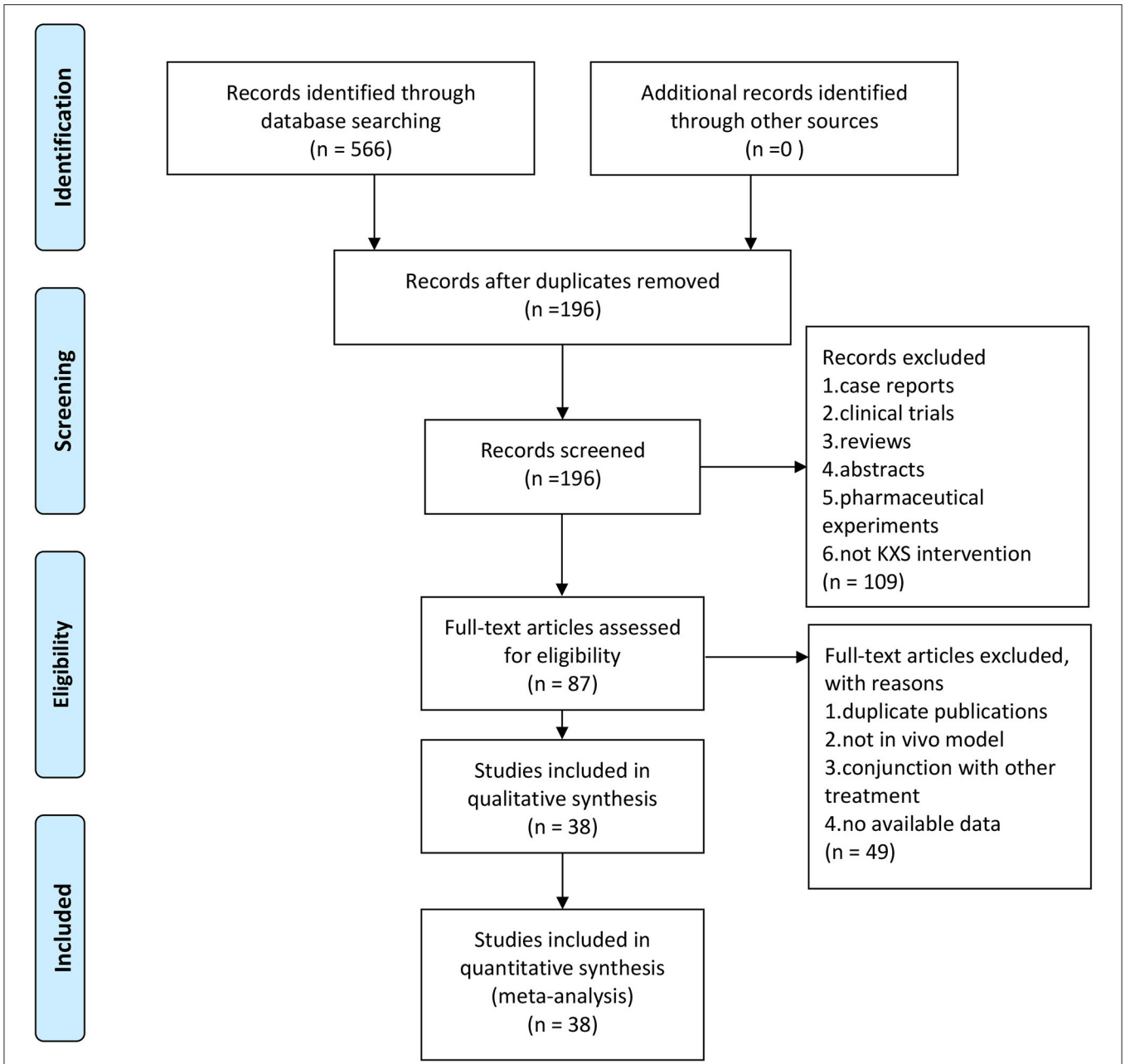

FIGURE 1 | The PRIMSA flow diagram of study selection.

of time spent in the target quadrants as an indicator of memory function. The pooled data showed that KXS treatment resulted in a marked difference in the length of time spent in the target quadrant between the KXS and control groups ($P < 0.00001$; SMD = 1.06, 95% CI [0.67, 1.46]; Heterogeneity: $\chi 2 = 4.39$, df = 4 ($P = 0.36$); $I^2 = 9\%$, **Figure 2C**).

As an indicator of depression, 9 (23.7%) studies (Wang et al., 2007; Dang, 2008; Dong et al., 2013, 2016, 2017; Liu W. W. et al., 2015; Yan et al., 2016; Zhang et al., 2016; Zhang, 2018) reported the number of rearing events in the open-field test. Kaixinsan induced a marked increase in the number of rearing events in the open-field test compared with that in the control group ($P = 0.0003$; SMD = 0.57, 95% CI [0.26, 0.88]; Heterogeneity: $\chi 2 = 15.39$, df = 9 ($P = 0.05$); $I^2 = 48\%$, **Figure 3A**). Three (7.9%) studies (Dang, 2008; Yan et al., 2016; Dou, 2017) reported total distance in the open-field test. The pooled data showed no significant difference between the KXS treatment groups and the control groups ($P = 0.10$; SMD = 1.04, 95% CI [−0.20, 2.27]; Heterogeneity: $\chi 2 = 10.50$, df = 2 ($P = 0.005$); $I^2 = 81\%$, **Figure 3B**). When only studies that used male animals were included, a meta-analysis of 2 studies (Yan et al., 2016; Dou, 2017) showed a significant difference between the KXS groups and the control groups, with the I^2 value dropping from 81 to 0% ($P < 0.00001$; SMD=1.63, 95%

TABLE 1 | Characteristics of the 38 included studies.

References	Species (Sex; *n* = experimental /control group)	Weight	Modeling approach	Anesthetic	Intervention trial group	Control group	Outcome measure	Intergroup differences
Bian et al. (2000)	SD rats (male and female,9/8)	180–230 g	Cognitive impairment induced by i.p. SCOP (5 mg/kg)	NR	KXS,i.g. 0.1, 0.6 g/kg/day for 7 days before the model	Distilled water	1. The number of errors in Y maze 2. 5-HT,5-HIAA, NE, DA 3. SOD, MDA	1. $p < 0.01$ 2. $p < 0.01$ 4. $p < 0.01$
Shang (2003)	Kunming mice (male and female,10/10)	16–20 g	Cognitive impairment induced by SCOP 2 mg/kg	NR	KXS,i.g. 118.5/237 mg/kg/day for 12 days before the model	Distilled water	1. Time of correct in SDT	1. $p < 0.01$
	ICR mice (male and female,12/12)	16–20 g	Cognitive impairment induced by SCOP 2 mg/kg	NR	KXS,i.g. 118.5/237 mg/kg/day for 17 days accompanying the model	Distilled water	1. The number of errors in MWM 2. Escape latency in water maze	1. $P > 0.05$ 2. $P < 0.05$
	ICR mice (male and female,12/12)	16–20 g	Cognitive impairment induced by SCOP 2 mg/kg	NR	KXS,i.g. 118.5/237/355.5 mg/kg/day for 23 days before the model	Distilled water	1. AchE 2. SOD	1. $p < 0.01$ 2. $p < 0.05$
	Kunming mice (male and female,12/12)	16–20 g	Cognitive impairment induced by SCOP 2mg/kg	NR	KXS,i.g. 118.5/237/355.5 mg/kg/day for 23 days before the model	Distilled water	1. ChAT	1. $P < 0.05$
Bian et al. (1999)	ICR mice (male,9/8)	18–22 g	Cognitive impairment induced by SCOP 5 mg/kg	NR	KXS,i.g. 0.1/0.3 g/kg/day for 7 days before the model	Distilled water	1. number of correct in Y maze	1. $p < 0.01$
	SD rats (male,10/10)	480–620 g	Aging model	NR	KXS,i.g. 0.1/0.3 g/kg/day for 7 days before the model	Distilled water	1. Number of correct in Y maze	1. $p < 0.01$
	ICR mice (male,9/8)	18–22 g	AD model induced by AlCl3 4 mg	NR	KXS,i.g. 0.1/0.3 g/kg/day for 3 months accompanying the model	Distilled water	1. Number of correct in Y maze 2. Number of correct in water maze	1. $p < 0.01$ 2. $p < 0.05$
Zhou et al. (2008)	Kunming mice (male,12/12)	18–22 g	Cognitive impairment model induced by D-gal 150 mg/kg	NR	KXS,i.g. 0.1/0.3/0.9 g/kg/day for 6 weeks	Normal saline	1. Escape latency in MWM 2. The number of error in MWM 3. AGEs 4. SOD, MDA	1. $p < 0.01$ 2. $p < 0.01$ 3. $p < 0.01$ 4. $p < 0.01$
Gao et al. (2010)	Kunming mice (male,15/15)	28–30 g	AD model induced by D-gal+SCOP	NR	KXS,i.g. 5, 10 g/kg/day for 12 weeks accompanying the model	Normal saline	1. Escape latency in MWM 2. Time spent in target quadrant 3. Percentage of finding the security desk 4. Escape latency in SDT 5. Number of errors in SDT 6. AchE,SOD,MDA	1. $p < 0.05$ 2. $p < 0.05$ 3. $p < 0.01$ 4. $p < 0.05$ 5. $p < 0.01$ 6. $p < 0.01$
Li et al. (2016)	Kunming mice (male and female,10/10)	18–22 g	AD model induced by D-gal+sodium nitrosum	NR	KXSE, i.g. 0.892/1.785/3.570 g/kg/day for 35 days after the model	Distilled water	1. Eacape latency in MWM 2. The number of target platform crossings 3. swimming distance in target quadrant 4. Ach 5. AchE 6. Tau 7. p-Tau 8. Aβ 9. NT-proBNP	1. $p < 0.05$ 2. $p < 0.05$ 3. $p < 0.05$ 4. $p < 0.01$ 5. $p < 0.05$ 6. $p < 0.01$ 7. $p < 0.05$ 8. $p < 0.01$ 9. $p < 0.05$
Xu and Jiang (2017)	Wistar rats (male and female, 12/12)	250–300 g	AD model induced by bilateral hippocampal injection Aβ1–42 with 5 ug	Sodium pentobarbital(50 mg/kg)	KXS,i.g. 1.6/2.4/3.6 g/kg/day for 28 days after the model	Distilled water	1. Escape latency in MWM 2. Time spent in target quadrant 3. The number of target platform crossing	1. $p < 0.05$ 2. $p < 0.05$ 3. $p < 0.01$

(Continued)

TABLE 1 | Continued

References	Species (Sex; *n* = experimental /control group)	Weight	Modeling approach	Anesthetic	Intervention trial group	Control group	Outcome measure	Intergroup differences
Zhong (2005)	Wistar rats (male and female, 12/12)	400–450 g	AD model induced by bilateral hippocampal injection Aβ25–35 with 5 ug	pentobarbital (40 mg/kg i.p.)	KXS,i.g. 0.1, 0.3 g/kg/day for 28 days after the model	Distilled water	1. Escape latency in MWM 2. AchE 3. APP 4. bax, bcl-2 5. Trib3	1. $p < 0.05$ 2. $p < 0.05$ 3. $p < 0.01$ 4. $p < 0.05$ 5. $p < 0.001$
Shi et al. (2017b)	SAMP8 mice/SAMR1 mice (male, 10/10)	24.5–34.2 g/30.2–37.6 g	Aging model induced by Gene knockout	No need	KXS,i.g. 0.195/0.78 g/kg/day for 8 weeks after the model	Normal saline	1. The number of target platform crossings 2. Time spent in target quadrant 3. The number of errors in STD 4. Escape latency in STD 5. mt-DNA	1. $p < 0.05$ 2. $p < 0.01$ 3. $p < 0.05$ 4. $p < 0.01$ 5. $p < 0.05$
Huang et al. (1999)	ICR mice (male, 13/13)	18–22 g	AD model induced by AlCl3	NR	KXS,i.g. 0.39, 0.13 g/kg/day for 3 months accompanying the model	Distilled water	1. Number of correct in Y maze 2. Number of correct in water maze	1. $p < 0.01$ 2. $p < 0.05$
Huang et al. (1998)	SD rats (male, 10/10)	480–620 g	Aging model	NR	KXS,i.g. 0.1/0.3 g/kg/day for 7 days before the model	Distilled water	1. Number of correct in Y maze 2. SOD, NE,5-HT,DA	1. $p < 0.01$ 2. $p < 0.05$
Dang (2008)	SD rats (male and female, 12/11)	190–250 g	Depression model induced by chronic stress	No need	KXS,i.g. 2.7, 0.9, 0.3 g/kg/day for 53 days accompanying the model	Distilled water	1. Weight 2. Average speed in open field 3. Total distance in open field 4. Number of rearing in open field	1. $p < 0.05$ 2. $p < 0.05$ 3. $p < 0.05$ 4. $p < 0.05$
Zhang et al. (2016)	Wistar rats (male, 10/10)	240 ± 20 g	Depression model induced by chronic stress	No need	KXS,i.g. 445 mg/kg/day for 6 weeks accompanying the model	Distilled water	1. Level of emotional arousal 2. The score of horizontal movement in open field test 3. The score of vertical movement in open field test 4. time of staying in center 5. ACTH, CRH, CORT 6. GR	1. $p < 0.05$ 2. $p < 0.05$ 3. $p < 0.05$ 4. $p < 0.05$ 5. $p > 0.05$ 6. $p < 0.01$
Wang et al. (2007)	Wistar rats (male, 10/10)	150–180 g	Depression model induced by chronic stress	No need	KXS,i.g. 4, 8 g/kg/day for 21 days accompanying the model	Distilled water	1. Sucrose consumption in sucrose preference test 2. The score of horizontal movement in open field test 3. The score of vertical movement in open field test	1. $p < 0.01$ 2. $p < 0.05$ 3. $p < 0.01$
Liu M. et al. (2012)	SD rats (male, 10/10)	180–220 g	Depression model induced by chronic stress	No need	KXS,i.g. 1,000, 500, 250, 125 mg/kg/day for 21 days accompanying the model	Distilled water	1. Sucrose preference index in sucrose preference test 2. Total distance in open field test 3. EL in MWM 4. Time spent in target quadrant 5. The number of target platform crossings 6. 5-HT, DA,NE 7. Ach, AchE	1. $p < 0.01$ 2. $p < 0.01$ 3. $p < 0.01$ 4. $p < 0.01$ 5. $p < 0.01$ 6. $p < 0.01$ 7. $p < 0.05$
Liu W. W. et al. (2015)	SD rats (male, 8/8)	180–220 g	Depression model induced by chronic stress	No need	KXS,i.g. 1.785 g/kg/day after the model	Distilled water	1. Weight 2. Sucrose preference index in sucrose preference test 3. The score of horizontal movement in open field test 4. The score of vertical movement in open field test 5. NE,DA,5-HT	1. $p > 0.05$ 2. $p > 0.05$ 3. $p > 0.05$ 4. $p > 0.05$ 5. $p > 0.05$

(Continued)

TABLE 1 | Continued

References	Species (Sex; *n* = experimental /control group)	Weight	Modeling approach	Anesthetic	Intervention trial group	Control group	Outcome measure	Intergroup differences
Duan et al. (2016)	ICR mice (male and female, 10/10)	20–22 g	Depression model induced by chronic stress	No need	KXS,i.g. 10 g/kg/day for 7 days after the model	Distilled water	1. Sucrose preference index in sucrose preference test 2. Duration of immobility in forced swim test 3. NGF 4. BDNF	1. $p < 0.05$ 2. $p < 0.01$ 3. $p > 0.05$ 4. $p > 0.05$
Zhang et al. (2018)	SD rats (male, 8/8)	170–200 g	Depression model induced by chronic stress	No need	KXS,i.g. 1.785 g/kg/day for 21 days after the model	Distilled water	1. Weight 2. Sucrose preference index in sucrose preference test 3. The score of horizontal movement in open field test 4. The score of vertical movement in open field test 5. Forced swimming test 6. SOD, MDA, CAT, GSH-Px, CRP, I-6,TNF-α	1. $P < 0.01$ 2. $p < 0.01$ 3. $p > 0.05$ 4. $p < 0.01$ 5. $p < 0.01$ 6. $p < 0.01$
Dou (2017)	SD rats (male, 10/10)	200 ± 20 g	Depression model induced by chronic stress	No need	KXS,i.g. 4.5 g/kg/day for 28 days accompanying the model	Distilled water	1. Weight 2. Sucrose preference index in sucrose preference test 3. Total distance in open field test 4. Forced swimming test	1. $p > 0.05$ 2. $p > 0.05$ 3. $p > 0.05$ 4. $p < 0.01$
Xu et al. (2019)	Kunming mice (male, 12/12)	35–40 g	Cognitive impairment induced by SCOP	NR	KXS,i.g. 0.7/1.4/2.8 g/kg/day for 14 days accompanying the model	Normal saline	1. Escape latency in MWM 2. The number of target platform crossings 3. Time spent in target quadrant 4. Y maze 5. Bax/Bcl-2,Ach,AchE,ChAT 6. SOD,MDA	1. $p < 0.01$ 2. $p < 0.01$ 3. $p < 0.01$ 4. $p < 0.05$ 5. $p < 0.05$ 6. $p < 0.01$
Chu et al. (2016b)	Wister rats (male, 10/10)	300 ± 10 g	AD model induced by D-gal+AlCl3	No need	KXS,i.g. 2.7, 5.4, 10.8 g/kg/day for 105 days accompanying the model	Normal saline	1. Escape latency in MWM 2. The number of target platform crossings 3. Aβ1–40 plaques level 4. Expression level of Bcl-2 and ChAT	1. $p > 0.05$ 2. $p < 0.01$ 3. $p < 0.05$ 4. $p < 0.05$
Lu et al. (2016)	Wistar rats (male, 12/12)	300–320 g	AD model induced by bilateral hippocampal injection Aβ1–40 with 5 uL	Chloral hydrate (3.5 ml/kg i.p.)	KXS,i.g. 0.72/1.44 g/kg/day for 35 days after the model	Water	1. Ach 2. Glu	1. $p < 0.01$ 2. $p < 0.05$
Dang et al. (2009)	SD rats (male and female, 12/11)	190–250 g	Depression model induced by chronic stress	No need	KXS,i.g. 2.7, 0.9, 0.3 g/kg/day for 53 days accompanying the model	Distilled water	1. Sucrose preference index in sucrose preference test 2. Latency for feeding 3. Number of crossing in shuttle box test 4. Total distance in shuttle box test 5. ACTH 6. NE, DA, DOPAC, HVA 7. 5-HT,5-HIAA 8. AchE	1. $p < 0.01$ 2. $p < 0.01$ 3. $p < 0.05$ 4. $p < 0.01$ 5. $p < 0.01$ 6. $p < 0.01$ 7. $p > 0.05$ 8. $p < 0.01$
Dong et al. (2016)	Wistar rats (male, 10/10)	180 ± 10 g	Depression model induced by chronic stress	No need	KXS,i.g. 370 mg/kg/day for 3 weeks accompanying the model	Distilled water	1. Sucrose consumption in sucrose preference test 2. Body weight 3. Number of crossing in open field test 4. Rearing count in open field test	1. $p < 0.05$ 2. $p < 0.05$ 3. $p < 0.01$ 4. $p < 0.05$

(Continued)

TABLE 1 | Continued

References	Species (Sex; *n* = experimental /control group)	Weight	Modeling approach	Anesthetic	Intervention trial group	Control group	Outcome measure	Intergroup differences
Dong et al. (2017)	Wistar rats (male, 12/12)	200 ± 10 g	Depression model induced by chronic stress	No need	KXS,i.g. 338, 676 mg/kg/day for 4 weeks accompanying the model	Distilled water	1. Weight 2. Sucrose preference index in sucrose preference test 3. Number of crossing in open field test 4. Rearing count in open field test 5. IL-6 6. TNF-α	1. $p < 0.01$ 2. $p < 0.01$ 3. $p < 0.05$ 4. $p < 0.05$ 5. $p > 0.05$ 6. $p < 0.05$
Huang et al. (2014)	Wistar rats (male, 12/12)	170–200 g	Depression model induced by chronic stress	3% sodium pentobarbital	KXS,i.g. 65, 130.260 mg/kg/day for 21 days accompanying the model	Distilled water	1. Weight 2. Sucrose consumption in sucrose preference test 3. Score in open field test 4. MT concentration	1. $p > 0.05$ 2. $p < 0.05$ 3. $p < 0.05$ 4. $p < 0.05$
Yan et al. (2016)	SD rats (male, 12/12)	150-180 g	Depression model induced by chronic stress	NR	KXS,i.g. 60.9, 182.7, 548.1mg/kg/day for 6 weeks before the model	Normal saline	1. Sucrose consumption in sucrose preference test 2. Cumulative immobility time in forced swimming test 3. Time spent in central area in open field test 4. Number of rearing in open field test 5. Total distance in open field test 6. NE 7. 5-HT 8. dopamine	1. $p < 0.01$ 2. $p < 0.01$ 3. $p < 0.01$ 4. $p < 0.01$ 5. $p < 0.01$ 6. $p < 0.01$ 7. $p < 0.01$ 8. $p < 0.01$
Zhou et al. (2012)	Kunming mice (male, 12/12)	21–30 g	Depression model induced by chronic stress	No need	KXS,i.g. 175, 350, 700, 1,400 mg/kg/day for 3 days before the model	Normal saline	1. Duration of immobility in tail suspension test 2. Duration of immobility in forced swim test 3. 5-HT 4. DA 5. NE	1. $p < 0.05$ 2. $p < 0.05$ 3. $p < 0.05$ 4. $p < 0.05$ 5. $p < 0.05$
Dong et al. (2013)	Wistar rats (male, 8/8)	180 ± 10 g	Depression model induced by chronic stress	10% chloral hydrate solution (3.5 ml/kg i.p.)	KXS,i.g. 338, 676 mg/kg/day for 4 weeks accompanying the model	Distilled water	1. Sucrose preference index in sucrose preference test 2. Number of crossing in open field test 3. Rearing times index in open field test 4. Body weight 5. 5-HT,5-HIAA 6. MAO-A, MAO-B	1. $p < 0.05$ 2. $p < 0.05$ 3. $p < 0.05$ 4. $p < 0.01$ 5. $p < 0.01$ 6. $p > 0.05$
Chu et al. (2016a)	Wistar rats (male, 10/10)	260 ± 20 g	AD model induced by D-gal+AlCl3	Sodium pentobarbital	KXS,i.g. 5.4 g/kg/day for 90 days accompanying the model	Normal saline	1. Escape latency in MWM 2. The number of target platform crossings	1. $p < 0.01$ 2. $p < 0.01$
Wang N. et al. (2017)	Wistar rats (male and female, 10/10)	200–240 g	AD model induced by bilateral hippocampal injection Aβ42 with 10 uL	Sodium pentobarbital (50 mg/kg i.p.)	KXS,i.g. 0.54, 1.08 g/kg/day for 21 days after the model	Normal saline	1. Proportion of injured neurons	1. $p < 0.01$
	Wistar rats (male and female,40/40)	200–240 g	AD model induced by bilateral hippocampal injection Aβ42 with 10 uL	Sodium pentobarbital (50 mg/kg i.p.)	KXS,i.g. 0.54, 1.08 g/kg/day for 21 days after the model	Normal saline	1. Aβ42 level 2. hippocampal IDE protein expression 3. IDE mRNA expression	1. $p < 0.01$ 2. $p < 0.01$ 3. $p > 0.05$
Wang X. J. et al. (2017)	APP/PS1 mice, C57BL/6J mice (male and female, 7/7)	NR	AD model induced by transgenosis	No need	KXS,i.g. 0.65 g/kg/day for 10 months after the model	Distilled water	1. Escape latency in MWM 2. The number of target platform crossings 3. discrimination index in 30 min 4. discrimination index in 24 h 5. Aβ1-42 plaques level	1. $p < 0.01$ 2. $p < 0.01$ 3. $p < 0.05$ 4. $p < 0.05$ 5. $p < 0.05$

(Continued)

TABLE 1 | Continued

References	Species (Sex; *n* = experimental /control group)	Weight	Modeling approach	Anesthetic	Intervention trial group	Control group	Outcome measure	Intergroup differences
Zhang et al. (2018)	ICR mice (male and female, 9/8)	25–35 g	AD model induced by lateral ventricle injection Aβ42 with 5 uL	Sodium pentobarbital (45 mg/kg i.p.)	KXS,i.g. 0.15 g/kg/day for 7 days before the model	Normal saline	1. Avoidance time in SDT 2. Error time in SDT	1. $p < 0.05$ 2. $p < 0.05$
	ICR mice (male and female, 7/6)	25–35 g	AD model induced by lateral ventricle injection Aβ42 with 5 uL	Sodium pentobarbital (45 mg/kg i.p.)	KXS,i.g. 0.15 g/kg/day for 7 days before the model	Normal saline	1. LTP	1. $P < 0.05$
	ICR mice (male and female,18/15)	25–35 g	AD model induced by lateral ventricle injection Aβ42 with 5 uL	Sodium pentobarbital (45 mg/kg i.p.)	KXS,i.g.0.15g/kg/day for 7 days before the model	Normal saline	1. Number of GluR2 IR cells	1. $p < 0.01$
Huang et al. (2001)	ICR mice (male and female,10/10)	18–21.5 g	AD model induced by SCOP 3 mg/kg	NR	KXS,i.g. 0.1, 0.3 g/kg/day for 7 days before the model	Distilled water	1. NO 2. NOS 3. ChE	1. $p < 0.01$ 2. $p < 0.01$ 3. $p < 0.05$
Wang et al. (2005)	Kunming mice (male,10/10)	22 ± 2 g	Depression model induced by chronic stress	NR	KXS,i.g. 1.5, 3.6 ml/kg/day for 14 days accompanying the model	Normal saline	1. Duration of immobility in forced swim test 2. GC 3. NE 4. DA 5. 5-HT 6. 5-HIAA	1. $p < 0.05$ 2. $p < 0.05$ 3. $p < 0.05$ 4. $p > 0.05$ 5. $p < 0.05$ 6. $p < 0.05$
Liu Y. M. et al. (2012)	Kunming mice (male,12/12)	22 ± 2 g	Depression model induced by chronic stress	NR	KXS,i.g. 1, 100, 550, 275 mg/kg/day for 7 days before the model	Normal saline	1. Duration of immobility in tail suspension test 2. NE 3. DA 4. 5-HT 5. BDNF	1. $p < 0.05$ 2. $p > 0.05$ 3. $p < 0.05$ 4. $p < 0.05$ 5. $p < 0.01$
Shi et al. (2017a)	SAMP8 mice/SAMR1 mice (male,10/10)	24.5–34.2 g/30.2-37.6g	Aging model induced by Gene knockout	No need	KXS,i.g.0.195/0.78 g/kg/day for 8 weeks after the model	Normal saline	1. 5-HT 2. 5-HIAA 3. NE 4. DA	1. $p < 0.01$ 2. $p < 0.01$ 3. $p < 0.01$ 4. $p < 0.01$
Shi et al. (2013)	SAMP8 mice/SAMR1 mice (male,10/10)	24.5–34.2 g/30.2–37.6 g	Aging model induced by Gene knockout	No need	KXS,i.g. 0.195/0.78 g/kg/day for 8 weeks after the model	Normal saline	1. TNF-α 2. IL-8 3. β-APP	1. $p < 0.01$ 2. $p < 0.01$ 3. $p < 0.01$

Ach, acetylcholine; AchE, Acetyl cholinesterase; ACTH, Adreno cortico tropic hormone; AD, Alzheimer's disease; AGEs, Advanced glycation end products; APP, Amyloid precursor protein; BDNF, brain derived neurotrophic factor; ChAT, choline acetyltransferase; CORT, Corticosterone; CRH, Corticotropin releasing hormone; CRP, Continuous Replenishment Program; DA, Dopamine; DOPAC, Hydroxyphenylacetic acid; GC, Glucocorticoids; Glu, Glucose; GR, Glucocorticoid; GSH-Px, glutathione peroxidase; HVA, Homovanillic acid; Ig, intragastrical administration; KXS, Kaixinsan; LTP, long-term potentiation (LTP); MAO-A, Monoamine oxidase-A; MAO-B, Monoamine oxidase-B; MDA, malondialdehyde; MT, Melatonine; MWM, Morris water maze; NE, Norepinephrine; NOS, Nitric oxide synthase; NR, Not report; SCOP, Scopolamine; SD rats, Sprague Dawley rats; SDT, Step down test; SOD, superoxide dismutase; TNF-α, Tumor Necrosis Factor α; 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, 5-hydroxytryptamine.

CI [0.92, 2.33]; Heterogeneity: $\chi 2 = 0.94$, df = 1 ($P = 0.33$); $I^2 = 0\%$). Six (15.8%) studies (Wang et al., 2005; Zhou et al., 2012; Fonarow, 2016; Yan et al., 2016; Dou, 2017; Zhang, 2018) evaluated duration of immobility in the forced swim test. The pooled data showed that KXS treatment resulted in a marked drop in the duration of immobility in the forced swimming test compared with that in the control groups ($P < 0.00001$; SMD=-1.92, 95% CI [−2.38, −1.47]; Heterogeneity: $\chi 2 = 9.89$, df = 5 ($P = 0.08$); $I^2 = 49\%$, **Figure 3C**). Thirteen (34.2%) studies (Wang et al., 2007; Dang, 2008; Dang et al., 2009; Liu M. et al., 2012; Dong et al., 2013, 2016, 2017; Huang et al., 2014; Liu W. W. et al., 2015; Fonarow, 2016; Yan et al., 2016; Dou, 2017; Zhang, 2018) evaluated sucrose consumption or sucrose preference index in the sucrose preference test. Treatment with KXS resulted in significantly different sucrose consumption or sucrose preference than that in the control group ($P < 0.00001$; SMD = 1.67, 95% CI [1.37, 1.97]; Heterogeneity: $\chi 2 = 23.66$, df = 12 ($P = 0.02$); $I^2 = 49\%$, **Figure 3D**).

Six (15.8%) studies (Wang et al., 2007; Dang, 2008; Dong et al., 2013, 2017; Yan et al., 2016; Zhang, 2018) that compared KXS with positive drug treatments reported the number of rearing events in the open-field test. There were no significant differences between the experimental groups and the drug groups ($P = 0.90$; SMD = −0.02, 95% CI [−0.38, 0.34]; Heterogeneity: $\chi 2 = 0.25$, df = 5 ($P = 1.00$); $I^2 = 0\%$, **Figure 4A**). Three (7.9%) studies (Dang, 2008; Yan et al., 2016; Dou, 2017) reported the total distance in the open-field test. The pooled data showed no significant differences between the KXS treatment groups and the positive drug groups ($P = 0.12$; SMD = −0.38, 95% CI [−0.87, 0.10]; Heterogeneity: $\chi 2 = 0.82$, df = 2 ($P = 0.66$); $I^2 = 0\%$, **Figure 4B**). Six (15.8%) studies (Wang et al., 2005; Zhou et al., 2012; Fonarow, 2016; Yan et al., 2016; Dou, 2017; Zhang, 2018) reported the duration of immobility in the forced

TABLE 2 | Risk of bias of the induced studies.

Study	A	B	C	D	E	F	G	H	I	J	Total
Bian et al. (2000)	√		√								2
Shang (2003)		√	√								2
Bian et al. (1999)	√					√	√				3
Zhou et al. (2008)	√		√			√					3
Gao et al. (2010)	√	√	√								3
Li et al. (2016)	√		√			√					3
Xu and Jiang (2017)	√		√			√					3
Zhong (2005)		√	√			√					3
Shi et al. (2017b)	√	√	√			√	√		√		6
Huang et al. (1999)	√		√								2
Huang et al. (1998)	√		√			√	√				4
Dang (2008)		√	√			√			√		4
Zhang et al. (2016)	√	√	√			√					4
Wang et al. (2007)	√	√	√			√					4
Liu M. et al. (2012)	√		√			√					3
Liu W. W. et al. (2015)	√		√			√					3
Fonarow (2016)	√	√	√			√					4
Zhang et al. (2018)		√	√			√					3
Dou (2017)		√	√			√					3
Xu et al. (2019)	√	√	√			√			√	√	6
Chu et al. (2016b)	√	√	√			√			√	√	6
Lu et al. (2016)	√	√	√			√			√	√	6
Dang et al. (2009)	√	√	√			√			√		5
Dong et al. (2016)	√	√	√			√			√	√	6
Dong et al. (2017)	√	√	√			√			√	√	6
Huang et al. (2014)	√	√	√			√			√	√	6
Yan et al. (2016)	√	√	√						√	√	5
Zhou et al. (2012)	√	√	√		√	√			√	√	7
Dong et al. (2013)	√	√	√						√		4
Chu et al. (2016a)	√	√	√			√			√		5
Wang N. et al. (2017)	√	√	√			√				√	6
Wang X. J. et al. (2017)	√	√	√			√			√	√	6
Zhang et al. (2018)	√	√	√			√			√	√	6
Huang et al. (2001)	√		√								2
Wang et al. (2005)	√		√								2
Liu Y. M. et al. (2012)	√	√	√								3
Shi et al. (2017b)	√	√	√			√	√		√		6
Shi et al. (2013)	√	√	√			√	√		√		6

Studies fulfilling the criteria of: A, peer reviewed publication; B, control of temperature; C, random allocation to treatment or control; D, blinded induction of model; E, blinded assessment of outcome; F, use of anesthetic without significant intrinsic neuroprotective activity; G, appropriate animal model; H, sample size calculation; I, compliance with animal welfare regulations; J, statement of potential conflict of interests.

swim test. The pooled data showed that there were no differences between the KXS treatment groups and the positive drug groups ($P = 0.26$; SMD = 0.21, 95% CI [−0.15, 0.56]; Heterogeneity: $\chi 2$ =7.10, df = 5 ($P = 0.21$); $I^2 = 30\%$, **Figure 4C**). Ten (26.3%) studies (Wang et al., 2007; Dang, 2008; Dang et al., 2009; Liu M. et al., 2012; Dong et al., 2013, 2017; Huang et al., 2014; Fonarow, 2016; Yan et al., 2016; Zhang, 2018) reported sucrose consumption or sucrose preference index in the sucrose preference test. There were no significant differences between the KXS treatment groups and the positive drug groups ($P = 0.29$; SMD = 0.15, 95% CI [−0.13, 0.42]; Heterogeneity: $\chi 2$ =8.67, df = 9 ($P = 0.47$); $I^2 = 0\%$, **Figure 4D**).

Mechanisms of Kaixinsan for Cognitive Impairment and Depression

Pooled data from 4 studies in 3 (7.9%) manuscripts (Li et al., 2016; Lu et al., 2016; Xu et al., 2019) showed that KXS significantly increased acetylcholine activity ($P < 0.00001$; SMD = 4.04, 95% CI [1.52, 6.57]; Heterogeneity: $\chi 2 = 28.68$, df = 3 ($P < 0.00001$); $I^2 = 90\%$, **Figure 5A**). To identify potential sources of heterogeneity, subgroup analysis of ACh activity was performed based on the duration of treatment. The results showed that longer periods of KXS treatment resulted in larger effect sizes (SMD = 6.79 vs. SMD = 1.70). Six studies in 5 (13.2%) manuscripts (Bian et al., 2000; Shang, 2003; Gao et al., 2010; Li et al., 2016; Xu et al., 2019) showed increased acetylcholinesterase (AchE) activity in response to KXS ($P < 0.00001$; SMD = −1.64, 95% CI [−2.06, −1.21]; Heterogeneity: $\chi 2 = 9.32$, df = 5 ($P = 0.10$); $I^2 = 46\%$, **Figure 5B**). Three (7.9%) studies (Shang, 2003; Chu et al., 2016b; Xu et al., 2019) showed increased ChAT activity in response to KXS ($P < 0.00001$; SMD = 1.24, 95% CI [0.68, 1.81]; Heterogeneity: $\chi 2 = 0.46$, df = 2 ($P = 0.80$); $I^2 = 0\%$, **Figure 5C**). Ten studies in 6 (15.8%) manuscripts (Huang et al., 1998; Bian et al., 2000; Shang, 2003; Zhou et al., 2008; Gao et al., 2010; Xu et al., 2019) showed increased levels of SOD in response to KXS ($P < 0.00001$; SMD = 1.41, 95% CI [1.09, 1.73]; Heterogeneity: $\chi 2 = 7.57$, df = 10 ($P = 0.58$); $I^2 = 0\%$, **Figure 5D**). Six studies in 4 (10.5%) manuscripts (Bian et al., 2000; Zhou et al., 2008; Gao et al., 2010; Xu et al., 2019) showed decreased levels of MDA in response to KXS ($P < 0.00001$; SMD = −1.87, 95% CI [−2.33, −1.42]; Heterogeneity: $\chi 2 = 8.66$, df = 5 ($P = 0.12$); $I^2 = 42\%$, **Figure 5E**).

To determine the mechanisms of KXS in treatment of depression, 2 studies in 1 (2.6%) article (Zhang, 2018) showed that KXS increased superoxide dismutase levels ($P = 0.0003$; SMD = 1.48, 95% CI [0.67, 2.29]; Heterogeneity: $\chi 2 = 0.04$, df = 1 ($P = 0.84$); $I^2 = 0\%$, **Figure 6A**). In addition, 2 studies in 1 (2.6%) article (Zhang, 2018) showed that KXS decreased malondialdehyde levels ($P = 0.001$; SMD = −1.33, 95% CI [−2.13, −0.53]; Heterogeneity: $\chi 2 = 1.07$, df = 1 ($P = 0.30$); $I^2 = 7\%$, **Figure 6B**). Two (5.3%) studies (Dang et al., 2009; Liu M. et al., 2012) showed that KXS treatment resulted in decreased AchE activity ($P < 0.0001$; SMD = −1.49, 95% CI [−2.19, −0.78]; Heterogeneity: $\chi 2 = 1.09$, df = 1 ($P = 0.30$); $I^2 = 9\%$, **Figure 6C**). Six studies in 4 (10.5%) articles (Dang, 2008; Liu Y. M. et al., 2012; Dong et al., 2016; Fonarow, 2016) showed decreased levels of brain-derived neurotrophic factor (BDNF) in response to KXS treatment ($P < 0.00001$; SMD = 1.48, 95% CI [1.11, 1.86]; Heterogeneity: $\chi 2 = 1.19$, df = 6 ($P = 0.98$); $I^2 = 0\%$, **Figure 6D**). Ten studies in 6 (15.8%) articles (Wang et al., 2005; Dang et al., 2009; Liu M. et al., 2012; Liu Y. M. et al., 2012; Liu W. W. et al., 2015; Yan et al., 2016) showed increased levels of NE in response to KXS ($P < 0.00001$; SMD = 2.99, 95% CI [1.99, 4.00]; Heterogeneity: $\chi 2 = 47.15$, df = 9 ($P < 0.00001$); $I^2 = 81\%$, **Figure 7A**). Eight studies in 6 (15.8%) articles (Wang et al., 2005; Dang et al., 2009; Liu M. et al., 2012; Liu Y. M. et al., 2012; Liu W. W. et al., 2015; Yan et al., 2016) showed increased

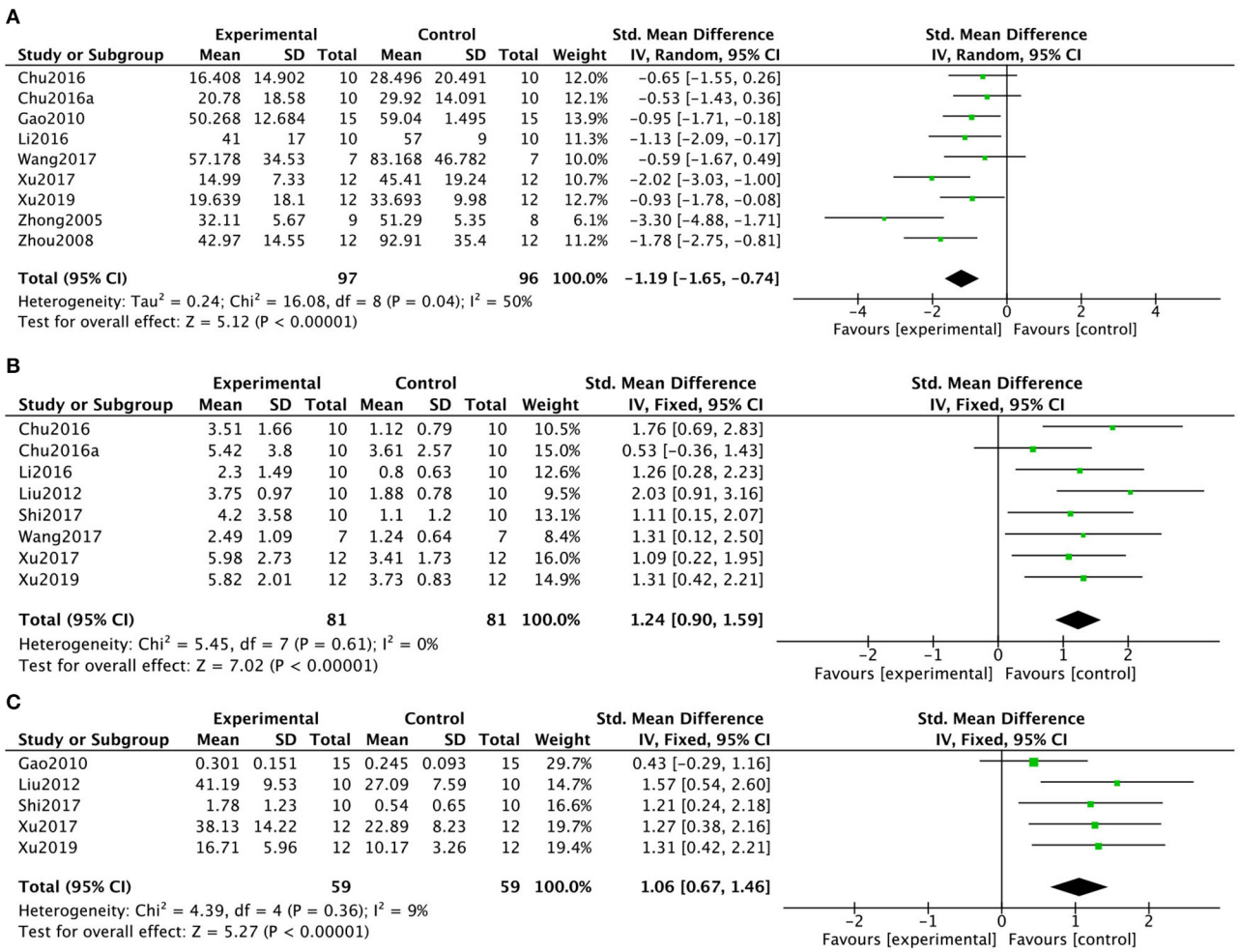

FIGURE 2 | Forest plot showing that KXS treatment decreased escape latency **(A)**, increased the number of target platform crossings **(B)**, and increased time spent on the target quadrants **(C)** in the Morris water maze test compared with the Control group.

levels of DA in response to KXS ($P < 0.00001$; SMD = 1.29, 95% CI [0.91, 1.68]; Heterogeneity: $\chi 2 = 6.58$, df = 7 ($P = 0.47$); $I^2 = 0\%$, **Figure 7B**). Twelve studies in 7 (18.4%) articles (Wang et al., 2005; Dang et al., 2009; Liu M. et al., 2012; Liu Y. M. et al., 2012; Dong et al., 2013; Liu W. W. et al., 2015; Yan et al., 2016) showed increased concentrations of 5-HT in response to KXS ($P < 0.00001$; SMD = 1.26, 95% CI [0.94, 1.58]; Heterogeneity: $\chi 2 = 21.54$, df = 11 ($P = 0.03$); $I^2 = 49\%$, **Figure 7C**).

DISCUSSION

Summary of Evidence

This is the first preclinical systematic review of KXS for cognitive impairment and depression based on 38 included studies with 1,050 animals. The methodological quality score was a mean of 4.24. The results demonstrated that KXS could significantly ameliorate both the behavioral performance of cognitive impairment and depression in animal models. The former included shortening the escape latency, decreasing the time spent on the target quadrants and increasing the number of target platform crossings in MWM, and the latter included raising the number of rearing in open-field test, decreasing the duration of immobility in forced swimming test and increasing the sucrose consumption or sucrose preference index in sucrose preference test. The meta-analysis of biochemical indicators illustrated that possible mechanisms of KXS include improvement of cognitive function via antioxidant, anti-inflammatory, antiapoptotic, neuroprotection, and synapse protection in cognitive impairment models, and antidepression effects through HPA axis regulation, antioxidant, anti-inflammatory, synapse protection and nervous protection in depression models. The findings of present study indicated that KXS exerted a consistent effect on improving the memory defects and depression symptoms in multiple animal models, indicating the therapeutic potential of KXS for treating AD-related BPSD.

Methodological Considerations

Currently, two major quality assessment tools are typically applied in preclinical systematic reviews: The CAMARADES checklist and the SYRCLE's risk of bias tool. The CAMARADES

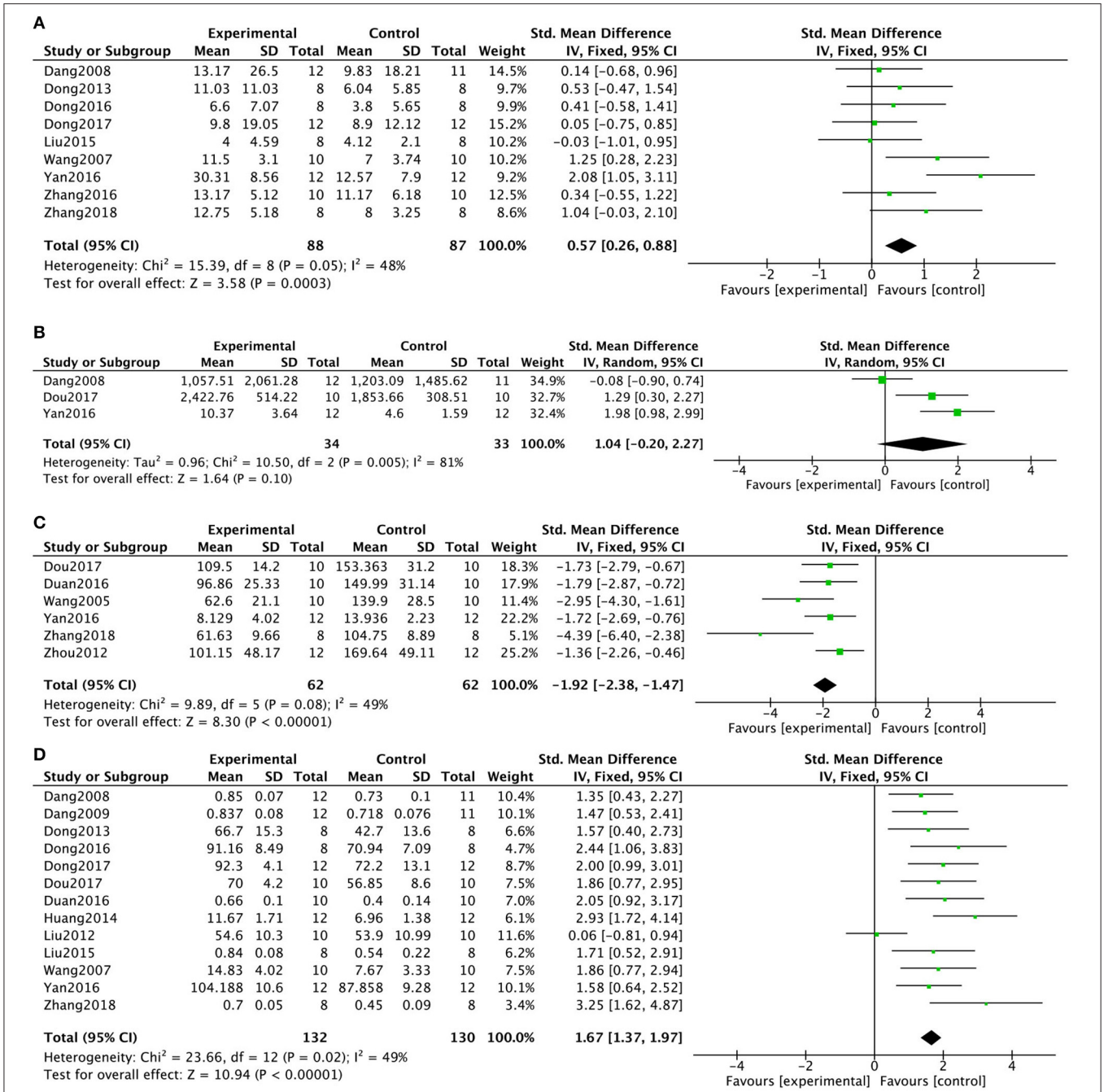

FIGURE 3 | Forest plot showing that KXS increased the number of rearing events **(A)** and total distance **(B)** in the open-field test, decreased the duration of immobility in the forced swimming test **(C)**, and increased sucrose consumption in the sucrose preference test **(D)** compared with the Control group.

checklist was designed as a tool to evaluate the methodological quality of interventional studies using stroke models. Subsequently, this checklist was used to evaluate other neurological diseases because the confounding factors are similar. The SYRCLE's risk of bias tool for animal studies originated from the Risk of Bias tool by Cochrane Collaboration (Hooijmans et al., 2014).

In this study, we used the CAMARADES checklist to assess quality because AD and depression are neurological disorders. The methodological quality score of the included studies were generally intermediate. The main concerns were as follows. Despite almost all statement randomly, no studies mentioned the detailed methods of random allocation in the present study. Randomization is a critical step to reduce selection bias, which ensures that comparisons are unbiased and that findings of studies are valid (Fonarow, 2016). Animal studies that do not use randomization are more likely to obtain positive results (Bebarta et al., 2003). However, randomization is often conducted poorly

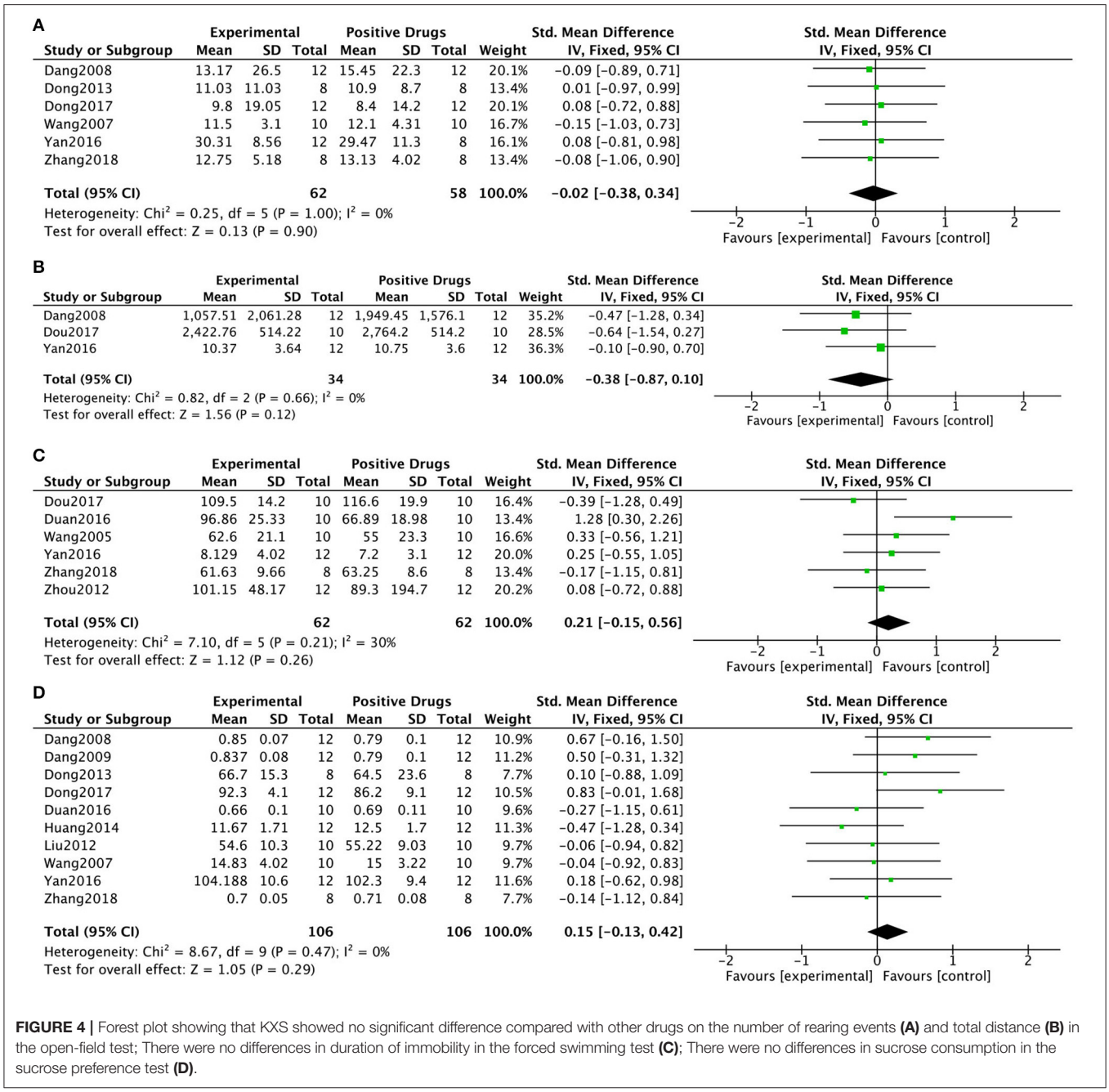

FIGURE 4 | Forest plot showing that KXS showed no significant difference compared with other drugs on the number of rearing events **(A)** and total distance **(B)** in the open-field test; There were no differences in duration of immobility in the forced swimming test **(C)**; There were no differences in sucrose consumption in the sucrose preference test **(D)**.

and reported incompletely (Doig and Simpson, 2005). According to the ARRIVE guidelines (Kilkenny et al., 2010), randomization procedures should be conducted appropriately, and reported in detail.

Results are more objective when using blind assessment (Schulz et al., 1995). Furthermore, the variability of observer make sense in outcomes (Bebarta et al., 2003). However, only a few studies use appropriate blinding procedures. Failure to blind studies may result in potential bias during modeling and outcome assessment. The ARRIVE guidelines (Kilkenny et al., 2010) state that steps taken to reduce the bias, such as blinding, should be detailed within manuscripts.

Calculation of sample size is important to ensure that enough participants are included to appropriately determine statistical significance (Khaled Fahim and Negida, 2018). Small sample sizes can result in not capturing true effect sizes, while inappropriately large sample sizes can be associated with ethical issues (Fitts, 2011). However, descriptions of how sample sizes are chosen are often inadequate (Baker et al., 2014). None of the included studies detailed how sample size was determined. The ARRIVE

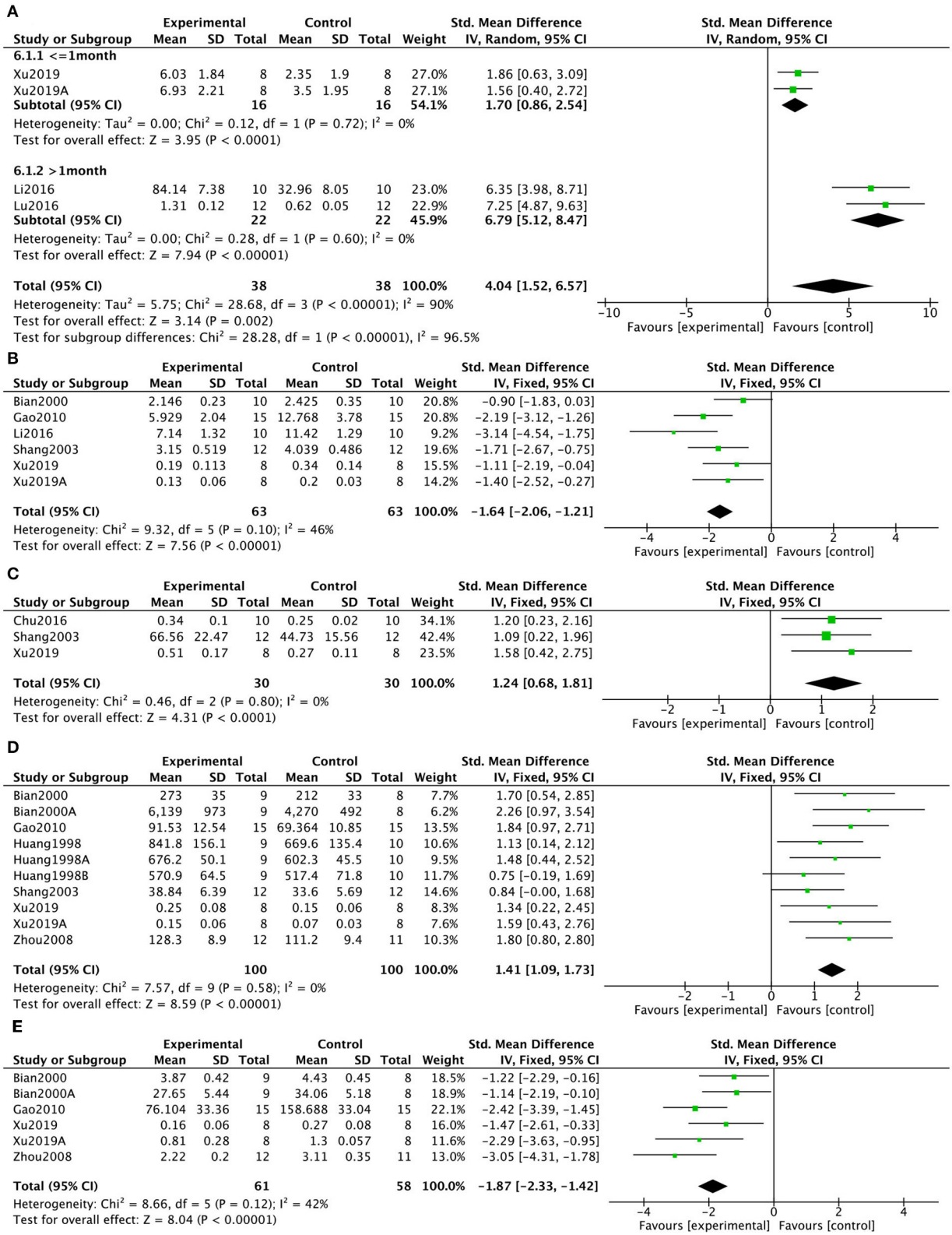

FIGURE 5 | Forest plot showing that KXS increased ACh levels **(A)**, decreased AchE activity **(B)**, increased ChAT activity **(C)**, increased SOD levels **(D)**, and decreased MDA levels **(E)** compared with controls in AD models.

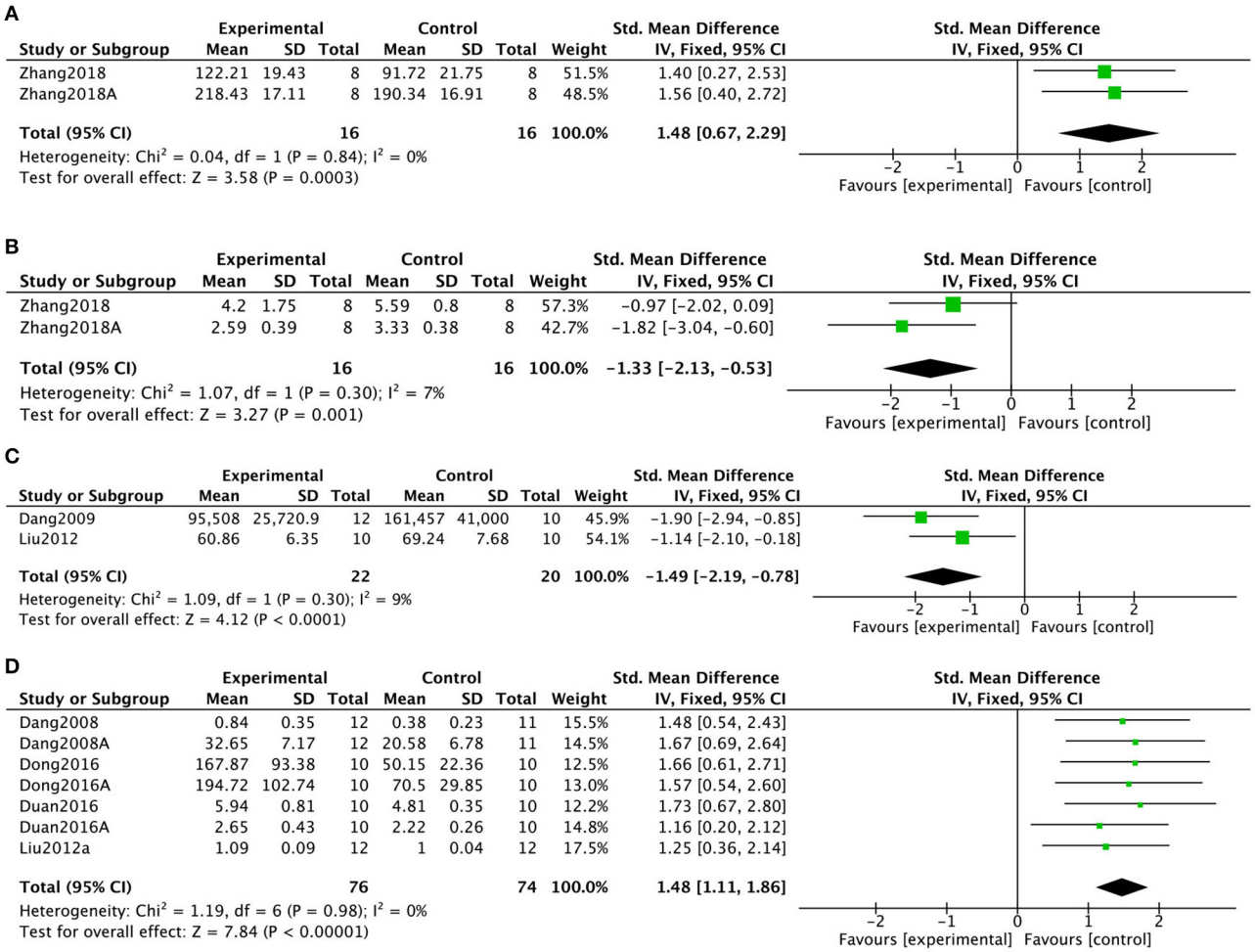

FIGURE 6 | Forest plot showing that KXS increased SOD levels **(A)**, decreased MDA levels **(B)**, decreased AchE activity **(C)**, and increased BDNF levels **(D)** compared with controls in depression models.

guidelines (Kilkenny et al., 2010) stated that the method by which sample size was determined should be appropriately detailed.

Seven studies used sodium pentobarbital as an anesthetic, and 2 studies used chloral hydrate. Pentobarbital is a commonly used barbiturate in animal studies. However, it must be used carefully because it can induce respiratory distress and deep sleep (Feustel et al., 1981; Warner et al., 1996). Furthermore, it is unknown whether barbiturates induce neuroprotective effects (Zwerus and Absalom, 2015). Although chloral hydrate has not been shown to induce neuroprotection in rats (Ozden and Isenmann, 2004), it has been shown to induce systemic toxicity in rodents (Huske et al., 2016). In addition, chloral hydrate may also be a carcinogen in rodents, which is an ethical issue (Maud et al., 2014). It is essential to select appropriate anesthetics in neurological studies.

Implications

Preclinical systematic review is a scientific approach to synthesize preclinical evidence with the goal of informing future studies. Preclinical systematic review provides an ethical approach and can increase sample sizes without increasing use of resources or number of animals. This systematic review synthesized preclinical evidence for KXS as a treatment for AD and depression. The results of our meta-analysis showed that KXS improved AD and depression symptoms in rats and mice. The results of the present study suggested that KXS may be a novel therapeutic agent for treatment of the behavioral and psychological symptoms of Alzheimer's dementia in preclinical and clinical studies.

Because AD is a chronic disease, it is important to assess the long-term effects and safety of KXS (Wimo, 2015). However, the progressive nature of AD makes long-term assessment of treatment strategies difficult (Rogers and Friedhoff, 1998). Thus, studies that evaluate the long-term efficacy and safety of KXS are needed.

The blood–brain barrier (BBB) is a physiological barrier that protects the central nervous system from harmful chemicals and peripheral biomolecules. In addition, the BBB prevents many drugs from entering the brain, resulting in low bioavailability in the brain and reduced pharmacological effects. Many drugs have failed to translate to clinical use despite being effective for

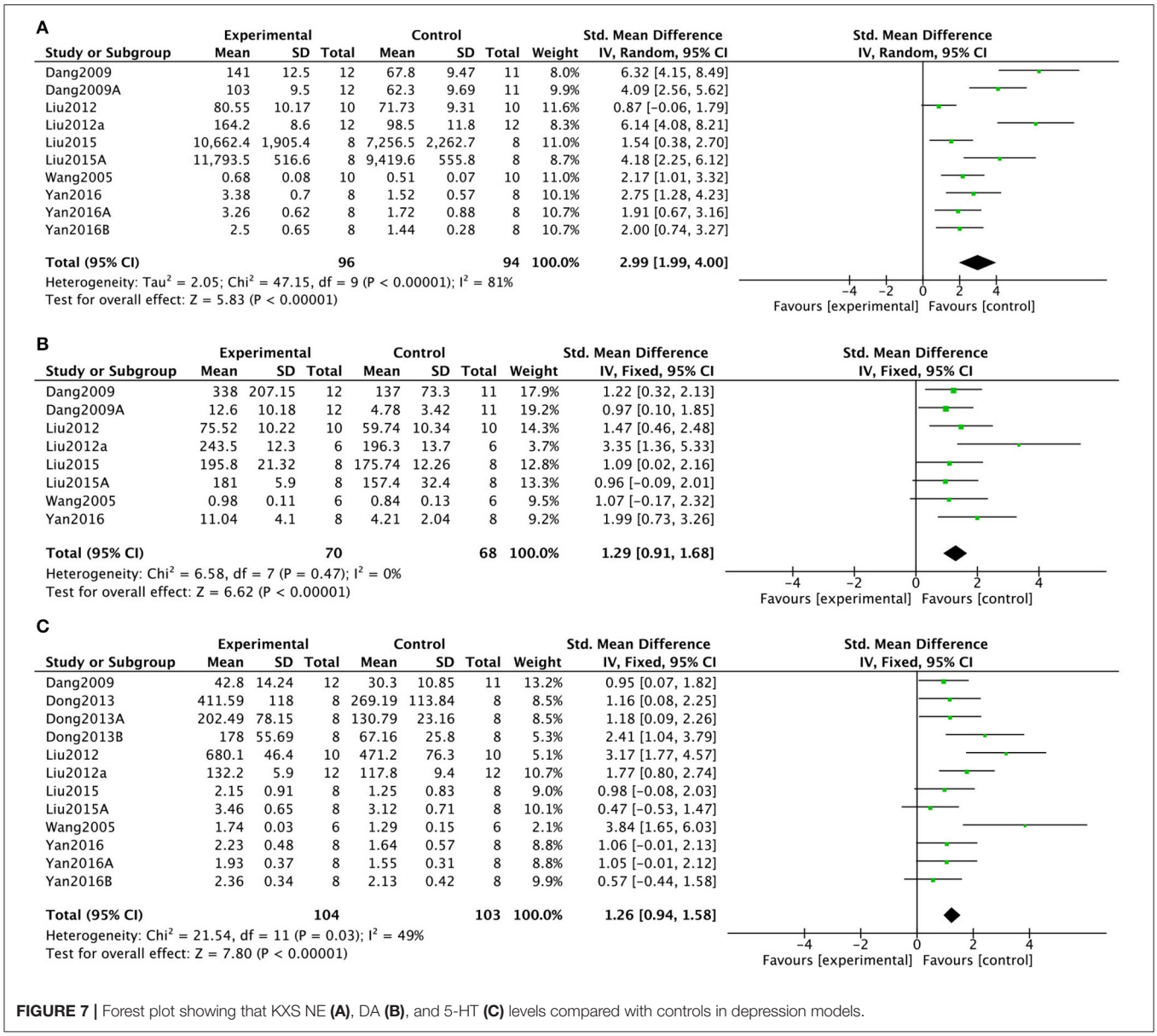

FIGURE 7 | Forest plot showing that KXS NE **(A)**, DA **(B)**, and 5-HT **(C)** levels compared with controls in depression models.

mitigation of CNS disorders because they are unable to cross the human BBB (Patel and Patel, 2017). Although the present systematic review provides evidence that KXS can improve cognitive impairment and depression, the mechanisms of KXS crosses the BBB is unknown. Further studies should evaluate KXS and its active ingredients crossing the BBB, and should focus on development of formulations that maximize brain bioavailability of KXS.

Animal models are essential for human disease research. Appropriate animal models should accurately reproduce the pathophysiology of human disease. There are 3 major types of AD models currently used: spontaneous models, chemically induced models, and transgenic animal models (Neha et al., 2014). Aging models and the SAMP8 mouse model were included as spontaneous models in our systematic review. Spontaneous models can accurately mimic human AD, but these studies are expensive and time-consuming. Chemically induced models were included in the present study, such as a scopolamine-induced model, an Aβ infusion-induced model, a D-gal-induced model, and an AlCl3-induced model. These models are widely used because they are easy to implement, and are relatively inexpensive. However, these models do not accurately mimic the pathophysiology of AD (Esquerda-Canals et al., 2017). APP/PS1 mice are a transgenic animal model included in our study. Transgenic animal models are frequently used due to advances in technology and the existence of well-established procedures (Esquerda-Canals et al., 2017). However, transgenic models are difficult to implement in rats (Do Carmo and Cuello, 2013).

The animal models of depression included in this systematic review were all induced by chronic stress, which is one of the most valid approaches for modeling depression (Willner, 1984). Depression is a disease with complex and varied etiology, and only one-fourth of patients develop depression due to stress (Willner, 1984). Because social stress results in varied responses,

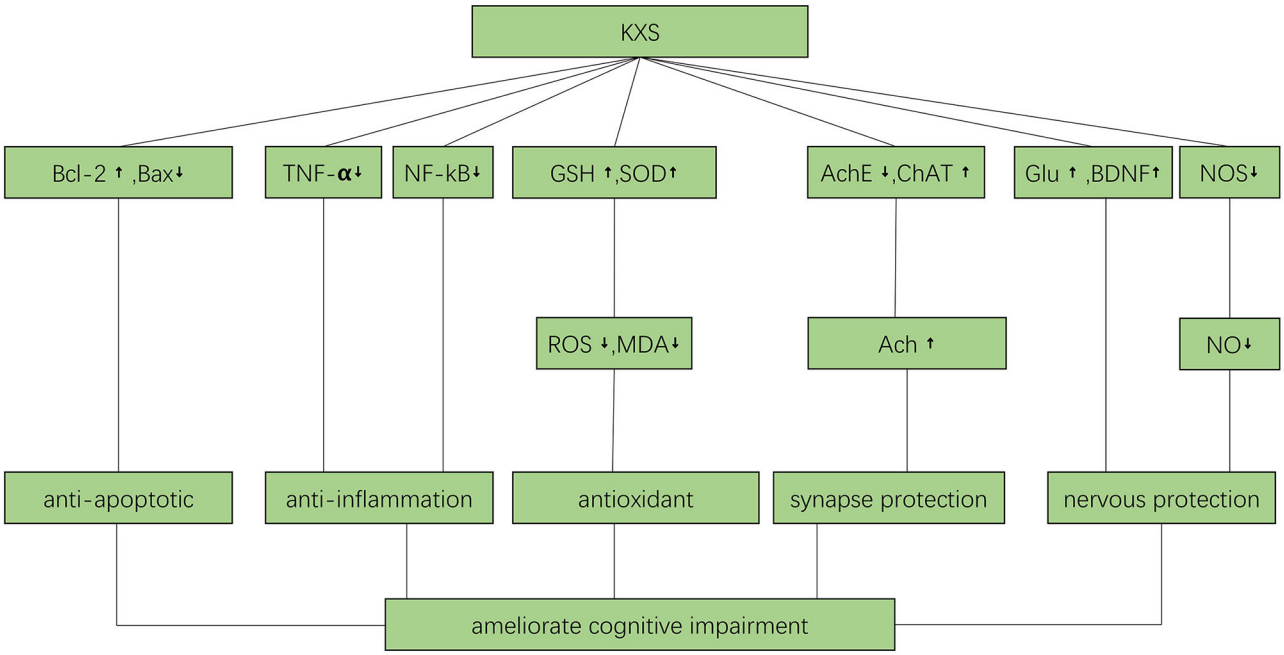

FIGURE 8 | The possible mechanisms by which KXS may improve cognitive function. Ach, acetylcholine; AchE, Acetyl cholinesterase; BDNF, brain derived neurotrophic factor; ChAT, choline acetyltransferase; Glu, Glucose; GSH, glutathione; MDA, malondialdehyde; NF-kB, nuclear factor-k-gene binding; NO, Nitric oxide; NOS, Nitric oxide synthase; ROS, reactive oxygen species; SOD, superoxide dismutase; TNF-α, Tumor Necrosis Factor α.

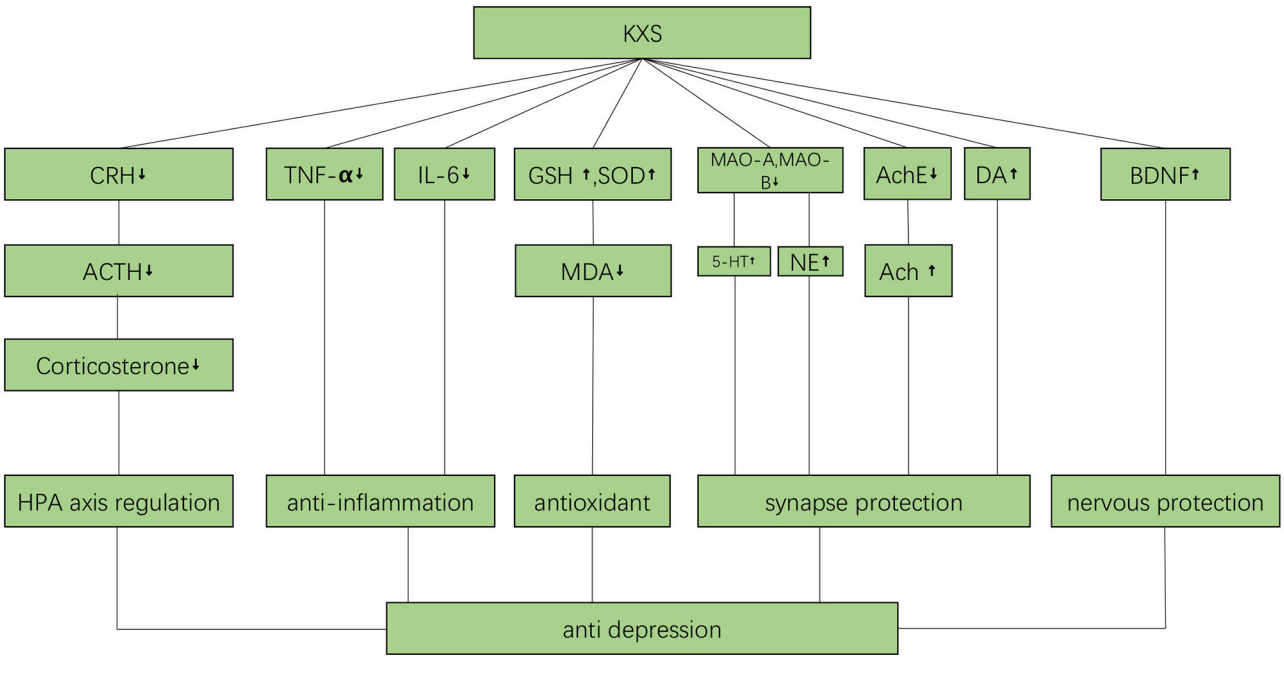

FIGURE 9 | The possible mechanisms by which KXS may ameliorate depression. Ach, acetylcholine; AchE, Acetyl cholinesterase; ACTH, Adreno cortico tropic hormone; BDNF, brain derived neurotrophic factor; CRH, Corticotropin releasing hormone; DA, Dopamine; GSH, glutathione; IL-6, interleukin-6; MAO-A, Monoamine oxidase-A; MAO-B, Monoamine oxidase-B; MDA, malondialdehyde; NE, Norepinephrine; TNF-α, Tumor Necrosis Factor α; 5-HT, 5-hydroxytryptamine.

it is of great importance to carefully evaluate associations between preclinical and clinical studies. Furthermore, common conditions that induce depressive behaviors in humans and animals should be considered when attempting to translate preclinical evidence to the clinic (McArthur and Borsini, 2006).

There is a lack of systematic research on models that mimic the combination of AD and depression. The ability of depression models to reproduce the pathophysiology of AD-related depression needs further study. Future studies should aim to develop better models to study BPSD.

Alzheimer's disease is a progressive disease that results in disability and death. Behavioral and psychological symptoms of dementia are a set of behaviors and neuropsychiatric symptoms associated with AD. Depression is one of the most common BPSDs associated with AD (Preuss et al., 2016), and correlates with accelerated AD-related cognitive impairment (Bassuk et al., 1998), increased mortality (Verkaik et al., 2007), and increased incidence of depression in caregivers (Barca et al., 2009). As a consequence, AD-related depression results in reduced quality of life of patients and increased social burden. Currently, the primary treatments for AD only control symptoms, but do not halt or cure AD. Behavioral and psychological symptoms of dementia are a diverse set of symptoms, which has prevented development of an appropriate single treatment approach for BPSD. Alzheimer's disease and depression are two conditions that often exist simultaneously in elderly individuals, they share many common symptoms (Novais and Starkstein, 2015), and both are associated with neurobiological changes such as cortical atrophy, limbic atrophy, and white matter lesions (Bennett and Thomas, 2014). The components of KXS act synergistically and interact with multiple targets, which may result in better treatment of AD and AD-related psychological symptoms. This systematic review synthesized preclinical evidence, and showed that KXS may be a promising therapeutic agent for treatment of AD and depression. However, the mechanisms by which KXS acts upon AD and depression are not clear.

Mechanisms

The mechanisms by which KXS ameliorated cognitive impairment were as follows (**Figure 8**). Kaixinsan may play a neurotrophic role by increasing glutamate (Glu) and brain-derived neurotrophic factor (BDNF) levels, and reducing nitric oxide-induced neurotoxicity via down-regulation of nitric oxide synthase activity. Kaixinsan also up-regulated the expression of Bcl-2 and down-regulated the expression of Bax, resulting in anti-apoptotic effects. Furthermore, KXS decreased TNF-α and NF-κB levels, resulting in anti-inflammatory effects. In addition, KXS decreased ROS and MDA levels via increased GSH and SOD levels. Finally, KXS protected synapses by increasing the concentrate of ACh through down-regulation of AchE activity and up-regulation of ChAT activity. The mechanisms by which KXS ameliorated depression were as follows (**Figure 9**). Kaixinsan down-regulated various components of the HPA axis such as CRH, ACTH, and corticosterone. Kaixinsan treatment also resulted in decreased release of TNF-α and IL-6. Furthermore, KXS reduced MDA levels via increased GSH and SOD levels. Moreover, KXS treatment resulted in increased levels of neurotransmitters such as NE, DA, 5-HT, and ACh, which may contribute to protection of synapses. Finally, KXS up-regulated BDNF, which is essential for protection of neurons.

The present study showed that KXS targeted pathways common to AD and depression. Identification of the physiological mechanisms of KXS activity has been limited by limitations of current models of AD and depression. Therefore, more, and diverse, animal models of AD, depression, and BPSD should be used to identify novel targets of KXS.

CONCLUSION

This study demonstrated that KXS could significantly protect cognitive function in AD models largely through antioxidant, anti-inflammatory, antiapoptotic, neuroprotective, and synapse protection mechanisms. Furthermore, KXS improved the symptoms of depression in animal models through HPA axis regulation, and antioxidant, anti-inflammatory, synapse protection, and nervous system protection mechanisms. The ability of KXS to effectively treat AD and depression symptoms in animal models suggests that it should be evaluated in clinical studies of AD and BPSD.

AUTHOR CONTRIBUTIONS

GZ designed the study, approved the manuscript, and is responsible for this published work. HF, ZX, and XZ collected the data, performed the analyses, and wrote the manuscript.

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Pharmacologic Approaches for the Management of Apathy in Neurodegenerative Disorders

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Apathy is one of the most frequent behavioral disturbances in many neurodegenerative disorders and is known to have a negative impact on the disease progression, particularly in Alzheimer's disease. Therapeutic options are currently limited and non-pharmacological approaches should constitute first line treatments. Pharmacological agents likely to reduce apathy levels are lacking. The objective of the present article is to review recent pharmacological treatments for apathy in neurodegenerative disorders. The Pubmed database was searched with a particular focus on articles published as of January 2017. Current main levels of evidence have been reported so far with cholinergic, glutamatergic and dopaminergic agents to reduce levels of apathy, despite several conflicting results. Treatment duration and samples sizes may have however decreased the validity of previous results. Ongoing studies involving more participants/treatment duration or distinct neural pathways may provide new insights in the treatment of apathy in neurodegenerative disorders.

Keywords: apathy, amotivation, pharmacology, treatment, Alzheimer's disease, neurodegenerative disorders

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INTRODUCTION

Apathy is the most frequent behaviorial disturbance in Alzheimer's disease (AD) and is prevalent in many other neurodegenerative disorders (Husain and Roiser, 2018). Despite apathy is considered a negative symptom in dementia, i.e. a non-demonstrative symptom, it does have negative consequences on the disease progression (Zhu et al., 2019) leading to increased risk of functional disability and institutionalization. The neural correlates of apathy are currently better understood. Brain imaging have shown the involvement of several areas such as anterior cingular and dorsolateral cortex, inferior frontal gyrus (Benoit and Robert, 2011; Kim et al., 2011), and of dopaminergic transmission (David et al., 2008), as well as the involvement of fronto-subcortical circuits (Riveros et al., 2018). Additionally, severity of apathy has been associated with lower CSF $A\beta_{42}$ concentrations in Alzheimer's disease (Vergallo et al., 2019). In this line, depression, that is often misdiagnosed with apathy, likely involves different structures (prefrontal orbitofrontal cortex (Lavretsky et al., 2007), cingulate, thalamus) (Starkstein et al., 2009; Zahodne et al., 2013), and neurotransmission pathways (5-HT transmission reduction in posterior cingulated and amygdala-hippocampus complex) (Benoit and Robert, 2011).

Considering the important negative impact of apathy in the evolution of AD, therapeutic options are needed. Current therapeutic treatments mainly rely on non-pharmacological approaches (Mueller et al., 2018). Moreover, conventional psychotropic drugs often overprescribed in AD, such as antipsychotics and Selective-Serotonin Reuptake Inhibitors (SSRI) antidepressants may increase levels of apathy in neurodegenerative disorders and may have overall insufficient effect to alleviate levels of BPSD (Anand et al., 2018). Weighing risks and benefits, it is recognized that psychotropic agents should be prescribed with caution in dementia (Azuar and Levy, 2018; Phan et al., 2019).

Previous articles have been published, including several randomized controlled trials (RCT), but pharmacological therapeutic options for the management of apathy are currently limited.

The present article makes a review of current pharmacological approaches available for the management of apathy in AD and related disorders.

METHOD

Previous reviews investigating management options for apathy have been recently published. Therefore, we focused our research on published articles as of 2017.

We searched the Pubmed online database between January 1st, 2017 and May 1st, 2019, for articles published in English, using the following method and keywords:

(((((apathy[Title/Abstract]) OR amotivation[Title/Abstract]) OR abulia[Title/Abstract])) AND ((treatment[Title/Abstract]) OR pharmacological intervention[Title/Abstract])) AND (((((((alzheimer[Title/Abstract]) OR vascular dementia[Title/Abstract]) OR mixed dementia[Title/Abstract]) OR lewy body [Title/Abstract]) OR parkinson[Title/Abstract]) OR dementia [Title/Abstract]) AND ("2017/01/01"[PDat]: "2019/12/31"[PDat])).

All abstracts were screened by two reviewers in order to assess their relevance to the topic.

See **Figure 1** for the study flow diagram.

RESULTS

Results are presented according to their level of evidence, respectively in Alzheimer's disease and in other neurological and/or neurodegenerative disorders. Main results are summarized in **Table 1**.

Alzheimer's Disease

Reviews and Meta-Analyses

One recent article from January 2017 reviewed recent pharmacological and non-pharmacological approaches for the management of apathy in AD (Theleritis et al., 2017) and reported the potential interest of cholinesterase inhibitors (ChEIs), methylphenidate and gingko biloba in reducing levels of apathy, whereas Sepehry et al's review did not reveal any significant treatment effect likely to reduce apathy in AD (Sepehry et al., 2017). In Theleritis, among 6 studies using galantamine (4 RCT and 2 open-label studies), five studies did show an improvement of apathy levels after treatment. Rivastigmine (8 open-label studies) showed improvements in apathy levels in all studies. Memantine (3 RCT, 1 open-label study, and 1 post marketing surveillance study) improved apathy in 4 studies. In the meta-analysis of Kishi (Kishi et al., 2017), memantine was not superior to controls for the management of negative symptoms, including apathy, in AD.

In Ruthirakukan's meta-analysis (Ruthirakuhan et al., 2018), methylphenidate (3 studies), compared to placebo, was likely to reduce apathy in AD, depending, however, on the assessment interview used (AES versus NPI-apathy domain).

In a review published in 2017, Lanctot et al. concluded that progress has been made in the phenomenology, the neurobiology and the treatment of apathy. Regarding the pharmacological treatment, they found evidence that ChEIs and memantine improve apathy, whereas ChEI withdrawal can worsen apathy. Modafinil improved apathy in 2 case reports, but a small RCT reported no significant improvement in apathy over 8-week treatment in AD. Methylphenidate was effective for apathy in mild to moderate AD as reported in 3 placebo-controlled trials (Lanctot et al., 2017).

Randomized Controlled Trials (RCT)

In the ongoing ADMET2 (Apathy in Dementia Methylphenidate Trial) phase III RCT study, authors reported the interest of using methylphenidate (Scherer et al., 2018) and planned to include 200 AD individuals (20 mg/day methylphenidate for 6 months and apathy assessed using the NPI apathy-domain). Results are expected as of 2020. The previous ADMET study showed a benefit of using methylphenidate after a 6-week treatment period among 60 participants (Rosenberg et al., 2013).

A memantine (20 mg/day)-citalopram (10 to 30 mg/day) combination (vs memantine + placebo) was significantly associated with a reduction of apathy in a group of AD individuals over a 12-week treatment period, using the NPI apathy-domain as outcome measure (Zhou et al., 2019).

In the ASCOMALVA study, comparing a subgroup of AD individuals (n = 56) receiving a combination of donepezil and choline alphoscerate (a cholinergic precursor) versus a subgroup (n = 57) with donepezil alone (24-month treatment period), the combined treatment was more effective on apathy levels than donepezil alone (Rea et al., 2015; Carotenuto et al., 2017).

Observational Studies

One observational study with AD individuals using ninjin'yoeito, a multicomponent drug with several effects including dopamine modulation, apathy (using the NPI apathy-domain) was significantly improved as of 4 weeks after treatment initiation (Ohsawa et al., 2017).

Animal Research

In a mice model of AD, the use of melatonin for 6 months (10 mg/kg) was efficient in reducing levels of apathy and anxiety as well amyloid and tau burden in transgenic AD mice, and could

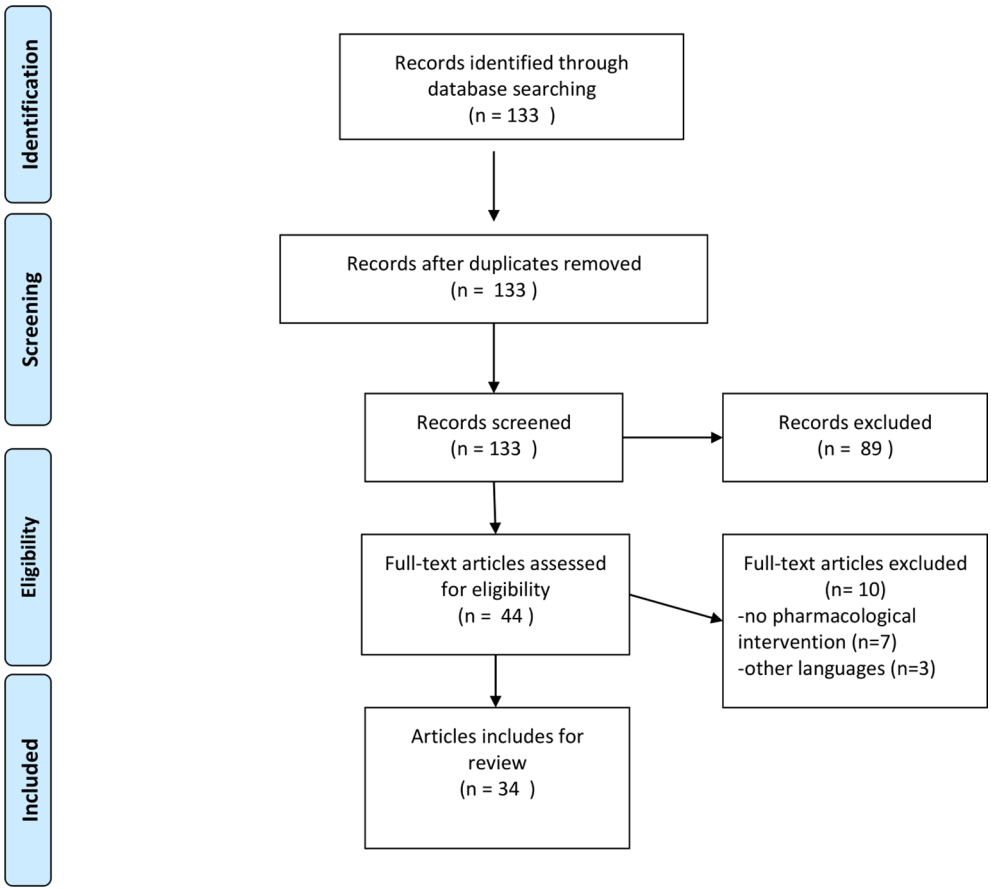

FIGURE 1 | Study flow diagram.

thus constitute a promising treatment opportunity in human research (Corpas et al., 2018).

Other Disorders

Parkinson's Disease

In several other neurodegenerative diseases, such as Parkinson's disease (PD) and Dementia with Lewy Body (DLB), dopaminergic agents, and cholinesterase inhibitors (ChEIs) have demonstrated an interest in reducing levels of apathy (Liu et al., 2019), but therapeutic options remain limited for the general management of nonmotor symptoms in PD, including apathy (Seppi et al., 2019). In an open-label observational study, targeting apathy as primary outcome (measured with NPI and AES), patients received transdermal rivastigmine (9,5 mg/day), one of the current available ChEIs. Rivastigmine did not improve apathy over a 12-month period (Moretti et al., 2017)

In Liu's meta-analysis, authors reviewed 19 articles regarding the pharmacological treatment of apathy in PD and 4 articles in DLB. In the selected studies, apathy was either the 1st or a 2nd outcome. In the PD population, 13 articles were RCT, 4 open-label studies, 1 case series and 1 case report. The Apathy was measured using different scales: apathy scale, the Non-Motor Symptoms Scale (NMSS), the Neuropsychiatric inventory (NPI), Lille Apathy Rating Scale (LARS) and Unified Parkinson's Disease Rating Scale (UDPRS) for PD, and the NPI for DLB.

The investigated drugs were: rotigotine, piribedil, methylphenidate, rivastigmine in double-blind placebo-controlled studies. Rotigotine, a dopamine agonist, improved apathy in all 4 RCTs. Piribedil, a D2 and D3 receptor agonist with alpha2- adrenergic antagonist properties, reduced apathy scores in PD patients who developed apathy after deep brain stimulation. Methylphenidate, a dopamine norepinephrine reuptake inhibitor, reduced apathy by 7 points on LARS compared to only 1-point reduction with placebo among 12 patients.

Rivastimine (ChEIs) reduced apathy on the LARS (8,5 points) compared to placebo (0,2-point reduction) in a 30-patient study. Five other RCT that assessed the pharmacological treatments of apathy in PD were analyzed. Rasagiline, an MAOI-B (monoamine oxidase B inhibitor) and atomoxetine, a SSNRI (selective serotonin-norepinephrine reuptake inhibitor), did not improve apathy levels. Decosahexaeonic acid (DHA), an omega-3 fatty acid, was not superior to placebo in the treatment of apathy. Amantadine, an agonist at many different receptors,

TABLE 1 | Summary of recent drug trials targeting apathy in different neurodegenerative disorders.

Study		Journal	n	disorder	Intervention	Treatment duration	Outcome and results	Comments
Authors	**Study design**							
Finger et al., 2018	RCT, Phase 1 + phase 2	Ongoing study	Total n = 60	FTD	Intranasal oxytocin different dosage between phase 1 and 2	18 weeks, phase 1, 18 weeks, phase 2 36 weeks	NPI Apathy-domain	Results not yet published
Scherer et al., 2018	RCT Phase 2	Ongoing study	200	AD	Methylphenidate 20mg/day	6 months	mADS-CGIC NPI DAIR	Results not yet published
Zhou et al., 2019	RCT	Experimental and Therapeutic Medicine	80 40/40	AD	Memantine 20 mg + Citalopram 30 mg/day vs Memantine 20 mg/day + placebo	12 weeks	NPI Apathy-domain: Reduction of apathy, p = 0,002	Memantine + citalopram superior to memantine + placebo
Gelderblom et al., 2017	RCT	PLOS One	40 20/20	Huntington	Bupropion 300 mg/day	10 weeks	Apathy primary outcome AES-I not efficient $p < 0.05$	
Lhommee et al., 2018	Open label randomized trial	The Lancet Neurology	251 127/124	PD	L-Dopa + dopa agonist/L-Dopa + dopa agonist + DBS The L-dopa equivalent daily dose increased by 21% (mean change 245·8 mg/day in patients allocated medical therapy alone) and decreased by 39% (–363·3 mg/day in those assigned DBS + medical therapy	2 years	NPI apathy-domain And Starkstein Apathy Scale	Apathy scores worsened in both groups, higher with DBS
Auffret et al., 2017	Observational study	Journal of the Neurological Sciences	12	PD	Apomorphine pump mean daily dose 57.7 ± 27.0 mg/day	6 months	Apathy: improvement on LARS- I $P < 0.05$	Patients advanced Parkinson's disease and contraindication to DBS
Oshawa et al., 2017	Observational	Journal of Alzheimer's Disease Reports	20	AD	ninjin'yoeito	12 weeks	NPI Significant improvement in Apathy after 4weeks $P < 0.001$	multicomponent drug, several effects including dopamine modulation
Nagayama et al., 2019	Open label	Journal of the Neurological Sciences	30	PD	Istradefylline, 40 mg	12 weeks	Apathy scale: significantly reduced at the 2^{nd}, 4^{th}, 8^{th}, 12^{th} w p = 0.02, 0.05, 0.01 and 0.005	Istradefylline = adenosine A2 receptor antagonist
Moretti et al., 2017	Open label, observational	Parkinson's Disease	48	Parkinson's dementia	Rivastigmine 9.5 mg/24h transdermal patch Add-on therapy	12 months	Apathy primary outcome, AES-S, AES-C, sub-item of NPI No efficacy	

decreased apathy levels by 0,9 compared with a 0,7 increase in the placebo group. For open-label studies, out of which only one included a control group, authors showed an improvement of apathy with galantamine on the NPI while rivastigmine did not decrease NPI-assessed apathy symptoms. A traditional Japanese medicine, yokukansan, significantly improved NPI apathy scores in 23 patients, but the exact scores were not reported.

Pump-based Parkinson therapies using apomorphine (non-selective dopamine agonist) infusion and levodopa-carbidopa intestinal gel allowing a more continuous dopaminergic stimulation tend to reduce several nonmotor symptoms in PD such as sleep, mood disorders, and apathy (Mundt-Petersen and Odin, 2017). Effects of add-on apomorphine in advanced PD were significant on apathy (assessed using the LARS-i) after 6 months of therapy (Auffret et al., 2017).

In late stages of PD, L-dopa showed significant improvements in levels of mood/apathy (Rosqvist et al., 2018). The use of Levodopa in individuals diagnosed with Parkinson's disease did not show significant reduction of apathy in the EARLYSTIM trial (Lhommee et al., 2018).

In an open-label trial including 30 PD individuals, the use of istradefylline (adenosine A2A receptor antagonist), an anti-parkinsonian agent, significantly reduced levels of apathy (assessed using the Apathy scale) after a 12-week treatment period (Nagayama et al., 2019).

In the meta-analysis, including recent RCT, from Wang et al. (2018), transdermal rotigotine significantly improved apathy in PD individuals.

In another recent review, dopamine agonists (piribedil, rotigotine and pramipexole) have been reported to improve levels of apathy in PD (Rektorova, 2019).

Fronto-Temporal Dementia (FTD)

Intranasal oxytocin for the management of neuropsychiatric symptoms in FTD is currently under trial (Finger et al., 2018). In this ongoing study, 60 individuals diagnosed with FTD will be included for a 6-week treatment period with oxytocin. Oxytocin is a neuropeptide, synthetized by magnocellular neurons in the hypothalamus (paraventricular and supraoptic nuclei), with behavioral effects in animals and humans. It has only one known receptor, OXYR, widely distributed throughout the brain (Lee et al., 2009). The use of psychostimulants may help to decrease levels of apathy in FTD (Young et al., 2018).

Huntington Disease

In Huntington disease, the use of bupropion (a norepinephrine dopamine reuptake inhibitor) did not show a significant effect in reducing levels of apathy, globally or by domain (cognitive, behavioral, and emotional) (Gelderblom et al., 2017). This RCT targeting apathy as primary outcome (using the Apathy Evaluation Scale AES) over a 10-week period of treatment with bupropion (150 or 300 mg/day vs placebo).

Other Disorders

One RCT investigating nefiracetam (a nicotinic, cholinergic, and NMDA receptor activity enhancer) was found relevant in reducing apathy in a post stroke population. Results were however not statistically significant at week 12 and only a limited number of individuals were included (n = 13) (Starkstein et al., 2016).

Aragona et al, however, reported an improvement in apathy levels (AES) with bupropion in a case report of post-stroke induced-apathy (left thalamus hemorrhagic stroke) (Aragona et al., 2018).

DISCUSSION

Despite the early and important prevalence of apathy in many neurodegenerative disorders, available pharmacological treatments remain currently limited. Non-pharmacological approaches have to be considered first line treatments for apathy as for all behavioral and psychological symptoms in dementia, eventually in association with pharmacological agents if required. To our knowledge and irrespective to the putative neural pathway, no pharmacological agent is currently recommended for the specific management of apathy in neurodegenerative. Investigated agents still remain so far off-label prescribing. Drug trials on apathy have mainly focused individuals with AD and PD. Despite conflicting results, agents involved in the cholinergic neural pathway (ChEIs), alone or in association with another pharmacological agent (cholinergic precursor) or glutamatergic agent (memantine) (alone or in association with SSRI) seems to be efficient in reducing levels of apathy, even for an extended treatment period. Agents having effects on the dopaminergic neural pathway (methylphenidate and bupropion, that inhibit the recapture of dopamine, dopamine agonists, L-Dopa) have also shown benefits in reducing apathy, but most of published results often included a limited number of participants over a limited treatment period. Results from the ADMET2 ongoing study (200 participants over a 6-month treatment duration) will likely provide insights on the interest of using dopaminergic agents for the treatment of apathy. The **Figure 2** summarizes the main neural pathways targeted so far for the treatment of apathy. Results from drug trials investigating distinct hypotheses such as oxytocin are also expected.

All aforementioned pharmacologic options for apathy are however likely to be associated with possible side effects that have to be taken into account when prescribed. Considering the cholinergic pathways, main side effects using CHEIs are digestive (nausea, diarrhea, vomiting), cardiogenic (mild decrease in the number of heart beats, rhythm disorders), and neuropsychologic (hallucinations, agitation, aggressiveness, seizure, fatigue, cephalalgia). With glutamatergic agents (memantine), the following side effects have been reported: fatigue, cephalalgia, digestive symptoms (nausea, constipation, vomiting), neuropsychologic symptoms (anxiety, hallucinations, sleep disorders, excessive sleepiness, confusion). Regarding dopamine-targeting agents, reported side effects are as follows, respectively with methylphenidate (addictive behaviors; amphetamine-like intoxication including hypertension, tachycardia, agitation, delusion, seizure,…; cardiogenic symptoms such as arrythmia and hypertension), with L-Dopa

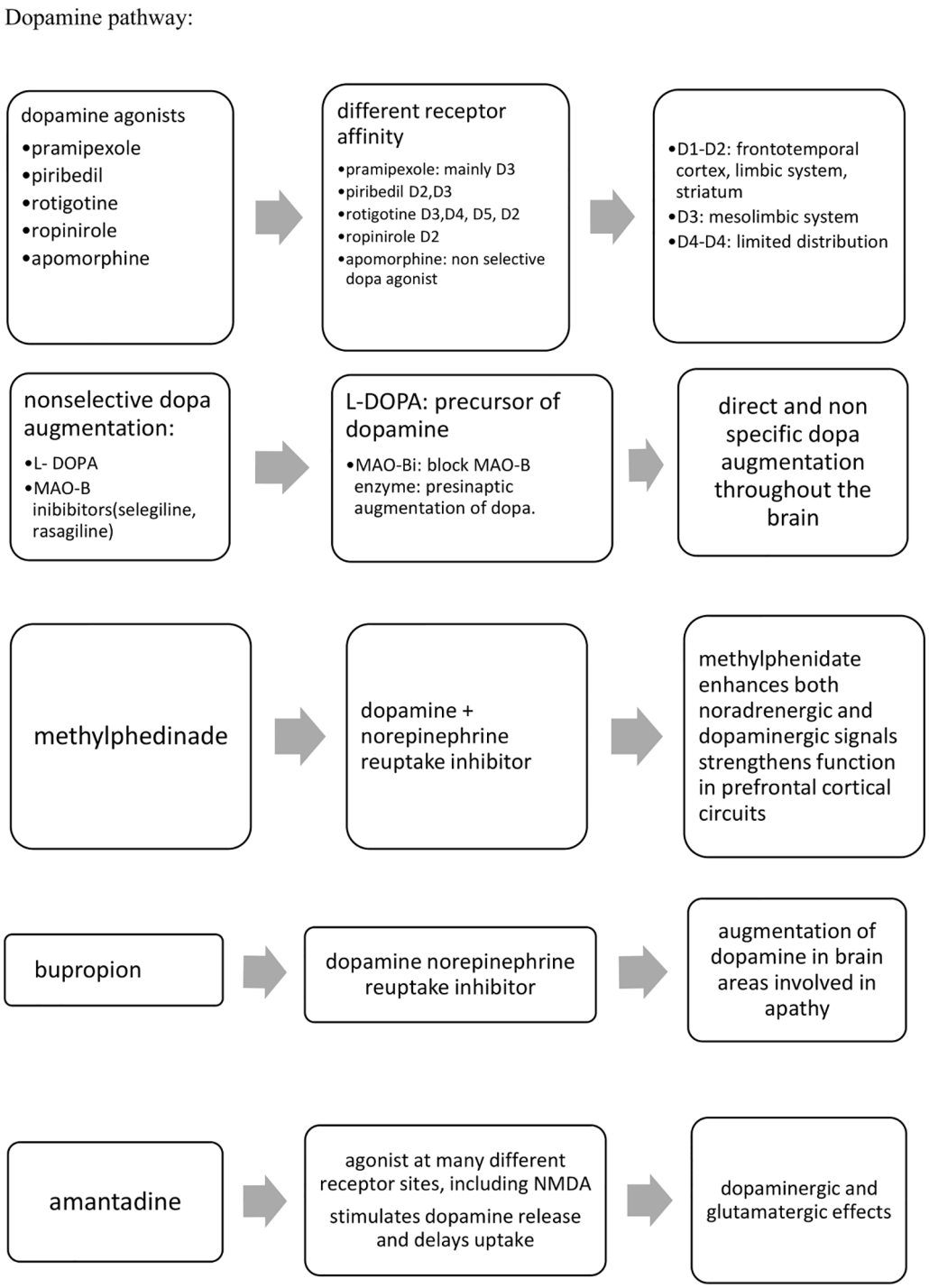

FIGURE 2 | Summary of pharmacological agents with higher levels of evidence for the management of apathy.

and dopa agonists (nausea and vomiting, anorexia, hypotension, excessive sleepiness or nightmares, anxiety, agitation, delusion, compulsive behaviors, and hypersexuality, dyskinesia).

Additionally, alternative therapeutic approaches such as transcranial direct current stimulation (tDCS) may constitute new options for the treatment of apathy, considering the fact that such techniques enable the possibility to directly stimulate deep cerebral structures (anterior cingular cortex for apathy). One study investigated this hypothesis with negative results on apathy (40 AD individuals with 6 tDCS sessions over 2 weeks) (Suemoto

et al., 2014). An optimized design with an increased and repeated number of sessions would probably be of interest.

On a more clinical point of view, apathy is sharing several overlapping symptoms with depression that could lead to inappropriate diagnoses, and thus consequently to an inappropriate treatment prescribing. Despite distinct neural pathways (Murakami et al., 2013; Eyre et al., 2017; Prange et al., 2019), apathy and depression are sharing similar symptoms such as diminished interests, psychomotor retardation, diminished decision making and initiatives. Apathy is frequently misdiagnosed with depression leading to antidepressant prescribing. In this line SSRIs (as well as SSNRIs selective serotonin and norepinephrine reuptake inhibitors such as duloxetine), usually prescribed as first line therapy in depression, might increase the severity of apathy, when inappropriately prescribed for apathy symptoms, whereas they are effective in reducing depressive symptoms (in a Parkinson's disease population) (Takahashi et al., 2019). Several authors suggest that the use of monoamine oxidase inhibitors (instead of other antidepressant drugs) should be initiated first in chronic neurodegeneration (Riederer and Muller, 2017).

Considering evidences from non-neurodegenerative diseases, others pharmacologic approaches showed benefits in reducing apathy-like behaviors (improvement of negative symptoms with aripiprazole, antidepressants, or topiramate in schizophrenia (Veerman et al., 2017).

Additionally, recent animal studies showed interests in using different pharmacologic targets such as antagonist of muscarinic acetylcholine receptors (Hailwood et al., 2019) or selective 5-HT2C receptor ligand (Bailey et al., 2018) to enhance amotivation and goal-oriented behaviors.

However, despite the different proposed approaches, the management of apathy and apathy-like behaviors remains challenging in daily clinical routine.

AUTHOR CONTRIBUTIONS

AB and RD participated in the review of the literature and the manuscript's writing. VM and AK participated in the manuscript's writing and editing.

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SYSTEMATIC REVIEW
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Sensing Technology to Monitor Behavioral and Psychological Symptoms and to Assess Treatment Response in People With Dementia. A Systematic Review

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Background: The prevalence of dementia is expected to rapidly increase in the next decades, warranting innovative solutions improving diagnostics, monitoring and resource utilization to facilitate smart housing and living in the nursing home. This systematic review presents a synthesis of research on sensing technology to assess behavioral and psychological symptoms and to monitor treatment response in people with dementia.

Methods: The literature search included medical peer-reviewed English language publications indexed in Embase, Medline, Cochrane library and Web of Sciences, published up to the 5th of April 2019. Keywords included MESH terms and phrases synonymous with "dementia", "sensor", "patient", "monitoring", "behavior", and "therapy". Studies applying both cross sectional and prospective designs, either as randomized controlled trials, cohort studies, and case-control studies were included. The study was registered in PROSPERO 3rd of May 2019.

Results: A total of 1,337 potential publications were identified in the search, of which 34 were included in this review after the systematic exclusion process. Studies were classified according to the type of technology used, as (1) wearable sensors, (2) non-wearable motion sensor technologies, and (3) assistive technologies/smart home technologies. Half of the studies investigated how temporarily dense data on motion can be utilized as a proxy for behavior, indicating high validity of using motion data to monitor behavior such as sleep disturbances, agitation and wandering. Further, up to half of the studies represented proof of concept, acceptability and/or feasibility testing. Overall, the technology was regarded as non-intrusive and well accepted.

Conclusions: Targeted clinical application of specific technologies is poised to revolutionize precision care in dementia as these technologies may be used both by patients and caregivers, and at a systems level to provide safe and effective care. To

highlight awareness of legal regulations, data risk assessment, and patient and public involvement, we propose a necessary framework for sustainable ethical innovation in healthcare technology. The success of this field will depend on interdisciplinary cooperation and the advance in sustainable ethic innovation.

Systematic Review Registration: PROSPERO, identifier CRD42019134313.

Keywords: dementia, sensoring, monitoring, behavior, therapy

INTRODUCTION

The global health challenge of dementia is exceptional in size, cost and impact (Wortmann, 2012). The World Health Organization estimates that 47 million persons live with dementia worldwide, a number expected to reach 75 million by 2030 and more than triple by 2045 (World Health Organization, 2017). According to the Alzheimer's Association, dementia-related costs range from $157 to $215 billion - higher than costs associated with cancer or cardiac disease — in the US alone, with roughly $42,000 to $56,000 spent per individual. These costs are driven to a significant extent by behavioral and psychological symptoms of dementia (BPSD) such as psychosis, apathy, hyperactivity, agitation, sleep disorders or depression (Ballard and Howard, 2006). This symptomatology may be caused or exaggerated by a range of conditions, such as hypoglycemia, pain and general discomfort, or they may arise secondary to the use of both psychotropic and non-psychotropic medications, which are known to precipitate a wide range of symptoms (Lyketsos et al., 2006). The prevalence of polypharmacy further adds to this clinical challenge (Gulla et al., 2016). Compounding this, no FDA approved pharmacologic treatments for BPSD exist and a wide range of psychotropic medications — including antipsychotics, mood stabilizers, antidepressants, and cholinesterase inhibitors — are regularly used to manage the symptoms, despite clear guidelines as to when and how to use them (Ballard and Corbett, 2010). This has led to vast variance in clinical practice around pharmacologic management of BPSD (Livingston et al., 2017). Polypharmacy and inappropriate prescribing can lead to significant adverse events, including increased fall risk, higher rates of inpatient care, loss of independence, and it increase the need for monitoring, which can significantly raise costs of dementia care, especially in nursing homes (Winblad et al., 2016).

Thus, there is an urgent need for tools that facilitate diagnoses that are more precise and a deeper understanding of patterns and triggers for BPSD (Kang et al., 2010). This includes tools that generate continuous data on behavior patterns, which may facilitate earlier detection of temporal events and guide more precise pharmacotherapy. Finally, there is a need for tools that can more closely monitor treatment response in dementia across care settings (Teipel et al., 2018).

A wide array of new technologies may provide solutions, especially those explicitly designed to support people with dementia and their formal and informal caregivers (Yang and Kels, 2017). The evidence around this has also been growing with research highlighting aspects of active and passive technology used in dementia (Pillai and Bonner-Jackson, 2015; Martinez-Alcala et al., 2016; Giggins et al., 2017; Brims and Oliver, 2018), the impact of safety equipment on wandering in dementia (Lin et al., 2014; Mangini and Wick, 2017), ethical considerations of surveillance technology in dementia (Sorell and Draper, 2012), or the need for real-world evidence-based solutions to conduct clinical trials (Teipel et al., 2018).

In this review paper, we present a synopsis of existing research studies in this space, including work on both commercially available as well as prototype technologies. This includes diagnostic technologies that utilize active and passive sensing in connection with smart housing, voice recognition and motion mapping (Teipel et al., 2018), and prognostic approaches that may inform clinicians about a range of potential responses, including alterations in circadian rhythm, changes in gait speed, falls, and variations in spatial location and reduction in resistance to care.

Finally, we discuss the potential pitfalls of this technology, specifically related to issues around ethics, privacy and security of data (Bantry-White, 2018; Chalghoumi et al., 2019) and the scalability of these technologies in terms to social living and activities.

METHODS

This systematic review presents a synthesis of previous research on sensing technology to assess behavioral and psychological symptoms and to monitor treatment response in people with dementia.

Literature Search

We initially searched for peer-reviewed English language publications indexed in the following databases: Embase, Medline, Cochrane library and Web of Sciences, published up to the 5thof April 2019. Keywords included MESH terms and phrases synonymous with "dementia", "sensor", "patient", "monitoring", "behavior", "therapy". See full search history in the supplementary material. We assessed papers for eligibility using the PICO criteria (P: population, I: intervention, C: comparison and O: outcome), (see **Table 1**). We included studies applying both cross-sectional and prospective designs, including randomized controlled trials, cohort studies, and case-control studies. Reviews, opinion papers, protocols, and conference abstracts were excluded from the main search results.

TABLE 1 | Inclusion and exclusion criteria.

Inclusion criteria according to PICO	Population	People with dementia
	Intervention	Use of sensor technology
	Comparison	No use of sensor technology
	Outcome	Changes in behavioral and psychological symptoms in dementia/neuropsychiatric symptoms in dementia. Validity of assessment of neuropsychiatric symptoms in dementia comparing sensor technology with proxy rated symptoms
Exclusion criteria	Studies published before 2009. Reviews, protocols, opinion, and conference papers. Publications in other languages than English.	

After removal of duplicates, one researcher (BH) screened all the manuscripts on title and abstract level to select relevant studies based on the inclusion and exclusion criteria. Potentially relevant studies were assessed for eligibility by all coauthors by evaluating the inclusion and exclusion criteria on the full-text manuscripts. Reference lists of manuscripts and reviews were screened to identify additional relevant publications. The final selection of included publications was by consensus among all authors. The study was registered in PROSPERO 3rd of May 2019.

RESULTS

The systematic search generated 1,337 potential publications from Embase (601), Cochrane (77) Medline (275), and Web of Science (384), of which 161 papers were identified as relevant for full-text evaluation (**Figure 1**). Of these, 127 papers were removed from the following results because they were either editorial review pieces or opinion articles, or because the studies involved use of technology but not for the primary goal of managing BPSD. Eighteen (53%) articles were published in Europe, 10 (29%) in the United States and 6 (18%) in Oceania.

Of the 34 studies selected, 23 focused on management of BPSD itself, while 11 studies that utilized sophisticated technological approaches for studying other factors. For example, one study (Whelan et al., 2018) assessed communication between caregivers and nursing home staff, while another utilized technology to assess ability to perform activities of daily living (ADLs) (Stucki et al., 2014). While these studies did not meet the original inclusion criteria, by consensus among the co-authors, we elected to include the studies since they reflect potentially meaningful applications of

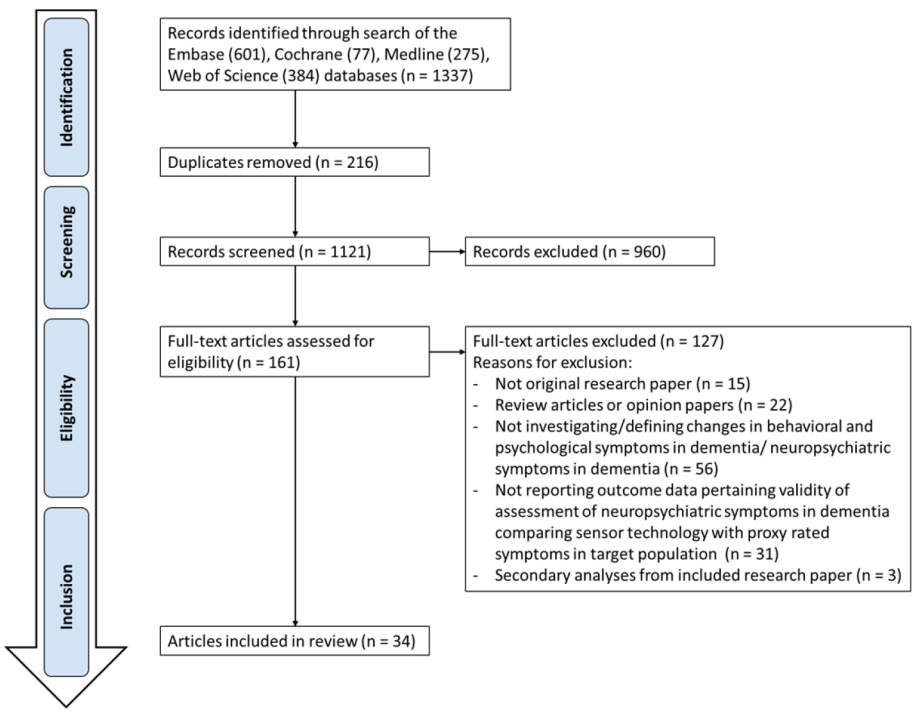

FIGURE1 | Flow Chart.

technology and may have implications for pharmacologic and non-pharmacologic management of BPSD.

For our final review, we assessed the full text from the 34 papers that were identified as relevant and divided studies into four broad categories, based on the type of technology used: (1) wearable technology, (2) non-wearable motion sensor technology, (3) assistive technology/smart home technology, and (4) other technologies not meeting criteria for the above three. We identified six papers that utilized more than one type of technology, and incorporated them into one of the above sections, based on the primary technology for each study.

Wearable Technologies

We identified seven studies that used wearable technologies — these included multiple sensor systems (two papers), ankle or wristbands (three papers), or a combination of both (two papers). We identified four prospective or retrospective cross-sectional studies along with two cohort studies and one case-control study. Study length ranged from 100 sec to 18 months. We noted that five studies utilized wearable technologies to primarily detect motion and two papers utilized wearable technologies that detected variables other than motion (body posture, stress). The details of the identified studies are summarized in **Table 2**.

Non-Wearable Motion Sensor Technologies

We identified 12 studies that utilized sensor-based motion detection approaches other than wearables. Only one of these was a randomized controlled trial, with one cohort study, four cross-sectional studies, two proof of concept studies, two case studies, and one longitudinal study. The sample sizes of the studies ranged vastly — from 1 to 265. This broad range reflects the heterogeneity of applications of motion sensor technologies for dementia. Study length ranged from two weeks to three years. Likewise, in the case of wearable technologies, we identified vast heterogeneity in study indications and purpose. Identified studies are summarized in **Table 3**.

Assistive/Smart Home Technologies

We identified 12 studies that utilized sensor rays placed in the living environment of study subjects. These were variously referred to as assistive or smart home technologies, since they required minimal active engagement by the patient or subject. The studies identified in this category included only one partial RCT — this study had 3 sites, but investigators were able to implement the RCT design at only one site. In addition, we identified three cross sectional/case-control studies, one cohort study, two case series and two open feasibility studies. We also identified three qualitative studies in this category. Study length ranged from 30 min interviews to 15 months and sample sizes ranged from four individuals to 65. Details of studies using these technologies are summarized in **Table 4**.

Other Technologies;

In addition, we identified three studies, each of which deployed a unique technological approach that could not be classified into one of the three categories above. One feasibility study (Khosla

TABLE 2 | Studies utilizing wearable technologies.

Author Country	Year	Study design	N	Study length	Domains studied	Outcome measures	Type of technology
Bankole et al., USA (Bankole et al., 2012)	2012	Cross-sectional	6	6 weeks	Agitation in dementia	Construct validity of BSN, tested against CMAI, ABS, MMSE	BSN - readings from wearables on wrist, waist, and ankle
Fleiner et al., Germany, (Fleiner et al., 2016)	2016	Cross-sectional	45	72 h	Agitation in dementia	Feasibility and acceptance of wearable uSense sensor	Wearable "uSense" 3D hybrid motion sensor on lower back which records body postures
Hsu et al. Taiwan, (Hsu et al., 2014)	2014	Cross-sectional	71	1 visit	Dementia	Validity of wearable device in sensing gait and balance problems during walking tasks	Inertial sensor-based wearable
Kikhia et al. Sweden, (Kikhia et al., 2016)	2016	Case series	6	37 days	Stress in dementia	Stress measurements (data was categorized into Sleeping, Aggression, Stress, and Normal) and GSR data	Wearable ("DemaWare@NH" wristband) - includes accelerometer, detects skin conductance and temperature, and environmental light and temperature
Merilahti et al. Finland, (Merilahti et al., 2016)	2016	Retrospective database study	16	12–18 months	Sleep patterns and functional status	Actigraphy, ADLs	Wearable (wristband)
Zhou et al. USA, (Zhou et al., 2017)	2017	Cohort study	30	1 visit	Motor-cognitive impairment	Feasibility of iTMT, performance on iTMT	iTMT
Zhou et al. USA, (Zhou et al., 2018)	2018	Cohort study	44	1 visit	Cognitive frailty (cognitive impairment and frailty)	Gait, iTMT performance, accuracy of iTMT system in detecting motor planning errors	iTMT

ABS, Aggressive Behavior Scale; ADL, Activities of Daily Living; BSN, Body sensor network; CMAI, Cohen-Mansfield Agitation Inventory; GSR, Galvanic Skin Response; iTMT, Instrumented trail-making task; MMSE, Mini-Mental-Scale Examination.

TABLE 3 | Studies utilizing motion-sensing technologies.

Author Country	Year	Study design	N	Study length	Domains Studied	Outcome measures	Type of technology
Akl et al., Canada, (Akl et al., 2015)	2015	Feasibility Study	97	3 years	Mild cognitive impairment	CDR), MMSE (tracking who remained cognitively intact vs. who experienced decline)	Passive infrared motion sensors, wireless contact switches (to track entrances/exits), and motion-activated sensors (to track walking speeds) installed in the home, machine learning algorithms
Alvarez et al. Spain (Alvarez et al., 2018)	2018	Cohort Study	18	10 weeks	Freezing of gait & abnormal motion behavior	Accuracy of Measurements	Multisensory band (wearable - temp, HR, motion data), binary sensor (doors open/close), RGB-D camera (extraction of depth information), Zenith camera (360-degree pano camera for movement tracking), WSN anchors/beacons (monitor signals from pts' wearables)
Dodge et al. USA, (Dodge et al., 2015)	2015	longitudinal	265	3 years	MCI	CDR; Neuropsychiatric scales (immediate & delayed recall; category fluency; trails, WAIS, Boston Naming Test)	Passive in-home sensor technology (specific motion sensors on the ceiling)
Enshaeifar et al. UK (Enshaeifar et al., 2018)	2018	Cross-sectional	12	6 month	Dementia (agitation, irritation, and aggression)	Motion data and level of engagement in activities	Wireless sensors (passive infrared sensors, motion sensors, pressure sensor, central energy consumption monitoring device)
Galambos et al. USA (Galambos et al., 2013)	2013	Case Series	5	7–12 months	Depression & Dementia in older adults	Congruence between health information (GDS, MMSE, SF-12) and activity level changes	Passive infrared motion sensors
Gochoo et al. USA (Gochoo et al., 2018)	2018	Cross-sectional	1	21 months	Dementia	Accuracy of classifier model in correlating travel pattern with dementia detection	Passive Infrared sensors & deep convolutional neural network (DCNN)
Jansen et al. Germany, (Jansen et al., 2017)	2017	Cross-sectional	65	2 consecutive days	motor & cognitive impairment in adults in 2 nursing homes (motion, gait, cognitive function)	MMSE, GDS, apathy evaluation scale, short falls efficacy scale international, movement tracking (time away from room, transits)	Wireless sensor network (nodes fixed to the walls that use radio signals)
Melander et al. Sweden (Melander et al., 2017)	2017	Feasibility & Observational	9	2 weeks	Dementia, agitation	Correlational analysis	EDA Sensor
Melander et al. Sweden, (Melander et al., 2018)	2018	Case Series	14	8 week study duration	Dementia, agitation	NPI-NH (Nursing home), Electro dermal activity (EDA)	EDA Sensor
Nishikata et al. Japan, (Nishikata et al., 2013)	2013	Cross-sectional	40	21-191 days	Moderate to advanced AD; BPSD		Integrated Circuit tag monitoring system (antennas set up on the ceiling that receive signals when patients moved under them)
Rowe et al. USA (Rowe et al., 2009)	2019	RCT	106	12 months	Nighttime wandering in dementia	Feasibility of system; prevention of dangerous nighttime events	Nighttime monitoring system
Yamakawa et al. Japan (Yamakawa et al., 2012)	2012	Cross-sectional	35	95 days	Nighttime wandering in dementia	Movement indicators (distance moved, number of hours with movement, etc.), agreement with nursing records; system data agreement with BPSD measured by NPI	Integrated circuit (IC) tag monitoring system - measures temporal and spatial movements

BPSD, Behavioral and Psychological Symptoms of Dementia; CDR, Clinical Dementia Rating scale; DCNN, Deep Convolutional Neural Network; EDA, Electro Dermal Activity; GDS, Geriatric Depression Scale; HR, Human Resources; IC, Integrated circuit; MMSE, Mini-Mental-State Examination; NPI, Neuropsychiatric Inventory; NPI-NH, Neuropsychiatric Inventory-Nursing Home version; SF-12, Short-Form Health Survey 12; WSN, Wireless Sensor Network.

et al., 2017) used a human-like robot to assess social and emotional responses to nonhuman caregivers. Another study utilized a suite of apps administered *via* a tablet device as a nonpharmacologic intervention for agitation in dementia (Vahia et al., 2017). We identified one study that utilized a text analysis tool to detect variance and patterns of communication between patients, staff, and caregivers (Whelan et al., 2018). The details of the studies are summarized in **Table 5**.

Finally, during the entire review process, we became increasingly aware of the discrepancies and lack of consensus

TABLE 4 | Studies utilizing assistive technologies.

Author Country	Year	Study design	N	Study length	Domains studied	Outcome measures	Type of technology
Aloulou et al. Singapore (Aloulou et al., 2013)	2013	Feasibility study	10	14 months	Wandering, falls, difficulty with ADLs	Acceptability, qualitative feedback	Ambient Assistive Living technologies (motion sensors controlled by a software)
Asghar et al. UK, (Asghar et al., 2018)	2018	Cross-sectional (questionnaire based)	327	2 months	Factors impacting use of assistive technology in people with mild dementia	Survey responses	AT included mobility supports, cognitive games, reminders or prompters, social applications, and leisure supports.
Collins ME. USA (Collins, 2018)	2018	qualitative study	8	30–45 min interviews	Alzheimer's & related dementia	AT with ADLs	AT included Wii, iPads, iPhones, computers, medication management systems, and alarms
Hattink et al. The Netherlands (Hattink et al., 2016)	2016	RCT at Germany site, pre-test/post-test design in Belgium and Netherlands	74	8 months	In-home assistive technologies' impact on autonomy, quality of life for both people with dementia and caregivers, sense of competence	Usefulness/user-friendliness, perceived autonomy (measured by the Mastery scale and WHOQOL), QoL (measured by QOL-AD and self-report for caregivers), caregiver competence (measured by SSCQ	Rosetta system
Jekel et al. Germany, (Jekel et al., 2016)	2016	Case-control study	21	1 day	MCI	IADL tasks, feasibility questionnaire	Assistive smart home technology
Lazarou et al. Greece (Lazarou et al., 2016)	2016	Case series	4	16 weeks	MCI/Dementia/Mild Depression	MMSE, MoCA, RBMT-delayed recall, NPI, Functional Rating Scale for Symptoms of Dementia, GDS, HDRS, Functional Cognitive Assessment Scale, Perceived Stress Scale, Beck Anxiety Scale, Trail B., Beck Depression Inventory, IADL, Rey-OCFT, Test of Everyday Attention., Map Search, Visual Elevator, Telephone Search	Smart home monitoring
Martin et al. Ireland (Martin et al., 2013)	2013	Cross-sectional	8	Varied, one patient stayed on 33 months through the lifespan of the project	Dementia	Self-report questionnaires	NOCTURNAL monitoring station
Meiland et al. The Netherlands (Meiland et al., 2014)	2014	Case series	50	15 months	Dementia	CANE, GDS, user feedback questionnaire	Monitoring and assistive ICT technologies
Nijhof et al., The Netherlands, (Nijhof et al., 2013)	2013	mixed methods (qualitative, cost analysis)	14	9 month	dementia; well-being	Feasibility, cost-saving, reduction of caregiver burden, increased independence and safety	AD life system
Olsson et al. Sweden, (Olsson et al., 2018)	2018	qualitative study (interviews about use of a technology)	8	Interview follow-up after 12 week intervention study	memory impairment due to stroke		Sensor and feedback technology
Sacco et al. France (Sacco et al., 2012),	2012	Cohort Study (prospective observational Study)	64	1 day	AD and MCI	DAS	Smart home

(Continued)

TABLE 4 | Continued

Author Country	Year	Study design	N	Study length	Domains studied	Outcome measures	Type of technology
Stucki et al. Switzerland (Stucki et al., 2014)	2014	Feasibility	11	20 days	Focus group healthy, explorative group AD	ADL	Monitoring system

AD, Alzheimer's Disease; ADL, Activities of Daily Living; AT, Assistive technology; CANE, Camberwill Assessment of Needs for the Elderly; DAS, Daily Activity Scenario; GDS, Geriatric Depression Scale; HDRS, Hamilton Depression Rating Scale; IADL, Instrumental Activities of Daily Living; MCI, Mild Cognitive Impairment; MMSE, Mini-Mental-State Examination; MoCA, Montreal Cognitive Assessment; NPI, Neuropsychiatric Inventory; RBMT, Rivermead Behavioral Memory Test; SSCO, Short Sense of Competence questionnaire; WHOQOL, World Health Organization Quality of Life assessment instrument; QoL, Quality of Life; QoL-AD, Quality of Life in Alzheimer's Disease; Wii, Wii Game Console.

TABLE 5 | Studies utilizing other technologies.

Author Country	Year	Study design	N	Study length	Domains studied	Outcome measures	Type of technology
Khosla et al. Australia, (Khosla et al., 2017)	2016	Longitudinal	115	3 years	Social engagement in dementia	Emotional engagement, Visual engagement, Behavioral engagement, Verbal engagement, Robot acceptability questionnaire, Anxiety questionnaire	Social human robot named "Matilda"
Vahia et al. USA, (Vahia et al., 2017)	2016	Feasibility	36	Duration of hospitalization	Agitation in dementia	Acceptability, staff report of agitation severity	iPads with 70 installed applications
Whelan et al. Australia (Whelan et al., 2018)	2017	Cross-sectional	34	10-min conversations	Communication difficulties between people with dementia and caregivers (e.g., topic shifts, interference, non-specificity, etc.)	Validity of Discursis software in detecting different types of "trouble-indicating behaviors" when checked against human coding	Discursis software (automated text-analytic tool which quantifies communication behavior

of the terminology used in this field. An overview of terminology and content are presented in **Table 6**.

DISCUSSION

The goal for this review was to identify and summarize the extent to which literature on technologies (specifically sensors) have been used in the assessment and management of behavioral and psychological symptoms of dementia. As these technologies become widely available, this role is likely to expand (Collier et al., 2018). We identified several ways in which these technologies are being studied. This body of literature will play a crucial role in helping researchers, clinicians and municipalities, and industry partners to develop precision approaches to dementia care. We did note, however, that even though we in our original search aimed at clinical intervention studies with control groups, the majority of the studies found are preliminary with relatively small sample sizes and small durations. Some studies with much larger sample

TABLE 6 | Terminology and content of different devices.

Terms	Devices	Tasks
Noninvasive body sensor network technology	Wearables on wrist, waist, and ankle e.g. accelerometer	Detect skin constitution; skin temperature; activities; environmental light and temperature
3D Hybrid motion sensors of body postures	Uni- and multi-axial accelerometers	Body posture
Unobtrusive sensing technologies with signal processing of real-world data (or monitoring system (TIHM) using Internet of Things, IoT)	Passive, wireless infrared motion sensors, analyzed by machine learning algorithms	Tracks entrances/exits and walking speeds in the home Track motion; pressure; central energy consumption
Integrated Circuit tag monitoring system	Antennas set up on the ceiling and related to a software platform	Register signals when patients moved under them
Passive, web-based, non-intrusive, proxy-free, assistive technology (AT)	Wii (Nintendo); iPads; iPhones; computers; video cameras; medication management, and alarms	Support of mobility and leisure; cognitive games; social robots; reminders or prompters; social applications, detection/ classification of ADL/IADL deficits
Sensor and feedback technology	Individually pre-recorded voice reminder	Memory support
Information and communication technology (ICT)	Imaging and video processing to improve assessments	Detect functional impairment and be more pragmatic, ecological and objective to improve prediction of future dementia
Tablet devices as novel non-pharmacologic tools	iPads	70 installed applications support challenging patient behavior
Discourse analysis software	Automated text-analytic tool	Quantify communication behavior by discriminating between diverse types of trouble and repair signalling behavior

sizes were not intervention studies; rather they represented large surveys of participants around technology use. This dearth in intervention studies suggests that the grounds for innovation, validation, and clinical transference of technology in the management of behavioral symptoms are fertile.

Though we classified technologies into three broad categories, we identified several common underlying themes. Firstly, almost half of studies across the three categories represent ways in which temporarily dense data on motion can be processed and aggregated as proxy for behavior. Findings from these studies indicate high validity of using motion data to detect and track behavioral symptoms such as sleep disturbances, agitation, and wandering (Rowe et al., 2009; Bankole et al., 2012; Sacco et al., 2012; Yamakawa et al., 2012; Aloulou et al., 2013; Galambos et al., 2013; Stucki et al., 2014; Fleiner et al., 2016; Hattink et al., 2016; Jekel et al., 2016; Lazarou et al., 2016; Merilahti et al., 2016; Alvarez et al., 2018; Enshaeifar et al., 2018). Continuous motion monitoring of people with dementia using sensor technology provides informal caregivers and health care providers with the ability to more immediately and accurately diagnose and manage behavioral disturbances and can help to delay admission to long-term care or inpatient facilities. In a prodromal population, data from 8 of the studies suggest that motion data can also be useful in early detection of mild cognitive impairment and/or mild Alzheimer`s disease (Sacco et al., 2012; Hsu et al., 2014; Akl et al., 2015; Dodge et al., 2015; Gochoo et al., 2018; Zhou et al., 2018). While the majority of identified studies focused on the assessment of behaviors, we also identified 8 studies that developed intervention approaches based on sensor data or other feedback (Rowe et al., 2009; Aloulou et al., 2013; Martin et al., 2013; Hattink et al., 2016; Vahia et al., 2017; Khosla et al., 2017; Melander et al., 2018).

In addition, out of 34 studies, we found that 16 studies represented proof-of-concept, acceptability, and/or feasibility testing for technologies that are new and have not been used in the dementia population previously. These studies demonstrated some usability issues for smart home and assistive systems, e.g., technological malfunctions and general user-unfriendliness; however, the technology used was predominantly non-intrusive and well-accepted (Hattink et al., 2016; Olsson et al., 2018).

In terms of data privacy and security, we noted that the majority of our identified articles conclude their discussion by encouraging stakeholders to respect users' privacy and autonomy. Several ask for legal frameworks and regulations to monitor the rapid development of this promising area (Yokokawa, 2012; Yang and Kels, 2017; Khan et al., 2018; Teipel et al., 2018). While we did not specifically identify clinical studies related to ethics, data privacy and security in our review, we present a synopsis of this topic, since the eventual acceptability of new technologies in dementia will be contingent on the development of transparency and trust around digital tools. This is highlighted in several opinion papers and review articles, which discuss ethical considerations in sensing technology for people with dementia or intellectual and developmental disabilities (**Table 7**).

Launched in May 2018, the General Data Protection Regulation (GDPR) is the novel European Union-wide law on data protection — a significant step towards more responsible protection of individuals (Crutzen et al., 2019). While it is recognized that participation in research is based on affirmative, unambiguous, voluntary, informed, and specific consent (Mendelson, 2018), people with advanced dementia or intellectual and developmental disabilities are not able to give informed consent or understand the consequences of data acquisition (Friedman and Rizzolo, 2017; Chalghoumi et al., 2019; Timmers et al., 2019). Article 6 of the GDPR addresses this issue by including provisions that protecting persons with dementia and their relatives from being coerced into providing consent without awareness of how their data will be used (Cool, 2019; Crutzen et al., 2019). Despite this regulation, local legislation differs between European countries (de Lange et al., 2019). In Norway, for, e.g., a family member or legal advocate may provide or refuse consent based on their determination around whether the person with dementia would agree or decline to participate in a given study (Husebo et al., 2019). In Germany, the inclusion of people with dementia is limited for only those who may directly benefit from research results. To further strengthen privacy protections, Article 35 of the GDPR requires the Data Protection Impact Assessment (DPIA) (**Figure 2**) (Donnelly and McDonagh, 2019), which mandates that only the most relevant personal data is collected (data minimization), and limits data access to those who are authorized or given permission by the individual (Yang and Kels, 2017). Overall, in this review, we did not specifically include search keywords relating to ethics in sensor technology but we recognized an engaged discussion in a considerable number of position papers and reviews around ethical considerations and especially, the need for data protection, proper transfer and storage (Holm and Ploug, 2013; Ploug and Holm, 2013).

Agencies that provide funding for research increasingly require patient and public involvement (PPI) in design, implementation, and dissemination of health research (**Figure 2**) (Melander et al., 2017; Melander et al., 2018). The goal of PPI is to ensure user-centered design so that persons who may benefit from it have an opportunity, especially in the early stages of their disease (Landau and Werner, 2012; Bantry-White, 2018) to understand the purpose of the technology (e.g. GPS) and to express values, wishes, and concerns to formal and informal caregivers, We noted that this principle was incorporated into at least three studies that we reviewed (Landau and Werner, 2012; Lariviere, 2017; Mangini and Wick, 2017; Bantry-White, 2018). This approach is also likely to optimize technology engagement in dementia (Nijhof et al., 2013; Mehrabian et al., 2014). A related principle, Responsible Research and Innovation (RRI) (**Figure 2**), is defined as a transparent, interactive process by which societal actors and innovators become mutually responsive to each other (von Schomberg, 2013). They are encouraged to assume a critical perspective when evaluating the innovation and marketability of products (Holthe et al., 2018; Lehoux and Grimard, 2018). This

TABLE 7 | Review and opinion articles on ethical considerations in sensing technology for people with dementia or intellectual and developmental disabilities.

Author	Year	Type of paper	Ethical considerations
Bantry-White et al. Ireland (Bantry-White E, 2018)	2018	Scope review on ethics of electronic monitoring in PWD	a) Autonomy/liberty: Who decides the person`s interests? Identification of past and present wishes for ethical decision making; liberty by electronic monitoring; b) Privacy: Monitoring may be less intrusive than constant caregiver presence; c) Dignity: May technology be a stigma in context to a social construct? d) Monitoring formal and informal caregiving may restrict harmful behaviour. e) Beneficence/non-maleficence: Monitoring may reduce costs, but increasing isolation.
Chalghoumi et al. Canada (Chalghoumi H, et al., 2019)	2019	Focus group interviews with 6 people with I/DD	People show awareness of privacy concerns but not due to the use of technology. Privacy breaches are a major risk in I/DD: they do not understand the use of personal information and are vulnerable to biases in data collection.
Friedman et al. USA (Friedman and Rizzolo, 2017)	2017	National I/DD survey on electric video monitoring	Video monitoring are effective methods to expand community care while being cost effective. However, it should also aim at improving care, not only serve as a substitute for personal care and interaction.
Kang et al. USA (Kang et al., 2010)	2010	Opinion paper on in situ monitoring of older adults	Monitoring can replace caregiver-patient interaction and social contact but also the opposite in providing increased opportunities in contact with family members because of larger awareness of patients` needs.
Landau et al. Israel (Landau et al., 2010)	2011	Mixed method recommendations for policy makers on ethics on GPS use for PWD	a) Maintain balance between the needs of PWD for protection and safety and their need for autonomy and privacy; b) Decision for GPS use together with PWD (informed consent) and family; c) Advance directives or earlier wishes in case of lack of informed consent; d) Involvement of formal caregivers in decision making.
Mehrabian et al. Bulgaria (Mehrabian et al., 2014)	2014	Semi-structured interviews with PWD & caregivers	Participants are positive to home telecare, cognitive stimulation program and devices' care of emergencies with potential to improve QoL. Ethical concerns (e.g. way of provision, installation, monitoring) are reported with needs for proper implementation and informed consent.
Robinson L et al. UK (Robinson et al., 2013)	2013	Scope review on practice & future direction	Summarize current use of assistive technology with focus on effectiveness, and potential benefits, and discuss the ethical issues associated with the use in elderly people including future directions.
Sorell et al., UK (Sorell and Draper, 2012)	2012	Position paper on telecare, surveillance and welfare state	Telecare may not be regarded as objectionable extension of a "surveillance state (Orwellian)," but a danger of deepening the isolation of those who use it. Telecare aims to reduce costs of public social and health care; correlative problem of isolation must be addressed alongside promoting independence.
Teipel et al. Germany (Teipel et al., 2018)	2018	Position paper on ICT devices and algorithms to monitor behavior in PWD	This paper discusses clinical, technological, ethical, regulatory, user-centred requirements for collecting continuously RWE data in RCTs. Data safety, quality, privacy and regulations need to be addressed by sensor technologies, which will provide access to user relevant outcomes and broader cohorts of participants than currently sampled in RCTs.
van Hoof et al. NL (van Hoof et al., 2018)	2018	Explorative study on RTLS in NHs	Interviews with formal caregivers; NH patients and family members, and researchers. Concerns differed between groups and addressed security, privacy of patients and carers, responsibility.
Wigg et al. USA (Wigg, 2010)	2010	Position paper on surveillance of pacing in PWD	Surveillance technologies such as locked doors dehumanise and frighten individuals, whereas motion detectors may increase QoL, health benefits and safe medication with less riskiness.
Yang et al. USA (Yang and Kels, 2017)	2017	Scope review on ethics of electronic monitoring for PWD	To protect and empower PWD, the decision-making capacity of the person has to be evaluated and a multidisciplinary process (including PWD, relatives and healthcare professionals) have to be conducted before electronic monitoring (GPS, radiofrequency, cellular triangulation) is used.

ICT, Information and Communication Technology; I/DD, Intellectual and developmental disabilities; GPS, Global Positioning System; NH, Nursing Home; PWD, People with Dementia; QoL, Quality of Life; RCT, Randomized Controlled Trial; RTLS, Real Time Location Systems; RWE, Real World Evidence.

approach may serve to promote awareness of technologies and related issues across both groups of stakeholders (van Haeften-van Dijk et al., 2015; Wu et al., 2017; Rostill et al., 2018).

LIMITATIONS

Our findings and recommendations must be interpreted in the context of some limitations. During the process, we recognized that the MESH terms and phrases synonymous with "dementia", "sensor", "patient", "monitoring", and "behavior", and " therapy" probably did not cover the whole range of interesting topics. For instance, items such as ethics, activities of daily living (ADL), and communication, may increase the understanding for and connection to the clinical aspects of this quickly developing area. Because of the vast heterogeneity of the literature, including terminology and definitions of sensing technology, a meta-analysis that may facilitate aggregated recommendations was not feasible. We also noted that the majority of the studies were open-label early-stage studies. Replication of these findings

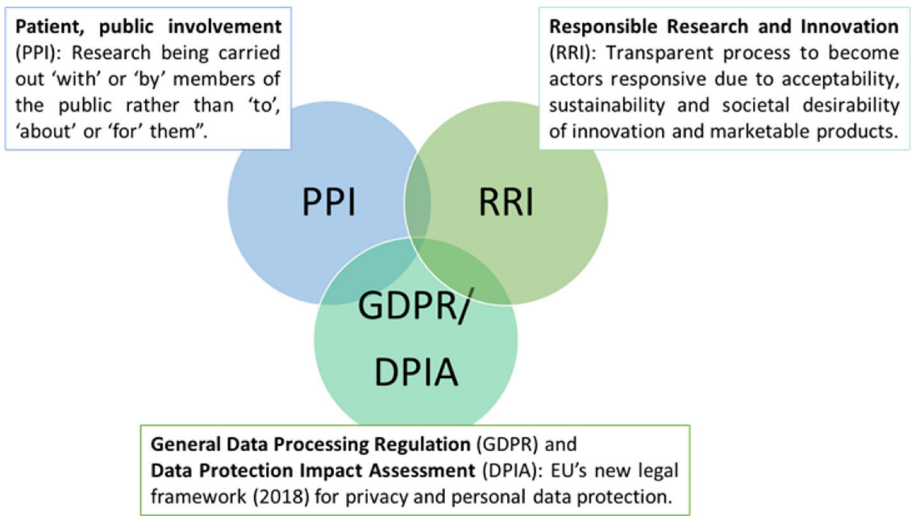

FIGURE 2 | Framework for sustainable ethic in healthcare technology.

in larger trials will be required before these findings can become the standard of care. Our search algorithm also has potential limitations. We restricted our search to the past decade, since we anticipate that future sensor-based care models will be built on contemporary technology. We determined that tools that are more than a decade old are unlikely to have relevance in the future.

CONCLUSION

Overall, our systematic review demonstrates that sensor technologies have a broad range of potential applications in dementia care, ranging from early detection of cognitive impairment to aid in the management of behavioral and psychological symptoms in late stage dementia. Targeted clinical application of specific technologies is poised to revolutionize precision care in dementia as these technologies may be used by patients themselves, caregivers, or even applied at a systems level (e.g., nursing homes) to provide more safe and effective care. As sensor technology matures in its ability to guide care in BPSD, it may generate novel ways to capture early symptomatology (e.g., social isolation), improve specificity for cognitive testing in-situ and facilitate cost effective research approaches. A small but rapidly growing body of evidence around sensors in dementia care is paving the early way for the field, bringing into focus both the potential and pitfalls of this approach. Next step in this field may be to investigate the validity of use not only for care purposes, but also for prognostics as well as acceptability, feasibility, and responsiveness in clinical trials. The eventual success of this field will depend on inter-disciplinary models of research, development by industry partners, and sustainable ethic innovation in healthcare technology and smart housing.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

AUTHOR CONTRIBUTIONS

BH and IV developed the study idea, designed the study protocol for the systematic search and BH applied for funding. BH screened all the manuscripts on title and abstract level to select relevant studies. All the co-authors assessed potentially relevant studies on full-text manuscripts for eligibility using inclusion and exclusion criteria. HH, LB, PO, and AR drafted the first version of the result evaluation with supervision from IV and BH. Contribution to the subsequent drafts were provided by BH, HH, LB, PO, AR, and IV. All authors approved the final version of the manuscript.

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CORRECTION
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Corrigendum: Sensing Technology to Monitor Behavioral and Psychological Symptoms and to Assess Treatment Response in People With Dementia. A Systematic Review

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A Corrigendum on

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In the original article, there was an error in the title. It was published as "Sensing Technology to Facilitate Behavioral and Psychological Symptoms and to Monitor Treatment Response in People With Dementia. A Systematic Review."

The correct title should be "Sensing Technology to Monitor Behavioral and Psychological Symptoms and to Assess Treatment Response in People With Dementia. A Systematic Review."

The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

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SYSTEMATIC REVIEW
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Depressive Symptoms in the Elderly—An Early Symptom of Dementia? A Systematic Review

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Background: Depression and dementia are common incapacitating diseases in old age. The exact nature of the relationship between these conditions remains unclear, and multiple explanations have been suggested: depressive symptoms may be a risk factor for, a prodromal symptom of, or a coincidental finding in dementia. They may even be unrelated or only connected through common risk factors. Multiple studies so far have provided conflicting results.

Objectives: To determine whether a systematic literature review can clarify the nature of the relation between depressive symptoms and dementia.

Methods: Using the Patient/Problem/Population, Intervention, Comparator, Outcome or PICO paradigm, a known framework for framing healthcare and evidence questions, we formulated the question "whether depressive symptoms in cognitively intact older adults are associated with a diagnosis of dementia later in life." We performed a systematic literature review of MEDLINE and PsycINFO in November 2018, looking for prospective cohort studies examining the aforementioned question.

Results: We critically analyzed and listed 31 relevant papers out of 1,656 and grouped them according to the main hypothesis they support: depressive symptoms as a risk factor, not a risk factor, a prodromal symptom, both, or some specific other hypothesis. All but three studies used clinical diagnostic criteria for dementia alone (i.e., no biomarkers or autopsy confirmation). Several studies contain solid arguments for the hypotheses they support, yet they do not formally contradict other findings or suggested explanations and are heterogeneous.

Conclusions: The exact nature of the relationship between depressive symptoms and dementia in the elderly remains inconclusive, with multiple studies supporting both the risk factor and prodromal hypotheses. Some provide arguments for common risk factors. It seems unlikely that there is no connection at all. We conclude that at least in a significant part of the patients, depressive symptoms and dementia are related. This may be due to common risk factors and/or depressive symptoms being a prodromal symptom of dementia

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and/or depression being a risk factor for dementia. These causal associations possibly overlap in some patients. Further research is warranted to develop predictive biomarkers and to develop interventions that may attenuate the risk of "conversion" from depressive symptoms to dementia in the elderly.

Keywords: depression, dementia, cognitive decline, Alzheimer, aging, biomarkers

INTRODUCTION

Rationale and Objectives

Neuropsychiatric diseases are a leading cause of disability worldwide, with numbers expected to increase dramatically in the coming decades, mainly due to aging populations (Alzheimer's Disease International, 2013). Possibly the most incapacitating of these illnesses is dementia—causing substantial physical and psychological disability, suffering, dependency, and economic costs for patients, caregivers, and society alike (Livingston et al., 2017). Several potentially disease-modifying drug trials may have failed because a disease like Alzheimer's (AD) is usually diagnosed clinically after underlying pathological processes have already been going on for years, or even decades (Jack et al., 2010; Jansen et al., 2015; Petersen, 2018). This, in turn, has led to a major interest in possible prodromal or (modifiable) risk factors for the development of dementia (Baumgart et al., 2015). Even though most forms of dementia are currently incurable, it has been hypothesized that a 10% reduction of known risk factors could result in a global decrease of more than one million future cases of dementia (Barnes and Yaffe, 2011).

Depressive symptoms have been linked to dementia. Indeed, clinicians have long acknowledged that depression in the elderly can mimic dementia in a situation known as depressive *pseudodementia* (Alexoupoulos et al., 1993). However, depressive symptoms may also be the first clinical manifestation of incipient dementia. Indeed, behavioral and psychological symptoms, such as depression, are highly prevalent in patients with dementia, leading to overlap in clinical presentations of cognitive impairment in the elderly (Savva et al., 2009). Others have suggested that depression and dementia share common risk factors and thereby frequently occur together without being causally linked themselves (Enache et al., 2011), or that psychological symptoms may occur (merely) as a reaction to incipient decline in patients who are aware of their cognitive disturbances. Another explication uses the "cognitive reserve" paradigm. This idea posits that intercurrent (physical or mental) illness in an already diseased and/or aged brain will lower the threshold for experiencing cognitive problems and therefore cause symptoms of the same pathophysiological process to manifest earlier (Stern et al., 1994). Multiple studies designed to assess risk and causality have provided conflicting results (Bennet and Thomas, 2014).

Depression in the elderly is more often associated with cognitive symptoms as compared to depressive disorders of earlier adulthood (Lam et al., 2014). On the other hand, depression itself may actually cause cognitive decline—conceivably related to certain pathophysiological processes of, for example, frontal and hippocampal atrophy possibly through glutamatergic or steroid-related toxicity (Peavy et al., 2007; Byers and Yaffe, 2011; Taylor et al., 2013). Still other studies have pointed out that even early-life depressive episodes increase the risk of later dementia (Dotson et al., 2010; Simões do Couto et al., 2016). The aforementioned possibilities are, of course, not mutually exclusive and quite possibly overlap in everyday clinical situations.

It is clear that the association between late-life depression and dementia is complex. To shed further light upon this issue, we conducted this systematic literature review. It focuses on the relationship between depressive symptoms that develop late in life and the subsequent development of dementia in general.

We acknowledge that depression (as in major depressive disorder) and depressive symptoms are not interchangeable terms. Identifying significant depressive symptoms, rather than limiting studies to those restricting themselves to clinician-ascertained major depressive episode alone, however, will broaden the scope of this review and include more large-scale epidemiological studies. Clinicians, also, will recognize the importance of depressive (and other neuropsychiatric) symptoms that are not severe enough to lead to a formal syndromal diagnosis. A similar rationale was used to examine dementia in a broad sense. Although AD is the most common and best studied form of dementia, vascular and mixed etiologies will not be excluded from our review as they contribute significantly to the aforementioned epidemiological and clinical problems (Alzheimer's Disease International, 2013; Livingston et al., 2017). Assessing the studies obtained will help identify the gaps in our knowledge that may guide specific future research.

METHODS

Research Question

To define our research question, we used the Patient/Problem/Population, Intervention, Comparator, Outcome or PICO paradigm—a well-acknowledged framework for framing healthcare and evidence questions, as well as a useful tool to develop concrete questions in complicated and multifactorial issues such as the one we set out to examine. Through a systematic literature review, we studied "whether depressive symptoms (I) in cognitively intact older adults (P) are associated with a diagnosis of dementia later in life (O), diagnosed using validated biomarkers or criteria, as compared to nondepressed matched controls (C)."

Design and Protocol

Using PRISMA as guidance (Moher et al., 2009), we included human longitudinal, prospective cohort studies reporting on a possible link between depression and depressive symptoms in the elderly (older than 65 years of age) and later development of dementia (not merely cognitive decline in a broader sense) in statistical, and not merely narrative, terms. We did not include case series or other designs to minimize bias, as prospective studies are acknowledged to be less vulnerable to certain forms of bias when ascertaining hazard and risk relationships, especially over longer periods of time. Comparator groups were defined as matched elderly subjects without depressive symptoms. We included memory clinic as well as general community-based population studies of the aforementioned types. No specific length of follow-up was required. There were no restrictions on diagnostic criteria nor rating scales used for detection of depression or dementia, as long as they were clearly defined and respected. We excluded studies ascertaining similar problems in highly specific pathological situations, such as Huntington's disease, Down syndrome, or prion diseases. No language or publication date restrictions were applied.

Medline and PsycINFO databases were searched in November 2018 using combinations of the following terms we identified through the PICO paradigm: depression (including variant wordings such as "depressive symptoms" in MeSH), dementia, Alzheimer, elderly, incidence, risk, hazard, cohort. We subsequently added search terms containing clinical diagnostic biomarkers such as magnetic resonance imaging (MRI), positron emission tomography (PET), cerebrospinal fluid (CSF), biomarkers, amyloid, tau, and neuropsychological test/examination (see **Supplementary Material Table** for these keywords and combinations used).

We collected and deduplicated references using EndNote software (*Clarivate Analytics*). Titles and abstracts were screened by carefully excluding publications irrelevant to our research question (mainly *in vitro* studies, cross-sectional designs, papers about highly specific other illnesses as mentioned above, case studies…—i.e., publications clearly incompatible with our inclusion criteria and research question). Studies with possibly relevant contents were fully read and considered for inclusion using the aforementioned inclusion and exclusion criteria and preparing to resolve possible conflicts on study inclusion or exclusion (which did not occur) among the three authors by consensus. We further screened the references of these articles for missed relevant publications. All were evaluated for possible objective errors. No studies found through PsycINFO were unlisted in Medline searches. As such, all (n = …) refer to references obtained from Medline. We used the Newcastle–Ottawa Scale (NOS) for cohort studies to assess risk of bias (obtained from ohri.ca/programs/clinical_epidemiology/oxford.asp) in prospective cohort studies.

RESULTS

Results are listed in **Figure 1**. Out of 1,656 search results, 1,601 titles and abstracts were excluded as clearly irrelevant. Fifty-five full articles were read and evaluated, of which 27 were excluded according to our predefined inclusion criteria. In our final assessment, 31 studies were included. We briefly mention seven additional publications that looked at cognitive decline *sensu lato* rather than dementia and five studies that included many patients deemed too young as per our cutoff of 65 years. Three papers by Wilson et al. (Wilson et al., 2003; Wilson et al., 2014; Wilson et al., 2016) described similar cohorts and neuropathological data and were merged into one additional reference. One additional study was added through follow-up for publication of an earlier abstract of interest the authors read at a conference (Ezzati et al., 2019). Two other papers were included from paper references. No data were extracted as we considered the obtained papers to be too heterogeneous to perform meta-analysis.

We grouped these references in five categories for review purposes—noting that their main conclusions are not mutually exclusive and many authors, indeed, suggest multiple explanations for their findings. Critical assessment of the papers' numerical results as well as their authors' main interpretation thereof in the respective discussion sections was used to classify the references in our different categories, as discussed further in this section. Additional substantiation is provided in the **Supplementary Material**.

A. Studies suggesting that depression is a risk factor for dementia A1 (n = 7) and studies suggesting that depression is not a risk factor for dementia or that they are linked without reaching statistical significance A2 (n = 8)
B. Studies that suggest that depression is an early symptom or prodrome of dementia (n = 10)
C. Studies that suggest that depression is both an early symptom and a risk factor (n = 1)
D. Studies demonstrating an association between depression and dementia, without clear conclusions concerning potential causality [n = 3 (one reference for three related papers)]

Results are listed by their aforementioned category in **Tables 1**–**4** (listing A1, A2, B, C&D).

Bias assessment using the NOS did not show any systematic difference in biases between categories, with all studies scoring relatively high on this design quality scale. We therefore conclude this had little influence on our findings. Results and additional comments are available in the **Supplementary Material Table**.

These studies propose that depressive symptoms confer an additional risk of a future development of dementia in cognitively healthy elderly individuals. This view has to be contrasted with the hypothesis that psychological symptoms simply accentuate or temporarily cause cognitive deficits, thereby accounting for that proportion of mild cognitive impairment (MCI) patients who do not "convert" to dementia but rather recover a normal cognitive status (Langa and Levine, 2014). Some studies (Irie et al., 2008; Ezzati et al., 2019) indeed corrected for baseline emotional and cognitive scores to address this possibility. We did not include studies evaluating the link

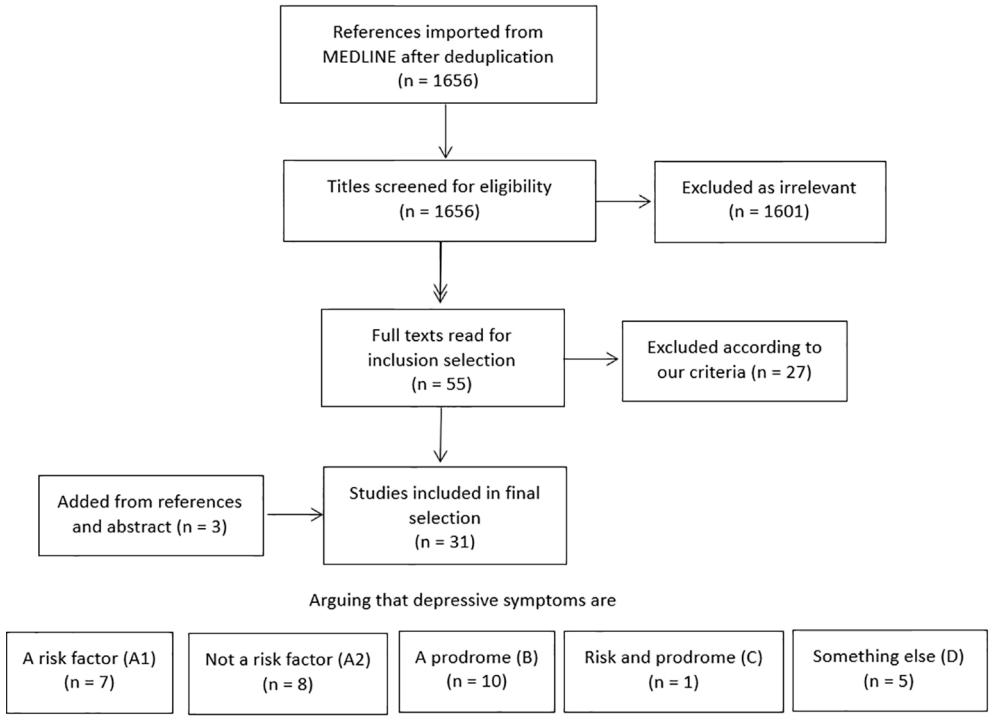

FIGURE 1 | Selection of studies included in this systematic review.

between early-life (onset before 65 years of age) depression and later dementia, even though this could be of interest to our research question; indeed, other review efforts appear to suggest this link (Ownby et al., 2006). Interestingly, several studies, including the largest one (Burke et al., 2016) in this category, suggest that dementia risk in people with depressive symptoms increases further when corrected for classically biasing factors such as age, education, or socioeconomic status, thus providing an argument against the position that depressive symptoms and dementia are linked solely through common risk factors and justifying classification in category A1. This relation becomes even stronger when associated with certain *APOE* genotypes, a well-known genetic risk factor for AD—a finding also reported by smaller samples (Irie et al., 2008; Kim et al., 2010).

Considering some of the proposed pathophysiological mechanisms (chronic inflammation, glucocorticoid toxicity, neuronal energetic dysregulation, etc.), a true biological risk relationship would imply that more severe and/or long-standing depression increases one's chance of cognitive deterioration due to a neurodegenerative or cerebrovascular brain disease. Although some reports (Wilson et al., 2003; Gatz et al., 2005; Saczynski et al., 2010; Langa and Levine, 2014) have shown such a link, most studies use depressive symptoms as a binary value (depressed–not depressed) and/or contain too many individuals with mild depressive symptoms to really establish a "dose–response" relationship of this kind. Furthermore, most studies did not evaluate these proposed mechanisms (e.g., through blood or CSF analysis, functional or advanced imaging). It is etiologically difficult to disentangle depression being a pure risk factor or an actual prodromal symptom of dementia, especially during the 2- or 3-year follow-up of most studies. However, some studies followed patients for up to 17 years and reported similar findings (Saczynski et al., 2010). One strong argument for the true risk hypothesis would be clinical trials indicating that successful treatment of major depressive episodes lowers the incidence of (solidly diagnosed) degenerative dementia. This is a controversial question, with multiple studies of different (mainly pharmacological) treatments providing conflicting results (Lee et al., 2016; Jacob et al., 2017; Almeida et al., 2017; Chu et al., 2018; Brauer et al., 2019). We further note that the successful treatment of clinical depression is a challenge in itself, as only one in three patients respond to first-line treatments and as many remain treatment resistant after multiple treatments, a situation that may be even more frequent in the elderly (Rush et al., 2006). Interestingly, some authors have even suggested that anti-amyloid therapies may have a role to play in treating late-life depressive syndromes (Mahgoub and Alexopoulos, 2016). Nevertheless, the studies we examined here fail to provide us with any additional evidence of this sort.

These studies did not find an increased risk of dementia in case of late-life depressive symptoms, as opposed to the first group of studies. The authors' point is generally based upon an absence of significant findings or results that lose statistical significance after correction for certain biasing factors. Some, however, do establish a risk relationship in specific situations,

TABLE 1 | (Category A1): Studies suggesting that depression is a significant risk factor for dementia.

Study	Cohort	N	Mean age (SD)	% Female	FU	Depression assessment	Diagnostic criteria of cognitive decline	Incidence of dementia	Risk?	Risk adjustments
(Brodaty et al., 2012)	Community of English speaking Australians	799 (480 NC, 319 MCI). 169 drop-outs	78 (4.7)	67.8%	2 years	NPI	Petersen MCI, DSM-IV Dementia	11 from MCI, 3 from NCI, too small for subtyping	OR 3.67 [1.1–12.5]	No difference (age, sex, education, NPI score)
(Burke et al., 2016)	Prospective UDS NACC: 80% White, 13% African, 6% Hispanic	11453 start, 8762 more than 1 visit	71 (10.89)	65.2%	Mean 3 years (1-10)	1) Recent 2) Earlier 3) Current episode (DSM-IV)	AD NINCDS/ ADRDA	330 AD. Subgroups not clearly reported	1) HR 2.35 [1.88–2.94] 2) HR 1.35 [1.06–1.73] 3) HR 2.82 [2.21–3.59]	Stronger after correction 1) HR 5.75 [3.28–10.07] 2) 3.20 [1.78–5.73] 3) HR 5.50 [3.09–9.64]
(Devanand et al., 1996)	Community in Manhattan 30% White, 41% Latino 27% African	852 NC at baseline, 478 one or more FU sessions	73 (7.1)	69.4%	1-5, mean 2.54 years (1.12 SD)	HAM-D >10 and 'mood' item	DSM-III-R	61 cases, (21% depressed vs 9% non), mostly AD (2 other, 1 PSP)	RR 2.94 [1.7-4.9]	Still significant (RR 2.05) after age, education, Moderate CI
(Ezzati et al., 2019)	Einstein Aging study: Bronx community, 65% white	1219	78 (5.4) 70+	62%	Yearly visits for 4.5 years (3.5 SD) up to 17 years	GDS-15	DSM-IV	132 cases, 111 AD	Per point HR 1.11 [1.03-1.19], not significant before 3 years	Age, sex, race, education, comorbidity and baseline cognition (BIMC)
(Irie et al., 2008)	USA Japanese in Hawaii	1932	76 (3.6)	0%	6.1 years mean	CES-D > 9	DSM-III-R, NINCDS/ ADRDA	6.3% (e4), 9.3% (dep) 13.7% (both) 4.2% (neither)	Dementia HR 2.2 [1.3–3.7] AD 2.9 [1.4–5.9]	Classic risk factors and self-reported memory
(Saczynski et al., 2010)	Framingham study: prospective community cohort	949	79 (5)	63.6%	Mean 8, up to 17 years	CES-D > 16	DSM-IV, CDR >1, NINCDS/ ADRDA	164 cases (136 AD)	Dementia HR 1.72 [1.04–2.84] AD 1.76 [1.03–3.01]	Age, education, homocysteine, APOE, MCI
(Spira et al., 2012)	Oldest old white (SOF WISE)	302	87 (2) > 85	100%	5 years after baseline	GDS-15 > 6	Petersen MCI, DSM-IV-TR dementia	84 cases 65% of GDS ≥6 & 37% < 6	MOR 3.15, [1.03-9.65]	Risk factors, alcohol, benzodiazepines

Values in square brackets are 95% confidence intervals. p-values are under 0.05 unless otherwise specified. UDS-NACC, Uniform Data Set - National Alzheimer's Coordinating Centre; NC, Normal cognition; MCI, Mild Cognitive Impairment; SD, Standard Deviation; GDS, Geriatric Depression Scale; HAM-D, Hamilton Depression Rating Scale; NPI, Neuropsychiatric Inventory; DSM, Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association); FU, follow-up, NINCDS; National Institute of Neurological and Communication Disorders and Stroke; ADRDA, Alzheimer's Disease and Related Disorders Association criteria; CES-D, Centre for Epidemiological Studies Depression scale; BIMC, Blessed Information Memory Concentration; CDR, Clinical Dementia Rating Scale; SOF-WISE, Study of Osteoporotic Fractures - Women; Cognitive Impairment Study of Exceptional Aging.

e.g., in combination with sex or *APOE* genotype (Lindsay et al., 2002; Kim et al., 2010). Others report an association with depressive episodes earlier in life as opposed to current symptoms (Pálsson et al., 1999; Geerlings et al., 2008). Several studied rather small populations, and their relatively low numbers of incident dementia cases may in itself account for a negative result (Geerlings et al., 2008; Becker et al., 2009; Blasko et al., 2010; Kim et al., 2010). This may also be the case for wide confidence intervals [e.g., in Geerlings et al. (2008), 0.82–6.69]. Some of these did not find any significant risk factors for dementia, apart from increasing age, which stands in apparent conflict with what is generally accepted in dementia research (Baumgart et al., 2015; Livingston et al., 2017) and quite possibly suggests insufficient power. We note that one study (Kim et al., 2010) reported an increased risk of dementia only for depressive males carrying an *APOE* ϵ4 allele. Lindsay et al. (Lindsay et al., 2002) looked only at syndromal (i.e., clinician-diagnosed) depression, as opposed to most of the other studies that utilized (self-reported) symptom scores. Two studies (41 and 44) report on the same cohort. The population studied in (Geerlings et al., 2008) was analyzed again in (Mirza et al., 2016), which is category B and supports the prodrome hypothesis (**Table 3**). Most population sizes in **Table 2** are smaller than those in other groups. In combination with other factors, as mentioned above, we conclude that several of these studies were probably underpowered to detect a connection and do not formally nor decisively contradict the notion that depressive symptoms and dementia are connected.

Considering that both neuropsychiatric illnesses may manifest themselves epidemiologically as hazard increasing, it can be difficult to distinguish between a causal risk factor and prodromal symptom in the years leading up to a diagnosis of dementia—as discussed above. Nevertheless, the authors in this category found support in their findings for the latter hypothesis. Several arguments in favor of this position are advanced by the authors of these studies. These include an increasing symptom burden over time (Mirza et al., 2016) and no effect of (the length of) episodes occurring earlier in life as opposed to current and

TABLE 2 | (Category A2): Studies not suggesting that depression is a significant risk factor for dementia.

Study	Cohort	N	Mean age (SD)	% Female	FU	Depression assessment	Diagnostic criteria of cognitive decline	Incidence of dementia	Risk?	Adjustments
(Becker et al., 2009)	CHS-CS Pittsburgh community	288	78 (3.65)	63%	7.1 years (1–9)	CES-D >10	3MSE, DSM-IV, NINCDS/ ADRDA	48, all AD	None found	All kinds of risk factors in CHS study
(Blasko et al., 2010)	VITA – 2 Vienna districts	331 never depressed undemented	76 (0.5)	56.5%	0 – 2.5 – 5 years	DSM-IV, sGDS	NINCDS/ ADRDA	33	Serum Ab42, male gender, age were risks	Multivariate logistic regression analyses
(Geerlings et al., 2008)	Rotterdam population Scan Study	486	74 (6.5)	49%	5.9 years (1.5 SD)	Interview-based (early vs. late (60y)) CES-D 16	CAMDEX and standard criteria	33 AD	EARLY history of depression risk factor	MRI volumetrics and WML
(Kim et al., 2010)	Korean community survey	518	72 (5) 65+	54.4%	2.4 years	Korean GDS	Standard criteria	45 (34 AD, 7 VaD, 4 other)	Strong risk of dep + APOE men (cf. Irie)	Vascular risk factors, APOE
(Lindsay et al., 2002)	Prospective Canadian Health & Aging study	4609	Cases 87 Controls 78 (70–100)	58%	5 years after initial visit	DSM-III-R (no symptoms only)!	NINCDS-ADRDA, DSM-III, NINDS-AIDEN	194 AD, 527 MCI and 'other' dementias	Age, education, APOE	Reduction by wine, coffee, NSAIDs, exercise,…
(Mossaheb et al., 2012)	VITA – 2 Vienna districts	437 (296 at 60 months) never depressed	76 (0.5)	55%	60 months	DSM-IV-TR questionnaire, HDRS, sGDS	NINCDS-ADRDA	65 (AD)	OR 5.27 [1.62-17.2] for loss of interest only	Risk factors, biochemical parameters, APOE
(Pálsson et al., 1999)	Gothenburg census of 85 year olds	227 healthy and 62 depressed	85 years old at baseline	Not explicitly stated in subgroups	3 years	DSM-III-R, history and records	Not clearly stated, MMSE	50 cases	Only early onset MDD	CT volumetrics
(Vinkers et al., 2004)	Leiden (NL) 85 year olds	500 (298 4th year)	85 years old at baseline	63%	Yearly for 4 years	GDS-15	MMSE, Stroop, LDCT, 12 Word Recall	Not explicitly stated	Correlation but no risk of decline	Mixed models

3MSE, Modified Mini Mental State Examination; WML, White Matter Lesions; AIDEN, Association Internationale pour la Recherche et l'Enseignement en Neurosciences; MDD, Major Depressive Disorder; LDCT, Letter Digit Coding Test.

recent symptoms (Fuhrer et al., 2003; Li et al., 2011). Others note a clear temporal relationship of both illnesses around diagnosis (Lenoir et al., 2011; Almeida et al., 2017) or a synergistic effect with white matter pathology (Verdelho et al., 2013). Concerning this last element especially, it is posited that in some proportion of elderly patients, depressive symptoms actually represent the organic effect of ongoing pathological processes (cerebrovascular and/or neurodegenerative) on affect-modulating networks in the brain (Thomas et al., 2002).

One must also consider here the possibility that depressive symptoms could be a reaction to patients' awareness of cognitive decline and thereby frequently manifest during prodromal and early stages of dementia. Several authors, however, reported no clear effect of baseline cognition and emotional symptoms to later dementia (Chen et al., 1999; Geerlings et al., 2000; Fuhrer et al., 2003; Irie et al., 2008; Li et al., 2011; Mirza et al., 2016; Ezzati et al., 2019), providing a solid argument against this position. Furthermore, other studies have reported that no clear or ubiquitously negative reaction to dementia in recently diagnosed subjects can be demonstrated (Carpenter et al., 2008). We therefore hypothesize that, even though this may occur in everyday clinical situations (e.g., someone worrying about future cognitive decline, possibly due to contact with the dementing illness of a relative), a negative affective response to noticing one's own decline alone cannot explain the association between depressive symptoms and dementia in all patients. Future and ongoing studies like the ABIDE project (van Maurik et al., 2019) will be of help to shed further light upon this association.

These studies propose multiple explanations or more complex associations between depression and dementia. Ganguli et al. (2006) (studying the same cohort as Chen et al. (1999) in category B, **Table 3**) hypothesized that, while depressive symptoms are indeed cross-sectionally associated with cognitive symptoms, they were unrelated to later cognitive decline, while noting that increasing cognitive symptoms associated with depression likely represent incipient dementia. Kaup et al. (Kaup et al., 2016) described that increasing severity of depressive symptoms on repeated assessments, rather than a one-time scoring, was associated with increased risk of dementia, thereby lending support to both risk factor and prodromal hypotheses. Luppa et al. (2013), through multiple interaction models, show that only major depressive episodes (i.e., depression in the strict sense) seem to increase risk of dementia as opposed to milder depressive symptoms whose effect disappears in multivariate analyses.

Wilson et al. (2003; 2014; 2016) have published three interesting studies. Their 2003 paper showed that, in a group of 130 elderly religious order members, each increase in depressive symptomatology increased the risk of being

TABLE 3 | (Category B): Studies suggesting that depression is a prodromal symptom of dementia.

Study	Cohort	N	Mean age (SD)	% Female	FU	Depression assessment	Criteria for cognitive decline	Incidence	Risk?	Adjustments
(Almeida et al., 2017)	Health in Men (Western Australia)	4922	77 (3.7) 71-89	0%	8.9 mean, up to 14 years	sGDS-15, history, health record	Healthcare records coding	903 cases (18%)	aSHR: Ever 1.3 [1.2-1.7] Past 1.3 [1.0-1.6] Current 1.5 [1.2-2.0]	Antidepressant use, stroke, risk factors. ONLY in the first 5 years
(Chen et al., 1999)	MoVIES cohort USA 97% white	954	65-85	54.6%	8 years with 2 yearly intervals	mCES-D	NINCDS-ADRDA, DSM-III, CERAD	78 (61 AD)	'Reverse' risk	Age, sex, education, self-reported cogn.
(Fuhrer et al., 2003)	Aquitaine France community	3777 (1500 at year 8)	75 (7) 65+	58.3%	8 years (1, 3, 5, 8)	CES-D (men 17 women 23)!	NINCDS-ADRDA, DSM-III-R, Hachinski	280 cases (200 AD)	OR men 3.5 [1.9–6.5] Women [1.2 0.7–2.0]	Hypertension in men 50% additional risk
(Gatz et al., 2005)	Manitoba Canada Community	766	75 (6) 65+	61.7%	5 years	CES-D (> 16 and other values)	Standard Criteria	56 (36 AD)	AD OR 2.75 [1.04–7.24] Dementia 2.37 [1.02–5.54)	Not earlier reported depression, not duration of symptoms
(Geerlings et al., 2000)	Two Netherlands cohorts	1911 + 1894	73 (5) and 70 (8)	62.3% and 52.9%	4 years	GMSS and CES-D respectively	"3 point MMSE drop" and criteria	53 AD AMSTEL	aOR >8y educated 5.3 [1.8-15]	Age, gender, education, psychiatric
(Lenoir et al., 2011)	Three French Cities (3C Study)	7989	74 (5) 65+	61%	2 times 2 years	MDE-MINI (DSM IV), CES-D	NINCDS-ADRDA, DSM-IV, Hachinski, AIREN	180 AD, 24 Vasc Dem, 29 mixed, 43 various	Dementia HR 1.5 [1.2–2.2] Vascular 4.8 [2.2–10.7	Risk factors and age, MRI WML, not earlier episodes
(Li et al., 2011)	Seattle ACT study	3410	75 (6) 65+	60%	7.1 average, Biennially up to 15 years	CES-D-11, history of past episodes	CASI, DSM-IV, NINCDS-ADRDA	658: 386 AD, 89 Vasc, 113 mix, 70 other	All cause aHR 1.61 [1.29- 2.01]	Age, gender, education, baseline CASI
(Mirza et al., 2016)	Rotterdam community scan study	3325	74.88 (IQR 71–80)	60%	3 times in 10 years	CES-D, HADS-D – 3 trajectories!	MMSE, GMS, CAMDEX, DSM-III-R, NINCDS-ADRDA	434 dementia – 348 AD, 26 Vasc, 60 other	Increasing trajectory dementia HR 1.42 [1·05–1·94]	Age, sex, *APOE*, education, medication, risk factors, cognition
(Palmer et al., 2007)	Stockholm community-based	185 (+47 MCI)	84 (5) 75-95 years	84.9%	3.4 years (0.6 SD)	Comprehensive Psychopathological Rating Scale	DSM-III-R, NINCDS-ADRDA	10 AD 7 dementia in healthy	AD RR 1.9 [1.0-3.6] per mood symptom	Corrected for age, sex, education. Anxiety in MCI
(Verdelho et al., 2013)	LADIS study of WML (clinic finding based)	639	74.1 +- 5y	55%	3 times annually	sGDS	NINCDS-ADRDA/AIREN	34 AD, 54 VD, 2 FTLD	GDS HR 2.4 [1.4 3.99]	Risk factors. Previous depression not significant

aSHR, Adjusted sub-hazard ratio; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; GMSS, Geriatric Mental State Schedule; MDE-MINI, Major Depressive Disorder part of the Mini International Neuropsychiatric Interview; CASI, Cognitive Abilities Screening Instrument; IQR, Interquartile Range; WML, White Matter Lesions.

diagnosed with AD. However, this did not seem to correlate well with the burden of AD neuropathology at autopsy, leading the authors to conclude that some other mechanism must drive the association between depression and dementia. They confirmed this finding in an expanded cohort of 1,750 people, 600 of whom underwent neuropathological examination, and again in a third paper. They found no support for depression being merely a psychological reaction to incipient cognitive decline but confirmed the association between depressive symptomatology and later dementia. They hypothesized that some mechanism, independent of the postmortem hallmarks of AD (i.e., plaques and tangles), must drive the association between depression and cognitive decline. Exactly what drives this intriguing finding remains to be elucidated in future studies. These should include newer biomarkers, as guided by fundamental scientific insights.

An amyloid-PET-based study has yielded similar results (i.e., showing no clear link with amyloid pathology) when evaluating hippocampal atrophy in a cohort of depressed people and matched controls (De Winter et al., 2017), even though others have pointed out that amyloid-positive individuals do have a tendency to progressively manifest more neuropsychiatric symptoms (Harrington et al., 2017; Donovan et al., 2018). It is clear that further research efforts could and should use the newer antemortem diagnostic techniques (e.g., LP and/or PET) to add to these findings.

DISCUSSION

Our systematic literature review yielded no conclusive arguments in support of or contradicting the exact nature of the etiological relationship between depression and dementia. Multiple studies, however, contain convincing arguments for the respective position on this topic (A1, A2, B, C, D) that their authors defend. Some issues raised in the *Results* section of category

TABLE 4 | (Categories C & D): Studies suggesting both or neither.

Study	Cohort	N	Mean age (SD)	% Female	FU	Depression assessment	Diagnostic criteria of cognitive decline	Incidence	Risk?	Adjustments
(Ganguli et al., 2006)	MoVIESBlue-collar rural U.S.A	1265	75 (5)	60.8%	Biannually for 12 years	mCES-D	CERAD, DSM-III-R	171 cases of dementia	Multiple interaction models finding no long-term association	Classic risk factors
(Kaup et al., 2016)	HABC Study, mixed USA	2488	74 (2.4)	53%	4 years	CES-D-10 and 'trajectories'	Records, medication, MMS decline	353 cases of dementia	High and increasing trajectory	Demographic and health factors, cognition
(Luppa et al., 2013)	LEILA 75+ Study	1265	75 years and older, mean 81	73%	Every 1.5 years over 8 years	CES-D	SIDAM - DSM IV	183 cases of dementia	Only for MD in multivariate	Classic risk factors
(Wilson et al., 2003; Wilson et al., 2014; Wilson et al., 2016)	Different prospective cohorts	130/ 1750/ 1965	76 (7.5) in 3rd study	73.8%	Differing per cohort/ paper	CES-D	DSM-III, NINCDS-ADRDA, Pathological criteria	346 cases of dementia in largest cohort	Cfr. text discussion.	Cfr. text discussion.

SIDAM, Structured Interview for Diagnosis of Dementia of Alzheimer type, Multiinfarct Dementia and Dementia of other Aetiology; MD, Major Depression.

A2 ("not a risk factor"), however, cast doubt on the power several of these studies to detect connections (or their absence). We deem it unlikely that there should be no connection at all, or that everything can be explained by subjects' emotional responses to incipient decline. We therefore conclude that depressive symptoms may be both a risk factor for and a prodromal symptom to dementia. They may sometimes be coincidental and/or stem from shared risk factors in the elderly. Exactly what mechanism(s) drive(s) this pathophysiological association remain(s) unclear and could not be elucidated by this systematic review. Limitations of our effort in this sense will be discussed in the next section of this article.

Multiple studies were excluded from our main results as they examined the relationship between depressive symptoms and cognitive decline, variously defined (Dufouil et al., 1996; Bassuk et al., 1998; Yaffe et al., 1999; Wilson et al., 2004; Barnes et al., 2006; Geda et al., 2014; Ritchie et al., 2016). Due to this heterogeneous construct (rather than the binary dementia–no dementia), these studies did not answer our research question. They remain, however, certainly of interest of the broader research area we considered in the *Introduction* section. Since these studies contain useful information for investigators looking into the cognitive effects of depression, they are listed here for further reading. Five of them report an increased risk of cognitive decline among depressed elders (Yaffe et al., 1999; Wilson et al., 2004; Barnes et al., 2006; Geda et al., 2014; Ritchie et al., 2016), whereas two of them do not (Dufouil et al., 1996; Bassuk et al., 1998).

As we wanted to study the interaction between late-life depression and dementia, studies including a large proportion of subjects younger than 65 years of age were excluded. Indeed, dementia is rare in this age group, and early- versus late-onset depression may differ clinically (Hall and Reynolds-Iii, 2014). As mentioned before (Ownby et al., 2006), some of these studies suggest that [severe (Simões do Couto et al., 2016)] early-life depressive episodes appear to have an "additive" effect on dementia risk, supporting depression as a causal factor or related to the same underlying pathology, such as vascular disease (Van Uden et al., 2016). Dal Forno et al. (2015) and Köhler et al. (2011) reported similar findings, albeit in older populations. These findings may be relevant to our review question and often imply a causal role for depression and depressive symptoms, much like the studies in Table 1. Even though the studies mentioned cannot be included in our systematic review, given our inclusion criteria, we briefly refer to these studies here (Dotson et al., 2010; Köhler et al., 2011; Dal Forno et al., 2015; Simões do Couto et al., 2016; Van Uden et al., 2016), as most do appear to support a link between depressive symptoms and dementia.

Neuropsychiatric symptoms in the elderly are common, pervasive, and incapacitating. In the search for validated biomarkers of (later) dementia, simple and cheap interventions, such as a structured mental health assessment or a quick screening tool for depressive symptoms, may complement expensive and/or invasive tools like imaging and laboratory tests in determining individual patients' risk profile. Hopefully, these can in turn lead to tailored risk mitigation strategies for individuals at risk that can be implemented on a large scale. Future research should aim at identifying novel techniques that are able to identify those depressed elders at high risk for "conversion" to dementia. There may be a role to play in unraveling this connection for certain issues raised in the papers we discussed. The effects of gender, genetics, cerebrovascular disease and inflammation, upon the interaction between depressive symptoms and (certain types of) dementia should be studied further using a combination of large datasets and modern technology. We believe that these areas of study may yield clues to understand the actual pathophysiological mechanisms driving the association between mood symptoms and cognitive decline and in turn guide future trials.

We hypothesize that newer diagnostic techniques—*in vivo* biomarkers through CSF analysis, targeted molecular imaging through positron emission tomography techniques, advanced (magnetic resonance) imaging analysis—unavailable during

many of the prospective study periods of the cohort studies we cited—may facilitate in this effort in overcoming the shortcomings of existing studies. The studies we included are mainly based on cohorts from years or even decades ago, when much fewer (para) clinical diagnostic tools were available. By increasing diagnostic accuracy and concordance with pathological diagnoses, disease-specific mechanisms may be identified more easily as compared to the more heterogeneous cohorts described above. We theorize that these techniques may facilitate an early identification of those depressed elders at an especially high risk of developing degenerative dementia. Second, future trials should examine whether and which treatments in the depressive elderly—with or without evidence of preclinical or prodromal neurodegeneration—may mitigate their risk of later dementia.

LIMITATIONS AND HETEROGENEITY

-Of the Studies Included

It is technically and ethically impossible to conduct a randomized, controlled trial to study the association between depression and dementia. Therefore, conclusions are based on observational studies. This means that the highest levels of evidence quality are not met. This is especially relevant when taking heterogeneity across studies into account in conducting systematic reviews and meta-analyses. We note that most studies are of similar quality when assessed using the NOS (see **Supplementary Material**). We therefore deem it unlikely that specific types of systematic bias in study design (apart from some concerns raised over the "negative" studies in Category A2) have influenced the categorization of studies and/or our general conclusions.

Related to the Diagnosis of Dementia

Dementia diagnoses were based on Diagnostic and Statistical Manual of Mental Disorders (DSM) (be it III or IV, revised or not) criteria in all but two studies (Kaup et al., 2016; Almeida et al., 2017), which relied on healthcare records and coding, prescription of cholinesterase inhibitors, and other "indirect" signs of a dementia diagnosis in their cohorts. AD diagnosis—if evaluated separately—was similarly based on National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria in most studies. Of note, almost no studies included additional "objective" biomarkers of AD or other dementias, which added to the heterogeneity of the investigated populations. The relatively low etiological diagnostic accuracy of non-biomarker-based clinical diagnostic criteria alone does not help this issue (Elahi and Miller, 2017). A minority of studies employed DNA analysis—mainly for *APOE* genotyping (Lindsay et al., 2002; Irie et al., 2008; Kim et al., 2010; Saczynski et al., 2010; Mossaheb et al., 2012; Mirza et al., 2016). While most criteria for "dementia" as such are quite clear, there are of course multiple causes for this clinical syndrome, and several studies do not formally differentiate between AD and other causes of dementia, very probably contributing to less clear results and precluding conclusions about specific types of dementia and their possible association with depressive symptoms. These issues may have influenced study findings and the conclusions of this systematic review.

Depression Measures

It is of interest to researchers and clinicians to differentiate between several elements of the depressive syndrome (anhedonia, low positive affect, motivational symptoms, vegetative or melancholic symptoms,…) to elucidate the role they have in causing clinical overlap between multiple disease states in the elderly: medical illness and pharmacological effects, major depression, apathy, incipient dementia, etc. (Hall and Reynolds-Iii, 2014). Rating scales differ in their focus on/attributing points to these elements of the depressive syndrome.

Fourteen studies used the Centre for Epidemiological Studies–Depression (CES-D) self-rating scale for assessing depressive symptoms at a given moment. Nevertheless, even they differ in the cutoff values used (e.g., 16, 11, 10, or 9 points); two studies use a modified scale, some use different cutoff values for men and women, while others did not. No less than nine other scales and evaluations were used, with or without a "regular" clinical psychiatric assessment of depression (generally based on DSM criteria). Ascertaining past episodes of depression was even harder due to recall bias and a general lack of recognition of multiple depressive symptoms and episodes in the general population (Patten, 2003). Although some of the included studies examined specific symptom trajectories of depression, most use a one-time screening tool inquiring about symptoms in the last few days or weeks, which is probably inadequate to distinguish true depression from subsyndromal depressive symptoms. This limits strong conclusions about what kind and/or severity of depressive symptoms are specifically related to future dementia and should, therefore, be actively identified and/or treated by clinicians.

Populations

Studied populations were relatively heterogeneous across cohorts. Participants' age was similar in most studies, with some studies focusing on the oldest old (Pálsson et al., 1999; Vinkers et al., 2004; Palmer et al., 2007). While a general female preponderance in studies of the elderly is to be expected and was indeed seen in most studies, some (29 and 47) looked at men only, with one (Spira et al., 2012) having an all-women cohort. Most (if not all) of these studies were conducted in the industrialized world. They do, however, contain populations from different continents and multiple ethnic backgrounds in rural as well as urban cohorts. Whether study findings can be extrapolated on a cross-cultural or global scale remains an open question.

Risk Analysis and Prospective Studies

While almost all studies corrected their results (concerning risk of developing dementia) for potentially confounding variables, almost none used an exactly identical list of confounders. Given that depressive symptoms and dementia are both common and have overlapping risk factors (e.g., socioeconomic status),

this lack of uniformity across studies further hampers the disentanglement of causal relationships.

As in all epidemiological studies, and especially those in old age, attrition bias (due to loss of follow-up, intercurrent illness, or death) is significant. Furthermore, multiple authors have suggested that dropped-out participants are more likely to suffer from depression and/or dementia (Brayne et al., 1999), possibly attenuating the risk found in study "survivors." Moreover, several authors have pointed out that people with depressive symptoms have more comorbid medical illnesses and die earlier (which is also true for people with dementia) (Almeida et al., 2010). We hypothesize that this attrition bias may underestimate some risk relationships and could produce false-negative results.

-Limitations of This Review

As can be expected from examining the complex association between depressive symptoms and dementia, major methodological differences exist between studies. There are profound and significant differences concerning the populations studied, diagnostic evaluations used, follow-up frequency and duration, corrections for bias, etc. These inconsistencies add to the difficulty of answering our research question (i.e., depression being a cause, effect, both, neither,… of dementia) that is in itself challenging to answer using prospective studies. Grouping studies and data that are this heterogeneous are a major limitation of the existing data. This also complicates hypothetical statistical analyses of data extracted from these studies.

We do not provide here a complete list of excluded studies, did not do the initial searches in duplicate, and cannot exclude any human errors in selection. Since the link between depression and dementia is a hotly debated one, with publications supporting multiple causal hypotheses, we do not think that (positive) publication bias has a major impact on our findings, although we cannot formally exclude this. We did not search all of the available literature databases, although it is unlikely they should have yielded important studies unlisted in Medline (as illustrated by our lack of additional findings in PsycINFO).

CONCLUSIONS AND FUTURE PERSPECTIVES

Despite our clear initial research question, this systematic review did not provide a single answer to the question of how depressive symptoms and later dementia are related. According to our review effort, grouping multiple large studies that provide conflicting results, it remains unclear whether depressive symptoms in the elderly are a risk factor for or a prodromal symptom of dementia. They still may be related mainly through common causal factors, e.g., aging or vascular disease. It seems unlikely that they are not at all related, or only in an indirect way–for example, evidence does not support the hypothesis that a negative emotional response to incipient cognitive symptoms alone can explain the connection between depressive symptoms and dementia.

Several interesting issues raised in some of the studies included, although outside the scope of this review, also deserve further evaluation. These include but are not limited to the role of gender and genetic factors, systemic inflammation and cerebrovascular disease, different etiologies of dementia developed (utilizing recent advances in pathological classification), the nature and severity of symptoms, in modulating the odds of developing dementia in depressive elders.

We deduce from this systematic review that depressive symptoms can be an independent risk factor for as well as a prodromal manifestation of dementia. In some cases, they may both stem from common risk factors such as cerebrovascular disease. In others, they may not have causal connections at all and simply occur together by chance—as two separate yet prevalent neuropsychiatric diseases with overlapping and prevalent risk factors. It remains, on the basis of these findings, challenging to identify those depressed elders at an increased risk of later dementia in clinical practice and, by extension, who would benefit from specific interventions to attenuate this risk.

Therefore, further research is needed to unravel the association between depression and dementia. Preferentially, this research should use a large database to have sufficient statistical power to determine which risk factors–possibly a combination of clinical characteristics and biomarkers, hardly available at all in the studies we examined—increase the risk of conversion to dementia in the depressed elderly. These risk factors should subsequently be validated in prospective, longitudinal clinical studies including elders with and without depressive symptoms in whom clinical, biochemical, and neuropsychological follow-up will decipher which (sub)group later develops cognitive deterioration and dementia. These risk factors can then be incorporated into a clinically useful risk score, of paramount importance for future efforts in the prevention of dementia—and therefore of interest to clinicians, researchers, and patients worldwide.

AUTHOR CONTRIBUTIONS

WW, CB, and SE conceived the idea for this manuscript. WW performed the database searches and wrote the first drafts. CB and SE critically reviewed and commented on these drafts. All authors contributed to manuscript revision. All authors read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2020.00034/full#supplementary-material

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frontiers in Pharmacology

REVIEW
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Alterations of Astrocytes in the Context of Schizophrenic Dementia

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The levels of the astrocyte markers (GFAP, S100B) were increased unevenly in patients with schizophrenia. Reactive astrogliosis was found in approximately 70% of patients with schizophrenia. The astrocytes play a major role in etiology and pathogenesis of schizophrenia. Astrocytes produce the components that altered in schizophrenia extracellular matrix system which are involved in inflammation, functioning of interneurons, glio-, and neurotransmitter system, especially glutamate system. Astrocytes activate the interneurons through glutamate release and ATP. Decreased expression of astrocyte glutamate transporters was observed in patients with schizophrenia. Astrocytes influence on N-methyl-d-aspartate (NMDA) receptors *via* D-serine, an agonist of the glycine-binding site of NMDA receptors, and kynurenic acid, an endogenous antagonist. NMDA receptors, on its turn, control the impulses of dopamine neurons. Therefore following theories of schizophrenia are proposed. They are a) activation of astrocytes for neuroinflammation, b) glutamate and dopamine theory, as astrocyte products control the activity of NMDA receptors, which influence on the dopamine neurons.

Keywords: schizophrenia, astrocyte, N-methyl-d-aspartate, glutamate, glial fibrillary acidic protein, S100B, kynurenic acid

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INTRODUCTION

Schizophrenia is a mental disorder, determined as a complex of positive, negative and cognitive symptoms (Carbon and Correll, 2014). Positive symptoms are the symptoms that present in patients with schizophrenia, but not healthy people, such as psychosis. Negative symptoms are the symptoms, associated with lack of functions, such as lack of motivation, reduction in spontaneous speech, and social withdrawal. Cognitive symptoms related to neurocognition: difficulties in memory, attention, and executive functioning (Van Os and Kapur, 2009). However, positive symptoms are more noticeable in patients than negative and cognitive symptoms, which helps in diagnosis of schizophrenia.

The dopamine theory of schizophrenia, based on hyperactive dopamine projections in the mesolimbic system and reduced dopamine projections in the mesocortical system

(Juárez Olguín et al., 2016), is the prevalent explanation of schizophrenia symptoms now. Alterations in striatal D2 receptors cause positive symptoms, and impairments in the prefrontal cortex D1 receptors cause negative and cognitive symptoms (Lau et al., 2013). Traditional pharmacotherapy, based on the dopamine theory of schizophrenia, has several significant limitations. The use of antipsychotics improves predominantly positive symptoms, although there is evidence of improvement of negative symptoms with the use of clozapine (Kane, 1988) and aripiprazole (Veerman et al., 2017). Approximately 25% of patients are resistant to therapy (Remington et al., 2017), in addition, the rate of metabolic syndrome among patients was 32.5% (Mitchell et al., 2013), which worsens life quality and predisposes to cardiovascular diseases.

Glutamate theory of schizophrenia is based on the ability of N-methyl-d-aspartate (NMDA) antagonists, such as ketamine, induced schizophrenia-like psychosis (Steeds et al., 2015). Disturbances in NMDA receptors in interneurons lead to the absence of inhibition impulses to the glutamate neurons, increasing glutamate activity especially in the prefrontal cortex, which can be related to negative symptoms of schizophrenia. The agonists of metabotropic glutamate receptors mGluR2 demonstrate the antipsychotic activity in clinical trials (Moghaddam and Javitt, 2012).

Neuroinflammation theory of schizophrenia is based on increased expression of proinflammatory agents and the presence of autoantibodies. Epidemiological studies associate schizophrenia with autoimmune disorders, autoantibodies affect synapses and NMDA-type glutamate receptors and cause damages in the brain (Sawa and Sedlak, 2016). Inflammation processes, in its turn, are connected with oxidative stress—the imbalance between the production of reactive oxygen species radicals and antioxidant system. Interconnections of neurons and glia mediate the inflammation processes, that means that altered glial state will be an important point in schizophrenia research (Leza et al., 2015).

The glial theory of schizophrenia assumes that initial disturbances in glial cells can lead to the abnormalities of the neurons and neurotransmitters. The glial theory of schizophrenia based on the proven inflammatory response and elevated levels of the characteristic markers of active glia—S100B and glial fibrillary acidic protein (GFAP) (Wang et al., 2015). In schizophrenia patients there is an accumulation of the metabolite of tryptophan—kynurenic acid (KYNA) (Plitman et al., 2017), acting as an antagonist of NMDA receptors and altered glutamate transport—which binds glial and glutamate theory, as well as due to the influence on interneurons. Obviously, astrocytes as the most abundant glial cells, are the objects of careful attention at the researchers of a lot of central nervous system (CNS) diseases. But its role in the development of schizophrenia is insufficiently studied. The concept of our paper is the generalization of previously obtained data in this field. This review analyses the action of astrocyte both on schizophrenia symptoms and on the related with them factors, such as inflammation processes, extracellular matrix, and different neurotransmitters.

Evidences of Alterations in Astrocyte System in Different Brain Areas

Patients with schizophrenia show increased activation of glia, especially astrocytes, which play a role in the development and functioning of synapses, glutamate release, water-electrolyte balance, regulation of blood circulation, and neuroprotection (Blanco-Suárez et al., 2017; Sullivan et al., 2018). The functions of astrocytes are related to the functions of other glial cells: protective functions of astrocytes can be changed by microglia, and also astrocytes, interacting with oligodendrocytes, play a role in myelination (Iglesias et al., 2017), which makes their role in schizophrenia even more significant.

The most part of *postmortem* human studies of astrocyte alterations in schizophrenia have focused on the number of glial cells. The number of astrocytes was reduced in the cingulate cortex (Williams et al., 2013a), motor cortex (Benes, 1986), medial, and ventrolateral regions of the nucleus accumbens (Pakkenberg, 1990), basal nuclei (Williams et al., 2013b), substantia nigra (Williams et al., 2014), but increased in the periventricular space (Bruton et al., 1990) and is not altered in the temporal and frontal cortex (van Kesteren et al., 2017), in the hippocampus (Schmitt et al., 2009), amygdala, and ventral pallidum in schizophrenia (Pakkenberg, 1990). The changes of the astrocyte density in the prefrontal cortex vary depending on the area of the dorsolateral prefrontal cortex of *postmortem* brain tissue (Rajkowska et al., 2002). Studies of the number of astrocytes in the mediodorsal nucleus of the thalamus vary: one study showed a decrease in the number of astrocytes (Pakkenberg, 1990), but another study showed increased GFAP expression in the mediodorsal nucleus of the thalamus and in the anteroventral, internal capsule, and putamen (Barley et al., 2009). A positive correlation has been found between the age of macaque monkey and the density of astrocytes in paralaminar nucleus (Chareyron et al., 2012) which suggests that different age of patients can contribute to the heterogeneity of astrocyte density.

Selemon et al. have found an increased density of glia in the prefrontal cortex in rhesus monkeys, chronically taking antipsychotics (Selemon et al., 1999). This is contradicted by the fact that the expression of clozapine- and haloperidol-induced Fos—protein in Sprague–Dawley rats is not colocalized with astrocytes, which suggests that haloperidol and clozapine do not act on these glial cells (Ma et al., 2003).

Individual astrocyte genes are associated with schizophrenia, which is proved by the increase in astrocyte Marker Gene Profile in the thalamic region in the transcriptomics analyses of *post-mortem* brain tissue (Toker et al., 2018). A significant number of changes in gene expression in schizophrenia patients occur in the anterior cingulate cortex, which is responsible for cognitive function, error recognition, and motivation, while very few or no significant expression differences in the dorsolateral prefrontal cortex and nucleus accumbens (Ramaker et al., 2017). Alterations in the expression of the two proteins are the most common among patients with schizophrenia—aldolase C (11 reports) and GFAP (9 reports), both expressed primarily by astrocytes (Davalieva et al., 2016). Adult astrocytes also express

calcium-binding protein S100B, glutamate-aspartate transporter/excitatory amino acid transporter 1 (EAAT1), and glutamate transporter (GLT-1) (Iglesias et al., 2017). Markers of enhanced astrocyte response are usually GFAP and S100B (Kim et al., 2018; Michetti et al., 2019).

Glucose metabolism finishes with the formation of oxidative radicals, and astrocytes normally increase mobilization of glycogen and glucose utilization in the case of oxidative stress (Lavoie et al., 2011). Destruction of astrocyte lactate transporters produces a loss of memory, suggesting the importance of lactate transport in astrocytes for the formation of long-term memory in rats (Xia et al., 2016). Inhibition of glycogenolysis in rats impairs memory, but it is improved by the use of lactate, which can be related to the impairments in working memory in patients with schizophrenia (Newman et al., 2011).

Marker of Enhanced Astrocyte Response GFAP

GFAP is expressed by the astrocytes, perisinusoidal stellate cells of the liver, Leydig cells, glomeruli of the kidney, and chondrocytes of elastic cartilage (Buniatian et al., 1998). GFAP is a marker of reactive astrocytes, many astrocytes normally do not release detectable GFAP levels (Kim et al., 2018). GFAP expression is different in patients with schizophrenia (Catts et al., 2014). It was elevated in the anteroventral and mediodorsal thalamic nuclei and putamen (Barley et al., 2009), and in dorsolateral prefrontal cortex in patients with neuroinflammation (Catts et al., 2014). GFAP expression was significantly reduced in the in the frontal cortex and cingulate cortex of *postmortem* brain tissue (Williams et al., 2013b; Wang et al., 2015). The level of GFAP and the number of GFAP-positive cells were not statistically different in the hippocampal and neocortical regions (Pantazopoulos et al., 2010; Schnieder and Dwork, 2011). However, animal models of schizophrenia showed an increase in the level of GFAP (Kim et al., 2018). Variation in the data may be related to differences in age, causes of death, the severity of the inflammatory response, genetic characteristics, heterogeneity of schizophrenia symptoms (Schmitt et al., 2009; Schnieder and Dwork, 2011; Catts et al., 2014). The latter is also confirmed by the difference in astrocyte activation of transgenic mice by alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) modulators (Höft et al., 2014). Moreover, multiple injections of the NMDA receptor antagonist that causes schizophrenia-like symptoms has led to increase in the level of GFAP in the hippocampus of rats (Yu et al., 2015) and in the medial prefrontal cortex of mice (Gomes et al., 2015).

Marker of Enhanced Astrocyte S100B

S100B is a calcium-binding protein, a biomarker of brain damage and stress that is synthesized by oligodendrocytes and astrocytes. It is also secreted by CD8T-lymphocytes and NK-cells during their stimulation, inducing microglial migration through increased cytokine expression (Michetti et al., 2019). The level of S100B was increased by almost two times compared to the healthy control groups, but its increase was observed in schizophrenia patients is not uniform (Aleksovska et al., 2014). The level of S100B was decreased in the *postmortem* brain tissue of deep layers of the anterior cingulate gyrus (Katsel et al., 2011) and in the corpus callosum (Steiner et al., 2014b). In the animal models, the level of S100B were heterogeneous (de Souza et al., 2015) in the hippocampus. S100B-immunopositive glia was elevated in paranoid as compared to residual schizophrenia patients (Steiner et al., 2008). There is evidence that S100B can be released by astrocytes in response to activation of 5-HT receptor, which means that an excess of serotonin can provoke the release of S100B, but this is opposed by serotonin and norepinephrine reuptake inhibitor in the hippocampus of rats (Michetti et al., 2019). Increased S100B expression can lead to metabolic disturbances in astrocytes and neurons, for example, reduced glucose uptake by astrocytes. The level of S100B in serum correlates with the development of insulin resistance in patients with schizophrenia (Steiner et al., 2014a). Intracellular S100B provokes proliferation, extracellular S100B provokes cell differentiation in small doses and induces cell death in large ones (Aleksovska et al., 2014). It was noted that antipsychotics (haloperidol and clozapine) reduce the level of S100B in the cell cultures (Steiner et al., 2010). The level of S100B in serum positively correlates with the manifestation of negative symptoms before treatment, while negative symptoms may be predictors of increased S100B. The level of S100B does not change during 6 months of treatment and the level of S100B also kept high after 6 months of treatment in patients with high rates of negative symptoms. Patients with increased S100B had problems with expression of emotions, communication with others, initiative, while mice with increased S100B showed impaired memory and learning ability (Rothermundt et al., 2004). Mice with S100B deletion had better fear memory in the contextual fear conditioning (Nishiyama et al., 2002).

Morphology of Astrocytes in Schizophrenia

Data about the presence of changes in the morphology of astrocytes in schizophrenia is also different: despite the hypertrophy of glial fibrillary acidic protein-containing cellular processes, the volume of tissue accessed by individual astrocytes of mice remains unchanged (Wilhelmsson et al., 2006). Reactive astrogliosis was found in approximately 70% of patients with schizophrenia in the thalamus, limbic system, and periventricular space (Mallya and Deutch, 2018), although reactive astrogliosis was not found in the entorhinal cortex (Casanova et al., 1990; Schnieder and Dwork, 2011). Gliosis at the rostral and caudal ends was more common in patients with late onset of schizophrenia (Nasrallah et al., 1983; Schnieder and Dwork, 2011). Differences in the data can be partly explained by differences in the age of the patients (Schmitt et al., 2009). The morphology of astrocytes depends on the measure of the inflammatory response in patients with schizophrenia, so the differences in morphology can partially explain the different data about the levels of GFAP (Kim et al., 2018). Morphological changes of astrocytes can also alter neuronal networks, which can apparently contribute to the development of schizophrenia symptoms (Poskanzer and Yuste, 2011). The appearance of astrogliosis can be expected due to the continuous patients neurodegenerative state, which can be predicted by altering the volume of brain areas (Brugger and Howes, 2017),

but the data on its manifestation is different, which can be explained by the presence of different types of astrogliosis and the short duration or blockade of astrocyte reactions in many people with schizophrenia (Catts et al., 2014). Normal astrogliosis has provided several significant benefits, including protection of neurons, recovery of the blood-brain barrier, and reducing inflammation in the central nervous system, while small and medium astrogliosis can look the same with healthy astrocytes of the CNS (Sofroniew, 2015). Pathological astrogliosis can lead to harmful effects: to provoke and increase inflammation, to produce molecules that destroy the blood-brain barrier and facilitate the migration of leukocytes into the CNS parenchyma (Leza et al., 2015; Sofroniew, 2015). The relationship between taking atypical antipsychotics and the suppression of astrogliosis, (including that caused by NMDA antagonist) have been also discovered (Catts et al., 2014).

Reactive hypertrophic astrocytes lose spontaneous Ca^{2+} oscillations *in situ* after stab wound injury, controlling the emission of gliotransmitters, which may be related to the neural network (Rossi, 2015). There is evidence that the release of high concentrations of tumor necrosis factor (TNF)-α by reactive microglia shows Ca^{2+}-dependent release of gliotransmitter glutamate by astrocytes, leading to neuronal damage (Bezzi et al., 2001).

Myoinositol is a marker of glial activation, for which the connection with astrocytes for schizophrenia spectrum disorders patients has been found (Chiappelli et al., 2015). Its level may be associated with inflammation and increased in untreated individuals. The level of myoinositol in the striatum positively correlates with the level of glutamate in untreated patients and positive symptoms, but not correlated with negative or symptoms at all (Plitman et al., 2016).

Prenatal Infection and Mother Deprivation Lead to Schizophrenia

Prenatal infection is one of the suspected causes of schizophrenia and it can make astrocytes hypersensitive to stimuli in the future, which may cause an enhanced response in the central nervous system (Takahashi and Sakurai, 2013). Maternal immune activation on day 12 of mice embryonic development leads to changes in astrocytes and microglia and increases the GFAP levels, which indicate astrogliosis in the amygdala (O'Loughlin et al., 2017), but in another study, mice prenatal immune activation did not change astrocyte density (Giovanoli et al., 2016). Activation of astrocytes during rat embryonic development can disrupt the cortical and thalamocortical formation (Beamer et al., 2017).

Mother deprivation in rats leads to specific behavioral symptoms of schizophrenia, which may be associated with corticosteroids. Mother deprivation provokes a higher level of GFAP and a large number of GFAP-positive astrocytes, which may indicate reactive gliosis (Llorente et al., 2009). At the same time, it has been found that mother deprivation provokes an increase in GFAP-positive cells only in male rats (López-Gallardo et al., 2008).

Contribution of Astrocytes in Neuron-Neuron and Neuron-Glia Interaction

Inflammatory Processes and Astrocytes

Oxidative and nitrostress are the main mechanisms by which inflammation can generate cell damage (Leza et al., 2015). Hypotheses of oxidative stress as a cause of schizophrenia suggest that inflammation can act in the embryonic period of development and induce oxidative stress in fetal cells through cytokines that cross the placenta; or an inflammatory agent, such as an infection that causes an immune response and oxidative stress, can act on the brain in adolescence, causing characteristic changes (**Figure 1**). At the same time, oxidative and nitro stress can be caused by non-inflammatory stimuli (mitochondrial dysfunction, dopamine, hyperhomocysteinemia, smoking, hypofunction of NMDA receptors, etc.) (Leza et al., 2015; Nedic Erjavec et al., 2018). Oxidative stress is observed in the prefrontal cortex, anterior cingulate cortex and hippocampus, which matches with the places of altered astrocyte activity in schizophrenia. Oxidative stress inhibits the activity of NMDA receptors, which can lead to the appearance of ketamine-like symptoms, and has inhibitory effects on glycogen metabolism in mice (Lavoie et al., 2011). In this case, free radicals can cross the blood-brain barrier, which becomes more permeable due to the product of lipid peroxidation 4-hydroxynonenal (Nedic Erjavec et al., 2018) and other agents, causing an inflammatory response and a decrease in pH as a result of chronic stress (van Kesteren et al., 2017). However, under the influence of certain circumstances astrocytes can emit molecules, such as sonic hedgehog, which provoke the repair of blood-brain barrier (Sofroniew, 2015)

Interneurons are very sensitive to damage from oxidative stress, especially at the beginning of postnatal development (Grace, 2016). Prolonged stress increases the activity of dopamine neurons through the ventral tegmental area and increases the level of dopamine in the prefrontal cortex and nucleus accumbens. The medial prefrontal cortex regulates the amygdala's response to stress. Stress-induced hyperreactivity of the amygdala leads to the loss of parvalbumin interneurons (Grace, 2016) and changes in their proportions in the hippocampus, which leads to even greater hyperexcitation of dopamine systems, and this causes symptoms of schizophrenia (Grace, 2016).

The main cells of the immune response in the CNS are astrocytes and microglia. In this case, microglia mainly produces type 1 cytokines, such as interleukin (IL)-12, and astrocytes inhibit the production of IL-12 and produce type 2 cytokines, for example, IL-10 (van Kesteren et al., 2017). The dysregulation of this balance can damage the neurons, cause a deficit of interneurons, leading to alteration of oligodendrocytes and inhibition of gamma-aminobutyric acid (GABA) interneurons (Nedic Erjavec et al., 2018). IL-1β and IL-6 promoted dopaminergic transmission (Purves-Tyson et al., 2019).

Stimulation of mGluR5 and a1-noradrenergic astrocyte receptors provokes mild inflammatory processes, including the

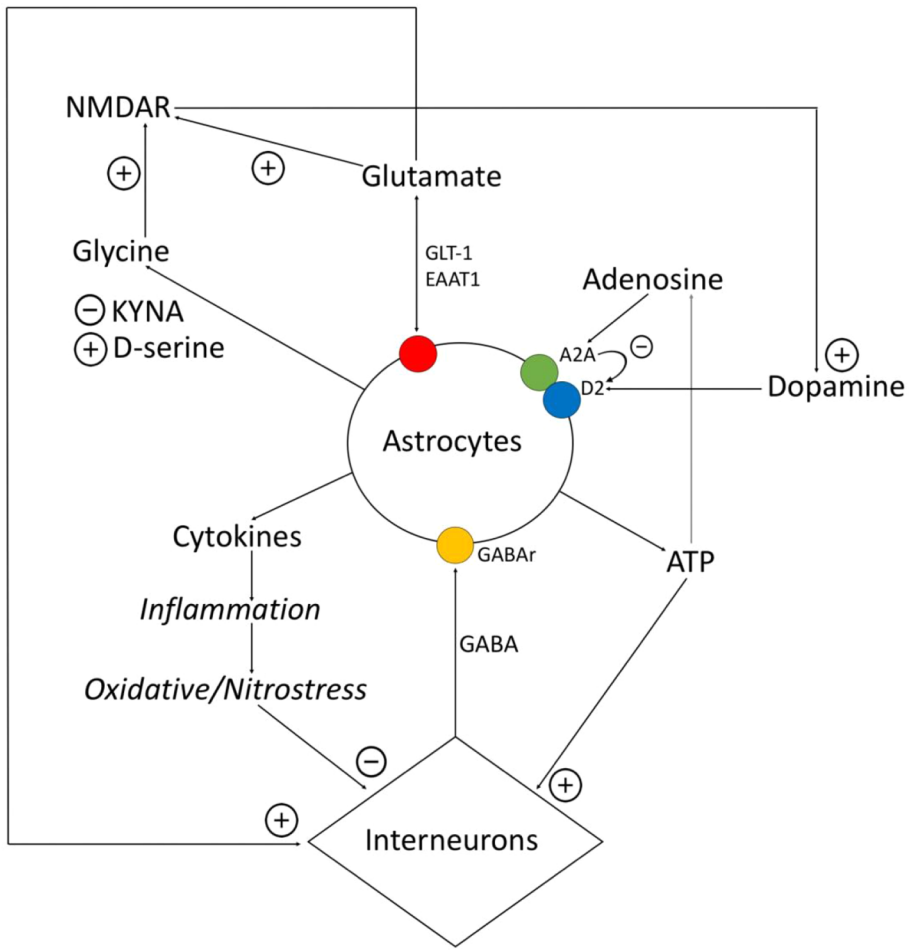

FIGURE 1 | Relationship between astrocytes, interneurons, and transmitters. Astrocytes express proinflammatory cytokines, which provokes the destruction of gamma-aminobutyric acid (GABA)ergic interneurons. GABA influences on astrocytes and *via* Ca^{2+}-dependent stimulates expression of different gliotransmitters (glutamate, ATP, cytokines). Glutamate and ATP have an activating impact on interneurons. Adenosine operates on A2A receptors of astrocytes, related with the dopamine receptors, and inhibits them. Astrocytes control the amount of glutamate *via* glutamate transporter (GLT)-1, excitatory amino acid transporter (EAAT)1, and also metabotropic glutamate receptors (mGluRs). Astrocytes express D-serine and kynurenic acid (KYNA), while D-serine is the agonist of N-methyl-d-aspartate (NMDA)-receptors, and KYNA is the antagonists of glycine site of NMDA-receptors. NMDA-receptors activate dopamine neurons.

release of prostaglandins and other eicosanoids, which can regulate communication between neurons and blood vessels (Rossi, 2015).

Experimental and clinical observations have shown that loss or dysfunction of astrocytes can seriously exacerbate CNS inflammation and tissue damage. Normal astrocytes produce pro-inflammatory agents, such as cytokine Il-6, IL-10, IL-17, and IL-1ß that attract leukocytes through vasodilation. Then the astrocytes exhibit a modulatory role to form the necessary barriers to limit the inflammation or enhancing the anti-inflammatory process through vasoconstriction mechanism. Hence astrocyte transcriptome changes that are shifted by pathogen-associated molecular patterns (PAMPSs) including LPS and associated cytokines (Sofroniew, 2015). Astrocytes also regulate the function of microglia during injury or recovery of the brain *via* secreted cytokines (Miyake et al., 2011; Bouzier-Sore and Pellerin,2013; Bernstein et al., 2015; Andrade 2016; Dean et al., 2016).

The Role of Astrocytes in the Functioning of the Extracellular Matrix

During pathogenesis of schizophrenia, glia loses the ability to form compartments and connections, which leads to disruption of perception and an inability to think, which can be included in the development of cognitive symptoms in schizophrenia. Supposing that astrocyte gap junctions are the site of memory formation and intentional programming, their functions must be essential for cognition and higher information processing (Mitterauer, 2011). This suggests changes in extracellular matrix system, plays a role in the pathogenesis of schizophrenia (Berretta, 2012; Takahashi and Sakurai, 2013). The extracellular matrix is synthesized by neuronal and glial

cells. In humans, unlike other mammals, there is a large number of astrocytes, synthesizing chondroitin sulfates as extracellular matrix in the amygdala. The patients with schizophrenia showed a large increase in chondroitin sulfate proteoglycan (CSPG) - positive glial cells in the deep amygdala and entorhinal cortex and the density of GFAP - positive cells was not changed at some studies (Pantazopoulos et al., 2010). CSPGs play a role in adult synaptic plasticity (Chelini et al., 2018). The extracellular matrix influences synapses' stabilization and maturation in different ways. Firstly, the rate of viscosity of the matrix and the interaction between the negatively charged chains of the glycosaminoglycan-proteoglycan and glutamate controls the diffusion of neurotransmitter in the extracellular space (Deutsch et al., 2010). Secondly, the extracellular matrix at the level of hyaluronan separates the surface of neurons, limiting the surface mobility of integral membrane proteins, including glutamate receptors in rats (Frischknecht et al., 2009). Also, the altered composition of extracellular matrix can lead to excessive diffusion of dopamine into the extracellular space from excessive stimulation extrasynaptic D2 receptors.

Reduced expression of Reelin, which is also a part of extracellular matrix, was noted in patients with schizophrenia in several brain regions, including the hippocampus, prefrontal and temporal cortex, cerebellum and caudate nucleus (Eastwood and Harrison, 2006; Guidotti et al., 2011). In adulthood, Reelin is expressed mainly by GABAergic interneurons (Dong et al., 2007). Reduction of Reelin regulation is usually accompanied by a decrease in glutamic acid decarboxylase expression, indicating a strong functional relationship between Reelin expression and GABAergic neurotransmission (Eastwood and Harrison, 2006). Therefore, the changes in extracellular matrix have an influence on release of neurotransmitters both directly and *via* inhibitory GABAergic interneurons.

Astrocyte-Related Changes in Transmitters Systems

Glutamate System

In schizophrenia, there is hypofunction of NMDA receptors, which leads to a decrease in prefrontal cortex functions (Herédi et al., 2017). Weakened prefrontal cortex function associated with NMDA receptor hypofunction may be involved in the development of negative and cognitive symptoms. This is confirmed by the detection of anti-NMDA antibodies in patients with the first episode of schizophrenia (Levite, 2014). The use of antagonists of NMDA receptors phencyclidine and ketamine, cause the psychotic reactions and leads to hyperactivation of dopamine (Rial et al., 2014). NMDA receptors are involved in synaptic plasticity, which plays a role in learning and memory (Parpura and Verkhratsky, 2012). MK-801 is an NMDA antagonist, increasing the number of GFAP-positive astrocytes in the prefrontal cortex (Gomes et al., 2015). Clozapine reduces the manifestations of these changes, however, an indirect connection through the dysfunction of GABAergic interneurons is possible. Also, an increase in the level of astrocytes can be compensation in response to a decrease in the level of glutamate.

The basis of the modified glutamate transmission is increased glutamate excretion in the hippocampus, in which the dysfunction of inhibitory interneurons in the hippocampus and prefrontal cortex also plays a role (Millan et al., 2016). Reduced activation of NMDA on inhibitory interneurons leads to increased release of glutamate by pyramidal hippocampal neurons (Tayeb et al., 2019).

The reason for the decrease in the activity of parvalbumin neurons in schizophrenia patients in the reduced access to glutamate (Chung et al., 2016). *Postmortem* studies of patients with schizophrenia showed a simultaneous decrease in the levels of parvalbumin interneurons (caused by changes in the expression of parvalbumin) and glutamic acid decarboxylase in the dorsolateral prefrontal cortex (Toker et al., 2018). In this case, NMDA antagonists cause a decrease in the level of mice parvalbumin neurons in the prefrontal cortex, but not in the hippocampus (Gomes et al., 2015). Astrocytes transformer at the activity of the inhibitory GABA from interneurons to excitatory glutamate activity increases synaptic transmission. Astrocytes also induce the increase of inhibitory synaptic connections of interneurons through glutamate release and activation kainate receptors in the inhibitory terminals (Perea et al., 2016), ATP secreted by astrocytes, has also an activating effect on mice interneurons (Bowser, 2004).

Ketamine, NMDA antagonist, decreases Ca2+ transients in astrocyte cell culture, which affects the secretory activity of astrocytes (Lasič et al., 2019). In this case, ketamine does not regulate exocytosis directly through cAMP. Ketamine-induced increase in the density of cholesterol domains in astroglial plasmalemma may stimulate the release of cholesterol molecules by astrocytes to neurons, which may be critical for the morphological plasticity of synapses. Structural changes in astroglial plasmalemma likely involve adenylate cyclase, which increases cAMP in the absence of stimulation of G-protein-coupled receptor (**Figure 1**).

Glutamate transporters GLT-1 and EAAT1 are localized in astrocytes and are responsible for glutamate uptake in astrocyte (Rial et al., 2014). Astrocytes are also responsible for the conversion of glutamate to glutamine, and changes in the glutamate/glutamine cycle that impact the energy exchange between neurons and astrocytes to cause schizophrenia (Sullivan et al., 2018).

In schizophrenia, there is a decreased expression of GLT-1 in the hippocampus of *postmortem* brain samples (Shan et al., 2013) and prefrontal cortex of genotyped patients (Spangaro et al., 2012). The blockade of GLT-1 increased the tonic activation of presynaptic metabotropic glutamate receptors (mGluRs) (Fleming et al., 2011), some of which protect neurons from excessive excitability and regulate the functioning of working memory of rhesus macaques (Jin et al., 2018). It was also noted that agonist mGluR2/3 ameliorates symptoms of schizophrenic psychoses (Segnitz et al., 2009).

In schizophrenia, there is also a decrease in the expression of EAAT1 in the prefrontal cortex. Mice with EAAT1 deficiency showed schizophrenia-like behavior and were more sensitive to locomotor hyperactivity caused by NMDA antagonists. Thus, the

locomotor hyperactivity caused by the lack of EAAT1 was reduced haloperidol. Mice with reduced EAAT1 levels also showed cognitive symptoms. The lack of EAAT1 makes the cells more sensitive to various traumatic factors (Mei et al., 2018).

Haloperidol and clozapine reduce GLT-1 and EAAT3 levels in rodents, while aripiprazole reduces EAAT1 expression but has minimal effect on GLT-1, which may further lead to differences in effects on positive, negative, and cognitive symptoms (Segnitz et al., 2009; Mei et al., 2018).

Glycine System

Glycine is an NMDA receptor agonist that can be released from astrocytes through activation of glutamatergic non-NMDA-type ionotropic receptors (Harsing and Matyus, 2013). In this case, the synaptic form of NMDA has a low affinity for glycine, and non-synaptic NMDA—high (Balu, 2016). Inhibitors of non-synaptic GlyT-1, which lead to an increase in the non-synaptic glycine concentration in rats (Harsing and Matyus, 2013), may participate in the actions of drugs on patients, including the previously described antipsychotic effect (Tsai et al., 2004) in positive, negative, and cognitive symptoms. D-serine, produced by astrocytes, is an agonist of the glycine-binding site of NMDA receptors (Möller and Czobor, 2015). The association of serine racemase, synthesizing serine enzyme, with schizophrenia was found, as well as mice with a lack of serine racemase gene showed behavior similar to schizophrenia (Takahashi and Sakurai, 2013).

Kynurenic Acid as N-Methyl-D-Aspartate Antagonist

Tryptophan is elevated in the cerebrospinal fluid of patients with schizophrenia, along with one of its metabolites—kynurenic acid (KYNA) (Linderholm et al., 2012; Kegel et al., 2017; Tayeb et al., 2019). Ninety percent of tryptophan is metabolized in KYNA. In schizophrenia discovered the lack of kynureninase in astrocytes that can be one of the reasons for increasing the level of KYNA in schizophrenia (Plitman et al., 2017). The conversion of kynuren to KYNA takes place primarily within astrocytes, as these cells contain KATs and therefore cannot degrade kynuren to its metabolites. Of the four existing KATs, KAT II is thought to be the main enzyme of KYNA production.

KYNA acts as an antagonist of all 3 ionotropic glutamate receptors, including NMDA, AMPA, and receptors kainate, while KYNA is the only currently known endogenous antagonist of NMDA (Plitman et al., 2017). KYNA presumably acts as an endogenous antagonist of the glycine site of the NMDA receptor and as a negative allosteric regulator of the nicotinic acetylcholine (nACh)-receptor α7 (Kozak et al., 2014). Both NMDAR and nACh-receptor α7 contribute to the functioning of working memory, and elevated levels of KYNA may contribute to NMDA-hypofunction, cognitive deficits, and negative symptoms. In high micromolar concentrations in rats KYNA acts as an NMDA antagonist, and in lower concentrations reduces the excitability of neurons through mechanisms independent of NMDA (Alkondon et al., 2011).

Conversion kynurenine to KYNA occurs mainly in astrocytes since these cells contain kynurenine aminotransferase (KAT) (Plitman et al., 2017). In adult mouse brain KAT-2 is expressed not only by astrocytes but also by neurons in several brain regions (hippocampus, substantia nigra, striatum, and prefrontal cortex), while the structure of the brain consisting mainly of GABAergic neurons (e.g., the substantia nigra), have the strongest neuronal expression of KAT-2 (Herédi et al., 2017). In rats KAT-2 inhibition reduces KYNA levels and improves cognitive function (Kozak et al., 2014). Activation of astrocytes can increase the production of KYNA (Plitman et al., 2017). The introduction of IL-6 and an increase of prostaglandin E2 level in cultured human astrocytes increases KYNA. Atrophic astrocytes also showed increased production of KYNA.

The possible role of KYNA as a functional link between the stimulation of dopamine receptors and the neurotoxicity of NMDA in the striatum was noted in rats (Poeggeler et al., 2007). An increase in KYNA leads to a decrease in the levels of dopamine, acetylcholine, GABA, and glutamate (Plitman et al., 2017). These inverse associations remain unclear in schizophrenia, as typical neurotransmitter disorders, such as increased synthesis and release of dopamine in the striatum, and elevated levels of subcortical glutamate, seem incompatible with the observed increase in KYNA levels. Antipsychotics normalize the level of tryptophan and reduce the production of KYNA (Müller et al., 2014). Pharmacologically important targets are the enzymes kynurenic way, and also cyclooxygenase-2, which reduces the level of KYNA.

The impact of the increased level of KYNA in schizophrenia symptoms is ambiguous. Elevated levels of KYNA provoked cognitive defects in animals: auditory sensory gating, prepulse inhibition, contextual discriminations, spatial working memory (Alexander et al., 2012). The level of KYNA in cerebrospinal fluid positively correlates with overall psychotic symptoms positive and negative symptoms. The symptom score included results from the scales measuring positive and negative psychotic symptoms (SAPS and SANS), the scale for schizotypal personality traits (SPQ-B), and the interview for schizoid, schizotypal, or paranoid personality traits (SCID-II interview cluster A section) (Kegel et al., 2017). In animal models, increased KYNA is associated with cognitive deficits, including deficits in spatial and working memory (Kozak et al., 2014). The higher initial level of KYNA in plasma was associated with a greater reduction in positive symptoms on the Positive and Negative Syndrome Scale as a result of therapy (Plitman et al., 2017). Thus, preclinical studies have demonstrated the effect of kynureninase acid as the behavior (e.g., cognitive function) and neurotransmission (e.g., glutamatergic, dopaminergic).

Gamma-Aminobutyric Acid System

GABA acts on astrocytes through GABA receptors, contributing to the release of chlorine and depolarization of astrocytes, and GABA receptors, activating calcium-dependent mechanisms and contributing to the growth of gliotransmitter (glutamate, ATP, cytokines) (Losi et al., 2014; Rossi, 2015). Activation of presynaptic GABA receptors increases the inhibitory effects of interneurons. At the same time, the activation of GABAb receptors leads to the activation of mGlu receptors of types 2 and 3, which leads to synaptic depression (Perea et al., 2016). There is evidence that mGlu2/3 receptor agonists can be used as atypical antipsychotics (Aghajanian, 2009).

GABA entering the astrocyte is mediated by a GABA-transporter operating on the principle of symport with sodium, increasing the content of intracellular sodium can contribute to the reversible operation of GABA-transporter (Losi et al., 2014). Reduced GABA release by reactive astrocytes may be important in reducing hippocampal synaptic plasticity, learning, and memory in mice (Rossi, 2015). The blockade of astrocyte GABA receptors improves cognitive abilities, and their complete removal destroys the ability to learn.

Adenosine System

Adenosine acts through two types of receptors—A1 and A2 (Rial et al., 2014). A1-receptors inhibit the release of neurotransmitters, including glutamate. Activating A2A-receptors increases the release of glutamate, supporting the activation of NMDA receptors and inhibits A1-receptors (Boison et al., 2012). At the same time, A2A receptors are not directly related to glutamate release mechanisms. A2A receptors are located in areas rich in dopamine: prefrontal cortex and striatum, and their activation leads to vasodilation and decreased dopaminergic innervation. The blockade of A2A receptors led to the delayed appearance of interneurons in the hippocampus and degradation of working memory (Kim et al., 2018). Activation of A1-receptors localized in oligodendrocytes stimulates myelination, and A2-receptors inhibit the proliferation of oligodendrocytes (Rial et al., 2014).

Recently gaining popularity adenosine theory of schizophrenia. It consists of the hyper-activation of adenosine kinase, which reduces the level of adenosine (Rial et al., 2014). It is shown that selective elimination of astrocyte A2A receptors in mice is related with deficits in GLT-1 activity (Matos et al., 2012; Kim et al., 2018). Also, ATP released by astrocytes is converted into adenosine, which inhibits the release of glutamate through presynaptic A1 receptors (Losi et al., 2014). Preclinical studies have shown that mice without adenosine A2A receptors in astrocytes demonstrate a potential response to the NMDA antagonist in the locomotor activity test (Kim et al., 2018).

Striatal astrocytes express the heterodimer native receptors A2A-D2 (Cervetto et al., 2017). D2 receptors inhibit presynaptic glutamate release, while A2A receptor activation eliminates the effect of D2 receptor activation (Aliagas et al., 2013). A study was carried out using a synthetic peptide VLRRRRRKRVN, corresponding to the receptor region involved in the electrostatic interaction between A2A and D2 receptors. It was shown that this peptide eliminated the ability of the A2A receptor to counteract the effect mediated by the D2 receptor (Azdad et al., 2009). Hypofunction of A2A receptors in the striatum can lead to hyperfunction of D2 receptors, which are involved in disorders associated with neuroinflammatory processes, stimulating immune responses and increasing the resistance of dopaminergic neurons to neurotoxic damage. Dysfunction striatal astrocytic A2A receptor, mediated damage of the D2 receptor, break down the homeostasis of glutamate and was presumably associated with schizophrenia (Ciruela et al., 2006).

Dopamine System

The morphological basis of the accepted dopaminergic theory of schizophrenia is the dysregulation of the dopaminergic system primarily in the striatum (Chuhma et al., 2017; Weinstein et al., 2017), which includes not only an excess of stimulation of dopaminergic neurons but also a violation of their communication and activity (Laruelle, 2014).

Postmortem examinations showed an increase in the level of dopamine in the striatum and an increase in the density of the D2 receptor but without changes in dopamine active transporter (DAT) densities (Howes et al., 2015). Interestingly, in individuals who do not receive antipsychotics, the density of D2 receptors has not been increased, unlike those treated with antipsychotics. Most likely, this is because all currently licensed antipsychotics bind to D2 and D3 receptors.

In schizophrenia, there was a decrease in the number of synapses in the striatum, which controls the lateral ventral part of the tegmental area and the black substance (Grace, 2016). Impulses of dopamine neurons in the ventral sides are controlled through NMDA receptors. Only in already activated NMDA receptors, dopamine neurons can emit neurotransmitters (Azdad et al., 2009).

Dopaminomimetic drugs, including amphetamine, in rodents provoke an increased release of dopamine from the striatum and induce positive symptoms similar to acute paranoid psychosis (Peleg-Raibstein et al., 2008; Rial et al., 2014). Injections of amphetamine in rats do not destroy cells or induce gliosis, as evidenced by the absence of an increase in the level of GFAP in dorsal caudate-putamen (Peleg-Raibstein et al., 2008). With increasing levels of dopamine in the cerebral cortex of rats in astrocytes, the co-localization of NMDA with GFAP significantly decreased (Ding et al., 2014).

Also, in schizophrenia, there was a lack of dopaminergic stimulation of the prefrontal cortex. This may be the result of impaired communication between the striatum and the prefrontal cortex, including a violation of NMDA receptors, a reduced level of which in schizophrenia is noted both in the prefrontal cortex and in the striatum in *postmortem* brain study (Errico et al., 2013).

CONCLUSION

As a result of our study, we can conclude that astrocytes allow us to look at the etiology and pathogenesis of schizophrenia from a new point of view. They can explain the disparate data on morphological, metabolic and transmitter changes in the brain in schizophrenia. Astrocytes perform a supporting function for neurons, which is reflected in their ability to influence the concentration of transmitters both inside and outside the synaptic gap. Astrocytes mold the effects of dopamine in the striatal and cortical pathways through the release of glutamate and its effect on NMDA receptors. Other different mediators (adenosine, GABA, glycine) also take part in it. The presence of markers of activation of glia (S100B, GFAP, myoinositol) in serum and cerebrospinal fluid indicates a growing activation of astrocytes. Isolation of pro-inflammatory agents (cytokines, interleukins, and chemokines) and KYNA indicates a violation in the metabolism of astrocytes and surrounding cells. As a

TABLE 1 | Association between symptoms of schizophrenia and metabolites, receptors, and pharmacological agents related with astrocytes.

Positive symptoms	Negative symptoms	Cognitive symptoms
Myoinositol in striatum ↑ (Plitman et al., 2016) Kynourenic acid ↑ (Kegel et al., 2017) EAAT1 ↓ (Mei et al., 2018)	S100B in serum ↑ (Rothermundt et al., 2004) Kynourenic acid ↑ (Kozak et al., 2014; Kegel et al., 2017)	S100B in serum ↑ (Nishiyama et al., 2002; Rothermundt et al., 2004) Kynourenic acid ↑ (Kozak et al., 2014) Destruction of lactate transporters ↑ (Xia et al., 2016) EAAT1 ↓ (Mei et al., 2018) A_2A receptors ↓ (Kim et al., 2018)
Agonists mGluR2/3 ↓ (Segnitz et al., 2009) Inhibitors GlyT1 ↓ (Tsai et al., 2004)	Inhibitors GlyT1 ↓ (Tsai et al., 2004)	Inhibitors GlyT1 ↓ (Tsai et al., 2004) Inhibitors KAT-2 ↓ (Kozak et al., 2014)

↑—*positive association, magnification of symptoms;* ↓—*negative association, diminution of symptoms.*

result, this leads to changes in the structure of the brain. Morphological manifestations include a decrease in astrocyte density in the frontal cortex, changes in the composition of the extracellular matrix and glial hypertrophy. Of course, in addition to the obvious changes in the brain, astrocytes make a significant contribution to the negative, positive, and cognitive symptoms of schizophrenia.

The number of astrocytes was reduced in the prefrontal cortex, that connects altered astrocyte system with mesocortical system, and nucleus accumbens, anterior cingulate cortex, which proves the changes in glial cells in the mesolimbic system, although in the hippocampus it was increased. The differences between the number of astrocytes in the mesocortical and mesolimbic system can affect on the manifestation of schizophrenia symptoms. Associations between GFAP and symptoms have not been found. At the same time the levels of another astrocyte markers, S100B and myoinositol, positively correlated with negative and positive symptoms, respectively. This finding suggests the dual alterations in astrocyte in brain regions, related with different symptom complexes.

The imbalance between microglia and astrocytes, which occurs in neuroinflammation, influence on different neurotransmitters, such as GABA and dopamine. GABAergic interneurons, affected by oxidative stress, modulate the activity of prefrontal cortex, hippocampus and amygdala, that worsen alterations in dopamine system and, therefore, symptoms of schizophrenia.

The contribution of glia to the development of cognitive symptoms was unexpected; normally it forms compartments and connections between neurons, but altered astrocyte themselves and extracellular matrix, affected by them, disturbs these interconnections.

NMDA receptors, related with all the groups of schizophrenia symptoms, associated also with astrocytes, since NMDA antagonist increased the number of GFAP-positive astrocytes in the prefrontal cortex. Astrocyte affects as on the glutamate system *via* KYNA and altered in schizophrenia glutamate transporters, as on the glycine system *via* non-synaptic GlyT-1 and D-serine. NMDA receptors and adenosine receptors, on its turn, control the dopamine release which is still considered the main schizophrenia neurotransmitter.

The study of the contribution of astrocytes to the etiology, pathogenesis, and symptoms of schizophrenia is associated with certain problems. The researches have been focused on the study of glia in different areas of the brain, which not only makes it difficult to generalize and analyze heterogeneous reactions of astrocytes but also eliminates the relationship between these areas and their respective astrocytes. In particular, the glia of "striatum-prefrontal cortex" axis, which supposedly plays a major role in the pathogenesis of schizophrenia, requires further analysis to study the contribution of NMDA receptors. Also, the study of the genetic patterns of astrocyte pathology is needed. Some problems are associated with the astrocytes themselves, for example, there is evidence of their heterogeneity, which means that it is impossible to accurately judge the suppression or activation of astrocytes in any structure of the brain. This problem is supplemented by the dependence of astrocyte functioning on the age of patients, which is not always taken into account in case-control studies.

Further study of the effect of astrocytes on neurotransmission may clarify the currently controversial aspects of brain function in schizophrenia and explain the characteristic symptoms. For example, it is not clear why a decrease in the expression of NMDA receptors is observed in both the prefrontal cortex and the striatum, if NMDA receptors have an activating effect on dopamine neurons. A separate role in this can play KYNA, NMDA receptor antagonist, an association of which was found with all types of symptoms of schizophrenia. Special attention should be paid to the study of GLT-1, whose effect on the symptoms of schizophrenia is heterogeneous (**Table 1**). The increased level of astrocyte activation markers in many areas of the brain indicates the need for further study of the theory of inflammation in schizophrenia in general and astroglial/microglial balance in particular. Finally, it is impossible to ignore data on changes in the metabolism of neurons and glia in schizophrenia, which can also contribute to the manifestation of the disease (**Table 1**).

AUTHOR CONTRIBUTIONS

VVT, AAS, VNC, SSS, PM, DL, SGS, CEK, SOB, and GA conceptualized and designed the study. PM and DL collected and analyzed the data. All of the authors discussed the analyses, the results, and their interpretation, revised and improved the various drafts. VT, AAS, VNC, SSS, PM, DL, SGS, CEK, SOB, and GA wrote the original draft. All authors have reviewed and approved the manuscript before submission.

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frontiers in Pharmacology

ORIGINAL RESEARCH
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Are Anticholinergic Medications Associated With Increased Risk of Dementia and Behavioral and Psychological Symptoms of Dementia? A Nationwide 15-Year Follow-Up Cohort Study in Taiwan

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Background/Objective: In previous reports, the usage of anticholinergic medications has been associated with an increased risk of dementia with prolonged usage or with a high Anticholinergic Cognitive Burden (ACB). This study aimed to investigate the association between anticholinergic medications and the risk of dementia using data from Taiwan's National Health Research Database (NHIRD).

Methods: A total of 790,240 patients, with 197,560 patients receiving anticholinergic medications and 592,680 control patients (1:3) matched for sex, age, and index-year, were enrolled from the two million Longitudinal Health Insurance Dataset, a subdataset of the NHIRD, between 2000 and 2015. The time-dependent Cox regression analysis was used to explore the hazard ratio (HR) with a 95% confidence interval for the association between anticholinergics and the risk of dementia during the 15-year follow-up. The behavioral and psychological symptoms of dementia (BPSD) were recognized by the usage of psychotropics. The ACB ranged from zero to three, divided as score <1, 1–1.9, 2–2.9, 3–4.9,and ≧5. The sensitivity analysis was done by excluding the diagnoses of dementia in the first 2 or 4 years after anticholinergic usage.

Results In the anticholinergic usage cohort, the HR was 1.043 (95% CI = 0.958-1.212, $p = 0.139$) without a significant difference. The sensitivity analysis revealed no association between the usage of anticholinergics and the risk of dementia. Anticholinergic usage was not associated with BPSD. Male sex, patients of ages of 60–64 and ≧80, usage of antiparkinsonian medications, a history of Parkinson's disease, epilepsy, urinary

incontinence, depression, bipolar disorder, and psychotic disorder were independent risk factors of dementia. Increased HRs for dementia were associated with an ACB ≥ 5 and an anticholinergic usage period ≥ 1,460 days.

Conclusion: In this study, the usage of anticholinergics was not associated with the risk of dementia or BPSD in a 15-year follow-up study. However, patients with the male sex, patients with ages of 65–79 and ≧80, patients with some comorbidities, high ACB scores, and long anticholinergic treatment duration were associated with the risk of dementia.

Keywords: anticholinergic, risk, dementia, behavioral and psychological symptoms of dementia, National Health Insurance Research Database

INTRODUCTION

Among those age-dependent mental disorders, dementia is probably the most devastating. It marks a broad range of abnormalities across different dimensions of cognitive deterioration and has approximately a 5%–7% lifetime prevalence in the global population (Prince et al., 2013). The prevalence in previous community studies was 4%–8% for the population aged ≥65 years (Liu et al., 1995; Liu et al., 1998a; Liu et al., 1998b; Sun et al., 2014), and dementia could result in a burden for these patients, their caregivers, and the community in Taiwan (Tzeng et al., 2015; Tzeng et al., 2017b; Wang et al., 2018; Yeh et al., 2019).

Behavioral and psychological symptoms of dementia (BPSD) are common in patients with different types of dementia, such as psychosis, agitations, mood disorders, disinhibited behavior, sleep-wake cycle disturbances, wandering, perseveration, pathological collecting, or shouting, which are related to more rapid progression of the disease, earlier institutionalization, use of physical restraints, and higher risk of mortality (Liperoti et al., 2008; Masopust et al., 2018). As the risk factors or leading causes of dementia and the BPSD are multifarious and largely undetermined, the treatment efficacy of this disease is unsatisfactory. Future efforts are therefore required to identify the risk factors and then reduce any possible exposure to those risk factors.

Anticholinergic medications are extensively employed in clinical medicine. They are well known for their cognitive side effects, including drowsiness, delirium, sedation, and memory problems (Ruxton et al., 2015), especially among frail, older patients (Tannenbaum et al., 2012). In patients with subjective cognitive decline or neurocognitive disorders, anticholinergic drugs are associated with functional impairment, cognitive impairment, and behavioral disturbances (Carnahan et al., 2017), while the reduction of the anticholinergic burden during treatment would decrease the BPSD (Dauphinot et al., 2017). Educational programs, such as the "Improving Antipsychotic Appropriateness in Dementia Patients Educational Program" and the "Centers for Medicare and Medicaid Services Partnership to Improve Dementia Care", were used and became effective in reducing the usage of antipsychotics and anticholinergics and reducing BPSD and delirium for patients in nursing homes (Jaidi et al., 2018).

By a prospective, population-based cohort study performed in an integrated health-care delivery system in the United States, Gray and colleagues (2015) reported that the cumulative usage of strong anticholinergic medications may well be associated with a risk of dementia (Gray et al., 2015). Richardson and colleagues (2018) performed a case-control design study and provided evidence to strengthen the association between some classes of anticholinergic drugs and the incidence of later dementia (Richardson et al., 2018).

However, as to whether anticholinergics were associated with dementia should be cautiously judged as this association may be influenced by several factors. First, a longer duration between the time of anticholinergic drug usage and the diagnosis of dementia was important since the development of most types of dementia is gradual and progressive (American Psychiatric Association, 1994; American Psychiatric Association, 2000). Gray and colleagues (2015) confirmed and justified that the dementia risk from anticholinergics is based on a prospective, population-based cohort study with a mean follow-up time of 7.3 years, which might be not enough for the long-term anticholinergic consequences to progress. Second, they found that higher scores of Anticholinergic Cognitive Burden (ACB) scale might have reflected polypharmacy and greater illness burden, which might be associated with the risk of dementia (Gray et al., 2015). One previous study has shown that anticholinergic polypharmacy with higher ACB score was associated with the anticholinergic-associated dementia (Richardson et al., 2018). Third, the anticholinergic medications might induce BPSD in the patients with dementia (Carnahan et al., 2017), but it is not clear as to whether the usage of anticholinergic medications is associated with the risk of BPSD. Therefore, we conducted this study to clarify this missing information.

In the present study, we used the Taiwan National Health Insurance Research Dataset (NHIRD) to examine whether there is an association between previous anticholinergic usage, late-onset dementia, and BPSD during the longer follow-up time of 15 years.

METHODS

Data Sources

The Taiwan National Health Insurance (NHI) Program was enacted in 1995. The enrolled participants exceeded 99% of the

population and were contracted with 97% of the medical providers (Ho Chan, 2010). The details of this program have been documented in previous studies (Huang et al., 2014; Tang et al., 2015; Yang et al., 2015a; Tzeng et al., 2016; Tzeng et al., 2017a; Tzeng et al., 2017c; Chao et al., 2018; Chu et al., 2018; Tzeng et al., 2018; Tzeng et al., 2019b). The data sources of the present study were two million randomly sampled patients from the Longitudinal Health Insurance Database (LHID), a subset of the NHIRD, over a 15-year period (2000-2015). Since several previous studies have revealed a high accuracy and validity of the diagnoses in the NHIRD (Cheng et al., 2011; Liang et al., 2011; Chou et al., 2013; Hsieh et al., 2015), it is therefore suitable to use the NHIRD to examine the longitudinal association between anticholinergic usage and the potential risk of developing dementia later in life.

The diagnostic coding employed in the present study is in accordance with the International Classification of Disease, 9th revision, Clinical Modification (ICD-9-CM) diagnostic criteria from the NHI Administration (Chinese Hospital Association, 2000). All diagnoses of dementia were made by board-certified psychiatrists or neurologists, according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) and its Text Revised Edition (DSM-IV-TR) (American Psychiatric Association, 1994; American Psychiatric Association, 2000). To verify the accuracy of the diagnoses, the NHI Administration randomly and regularly reviews the records of one in 100 ambulatory care visits and one in 20 in-patient claims (Ministry of Justice, 2014). In addition, licensed medical records technicians verified the coding before claiming the reimbursements in hospitals and clinics (Tzeng et al., 2016; Tseng et al., 2019). Therefore, while only a small number of validation studies with small sample sizes have been undertaken, they have generally reported positive predictive values of over 70% for various diagnoses, thus, the NHIRD is a large, powerful data source for biomedical research (Lin et al., 2018c).

Study Design and Sampled Participants

The present study was designed as a nationwide, matched cohort study. A total of 790,240 patients, with 197,560 anticholinergic patients and 592,680 control patients. To avoid the survival bias as possible, we used the CICR analysis. The definition of exposed group was that the patients who first started to use anticholinergics in the study period, between January 1, 2000 and December 31, 2015. The matched control, or unexposed group, was 1:3 sex, age, and index-year matched individuals. Both exposed and unexposed groups were enrolled from the 2 million LHID. The anticholinergic exposed group, or the users, were individuals who ever used an anticholinergic during the whole 15-year period. The unexposed (control) group, or nonusers, individual who never used an anticholinergic during the 15-year period. The subjects with dementia or anticholinergic usage before 2000, becoming control, or the entry date were excluded in this study.

Anticholinergic drugs are classified into several categories according to the clinical effects: antidepressants, antipsychotic, antiparkinsonian, analgesics, cardiovascular, gastrointestinal, respiratory, urological, and other anticholinergic drugs (Gray et al., 2015; Richardson et al., 2018). The exclusion criteria were those using anticholinergics before 2000, those aged <50 years, and those diagnosed with dementia before January 1, 2000 or their cohort entry date. Patients with one of the following diagnoses before January 1, 2000 were excluded from the present study, including HIV infections (ICD-9 codes of 042, 043, 044, V08), motor neuron diseases (ICD-9-CM 335), multiple sclerosis (340), alcohol-related disorders [ICD-9-CM alcohol-induced psychosis (291.x), alcohol dependence (303.x), alcohol abuse (305.0), alcoholic polyneuropathy (357.5), alcoholic cardiomyopathy (425.5), alcoholic gastritis (535.3), alcoholic liver diseases (571.0, 571.1, 571.2, and 571.3)], Down syndrome (ICD-9-CM 758.0), and dementia (ICD-9-CM 290.0, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.3, 290.41, 290.42, 290.43, 290.8, 290.9, and 331.0), with references from the two aforementioned studies (**Figure 1**) (Gray et al., 2015; Richardson et al., 2018).

In addition, we included the antipsychotics, antidepressants and sedative-hypnotics of estimated treatment duration ≧30 days, to represent the occurrence of BPSD in both cohorts. We have excluded the mental health conditions before dementia diagnoses that might prompt continued use of psychotropics, such as schizophrenia or bipolar disorder.

The Classification of Anticholinergic Medications

The anticholinergic medications could be categorized as the following types of drugs: antidepressants, antipsychotics, antiparkinsonian drugs, analgesics, cardiovascular, gastrointestinal (anti-spasmodic and anti-ulcer), respiratory (anti-asthmatics), urological (for urinary incontinence), and other anticholinergics (Gray et al., 2015; Richardson et al., 2018). The present study used the Anticholinergic Cognitive Burden (ACB) as an index to quantify the degree of the anticholinergic exposure by the same score employed by others (Campbell et al., 2013): A score of 1 refers to drugs without the clinically relevant negative cognitive effects. A score of 2 refers to drugs with established and clinically relevant anticholinergic effects. A score of 3 refers to drugs with a score of 2 and are reported to be associated with delirium. All other drugs were scored as 0 (Salahudeen et al., 2015). In addition, the cumulative dosage of the anticholinergic medications was calculated as the sum of the dispensed doses of any anticholinergics from the LHID.

The Calculation of Duration and Cumulative Doses of the Medications

The data of the defined daily dosage (DDD) were obtained from the WHO Collaborating Center for Drug Statistics Methodology 2018 (https://www.whocc.no/) (World Health Organization, 2018), and the duration of the usage of anticholinergics, antidepressants, and hypnotics was calculated by dividing the cumulative doses by the DDD of these medications. For the usage of antipsychotics in the treatment of BPSD, the average daily doses of haloperidol (1.0 mg a day), risperidone (1.0 mg a day), olanzapine (7.5 mg a day), quetiapine (75 mg a day), and aripiprazole (10 mg a day), were used to calculate the duration of

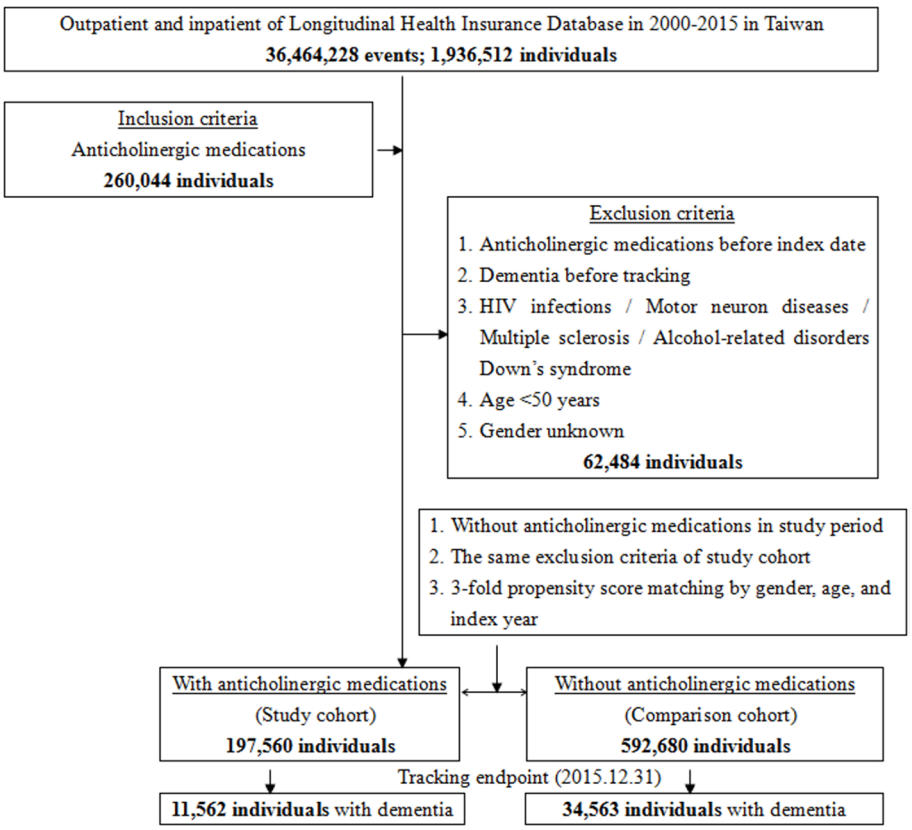

FIGURE 1 | The flowchart of study sample selection from National Health Insurance Research Database in Taiwan.

the antipsychotic usage (Chan et al., 2001; Brodaty et al., 2003; Lee et al., 2004; National Resource Center for Academic Detailing, 2013).

Covariates

Covariates included the following: sex, age group (50–64, 65–79,≧80), geographical area of residence (northern, central, southern, and eastern Taiwan), urbanization level (levels 1 to 4, as described below), monthly income (in New Taiwan dollars (NT$): < 18,000, 18,000–34,999, ≥35,000), and comorbidities. The urbanization of a patient's residence was defined by the population and indicators of the area's level of development. Level 1 urbanization was defined as a population of >1,250,000. Level 2 was defined as a population between 500,000 and 1,250,000. Urbanization levels 3 and 4 were defined as having a population between 150,000 and 500,000 and less than 150,000, respectively. Taiwan's NHI insurance premiums are based on their work salaries. Those with insurance premiums of < NT $18,000 (around US$563) a month are mostly people with lower-than-average monthly incomes or people who are not in the labor force, such as retirees, housewives, or students; those with insurance premiums of NT$18,000–NT$34,999 a month are considered to be in the mean income range (Lin et al., 2013).

In addition, baseline comorbidities with the code ICD-9-CM are listed in **Table S1** with references from the two previous studies (Gray et al., 2015; Richardson et al., 2018). These comorbidities, which were collected at the entry time in the study period in the exposed or unexposed groups, included the following: diabetes mellitus, hypertension, hyperlipidemia, stroke and transient ischemic attack, hemorrhagic stroke, transient ischemic attack, heart failure, peripheral vascular disease, coronary artery disease, atrial fibrillation, angina, myocardial infarction, deep vein thrombosis, Parkinson's disease, epilepsy, fatigue, hemiplegia and paraplegia, headache, tension-type headache, other headache syndromes, back or neck pain, peripheral neuropathy, Meniere's disease, restless leg syndrome, chronic obstructive pulmonary disease, asthma, rhinitis, gastroesophageal reflux disease, peptic or gastric ulcer, irritable bowel syndrome, inflammatory bowel disease, liver disease (except alcoholic liver diseases), osteoarthritis, rheumatoid arthritis, eczema and dermatitis, psoriasis, urinary incontinence, chronic kidney disease, cancer, prostatism, falls, fractures, obesity, depressive disorder, bipolar disorder, anxiety disorder, nonorganic sleep disorder, organic sleep disorder, and psychotic disorder, with references from the two previous studies (Gray et al., 2015; Richardson et al., 2018).

Outcome Measures

All of the participants enrolled in the present study were followed from the index date until the onset of dementia, withdrawal from

the NHI program, death, or the end of 2015. Dementia was identified by the ICD-9-CM codes of 290.0, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.3, 290.41, 290.42, 290.43, 290.8, 290.9, and 331.0. The types of dementia are grouped as follows: Alzheimer dementia (AD, ICD-9-CM 331.0), vascular dementia (VaD, ICD-9-CM 290.41-290.43), and other dementia (ICD-9-CM 290.0, 290.10-290.13, 290.20-290.21, 290.3, and 290.8-290.9).

A total of 197,560 patients who had used anticholinergics were enrolled (the study cohort), and another 592,680 patients who had not used anticholinergics were enrolled as the non-users (the comparison cohort) (**Figure 1**); thus, there was a relative 1:3 ratio of the anticholinergic cohort and the control cohort. In the anticholinergic usage cohort, 1,818 in 1975,60 individuals (0.92%) were missing due to loss of tracking and 5,394 in 592,680 (0.91%) were loss of tracking in the comparison cohort, during the 15-year of study period.

Statistical Analysis

All analyses were performed using the SPSS software version 22.0 for Windows (IBM Corp., Armonk, NY). χ^2 and t-tests were used to evaluate the distributions of the categorical and continuous variables between the patients who did and did not use anticholinergics. The time-dependent Cox regression model was used to determine the risk of dementia, and the results are presented as a hazard ratio (HR) with a 95% confidence interval (CI), censoring with death. The differences in the risk of dementia between the two groups were estimated using the CICR model method, using the computer program as STATS_COMPRISK,spe, with the log-rank test. The HR analyses were for the types, duration of usage, and cognitive burden of the anticholinergic medications. The risk of BPSD was also analyzed, and the HR analyses were for the usage of anticholinergic medications and the usage of psychotropic drugs in the patients. In addition, the interaction tests were conducted to reveal the interactions between age, sex, and comorbidities and the risk of dementia in patients with anticholinergic usage, and the sensitivity analysis was used by excluding the diagnoses of dementia in the first 2 or 4 years, to eliminate any potential protopathic bias. A two-tailed p-value < 0.05 was considered to be statistically significant.

Ethical Approval

This study was carried out in accordance with the recommendations of the NHI Administration, which has given general approval for the use of their data in this research (Chen et al., 2011).

According to the Declaration of Helsinki (World Medical Association, 2013), The protocol was approved by the Institutional Review Board and the Ethical Committee (IRB/EC) of the Tri-Service General Hospital (IRB No. 2-107-05-026), and the IRB/EC of the Tri-Service General Hospital has exempted the requirement for written informed consents in this study, since any identifiable, personal information included in the NHIRD was encrypted to protect the patient's individual privacy (Chen et al., 2011).

RESULTS

Baseline Characteristics of the Study Population

Table 1 shows the sex, age, comorbidity, level of urbanization, and geographical location of the anticholinergic users and the non-users. The anticholinergic users were associated with lower comorbidity rates of diabetes mellitus, stroke, heart failure, Parkinson's disease, epilepsy, hemiplegia and paraplegia, back or neck pain, Meniere's disease, chronic obstructive pulmonary syndrome, asthma, peptic or gastric ulcer, liver disease, chronic kidney disease, and cancer than the non-users. In contrast, the anticholinergic users were associated with higher comorbidity rates of hypertension, hyperlipidemia, myocardial infarction, headache, rhinitis, a fall injury, a fracture, obesity, depression, bipolar disorder, anxiety, and nonorganic sleep disorders than the non-users. In addition, the patients who used anticholinergics received more hospital-based care.

CICR Curves for Dementia in Patients With the Usage of Anticholinergic Medications

At the end of the present study, 46,820 of the 790,240 enrolled patients developed dementia, including 11,737 of the 197,560 (523.84 per 100,000 person-years) patients who used anticholinergics and 35,083 of the 592,680 (482.31 per 100,000 person-years) non-users patients (**Figure 1**). **Figure 2** shows the CICR curves, by using the computer program as STATS_COMPRISK,spe, for the CICR of dementia for the study cohort and for the comparison cohort with the log-rank test. There was no difference between the anticholinergic users and the non-users in the risk of development of dementia over the 15-year follow-up period ($p = 0.178$).

The Usage of Anticholinergic Medications Is Not Associated With an Increased HR for Dementia

Table 2 shows that the anticholinergic usage was not associated with the increased risk of dementia as the HR was 1.043 (95% CI = 0.958-1.212, $p = 0.139$). **Table S3** shows that hazard ratios was 1.054 (95% CI = 0.930-1.175, $p = 0.088$) with the analysis by using only the level 2 and level 3 anticholinergic medications. In this study, most of the comorbidities are as mentioned above, and the locations in Taiwan, urbanization levels, and levels of medical care were not associated with the increased risk of dementia (data not shown). Male patients, patients of age of 65–79 and ≥ 80 years, and comorbidities, such as stroke, Parkinson's disease, epilepsy, hemiplegia and paraplegia, asthma, urinary incontinence, depression, bipolar disorder, and psychotic disorder, were independent risk factors of dementia, in both all levels of ACB (**Table 2**) and ACB of Level 2 and Level 3 rated drugs (**Table S3**). In addition, the interaction test revealed that age male patients and patients of age of 65-79 and ≥ 80 years in the anticholinergic usage cohort were associated with the risk of dementia. However, the association between several comorbidities, such as stroke,

TABLE 1 | Characteristics of study at the baseline.

Anticholinergic medications	With		Without		P
Variables	**n**	**%**	**n**	**%**	
Total	197,560	25.00	592,680	75.00	
Sex					0.999
Male	101,059	51.15	303,177	51.15	
Female	96,501	48.85	289,503	48.85	
Age (years)	64.32 ± 9.99		64.35 ± 9.89		0.244
Age group (years)					0.999
50–64	100,465	50.85	301,395	50.85	
65–79	58,012	29.36	174,036	29.36	
≧80	39,083	19.78	117,249	19.78	
Education (years)					0.576
< 12	108,345	54.84	325,632	54.94	
≧12	89,215	45.16	267,048	45.06	
Insured premium (NT$)					0.286
< 18,000	164,558	83.30	493,129	83.20	
18,000–34,999	20,090	10.17	61,208	10.33	
≧35,000	12,912	6.54	38,343	6.47	
Diabetes mellitus	33,513	16.96	107,557	18.15	<0.001
Hypertension	51,933	26.29	131,234	22.14	<0.001
Hyperlipidemia	8,869	4.49	18,374	3.10	<0.001
Stroke	16,884	8.55	59,213	9.99	<0.001
Heart failure	5,238	2.65	20,211	3.41	<0.001
Peripheral vascular disease	115	0.06	412	0.07	0.996
Atrial fibrillation	3,578	1.81	11,103	1.87	0.186
Angina	3,294	1.67	9,788	1.65	0.737
Myocardial infarction	6,475	3.28	17,677	2.98	<0.001
Deep vein thrombosis	496	0.25	1,325	0.22	0.124
Parkinson's disease	1,347	0.68	4,533	0.76	0.006
Epilepsy	441	0.22	1,791	0.30	0.001
Hemiplegia & paraplegia	2,568	1.30	10,927	1.84	<0.001
Headaches	1,024	0.52	2,718	0.46	0.013
Back or neck pain	477	0.24	1,831	0.31	0.002
Peripheral neuropathy	2,113	1.07	6,755	1.14	0.062
Meniere's disease	619	0.31	3,201	0.54	0.001
Restless leg syndrome	0	0	0	0	–
Chronic obstructive pulmonary syndrome	12,753	6.46	55,060	9.29	<0.001
Asthma	4,171	2.11	17,827	3.01	<0.001
Rhinitis	1,077	0.55	1,904	0.32	<0.001
Gastroesophageal reflux	659	0.33	5	<0.01	<0.001
Peptic or gastric ulcer	13,322	6.74	47,185	7.96	<0.001
Irritable bowel syndrome	212	0.11	680	0.11	0.998
Inflammatory bowel disease	139	0.07	501	0.08	0.184
Liver disease	6,378	3.23	35,096	5.92	<0.001
Osteoarthritis	6,804	3.44	16,088	2.71	<0.001
Rheumatoid arthritis	767	0.39	2,333	0.39	0.865
Eczema & dermatitis	1,010	0.51	3,113	0.53	0.682
Psoriasis	176	0.09	509	0.09	0.797
Urinary incontinence	154	0.08	379	0.06	0.257
Chronic kidney disease	6,759	3.42	35,768	6.03	<0.001
Cancer	17,149	8.68	55,829	9.42	<0.001
Prostatism	0	0	0	0	–
Falls	8,180	4.14	20,135	3.40	0.002
Fractures	18,795	9.51	44,736	7.55	<0.001
Obesity	96	0.05	172	0.03	0.014
Depression	1,425	0.72	330	0.06	<0.001
Bipolar disorder	201	0.10	469	0.08	0.042
Anxiety	1,562	0.79	3,811	0.64	0.002
Non-organic sleep disorders	1,939	0.98	4,442	0.75	0.001
Organic sleep disorders	3	<0.01	1	<0.001	<0.001
Psychotic disorders	1,495	0.76	4,720	0.80	0.297
Location					<0.001
Northern Taiwan	77,954	39.46	229,607	38.74	
Middle Taiwan	56,611	28.66	168,415	28.42	
Southern Taiwan	51,434	26.03	154,980	26.15	
Eastern Taiwan	10,674	5.40	36,810	6.21	
Outlets islands	887	0.45	2,868	0.48	
Urbanization level					<0.001
1 (The highest)	63,609	32.20	195,570	33.00	
2	89,528	45.32	259,075	43.71	
3	13,068	6.61	42,383	7.15	
4 (The lowest)	31,355	15.87	95,652	16.14	
Level of care					<0.001
Medical center	74,815	37.87	212,693	35.89	
Regional hospital	78,602	39.79	203,733	34.37	
Local hospital	44,143	22.34	176,254	29.74	

P, Chi-square test on category variables and t-test on the continuous variables; NT$, New Taiwan Dollars.

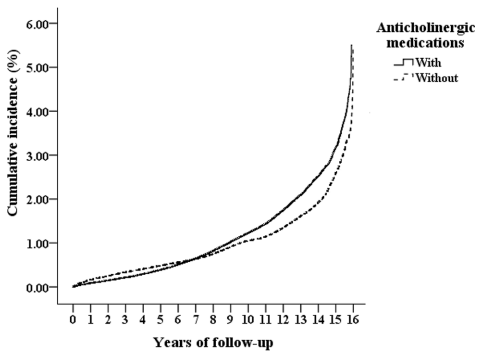

FIGURE 2 | Cumulative incidence competing risk (CICR, the vertical axis) of dementia aged 50 years and over, stratified based on the exposure of anticholinergic medications, in the 15-year of follow up (the horizontal axis), with log-rank test (Log-rank $p = 0.178$).

hemiplegia and paraplegia, and asthma, and the risk of dementia, were statistically insignificant (**Table 2**).

HR Analyses of the Types, Duration, Cognitive Burden of Anticholinergic Medications, and the Risk of Dementia

In this study, most of the types of the anticholinergic medications, the duration of the anticholinergic usage <1,460 days, and the Anticholinergic Cognitive Burden scale (ACB scale) < 5, were not associated with the risk of dementia. The time-dependent Cox regression hazards risk model showed significant findings in the usage of antiparkinsonian drugs were associated with the risk of dementia, HR: 1.328 [95% CI, 1.038–1.677, $p = 0.015$]. In addition, the longer duration of the

TABLE 2 | Hazard ratios of dementia in different factors, analyzed by using time-dependent Cox regression analysis.

Variables	Time-dependent Cox regression								Interaction test
	Crude HR	95% CI	95% CI	*P*	aHR	95% CI	95% CI	*P*	*P*
Anticholinergic medications									
Without	Reference				Reference				
With	1.095	0.966	1.225	0.127	1.043	0.958	1.212	0.139	
Male *(Reference: female)*	1.083	1.015	1.146	0.017	1.019	1.005	1.033	0.045	0.025
Age 65-79 *(Reference: age 50–64)*	1.085	1.025	1.139	0.026	1.031	1.012	1.056	0.031	0.006
Age ≧ 80 *(Reference: age 50–64)*	2.201	2.167	2.286	<0.001	1.429	1.400	1.456	<0.001	
Stroke *(Reference: without)*	3.253	3.172	3.337	<0.001	1.656	1.633	1.680	<0.001	0.058
Parkinson's disease *(Reference: without)*	4.399	4.200	4.607	<0.001	1.652	1.612	1.690	<0.001	0.002
Epilepsy *(Reference: without)*	3.745	3.434	4.073	<0.001	1.485	1.423	1.552	<0.001	0.009
Hemiplegia & paraplegia *(Reference: without)*	2.836	2.626	3.063	<0.001	1.100	1.057	1.147	<0.001	0.235
Asthma *(Reference: without)*	1.833	1.766	1.904	<0.001	1.102	1.025	1.188	0.022	0.179
Urinary incontinence *(Reference: without)*	2.419	1.657	2.786	<0.001	1.249	1.095	1.424	<0.001	0.042
Depression *(Reference: without)*	2.614	2.108	3.243	<0.001	1.410	1.359	1.463	<0.001	<0.001
Bipolar disorder *(Reference: without)*	2.614	2.108	3.243	<0.001	1.442	1.295	1.609	<0.001	0.001
Psychotic disorders *(Reference: without)*	2.254	2.059	2.467	<0.001	1.296	1.236	1.355	<0.001	<0.001

HR, hazard ratio, CI, confidence interval, aHR, Adjusted hazard ratio: Adjusted for the variables listed in the table.
T_Cov × Anticholinergic medications: The analysis of the interaction between anticholinergic medications and dementia in different time-periods, the P was 0.007 (Crude HR model), the P was 0.053 (aHR model), after adjusted all the covariates, which is statistically insignificant.

anticholinergic exposure ≥1,460 days, HR: 1.191 [95% CI, 1.005–1.386, $p = 0.045$], and a higher level ACB scale scores, ≥5,HR: 1.317 [95% CI, 1.041–1.530, $p = 0.001$], were associated with the risk of dementia (**Table 3**).

A Sensitivity Analysis for the Association Between the Usage of Anticholinergic Medications and Dementia

We have conducted the sensitivity analysis to evaluate the risk of dementia. We have excluded the patients diagnosed with dementia within the first 2 and the first 4 years after the usage of anticholinergics. No association between anticholinergic usage was found after excluding the diagnosis of dementia with the first 2 and the first 4 years after the usage of anticholinergics (**Table 4**).

HR Analysis for the Usage of Anticholinergic Medications and the Usage of Psychotropic Drugs

There were no direct codes in the ICD-9-CM system for the BPSD, however, we identified a substitute for the BPSD by recording the usage of psychotropics, such as antipsychotics, antidepressants, and hypnotics after the dementia diagnosis in the anticholinergic cohort or the control group. **Table 5** shows that in the patients who developed dementia during this study, there were no significant differences in the usage of overall psychotropic drugs, antipsychotics, and antidepressants between the patients from the anticholinergic cohort and the non-users. The only exception was the marginal difference between the usage of hypnotics in the anticholinergic cohort and the non-users as follows: 40.03% (N = 79,083) vs 38.44% (N = 227,855), respectively, ($p = 0.015$). In addition, there were no differences between the usage of combination drugs, monotherapy drugs, or none of the psychotropic drugs in these two groups.

DISCUSSION

No Association Exists Between the Usage of Anticholinergic Medications and the Risk of Dementia

In this 15-year follow-up cohort study, the usage of anticholinergic medications was not associated with the risk of dementia. At the end of the study, the rate of patients with dementia was 5.92%, which is within the range of the finding of 4%–8% in the previous community studies on dementia prevalence in Taiwan in those aged ≥65 years (Liu et al., 1995; Liu et al., 1998a; Liu et al., 1998b; Sun et al., 2014); thus confirming that this study was conducted on a representative sample population.

Protopathic bias arises when the initiation of a drug (exposure) occurs in response to a symptom of the (at this point undiagnosed) disease under study (outcome), which reflects a reversal of cause and effect. This is particularly a problem in studies of drug-cancer associations and other outcomes with long latencies We handled this bias by the sensitivity analysis (Gerhard, 2008; European Network of Centres for Pharmacoepidemiology and Pharmacovigilance, 2018). Based on the sensitivity analysis in **Table 4** and the year-tracking comparison between anticholinergic users and no-users in **Table S2**, the usage of anticholinergic medications was not found to be associated with overall dementia. Also, when protopathic bias and the carry-over effects (Schuemie et al., 2012) were removed by excluding the first two and four years of dementia, there was no statistical significance. To the best of our knowledge, this is the first nationwide, population-based, matched-cohort study with a 15-year follow-up on the topic of the association between the usage of anticholinergic medications and the risk of dementia. The results from this study are different from the findings of previous studies, which revealed the association between the usage of anticholinergic medications

TABLE 3 | Factors of dementia by using time-dependent Cox regression analysis among different models.

Model		Anticholinergic medications				Time-dependent Cox regression			
	Subgroup	Events	Population	PYs	Rate (per 10^5 PYs)	aHR	95% CI	95% CI	*P*
Model 1	Without	34,563	592,680	7,274,012	475.16	Reference			
With/Without	With	11,562	197,560	2,240,667	516.01	1.043	0.958	1.212	0.139
Model 2	Antidepressants	1,683	13,755	193,180	871.21	1.127	0.926	1.395	0.196
Types of anticholinergics	Antipsychotic	2,874	35,121	454,513	632.33	1.108	0.881	1.361	0.213
(Reference: without)	Antiparkinsonian drugs	512	1,836	23,444	2,183.93	1.328	1.038	1.677	0.015
	Analgesics	6,274	110,040	1,317,079	476.36	0.997	0.805	1.277	0.633
	Cardiovascular drugs	8,195	98,192	1,300,518	630.13	1.077	0.865	1.434	0.434
	Gastrointestinal drugs	5,198	69,898	907,841	572.57	1.049	0.883	1.270	0.166
	Respiratory drugs	6,471	73,617	965,142	670.47	1.086	0.891	1.146	0.197
	Urological drugs	603	4,542	66,038	913.11	1.129	0.929	1.234	0.135
	Other drugs	6,210	76,643	1,001,697	619.95	1.048	0.831	1.121	0.304
Model 3	0	34,563	592,680	7,274,012	475.16	Reference			
Anticholinergic medications durations	1–3 days	1,514	28,442	337,055	449.18	0.995	0.819	1.211	0.397
(drug exposure period)	14–89 days	2,006	37,643	437,136	458.90	1.056	0.921	1.240	0.284
	90–364 days	2,391	43,490	488,266	489.69	1.126	0.955	1.293	0.142
	365–1,459 days	2,888	54,292	528,679	546.27	1.158	0.979	1.315	0.079
	≧1,460 days	2,763	33,693	449,531	614.64	1.191	1.005	1.386	0.045
Model 4	0	34,563	592,680	7,274,012	475.16	Reference			
Anticholinergic Cognitive Burden scale	<1	1,865	36,654	398,053	468.53	1.032	0.759	1.044	0.597
	1–1.9	2,297	42,781	475,926	482.64	1.042	0.848	1.084	0.422
	2–2.9	3,432	52,222	697,301	492.18	1.132	0.935	1.291	0.126
	3–4.9	1,981	34,820	352,483	562.01	1.206	0.990	1.359	0.056
	≧5	1,987	31,083	316,904	627.00	1.317	1.041	1.530	0.001

*PYs, Person-years; aHR, Adjusted hazard ratio: Adjusted for the variables listed in **Table 1**; CI, confidence interval; P, Chi-square test on category variables and t-test on the continuous variables.*

TABLE 4 | Factors of dementia subgroup and sensitivity analysis by using time-dependent Cox regression analysis.

Anticholinergic medications (With vs. Without)		Time-dependent Cox regression			
Sensitivity analysis	**Dementia subgroup**	**aHR**	**95% CI**	**95% CI**	***P***
Overall	All dementia	1.043	0.958	1.212	0.139
	AD	1.115	0.990	1.296	0.060
	VaD	1.039	0.975	1.208	0.149
	Other degenerative dementia	1.031	0.964	1.207	0.178
First 2 years excluded	All dementia	1.040	0.977	1.208	0.089
	AD	1.112	0.987	1.290	0.075
	VaD	1.023	0.961	1.188	0.224
	Other degenerative dementia	1.036	0.973	1.205	0.138
First 4 years excluded	All dementia	1.024	0.962	1.190	0.162
	AD	1.087	0.982	1.263	0.077
	VaD	0.994	0.934	1.155	0.394
	Other degenerative dementia	1.023	0.961	1.189	0.248

*PYs, Person-years; aHR, Adjusted hazard ratio: Adjusted for the variables listed in **Table 1**.; CI, confidence interval; AD, Alzheimer dementia; VaD, Vascular dementia; P, Chi-square test on category variables and t-test on the continuous variables.*

TABLE 5 | Usage of psychotropic drugs in the dementia patients.

Dementia	With anticholinergics (N = 197,560)	Without anticholinergics (N = 592,680)	P
Overall psychotropic drugs	188,927 (95.63%)	564,409 (95.23%)	0.196
Antipsychotics	103,028 (52.15%)	306,239 (51.67%)	0.484
Antidepressants	89,176 (45.14%)	271,625 (45.83%)	0.322
Hypnotics	79,083 (40.03%)	227,855 (38.44%)	0.015
Combination of different classes of drugs			0.346
≧2	73,354 (37.13%)	216,862 (36.59%)	
1	115,572 (58.50%)	347,547 (58.64%)	
0	8,634 (4.37%)	28,271 (4.77%)	

P, Chi-square test on category variables and t-test on the continuous variables.

and the increased risk of dementia (Carriere et al., 2009; Jessen et al., 2010; Gray et al., 2015; Richardson et al., 2018).

Comparison of This Study With the Previous Literature

Two cohort studies (Jessen et al., 2010; Gray et al., 2015) and two case control studies (Carriere et al., 2009; Richardson et al., 2018) have reported the association between anticholinergic medication usage and the risk of dementia. In comparison to

these studies, our study has several advantages: First, it was conducted in a nationwide, population-based sample, instead of in regional samples like the other studies. Second, we used a larger sample size of approximately 400,000 patients, which outnumbered those of other studies. Third, our study spanned a 15-year follow-up, longer than the other studies with either a 4-year (Jessen et al., 2010) or 10-year follow-up period (Gray et al., 2015).

In the present study, the risk of dementia was found to be increased with a longer duration of anticholinergic usage (≥1,460 days) or a higher ACB scores (a score of 5 or higher), and these results were similar to the findings of Gray and colleagues (2015) (≥1,095 days) (Richardson et al., 2018) and Richardson and colleagues (2018) (Gray et al., 2015). In addition, cardiovascular drugs, analgesics, and respiratory drugs were the three leading medications with anticholinergic effects in the present study. It is highly possible that it is the physical problems themselves, or certain comorbidities that increase with aging, which needed to be treated with anticholinergic medications, were responsible for the risk of dementia. Thus, we might design a multicenter prospective cohort study, to include different indications and stratify by different indications. This may allow to conclusively show that the results are caused by the exposure rather than the indication (Catalogue of bias collaboration, et al., 2018). In addition, there was an apparent "dose-response effect" with the increased risk for higher ACB, and longer duration of anticholinergic exposure; however, the medical conditions that led the patients to take the anticholinergic medications might also contribute to the risk factors for dementia. Nonetheless, this observation should remind clinicians to be cautious when prescribing medications with a high ACB score and a longer duration of anticholinergic usage.

A similar finding in a recent nested case control study found that the anticholinergic antidepressants, antiparkinsonian drugs, antipsychotics, bladder antimuscarinic drugs, and antiepileptic drugs were associated with the risk of dementia. All anticholinergic medications with longer duration of the usage for more than 1,095 total standardized daily doses (TSDDs) were associated this risk. These associations were stronger in cases diagnosed before the age of 80 years (Coupland et al., 2019).

Sex and the Risk of Dementia

In this study, male sex was associated with risk of dementia. Previous studies have shown that, in AD, low education has been historically a risk factor for women, bilateral oophorectomy is a factor associated with women, and the apolipoprotein E genotype is equally common in men and women but has a stronger effect in women (Rocca et al., 2014). On the other hand, male patients with Parkinson's disease progressed more rapidly than females in the transition from no cognitive impairment to Parkinson's disease dementia (Cholerton et al., 2018). However, the influences of sex on the risk of dementia remains unclear and further studies may well be needed to examine the association among male patients, anticholinergic usage, and the risk of dementia.

Aging, Comorbidities and the Risk of Dementia

In our study, the patients with anticholinergic exposure aged 65–79 and ≥80 years were associated with a higher risk of dementia, in comparison to the patients with aged 50–64 years. Several previous studies have reported that aging itself is a risk factor of dementia development (Liu et al., 1995; Liu et al., 1998a; Liu et al., 1998b; Sun et al., 2014).

Along with previous evidence, our data also demonstrate that, in certain patient groups with several comorbidities, anticholinergics treatment had associations with the risk of dementia. These comorbidities themselves may serve as independent risk factors for dementia, including stroke (Yang et al., 2015b; Corraini et al., 2017; Shih et al., 2017), Parkinson's disease (Breteler et al., 1995; Riedel et al., 2008; Jessen et al., 2010), epilepsy (Breteler et al., 1995; Sen et al., 2018), hemiplegia and paraplegia (Bejot et al., 2011; Huang et al., 2017), asthma (Rusanen et al., 2013; Su et al., 2014; Peng et al., 2015), depression (Yang et al., 2015b; Yang et al., 2015c; Huang et al., 2017), bipolar disorder (Wu et al., 2013; Yang et al., 2015b), and psychotic disorder (Lin et al., 2018a; Almeida et al., 2019). Notice that urinary incontinence was one of the key components of impaired activity daily living (ADL) (Gosch et al., 2015; Greer et al., 2015), which is a predictor of the risk of dementia (Fauth et al., 2013). However, the association between several comorbidities, such as stroke, hemiplegia and paraplegia, and asthma, and the risk of dementia, were statistically insignificant in this study.

Overall, we might well attribute the risk of dementia to aging and the comorbidities themselves, instead of the impact from the usage of anticholinergic medications, per se. Since anticholinergic usage could be related to drowsiness, delirium, sedation, and memory problems (Ruxton et al., 2015), especially among frail, older patients (Tannenbaum et al., 2012), clinicians are advised to balance the risks against benefits when considering the usage of anticholinergic medications for the elderly.

The Different Types of Anticholinergic Medications and Their Impact on Cognitive Function

In this study, the usage of antiparkinsonian anticholinergics was associated with the increased risk of dementia. Antiparkinsonian drugs were mostly used for Parkinson's disease (Leoni et al., 2002; De Germay et al., 2016) and for managing the extrapyramidal side effects with antipsychotic usage for psychotic disorders (Hunter, 1981; Xiang et al., 2007). Therefore, this finding might also be related to the fact that Parkinson's disease and psychotic disorders have been associated with the risk of dementia as aforementioned. Several previous studies have reported the association between antidepressant usage and the risk factor for dementia (Lee et al., 2016; Then et al., 2017); nevertheless, our study revealed no such association between antidepressants with anticholinergic effects (most tricyclic antidepressants) and the risk of dementia. In addition, one study using the NHIRD database reported the association between antimuscarinics for an overactive bladder (OAB) and

the subsequent dementia risk in patients with diabetes mellitus (Yang et al., 2017). However, in our study, the usage of urological drugs (antimuscarinics, such as oxybutynin, solifenacin, and tolterodine) was not associated with the risk of dementia. In addition, a recent study found that OAB, instead of the use of antimuscarinic urological drugs, was associated with the increased risk of psychiatric disorders, including dementia (Tzeng et al., 2019a).

The Use of Anticholinergic Medications and BPSD

It is needed to appraise the influences of anticholinergic usage on BPSD, since the exposure to some medications could result in long term effects. For example, antipsychotics might cause long-term effects such as tardive dyskinesia. Antipsychotics and anticholinergic might share some mechanisms, which were underscored by the proposed use of anticholinergics to treat tardive dyskinesia (Bergman and Soares-Weiser, 2018). For collecting the data of long-term side effects, the post-marketing pharmacovigilance is necessary regarding newer muscarinic antagonists, such as glycopyrronium, aclidinium, and umeclidinium (Tashkin, 2015), since the anticholinergic drugs are related to the side effects as tooth decay, cardiac side effects (Rogliani et al., 2018), and the increased risk of cancer in patients with chronic obstructive pulmonary disease (COPD) (Lin et al., 2018b).

Furthermore, while we recognized BPSD from the records of usage of psychotropics, such as antipsychotics, antidepressants, and hypnotics, after dementia was diagnosed in the anticholinergic cohort or the non-users, there were no significant differences between the anticholinergic and the comparison cohorts in the overall usage of the psychotropic drugs, antipsychotic drugs, and antidepressants in this study; in addition, there was quite a marginal difference between the usage of hypnotics at 40.03% vs 38.44% (p = 0.015) in the anticholinergic cohort and the non-users, respectively. Monotherapy or polypharmacy showed no significant difference between the anticholinergic usage and psychotropic usage in both groups. In other words, the anticholinergic drugs were not associated with BPSD, which was represented by the usage of the psychotropic medications after the diagnosis of dementia. Antiepileptic medications were not included in this analysis since antiepileptics, such as carbamazepine and valproic acid, had limited or conflicting effects for the treatment of BPSD (Sink et al., 2005; Franco and Messinger-Rapport, 2006; Yeh and Ouyang, 2012; Tzeng et al., 2017b), and one previous study in Taiwan has shown that only 1% of the patients with BPSD received antiepileptics as a treatment (Tsai et al., 2010). A multicenter, prospective follow-up study might be necessary to clarify the association between the previous use of anticholinergic medications and the risk of BPSD.

The reason why the anticholinergic usage was not associated with the risk of BPSD remains unclear. We hypothesize that the upregulation of muscarinic receptors, in the long-term use of anticholinergic medications (Hori et al., 2014), might play a role in such a phenomenon. However, more studies are needed to clarify the underlying mechanisms.

Limitations

Several limitations/concerns of the present study should be addressed. First, as in many previous NHIRD-based studies, our study is retrospective and dependent upon the ICD-9-CM codes instead of the direct medical records or the interview data. It is necessary to conduct a study, with a prospective cohort study design, to achieve a more accurate and consistent finding. Therefore, the lack of detailed records and misdiagnosis-related errors may have occurred. Second, the NHIRD database does not contain genetic, nutritional, or habitual factors, such as the apolipoprotein E genotype, record of smoking, and body mass index that were not included in this database, and in such a claims database study, we could only estimate the treatment durations of each anticholinergics by dividing the cumulative doses of individual medications by DDD. The role of blood brain barrier (BBB) plays an important role in the central nervous system side effects of anticholinergic medications. The factors determining the penetration of anticholinergic medications might include passive diffusion, active transport, lipophilicity, the polarity of the chemical, and molecular size (Staskin and Zoltan, 2007). Small, lipophilic, noncharged molecular compounds (tertiary ammonium groups) pass the BBB more readily than those containing a quaternary ammonium group (van de Waterbeemd et al., 1998). Furthermore, the data such as serial amyloid scans or some more sensitive measure of dementia were not available in this NHIRD claims database. Third, this national review insurance database cannot provide detailed information, including the severity, stage, and care-giver burden of the patients with dementia. Fourth, the use of the ACB scale has some limitations as it includes drugs without clinically relevant negative cognitive effects, and there is a lack of serum anticholinergic activity levels validation. Fifth, the recognition of BPSD by the records of psychotropic usage is also a limitation. However, in one study in Taiwan, only 7% of patients with dementia did not receive any psychiatric medication (Lin, 2011). Sixth, the records of the medications obtained from the NHIRD for big data studies, including the anticholinergic study, were listed as the total dose(s) of the referred medication(s) in this database. Therefore, we identified the use of the patients who first started an anticholinergic regimen between January 1, 2000 and December 31, 2015, instead of the exact date of anticholinergic usage. Seventh, it is not easy to distinguish the effects of anticholinergic drugs, and know the underlying disease and permeability of crossing the blood brain barrier types of anticholinergics in the present study. Seventh, since the nonusers were individual who never used an anticholinergic during the 15-year period, there could be a limitation producing the conditioning on future exposure and risk of bias (Lund et al., 2017). Finally, the timing of the records of the use of psychotropics (i.e., antipsychotics, antidepressants, and hypnotics) to recognize BPSD could not be identified, since these were also listed as the total dose(s) of the referred

medication(s) in this database. The survival bias might occur by using this method of estimation of duration of the anticholinergic usage to investigate the risk of dementia, with the reference from one previous study of a similar design (Gray et al., 2015). However, we used the time-varying cumulative exposure analysis, to avoid the survival bias possible. Therefore, a multicenter, prospective observational study might well be necessary to clarify the association between the previous use of anticholinergic medications and the risk of BPSD.

CONCLUSION

The strength of the present study lies in the large population dataset with strong attempts to control the disease-related protopathic bias. In this study, the usage of anticholinergics was not associated with the risk of dementia or BPSD from a 15-year follow-up study in Taiwan. However, the groups of male patients, patients of age of 65–79 and ≥ 80 years, with comorbidities as Parkinson's disease, epilepsy, urinary incontinence, depression, bipolar disorder, and psychotic disorder, higher ACB scores, and the long duration of treatment, were associated with the risk of dementia. Based on the results of this study, clinicians are advised to balance the risks and benefits when considering the usage of anticholinergic medications.

ETHICS STATEMENT

In comparison to the Code of Ethics of the World Medical Association (Declaration of Helsinki) (World Medical Association, 2013), a written informed consent was not obtained from the participants in the encrypted data for this study. Since the identifiable database of the individuals included in the NHIRD were all encrypted in order to protect individual privacy (Chen et al., 2011), the NHI Administration has given general approval for their data to be used in this research (Chen et al., 2011). Because the NHIRD has the advantage in providing a large-scale, longitudinal, reliable dataset, leading to extensive uses for the population-based researches in Taiwan (Hsiao et al., 2007; Chen et al., 2011; National Health Research Institutes, 2015), the Institutional Review Board (IRB, the ethical committee) of the Tri-Service General Hospital was aware of this and approved the research to proceed, and also agreed that the benefit justified waiving the need for individual written informed consent in such a study (IRB No. 2-107-05-026).

AUTHOR CONTRIBUTIONS

Y-PL and N-ST conceived and conducted this study. Y-PL, W-CC, N-ST, and C-HC conducted data collection, data analysis, and data interpretation. H-AC and Y-CK conducted data interpretation. Y-PL and N-ST wrote the manuscript. All authors approved this manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2020.00030/full#supplementary-material

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Large Sample Size Fallacy in Trials About Antipsychotics for Neuropsychiatric Symptoms in Dementia

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Background: A typical antipsychotics for neuropsychiatric symptoms in dementia have been tested in much larger trials than the older conventional drugs. The advantage of larger sample sizes is that negative findings become less likely and the effect estimates more precise. However, as sample sizes increase, the trials also get more expensive and time consuming while exposing more patients to drugs with unknown safety profiles. Moreover, a large sample size might yield a statistically significant effect that is not necessarily clinically relevant.

Objective: To assess (1) the variation in sample size and sample size calculations of antipsychotic trials in dementia, (2) the size of reported treatment effects and related statistical significance, and (3) general study characteristics that might be related to sample size.

Study Design and Setting: We performed a meta-epidemiological study of randomized trials that tested antipsychotics for neuropsychiatric symptoms in dementia. The trials compared conventional or atypical antipsychotics with placebo or another antipsychotic. Two reviewers independently extracted sample size, sample size calculations, reported treatment effects with p-values, and general study characteristics (drug type, trial duration, type of funding). We calculated a reference sample size of 83 and 433 per study group for the placebo-controlled and head-to-head trials respectively.

Results: We identified 33 placebo-controlled trials, and 18 head-to-head trials. Only 14 (42%) and 2 (11%), respectively, reported a sample size calculation. The average sample size per arm was 34 (range 6–179) in placebo-controlled trials testing conventional drugs, 107 (8–237) in such trials testing atypical drugs, and 104 (95–115) in such trials testing both drug types; it was 31 (10–88) in head-to-head trials. Thirteen out of 18 trials with sample sizes larger than required (72%) reported a statistically significant treatment effect, of which two (15%) were clinically relevant. None of the head-to-head trials reported a statistically significant treatment effect, even though some suggested non-inferiority. In placebo-controlled trials of atypical drugs, longer trial duration (>6 weeks) and commercial funding were associated with higher sample size.

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Conclusion: Sample size calculations were poorly reported in antipsychotic trials for dementia. Placebo-controlled trials of atypical antipsychotics showed large sample size fallacy while head-to-head trials were massively underpowered.

Keywords: sample size, power, antipsychotics, dementia, placebo-controlled trials, head-to-head trials, meta-epidemiological study

INTRODUCTION

Over the years the sample sizes of antipsychotic trials in dementia have increased from as low as 18 in the 1960s to as high as 652 in the 1990s (Schneider et al., 2005; Cox Grad, 2009; Hulshof et al., 2015). The increase in sample sizes is generally viewed as a favorable development. Larger sample sizes provide more power to identify a treatment effect that is really present. In addition, the effect is estimated more precisely (smaller confidence intervals). Larger trials are also a natural consequence of head-to-head trials because the difference between two active drugs is generally expected to be small, and therefore, the required sample size needs to be relatively high.

However, larger sample sizes also make trials expensive and time consuming (Cox Grad, 2009). This can be barrier for non-commercial investigators to perform a trial. Moreover, it can be ethically questionable to ask more patients to participate, especially when the safety of the tested drug has not yet been established (Schipper and Weyzig, 2008). Another disadvantage of (very) large sample size is that a difference in outcomes between the groups will become (very) statistically significant, no matter how small or clinically meaningless it is (Sullivan and Feinn, 2012). If such results are nevertheless interpreted as clinically relevant, the 'large sample size fallacy' occurs (Lantz, 2013).

Sample size calculations for trials are based on four parameters if the response rate is the outcome. These are alpha, beta, the expected response rate in the active treatment groups, and the expected response rate in the comparison group (e.g. placebo) (Noordzij et al., 2010). Alpha is the probability of identifying a treatment effect that is not really present, which is usually set at 5%. Beta is the risk of not identifying a treatment effect that is really present, and is usually set at 20%. Sample size calculations for trials with continuous outcomes, such as the reduction of neuropsychiatric symptoms (NPS), are based on alpha, beta, the expected (difference between) means in the active and comparison group, and the population variance around the mean. Furthermore, the expected number of participants dropping out should be taken into account when determining the final target sample size of a trial.

A different expected treatment effect might explain why the sample sizes of antipsychotic trials increased over time. Perhaps, atypical antipsychotics were expected to be less effective than conventional antipsychotics, even before it was shown in systematic reviews that they did not affect psychotic symptoms compared to placebo (Schneider et al., 2006; Smeets et al., 2018). Alternatively, drop-out could have increased because recent trials lasted longer and participants have become more assertive.

On the other hand, general study characteristics, which are not directly related to sample size calculation might have contributed to the increase in trial sample sizes over the years. Large sample size is generally considered a sign of high trial quality, and this increases the probability of publication and citation (Dickersin et al., 1992). In addition, pharmaceutical companies will have more resources to fund larger trials than non-commercial organizations. Therefore, the aim of this meta-epidemiological study was to assess (1) the variation in sample size and sample size calculations of antipsychotic trials in dementia, (2) the size of the reported treatment effects and related statistical significance, and (3) general study characteristics that might be related to sample size.

METHODS

Search Strategy

Two reviewers (TAH, HJL) used a list of conventional and atypical antipsychotics from the websites of the World Health Organization, Food and Drug Administration, and Wikipedia to search the literature (US Food and Drug Administration, 2013; World Health Organization, 2013; Wikipedia, 2015). First, we first searched for studies in the electronic databases PubMed, CINAHL, EMBASE, and Cochrane library with the string 'generic name of atypical/conventional antipsychotic' and trial and dementia (see online supplement). We restricted the position of the drug name to title and abstract. Subsequently, we manually searched the references of published systematic reviews, which were identified with the same electronic databases. Titles and abstracts of potentially eligible studies were retrieved from PubMed. In addition, we sought trials in trial registration websites with the abovementioned search terms if possible; otherwise we used only the term dementia. These three searches were last re-run in June 2019. Finally, we had used the databases of the Dutch Medicines Evaluation Board and the FDA to find unpublished trials as part of a previous search performed in 2015 (Hulshof et al., 2019).

Study Selection

We screened the title and abstract of the hits. Full texts of potentially eligible published studies and online protocols for unpublished studies were retrieved. Two reviewers used the full texts to determine definitive eligibility (TAH, HJL). The selected trials had to have been randomized and double-blind. They should have tested the efficacy of antipsychotics on NPSs in persons diagnosed with Alzheimer or vascular dementia. The trial had to compare conventional or atypical antipsychotics with

placebo or another antipsychotic (head-to-head trial). We excluded studies with multiple drugs in a single intervention arm, studies that were stopped early and thus did not reach the targeted sample size, and studies with a cross-over design as other than standard sample size calculations need to be applied for this design. There were no restrictions with respect to publication date, language, and duration of the study.

Data Extraction

Two reviewers (TAH or SIMJ and HJL) independently extracted the following general study characteristics besides the sample size from the included studies: placebo-controlled or head-to-head trial, type of dementia (Alzheimer's disease, vascular dementia, mixed, unspecified), type of NPS (agitation, psychosis, diverse), setting (nursing home, hospital, outpatient clinic), active drug tested (conventional, atypical, or both), trial duration, type of funding (not-for-profit or commercial), and whether a sample size calculation was reported.

If the sample size calculation was reported, we extracted the input for sample size calculations: alpha, beta, expected treatment effects in the comparison groups (response rate, or mean symptom reduction with population variance at endpoint), and the expected drop-out rates. For trials that had been published in an abstract or online trial registration only, this data-extraction was considered inapplicable.

In addition, we extracted the reported treatment effects and related statistical significance. The primary outcome of trials that test antipsychotics for NPS in dementia is most often the difference in response rate or difference in reduction of target symptoms between the treatment groups. We extracted both for each trial with the related p-value. For the response rate, we extracted the number of patients with a clinically relevant improvement as defined by the authors. For reduction in symptoms, we extracted the difference in mean change from baseline to endpoint as measured with a symptom scale, such as the Cohen-Mansfield Agitation Inventory (CMAI) for agitation and Neuropsychiatric Inventory-Nursing Home (NPI-NH) for mixed symptoms. Initially, we also set out to extract standard deviations to calculate standardized mean differences, so that we could compare trial results. However, as many SDs turned out to be missing, we decided to extract the mean on the symptom scale at baseline as a reference instead (see data-analysis).

The primary source of extracted data was the published main results article. If that was not available, then conference abstracts or online published results were used. We received the individual patient data of two trials (Schneider et al., 2006; Paleacu et al., 2008), and additional meta-data of two others for use in another study (De Deyn et al., 1999; De Deyn et al., 2005; Hulshof et al., 2019).

Data Analyses

First, we described the variation in sample sizes for the different types of trials by plotting the mean number of participants per comparison group against the publication year of the trial. We present these data for the conventional and atypical placebo-controlled trials and head-to head trials separately.

To assess the adequacy of the reported sample sizes, we calculated reference sample sizes for trials with the response rate as outcome. For the placebo-controlled trials, we used an alpha of 0.05, beta of 0.20, a treatment response rate in the antipsychotic group of 55% and in the placebo group of 30%, and an expected drop-out of 30% (Brant, 2016). A treatment effect of 25% (NNT = 4) and drop-out rate of 30% is in line with previous literature and the reported response rates in antipsychotic trials in dementia (Schneider et al., 2006; Jeste et al., 2008; Drouillard et al., 2013). We used a conservative drop-out rate of 30% (it was 26% on average in the included trials), so that the reference sample size would not be an underestimation. The required sample size per study group was 58 without loss to drop-out, and 83 with loss.

For the head-to-head trials (no placebo group), we used a treatment effect of 55% for the drug of interest and 45% for the control antipsychotic drug, because a 10% difference seems the upper limit of no difference. The expected drop-out rate was set at 10%, which is in line with the average drop-out rate in the included head-to-head trials. The required sample size was 389 per group without loss, and 433 with loss. We used the ssi command in Stata version 15.0 to calculate the reference sample sizes (StataCorp., 2017).

To calculate reference sample sizes based on the outcome mean symptom reduction, the minimal clinically important difference (MCID) is required. However, the MCID is not known for most symptom scales used in this field (Shabbir and Sanders, 2014). The exception is the NPI, which was found to have an MCID of at least 8.0 (Howard et al., 2011; Zuidema et al., 2011). Nine of the included placebo-controlled trials in our study used this instrument, and we used the reported data to check our calculated reference sample size based on response rates. The reported mean reduction in symptoms was 19 (SD 14) for the placebo group (see **Supplementary Table 1**), and hence, assuming an MCID of 8.0, 27 (SD 16) for the antipsychotic group. We calculated a required sample size of 80 based on these data, and this finding confirms the reference sample size of 83 based on response rates. In addition, the MCID of 8.0 reflects an SMD of 0.500 given the SD of 16 reported in the included trials. This is in line with the lower limit for a visible (medium) treatment effect suggested by Cohen (2007).

The next step was to assess whether studies with larger sample size reported statistically significant treatment effects that were not clinically relevant (difference in response rate <25%; difference in symptom reduction < MCID or SMD <0.5), which would suggest the presence of large sample size fallacy. Treatment effects in terms of reported response rates can be compared between trials with varying sample sizes. However, it was not possible to use MCIDs or SMDs to compare reported reductions in symptoms across different symptoms scales. Therefore, we calculated the relative symptom reduction as the ratio of the difference in symptom reduction between the study groups relative to the baseline mean in the groups. This approach has been used before (Smith et al., 1974). Moreover, the MCID of 8.0 on the NPI and a mean baseline of 39 (see **Supplementary Table 1**) would translate into a relative symptom reduction of

21%. Hence, a relative symptom reduction of > = 20% seems appropriate.

Finally, we analyzed the association between other general study characteristics and mean sample size per group. The characteristics were type of drug tested (category: conventional, atypical, or both), trial duration (< = 6 weeks, > 6 weeks), and type of funding (non-for-profit, commercial). We calculated mean sample sizes of comparison groups per category, and used the two-sample t-test to determine whether the means differed between the first (reference) category and other categories. The analyses were performed for the placebo-controlled and head-to-head trials separately. All analyses were carried out with Stata version 15.0 (StataCorp., 2017).

RESULTS

Our search yielded 2,768 potentially relevant hits (**Figure 1**). We obtained the reports of 92 studies for full text review. We considered 57 studies eligible, but 6 had no useable data at the time of assessment. Hence, we used 51 studies in the current study (Hamilton and Bennet, 1962; Sugerman et al., 1964; Smith et al., 1974; Rada and Kellner, 1976; Rosen, 1979; Vergara et al., 1980; Götestam et al., 1981; Barnes et al., 1982; Petrie et al., 1982; Spagnolo et al., 1983; Morris and Rickels, 1984; Stotsky, 1984; Ather et al., 1986; Lovett et al., 1987; Carlyle et al., 1993; Finkel et al., 1995; Auer et al., 1996; Auchus and Cheryl Bissey-Black, 1997; Devanand et al., 1998; De Deyn et al., 1999; Katz et al., 1999; Allain et al., 2000; Street et al., 2000; Howanitz and Wisotzek, 2001; Herz et al., 2002; Pollock et al., 2002; Brodaty et al., 2003; Fontaine et al., 2003; De Deyn et al., 2004; Garerl et al., 2004; Mulsant et al., 2004; Sheng, 2004; Sun et al., 2004; Ballard et al., 2005; De Deyn et al., 2005; Deberdt et al., 2005; Verhey et al., 2006; Tariot et al., 2006; Mintzer et al., 2007; Rainer et al., 2007; Zhong et al., 2007; Paleacu et al., 2008; Streim et al., 2008; Teri et al., 2000). Online or other clinical trial reports of the following studies were used: NCT00287742, NCT01862640, NCT01922258, NCT02992132, ZIP-128-105, RIS-BEL-14, RIS-INT-83.

Table 1 shows the general study characteristics. Eleven trials compared conventional antipsychotics to placebo and 19 trials atypical antipsychotics to placebo. Six of the latter 19 trials tested multiple doses of one atypical drug, so they had more than one drug group (range 2–4). Three placebo-controlled trials tested both conventional and atypical antipsychotics. Eighteen trials compared an antipsychotic drug with another antipsychotic drug. The studies were performed in outpatients, nursing

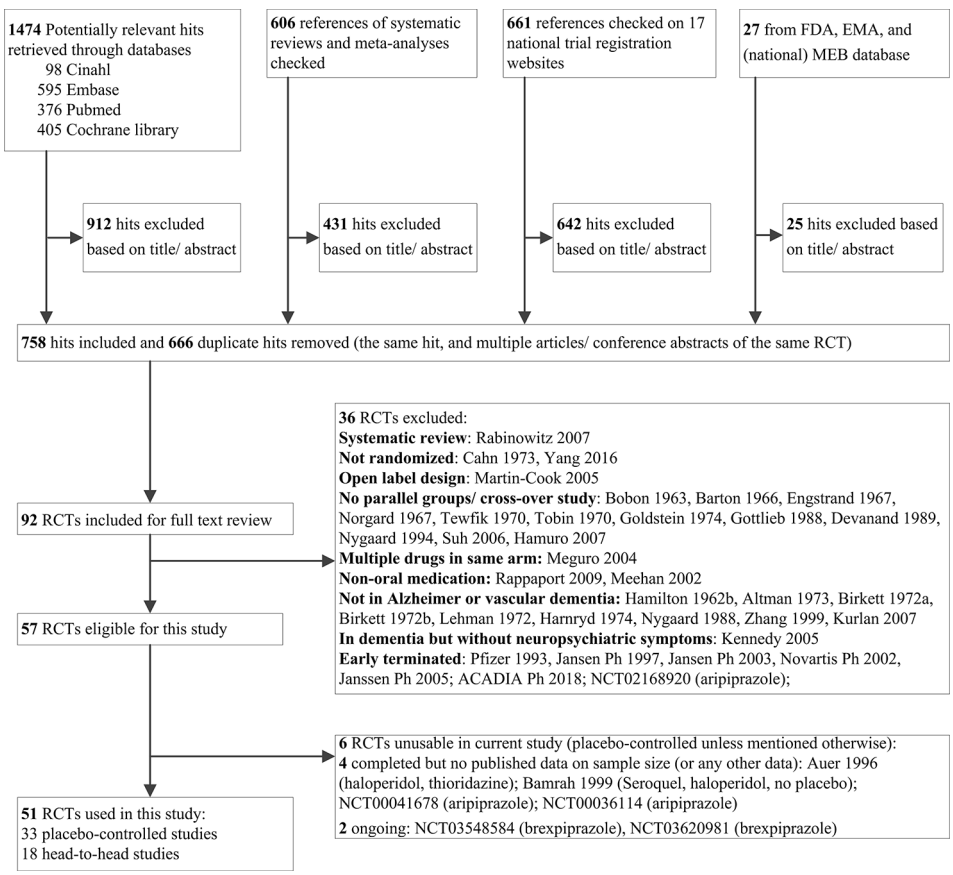


FIGURE 1 | Flow diagram of literature search and study selection.

TABLE 1 | Characteristics of randomized placebo-controlled and head-to-head trials of antipsychotics in patients with dementia.

Study	Drug(s) studied	Type of dementia	Type of NPS (at least)	Setting	N, total randomized	Duration, weeks	Sample size calculation reported	Commercial funding (drug of sponsor)
Antipsychotic versus placebo (33)								
Auchus and Cheryl Bissey-Black, 1997	Haloperidol	AD	Agitation	OUTP	12	6	–	– (non-commercial)
Howanitz and Wisotzek, 2001	Olanzapine	VAS	Diverse NPS	NR	16	6	– (abstract)	NR
Sugerman et al., 1964	Haloperidol	CBS	Psychosis	HOS	18	6	–	+ (haloperidol)
Herz et al., 2002°	Risperidone, olanzapine	AD	Agitation	NR	29	6	– (abstract)	NR
Hamilton and Bennet, 1962	Trifluoperazine	CBS	Psychosis	HOS	27	8	–	NR
Finkel et al., 1995	Thiothixene	NR	Agitation	NH	35	11	–	+ (thiothixene)
Barnes et al., 1982	Loxapine, thioridazine	NR	Diverse NPS	NH	60	8	–	+ (loxapine)
Petrie et al., 1982	Loxapine, haloperidol	NR	Diverse NPS	HOS	63	8	–	+ (loxapine)
Paleacu et al., 2008	Quetiapine	AD	Diverse NPS	NR	40	6	+	+ (quetiapine)
Rada and Kellner, 1976	Thiothixene	CBS	Diverse NPS	HOS	63	4	–	NR
Devanand et al., 1998	Haloperidol	AD	Diverse NPS	OUTP	66	6	–	– (non-commercial)
Ballard et al., 2005	Quetiapine	AD	Agitation	NH	62	6	+	+ (commercial)#
Pollock et al., 2002	Perphenazine	AD, VAS, and MIX	Diverse NPS	NH	54	2,5	–	– (non-commercial)
Teri et al., 2000	Haloperidol	AD	Agitation	HOS	70	16	+	+ (trazodone)
Street et al., 2000	Olanzapine	AD	Diverse NPS	NH	206	6	+	+ (olanzapine)
Ballard et al., 2018	Pimavanserin	AD	Psychosis	NH	181	12*	+	+ (pimvaserin)
Tariot et al., 2006	Quetiapine, haloperidol	AD	Psychosis	NH	284	10	+	+ (quetiapine)
Allain et al., 2000	Tiapride, haloperidol	AD, VAS, and MIX	Agitation	NH-HOS	306	3	+	+ (tiapride)
De Deyn et al., 2005	Aripiprazole	AD	Psychosis	OUTP	208	10	–	+ (aripiprazole)
Zhong et al., 2007	Quetiapine	AD and VAS	Agitation	NH	333	10	+	+ (quetiapine)
Schneider et al., 2006	Olanzapine, quetiapine, risperidone	AD	Diverse NPS	OUTP	421	12^	+	+ (olanzapine, quetiapine, risperidone)
De Deyn et al., 1999	Risperidone, haloperidol	AD, VAS, and MIX	Diverse NPS	NH	344	12	+	+ (risperidone)
Satterlee et al., 1995°	Olanzapine	AD	Diverse NPS	NR	238	8	–	+ (olanzapine)
Mintzer et al., 2007	Aripiprazole	AD	Psychosis	NH	487	10	–	+ (aripiprazole)
Streim et al., 2008	Aripiprazole	AD	Psychosis	NH	265	10	–	+ (aripiprazole)
De Deyn et al., 2004	Olanzapine	AD	Psychosis	NH-HOS	652	10	+	+ (olanzapine)
Otsuka Ph, 2017a†	Brexpiprazole	AD	Agitation	NH	413	12	– (online)	+ (brexpiprazole)
Otsuka Ph, 2017b	Brexpiprazole	AD	Agitation	NH –OUTP	270	12	– (online)	+ (brexpiprazole)
Deberdt et al., 2005	Olanzapine, risperidone	AD, VAS, and MIX	Psychosis	NH –OUTP	494	10	–	+ (olanzapine)
Katz et al., 1999	Risperidone	AD, VAS, and MIX	Diverse NPS	NH	625	12	+	+ (risperidone)
Brodaty et al., 2003	Risperidone	AD, VAS, and MIX	Aggression	NH	345	12	+	+ (risperidone)
Stotsky, 1984	Thioridazine	NR	Diverse NPS	NH-HOS	358	4	–	NR
Mintzer et al., 2006	Risperidone	AD	Psychosis	NH	473	8	+	+ (risperidone)
Head-to-head trials (18)								
Vergara et al., 1980	Clomacran vs. thioridazine	CBS	Diverse NPS	HOS	20	12	–	+ (clomacran)
Spagnolo et al., 1983	Clomacran, thioridazine	VAS	Diverse NPS	HOS	30	3	–	NR
Fontaine et al., 2003	Etoperidone, thioridazine	NR	Agitation	NH	39	2	–	+ (olanzapine)
Carlyle et al., 1993	Olanzapine, risperidone	AD, VAS, and MIX	Aggression	HOS	40	4	–	NR
Garerl et al., 2004	Loxapine, haloperidol	AD, VAS, and MIX	Diverse NPS	NR	60	8	–	– (non-commercial)

(Continued)

TABLE 1 | Continued

Study	Drug(s) studied	Type of dementia	Type of NPS (at least)	Setting	N, total randomized	Duration, weeks	Sample size calculation reported	Commercial funding (drug of sponsor)
Morris and Rickels, 1984	Risperidone, olanzapine, promazine	NR	Diverse NPS	NH	41	8	–	+ (loxapine)
Rosen, 1979	Loxapine, thioridazine	Organic cerebral disease#	Diverse NPS	OUTP	56	6	–	+ (haloperidol)
Smith et al., 1974	Haloperidol, thioridazine	CBS	Psychosis	NH	46	6	–	NR
Götestam et al., 1981	Haloperidol, thioridazine	(Pre)senile and VAS	Diverse NPS	HOS	47	8	–	NR
Lovett et al., 1987	Cis(Z)–clopenthixol, haloperidol	CBS	Psychosis	NH	54	6	–	+ (trifluoperazine)
Chan et al., 2001	Trifluoperazine, haloperidol	AD, VAS, and MIX	Diverse NPS	OUTP –HOS	58	12	–	+ (risperidone)
Verhey et al., 2006	Risperidone, haloperidol	NR	Agitation	OUTP-NH	59	5	+	NR
Ather et al., 1986	Olanzapine, haloperidol	NR	Diverse NPS	NR	68	4	–	+ (chlormethiazole)
Sheng et al., 2004	Chlormethiazole, thioridazine	AD and VAS	Diverse NPS	NR	60	8	–	+ (risperidone)
Rainer et al., 2007	Risperidone, haloperidol	AD, VAS, MIX, FTD	Diverse NPS	OUTP	68	8	+	+ (quetiapine)
Mulsant et al., 2004	Quetiapine, risperidone	AD, VAS and MIX	Diverse NPS	NH	86	6	–	+ (risperidone)
Sun et al., 2004	Risperidone, olanzapine	DSM-IV dementia	Diverse NPS	HOS-OUTP	116	8	–	+ (risperidone)
Gutzmann et al., 1997	Risperidone, haloperidol	NR	Restlessness	HOS	176	4	–	+ (tiapride)

AD stands for Alzheimer's disease; CBS for chronic brain syndrome; HOS for hospital; MIX for mixed dementia (Alzheimer/vascular); NH for nursing home; NPS for neuropsychiatric symptoms; OUTP for outpatients; Ph for Pharmaceutical company; NR for not reported; and VAS for vascular dementia.

*° abstract only; * reduction in NPI Psychosis items at 12 weeks was the original primary outcome (clinicaltrials.gov); ^ discontinuation rate at week 36 was the primary outcome, but as it is incomparable to other trials, we used response rate and reduction of symptoms at 12 weeks (see **Table 3**); † results of 0.5 mg group (n = 20) were not reported; # the term senile brain disease was also used.*

homes, or hospitals. The target symptom for treatment consisted of agitation, psychosis, or diverse NPSs.

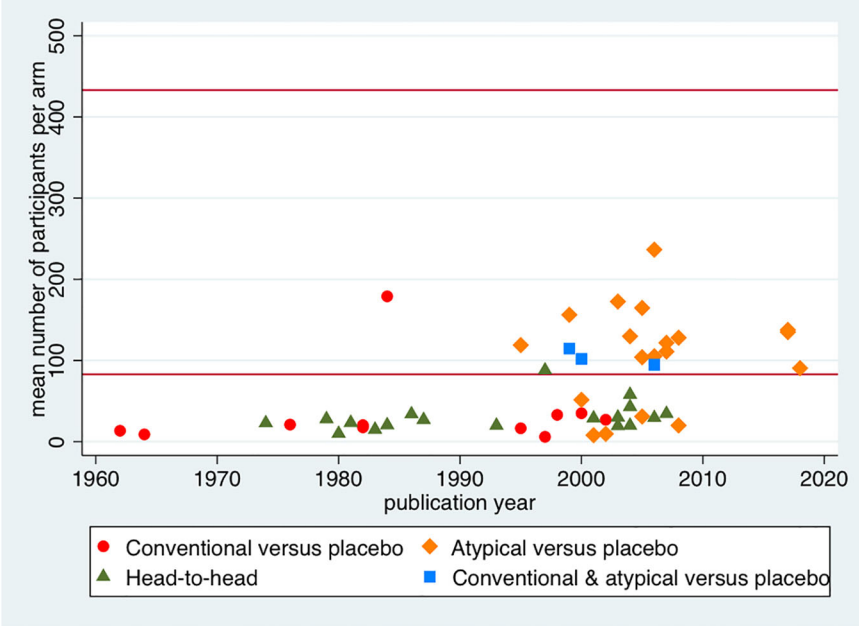
Sample Size Variation and Calculations

Figure 2 shows the mean number of participants per comparison group in each trial against publication year. The symbols indicate the type of drug tested (conventional, atypical, or both) and type of study (placebo-controlled or head-to-head). In the conventional antipsychotic placebo-controlled studies, the mean number per group was 34 patients (range 6–179), while those comparing atypical antipsychotics to placebo included on average 107 patients per group (range 8–237). The three trials that included both conventional and atypical antipsychotics and compared these to placebo included 104 patients per group (range 95–115). Head-to-head trials included a mean number of 31 patients per group (range 10–88). The increase in sample size over time seems to be related to type of drug tested.

We calculated a reference sample size of 83 patients per group for the placebo-controlled trials and 433 patients for the head-to-head trials, as explained above. The group sample size was lower than the reference sample size in 10 placebo-controlled trials of conventional antipsychotics (small sample size) and higher in one such trial (large sample size), whereas 5 of the 19 atypical antipsychotic trials and none of the 3 trials including both conventional and atypical antipsychotics had small sample sizes. At least four of the five atypical underpowered antipsychotic trials were investigator initiated, although one was performed with commercially acquired funds. All head-to-head trials had a small sample size that was lower than the reference sample size of 433.

Sixteen of 47 articles (excluding 2 abstracts and 2 reports on online trial registers) reported a sample size calculation (34%), which was often called a power analysis (**Table 1**). Fourteen were placebo-controlled trials and two head-to-head trials (**Table 2**). **Table 2** shows, which input for these sample size calculations was reported. There were only three studies that reported sufficient information (Ballard et al., 2005; Mintzer et al., 2006; Schneider et al., 2006). Two studies reported an alpha that differed from 5% (2.5% and 7%). Eight studies reported a beta that differed from 20% and it varied between 1% and 15%. Except for the alpha of 2.5%, this input will yield higher sample sizes. Expected drop-out rates were reported in seven studies and varied between 10% and 30%.

There were seven placebo-controlled trials that postulated an expected treatment effect in terms of symptom reduction, four of which reflected a relative symptom reduction below 20%. The expected differences in relation to baseline means (relative



* Red lines indicate calculated reference sample sizes per arm for the placebo-controlled trials (N=83) and head-to-head trials (N=433).

FIGURE 2 | Scatter plot of sample sizes per arm over the years per treatment group.

symptom reduction) were: 10% (Ballard et al., 2005); 11% (Tariot et al., 2006); 12% (Brodaty et al., 2003); 14% (Street et al, 2000); 20% (Mintzer et al., 2006); 31% (De Deyn et al., 2004); 31% (Ballard et al., 2018). For a head-to-head trial, the expected relative risk reduction was 16% (Verhey et al., 2006).

Reported Treatment Effects In Relation To Sample Size

Table 3 presents the reported treatment effects in order of sample size per study group. A positive difference in response rate and negative difference in symptom reduction means that

TABLE 2 | Input for sample size calculations*.

Study	Alpha, %	Beta, %	Response rate or mean symptom change in drug group	Response rate or mean symptom change in control group	Difference in rates or means (SD) between groups¶	Expected dropout, %
Placebo-controlled trials						
Teri et al., 2000†	5	20	70%	30%	40%	NR
Katz et al., 1999	5	20	50%	30%	20%	NR
Street et al., 2000	5	20	NA	NA	–2.0 pts (NR)	NR
Brodaty et al., 2003	5	20	NA	NA	–4.15 pts (NR)	30
De Deyn et al., 2004	5	15	NA	NA	–3.0 pts (NR)	NR
Ballard et al., 2005	5	10	NA	NA	–6.0 pts (6)	25
Schneider et al., 2006	5	1^	27%#	60%#	–33%#	NA#
Mintzer et al., 2006	5	5	45%	25%	20%	20
Zhong et al., 2007	2.5	20	NR	NR	NR	10
Paleacu et al., 2008	7	10	NR	NR	–25% pts (NR)	NR
Ballard et al., 2018	5	10	NA	NA	–3.0 (6)	20
De Deyn et al., 1999	5	20	NR	NR	20%	20
Allain et al., 2000	5	20	55%	30%	25%	NR
Tariot et al., 2006	5	10	NA	NA	–4.5 (9)	NR
Head-to-head trials						
Verhey et al., 2006	5	10$	–14 pts	–2.8 pts	<–11.2 (NR)	25
Rainer et al., 2007	5	20	NR	NR	NR	NR

*NA stands for not applicable, NR for not reported, pts for points (on instrument used to measure neuropsychiatric symptoms); * this table presents the 16 studies that reported a sample size calculation ('power analysis') were included in this table; ¶ a difference in means needs to be accompanied by the population variance to calculate a sample size; † except for Teri et al., 2000, all calculations were based on the comparison of the atypical antipsychotic group versus placebo; ^ beta was reported to be 20% for a difference in rates of -20%; # discontinuation (not response) was the outcome; $ text also mentions 20%.*

TABLE 3 | Results of randomized trials in order of group sample size.

Study	Comparison groups	N per group	Reported effect in terms of response rate			Reported effect in terms of symptom reduction		
			Definition/measurement (bold if primary outcome)	Difference between groups	p-value	Symptom scale (bold if primary outcome)	Difference between groups (baseline mean); relative symptom reduction	p-value
Antipsychotic versus placebo (33)								
Auchus and Cheryl Bissey-Black, 1997	Haloperidol vs. placebo	6–6	—	—	—	**CMAI**	−1.0 (35.2); 5%	.82
Howanitz and Wisotzek, 2001	Olanzapine vs. placebo	8–8	—	—	—	—	—	—
Sugerman et al., 1964	Haloperidol vs. placebo	9–9	**improvement on psychiatric observation**	**22%**	nr	'symptom checklist'	−2.5 (nr); nr	nr
Herz et al., 2002°	Risperidone vs. placebo	14–8	—	—	—	**BPRS Excitement**	Nr (nr); nr	ns .0001
	Olanzapine vs. placebo	7–8	—	—	—		Nr (nr); nr	
Hamilton and Bennet, 1962	Trifluoperazine vs. placebo	18–9	**improvement on psychiatric observation**	**22%**	nr	MACC	−0.7 (31.4); 2%	ns
Finkel et al., 1995	Thiothixene vs. placebo	17–18	> 5 points on CMAI	51%	nr	**CMAI**	−9.0 (30.5); 55%	<.001
Barnes et al., 1982	Loxapine vs. placebo	19–17	improvement on CGI	17%	ns	**BPRS**	−2.9 (45.8); 6%	ns
	Thioridazine vs. placebo	17–17		12%	ns		0.0 (45.8); 0%	ns
Petrie et al., 1982	Loxapine vs. placebo	19–22	**> = moderate**	23%	nr	BPRS	−9.5 (47.9); 20%	<.05
	Haloperidol vs. placebo	20–22	**improvement on CGI**	26%	nr		−9.3 (47.9); 19%	<.05
Paleacu et al., 2008	Quetiapine vs. placebo	20–20	Improved on CGIC	−5%	ns	**NPI-NH**	−5.2 (41.0); 13%	ns
Rada and Kellner, 1976	Thiothixene vs. placebo	22–20	improved on global rating	4%	ns	**BPRS**	Nr (nr); nr	ns
Devanand et al., 1998	Haloperidol 0.5–0.75 mg vs. placebo	21–24	> = 25% reduction BPRS	0%	nr	**BPRS Psychosis**	0.0 (6.8); 0%	ns
	Haloperidol 2–3 mg vs. placebo	21–24	Psychosis items	30%	<0.06		−1.2 (6.8); 18%	<.03
Ballard et al., 2005	Quetiapine vs. placebo	31–31	—	—	—	**CMAI**	3.5 (57.7); 8%	.30
Pollock et al., 2002	Perphenazine vs. placebo	33–21	—	—	—	**NRS**	−4.9 (57.6); 9%	.14
Teri et al., 2000	Haloperidol vs. placebo	34–36	**improvement on ADCS-CGIC**$	**1%**	0.81	CMAI	−1.3 (49.2*); 3%	>.25
Street et al., 2000	Olanzapine 5 mg vs. placebo	56–47	—	—	—	**NPI-NH Agitation + Psychosis**	−3.9 (14.2); 27%	<.001
	Olanzapine 10 mg vs. placebo	50–47	—	—	—		−2.4 (14.2); 17%	.006
	Olanzapine 15 mg vs. placebo	53–47	—	—	—		−1.2 (14.2); 8%	.24
Ballard et al., 2018¶	Pimavanserin vs. placebo	90–91	> = 30% decrease on NPI-NH Psychosis items	nr	nr	**NPI-NH Psychosis**	−0.5 (9.8); 5%	.561
Tariot et al., 2006	Quetiapine vs. placebo	91–99	> = 30% decrease on BPRS	11%	.265	BPRS	−2.3 (39.5); 6%	.217
	Haloperidol vs. placebo	94–99		7%	nr		−0.4 (39.5); 1%	.354
Allain et al., 2000	Tiapride vs. placebo	102–103	**> = 25% decrease on MOSES irritability/ aggression items**)	14%	.04	MOSES irritability/ aggression	−1.9 (20.3); 9%	.009 .005
	Haloperidol vs. placebo	101–103		20%	.004		−2.1 (20.3); 10%	
Deberdt et al., 2005	Aripiprazole vs. placebo	106–102	improvement on CGI-I	8%	.18	**NPI Psychosis**	−1.03 (12.4); 8%	.017
Zhong et al., 2007	Quetiapine 100 mg vs. placebo	124–92	moderate and marked	8%	ns	**PANSS-EC**	−0.8 (23.0); 3%	.457
	Quetiapine 200 mg vs. placebo	117–92	improvement on CGI-C	22%	.002		−2.7 (23.0); 12%	.014
Schneider et al., 2006	Olanzapine vs. placebo	100–142	improvement on CGIC†	11%	.05	NPI	−5.0 (36.9); 14%	nr nr
	Quetiapine vs. placebo	94–142		5%	.37		−7.6 (36.9); 21%	nr
	Risperidone vs. placebo	85–142		8%	.21		−7.4 (36.9); 20%	
De Deyn et al., 1999	Risperidone vs. placebo	115–114	**> = 30% decrease on BEHAVE-AD**	11%	.13	BEHAVE-AD	−2.4 (16.5); 15%	.05
	Haloperidol vs. placebo	115–114		8%	.25	BEHAVE-AD	−1.3 (16.5); 8%	nr
Satterlee et al., 1995°	Olanzapine vs. placebo	120–118	—	—	—	BEHAVE-AD	−0.4 (19.8); 2%	ns

(Continued)

TABLE 3 | Continued

Study	Comparison groups	N per group	Reported effect in terms of response rate			Reported effect in terms of symptom reduction		
			Definition/measurement (bold if primary outcome)	Difference between groups	p-value	Symptom scale (bold if primary outcome)	Difference between groups (baseline mean); relative symptom reduction	p-value
Mintzer et al., 2007	Aripiprazole 2 mg vs. placebo	118 –121	> = 50% decrease NPI-NH Psychosis	5%	ns	**NPI-NH Psychosis**	–0.5 (11.6); 4%	ns
	Aripiprazole 5 mg vs. placebo	122–121		13%	ns		–1.2 (11.6); 10%	ns
	Aripiprazole 10 mg vs. placebo	126–121		15%	.019		–1.8 (11.6); 16%	.013
Streim et al., 2008	Aripiprazole vs. placebo	131–125	> = 50% decr NPI-NH	18%	.006	**NPI-NH Psychosis**	+0.1 (10.6); 1%	ns
De Deyn et al., 2004	Olanzapine 1mg vs. placebo	129–129	—	—	—	**NPI—NH Psychosis**	–1.0 (9.7); 10%	.171
	Olanzapine 2.5 mg vs. placebo	134–129	(CGI—C was administered)	—	—		–0.8 (9.7); 8%	.089
	Olanzapine 5 mg vs. placebo	125–129		—	—		–0.6 (9.7); 6%	.274
	Olanzapine 7.5 mg vs. placebo	132–129		—	—		–1.2 (9.7); 12%	.032
Otsuka Ph, 2017a^	Brexpiprazole 1 mg vs. placebo	137–136	—	—	—	**CMAI**	+0.2 (nr); nr	.902
	Brexpiprazole 2 mg vs. placebo	140–136					–3.8 (nr); nr	.040
Otsuka Ph, 2017b	Brexpiprazole vs. placebo	133–137	—	—	—	**CMAI**	–2.4 (nr); nr	.145
Deberdt et al., 2005	Olanzapine vs. placebo	204–94	> = 30% decr NPI-NH	–4%	ns	**NPI Psychosis**	–0.7 (11.3); 6%	0.421
	Risperidone vs. placebo	196–94	Psychosis	–3%	ns		–0.5 (11.3); 4%	0.585
Katz et al., 1999	Risperidone 0.5 mg vs. placebo	149–163	> = 50% reduction on	nr	nr	**BEHAVE-AD**	–1.2 (15.8); 8%	.13
	Risperidone 1 mg vs. placebo	148–163	BEHAVE-AD	12%	.02		–2.2 (15.8); 14%	.02
	Risperidone 2 mg vs. placebo	165–163		17%	.002		–3.3 (15.8); 21%	<.001
Brodaty et al., 2003	Risperidone vs. placebo	173–172	improvement on CGI-I	22%	< .001	**CMAI aggression**	–4.4 (33.5); 23%	<.001
Stotsky, 1984	Thioridazine vs. placebo	183–175	—	—	—	**Modified HAS**	–4.3 (nr); nr	<.001
Mintzer et al., 2006	Risperidone vs. placebo	235–238	improvement on CGI-C	10%	.019	**BEHAVE-AD Psychosis**	–0.6 (7.9); 8%	.118
Head-to-head trials (18)								
Vergara et al., 1980	Clomacran vs. thioridazine	20 total	Improvement on CGI	0%	nr	**VTSRS**	nr (nr); nr	ns
Spagnolo et al., 1983	Etoperidone vs. thioridazine	15–15	clinical judgment	0%	nr	**SHGRS**	nr (nr); nr	nr
Fontaine et al., 2003	Olanzapine vs. risperidone	20–19	— (CGI-C was administered)	nr	ns	**NPI**	+8 (51.8); 15%	ns
Carlyle et al., 1993	Loxapine vs. haloperidol	20–20	Any decrease in weekly # of aggressive acts	15%	nr	**weekly # of aggressive acts**	–1.1 (6.9); 16%	ns
Garerl et al., 2004	Risperidone vs. promazine	20–20	**> = 50% decrease on NPI**	5%	nr		—	—
	Olanzapine vs. promazine	20–20		15%	nr		—	—
Morris and Rickels, 1984	Loxapine vs. thioridazine	21–20	global improvement	nr	nr	**BPRS**	+1.7 (63.6); 3%	ns
Rosen, 1979	Haloperidol vs. thioridazine	24–18	—	—	—	**Modified BPRS**	+0.1 (3.2); 3%	ns
Smith et al., 1974	Haloperidol vs. thioridazine	23–23	CGI	22%	nr	**BPRS**	nr (nr); 11%	.01
Götestam et al., 1981	Cis(Z)-clopenthixol vs. haloperidol	25–22	improvement on CGI	–6%	nr	**GCGRS**	–4.1 (26.9); 15%	<.05
Lovett et al., 1987	Trifluoperazine vs. haloperidol	26–28	improvement on CGI	18%	ns	**BPRS**	–1.2 (50.4); 2%	ns
Chan et al., 2001	Risperidone vs. haloperidol	29–29	—	—	—	**CMAI**	+2.0 (47.7); 4%	ns
Verhey et al., 2006	Olanzapine vs. haloperidol	30–28	— (CGI was administered)	—	—	**CMAI**	+6.5 (70); 9%	0.338

(Continued)

TABLE 3 | Continued

Study	Comparison groups	N per group	Reported effect in terms of response rate			Reported effect in terms of symptom reduction		
			Definition/measurement (bold if primary outcome)	Difference between groups	p-value	Symptom scale (bold if primary outcome)	Difference between groups (baseline mean); relative symptom reduction	p-value
Ather et al., 1986	Chlormethiazole vs. thioridazine	30–30	—	—	—	**CGBRS**	−1.9 (37.1); 5%	nr
Sheng et al., 2004	Risperidone vs. haloperidol	30–30	**improvement on CGI**	10%	>.05	**BEHAVE-AD**	0 (15); 0%	>.05
Rainer et al., 2007	Quetiapine vs. risperidone	36–32	improvement on CGI	−3.4%	nr	**NPI**	+2.2 (57.9); 4%	ns
Mulsant et al., 2004	Risperidone vs. olanzapine	42–43	—	—	—	**NPI**	Nr (nr); nr	ns
Sun et al., 2004	Risperidone vs. haloperidol	57–59	**> = 30% decrease on BEHAVE-AD**	1%	nr	**BEHAVE-AD**	+0.1 (17.5); 1%	ns
Gutzmann et al., 1997	Tiapride vs. melperone	88–87	**improvement on CGI**	1%	.675	restlessness	−1.4 (56.2); 2%	ns

nr stands for not reported, ns means that the effect was reported as not statistically significant but no p-value was given; ADCS-CGIC stands for Alzheimer's Disease Cooperative Study Clinical Global Impression of Change; BEHAVE-AD for Behavioural pathology in Alzheimer's disease scale; BPRS for Brief Psychiatric Rating Scale; CMAI for Cohen-Mansfield Agitation Inventory; CGBRS for Crichton Geriatric Behavioral Rating Scale; GCGRS for Gottfires-Cronholm Geriatric Rating Scale; MACC for Motility affect communication cooperation behavioral adjustment scale; NPI (-NH) for Neuropsychiatric Inventory (- Nursing Home version); NRS for Neurobehavioral Rating Scale; PANSS for Positive and Negative Syndrome Scale; SHGRS for Stuard Hospital Geriatric Rating Scale; and VTSRS for Verdun Target Symptom Rating Scale.

*° abstract only; * 49.2 is the weighted mean of baseline mean of all studies with CMAI total; ¶ reduction in NPI Psychosis at 12 weeks was originally the primary outcome (clinicaltrials.gov); † Discontinuation rate at week 36 is primary outcome of trial, but as it is incomparable to other trials, we used response rate and reduction of symptoms at 12 weeks; ^ results of 0.5mg group (n = 20) were not reported.*

the investigated drug performed better than the control group. Six trials did not report what the effect of treatment on the primary outcome was: four studies were old, published between 1974–1983, but two were relatively new, published after 2000 (Smith et al., 1974; Rada and Kellner, 1976; Vergara et al., 1980; Spagnolo et al., 1983; Herz et al., 2002; Mulsant et al., 2004). Five placebo-controlled studies reported only p-values without effect sizes in the abstract (Katz et al., 1999; Brodaty et al., 2003; Deberdt et al., 2005; Mintzer et al., 2006; Zhong et al., 2007).

Thirteen of 18 overpowered trials (72%) versus seven of 15 underpowered placebo-controlled trials (47%) yielded a statistically significant difference between the study groups in either response rate or symptom reduction. Two of 13 (15%) and four of seven (57%) of these treatment effects respectively were clinically relevant (difference in response rate > = 25%, or relative symptom reduction > = 20%). The statistically significant response rates were 10–22% and reported by studies with large sample sizes. The two studies with a difference in response rate of > = 25%, which is the difference deemed clinically relevant (Cohen, 2007), were underpowered and did not report a statistically significant result. In addition, large sample size trials reported statistically significant relative symptom reductions between 10% and 23%, and small sample size trials reported statistically significant relative symptom reductions varying between 17% and 55%.

Many placebo-controlled trials had more than one intervention group, adding up to a total of 54 individual comparisons. Thirteen of the 33 overpowered comparisons (39%) from 18 trials yielded a statistically significant treatment effect on either response rate or symptom reduction, versus seven of the 21 underpowered comparisons (33%) from 15 trials.

Five of 18 head-to-head trials reported a difference in response rate of 10%, the lower limit that we set for non-inferiority in our reference sample size calculation, and four a relative symptom reduction of 10%. Yet, none of these results were statistically significant.

The reported treatment effect was lower than the expected treatment effect in the 14 studies that presented an expected treatment effect in a sample size calculation, except in two studies (Street et al., 2000; Brodaty et al., 2003). The reported drop-out rates varied between 6% and 37% (not shown), which was higher than the expected drop-out rate in most studies.

Study Characteristics and Sample Size

Table 4 shows the mean sample size per comparison group by type of drug tested, trial duration, and type of funding. The mean sample size per study group was statistically significantly higher in placebo-controlled trials that tested an atypical antipsychotic drug (107.0) or both a conventional and an atypical drug (103.8) in comparison to placebo-controlled trials of conventional antipsychotics (34.4; $p < .05$). The mean sample size per study group was also statistically significantly higher in trials that lasted more than 6 weeks (109.2) compared to less than 6 weeks (28.9; $p < .001$), and that were commercially (100.3) versus non-commercially (18.1; $p < .001$) funded. Head-to-head-trials that tested atypical drugs only had a significantly larger mean sample size (46.3) than trials that tested conventional drugs (22.3; $p < .05$). Trial duration and commercial funding did not seem to be related to the sample size of head-to-head trials.

DISCUSSION

We assessed the presence of large sample size fallacy in 51 antipsychotic trials in dementia. Most placebo-controlled trials

TABLE 4 | Mean sample size by study characteristic.

Study characteristic		Placebo-controlled trials		Head-to-head trials	
		n	Mean (SD)	n	Mean (SD)
Type of drug	Conventional antipsychotic (ref)	11	34.4 (48.8)	9	22.3 (7.1)
	Atypical antipsychotic	19	107.0 (60.5)^	4	46.3 (29.5)^
	Conventional and atypical antipsychotic	3	103.8 (94.7)^	3	33.3 (14.4)
Trial duration	= < 6 weeks (ref)	11	28.9 (4.4)	10	32.7 (21.0)
	> 6 weeks	22	109.2 (12.6)*	8	28.2 (14.2)
Type of funding	Non-commercial (ref)	7	18.1 (9.6)	5	21.6 (5.4)
	Commercial	24	100.3 (57.5)*	13	34.2 (20.0)

*^p < .05 compared to reference group; *p < .001 compared to reference group.*

of conventional antipsychotics had small sample size, i.e. smaller than the calculated reference sample size, but most trials of atypical antipsychotics had large sample sizes. All head-to-head trials had very small sample sizes. Only one third of trials reported a sample size calculation. Thirteen of 18 trials with large sample sizes (72%) reported a statistically significant treatment effect, of which two (15%) were clinically relevant. In contrast, seven of 15 placebo-controlled trials with small sample sizes (47%) yielded a statistically significant treatment effect, and four were clinically relevant (57%). None of the head-to-head trials reported a statistically significant treatment effect, even though some suggested non-inferiority.

Large Sample Size Fallacy

Sample sizes need to be large enough to guarantee a minimum level of discriminative power to detect a real treatment effect. Moreover, precision of an estimate increases with sample size. Studies based on small sample size may yield a non-statistically significant but clinically relevant treatment effect. On the other hand, studies based on large sample size—larger than necessary—may yield statistically significant but clinically insignificant treatment effects (Roggla and Fortunat, 2004; Chan et al., 2008). Large sample size fallacy occurs when such results are interpreted as relevant for medical practice (Lantz, 2013; Lin et al., 2013). Nevertheless, pharmaceutical companies and academic scholars benefit from statistically significant treatment results being interpreted as clinically relevant (Dickersin et al., 1992). The emphasis on statistical significance was confirmed by six trials in our review that did not report effect sizes, and five trials that reported just p-values in the abstract.

The sample sizes of trials testing atypical antipsychotics versus placebo, whether or not simultaneously with a conventional antipsychotic, were generally larger than necessary. These trials were commercially funded by the manufacturer of the atypical antipsychotic drugs. Only investigator-initiated trials were too small. The majority of large trials reported a statistically significant treatment effect, despite lack of clinical relevance, which confirms the presence of large sample size fallacy. The mean sample size was also higher when the study lasted longer than 6 weeks and was commercially funded, but this might be explained by the fact that placebo-controlled trials of atypical antipsychotics were generally longer and often industry-initiated. The chance of statistically significant findings was further enhanced by the use of multiple comparisons per study and multiple measurement scales per outcome in a number of the larger trials.

Many placebo-controlled trials of conventional antipsychotics had small sample sizes. Most were relatively old (published before 1990) and seemed to be investigator-initiated. Some of these trials reported clinically relevant results, but most were not statistically significant. That small placebo-controlled trials yielded statistically significant and clinically relevant effects relatively often might reflect publication bias.

Head-to-head trials had sample sizes that were (much) smaller than required, and these studies yielded non-statistically significant results that sometimes suggested a substantial effect. Even if we had set the limit for non-inferiority at 15%, the required sample would have been a lot higher than the sample sizes of the included studies were (346 without loss, and 385 with loss). It is unclear why these trials were so clearly underpowered. Perhaps, industry has little to gain from properly testing their own product against that of competitors. Non-commercial funds might not be interested in a trial with at least 2 × 433 patients to show that the tested drugs are non-inferior, even if patients might be quite willing to participate in a study that ensure treatment with an active drug.

Sample Size Requirements

It is generally agreed that a trial protocol and report should report a sample size calculation (CONSORT Group, 2010). Nevertheless, only a third of trials in our review reported a sample size calculation and just three were complete. Although some trials can be considered old, most were published in the 1990s or later when it had become common to report trial methods in detail. Sample size calculations are often not (completely) reported in randomized trials in other fields of research was well (Chan et al., 2008; Charles et al., 2009). One review found that articles about newer randomized controlled trials included sample size calculations more often, and showed positive results more often (76%) than older studies (55%) (Latif et al., 2011).

Some studies in our review reported a lower alpha (2.5%) or beta (5%) than is usual in sample size calculations (5% and 20% respectively). In addition, the MCID proposed in the sample size calculations seemed rather small: difference in response rates <25% in 3/6 trials, and in relative risk reduction of <20% in 4/7 trials. The lower the alpha, beta, and MCID, the higher the

calculated sample size will be and hence the power to detect a statistically significant but not clinically relevant treatment effect. Moreover, even if the expected difference is equal to the MCID, a proportion of the patients will not have a clinically relevant effect on the individual level. On the other hand, the expected drop-out rate in the sample size calculations was mostly lower than the (mean) reported drop-out, and this would have led to a spuriously smaller calculated sample size. Real drop-out might have been high because trial duration was long on average. Most trials lasted more than a month, even though in clinical practice, antipsychotics usually show an effect within 2 weeks, four at the most. It has been estimated that up to 64% of trials with continuous outcomes are underpowered or overpowered because of imprecise input (Tavernier and Giraudeau, 2015).

Strengths and Limitations

To our knowledge determinants of sample size in trials testing antipsychotics for NPSs in dementia have not been studied previously. Our study showed that sample size calculations in the reports of these trials were missing on a large scale as was the correct interpretation of effect size. A limitation of our study is its focus on antipsychotic trials in dementia, which might be perceived as a small field of research. In addition, the interpretation of our results is limited by the possible presence of multiple testing. Many trials used multiple comparisons of either different drugs, different dosages, multiple outcomes, and sometimes multiple measurement instruments per outcome. Such multiple testing might reinforce the large sample size fallacy.

With our study, we do not want to suggest that large sample sizes should be avoided. It is important for clinical practice that study results are precise. Moreover, large sample sizes are very useful for identification of adverse effects. Small trials should not be avoided either, as long as they are published irrespective of results and available for pooling in meta-analyses.

The implication of our study is that researchers need to be encouraged to report and consider effect sizes in line with p-values to avoid the large sample size fallacy. Journals should probably mention this in their author instructions.

CONCLUSION

Placebo-controlled trials that tested atypical antipsychotics showed large sample size fallacy. Placebo-controlled trials of conventional antipsychotics and head-to-head trials had insufficient power to detect a real difference between the treatment groups. Sample size calculations in antipsychotic trials for dementia need to be reported adequately.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

TH, SJ, and HL extracted the data. TH and HL searched and selected the trials, performed the data analysis, and drafted the manuscript. SJ and SZ critically reviewed the manuscript and suggested revisions. HL designed the study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2019.01701/full#supplementary-material

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MINI REVIEW
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Pimavanserin: A Novel Antipsychotic With Potentials to Address an Unmet Need of Older Adults With Dementia-Related Psychosis

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Dementia affects more than 40 million people worldwide. When it is accompanied by psychosis, symptom management is especially challenging. Although no drug has been approved by the US Food and Drug Administration (FDA) for psychosis in patients with dementia, atypical antipsychotics are used off-label in severe cases in patients who do not respond to non-pharmacological interventions. However, antipsychotic use in elderly patients with dementia-related psychosis (DRP) is associated with adverse reactions including motor function disorders, cognitive impairment, cerebrovascular events, and increased risk of death. In 2017, the US FDA granted breakthrough therapy designation to the new antipsychotic pimavanserin for the treatment of DRP. Topline result of the pivotal phase III HARMONY (NCT03325556) trial suggests that pimavanserin reduces the relapse of psychosis by 2.8-folds compared to placebo. This favorable result may open path for the potential approval of pimavanserin in DRP. In this review, we discuss the pharmacological activity, clinical efficacy and safety of pimavanserin as a novel atypical antipsychotic with potentials to address the unmet needs of older adults with DRP.

Keywords: pimavanserin, dementia, behavioral and psychological symptoms of dementia, dementia-related psychosis, neuropsychiatric symptoms of dementia, Alzheimer's disease, Antipsychotic, Atypical antipsychotic

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BACKGROUND

It is estimated that 44 million people worldwide are currently living with dementia and this number is expected to triple by 2050 (Alzheimers.net, 2013). In addition to cognitive impairment, dementia is often accompanied by behavioral and psychological symptoms. Indeed, up to 90% of people with dementia experience behavioral and psychotic symptoms of dementia (BPSD) throughout the course of the disease (Selbæk et al., 2013). These symptoms include depression, psychosis, aggression, and agitation and they can lead to complications that further reduce the patient's quality of life. Different subtypes of dementia diseases including Alzheimer's disease (AD), dementia with Lewy bodies, frontotemporal dementia, and vascular dementia exhibit dementia-related psychosis (DRP). These psychotic symptoms present as delusions, with a reported prevalence ranging between 30%–40% and hallucinations, with a prevalence of 5%–20% (Flint, 1991;

Sultzer, 2004). According to Reeves and colleagues (2012), DRP is a "logical attempt to understand the environment" in the context of a degraded cognitive integrity. Psychosis aggravates the clinical course of dementia and creates profound stress on caregivers and family members, which may lead to placing patients in long-term care facilities earlier in the course of the illness (Koppel and Greenwald, 2014).

To date, no drug has received approval by the US Food and Drug Administration (FDA) for treating DRP. Given the severity and high prevalence of BPSD and the lack of FDA-approved pharmacological treatment, many classes of drugs (antipsychotics, antidepressants, and anticonvulsants) have been utilized off-label for the management of BPSD. The most widely used and most effective drugs for this purpose are the atypical antipsychotics, including aripiprazole, risperidone, olanzapine, and quetiapine (Alzheimer's Association, 2013.). However, antipsychotic use in elderly patients with DRP is associated with adverse reactions that include motor function disorder, cognitive impairment, cerebrovascular events (stroke and transient ischemic attack), and increased risk of death (Schneider et al., 2006; Huybrechts et al., 2012; Zhai et al., 2016). In this review, we focus on pimavanserin, a novel antipsychotic that was granted the FDA's breakthrough therapy designation for the treatment of DRP in 2017 (Tan, 2019). This designation indicates the FDA will fast-track its review and development.

PHARMACOLOGY OF PIMAVANSERIN

Pimavanserin is the active pharmaceutical ingredient of Nuplazid®, which was approved by the FDA in 2016 for the treatment of hallucinations and delusions associated with psychosis in patients suffering from Parkinson's disease. Its exact mechanism of action is unclear. The drug exhibits a combination of inverse agonist and antagonist activity at the serotonin 2A receptors (5-HT2A) and, to a lesser extent, at the 5-HT2C receptors in the central nervous system, which is believed to contribute to its antipsychotic activity. Pimavanserin is absorbed in the gastrointestinal tract and is highly bound to plasma protein (approximately 95%). Following the administration of a single 34-mg dose of pimavanserin, the time to maximum plasma concentration is six hours, the half-life is approximately 57 h and the mean (standard deviation, SD) apparent volume of distribution is 2,173 (307) L. Pimavanserin is metabolized in the liver predominantly by cytochrome P450 (CYP3A4 and CYP3A5) and does not cause significant CYP3A4 inhibition or induction. It has a major active N-desmethylated metabolite AC-279, whose half-life is 200 h (Paspe Cruz, 2017).

Pimavanserin is the first atypical antipsychotic that does not induce clinically significant antagonism of adrenergic, dopaminergic, histaminergic, or muscarinic receptors (see **Table 1** for comparison with other atypical antipsychotics) (Paspe Cruz, 2017). This may explain the absence of movement-related disorders seen with other antipsychotics. The most frequent adverse reactions are peripheral edema (7%), nausea (7%), and state of confusion (6%) (FDA, 2018).

APPROVAL FOR TREATING PARKINSON'S DISEASE-RELATED PSYCHOSIS

The efficacy of pimavanserin for treating hallucinations and delusions associated with Parkinson's disease was demonstrated in a 6-week, randomized, placebo-controlled, parallel-group phase III study by Cummings et al. The study randomized 199 patients (mean age 72 years) with Parkinson's disease psychosis (hallucinations and/or delusions) to receive either pimavanserin 34 mg daily or placebo. The outcome was assessed with the

TABLE 1 | Receptor selectivity of pimavanserin and other atypical antipsychotics (Nasrallah, 2008; Hacksell et al., 2014; Mauri et al., 2014; Kusumi et al., 2015; Siafis et al., 2018).

Atypical Antipsychotic*	Receptors																	
	5-HT$_{1A}$	5-HT$_{2A}$	5-HT$_{2B}$	5-HT$_{2C}$	α1A	α1D	α2A	α2B	α2C	D1	D2	D3	H1	M1	M2	M3	M4	M5
Amisulpride	✓	✓		✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
Aripiprazole	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Asenapine	✓			✓	✓	✓				✓	✓	✓	✓					
Brexpiprazole	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓					
Clozapine	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓		✓	✓	✓	✓	✓	✓
Iloperidone	✓	✓		✓	✓	✓					✓	✓	✓					
Lurasidone	✓	✓		✓	✓	✓												
Olanzapine		✓	✓	✓			✓	✓	✓	✓	✓	✓	✓	✓			✓	✓
Quetiapine		✓	✓		✓				✓		✓	✓	✓	✓			✓	✓
Paliperidone	✓	✓		✓		✓	✓				✓	✓		✓				
Pimavanserin		✓		✓														
Risperidone	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Ziprasidone	✓	✓		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

D, dopamine; M, muscarinic; 5-HT, serotonin; α, alpha adrenergic receptor.

**The symbol ✓ indicates that the antipsychotic has an affinity for the receptor in the corresponding column.*

Parkinson's disease-adapted scale for assessment of positive symptoms (SAPS-PD). The group receiving pimavanserin showed a significantly improved SAPS-PD score at week 6 compared to the group receiving placebo. Indeed, a 5.79 point improvement [least square (LS) mean change] in the SAPS-PD score was observed with pimavanserin compared to a 2.73-point improvement for placebo (treatment difference of 3.06 points; p = 0.001). Overall, pimavanserin was well tolerated with no significant safety concerns or worsening of motor function (Cummings et al., 2014).

A post-hoc subgroup analysis of the results revealed a significant improvement in the SAPS-PD score of PD patients with cognitive impairment (n = 50) treated with pimavanserin compared to those on placebo, with no adverse effect on cognition. Moreover, pimavanserin led to better improvement in the SAPS-PD score in the subgroup of patients with cognitive impairment (treatment difference of 5.71 points; p = 0.002) than in the overall PD population (treatment difference of 3.06 points; p = 0.001), suggesting a more robust effect in the former group than the latter (Cummings et al., 2018). Based on this finding, it was extrapolated that pimavanserin may also be a potential treatment for dementia with Lewy bodies, which is also characterized by movement disorders and is associated with psychotic symptoms in 75% of patients (Lyketsos et al., 2002). Despite data from this subgroup analysis suggesting a better safety profile, pimavanserin, like other antipsychotics, carries a black box warning stating that "elderly patients with DRP treated with antipsychotic drugs are at an increased risk of death" (FDA, 2018).

CLINICAL EVIDENCE FROM TRIALS IN DEMENTIA-RELATED PSYCHOSIS

A phase II randomized, double-blind, placebo-controlled, single-center clinical trial assessed the safety and efficacy of pimavanserin 34 mg daily versus placebo for the treatment of AD psychosis. Completed in 2016, the study included 181 participants (mean age 86 years) from multiple affiliated nursing-home sites across the United Kingdom (UK). The primary endpoint was the mean change in the Neuropsychiatric Inventory-Nursing Home version (NPI-NH) psychosis score, from baseline to week 6. At week 6, patients in the pimavanserin group showed significant improvement in the NPI-NH psychosis score compared to patients in the placebo group. Mean change in the NPI-NH psychosis score from baseline at week 6 was −3.76 points [standard error (SE), 0.65] for pimavanserin and −1.93 points (SE, 0.63) for placebo [mean difference −1.84 (95% CI −3.64 to −0.04); p = 0.045] (Ballard et al., 2018). However, in this trial, a significant difference in efficacy between pimavanserin and placebo was not seen at 12 weeks of treatment (**Table 2**). Although agitation was higher in patients receiving pimavanserin (21%) than in those receiving placebo (14%), the overall adverse event profile was similar in the two groups. No detrimental effect was observed on cognition or motor function in either group (Ballard et al., 2018).

Two other trials are currently evaluating pimavanserin in patients with dementia: the SERENE trial (ClinicalTrials.gov number: NCT02992132) and the HARMONY trial

TABLE 2 | Summary of completed and ongoing clinical trials for pimavanserin in dementia-related psychosis.

Trial	Treatment Comparison		Trial Phase	Blinding	Sample size	Symptom	Outcome	Relative Treatment Effect (95% CI)	
	Intervention	Comparator						Effect size (95% CI)	P-value
SERENE (ClinicalTrials.gov identifier: NCT02992132)	Pimavanserin 20 mg (PO, qd) and 34mg (PO, qd)	Placebo (PO, qd)	2	Double-blind	111	Aggression and Agitation	**Primary:** Cohen-Mansfield Agitation Inventory (CMAI) **Secondary:** Zarit Burden Interview	N/A	N/A
HARMONY (ClinicalTrials.gov identifier: NCT03325556)	Pimavanserin 20 mg (PO, qd) and 34mg (PO, qd)	Placebo (PO, qd)	3	Double-blind	392	Psychosis	**Primary:** Time from randomization to relapse in the double-blind period **Secondary:** Time from randomization to discontinuation from the double-blind period for any reason	Primary endpoint HR, 0.353 Secondary endpoint HR, 0.452	Primary endpoint, 0.0023* Secondary endpoint, 0.0024*
ClinicalTrials.gov identifier: NCT03118947	Pimavanserin 20 mg (PO, qd) and 34mg (PO, qd)	N/A	2	Open label	79	Aggression and Agitation	**Primary:** Treatment emergent adverse events (TEAEs)	N/A	N/A
ClinicalTrials.gov identifier: NCT02035553	Pimavanserin tartrate 40 mg (PO, qd)[a]	Placebo (PO, qd)	2	Double-blind	181	Psychosis	**Primary:** Neuropsychiatric Inventory-Nursing Home Version (NPI-NH)	At 6 weeks: MD, −1·84 (−3·64, −0·04) At 12 weeks: MD, −0·51 (−2·23, 1·21)	0·045 (at 6 weeks) 0·561 (at 12 weeks)

CI, confidence interval; HR, hazard ratio; MD, mean difference; N/A, not available or not applicable; PO, taken orally; qd, daily.
[a]*Pimavanserin tartrate 40 mg is equivalent to 34 mg free base pimavanserin.*
**one-sided p value.*

(ClinicalTrials.gov number: NCT03325556). The SERENE trial is a double-blind, placebo-controlled phase II trial examining the safety and efficacy of pimavanserin to treat agitation and aggression in people with AD. Patients are given either 34 or 20 mg of daily pimavanserin, or a placebo for three months. Patients who successfully complete the SERENE trial are eligible to take part in an open-label extension study (ClinicalTrials.gov number: NCT03118947) that assesses the safety and tolerability of 34 or 20 mg of pimavanserin taken for a year. The SERENE trial was completed in February 2018, and its extension was completed in February 2019 (ClinicalTrials.gov, 2019a; ClinicalTrials.gov, 2019b; Tan, 2019). To our knowledge, no data from this phase II clinical trial and its extension have been published to date.

The HARMONY trial is a phase III, double-blind, placebo-controlled study evaluating the efficacy of pimavanserin versus placebo in preventing a relapse of psychotic symptoms in patients with DRP who are stabilized after 12 weeks of open label pimavanserin treatment. Unlike the phase II trials that were restricted to patients with AD, this phase III trial also includes patients with Lewy body dementia, Parkinson's disease dementia, frontotemporal dementia, and vascular dementia. During an initial open-label, 3-month period, all patients receive 34 mg of pimavanserin daily. After this period, patients are randomized to continue receiving 34 mg of pimavanserin daily, to switch to 20 mg daily, or to be given a placebo. HARMONY started in September 2017, and recent topline results suggested that pimavanserin reduced the risk of relapse of psychosis by 2.8-fold compared to placebo in patients with DRP (see **Table 2**) (Acadia Pharmaceuticals, 2019; Tan, 2019).

POTENTIAL OFF-LABEL USE

An International Delphi consensus panel of 11 experts in the management of BPSD chose risperidone as the recommended pharmacological option for this indication, and regarding future treatments, the greatest priority was placed on pimavanserin (Kales et al., 2019). Given its approval for Parkinson's-related psychosis, its selection by the consensus panel for future treatments, and the promising published results from the phase II and III clinical trials indicating pimavanserin's favorable efficacy/safety profile over placebo than the current pharmacological options, pimavanserin is likely to be used off-label for the treatment of DRP pending its potential approval. However, to our knowledge, there is no published data on the status of its likely off-label use in clinical practice.

CONCLUSION

Preliminary clinical evidence suggest that pimavanserin may have a positive benefit-risk profile for the short-term treatment of DRP, which contributed to it's designation by the FDA as a breakthrough therapy for this indication. Results from the phase III HARMONY trial will open the path for the FDA's priority review and a potential approval of pimavanserin for DRP.

AUTHOR CONTRIBUTIONS

IY, ME, and SA determined the outline, reviewed the literature, wrote, verified, and approved the manuscript.

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REVIEW
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Pathways Connecting Late-Life Depression and Dementia

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Late-life depression is associated with significant cognitive impairment. Meta-analyses showed that depression is associated with an increased risk for Alzheimer's disease (AD) and it might be an etiological factor for AD. Since late-life depression is often connected with cognitive impairment and dementia is usually associated with depressive symptoms, a simple diagnostic approach to distinguish between the disorders is challenging. Several overlapping pathophysiological substrates might explain the comorbidity of both syndromes. Firstly, a stress syndrome, i.e., elevated cortisol levels, has been observed in up to 70% of depressed patients and also in AD pathology. Stress conditions can cause hippocampal neuronal damage as well as cognitive impairment. Secondly, the development of a depression and dementia after the onset of vascular diseases, the profile of cerebrovascular risk factors in both disorders and the impairments depending on the location of cerebrovascular lesions, speak in favor of a vascular hypothesis as a common factor for both disorders. Thirdly, neuroinflammatory processes play a key role in the etiology of depression as well as in dementia. Increased activation of microglia, changes in Transforming-Growth-Factor beta1 (TGF-beta1) signaling, production of pro-inflammatory cytokines as well as reduction of anti-inflammatory molecules are examples of common pathways impaired in dementia and depression. Fourthly, the neurotrophin BDNF is highly expressed in the central nervous system, especially in the hippocampus, where it plays a key role in the proliferation, differentiation and the maintenance of neuronal integrity throughout lifespan. It has been associated not only with antidepressant properties but also a reduction of cognitive impairment and therefore could be involved also in AD. Another etiologic factor is amyloid accumulation, as plasma amyloid beta-42 independently predicts both late-onset depression and AD. Higher plasma amyloid beta-42 predicts the development of late onset depression and conversion to possible AD. However, clinical trials with antibodies against beta amyloid recently failed, i.e., Solanezumab, Aducanumab, and Crenezumab. An overproduction of amyloid-beta might simply reflect a form of synaptic plasticity to compensate for neuronal dysfunction in different kind of neurological and psychiatric diseases of multiple etiologies. The tau hypothesis, sex/gender specific differences, epigenetics and the gut microbiota-brain axis imply other potential common pathways connecting late-life depression and dementia. In conclusion, different potential pathophysiological links between dementia and depression highlight several specific synergistic and multifaceted treatment possibilities, depending on the individual risk profile of the patient.

Keywords: late-life depression, dementia, endocrine hypothesis, vascular hypothesis, neuroinflammation, amyloid hypothesis

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INTRODUCTION

Older adults with late-life depression often suffer from serious cognitive impairment without full recovery after successful antidepressant treatment. A relationship has been shown between history of depression and increased risk of dementia. Recent meta-analyses found that depression was associated with an increased risk for dementia and Alzheimer's disease (AD).

Dementia is a clinical syndrome characterized by a progressive deterioration of cognitive function associated with impairment in activities of daily living (van der Flier and Scheltens, 2005) commencing mostly in late life. It is estimated that there will be approximately 4.6 million new cases every year worldwide, doubling every 20 years to 81.1 million by 2040 (Ferri et al., 2005). It is increasing in high-income countries and even more so in low- and middle-income countries (Kalaria et al., 2008). In late life the prevalence of depression is expected to rise and thus denotes new challenges for the mental health system. Mutual hypotheses to explain comorbidity suggest that depression might either be an early symptom of dementia, or a reaction to cognitive decline, or due to an overlap of both syndromes. Other hypotheses suggest that depression might increase susceptibility to dementia or act as a predictor, if not a causal factor for dementia (Lenoir et al., 2011). So far, no particular and distinctive symptom profile with substantial usefulness in the clinical setting has emerged as characteristic of late-life depression (Gallagher et al., 2010). More importantly, the intensity and the reporting of depressive symptoms in the elderly are suspected to be covert and not properly meeting the diagnostic criteria. Since late-life depression is often coupled with cognitive impairment and dementia may be associated with depressive symptoms, a simple differential diagnostic approach to distinguish between those syndromes is not always possible (Steffens and Potter, 2008). Depressive symptoms are reported in 30–50% of AD patients (Zubenko et al., 2003) and severe depressive episodes are reported in more than 10% of patients suffering from AD (Lopez et al., 2003) and in about 50% of patients with vascular dementia (Ballard et al., 2000; Park et al., 2007). The definitions of the terms "depression" and "dementia" are heterogeneous with blurred boundaries. Depression and dementia are not dichotomous symptoms or diagnoses. Depression can be considered as a symptom of dementia. Neuropsychiatric symptoms or behavioral and psychological symptoms are almost universal parts of dementia, as reviewed by van der Linde et al. (2016). The Cache County Study (Steinberg et al., 2008) revealed point and 5-year period prevalence of neuropsychiatric symptoms in dementia and found that participants most likely developed depression (77%), apathy (71%) and anxiety (62%). A 5-year longitudinal study of 223 patients with mild dementia and annual assessments in Western Norway (Vik-Mo et al., 2018) revealed that the most common symptoms were apathy (83%), depression (63%), appetite (63%), and aberrant motor behavior (60%). Connors et al. (2018) investigated the stability of neuropsychiatric subsyndromes in AD by principal component analyses and multiple-group confirmatory factor analyses. The findings suggest that the neuropsychiatric symptoms do not appear in distinctive subsyndromes that are stable over time. Neuropsychiatric symptoms in dementia have multiple overlapping relationships with one another. It is well-known that cognitive decline limits language skills as well as self-awareness of depressive symptoms. Depression and apathy due to dementia are difficult to differentiate. The problem of the correct diagnosis is foreshadowed by the large range of published prevalence rates for depression in AD from under 5% to nearly 50% (Weiner et al., 1994, 2002). Forgetfulness, difficulties in concentration, sleeping too much or not enough, reducing social contacts as well as loss of interest in hobbies mark additional areas of overlap for depression and dementia. Clinically, depression may masquerade as dementia, dementia may pose as depression, and dementia and depression may coexist. Neuropsychological tests and psychiatric exploration may not differentiate between reversible cognitive deficits due to depression and persistent cognitive impairment due to dementia. Widely used rating scales – in studies as well as in clinical daily routine – assessing the severity of depression are not always helpful for demented patients. The Montgomery–Asberg Depression Rating Scale – MADRS (Montgomery and Asberg, 1979) is not validated for demented patients (Holroyd and Clayton, 2000; Conn and Thorpe, 2007). The Hamilton Depression Rating Scale – HAM-D (Hamilton, 1960) has not been validated in severely demented patients (Lichtenberg et al., 1992). Interestingly, antidepressant drugs have proven efficacy in non-demented populations (Cipriani et al., 2018), but revealed negative outcomes in randomized placebo-controlled trials with antidepressants in dementia (Leong, 2014; Leyhe et al., 2017): venlafaxine (75 mg daily) for 6 weeks, assessed by MADRS in 31 patients (de Vasconcelos Cunha et al., 2007); fluoxetine (maximum 40 mg daily) for 6 weeks, assessed by HAM-D in 41 patients (Petracca et al., 2001) and imipramine (83 mg daily) for 8 weeks, assessed by HAM-D in 61 patients (Reifler et al., 1989). Pharmacological interventions based on serotonergic and noradrenergic etiology were mostly disappointing. A promising overlap between dementia and depression might be the glutamatergic signaling, namely the dysfunction of *N*-methyl-D-aspartate (NMDA) receptor complex signaling. NMDA receptor antagonists feature antidementia and antidepressant potential [for review see Khundakar and Thomas (2015)]. In a review by Butters et al. (2008), the hypothesis has been postulated that depression leads to subsequent cognitive impairment and dementia.

THE ENDOCRINE HYPOTHESIS

One of the most important endocrine components to respond to stress is the secretion of corticosteroid hormones. The neuroendocrinology of depressive patients – as far as the hypothalamic-pituitary adrenal (HPA) axis is concerned – shares common characteristics with that of rats that are chronically stressed (Checkley, 1996). Moreover, there is evidence for an increased central HPA axis activation in animal models of chronic stress (Herman et al., 1989; Angulo et al., 1991; de Goeij et al., 1992; Bartanusz et al., 1993; Harbuz et al., 1993) as well as in human depression (Ur et al., 1992; Raadsheer et al., 1994; Young et al., 1994). Secondly, the impaired negative feedback can be

observed in animal models of chronic stress (Sapolsky et al., 1984; Young et al., 1990) as well as in depression (Carroll et al., 1981; Young et al., 1991). Thirdly, the hypertrophy of the adrenal gland can be found in chronically stressed animals (Herman et al., 1995) as well as in depressive patients (Dorovini-Zis and Zis, 1987; Nemeroff et al., 1992; Rubin et al., 1995). In line with these observations, the dexamethasone suppression test can be striking in depressive patients (Arana and Mossman, 1988). The hippocampus contains corticosteroid receptors (McEwen, 1999). Stress conditions as well as an exogenous application of glucocorticoids can cause hippocampal neuronal damage as well as cognitive impairment (Levy et al., 1994; Cereseto et al., 2006). Stress exposure causes volume reductions of the hippocampus, impairs dendritic complexity of neurons in the CA3 and affects neurogenesis in the dentate gyrus (Gould et al., 2000; Czeh and Lucassen, 2007). Increased levels of cortisol serum are associated with AD biomarkers in CSF and serum cortisol and CSF tau levels are negatively correlated (Laske et al., 2009). Similarly, hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis and increased levels of cortisol are most consistently observed findings in up to 70% of depressed patients (Porcelli et al., 2011). Impaired hippocampal plasticity may be related to cognitive impairment due to depression. A large number of MRI studies investigated the hippocampus subfield volumetrics in depressive patients compared to controls: As summarized by Maller et al. (2018), the findings were partly inconsistent. No significant differences concerning various hippocampal subfields in depressive patients compared to controls or correlations with illness duration or number of episodes have been found (Cho et al., 2010; Cole et al., 2010; Huang et al., 2013; Lindqvist et al., 2014; Na et al., 2014; Travis et al., 2015; Treadway et al., 2015; Han et al., 2016; Maller et al., 2018). Hippocampal tail volume was discussed as being a biomarker for sensitivity to treatment with antidepressant medication (Maller et al., 2018). The association of hippocampal volume and dementia, especially AD, is well known and has been refined several times (Allison et al., 2019).

THE VASCULAR HYPOTHESIS

Clinically, the onset or worsening of a depression after the onset of vascular disease, the profile of cerebrovascular risk factors in depressive patients, and the impairments depending on the location and extent of a cerebrovascular lesion, as well as a poor response to antidepressant medication speak in favor of a vascular depression hypothesis (Alexopoulos, 2019). Several neuroimaging findings also support this hypothesis, namely – amongst others – low blood flow in the precuneus, cuneus, in fronto-cingulate-striatal areas as well as temporal, occipital, and parietal lobes, a resting functional connectivity pattern as postulated in depression and changes suggesting limbic hyperactivation. Circulating markers of endothelial dysfunction and flow mediated vascular dilatation also support the vascular depression hypothesis. However, the change of depressive symptoms over time, and the fact that infarcts were not associated with the severity of depression, cannot be readily brought in line with this hypothesis (Alexopoulos, 2019). Moreover, patients suffering from ischemic lesions do not necessarily develop a depression. Epidemiological investigations focus on the comorbidity of depression and dementia with cardiovascular diseases, i.e., heart failure, however, the prognostic role of depression and the impact of heart failure as a risk factor for dementia needs further investigation (Adelborg, 2018).

THE NEUROINFLAMMATION HYPOTHESIS

Neuroinflammatory processes play an important role in the etiology of depression (Bhattacharya et al., 2016) as well as dementia (Knezevic and Mizrahi, 2018). Increased activation of microglia could be detected in depression (Setiawan et al., 2015) and in AD (Knezevic and Mizrahi, 2018). The anti-inflammatory cytokine Tumor Necrosis Factor-beta1 (TGF-beta1) is important for memory formation and synaptic plasticity and is reduced in depression in correlation with depression severity. A deficit in TGF-beta1 signaling pathway is common in depression and AD (Caraci et al., 2018). In a nutshell, the inflammation hypothesis of late life depression is underpinned by typical old-age immune responses [for summary see Alexopoulos (2019)] like production of pro-inflammatory cytokines as well as reduction of anti-inflammatory molecules, the insufficient clearance of neurotoxic molecules, neuronal loss and reduced neurogenesis. Cytokines lead to (1) the induction of enzymes that reduce the production of serotonin, (2) dysregulation of the glutamate system, (3) excitotoxicity and a reduced production of neurotrophic factors that are important for neuroplasticity and neurogenesis, and (4) oxidative stress, affecting glial cells in the prefrontal cortex and the amygdala. Inflammation impairs the function of glucocorticoid receptors. The increase of inflammatory markers is associated with depression severity as well as with cognitive impairment in depression. A treatment with antidepressant medication reduces inflammation markers, as well as non-steroidal anti-inflammatory drugs might have antidepressant effects in depressive persons.

The role of the gut microbiota-brain axis in affective disorders is subject of promising interventions with pro- and prebiotics as well as fecal microbiota transplants [as reviewed by Carlessi et al. (2019) and Peirce and Alvina (2019)]. The gut microbiota-brain axis could be a common pathway in late life depression and dementia. The recent review by Panza et al. (2019c) provided evidence for a gut microbial hypothesis in dementia with the appeal to test antibacterial therapy in AD.

THE NEUROTROPHIN HYPOTHESIS

The neurotrophin BDNF is highly expressed in the central nervous system, particularly in the hippocampus where it plays a key role in the proliferation, differentiation and the maintenance of neuronal integrity throughout lifespan (Lipsky and Marini, 2007). In AD, there is an association between the rate of cognitive decline and BDNF serum levels, amyloid beta (Aβ1-42) plasma levels and the degree of platelet activation

(activated GP IIb-IIIa and P-selectin) (Laske et al., 2010; Stellos et al., 2010; Laske et al., 2011). Furthermore, up-regulation of serum BDNF after pharmacotherapy in AD patients revealed a reduction of cognitive impairment and therefore could mirror a neuroprotective effect (Leyhe et al., 2008, 2009). Synaptic plasticity in neuronal networks playing a role in depression is regulated by BDNF (Schinder and Poo, 2000; Pittenger and Duman, 2008). Moreover, stress-induced deficits in structural and synaptic plasticity may be reversed by up-regulation of BDNF, enhancing cognitive flexibility and resilience against depression. Depressed and demented patients show reduced BDNF levels which are increased by antidepressant treatment (Karege et al., 2002; Shimizu et al., 2003; Aydemir et al., 2005; Gervasoni et al., 2005; Lee et al., 2006, 2011; Kim et al., 2007; Brunoni et al., 2008; Sen et al., 2008; Deuschle et al., 2013; Ricken et al., 2013). BDNF polymorphism and serum level are related to depression, anxiety, neuroticism and serotonergic neurotransmission (Hellweg et al., 2002, 2008; Lang et al., 2002, 2004, 2005, 2006, 2007, 2009). An augmentation with lithium is an evidence-based antidepressant therapy and leads to increasing BDNF levels (Ricken et al., 2013). Of note, a common feature among depressed patients is insomnia (Steiger and Kimura, 2010). Giese et al. (2014) present data on the relation between BDNF levels and sleep disturbances, whereas patients suffering from insomnia revealed reduced BDNF levels.

THE SENESCENCE HYPOTHESIS

Various stimuli cause cellular senescence and a senescence-associated secretory phenotype, i.e., short/dysfunctional telomeres, non-telomeric DNA damage, oncogenes/oncogenic mutations, mitogenic/stress signals, overexpressed cell cycle inhibitors, and chromatin instability (Coppe et al., 2010). Senescence is linked to depression and could be a future therapeutic target (Diniz, 2018).

The role of telomere length and shortening as an indicator of cellular aging is discussed as a mechanism for stress-related depression (Boccardi and Boccardi, 2019) as well as for Alzheimer's dementia (Boccardi et al., 2015; Nudelman et al., 2019).

Another link for the conversion of affective disorders to dementia is glycogen synthase kinase 3 (GSK-3) that might be an etiological factor for depression and dementia (Terao et al., 2019). Lithium inhibits GSK-3 and is effective for affective disorders and cognitive impairment (Terao et al., 2006; Nunes et al., 2007; Kessing et al., 2008; Gerhard et al., 2015).

THE AMYLOID HYPOTHESIS

According to Mahgoub and Alexopoulos (2016), amyloid accumulation is related to depression by means of frontolimbic impairment. Higher plasma amyloid beta-42 predicts the development of late-life depression and conversion to AD (Blasko et al., 2010). Increased levels of amyloid beta peptides could be associated with an amyloid-related depression (Morgese et al., 2015, 2017; Schiavone et al., 2017). In elderly persons without cognitive deficits, increased amyloid burden was related to depression (Yasuno et al., 2016; Donovan et al., 2018). The amyloid hypothesis is extensively discussed as primary cause for synaptic dysfunction and neurodegeneration in AD (Hardy and Higgins, 1992; Hardy and Selkoe, 2002). There is a huge amount of data that supports the hypothesis that amyloid beta related toxicity plays a role in AD [summarized in Herrup (2015)]: For example, APOE variants are a known risk factor for AD and demonstrated an effect on amyloid beta clearance; overexpression of human APP in mice results in the formation of plaques; transgenic mice for human APP demonstrate memory impairment; amyloid beta shows toxicity for cultured neurons; human APP overexpressed in fruit flies leads to neurodegeneration; amyloid plaques can be detected more frequent in AD brains; presence of plaques is related to greater risk for developing AD. There is, however, also a large amount of recent data underpinning that the claim for the absolute truth of this hypothesis as the primary cause for AD cannot be maintained, as summarized by Herrup (2015). Most importantly, several clinical trials with antibodies against beta amyloid based on this hypothesis failed. Solanezumab was not successful in phase 3 clinical trials (McCartney, 2015). Phase 3 clinical studies with Aducanumab were canceled in March 2019 because an interim analysis revealed that the trials were unlikely to meet the primary endpoint. However, after a reanalysis in October 2019, Biogen announced that the company intends to seek regulatory approval (Biogen, 2019). Concerning Crenezumab, Roche has recently announced discontinuation of the Phase III studies after a pre-planned interim analysis (Hoffmann-La Roche, 2019).

Amyloid beta has an important physiological role for the brain function, e.g., for neurogenesis, synaptic plasticity, memory and neuronal survival; and an overproduction of amyloid-beta might simply reflect a form of synaptic plasticity to compensate for neuronal dysfunction in different kind of neurological and psychiatric diseases of multiple etiologies, including cognitive (e.g., AD) as well as affective disorders, as reviewed by Panza et al. (2019b). This hypothesis of an amyloid beta overexpression as a compensatory attempt in terms of a repair mechanism is in line with observations that anti-amyloid beta drugs, e.g., beta-site amyloid precursor protein-cleaving enzyme 1 (BACE-1) inhibitors, may induce or worsen psychiatric disturbances in cognitively impaired patients (Egan et al., 2019a,b; Henley et al., 2019; Panza et al., 2019a).

THE TAU HYPOTHESIS

Rapp et al. (2006, 2008) investigated the interaction between depression and neurofibrillary tangles in AD patients and indeed found increased neurofibrillary tangles in AD patients with a comorbid depression. However, Tsopelas et al. (2011) found that a history of late-life depression was not associated with neurofibrillary tangles in brains whose donors had no history of dementia. Longitudinal clinical-pathologic cohort studies with almost 2000 participants do not support the tau

hypothesis that depression is associated with neurofibrillary tangles (Wilson et al., 2016).

GENDER DIFFERENCES

Gender specific associations and differences in resilience to stress (Hodes and Epperson, 2019) and in depression and dementia are widely discussed, with partly divergent results (Fuhrer et al., 2003; Kessing and Nilsson, 2003; Dal Forno et al., 2005; Simons et al., 2006; Artero et al., 2008; Chen et al., 2008; Noale et al., 2013; Mirza et al., 2014; Kim et al., 2015; Heser et al., 2020). A female to male prevalence ratio of 2:1 is described for depression (Bromet et al., 2011) and dementia (Ferretti et al., 2018). The gender differences in published prevalence rates of depression might be partly explained by the fact that men are less willing to seek psychiatric help (Kessler et al., 1981; Ferretti et al., 2018), leading to a possible underestimation of depression in men. The sex differences in life expectancy might also have an influence on the ratio for dementia. Nevertheless, sex-specific biological features, e.g., the effect of estrogens on mood and/or cognition (Kawas et al., 1997; Waring et al., 1999; Wang et al., 2000), might modulate the risk for affective and cognitive disorders. Dal Forno et al. (2005) and Heser et al. (2020) provided evidence that the association between depression and dementia is stronger in the male population.

EPIGENETICS

Several reviews exist about the role of epigenetics (meaning "on top of" genetics and without changes of DNA sequence), in the pathogenesis of depression (e.g., Menke and Binder, 2014; Nestler, 2014; Saavedra et al., 2016; Lin and Tsai, 2019) and dementia (e.g., Maloney and Lahiri, 2016; Fenoglio et al., 2018; Lemche, 2018; Stoccoro and Coppede, 2018; Sujeetha et al., 2018). To be honest, epigenetic results are fairly variable for depression and dementia, and the lack of common stable epigenetic patterns makes it difficult to relate reliable epigenetic factors in depression with the risk of AD, as summarized by Herbert and Lucassen (2016). Further limitations addressing epigenetic research with correlational studies are discussed in the following section.

LIMITATIONS

When assessing correlational studies, it is always important to keep in mind the advantages and limitations of this approach (Asamoah, 2014): A correlation does not necessarily imply causation. Moreover, the dilemma of directionality (the "chicken-and-egg problem") cannot be sufficiently addressed by a correlational approach: It cannot be concluded that changes in variable A might cause changes in variable B, but that also changes in variable B might cause changes in variable A. With respect to a multifactorial complexity of affective symptoms and cognitive impairment in humans, the variables A and B are supposed to be related to variables C, D, E, ...

On the other hand, causation does indeed imply a correlation. This makes it an important tool for the falsification of a hypothesis. Bearing this consideration in mind, the results of correlational studies can offer interesting ideas for further research or improved diagnostic and/or therapeutic steps. Correlational studies are extremely helpful to formulate an interesting hypothesis for experimental research. However, experimental approaches in the field of pathogenesis of depression and dementia in humans are challenging or impossible because important variables cannot be manipulated or their manipulation would be unethical. Moreover, an experimental approach using animal models for affective and cognitive diseases is limited and cannot cover all aspects of human pathology. Another challenge is the use of a representative sample and the generalization to the population of patients with depression and/or dementia.

CONCLUSION

The pathogenesis of both syndromes themselves is not understood so far – making it more difficult to describe common pathways. There is a vast amount of literature showing several potential links between dementia and depression highlighting the multifactorial complexity of both syndromes. In accordance with these multifaceted pathologies different individualized strategies (antiinflammatory, psychotherapeutic, antidepressant, antihypertensive, and endocrinological) might help to overcome the pathophysiology of dementia and depression in an individualized treatment regimen depending on the individual risk factors. However, a common drawback of all links between affective and cognitive impairments mentioned and discussed above is the lack of specificity for depression and/or dementia. When searching the literature for links between these fields, many interesting intersections can be found – but also many limitations and downsides that do not the support the respective hypotheses. To be honest, all pathways connecting dementia and late life depression that are found so far can only explain a small part of the story and have strong limitations. Correlational approaches have severe limitations, as a correlation does not necessarily imply causation. The dilemma of directionality (the "chicken-and-egg problem") as well as the third-variable problem cannot be solved. Experimental research in humans is impeded by ethical limits or the fact that certain variables cannot be manipulated. Moreover, animal models cannot address all relevant aspects of the human pathology in depression and dementia. The review of the literature shows that most publications in this field end with an outlook and perspective for prevention and/or therapy of cognitive or affective disorders that are somehow contrived and artificial hypotheses – far away from a quantum jump and breakthrough for applied therapies – due to the multifactorial complexity of both syndromes.

AUTHOR CONTRIBUTIONS

CL and UL performed the literature research and wrote the manuscript.

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frontiers in Pharmacology

BRIEF RESEARCH REPORT
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Effects of Aging on Formalin-Induced Pain Behavior and Analgesic Activity of Gabapentin in C57BL/6 Mice

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Improved living conditions have induced an increase of lifespan often accompanied by comorbidities, responsible for pain, and by cognitive impairment and dementia, impairing communication capabilities. In most cases, the elderly do not receive pain relief because of underdiagnosis and of aging-induced changes of systems affecting nociceptive response. Unrelieved pain is involved in the development of behavioral symptoms, as agitation, representing a difficult challenge in this fragile population. Aged C57BL/6 mice and amyloid precursor protein (APP) mice display behavioral disturbances that mimic behavioral and psychological symptoms of dementia (BPSD). Therefore, this original study focuses on the influence of aging on nociception to provide insight into the occurrence of BPSD. We have investigated how aging can affect nociception after formalin administration and gabapentin effect in C57BL/6 mice, since it represents one of the treatments of choice for chronic neuropathic pain. Based on our results, changes of nociceptive behavior in response to an algogen stimulus occur during aging. Formalin-induced behavioral pattern in older C57BL/6 mice presents a temporal shift and an increase in the peak amplitudes. Our data show that the effectiveness of gabapentin is influenced by the age of the animal; though preliminary, the latter provide evidence upon which formalin test induced long-lasting mechanical allodynia might be a reliable as rapid and viable persistent pain model. The disclosed differences in effectiveness of gabapentin according to age can form the rational basis to deepen the study of pain treatment in the elderly.

Keywords: aging, behavioral and psychological symptoms of dementia, dementia, pain, gabapentin, formalin test

INTRODUCTION

During the last 150 years the improvements in medicine and in standards of living induced an increase of three months per year in life expectancy at birth (Scully, 2012). Unfortunately, longevity and aging predispose to chronic and progressive neurodegenerative conditions. In particular, 50 million people worldwide suffer from dementia and this number will likely triple by 2050 (Patterson, 2018). The most affected segment of population is represented by adults older than 65 years, often

presenting comorbidities responsible for pain states, (see (Scuteri et al., 2018b)) e.g. arthritis, herpes zoster, diabetes accompanied by neuropathy and retinopathy (see (Scuteri et al., 2019b)) and migraine, disabling (see (Scuteri et al., 2019a)), and difficult to treat (see (Scuteri et al., 2020)). Up to 80% of patients resident in nursing homes often shows moderate to severe pain (see (Sandvik et al., 2014)). Unrelieved pain might be a contributory factor for the development of agitation (Husebo et al., 2011; Sampson et al., 2015). Poor communication skill of patients affected by dementia is an important determinant of underdetected pain (Kovach et al., 2005; Scuteri et al., 2017a). The latter problem makes the assessment of pain very difficult in this fragile population, thus receiving less pain medication than cognitively intact elderly (Horgas and Tsai, 1998; Achterberg et al., 2013). Indeed, the treatment of pain with a stepwise protocol is demonstrated to reduce agitation at the Cohen-Mansfield agitation inventory of the 17% (Husebo et al., 2011). Intense agitation and anxiety are the main features of the behavioral and psychological symptoms of dementia (BPSD) known under the definition of sundowning syndrome, frequent challenge in institutionalized demented and normal elderly (Evans, 1987; Bachman and Rabins, 2006; Bedrosian et al., 2011). Mice subjected to spared nerve injury develop depressive-like behavior and cognitive dysfunction with significant enhancement in β-amyloid 1–40 serum peptide levels (D'Aniello et al., 2017). Incidentally, aged C57BL/6 mice and amyloid precursor protein (APP) mice both present an anxiety pattern of behavior that mimics this BPSD (Bedrosian et al., 2011). Aging is associated with changes of the systems involved in nociception (Hamm and Knisely, 1985; Hamm and Knisely, 1986), as well as dementia (Parvizi et al., 2000; Zarow et al., 2003). How aging impacts on pain processing and on painkillers effectiveness has not been well understood yet. Indeed, the lack of homogeneous results yielded so far may stem from differences in strain, age, and test for sensitivity assessment (Yezierski, 2012). Aged Lou/c/jall rats present increased mechanical sensitivity to Von Frey's test and paw pressure test (Jourdan et al., 2000; Jourdan et al., 2002). Older rats show more sensitivity to cold and morphine is less effective in producing antinociception during thermal, hot, stimulation. In particular, aged Fischer 344 × Brown Norway F1 rats placed in an apparatus with temperature-controlled floor plates spend more time in the floor at the neutral temperature of 30°C as compared to hot (45°C) and cold (15°C) temperatures. Aversion is greater to cold than to heat, but it is increased by exposure to extreme hot and cold temperatures with significant influence of age (Morgan et al., 2012). Among others, we have used the formalin test (Dubuisson and Dennis, 1977) because of favorable features. In fact, following a period of inflammation, it induces longer lasting hyperalgesia. In particular, peripheral inflammation and nocifensive behavior ensue immediately after the administration of formalin, whilst hyperalgesic response occurs after 2 h and builds up from the first to the third day lasting 3 to 4 weeks (Fu et al., 2001; Guida et al., 2012). Formalin-induced licking/biting behavior is characterized by an early nociceptive phase and a late phase in which central sensitization occurs (see (Scuteri et al., 2018a)). Interestingly, the α2δ-1 calcium channel subunit, important for channel assembly, is overexpressed during central sensitization and allodynia in a number of specific pain models (Luo et al., 2002). The α2δ-1 ligands, known as gabapentinoid drugs, represent a largely validated approach for chronic neuropathic pain treatment (Scuteri et al., 2017b). Therefore, here we aim at characterizing the impact of aging on formalin evoked nociception and gabapentin efficacy in C57BL/6 mice.

MATERIALS AND METHODS

Animals

Male C57BL/6 mice (Charles River, Italy) of 2, 6, 13, and 20 months of age at the beginning of the experiment have been used. Mice have been housed in groups of 4 per cage on a 12 h:12 h light dark cycle at constant room temperature of 22 ± 1°C and in conditions of relative humidity of the 65% and provided with food and water *ad libitum*.

Ethical review and approval was not required for the animal study because the experimental protocol is in accordance to the European Community Council Directive of 24 November 1986 (86/609/EEC) and L.D. 4 March 2014 No. 26 has been followed to minimize the number of animals used still generating reliable results. Since this project has been approved when the D.M. 116 was still in validity, no other approval was required.

The severity of the formalin test procedure is slight (for pain intensity and duration) according to the annex VII of the L.D. 26 quoted in the experimental procedure section. More importantly, our work has used this test to replace more severe surgical procedures to mimic persistent pain. Similarly, the very low number of animals used in this behavioral study cannot be reduced further. Indeed, the experimental design, considering group sizes and statistical power analysis, balances the need for reliable results while keeping the number of animals as low as possible. Accordingly, we meet with the scope of the 3R approach to refine, reduce, and, at least in part, replace. Based on statistical power calculation and according to similar studies in literature, n=5 animals per group subjected to gabapentin treatment is sufficient to obtain 30% reduction of formalin-induced mechanical allodynia. Therefore, this n has been chosen to use the minimum number of animals still generating reliable results.

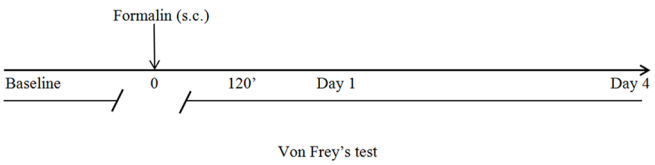
Experimental Pain Model

The experimental pain model is the formalin test (Dubuisson and Dennis, 1977). Mice are allowed to acclimatize in a plexiglas box (30 x 30 x 35 cm^3) for up to 60 min maintaining room temperature and humidity stable. Twenty µl of a 5% solution of fresh formalin obtained from a solution of saturated formaldehyde at 36.5–38% (Sigma F8775) were administered subcutaneously (s.c.) into the left hindpaw of the mouse. The

licking/biting/flinching behavior is monitored for 90 min at intervals of 5 min.

Behavioral Test

The Von Frey's test (Chaplan et al., 1994) is performed to assess mechanical allodynia. For acclimation, mice are placed inside perspex chambers (75 mm x 90 mm) on a wire mesh floor for up to 60 min. This test uses calibrated filaments, the Von Frey's hairs (Ugo Basile, Comerio, Italy), through the up-down method (Dixon, 1980; Chaplan et al., 1994) that allows to determine the value corresponding to the 50% of the withdrawal threshold. The method for calculation is based on "k value" and "log final hair", considering the stiffness of the Von Frey's hair. In particular, the 50% response threshold is interpolated through the formula "50% g threshold = $(10^{[Xf+k\delta]})/10.000$" where: Xf = value (in log units) of the final Von Frey's hair used; k = tabular value for the pattern of positive/negative responses; δ = mean difference between stimuli expressed in log units. Von Frey's hairs have logarithmically incremental stiffness (0.41, 0.70, 1.20, 2.00, 3.63, 5.50, 8.50, and 15.10 g) (Chaplan et al., 1994). During the behavioral tests the room temperature and humidity are maintained constant. The timeline of the behavioral tests is as follows:



Drug Treatment

Gabapentin/vehicle is administered intraperitoneally (i.p.) 15 min before formalin injection. Gabapentin is used in two different doses: 10 mg/kg or 100 mg/kg. Based on the existing literature, the dose of 100 mg/kg has been selected and compared with a second 10-fold lower dose (10 mg/kg) and a vehicle. Gabapentin is dissolved in depurated water (vehicle) according to its solubility (10 mg/ml). The Von Frey's test is performed before the administration of formalin in order to get the baseline threshold. To assess the effect of gabapentin on formalin-induced mechanical allodynia in mice of different ages, the Von Frey's test is performed 2 h after the administration of formalin, on the following day and on the 4th day after formalin test. In view of the reported circadian oscillation of α2δ-1 subunit expression and variability of response to gabapentin, our experiments started at 9:30 a.m. in all instances (Kusunose et al., 2010).

Statistical Analysis

Data are expressed as mean ± SEM and assessed statistically for differences by two way analysis of variance (ANOVA) followed by Bonferroni's multiple comparisons test (GraphPad Prism). p values < 0.05 are considered statistically significant.

RESULTS

Effect of Aging on Formalin-Induced Licking/Biting/Flinching Behavior

The formalin test provides an initially inflammatory stimulus turning into a persistent pain trigger in the long-term and formalin-induced nocifensive behavior undergoes modifications both in the intensity and in the duration with increasing age of the animal. While the 2 month-old mice show the behavioral pattern typically induced by formalin (Dubuisson and Dennis, 1977), the curves of older mice show a temporal shift (**Figure 1A**) with an increase in the peak amplitudes (**Figure 1B**).

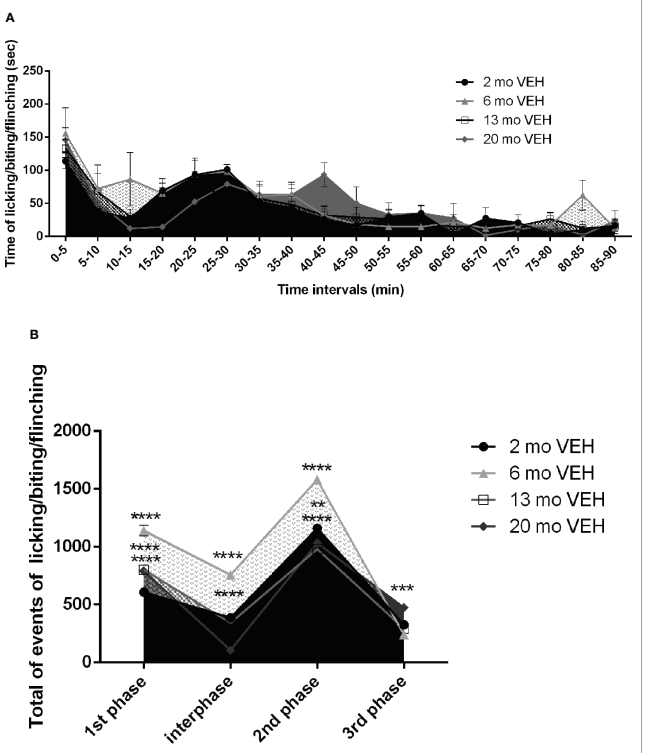


FIGURE 1 | Effect of aging on formalin-induced licking/biting/flinching behavior. The first phase occurs in the first 5 min in all the age groups, while the second phase is shifted and prolonged (30–45 min) in aged 20 months mice (**A**. Two-way ANOVA F (17, 216) = 15,69; p < 0,0001**** for time points factor). The amplitude of the peak in the first phase increases in 13 and 20 month-old mice, but it reaches the highest level in mice of 6 months (**B**. Two-way ANOVA F (9, 52) = 60,02; p < 0,0001****: 2 vs 6 months p< 0,0001****; 2 vs 13 months p< 0,0001****; 2 vs 20 months p< 0,0001****). Also in the interphase (**B**. Two-way ANOVA F (9, 52) = 60,02; p < 0,0001****: 2 vs 6 months p< 0,0001****; 2 vs 20 months p< 0,0001****) and in the second phase (**B**. Two-way ANOVA F (9, 52) = 60,02; p < 0,0001****: 2 vs 6 months p< 0,0001****; 2 vs 13 months p< 0,0001****; 2 vs 20 months p< 0,01**) the highest amplitude occurs in 6 month-old mice. The 20 month-old mice, they develop a higher third phase (**B**. Two-way ANOVA F (9, 52) = 60,02; p < 0,0001****: first phase 2 vs 20 months p< 0,001***). Data are expressed as mean ± SEM of the nociceptive reaction. p values <0.05 were considered statistically significant.

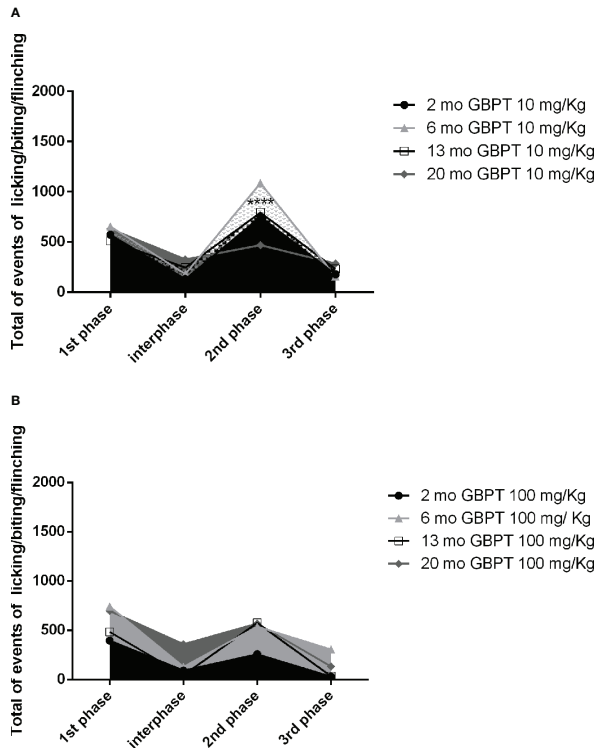


FIGURE 2 | Influence of aging on gabapentin effects in formalin test. In the second phase the low dose of 10 mg/kg of gabapentin is more active in 20 than in 2 month-old mice (**A**. Two-way ANOVA F (9, 56) = 88,16; p < 0,0001****: 2 vs 20 months p< 0,0001****). On the contrary, the higher dose of 100 mg/kg is more effective in the 2 month-old mice rather than in all the groups of older mice (**B**. Two-way ANOVA F (9, 64) = 56,54; p < 0,0001****). Data are expressed as mean ± SEM of the nociceptive reaction. p values <0.05 were considered statistically significant.

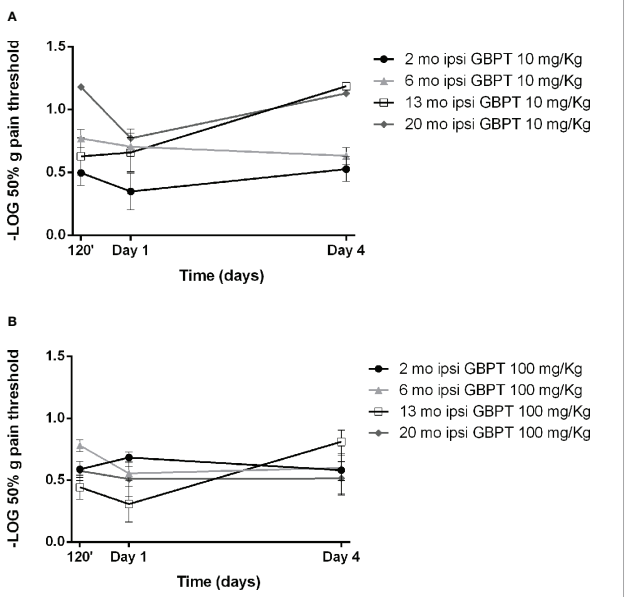


FIGURE 3 | Influence of aging on gabapentin effects in formalin-induced mechanical allodynia. The lower dose of gabapentin is not active (**A**. Two-way ANOVA F (9, 56) = 2,925; p = 0,0065 **) and the higher dose is more effective in aged mice (**B**. Two-way ANOVA F (9, 64) = 1,930; p = 0,0633). Data are expressed as –LOG of the mean ± SEM of the 50% pain threshold. p values <0.05 were considered statistically significant.

Under these experimental conditions, due to the detected different duration of the behavioral pattern in aged mice, the latter has been monitored for 90 min, instead of the classic 60 min. While the first phase occurs in the first 5 min in all the age groups, the second phase, presented by 2 month-old mice from 25 to 30 min since formalin injection, is shifted and prolonged (30–45 min) in 20 months mice (**Figure 1A**. Two-way ANOVA F (17, 216) = 15,69; p < 0,0001**** for factor time). This likely indicates an increased latency to recovery. Moreover, the amplitude of the peak in the first phase increases in 13 and 20 month-old mice, but it reaches the highest level in mice of 6 months (**Figure 1B**. Two-way ANOVA F (9, 52) = 60,02; p < 0,0001****: 2 vs 6 months p< 0,0001****; 2 vs 13 months p< 0,0001****; 2 vs 20 months p< 0,0001****). Also in the interphase (**Figure 1B**. Two-way ANOVA F (9, 52) = 60,02; p < 0,0001****: 2 vs 6 months p< 0,0001****; 2 vs 20 months p< 0,0001****) and in the second phase (**Figure 1B**. Two-way ANOVA F (9, 52) = 60,02; p < 0,0001****: 2 vs 6 months p< 0,0001****; 2 vs 13 months p< 0,0001****; 2 vs 20 months p< 0,01**) the highest amplitude occurs in 6 month-old mice. It is conceivable that the prolonged response of 20 month-old mice may yield the observed higher third phase (**Figure 1B**. Two-way ANOVA F (9, 52) = 60,02; p < 0,0001****: first phase 2 vs 20 months p< 0,001***).

Influence of Aging on Gabapentin Effects in Formalin Test

The effect of gabapentin on the nociceptive response induced by formalin is influenced by the age of the mice. A low dose, poorly effective or ineffective (Dixit et al., 1999) in young adult rodents, shows increased efficacy in aged mice. In fact, in the second phase the low dose of 10 mg/kg is more active in 20 month-old than in 2 month-old mice (**Figure 2A**. Two-way ANOVA F (9, 56) = 88,16; p < 0,0001****: 2 vs 20 months p< 0,0001****). At variance with the latter, the dose of 100 mg/kg results more effective in 2 month-old (**Figure 2B**. Two-way ANOVA F (9, 64) = 56,54; p < 0,0001****) mice but not in all of the other age groups of mice.

Influence of Aging on Gabapentin Effects in Formalin-Induced Mechanical Allodynia

The effects of systemic pretreatment with gabapentin have been studied on tactile allodynia induced by formalin. A pretreatment with 10 mg/kg of gabapentin is ineffective in all age groups (**Figure 3A**. Two-way ANOVA F (9, 56) = 2,925; p = 0,0065 **). The higher dose (100 mg/kg) appears to be more effective in aged mice, though this effect does not reach statistical significance (**Figure 3B**. Two-way ANOVA F (9, 64) = 1,930; p = 0,0633).

DISCUSSION

Aging and dementia are often accompanied by comorbidities responsible for underdiagnosed chronic pain which is often associated to the development of BPSD, in particular agitation (Husebo et al., 2011). Memantine, through an uncompetitive/fast-off rate action mainly on extrasynaptic N-methyl-D-aspartate (NMDA) receptors (see (Scuteri et al., 2017c)), delays progression of disease but does not prevent agitation from occurring. Aged mice show behavioral disturbances comparable to those displayed by APP mice (Bedrosian et al., 2011; Bedrosian and Nelson, 2013). Therefore, the purpose of this preclinical study is to deepen the knowledge concerned with the effects of aging on a persistent pain condition alluding to a clinically relevant state and on the efficacy of gabapentin. Aged C57BL/6 mice show a different trend of the classical formalin-induced behavioral pattern with a shift in time and amplitude, thus supporting the occurrence of modifications in the mechanisms of central sensitization. These results are in agreement with the evidence that aged animals develop heightened hypersensitivity in several experimental pain models (Crisp et al., 2003; Bishay et al., 2013) and that formalin test behavioral pattern is influenced by age (Gagliese and Melzack, 1999). Also under different experimental conditions (10 µl of 4% formalin solution (Kolber et al., 2010)), C57BL/6 mice display enhanced nociceptive behavior and increased variability among different ages in the second phase and mechanical allodynia (Sadler et al., 2017). Aged C57BL/6J mice present a mitochondrial impairment (Kadoguchi et al., 2020) and a decrease in oxidative phosphorylation as well as alteration in apoptosis regulation (see (Azzu and Valencak, 2017)). Caspase activation and apoptosis is involved in the neuropathogenesis of Alzheimer's disease (Su et al., 1994; Su et al., 1997; Barnes et al., 1998; Mattson, 2002; Shao et al., 2014). Interestingly, aged C57BL/6 mice also display neurobehavioral changes (Dean et al., 1981; Traschutz et al., 2018). In the clinic, aging causes a decrease of pain tolerance threshold (Lautenbacher, 2012; Paladini et al., 2015) and an impairment of descending modulatory pathways (Washington et al., 2000; Riley et al., 2010; Paladini et al., 2015). Neuropathological alterations can impact nociception at a great extent and according to the type of dementia (Scherder et al., 2003). Central sensitization and plastic modifications occurring at level of the dorsal horn (Tjolsen et al., 1992), likely implicated in the formalin-induced second phase and late long-term mechanical allodynia (Fu et al., 2001; Guida et al., 2012), could undergo modifications with the increase of age of the animal. Formalin test, using mainly 5% formalin induces concentration-dependent hypersensitivity resembling neuropathic pain induced by spinal nerve injury enhancing α2δ–1 subunit protein levels in dorsal root ganglia (Salinas-Abarca et al., 2017). Moreover, formalin-induced allodynia is reversed by gabapentin as allodynia induced by spinal nerve ligation (Salinas-Abarca et al., 2017). In our experimental setting, mechanical allodynia induced by formalin test shows different features according to the age of the animal, with an apparent more difficult recovery from injury in 13 and 20 month-old mice; this is likely linked to the observed different basal threshold of these mice according to their age. In agreement with previous data (Fu et al., 2001; Guida et al., 2012), here we have reported that the hindpaw contralateral to formalin injection develops mechanical allodynia on the day 4th, supporting the deduction that central sensitization mechanisms are implicated. Quite importantly, a reportedly poorly active or inactive (Dixit et al., 1999) dose of gabapentin here shows stronger efficacy in formalin-induced nociceptive, but not in mechanical allodynia, response in aged mice. The latter pharmacological responses may be suggestive of the expression of a behavioral component depending on α2δ-1 subunit expression, conceivably subjected to quantitative variability according to age and phase of the formalin test. Additional studies are needed to strengthen our preliminary evidence and to dissect the molecular basis of the behavioral and pharmacological responses described here. It is conceivable that performing formalin test in transgenic 3xTg-AD mice, bearing an age-dependent cognitive and behavioral profile (Baeta-Corral et al., 2018), might help disclosing the effect of pain on behaviors recapitulating BPSD.

DATA AVAILABILITY STATEMENT

All datasets generated and analyzed for this study are included in the manuscript.

AUTHOR CONTRIBUTIONS

LB, GB, PT, LM, and MC conceived the study. DS participated in the conceptualization of the study, carried out the experiments, analyzed the results, and wrote the manuscript. LR participated to the analysis of literature and of data. All authors read and approved the final manuscript.

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REVIEW
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The Use of Risperidone in Behavioral and Psychological Symptoms of Dementia: A Review of Pharmacology, Clinical Evidence, Regulatory Approvals, and Off-Label Use

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Dementia represents a global health challenge due to the increase in elderly population worldwide. In addition to memory loss, dementia often results in severe behavioral and psychological changes where pharmacological treatments might be considered in addition to nonpharmacological strategies for optimal symptomatic control. Risperidone, the second oldest atypical antipsychotic, has been widely used off-label to treat behavioral and psychological symptoms of dementia (BPSD), including agitation, aggression, and psychosis. Several studies have indicated that risperidone offers a modest and statistically significant effectiveness in the clinical setting. However, in the past decade, safety concerns emerged due to increased risk for cerebrovascular adverse events and death following the use of risperidone in the elderly population. Clinical guidelines suggest that, in severe dementia where an older adult is threatening to harm himself or others, pharmacological treatments might be considered when nonpharmacological treatments fail. Risperidone was approved for BPSD in some countries (Australia, Canada, United Kingdom and New Zealand) but not in the United States. This article reviews risperidone's pharmacological activity, clinical effectiveness and safety, marketing approval, and off-label use in BPSD.

Keywords: behavioral and psychological symptoms of dementia, risperidone, Alzheimer's disease, review (article), dementia

INTRODUCTION

More than 40 million people live with dementia worldwide, and this number is projected to triple by 2050 (Prince et al., 2015). It occurs more commonly in persons 65 or older, and with the growing elderly population in developed countries, dementia represents a global health challenge (Plassman et al., 2007; Livingston et al., 2017). Dementia is characterized by progressive memory decline with different underlying causes, including Alzheimer's disease, vascular dementia, and Lewy bodies, among others. In addition to memory loss, behavioral symptoms common to dementia which are

thought to be targets for antipsychotic drugs include: declined ability to solve problems, difficulty in maintaining emotional control, agitation, aggression, delusion, apathy, impulsivity, depression, and hallucinations (Dementia Society of America, 2019). Behavioral and psychological symptoms of dementia (BPSD) add to the burden of the disease and further reduce the quality of life of the patients and their caregivers (Anderson et al., 2019).

Acetylcholinesterase inhibitors (galantamine, donepezil, rivastigmine) and memantine are the mainstay treatment for dementia-related cognitive symptoms. The first-line treatment of BPSD are nonpharmacological treatments including environmental (e.g., use of familiar objects) and social techniques (redirection and frequent re-orientation). However, medications like antidepressant and antipsychotics are sometimes considered as treatment options at later stages for optimal management of severe BPSD (Motsinger et al., 2003; Bessey and Walaszek, 2019; Ringman and Schneider, 2019). Among antipsychotics, atypical drugs (including clozapine, risperidone, olanzapine, aripiprazole, quetiapine, etc.) are favored over typical due to less extrapyramidal side effects (EPS). Although, clozapine is the first atypical antipsychotic to be approved for other indications; it did not gain widespread use over risperidone because of its increased risk of agranulocytosis (Liperoti et al., 2008). Moreover, among all the atypical antipsychotics, risperidone has the most clinical trial-related evidence to support its use in BPSD (Lee et al., 2006).

In this review, we will focus on the role of risperidone, one of the oldest and most widely used atypical antipsychotics in the management of BPSD. We will first review risperidone's pharmacological activity, secondly, we will explore the clinical evidence behind its use in BPSD and finally, we will examine its worldwide regulatory approval and off-label use in BPSD.

PHARMACOLOGY OF RISPERIDONE

Risperidone is a benzisoxazole derivative. It was the second atypical antipsychotic developed following clozapine. It quickly became a first-line treatment for schizophrenia because of its favorable side effect profile compared to clozapine (Chopko and Lindsley, 2018). Like other atypical agents, its antipsychotic activity is believed to be linked primarily to central antagonism of dopamine-2 (D2) and serotonin-2C (5HT2C) receptors (Love and Nelson, 2000). Compared to conventional antipsychotics like haloperidol, risperidone bocks 5-HT2 receptors with a higher affinity than D2 receptors. The blockade of 5-HT2A receptors is thought to confer increased dopaminergic transmission in the nigrostriatal pathway and hence results in reduced risk of EPS compared to conventional antipsychotics (Álamo and López-Muñoz, 2013). However, in clinical practice, it should be noted that risperidone can cause EPS in a dose-dependent manner, especially with doses above 6 mg/d (Motsinger et al., 2003; Calsolaro et al., 2019). While EPS is a grossly overused and poorly understood term, risperidone-related EPS such as akathisia and parkinsonism are extremely under-recognized in elderly patients with dementia (Thomson et al., 2017; Duma and Fung, 2019).

Moreover, risperidone blocks α1 and α2 adrenergic receptors as well as H1 histaminergic receptors, which contributes to other pharmacological properties (FDA, 2009). Antagonism of α2 adrenergic receptors is believed to contribute to antidepressant activity and blockade of H1 receptors leads to sedation. Antagonism of α1 adrenergic receptors accounts for orthostatic hypotension. Also, several lines of evidence suggest that antagonizing 5-HT2C receptors results in antidepressant and anxiolytic properties. Risperidone has little or no in vitro affinity on cholinergic muscarinic receptors, which is translated in clinical practice as minimal anticholinergic side effects (Jensen et al., 2010). This is of particular interest in the elderly population where anticholinergic burden (risk of fall, delirium, and confusion) is an important safety concern.

Risperidone has a fast onset of action due to its rapid gastrointestinal absorption and quickly reaches a steady-state plasma concentration due to its short half-life (2.8 h). This property favors its use for the management of severe acute psychosis (Claus et al., 2006; Álamo and López-Muñoz, 2013), with similar pharmacological properties and a significantly longer long half-life (24.8 h) is responsible for the extended duration of action, which allows for a once-daily administration (Mauri et al., 2014).

CLINICAL USE OF RISPERIDONE IN DEMENTIA-RELATED PSYCHOSIS, AGGRESSION, AND AGITATION

Table 1 presents a summary of findings from notable systematic reviews and meta-analyses of clinical trials that compared risperidone with other atypical antipsychotics or placebo. Clinical evidence from systematic literature reviews and meta-analyses suggests that risperidone as other atypical antipsychotics, provides a small but statistically significant benefit compared to placebo in treating psychosis, aggression, and agitation in individuals with dementia. However, like other antipsychotics, risperidone is accompanied by potentially serious adverse effects. These include, parkinsonism, falls, an increased risk of death, and cerebrovascular adverse events (CVAE [including stroke and transient ischemic attack]) (Maher et al., 2011; Tampi et al., 2016). An increase in the risk of CVAE and deaths with antipsychotics in the elderly population has been widely reported in the literature and resulted in a boxed warning by the US Food and Drug Administration (FDA) placed on risperidone's package as well as all other antipsychotics' package (Chatterjee et al., 2012). Some studies have argued that the risk of CVAE in patients with BPSD is overestimated and evidence came from patients with predisposing risks such as underlying vascular type of dementia, previous stroke, and insufficient management of hypertension (Herrmann and Lanctôt, 2005; Shin et al., 2013). However, according to a network meta-analysis (NMA) comparing different atypical antipsychotics (risperidone, olanzapine, aripiprazole, and quetiapine) for the

TABLE 1 | Findings from some notable systematic reviews and meta-analyses comparing risperidone with other atypical antipsychotics or placebo (Schneider et al., 2006; Schneider et al., 2005; Maher et al., 2011; Farlow and Shamliyan, 2017; Jin and Liu, 2019; Yunusa et al., 2019).

Study	Study Type	Study objective	Comparison[a]	Summary of Findings	
				Efficacy	Safety[b]
Schneider et al., 2006	SR/MA	Assess the evidence for efficacy and adverse events of atypical antipsychotics for people with dementia.	Risperidone vs Placebo	Behave-AD; risperidone significantly improved Behave-AD compared with placebo (WMD, −1.48; 95% CI, −2.35, −0.61; 4 studies). CMAI; risperidone significantly improved CMAI compared with placebo (WMD, −3.00; 95% CI, −4.22, −1.78; 3 studies) BPRS; risperidone did not significantly improve BPRS compared with placebo (WMD, 0.60; 95% CI, −1.82, 3.02; 1 study). NPI; risperidone did not significantly improve NPI compared with placebo (WMD, 2.60; 95% CI, −2.70, 7.90; 1 study). CGI-S; risperidone did not significantly improve CGI-S compared with placebo (WMD, −0.09; 95% CI, −0.21, 0.02; 3 studies).	CVAE; There was a significant increase in the risk of CVAE for risperidone compared with placebo (OR, 3.43; 95% CI, 1.60, 7.32; 4 studies). Death; There was no significant increase in the risk of death for risperidone compared with placebo (OR, NR; 95% CI, NR; 5 studies).
Schneider et al., 2005	SR/MA	Assess the evidence for increased mortality from atypical antipsychotics for people with dementia.	Risperidone vs Placebo	N/A	CVAE; N/A Death; There was no significant increase in the risk of death for risperidone compared with placebo (OR, 1.30; 95% CI, 0.76, 2.23; 5 studies).
Maher et al., 2011	SR/MA	Assess the efficacy and safety of atypical antipsychotic medications for use in conditions lacking approval for labeling and marketing by the US Food and Drug Administration.	Risperidone vs Placebo	Global score[c]; risperidone did not significantly improve global scores compared with placebo (SMD, 0.19; 95% CI, 0, 0.38; 6 studies).	CVAE; There was a significant increase in the risk of CVAE for risperidone compared with placebo (OR, 3.12; 95% CI, 1.32, 8.21; 4 studies). Death; NR
Farlow and Shamliyan, 2017	SR/MA	Assess the efficacy and safety of atypical antipsychotics for people with dementia.	Risperidone vs Placebo	Behave-AD; risperidone did not significantly improve Behave-AD compared with placebo (SMD, −0.20; 95% CI, −0.40, 0.00; 4 studies). BPRS; risperidone did not significantly improve BPRS compared with placebo (SMD, −0.10; 95% CI, −0.60, 0.30; 2 studies). NPI; risperidone did not significantly improve NPI compared with placebo (SMD, −0.10; 95% CI, −0.60, 0.40; 2 studies). CGI; risperidone significantly improved CGI-T compared with placebo (SMD, −0.40; 95% CI, −0.70, −0.10; 4 studies).	CVAE; There was a significant increase in the risk of CVAE for risperidone compared with placebo (OR, 4.53; 95% CI, 1.75, 11.72; 4 studies). Death; There was no significant increase in the risk of death for risperidone compared with placebo (RR, 3.70; 95% CI, 0.20, 88.5; 1 study).
Yunusa et al., 2019	SR/NMA	Assess the relative benefits and safety of atypical antipsychotics in the treatment of BPSD shown in randomized clinical trials using network meta-analysis.	Risperidone vs Placebo vs Aripiprazole vs Olanzapine	CMAI; There was no statistically significant difference between risperidone and other atypical antipsychotics based on CMAI. Risperidone significantly improved CMAI compared with placebo (SMD, −0.30; 95% CI, −0.55, −0.05)	CVAE; There was no statistically significant difference between risperidone and other atypical antipsychotics based on CVAE.There was a significant increase in the risk of CVAE for risperidone compared with placebo (OR, 3.85; 95% CI, 1.55, 9.55). Death; There was no statistically significant

(Continued)

TABLE 1 | Continued

Study	Study Type	Study objective	Comparison[a]	Summary of Findings	
				Efficacy	Safety[b]
			vs Quetiapine	BPRS; There was no statistically significant difference between risperidone and other atypical antipsychotics based on BPRS. Risperidone did not significantly improved BPRS compared with placebo (SMD, –0.10; 95% CI, –0.29, 0.09). NPI; There was no statistically significant difference between risperidone and other atypical antipsychotics based on NPI. Risperidone did not significantly improved NPI compared with placebo (SMD, –0.01; 95% CI, –0.19, 0.18).	difference between risperidone and other atypical antipsychotics based on mortality. No significant increase in the risk of death for risperidone compared with placebo (RR, 1.32; 95% CI, 0.77, 2.27).
Jin and Liu, 2019	SR/ NMA	Assess the comparative efficacy and safety of pharmacological and nonpharmacological therapies for the BPSD.	Risperidone vs Placebo vs Aripiprazole vs Olanzapine vs Quetiapine vs Haloperidol vs Other antipsychotic agents	CMAI; There was no statistically significant difference between risperidone and other atypical antipsychotics based on CMAI. Risperidone significantly improved CMAI compared with placebo (MD, –2.58; 95% CrI, –5.20, –0.60) NPI; There was no statistically significant difference between risperidone and other atypical antipsychotics based on NPI. Risperidone did not significantly improved NPI compared with placebo (MD, –3.20; 95% CrI, –6.08, –0.31).	CVAE; There was no statistically significant difference between risperidone and other atypical antipsychotics based on CVAE. There was a significant increase in the risk of CVAE for risperidone compared with placebo (OR, 3.94; 95% CrI, 1.85, 10.73). Death; NR

BPDS, behavioral and psychological symptoms of dementia; BPRS, Brief Psychiatry Rating Scale; CGI, Clinical Global Impression (total score); CGI-S, Clinical Global Impression – Severity scale; CMAI, Cohen-Mansfield Agitation Inventory; CVAE, cerebrovascular adverse events; CI, confidence interval; CrI, credible interval; MD, mean difference; N/A, not applicable or not available; NMA, network meta-analysis; NR, not reported; NPI, neuropsychiatry inventory; OR, odds ratio; RR, relative risk; SR/MA, systematic review and meta-analysis (pairwise); SR/ NMA, systematic review and network meta-analysis; SMD, standardized mean difference; WMD, weighted mean difference.

[a]*Refers to only comparisons involving risperidone.*

[b]*Safety outcomes limited to death and cerebrovascular adverse events for which there are regulatory warnings across the world.*

[c]*Refers to a total global score that included cumulative psychiatric symptoms of delusions, hallucinations, suspiciousness, dysphoria, anxiety, motor agitation, aggression, hostility, euphoria, disinhibition, irritability, apathy, and other behavioral disturbances.*

treatment of BPSD, no statistically significant difference was seen between antipsychotics in terms of effectiveness, death, or CVAE (Yunusa et al., 2019). This NMA found that risperidone only provided a superior improvement over placebo on Cohen-Mansfield Agitation Inventory (CMAI) scale while aripiprazole improved Neuropsychiatric Inventory and Brief Psychiatric Rating Scale in addition to CMAI (Overall and Gorham, 1962; Cummings et al., 1994; Cohen-Mansfield, 1996; Wood et al., 2000). In this NMA, simultaneous ranking of effectiveness and safety suggests that aripiprazole could be a safer treatment option in patients with a history of stroke or other risk factors of CVAE.

In another study that compared all available interventions for BPSD, it was found that pharmacological treatment with both risperidone and aripiprazole are superior to nonpharmacological treatment showing significant efficacy on CMAI (Jin and Liu, 2019). Some evidence suggests that safety concerns in the elderly population may be less prevalent with lower doses (0.25-2mg/ day) of risperidone over a short-term period of 6–12 weeks (Oshima, 2008; Ballard et al., 2009; Torres-Lista et al., 2019). Following a review of clinical studies, on January 1, 2020, the Australian Pharmaceutical Benefits Scheme recommended that the use of risperidone should be limited to 12 weeks (National Prescribing Services, 2020).

REGULATORY APPROVALS AND OFF-LABEL USE

The rate of off-label use of antipsychotics worldwide is still high (Kirkham et al., 2017). Risperidone is reportedly the antipsychotic the most commonly prescribed off-label (Leslie et al., 2009; Leslie and Rosenheck, 2012). This can be partly explained by the fact that the US FDA has not yet approved any medication for treating BPSD (Maher et al., 2011). Despite clinical evidence supporting the efficacy of antipsychotics in the management of BPSD, so far, safety concerns appear to prevent FDA approval. Warnings started in 2002 with Health Canada advising physician to assess the risks and benefit of antipsychotic drugs in elderly patients and to immediately report signs and symptoms of CVAE (Health Canada Therapeutic, 2002). The FDA followed with warnings of increased CVAE for

risperidone in April 2003 and for aripiprazole in February 2005. In addition, in April 2005, the FDA issued a health advisory warning of an increased risk for death with atypical antipsychotics in persons with dementia (Schneider et al., 2005; US Food Drug and Administration, 2005).

Despite safety concerns, risperidone remains a popular therapeutic choice for patients with Alzheimer's disease and behavioral symptoms, especially those with more severe agitation and aggressive behaviors and has been approved for this indication in many countries (McNeal et al., 2008). Indeed, in 2008, the European Union approved risperidone for the short-term for up to 6 weeks management of persisting and severe aggression in individuals with Alzheimer's disease who have failed nonpharmacological treatment. Health Canada and The Australian's Therapeutic Goods Administration (2020) who had previously approved risperidone for behavioral disturbances in dementia reviewed this indication in 2015 following the safety issues and restricted risperidone's indication for severe dementia of the Alzheimer type. It should be noted that risperidone is the only antipsychotic approved for the treatment of severe BPSD despite positive clinical evidence for other antipsychotics such as aripiprazole and quetiapine. This may be partly because risperidone is the oldest atypical antipsychotic on the market after clozapine and has well established use.

While risperidone is currently the only atypical antipsychotic approved in some countries for the treatment of BPSD, it is worthy to note that, another drug, pimavanserin, a selective serotonin-2A (5HT2A) receptor inverse agonist and already approved by the US FDA for Parkinson's disease-related psychosis (PDP) is currently under development for dementia-related psychosis after a favorable phase II clinical trial result (Hacksell et al., 2014; Ballard et al., 2018). It should be noted that the effectiveness of pimavanserin in PDP was demonstrated at 4–6 weeks; however, there is no robust data on the onset of efficacy of the off-label use of risperidone in PDP (Cummings et al., 2014). An international Delphi consensus formed to prioritize existing and emerging treatments for BPSD placed a priority for risperidone for existing treatments and gave the greatest priority for future treatments to pimavanserin (Kales et al., 2019). A recent topline result from the pivotal phase III trial (the HARMONY trial, ClinicalTrials.gov number: NCT03325556) suggested that, in patients with dementia-related psychosis, pimavanserin reduced the risk of relapse of psychosis by 2.8 fold in comparison to placebo (Acadia Pharmaceuticals, n.d.). It remains to be seen whether this positive finding will pave a way for pimavanserin to secure a regulatory approval and subsequently become more favorable than risperidone.

CONCLUSION

In patients with BPSD, treatment choices should be based on a positive risk-benefit ratio. Given the current evidence on the clinical effectiveness and safety of risperidone in the management of BPSD, its use should be restricted to patients with severe symptoms (aggression, agitation, or psychosis) who fail to respond adequately to nonpharmacological treatments. In this case, a low dose (0.25-2 mg daily) and short treatment duration (6-12 weeks) must be favored. Moreover, risperidone must be avoided in patients with a history of CVAE or with risk factors for stroke. Clinicians should also monitor patients for parkinsonism and risk of fall, using a fall rating scale. Risperidone should be stopped after 12 weeks if the risk of adverse events increases, or no benefit is observed.

Consistent with the best practice, before clinicians consider prescribing risperidone to patients with BPSD, the implementation of DICE (describe, investigate, create, and evaluate) approach should come first (Kales et al., 2015). In this approach, clinicians, and caregivers can better identify patients who might benefit from a pharmacological treatment. Since the US FDA has not yet approved any medication for BPSD and risperidone is the only approved drug for BPSD in some regions/countries (Europe, Australia, Canada, and the United Kingdom), research on other more effective and safer alternatives for BPSD is highly needed.

AUTHOR CONTRIBUTIONS

IY and MH determined the outline, reviewed the literature, wrote, and approved the manuscript.

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Serum Concentrations of Cholinesterase Inhibitors in Patients With Alzheimer's Dementia Are Frequently Below the Recommended Levels

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Background: Acetylcholinesterase inhibitors (AChE-I) are recommended for the treatment of cognitive symptoms but also of behavioral and psychological symptoms in dementia. They are widely used not only in Alzheimer's disease, but also in other forms of dementia. Efficacy of treatment might depend on serum concentration of the respective AChE-I.

Objective: In patients with mild to moderate Alzheimer's dementia, we measured serum concentrations of hepatically metabolized donepezil and renally excreted rivastigmine and investigated possible modifiers. Additionally, we looked at correlations between serum concentrations and efficacy for both drugs.

Methods: Serum concentrations of donepezil and rivastigmine were measured by liquid chromatography – tandem mass spectrometry (LC-MS/MS). Real-time quantitative polymerase chain reaction (PCR). Allele specific PCR were performed to determine CYP2D6 genotype and gene dose. Clinical efficacy was assessed by changes of the subtest wordlist delayed recall of the Consortium to Establish a Registry for Alzheimer's Disease-Neuropsychological Assessment Battery (CERAD-NAB).

Results: Sixty-seven patients treated with a stable dosage of donepezil 10 mg (n=41) or rivastigmine 9.5 mg (n=26) were included. Mean serum concentration of donepezil and rivastigmine were 41.2 and 6.5 ng/ml, respectively. Serum concentrations were below the recommended range in 73% of the subjects in the donepezil group and in 65% of the participants in the rivastigmine group. When applying a dose-related reference, ranges 63% of patients in the donepezil group and 32% in the rivastigmine group had concentrations below the expected range. Gene dose, sex, and duration of treatment significantly predicted donepezil serum concentration (p=0.046, p=0.001, p=0.030 respectively). Only for rivastigmine did the serum concentration significantly contribute

to the regression model predicting changes on the subtest word list delayed recall (β=0.472; p=0.019).

Conclusions: Serum concentrations of about two thirds of the patients were below the recommended range. When not looking at absolute values but at the dose-related reference ranges, these numbers improved but still 32%, respectively 63% of patients had low serum concentrations. High serum concentrations of rivastigmine predicted clinical response to cognition. Therapeutic drug monitoring might help to identify the cause of poor clinical response to cognition and behavioral and psychological symptoms in patients with AChE-I treatment.

Keywords: Alzheimer's disease, Alzheimer's dementia, cholinesterase inhibitors, serum concentration, therapeutic drug monitoring, treatment efficacy, gene dose, CYP2D6 polymorphism

INTRODUCTION

Over 75% of dementia patients are affected by behavioral and psychological symptoms in dementia (BPSD) over the course of the disease. BPSD constitute a significant burden to caregivers and nursing staff (Lyketsos et al., 2002; Steinberg et al., 2008; Torrisi et al., 2017; Hessler et al., 2018). Symptoms like depression and anxiety are even associated with an increased suicide risk (Seyfried et al., 2011). For mild to moderate dementia due to Alzheimer's disease (ADD), the most common cause of dementia (van der Flier and Scheltens, 2005), symptomatic treatment with acetylcholinesterase inhibitors (AChE-I) such as donepezil, galantamine, or rivastigmine is recommended (Doody et al., 2001; Dimentia, 2007; Gauthier et al., 2012; Deuschl, 2016; Dyer et al., 2016). Rivastigmine additionally pseudo-irreversibly inhibits butyrylcholinesterase (BChE) (Weinstock, 1999), an enzyme that, like AChE, catalyzes the hydrolysis of acetylcholine. Besides the effect of AChE-I on cognitive symptoms, they can also improve BPSD not only in ADD (Cummings et al., 1994; Birks, 2006; Tan et al., 2014; Matsuzono et al., 2015; Kratz, 2017), but also in dementia in idiopatic Parkinson's disease (PDD) and dementia with Lewy bodies (DLB) (Rolinski et al., 2012; Mori et al., 2016). However, no improvement of BPSD has been detected under treatment with rivastigmine in one study (Birks et al., 2015). There is no evidence for the efficacy of AChE-I in frontotemporal lobar degeneration, multiple sclerosis, or supranuclear palsy (Li et al., 2015). As the efficacy of AChE-I probably depends on drug serum or plasma concentration (Rogers et al., 1998; Chou et al., 2012; Yang et al., 2013; Hefner et al., 2015; Manabe et al., 2016; Chen et al., 2017; Miranda et al., 2017), inconclusive results might be due to insufficient drug blood concentrations in some subjects.

Factors affecting plasma concentrations are sex (Noetzli et al., 2014), age (Coin et al., 2016; Mori et al., 2016), weight (FDA, 2012; FDA, 2015), dosage (Darreh-Shori et al., 2006; Mori et al., 2016), and duration of treatment (Miranda et al., 2017). The metabolism of the respective AChE-I, particularly for donepezil, might also have an impact on serum concentration. While rivastigmine is mainly hydrolyzed and renally excreted (FDA, 2012), donepezil is hepatically metabolized mainly by the cytochrome P450 isoenzyme CYP2D6 and, to a lesser extent, by CYP3A4 and undergoes glucuronidation (FDA, 2015). Treatment with CYP2D6 inhibitors or CYP2D6 inducers (FDA, 2015) as well as CYP2D6 polymorphisms can result in altered enzyme activity and thus altered metabolism rates (Meyer and Zanger, 1997; Sachse et al., 1997; Raimundo et al., 2004; Hicks et al., 2013). Depending on the genetically determined enzyme activity, patients can be classified by their phenotype as poor metabolizer (PM) with no enzyme activity, intermediate metabolizer (IM) with reduced enzyme activity, extensive metabolizer (EM) with normal enzyme activity, and ultra-rapid metabolizer (UM) with increased enzyme activity. Instead of correlating the phenotype with the genotype, Steimer et al. recommend to correlate the phenotype with a semiquantitative gene dose that depends on the number and the activity of detected CYP2D6 alleles (Steimer et al., 2004).

Which AChE-I is prescribed at what dose depends on local drug approval and patients' preferences, e. g. if an oral application or a transdermal patch is preferred, but mainly it is in the physician's responsibility to choose the best drug at the right dosage for the individual patient. To support this decision, guidelines provide information about recommended therapeutic reference ranges for blood concentrations (Hiemke et al., 2018).

In this study, we measured serum concentrations of the hepatically metabolized donepezil and the renally metabolized rivastigmine, looked at potential factors influencing serum concentrations such as CYP2D6 polymorphisms and investigated correlations between serum concentrations and clinical efficacy for both drugs.

MATERIALS AND METHODS

Ethics Statement

The study protocol was approved by the ethics committee of the Faculty of Medicine of the Technical University of Munich, Munich (reference number 673/02). All patients provided written informed consent prior to any study specific procedures. All clinical investigations have been conducted in accordance with the principles of the Declaration of Helsinki, sixth revision.

Patient Recruitment and Study Design

The study was conducted at the outpatient unit of the Centre for Cognitive Disorders at the Department of Psychiatry, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany and at the Memory Clinic at the Institute for Stroke and Dementia Research, Klinikum der Universitaet Muenchen, Munich, Germany between October 2012 and December 2014. Patients had initially been referred for the diagnostic evaluation of cognitive impairments by self-referral, general practitioners, neurologists, psychiatrists, or other institutions, and had undergone a standardized diagnostic procedure that has been described previously (Ortner et al., 2015). It included an interview with the patient and an informant, obtaining demographic data, medical history, concomitant medication, physical, neurological, and psychiatric examinations, a neuropsychological evaluation including the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Assessment Battery (CERAD-NAB) (Morris et al., 1989), as well as a routine laboratory screening test.

The treating physician started patients diagnosed with mild to moderate Alzheimer's dementia (McKhann et al., 2011) on treatment with an AChE-I by his own choice in accordance with the German treatment guidelines for Alzheimer's dementia (Deuschl, 2016). Mild dementia was defined by a MMSE of 26–20 points, moderate dementia by 19–10 points. German treatment guidelines for Alzheimer's disease recommend AChE-I such as donepezil, rivastigmine, or galantamine for symptomatic treatment of mild and moderate Alzheimer's dementia (Deuschl, 2016). Memantine is recommended for moderate and severe Alzheimer's dementia. Each doctor is independent in his or her choice which of the approved drugs is prescribed. At a routine follow-up appointment after 3–6 months, patients were informed about the study and asked to provide written informed consent if they met the inclusion criteria.

Patients needed to be able to provide written informed consent, actually have started treatment and be on stable medication for at least five half-times with either donepezil capsules 10 mg or rivastigmine transdermal patch 9.5 mg per day. They should be compliant in taking their medication as ascertained by caregiver information. The only study specific procedure consisted in a venous blood draw in order to assess serum concentrations of donepezil and rivastigmine and the genotype and gene dose of CYP2D6 alleles for subjects treated with donepezil. Routine follow-up procedures included a patient and caregiver interview with an assessment of the current medication, the start of AChE-I treatment, the time point when the dose of AChE-I was increased, side effects of AChE-I treatment, a neuropsychological assessment (CERAD-NAB, MMSE), and a psychiatric and neurological examination.

Patients were excluded from study participation if they were incapable to provide written informed consent, were not started or not on a stable dosage of donepezil or rivastigmine, or if dementia was due to any other disease than Alzheimer's disease, for instance Parkinson's disease. Further exclusion criteria were other possible causes of cognitive impairment such as sedating psychotropic medication (e.g. tricyclic antidepressants, low-potent antipsychotics), substance misuse, clinical signs of major depression, or major abnormalities in the routine blood testing at the initial presentation of the patient.

Blood Sample Collection and Analyses

To measure steady-state trough drug levels patients needed to be on the respective AChE-I for at least five half-times and blood was drawn as close as possible to the time the next dose would have been due. If the blood sample could not be drawn prior to the next scheduled time point for dosing, medication was held until after the blood draw.

Serum concentrations of donepezil and rivastigmine were measured by liquid chromatography – tandem mass spectrometry (LC-MS/MS). Standard procedures were used for genotyping. Depending on allele status subjects were classified into PM, IM, EM, and UM (**Supplementary Table 1**). Additionally, as proposed by Steimer et al. (2004), to each allele an individual gene dose was assigned to calculate a semiquantitative gene dose (**Supplementary Tables 1–3**). Details of blood sample collection, LC-MS/MS method and genotyping and gene dose assignment are provided in **Supplementary Materials**.

In addition to the absolute serum concentrations, we also looked at the dose-related reference ranges for both treatment groups as defined by the Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology (Hiemke et al., 2018). The dose-related reference range gives information about serum concentrations that can be expected for 68% of patients aged 18–65 years with a body weight of 70 kg at a given dose.

Cognitive Assessments and Evaluation of Treatment Efficacy

Efficacy of the treatment with donepezil or rivastigmine was evaluated by changes of the CERAD-NAB sub-test wordlist delayed recall before initiation of an AChE-I and under stable treatment. The absolute difference in points scored in the initial and follow-up assessment was calculated. Negative values indicated worsening, positive values indicated improvement.

Statistical Analyses

Subjects under treatment with donepezil 10 mg or rivastigmine 9.5 mg, respectively, were characterized using descriptive statistics. All statistics were calculated using SPSS Statistics 23 (SPSS Inc., Chicago, Il, USA). Group comparisons for normally distributed variables were calculated using t-test, for not normally distributed variables, Mann-Whitney U test was applied. A significance threshold of $p < 0.05$ (two sided) was applied.

In the donepezil group only, we assessed the correlation between serum concentration of donepezil and gene dose of CYP2D6 using multivariate linear regression analysis. The dependent variable was donepezil serum concentration; independent variables were chosen based on their known influence on donepezil concentration and consisted of gene dose, concomitant medication with CYP2D6 inhibitors, sex, age, weight, duration of treatment with donepezil, and time

since last dosing. As a confirmative analysis, the same model was calculated using metabolism type instead of gene dose.

To investigate correlations between serum concentration and efficacy of the respective treatment, linear regression analyses with the difference between baseline to follow-up in the sub-test word list delayed recall as the dependent variable were calculated. Independent variables were serum concentration, results of delayed recall at the initial assessment, time between initial assessment and follow-up, sex, and age. To further investigate correlations between serum concentration and clinical efficacy, we repeated the regression analyses using low/high serum concentration of the respective AChE-I as a factor. The "low concentration" group consisted of the third of subjects with the lowest serum concentrations and the "high concentration" group of the third of subjects with the highest serum concentrations for the respective AChE-I.

We chose the sub-test word list delayed recall as endpoint for treatment efficiency. The rationale behind that decision was that (i) most variability could be expected in this test and it discriminates best between healthy controls and even mildly demented subjects (Welsh et al., 1991) and (ii) by focusing on a single endpoint, we wanted to avoid multiple comparisons. All statistical models were tested for interaction. There was no imputation of missing data.

RESULTS

Characteristics of Participants

Characteristics of participants are shown in **Table 1**. Forty-one subjects were included in the donepezil group and 26 in the rivastigmine group. There were no statistically significant differences between the groups regarding sex, age, time between initial and follow-up assessment, duration of treatment with an AChE-I, weight, BMI (**Table 1**), or results of the neuropsychological assessments at baseline and follow-up (**Supplementary Table 4**). The progress of participants is shown in **Supplementary Figure 1**.

TABLE 1 | Characteristics of participants: where applicable: mean ± standard deviation (minimum - maximum).

	Donepezil	Rivastigmine	p-value
Numbers	41	26	–
Sex: male:female	21: 20 (51%: 49%)	16:10 (61.5%: 38.5%)	0.458[a]
Age [years]	72.7 ± 9.51 (53-88)	72.1 ± 7.0 (53-86)	0.772[b]
Time baseline to follow up [days]	217.7 ± 64.8 (96-441)	228.7 ± 80.2 (122-442)	0.990[c]
Duration from start of AChE-I treatment to follow up [months]	5.7 ± 2.4 (3-13)	5.7 ± 2.1 (2-12)	0.825[c]
Number of participants taking CYP2D6 inhibitors	6 (5 x Citalopram; 1 x Carvedilol)	n.a.	–
Number of participants taking CYP2D6 inducers	none	n.a.	–
Weight [kg] n=37 (Donepezil) n=24 (Rivastigmine)	69.5 ± 8.5 (50-83)	68.2 ± 13.8 (47-90)	0.671[b]
BMI [kg/m²] n=37 (Donepezil) n=24 (Rivastigmine)	23.8 ± 3.0 (17.2-34.5)	23.5 ± 3.6 (16.5-30.9)	0.743[b]

AChE-I, acetylcholinesterase inhibitor; n.a., not applicable; kg, participants' weight in kilogram; BMI, body mass index; p-values calculated from [a]Chi-squared test, [b]t-test or [c]Mann-Whitney-U-test.

TABLE 2 | Serum concentrations of AChE-I: Daily drug dose, serum concentration, and variance of blood serum concentration for donepezil and rivastigmine group, respectively.

Variables	Donepezil 10 mg/d	Rivastigmine 9.5 mg/d	p-value
Serum concentration [ng/ml]	41.22 ± 15.56 (18.8-87.6)	6.53 ± 5.14 (0.47-17.50)	
Variance of serum concentration	242.0	26.5	<0.001[a]
Variation coefficient of serum concentration measurement	5.11 ± 2.58 (0.57-10.32)	5.57 ± 3.61 (1.00-17.40)	0.990[b]
Time since last dosing [h]	22.0 ± 2.2 (14-26)	23.6 ± 3.0 (15-28)	0.002[b]

h, hours; ng, nanogram; ml, milliliter; mg, milligram; d, day; where applicable: mean ± standard deviation (minimum – maximum). [a]calculated from F-test. [b]calculated from Mann-Whitney U test.

Drug Serum Concentrations and Gene Dose

Serum Concentrations of Donepezil and Rivastigmine

The next AChE-I administration was held until after the blood draw. On average, blood was drawn 1.32 ± 2.4 (-10 to +4) hours before the next scheduled drug administration. Drug serum concentrations are shown in **Table 2**. The variance of serum concentration of donepezil differed significantly from that of rivastigmine ($p < 0.001$) while variation coefficients did not significantly differ (p=0.775; **Table 2**).

Female subjects had significantly higher donepezil serum concentrations (p=0.004) and lower absolute body weight ($p < 0.001$), while BMI did not statistical significantly differ between sexes (**Table 3**). In the rivastigmine group, serum concentrations did not differ between sexes (**Supplementary Table 5**). Female subjects had a significantly lower body weight (p=0.004) and borderline significantly lower BMI (p=0.050).

Characteristics and serum concentrations for the respective low and high concentration subgroup for donepezil and rivastigmine are shown in **Supplementary Table 6**. Serum concentrations differed significantly ($p < 0.001$) between the respective low concentration and high concentration subgroup. In the donepezil group only, there also was a statistically significant difference in the distribution of sex (p=0.008) with more males in the low concentration subgroup and more females in the high concentration subgroup.

Dose-Related Reference Range

According to the Consensus guidelines, the dose-related reference range for donepezil 10 mg daily is 44.20–63.80 ng/ml and for rivastigmine patch 9.5 mg it is 3.42–9.69 ng/ml (Hiemke et al., 2018). In the donepezil group, 63% (n=26) of participants

TABLE 3 | Sex differences *donepezil*: Serum concentration and BMI of male and female participants, respectively, in the *donepezil* group.

Variables	male (n=21)	female (n=20)	p-value
Serum concentration donepezil [ng/ml]	34.75 ± 11.17 (18.75-56.65)	48.02 ± 16.83 (23.40-87.55)	0.004[b]
Body weight [kg]	74.4± 5.9 (60-83)	64.3 ± 7.8 (50-83)	<0.001[a]
BMI [kg/m²]	23.8 ± 2.4 (17.2-26.5)	23.8 ± 3.7 (18.6-34.5)	0.663[b]

ng, nanogram; ml, milliliter; kg, participants' weight in kilogram; BMI, body mass index; m^2, square of body hight in meters. Where applicable: mean ± standard deviation (minimum - maximum). p-value calculated from [a]t-test for normally distributed data and [b]Mann-Whitney U test for not normally distributed data.

had serum concentrations below that range, 32% (n=13) were within the range, and 5% (n=2) were above the range. In the rivastigmine group, 23% (n=6) were below the range, 54% (n=14) within, and 23% (n=6) above.

Genotype and Gene Dose

Supplementary Table 7 shows tested alleles, the respective gene doses, and allele frequencies. For one subject, the analysis could not be completed. Gene dose distribution, type of metabolizer, and respective donepezil serum concentrations are shown in Supplementary

Table 1. Serum concentration in relation to gene dose and type of metabolizer is displayed in **Figure 1**.

Correlation Between Donepezil Serum Concentration and CYP2D6 Gene Dose

Gene dose (β=-0.375; p=0.046), sex (β=-0.742; p=0.001), and duration of donepezil treatment (β=0.341; p=0.030) were significant predictors of donepezil serum concentration and the applied regression model explained 35.1% of the variability of drug serum concentration (p=0.005) (**Table 4**). Sex explained most of the variability and differed significantly between the low and high concentration group (p=0.008). Serum concentrations in relation to sex and the therapeutic range are presented in **Figure 2**.

We found no indication for significant interactions, and the quality of the model did not improve after forcing interaction terms into the model. A table with the univariate regression analyses is shown in **Supplementary Table 8**.

To further explore variability of drug serum concentration, gene dose was replaced by metabolizer status in the multivariate regression model. This model yielded similar results with type of metabolizer and sex as significant predictors for donepezil concentration (**Supplementary Table 9**). The model was statistically significant (p=0.005) and explained 35.2% of the variability of serum drug concentration.

To rule out spurious correlation caused by differences in body weight between sexes, an additional linear regression analysis with BMI instead of body weight was calculated. The model was significant (p=0.005) and explained 34.9% of variability of serum drug concentration, with a similar pattern compared with the previous analysis. The effect of the gene dose just failed to reach significance (β=-0.354; p=0.061). Neither body weight nor BMI contributed significantly to the respective model (β=0.171 p=0.343 and β=0.127 p=0.372, respectively; **Table 4** and **Supplementary Table 10**).

Explorative Analyses of Influence Factors on Rivastigmine Drug Serum Concentration

As plausibility check, a regression analysis to explore possible predictors on serum concentration in the rivastigmine group was

TABLE 4 | Prediction of serum concentration of *donepezil: Multivariate* regression model; n = 37.

	Beta	p-value
Gene dose	-0.375	0.046
CYP2D6-Inhibitors	0.229	0.126
Age	0.195	0.186
Sex	-0.742	0.001
Duration of AChE-I treatment	0.341	0.030
Time since last dosing	-0.079	0.650
Body weight	0.171	0.343

AChE-I, acetylcholinesterase inhibitor.
corr. R^2= 0.351, p = 0.005.

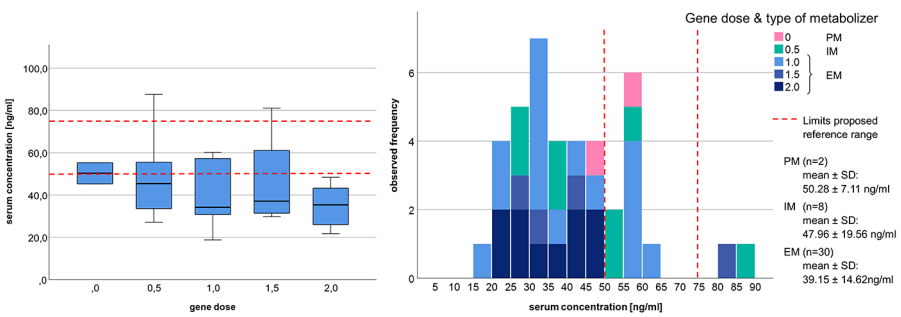

FIGURE 1 | Distribution of donepezil serum concentration in regards to gene dose and the proposed therapeutic reference range (Hiemke et al., 2018). PM, poor metabolizer; IM, intermediate metabolizer; EM, extensive metabolizer; n, number of subjects; SD, standard deviation.

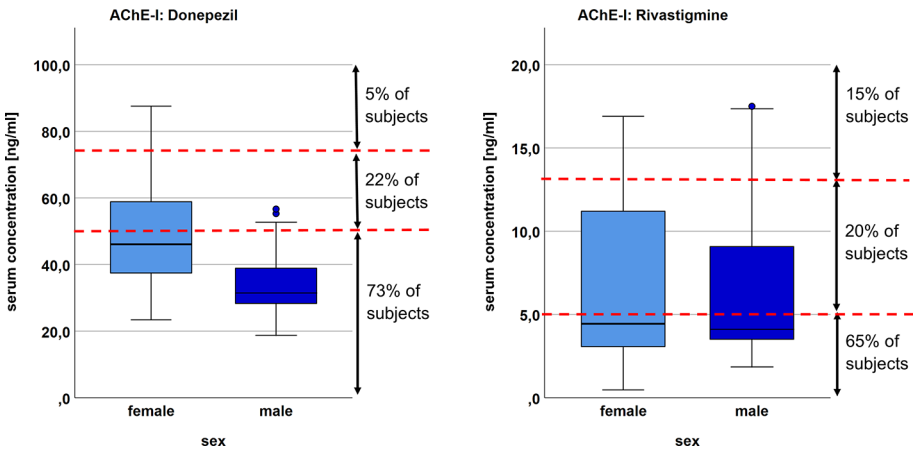

FIGURE 2 | Distribution of serum concentration for female and male subjects in the donepezil and rivastigmine group, respectively. Red dotted line marks the limits of the proposed therapeutic reference range (donepezil 50–75 ng/ml; rivastigmine 5-13 ng/ml (Hiemke et al., 2018).

conducted including concomitant medication with CYP2D6 inhibitors, age, sex, duration of treatment with rivastigmine, time since last dosing, and body weight as independent variables. Neither the regression model (p=0,718; R^2=-0,113) nor any of the variables were statistically significant (**Supplementary Table 11**). The models remained not significant after using BMI instead of body weight as independent variable (**Supplementary Table 12**).

Correlations Between Changes in the Neuropsychological Test Results and Serum Concentrations of Donepezil and Rivastigmine

Changes in Neuropsychological Assessments Between Initial and Follow Up Assessment

There were no statistically significant differences between the donepezil and rivastigmine group regarding efficacy of AChE-I treatment based on the results of the CERAD-NAB subtest word list delayed recall (**Supplementary Table 4**).

Correlation Between Cognitive Changes and Drug Serum Concentration

Results of multivariate regression analyses for changes in the CERAD-NAB word list delayed recall subtest as dependent variable are shown in **Supplementary Table 13** for the donepezil and rivastigmine group.

The linear regression models to predict the word list delayed recall subtest were significant for both treatment groups. In both groups, the baseline results significantly predicted results at follow-up. Only in the rivastigmine group did drug serum concentration significantly contribute to the model (β = 0.472; p = 0.019) (**Supplementary Table 13**). When using "low/high serum concentration" as a factor, the goodness of fit for the model was similar for rivastigmine but no longer statistically significant (adjusted R^2=0.294, p=0.098; **Supplementary Table 14**). For donepezil, the model got worse (adjusted R^2=0.096, p=0.208) when using low/high serum concentration as a factor (**Supplementary Table 14**).

DISCUSSION

We investigated the correlation between donepezil serum concentration and the gene dose as a marker for CYP2D6 metabolism rate, and compared associations of serum concentrations and clinical efficacy of the hepatically metabolized donepezil and the renally excreted rivastigmine. Serum concentrations were below the recommended range in 73% of the subjects in the donepezil group and in 65% of the participants in the rivastigmine group. The gene dose significantly predicted donepezil serum concentration. Multiple linear regression models for changes in the subtest word list delayed recall were significant for both donepezil and rivastigmine, however, only serum concentration of rivastigmine significantly predicted changes in the test results. When using high or low rivastigmine serum concentration as a factor, the goodness of fit for the model with rivastigmine was similar, but the model was no longer significant.

Drug Serum Concentrations and Gene Dose

Noteworthy, about two thirds of subjects in both groups had serum concentrations below the therapeutic range recommended by the AGPN Consensus Guidelines (Hiemke et al., 2018). As participants were either on a stable dosage of donepezil 10 mg or rivastigmine 9.5 mg, variability due to different dosages within one group can be ruled out.

More subjects in the donepezil group had lower than expected drug serum concentrations (73 vs. 65% in the rivastigmine group) and all but one of the subjects with a gene dose >1 fell in that category (compare **Figure 1**). Vice versa, being a poor metabolizer with a gene dose of 0 or 0.5 did not necessitate in a

serum concentration within or above the recommended range. While in our study the gene dose, respectively type of metabolizer, significantly predicted donepezil serum concentration, previous studies investigating correlations between CYP2D6 mutations and donepezil concentration showed inconsistent results (Varsaldi et al., 2006; Seripa et al., 2011; Lu et al., 2014; Sonali et al., 2014; Miranda et al., 2017).

As 65% of the subjects treated with rivastigmine had low drug serum concentrations as well, we assumed that other factors than gene dose, such as sex or adherence, might contribute to the finding of lower than expected drug serum concentrations in this many subjects.

Donepezil and Rivastigmine Serum Concentration in Context of the Recommended Therapeutic Range

Concerning donepezil, one reason might be that the current guideline increased the recommended lower limit from 30 to 50 ng/ml (Hiemke et al., 2011; Hiemke et al., 2018). Even adhering to the previous guideline, 25% of our subjects would have had serum concentration below the formerly recommended lower limit. Establishing a therapeutic range for each drug is not mandatory for pharmaceutical companies, so guidelines are subject to constant change and adaption, based on the availability of data. Within its therapeutic range, a drug should have a definite therapeutic effect while being tolerable and not harmful.

The Consensus Guidelines are based on published data about the respective drugs, were obtained from drug concentrations at therapeutically effective doses and related to clinical effects, and cut-off values were identified by receiver operating characteristic (ROC) analysis when possible (Hiemke et al., 2018).

Hefner et al. (2015) investigated in over 100 patients if donepezil serum concentration was associated with clinical improvement measured on the clinical global impression rating scale (CGI). They provided ROC analyses suggesting a serum concentration of at least 50 ng/ml was necessary for a good clinical response. Subjects that "very much improved" on the CGI actually had a mean serum concentration of 60 ng/ml. As Koeber et al. (2012) already suggested and as can be seen in our sample, a dosage higher than 10 mg might be necessary to achieve such serum concentrations of donepezil. We did not find comparable data on rivastigmine.

Although it has not specifically been investigated for AChE-I, most plasma and serum samples for measuring antidepressants or antipsychotics can be stored at 4°C in the dark for 24 h without affecting measuring of the respective drugs (Heller et al., 2004). Even if donepezil or rivastigmine were unstable at room temperature, it is unlikely that this would be the cause for the low serum concentrations we measured. In our study, blood samples were immediately stored at 4°C and centrifuged within 60 min of collection. Following centrifugation serum samples were stored at -20°C.

80% of subjects in our study had rivastigmine serum concentrations outside the recommended therapeutic range which is between 5–13 ng/ml (65% below, 15% above that range). We were surprised to not see a statistically significant association between rivastigmine serum concentration and body weight as this is described in the drug label information (FDA, 2012). Neither did we find another factor predicting serum concentration.

That an estimated half of medication in chronic diseases is not taken as prescribed might have contributed to overall low drug serum concentrations in this study (Zullig et al., 2013). Therefore we additionally looked at the dose-related reference range (Hiemke et al., 2018). In the rivastigmine group 54% of subjects were within recommended limits and each 23% above or below that range. Only 32% of participants in the donepezil group had serum concentrations within the dose-related reference range, 63% were below, and 5% above. Beside genetic abnormalities or drug interactions, low drug adherence is a likely cause for this finding. Noteworthy in this context seems the fact, that subjects treated with oral donepezil were 2.7 times as likely to have serum concentrations beneath the dose-related reference range as those treated with a transdermal rivastigmine patch (63 vs. 23%).

Another possible factor resulting in relatively more subjects with a sub-therapeutic concentration of donepezil might be found in the substrates of the respective medication. While donepezil causes a rapidly reversible inhibition of AChE, rivastigmine pseud-irreversibly inhibits both, AChE and BChE. When analyzing serum, a large proportion of AChE that is bound to the surface of RBC will have been removed from the sample, as will have the AChE-I that is bound to the enzyme. BChE as a soluble enzyme, on the other hand, will remain in serum and plasma. However, as rivastigmine binds quasi irreversibly to its target enzymes and is degraded during its interaction with the enzyme, measuring free rivastigmine in serum means that its binding sites are saturated. Measuring unchanged donepezil and rivastigmine-metabolites in whole blood might yield more precise results when investigating drug concentrations in terms of bioavailability. While a large number of studies investigated serum and plasma concentrations like we did and available data in the drug label information and guidelines report plasma or serum concentrations, some authors directly measured the activity and protein levels for AChE and BChE (Darreh-Shori et al., 2006; Nordberg et al., 2009; Darreh-Shori and Soininen, 2010; Darreh-Shori et al., 2014). Important findings from these studies are that donepezil, as a reversible, noncarbamylating AChE-I, more than doubles AChE protein expression and increases AChE activity in both, RBC and cerebro spinal fluid (CSF), and favors AChE-driven Aβ aggregation (Darreh-Shori et al., 2006; Nordberg et al., 2009; Darreh-Shori and Soininen, 2010; Darreh-Shori et al., 2014). This raises the question if increasing the dosage of donepezil would accelerate the progression of Alzheimer's pathology? Interestingly, Darreh-Shori et al. observed that adding low-dose phenserine, a carbamylating AChE, to donepezil treatment, the higher expression of AChE was counteracted (Darreh-Shori et al., 2014). Darreh-Shori et al. also found that CSF donepezil concentrations were higher after 24 months than after 12 month of treatment and that the

inhibition of CSF AChE was 20% higher than RBC AChE inhibition, even though donepezil concentrations were almost 10 times lower in CNS as compared to plasma (Darreh-Shori et al., 2006). In contrast, rivastigmine, a pseudo-irreversible, carbamylating AChE-I and BChE-I, was associated with a decreased activity and decreased protein levels for both AChE and BChE (Nordberg et al., 2009; Darreh-Shori and Soininen, 2010).

Drug Serum Concentration and Clinical Efficacy

Cognitive Symptoms

Rivastigmine serum concentration was the only significant predictor of changes in the subtest wordlist delayed recall. When using low/high serum concentration as a factor, regression models for both groups were no longer significant. However, roughly two thirds of study participants had drug serum concentrations below the recommended therapeutic range. As a result, when looking at the third of subjects with the highest serum concentrations in the donepezil group, some already had serum concentrations below the recommended range. In the rivastigmine group, the "high serum concentration" group comprised of all participants within or above the recommended reference range.

As a dose dependent, respectively blood concentration dependent effect has been suggested for both, donepezil and rivastigmine, low serum concentrations in our sample might explain lack of seen drug efficacy (Rogers et al., 1998; Chou et al., 2012; Yang et al., 2013; Hefner et al., 2015; Chen et al., 2017). In the US and some Asian countries, a 23 mg dosage of donepezil has been approved by regulation authorities (FDA, 2015) and although there were more adverse drug reactions, particularly of the gastrointestinal system, participants treated with 23 mg donepezil daily also showed significantly more improvement in cognition as compared to patients receiving a dosage of donepezil 10 mg (Farlow et al., 2010).

We looked at changes of cognitive symptoms between baseline and follow-up. As concomitant medication in subjects was stable between both assessments, we did not adjust test results for potential anticholinergic side effects of concomitant medication. Furthermore, the anticholinergic burden (ACB) score was low in our cohort (mean 0.42 ± 0.72) (Kiesel et al., 2018). Only one subject had an ACB score >2, a value above which a switch to alternative drugs is recommended (Boustani et al., 2008). Besides, the ACB scores did not significantly differ between groups ($p = 0.487$).

BPSD

A dose dependent treatment response has also been shown for BPSD in DLB. In patients with worsening of BPSD under treatment with 5 mg donepezil, Manabe et al. found that increasing the dosage to 10 mg led to statistically significant improvements on the Neuropsychiatric Inventory (NPI) (Manabe et al., 2016). Tan et al. also saw a dose dependent effect of donepezil on behavioral symptoms that was significant for 10 mg daily, but not for 5 mg (Tan et al., 2014). Beside Alzheimer's dementia, AChE-I are effective in dementia due to other neurodegenerative diseases. A Cochrane review found evidence of a positive impact of AChE-I for DLB, PDD, and cognitive impairment in PD (Rolinski et al., 2012). Beside cognitive functions, behavioral symptoms improved under treatment with AChE-I as well (Rolinski et al., 2012). Jin and Liu looked at the efficacy and safety of different drugs used to treat BPSD (Jin and Liu, 2019). They also found a positive effect for AChE-I. However, they also saw an increase in the risk of adverse events such as nausea and vomiting. Additionally, there might be sex-specific effects. On one hand, Matsuzono et al. (2015) described significantly improved scores on the Abe's Behavior and Psychological Symptom of Dementia Score (ABS) for female patients after three months of treatment with rivastigmine, but not for male patients. ABS for male patients, on the other hand, were stabilized under treatment with galantamine, while females deteriorated.

Limitations

Sample size and variation of the time from baseline to follow-up appointments are the biggest limitations of this study. Due to the relatively small sample size, especially when further dividing treatment groups into a low and high serum concentration subgroup, weak correlations and small effects might not have been detected. Concerning time to follow-up, routine follow-up appointments were supposed to take place 3–6 months after the initial visit. However, there was much variability in the actual time span to follow-up appointments. As duration of treatment had a statistically significant influence on donepezil serum concentration in our regression model, a longer treatment period might have resulted in higher serum concentrations and possibly higher efficacy. Although according to drug label information, steady state is reached after about 15 days of treatment with donepezil (FDA, 2015), Miranda et al. also described increasing serum concentrations over a study period of one year (Miranda et al., 2017) and Darreh-Shori et al. reported a further increase of donepezil concentration in CSF after 24 months of treatment.

Some cited studies measured drug concentrations in serum, some in plasma. We decided to use serum, as this constitutes the standard for measuring drug concentrations in Germany. As serum equals plasma without fibrinogen, measurements should be identical, especially when using Liquid Chromatography Mass Spectrometry. We are not aware of any studies comparing donepezil or rivastigmine concentrations in plasma to that in serum and the current Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology considers both, serum and plasma, as equal (Hiemke et al., 2018).

We aimed to measure drug serum concentration in the trough state as close to the next scheduled dosing as possible. In some cases, however, this was not possible. While the effect on the serum concentrations of donepezil with a half-life of 70 h (FDA, 2015) might have been small, holding the next dose of rivastigmine with a half-life of 3.4 h after patch administration

(FDA, 2012) for up to 4 h might have had a bigger effect on rivastigmine concentrations.

Another limitation is that we did not measure mutations in the BChE gene. As BChE wild-type carriers have been reported to show greater response to rivastigmine than donepezil (Blesa et al., 2006) and as some variants, such as BChE-K, cause reduced AChE activity (O'Brien et al., 2003) and thereby reduced degradation of rivastigmine, this might have affected measures of efficacy as well as rivastigmine serum concentration.

Assessing efficacy on cognition in a steadily progressing disease with day to day fluctuation poses a challenge. Even if no improvement is seen, slower worsening has to be considered as treatment effect. In small samples and without a placebo group, however, the effect might be easily missed. While the CERAD-NAB is a well-established test for Alzheimer's disease, it does not assess activities of daily living or BPSD. It would have been of use if additional tests for the ability of daily living and BPSD would have been administered for this study. Improvement in these fields may have occurred even in the absence of improvement on the CERAD-NAB sub-score for word list delayed recall.

Last but not least, information about treatment adherence was obtained from the caregivers and may have been flawed as indicated by low serum concentrations compared to the dose-related reference ranges. Questions regarding drug adherence may have been answered to please the treating physician.

Conclusions

Since there are signs that a substantial number of subjects treated with AChE-I have drug serum concentrations below the recommended reference range, therapeutic drug monitoring might improve the efficacy of AChE-I when treating cognitive and behavioral symptoms in dementia. This might be true not only for ADD, but also for PDD, DBL, and possibly vascular dementia. Studies on different forms of dementia investigating drug blood concentration while assessing not only cognitive tests, but also scales for activity of daily living, BPSD and caregiver burden would be of value. As donepezil and rivastigmine have fundamentally different effects on AChE concerning protein concentration and activity, measuring plasma or serum concentrations might not be quite as meaningful when assessing the effect of AChE-I. There also might be room for improvement on medication adherence. Thorough education of patients and caregivers or the involvement of home nursing might be of benefit when seeking top treatment result. In addition, drug adherence seems to be better in a transdermal application of the AChE-I.

DATA AVAILABILITY STATEMENT

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. However, due to the nature of pseudonymized patient data, a material transfer agreement is required to meet ethical standards and data privacy laws of Germany.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Faculty of Medicine of the Technical University of Munich, Munich (reference number 673/02). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MO: Design of the study, analysis and interpretation of data, drafting the manuscript. MS: Acquisition, analysis and interpretation of data, drafting the manuscript. HS: Analysis and interpretation of data, drafting the manuscript, revising the manuscript for intellectual content. CS: Analysis and interpretation of data, revising the manuscript for intellectual content. KB: Acquisition and analysis of the data, revising the manuscript for intellectual content. CM: Acquisition and analysis of data, revising the manuscript for intellectual content. BD: Collecting data, revising the manuscript for intellectual content. OG: Collecting data, revising the manuscript for intellectual content. JD-S: Acquisition and interpretation of data, and revising the manuscript for intellectual content. HF: Interpretation of data and revising the manuscript for intellectual content. WS: Conceptualization of the study, interpretation of data, and revising work for intellectual content. TG: Conceptualization of the study, analysis and interpretation of data, drafting and revising the manuscript for intellectual content. All authors approved of the final version of the manuscript and agreed to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2020.00691/full#supplementary-material

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REVIEW
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Role of Neuroinflammation in Autism Spectrum Disorder and the Emergence of Brain Histaminergic System. Lessons Also for BPSD?

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Many behavioral and psychological symptoms of dementia (BPSD) share similarities in executive functioning and communication deficits with those described in several neuropsychiatric disorders, including Alzheimer's disease (AD), epilepsy, schizophrenia (SCH), and autism spectrum disorder (ASD). Numerous studies over the last four decades have documented altered neuroinflammation among individuals diagnosed with ASD. The purpose of this review is to examine the hypothesis that central histamine (HA) plays a significant role in the regulation of neuroinflammatory processes of microglia functions in numerous neuropsychiatric diseases, i.e., ASD, AD, SCH, and BPSD. In addition, this review summarizes the latest preclinical and clinical results that support the relevance of histamine H1-, H2-, and H3-receptor antagonists for the potential clinical use in ASD, SCH, AD, epilepsy, and BPSD, based on the substantial symptomatic overlap between these disorders with regards to cognitive dysfunction. The review focuses on the histaminergic neurotransmission as relevant in these brain disorders, as well as the effects of a variety of H3R antagonists in animal models and in clinical studies.

Keywords: behavioral and psychological symptoms of dementia, Alzheimer's disease, schizophrenia, autism spectrum disorder, cytokines, neuroinflammation, central histamine receptors, H3R antagonists

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Abbreviations: ASD, Autism Spectrum Disorder; AβP, Amyloid beta peptide; ACh, Acetylcholine; AChE, Acetylcholine esterase; ACEI, Acetylcholine esterase inhibitor; AD Alzheimer's disease; ADHD, Attention deficit hyperactivity disorder; APP, Amyloid protein precursor; BPSD, Behavioral and Psychological Symptoms of Dementia; CNS, Central Nervous System; COX, Cyclooxygenase; H3R, Histamine H3 Receptor; HA, Histamine; GSK-3β, Glycogen synthase kinase 3 beta; GM, Grey matter; DSM, Diagnostic and Statistical Manual of Mental Disorders; EMA, European Medicines Agency; FDA, Food and Drug Administration; H_2O_2, Hydrogen peroxide; HDC, Histidine Decarboxylase; HR, Histamine Receptor; HNMT, Histamine Nmethyl Transferase; HS, Histaminergic System; IL, Interleukin; IFN-γ, interferon gamma; LPS, Lipopolysaccharide; MCI, Mild cognitive impairment; NF-κB, Nuclear Factor kappalight-chain-enhancer of activated B cells; iNOS, Inducible nitric oxide synthase; NO, Nitric Oxide; NRXN, Neurexin; NMDA, NMethyl-D-aspartate; PCP, Phencyclidine; PD, Parkinson's disease; PGE_2, Prostaglandin E_2; ROS, Reactive Oxygen Species; SCH, Schizophrenia; TNF-α, Tumor necrosis factor alpha; TS, Tourette syndrome; SOD, Superoxide dismutase 1; TGF-β, Transforming growth factor beta; ToM, Theory of Mind; VPA, Valproic Acid; i.p., Intraperitoneally; WM, White matter.

INTRODUCTION

ASD as a Prototype for Neuropsychiatric Disorders

Alzheimer's disease (AD) patients are often found to show apathy, depression, eating, and sleeping disorders, aggressive behavior, as well as other non-cognitive symptoms (Selles et al., 2018). These symptoms are usually associated with AD pathology but are often neglected as part of disease progression due to the early and more profound disturbances of memory centers in the hippocampus and entorhinal cortex. AD comprises up to 80% of all dementias. Behavioral and psychological symptoms of dementia (BPSD) in AD are known recently to correlate with gray matter (GM) atrophy and, also with white matter (WM) damage. WM damage and its relationship with GM atrophy are reported in AD (Makovac et al., 2016). Additionally, Sokol et al. reported that Amyloid-β protein precursor (βAPP) and its metabolites to be dysregulated not only in AD, but also in Autism spectrum disorder (ASD), and that the secreted variant of APP may lead to increased brain WM. WM structure is dynamic and is essential to cognitive function (Courchesne et al., 2003; Dawson et al., 2007). WM is largely composed of glia including microglia and it was proposed that neuroinflammation along with increased myelination, may contribute more to the WM enlargement in ASD (Herbert, 2005; Fields, 2008; Aoki et al., 2017; Sokol et al., 2019). Neuroinflammation appears to be similar in ASD and AD (Herbert, 2005), hence, applying known pathways in AD to ASD as proposed, should provide drug targets for ASD. Therefore, knowledge from better developed field as AD opens the door to better understand ASD.

Interestingly, BPSD are present in almost 90% of patients diagnosed with AD, characterized as a disorder of heterogeneous degenerative symptoms with memory and cognitive deficits considered as the core symptoms across multiple symptom domains (Chakraborty et al., 2019). Many BPSD share similarities with symptoms observed in AD, schizophrenia (SCH), and ASD including depression, anxiety, executive functioning deficits, and communication deficits (Wallace et al., 2016; Rhodus et al., 2019). ASD is a biologically based persistent neurodevelopmental disorder of which the core symptoms include impaired social interaction and repetitive behaviors with restricted interests (Baronio et al., 2015). The term ASD became much more used in the medical literature with the publishing of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). The history of the concept of ASD was rather well described by Ousley and Cermak (Ousley and Cermak, 2014). The core symptoms of ASD, e.g., stereotypy, repetitive behavior, and restricted interests, can be typically diagnosed in early developmental period in childhood that are persistent for the whole lifetime (Andres, 2002). The incidence of ASD has been reported to be increasing, which attracted the attention of the public but also scientists (Sheldrick and Carter, 2018; Xu et al., 2018). As estimated worldwide, prevalence of patients with ASD diagnosis is remarkably high. Current prevalence for ASD is approximately one in 160 children worldwide, and is expected to rise (Arvidsson et al., 2018). Despite the high prevalence rate, the etiology and pathogenesis of this disorder are still largely unknown and remain a matter of speculation. The lack of a specific etiologic diagnosis can be attributed to limited human brain accessibility and the complexity of the neurobiology of its activity (Nestler and Hyman, 2010). ASD is a heterogeneous group of neurobehavioral abnormalities with different recognized genetic and environmental origins. Genetic and environmental factors are strongly suggested to be involved in incidence of ASD (Baronio et al., 2015). Additionally, the heterogeneous behavioral symptoms and neuropsychiatric comorbidities in autistic children make it difficult to decipher the pathophysiology of this disorder, and consequently to develop a fundamental therapeutic approach to ASD. Therefore, subgrouping of ASD children with shared symptoms and shared molecular changes into several categories and observing their response to intervention is essential (James et al., 2009). Pharmacological treatments addressing core symptoms in ASD still remain challenging. Despite expanding awareness and advances in early age, efficacious reversal of these persistent autistic symptoms is not yet achieved. To date, risperidone and aripiprazole are the only two ASD-specific drugs approved by the US Food and Drug Administration (FDA) for improving behavioral ASD associated symptoms, such as irritability (Matson et al., 2011). There is lack of effective therapeutic interventions that address ASD hallmark symptoms (Sheldrick and Carter, 2018; Xu et al., 2018). Pharmacotherapeutic options that are currently used target accompanying symptoms in ASD, but are not disease-modifying and do not provide symptomatic control of core symptoms (Wong and Smith, 2006; Hanson et al., 2007). These accompanying physiological and psychiatric symptoms of ASD include attention deficit, anxiety, irritability, hyperactivity, self-injuries, aggression, in addition to sleep, sensory, and gastrointestinal disturbances (Lai et al., 2014; Summers et al., 2017). Psychiatric drugs are frequently used for treating these symptoms in autistic children (Findling, 2005). Despite the outstanding research that has been accomplished on ASD, complete and effective treatments targeting ASD core symptoms has been challenging and not yet achieved, as mentioned earlier. Therefore, significant progress toward the goal of identifying treatments for improving and potentially even curing core symptoms of ASD is of high importance, aiming to provide better quality of life for the suffering individuals and relieving the burden on their families. This heterogeneity may be due to the display of a wide spectrum of symptoms. The risk architecture of ASD included both genetic as well as environmental factors, however, there is not any unifying genetic or environmental factor linked to this disorder (Hassan and Mokhtar, 2019) (Stubbs et al., 2016). Also, the variety of interactions between genes, epigenetics, and the exposure to environmental factors all play critical and definite roles in developing ASD (Muhle et al., 2004). The risk of developing ASD was reported to be 35–40% due to genetic variability and around 60% due to pre,- peri-, and postnatal environmental factors (Hallmayer et al., 2011). Accordingly, environmental

factors in terms of ASD risk included prenatal and perinatal complications (Glasson et al., 2004; Maramara et al., 2014), birth and neonatal complications (Gardener et al., 2011; Guinchat et al., 2012), advanced parental age, assisted reproductive technologies, nutritional factors, maternal viral infection, autoimmune diseases, and exposure to environmental chemicals, toxins, and medications such as the anticonvulsant valproic acid (VPA) (Kern and Jones, 2006; Kolevzon et al., 2007; Emberti Gialloreti et al., 2019). Therefore, a better understanding of gene-environmental interplay in the pathogenesis of ASD may explain better the pathophysiology of ASD, hence lead to an optimized therapeutic strategy.

Common Neurotransmitter Changes in ASD, BPSD, and SCH

The reported interplay between ASD and late life dementia highlights shared neuroanatomic areas between ASD and late life dementias, that could help to provide valuable insights for the development of therapeutic strategies for both ASD and behavioral features seen in mild cognitive impairments (MCIs) and states of dementia (Crawford et al., 2014). Recognition of possible relationships between clinical features of dementia and ASD has sparked a recent scientific research. Along with the genetic factors and environmental influences, growing evidences suggested an association between the onset and progression of ASD and a variety of brain neurotransmitter systems such as acetylcholine (ACh), dopamine, serotonin, glutamate, γ-amino butyric acid, and histamine (HA) (Shah and Wing, 2006; Bacchelli et al., 2015; Ellenbroek and Ghiabi, 2015; Wang et al., 2015; Chen et al., 2017; Hellings et al., 2017; Hellmer and Nystrom, 2017; Naaijen et al., 2017; Nakai et al., 2017; Paval, 2017; Paval et al., 2017). Histaminergic and cholinergic altered neurotransmission are thought to play a crucial role in the ASD-related behavioral phenotype (Karvat and Kimchi, 2014; Baronio et al., 2015; Wright et al., 2017). Previous reports suggested that an impaired cholinergic system causes cognitive problems that may include social problems, which were reversed by donepezil treatments, an acetylcholinesterase inhibitor (ACEI) (Riedel et al., 2009; Karvat and Kimchi, 2014). Mounting evidence from preclinical studies indicated notably that H3R antagonists/inverse agonists exhibited cognition-enhancing properties (Witkin and Nelson, 2004; Passani and Blandina, 2011; Sadek et al., 2016b; Sadek and Stark, 2016). Both AChE and histamine H3 receptors (H3R) auto- and heteroreceptors are suggested to be involved in the modulation of several central neurotransmitters, including ACh and HA, which are associated with cognition. Moreover, BPSD represent a heterogeneous group of neuropsychiatric and behavior symptoms occurring in patients with dementia, and are clinically relevant as cognitive symptoms which correlate strongly to the degree of functional and cognitive impairment (Cerejeira et al., 2012). Furthermore, it has been revealed that several brain neurotransmitters are involved in a particular behavioral syndrome of BPSD and ASD. The imbalances of different neurotransmitters and their role in BPSD clinical manifestation have been extensively investigated. Findings of recent trials of ACEIs, supported that this class of drugs may be effective in managing BPSD (Lanari et al., 2006). Dementia is a consequence of neurodegeneration in brain, and AD is the most common form of dementia which is characterized by progressive cognitive and behavioral impairments (Dillon et al., 2013). The cholinergic neurotransmitter system has long been known to have an important role in the cognitive decline and memory deficits of AD (Sultzer, 2018). This view supports the recent findings of promising improvements in BPSD by ACEIs, highlighting the significant role of ACh in enhancing not only cognition and memory but also behavioral symptoms. Moreover, social functioning impairment common in ASD and SCH may be due to underlying mechanisms such as deficits in theory of mind (ToM), that are common in both disorders, as both overlap genetically and symptomatically (De Crescenzo et al., 2019). Lack of ToM skills has been also proposed to be an important part of AD. ToM refers to the ability of an individual to understand the mental states of oneself and others, and depends on executive functions and memory (Castelli et al., 2011). It was reported that 65% of AD dementia patients exhibited cognitive ToM deficits, and these deficits were associate with multiple domains of cognitive impairments (Yildirim et al., 2020). Similar to ACEIs, H3R antagonists are reported to have cognitive enhancing effects with positive results in memory and attention (Nathan et al., 2013), suggesting the important role of histamine in disorders associated with memory and cognitive impairments, and proposing the special role it might have in ToM. In addition, Passani et al. reported preclinically, that several neurotransmitters including histamine regulated social recognition and memory consolidation in amygdala and hippocampus (Passani et al., 2017). In line with these findings, the significance of this research area to disclose the etiology of ASD and BPSD is substantially important, for developing novel agents with multiple pharmacological effects for treatment of neuropsychiatric disorders of a multifactorial nature, such as ASD.

SIMILARITIES BETWEEN ASD AND OTHER NEUROPSYCHIATRIC DISORDERS INCLUDING BPSD

ASD, SCH, and BPSD are all significant public health problems. Scientists have recently explored the association between ASD and SCH, but the outcomes are inconsistent (Zheng et al., 2018). The relationship between ASD and SCH is complex and has experienced significant reconsiderations over the past seven decades. In the mid-twentieth century, the two neuropsychiatric disorders were in fact regarded as being one condition, however, from the early 1970s, the two began to be looked at as separate conditions. Subsequently, the separation of the two disorders was justified, with the age at onset being the most evident example where the disorders differ. However, it is now widely recognized that there is substantial overlap between

the two conditions, based on genetic underpinnings, epidemiological similarities, and the high rates of co-occurrence (Wood, 2017).

Interestingly, behavioral characteristics of ASD have been described in individuals with MCI or early dementia, demonstrating the possibility of late-life emergence of behaviors characteristic of ASD as part of MCI or AD (Rhodus et al., 2019) (**Table 1**). Moreover, the genetic basis of ASD and AD implies common associations like memory deficits, cognition changes, demyelination, oxidative stress and inflammation, a fundamental part of both disorders (**Table 1**) (Khan et al., 2016). Involvement of microglial function is increasingly recognized in the mechanism of AD and has been discussed in relation to BPSD, although there is a debate whether glial activation is cause or consequence of AD, or even a protective response (Selles et al., 2018). The similarities between ASD and BPSD as well as the common mechanisms of ASD and AD are summarized in **Table 1**.

NEUROINFLAMMATION IN ASD AND COMPARISON WITH OTHER NEUROCOGNITIVE DISORDERS

Neuroinflammation is a response that involves neurons, microglia and macroglia, which are cells that are present in the central nervous system (CNS) (Bradl and Hohlfeld, 2003; Carson et al., 2006a). Neuroinflammation has been reported to characterize many neurodegenerative diseases and neuropsychiatric conditions such as multiple sclerosis, narcolepsy, AD, Parkinson's disease (PD), and ASD (Carson et al., 2006b; Frick et al., 2016). Autistic individuals often show signs of altered inflammatory responses and neuro-immune system abnormalities throughout life, which implicates a potential role of inflammation in the etiology of ASD. This is further confirmed by increasing clinical and experimental evidence that links altered immune and inflammatory responses with the pathogenesis of ASD (Lucchina and Depino, 2014). Moreover, post mortem studies have supported this hypothesis, documenting substantial neuroinflammation in several brain regions of patients with ASD (Vargas et al., 2005).

Mounting evidences supported a link between inflammation and neuropsychiatric disorders. ASD and SCH share several behavioral symptoms that might reflect the same biological basis, including inflammation. Both disorders share impairments in social communications and some degree of genetic overlap (Prata et al., 2017). Delusions and hallucinations represent the positive symptoms of SCH, while autistic traits are features of negative symptoms of SCH, that include motivational deficits, social withdrawal, poverty of speech, diminished emotional reactivity, and psychomotor expression (Kirkpatrick et al., 2006; Strauss et al., 2013; Harvey et al., 2019). Recently, Goldsmith et al. reported the associations between inflammatory markers and negative symptoms of SCH, and that inflammation is one mechanism that may underlie these negative symptoms (Goldsmith and Rapaport, 2020). Since SCH and ASD have been associated with chronic and low-grade inflammatory states, hence, a considerable number of pro-inflammatory biomarkers, including cytokines such as IL-6, TNF-α, IL-1β, IL-8, IFN-γ, have been identified in both, suggesting the related symptomatic overlap (Cox et al., 2015; Lv et al., 2015; Masi et al., 2015). Microglia, the brain's resident inflammatory cells, have a critical role in mediating neuroinflammation and regulating brain development and homeostasis. In fact, they play a critical role in defence and tissue repair. Microglia activation is the first sign of neuroinflammation, and abnormalities in microglia have been implicated in autism (Carson et al., 2006a; Frick et al., 2016). When being activated, microglia may cause a neuronal dysfunction and cell death (neurodegenerative role). Some of the biological effects and consequences of activated microglia include rounding-up, proliferation, migration, phagocytosis, presentation of antigens to T-cells, release of a variety of oxidants such as reactive oxygen species, and activation of several genes and proteins, such as inducible nitric oxide synthase (iNOS), cyclooxygenase 1 (COX1), cyclooxygenase 2 (COX2), and a variety of proinflammatory cytokines including interleukin-1β (IL-1β), tumor necrosis factor alpha (TNF-α) (**Figure 1**). Notably, these effects are also observed in autism (Monnet-Tschudi et al., 2011). Chronic or excessive neuroinflammation has been diagnosed in ASD (Kern et al., 2015), this observed chronic glia activation and altered inflammatory function may be partly responsible for the behavioral features in ASD, as chronic peripheral inflammation and abnormal inflammatory responses in the brain may lead to cognitive dysfunction (Lucchina and Depino, 2014).

During pregnancy, both environmental and genetic risk factors may affect inflammatory response of new-borns, hence altering postnatal brain development (Adams-Chapman and Stoll, 2006). These genetic and environmental factors can directly elicit chronic neuroinflammation which in turn may

TABLE 1 | Relationship between ASD, BPSD and AD.

Diagnostic criteria for ASD in the Diagnostic and Statistical Manual of Mental Disorders (Rhodus et al., 2019)	Similarities of ASD and BPSD (Rhodus et al., 2019)	Common mechanisms of ASD and AD (Khan et al., 2016)
- Deficits in social communication and social interaction	- Anxiety	- Inflammation
- Restricted, repetitive patterns of behavior, interests, or activities including repetitive movements, use of objects, or speech	- Depression	- Oxidative Stress
- Inflexibility in terms of routines	- Executive functioning deficits	- Synapse formation
	- Communication deficits	- Myelination
		- Methylation
		- Impaired cholinergic system

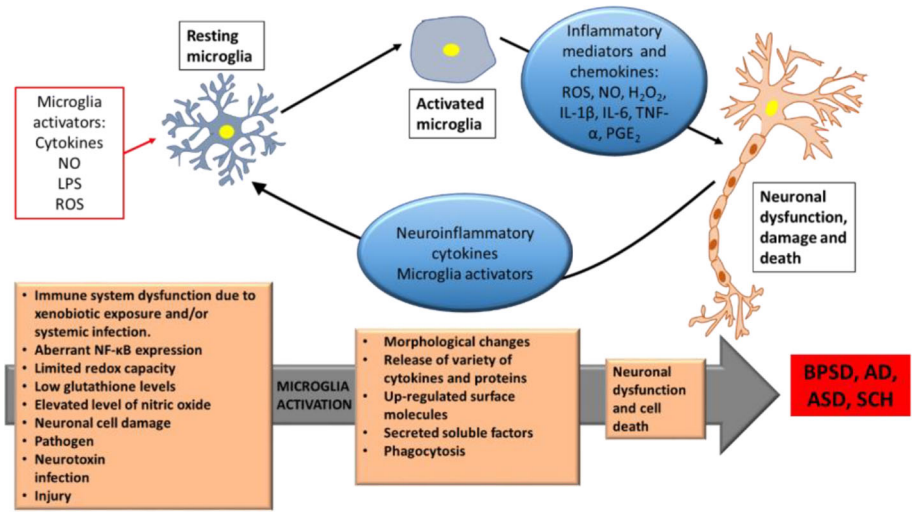

FIGURE 1 | Schematic depiction of microglia activation neuronal cell death in BPSD, AD, ASD, and SCH. Neuroinflammatory proteins and cytokines due to microglia activation by genetic and different environmental activators, leading to neuron dysfunctions and cell death. BPSD, Behavioral and Psychological Symptoms of Dementia; AD, Alzheimer's disease; ASD, Autism Spectrum Disorder; SCH, Schizophrenia; NO, Nitric Oxide; LPS, Lipopolysaccharide; ROS, Reactive Oxygen Species; H_2O_2, hydrogen peroxide; IL-1β, Interleukin-1β; IL-6, Interleukin-6; TNF-α, tumor necrosis factor-α; PGE_2, Prostaglandin E2; NF-κB, Nuclear Factor kappa-light-chain-enhancer of activated B cells. Modified after (Shabab et al., 2017).

modulate neuronal function and immune response *via* glia activation, or directly by affecting neuronal function (Depino, 2013) (**Figure 2**). Valproic acid (VPA), as an environmental risk factor, elicited activation in different brain regions, with evidence of long-lasting glia activation in the hippocampus and the cerebellum (Lucchina and Depino, 2014). The hippocampus (Depino et al., 2011) and cerebellum (DeLorey et al., 2008; Martin et al., 2010) are two brain regions linked to autism-related behavior, namely, limited social interaction and repetitive behaviors. Additionally, several studies showed that altered social behavior in adult mice may be due to cerebellar inflammation as the cerebellum is considered to be involved in executive and cognitive functions (Shi et al., 2009; Koziol et al., 2014; Lucchina and Depino, 2014; Wang et al., 2014). Furthermore, evidences

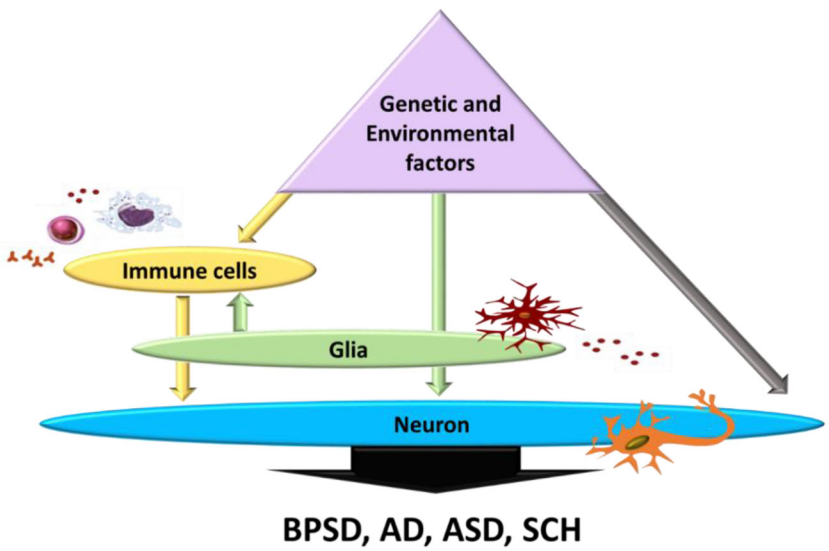

FIGURE 2 | Effect of genetic and environmental factors on neuronal dysfunction and immune response modulating BPSD, AD, ASD, and SCH symptoms. All possibilities contributing to ASD through glia activation (grey arrow), or through directly altering peripheral immune cells (white arrows) which in turn activates glia affecting the neuronal function (black arrows). BPSD, Behavioral and Psychological Symptoms of Dementia; AD, Alzheimer's disease; ASD, Autism Spectrum Disorder; SCH, Schizophrenia. Adapted from (Depino, 2013).

suggested that astrocyte and microglia activation in the cortex and cerebellum increase expression of cytokines, including IL-6, TNF-α, MCP-1, TGF-β1, IFN-λ, interferon gamma, IL-8, and other associated genes involved with the immune response in different brain regions of autistic subjects (Vargas et al., 2005; Chez et al., 2007; Garbett et al., 2008; Li et al., 2009; Chez and Guido-Estrada, 2010). Alternatively, both these environmental and genetic factors could chronically alter immune response through increasing production of free radicals, which consequently activate glia cells, increasing the inflammatory response and then affecting neurons, thus mediating clinical symptoms of autism (Depino, 2013) (**Figure 2**). These findings suggest that neuroinflammation may contribute to ASD behavioral effect, hence, controlling microglia activation and inhibiting cytokine and free radical production might be a therapeutic strategy for treating ASD. Moreover, exploration of mechanisms involved in neuroinflammation, immune-mediated pathways and targeting their modulation as a strategy for disease-modifying treatment, are promising research approaches in neurodegenerative diseases such as AD and BPSD, where the memory and cognitive deficit domain are the most prominent across several symptom domains (Chakraborty et al., 2019). AD is characterized by neuroinflammatory processes in which microglia are over-activated, resulting in the elevated production of pro-inflammatory cytokines. Increased expression of IL-1 has been reported in AD brain where several variants in genes of IL-1A and IL-1B have been found to influence AD risk. Increased IL-6 expression has been identified in AD patients, both in the periphery and CNS. Elevated levels of TNF-α has been also reported in AD patients (Su et al., 2016; Decourt et al., 2017). Moreover, increases in IL-1, IL-6, TNF-α, IL-8, IFN-γ, IL-4, and TGF-β have been reported in patients with SCH, and have been associated with negative symptoms (Potvin et al., 2008; Goldsmith et al., 2018; Momtazmanesh et al., 2019). All of which are inflammatory markers reported to be altered in ASD (Novellino et al., 2020). A recent clinical study suggested that the behavioral phenotype of ASD may develop as a consequence of neurodegenerative processes, since the frequency of ASD-like behaviors directly correlate with the progressing severity of cognitive impairment (Rhodus et al., 2019). In addition to this, another clinical study reported the association between ASD-linked symptoms and late-life degenerative dementia, where such symptoms are more prevalent in those with early onset dementia (Crawford et al., 2014). Multiple lines of evidence support neuroinflammation as a common feature of dementia, AD, and ASD, and suggest a central role of microglia in the progression of the disorder (Lucchina and Depino, 2014; Pasqualetti et al., 2015). A broader approach to the complexity of microglial subpopulations provides an opportunity to explore the phenotypic landscape of microglia-driven neuroinflammation in ASD, AD, and BPSD, hence, may assist in the identification of targets for therapeutic interventions.

Moreover, the amyloid hypothesis predicts clinical disease associated with amyloid-β loaded plaques resulting in brain atrophy in patients with AD.

IMPLICATION OF HISTAMINE IN TOURETTE'S SYNDROME, SCH AND ASD

Central histaminergic system (HS) was found to exhibit a critical role in cognition and sleep disorders, and has been reported to be involved in various brain disorders such as AD, SCH, drug dependence, and PD (Baronio et al., 2014; Wright et al., 2017).

In previous studies, it was reported that genetic histaminergic signaling abnormalities may lie behind some cases of rare diseases such as Tourette syndrome (TS) (Paschou et al., 2013). TS was also reported to be among the most prevalently comorbid neurodevelopmental disorders with ASD (Gillberg and Billstedt, 2000), sharing genetic risk factors (Clarke et al., 2012; Fernandez et al., 2012). Additionally, both conditions share upregulation of neuroinflammation (Muller, 2007; Kern et al., 2015; Theoharides et al., 2016), and increased microglia activation (Frick et al., 2016). HA has a remarkable role in neuroinflammation (Jutel et al., 2005; Theoharides et al., 2016), as well as microglia regulation (Ferreira et al., 2012; Dong et al., 2014; Rocha et al., 2014; Frick et al., 2016), suggesting that the HS may partly mediate these abnormalities. Also, a recent preclinical study revealed that HA induces microglia activation and the release of several proinflammatory mediators in rat brain through activation of H1- or H4Rs (Zhang et al., 2019). A study of TS reported a rare non-sense mutation in HDC, a gene encoding for the histidine decarboxylase enzyme that synthesizes HA from histidine (Karagiannidis et al., 2013). Other recent studies suggested *de novo* deletions overlap in HNMT, a gene which encodes the enzyme histamine-*N*-methyl transferase that inactivates HA (Griswold et al., 2012; Mulatinho et al., 2012). Furthermore, analysis of gene mapping within rare copy number variants in TS reported a significant overlap with those revealed in ASD, and some of them were in histamine pathways (Fernandez et al., 2012). All these findings of overlaps between the two disorders raised the possibility of the involvement of the HS in ASD. Furthermore, ASD and SCH were reported to share similar clinical symptoms and significant genetic overlap (Konstantareas and Hewitt, 2001; Carroll and Owen, 2009; Naguy and Naguy, 2018). Replicated findings suggested that SCH and ASD may share similar biological pathways, demonstrating that both conditions have a structural variant in chromosomal regions 16p11.2 (Weiss et al., 2008; McCarthy et al., 2009), 22q11.2 (Guilmatre et al., 2009; Vassos et al., 2010), 1q21 (Brunetti-Pierri et al., 2008; Stefansson et al., 2008; Ikeda et al., 2010; Mefford et al., 2010), and the gene neurexin (NRXN) and SHANK (Leblond et al., 2012; Sato et al., 2012). Other recent publications of copy number variations revealed rare variants at NRXN1 and catenin alpha3 loci suggesting a risk factor overlap with both ASD and SCH. In addition to the genetic overlap between both disorders, they also share behavioral symptoms as mentioned earlier. Social cognitive impairments are hallmark behavioral deficits in both, ASD and SCH (Couture et al., 2006; Meyer et al., 2011). Furthermore, neuroinflammation as a consequence of microglia activation plays an important role in both SCH and ASD (Nakagawa and Chiba, 2016). These findings suggest that HS dysfunction may be

involved in the etiology of ASD, since both SCH and TS disorders have substantial genetic and symptomatic overlap with ASD. Therefore, the emergence that the HS may be implicated in ASD and may contribute to the core symptoms, necessitates further research to investigate what role the HS may or may not have in enhanced neuroinflammation.

Histamine and Inflammation in Neurodegenerative Disorders

The possible implication of central HA to regulate neuroinflammation has received some scientific attention, but more recently, the fact that both the HS and microglial dysregulation are involved in a range of neurodegenerative pathologies and neurological conditions, highlighted the importance of HA in the regulation of microglia (Rocha et al., 2014). Evidence has been pointing to neuroinflammation as a triggering factor in neurodegenerative disorders and cognitive decline. In the brain, histamine can act either as neurotransmitter or as modulator of the innate immune system, hence modulating brain inflammatory responses (Saraiva et al., 2019). Several studies demonstrated the ability of histamine to counteract LPS-induced inflammation through the decrease of microglial migration, phagocytosis and ROS production induced by LPS, as well as the release of IL-1β (Ferreira et al., 2012) A recent finding reported microglial abnormalities in HDC knockout mouse, a validated model of TS (Baldan et al., 2014), which further supported the importance of understanding the role of HA in regulating microglial function, especially as TS and ASD have a high degree of overlap. An *in vitro* study demonstrated that microglia cells expressed all known HRs (Ferreira et al., 2012). Another experimental study suggested the role of HA in microglial inflammatory response modulation, demonstrating a dual role of HA in neuroinflammation regulation. Activated microglia modulate cell recruitment and proinflammatory cytokine release, such as IL-1β and TNF-α (Ferreira et al., 2012).

This evidence is complemented by a recent study demonstrating that HA reduces the proinflammatory microglia phenotype in the SOD1-G93A mouse model of Amyotrophic Lateral Sclerosis. It was reported that HA exerts its beneficial action only in inflammatory SOD1-G93A microglia, and on the other hand elicits a pro-inflammatory effect in non-transgenic cells (Apolloni et al., 2017). These findings demonstrated a different role for HA under physiological conditions and during an inflammatory response (Barata-Antunes et al., 2017). Another recent study demonstrated the dual role of HA in the modulation of microglial responses, suggesting that while histamine *per se* triggers microglia pro-inflammatory injurious phenotype, it can revert them oppositely under inflammatory challenge (Barata-Antunes et al., 2017), opening a new perspective for the therapeutic potential of HA to selectively improve inflammation-associated processes in disorders associated with microglia-derived inflammation. The role of H3R antagonists in stimulating the synthesis and release of HA in brain, as mentioned earlier, suggests that therapeutic use of H3R antagonists may ameliorate neuroinflammation and consequently, improving ASD behavioral symptoms. Moreover, the antioxidant effect of H3R antagonists, as demonstrated in a previous study strongly suggests that H3R antagonists may have therapeutic potential in the management of ASD (Mahmood et al., 2012; Mani et al., 2017). Previous studies have found elevated expression of proinflammatory molecules, including IL-1ß, TNF-α, IL-6, and TGF-ß in the autistic brain (Vargas et al., 2005; Depino, 2013; Goines and Ashwood, 2013; Deckmann et al., 2018). IL-1ß disruption was reported to have several neurological consequences relevant to ASD. It was also reported earlier that IL-6 overexpression in the mice CNS showed cognitive alterations, including avoidance behaviors (Heyser et al., 1997). Additionally, Vargas et al. found that transforming growth factor beta (TGF-β) was one of the most prevalent cytokines in brain tissues of individuals with ASD and is involved in social behavior. A previous study demonstrated that JNJ10181457, a H3R receptor inverse agonist reverted LPS-induced microglial IL-1ß, IL-6, and TNF-α expression, indicating that the compound inhibited microglial activation associated with inflammation (Iida et al., 2017). Similarly, another study showed that ciproxifan (1 mg/kg, i.p.) reduced the level of IL-1ß and IL-6 cytokines in the transgenic mouse brain of B6.129-Tg(APPSw)40Btla/J mice (Mani et al., 2017). Moreover, a recent study reported that H3R inverse agonist BF 2649, or selective H3R antagonist with partial H4R receptor agonist clobenpropit, significantly showed reduction in amyloid beta peptide (AβP) deposits along with marked reduction in neuronal or glial reactions in AβP infusion-induced brain pathology in a rat model (AD like pathology). However, clobenpropit showed superior effects than the BF2649 in this AD model. The results suggested that H3 and H4 receptor modulation may induce neuroprotective effect resulting in less deposition of the peptide and reduction in glia activation (Patnaik et al., 2018). Also, earlier preclinical findings showed that activation of brain histaminergic neurotransmission may be a mechanism for cognitive effects of memantine, an NMDA-receptor antagonist widely used for the treatment of AD (Motawaj et al., 2011), demonstrating the role of neurotransmission to NMDA receptors and in BPSD (Lin and Lane, 2019). Thus, these multiple lines of evidence demonstrate a strong impact of the histaminergic neurotransmission on modulation of microglia-induced neuroinflammation and associated pro-inflammatory cytokine expression. This may also suggest that cytokine imbalances could impact neural activity and mediate behavioral aspects of ASD. H3R antagonists may serve as potential therapeutics for ASD and other brain disorders with microglia-driven neuroinflammation, such as AD, SCH, and BPSD.

ANTAGONISTS OF HISTAMINE RECEPTOR SUBTYPES IN ASD AND OTHER NEUROPSYCHIATRIC DISORDERS

Several clinical studies revealed the positive effects of H1R and H2R antagonists in children and adolescents with ASD and suffering from behavioral and sleep disturbances (Rossi et al.,

1999; Linday et al., 2001). Moreover, numerous preclinical studies improved social behaviors and stereotyped repetitive behaviors of several imidazole- as well as non-imidazole–based H3R antagonists in different rodents (Witkin and Nelson, 2004; Esbenshade et al., 2008; von Coburg et al., 2009; Brown et al., 2013; Sadek et al., 2016b; Eissa et al., 2018a; Eissa et al., 2019), and are discussed below.

H1R Antagonists

Among numerous H1R antagonists, niaprazine with noticeable sedative properties has been clinically used in subjects with behavior and sleep disorders (Rossi et al., 1999). A promising effect was found in 52% of autistic patients with associated behavior and sleep disorders, with specific efficacy on attention deficit, hyperkinesia, rigidity, hetero-aggressiveness, mild anxiety, and sleep disturbances. Rossi et al. concluded that niaprazine can be used as a first-choice drug to improve behavior and sleep disorders in patients with ASD due to its good tolerability and the presence of sedative effects. Moreover, the clinical use of the H1R antagonist cyproheptadine was reported to decrease stereotypical behaviors and to improve expressive speech in children with ASD, when compared with a group receiving haloperidol and placebo (Gudarzi et al., 2002; Akhondzadeh et al., 2004).

H2R Antagonists

Several studies speculated that the H2R antagonist famotidine might be effective for certain ASD symptoms because it has been shown to improve certain symptoms in SCH, including improvements in eye contact avoidance, repetitive behaviors, social communication, and social interaction in children with ASD who had no history of gastrointestinal problems (Linday, 1997; Linday et al., 2001). Moreover, a very recent study showed that pretreatments of animals with famotidine prevented cell death induced by the NMDA antagonist MK-801, and therefore provided neuroprotective effects *via* modulation of the Akt/GSK-3β/β-catenin signaling pathway, an important mechanism in SCH neurobiology (Unal et al., 2019).

H3R Antagonists

H3Rs in the CNS act as presynaptic auto- or hetero-receptors that regulate the biosynthesis and release of HA and a variety of neurotransmitters form histaminergic neurons and non-histaminergic neurons, respectively. Hence, H3Rs play a role in cognitive function and homeostatic processes, as shown in (**Table 2**). This suggests that selective and potent H3R antagonists could lead to a therapeutic approach for the improvement of cognitive decline accompanied with SCH and ASD (Witkin and Nelson, 2004; Esbenshade et al., 2008; von Coburg et al., 2009; Brown et al., 2013; Sadek et al., 2016b). To date, few studies have investigated the association of H3R antagonists and the underlying mechanism for treatment of ASD behavioral deficits (**Table 2**).

Preclinical animal experiments have widely used thioperamide and ciproxifan which are selective and potent imidazole-based H3R antagonists (Ligneau et al., 1998; Stark et al., 2000; Brown et al., 2013). A preclinical study reported that thioperamide and ciproxifan reinforced the decreased prepulse inhibition in an animal model of SCH (Browman et al., 2004) (**Table 2**). Interestingly, H3R antagonists have shown to possess an antioxidant effect which could enhance their therapeutic use, since oxidative stress is considered to be involved in pathogenesis and pathophysiology of SCH and ASD (Mahmood et al., 2012). Moreover, considering the pro-cognitive effect of non-imidazole H3R antagonist ABT-288 in several preclinical models, a further study revealed that treatment of dysregulated cognitive function associated with SCH, the schizophrenic features remained constant for the duration of the study (Hsieh et al., 2010; Coruzzi et al., 2012).

H3R antagonist have also showed amelioration in spatial working memory deficit observed in animal model of SCH, a deficit which also characterizes patients with ASD (Steele et al., 2007). However, these initial data still need further research efforts to expand, corroborate, and achieve a better understanding of pathophysiology and therapeutic management of ASD.

Exploring the potential role of H3R antagonists in a number of CNS diseases like AD, epilepsy, attention deficit hyperactivity disorder (ADHD), narcolepsy (Witkin and Nelson, 2004; Savage et al., 2010; Kasteleijn-Nolst Trenite et al., 2013), SCH (Passani and Blandina, 2011; Baronio et al., 2015), and recently in TS (Rapanelli and Pittenger, 2016) and ASD (Baronio et al., 2015), suggest that H3R antagonists may be a potential therapeutic approach for treatment of several neurological disorders that are linked to cognitive impairment. Preclinical studies reported that ciproxifan, an imidazole-based H3R antagonist demonstrated improvements in hyperactivity and associated memory impairment after administration of this drug in a mouse model of AD (Bardgett et al., 2011). Treatment with JNJ-10181457, a selective non-imidazole H3R antagonist reversed cognitive deficits induced by scopolamine, and re-balanced the dysregulation of ACh neurotransmission (Galici et al., 2009). Impairments in cognitive functions that are commonly featured in ASD include self-regulation and social cognition. These allow people to appropriately regulate actions related to social issues and to make plans. H3R antagonists may have a potential role in rescuing such core symptoms of ASD (Heatherton and Wagner, 2011). Moreover, recent wakefulness clinical trials reported the successful effect of pitolisant (Wakix®), a H3R antagonist/inverse agonist marketed for the treatment of narcolepsy (Baronio et al., 2014). Pitolisant is approved by the European Medicines Agency (EMA) as well as the FDA and is the first-in-class drug to be introduced into clinics. Preclinical data suggested that pitolisant may also be a valuable drug candidate to enhance memory deficits and to treat other cognitive disorders (Ligneau et al., 2007). Pitolisant was suggested to be effective in epilepsy, which is highly comorbid with ASD (Kasteleijn-Nolst Trenite et al., 2013). Again, all these accumulated evidences support the implication of the HS in ASD. Additionally, a recent study revealed that impairments in social behavior was ameliorated by H3R antagonists in rodents exposed to phencyclidine (PCP), suggesting its therapeutic value for ASD (Griebel et al., 2012). Based on these findings, Baronio et al. assessed for the first time the effect of imidazole-based H3R antagonist ciproxifan in animal model of autism induced by maternal VPA exposure

TABLE 2 | Summary of H3R antagonists that have been in clinical and preclinical trials in ASD and related brain disorders.

Disorder	H3R antagonist	Clinical phase	Pharmacological effect	Reference
ASD	Ciproxifan	Preclinical	Improving some social impairments and stereotypies in mice.	(Baronio et al., 2015)
	DL77	Preclinical	Palliated sociability deficits and stereotypies.	(Eissa et al., 2018a)
	ABT-239	Preclinical	Improvement in social memory.	(Fox et al., 2005)
	E100	Preclinical	Ameliorated repetitive compulsive behaviors in a mouse model of ASD.	(Eissa et al., 2019)
ADHD	JNJ-31001074	Clinical	No significant improvements in adult patients.	(Weisler et al., 2012; Sadek et al., 2016c)
AD	ABT-288	Clinical	A randomized study did not demonstrate any significant improvements in mild to moderate AD dementia.	(Haig et al., 2014b)
	Ciproxifan	Preclinical	Improvement in increased locomotor activity in transgenic mice. Enhancement in memory deficit.	(Bardgett et al., 2011)
	GSK239512	Clinical	Positive improvement in episodic memory in patients with mild to-moderate AD. No improvement in executive function/working memory for subjects with mild to- moderate AD.	(Nathan et al., 2013; Grove et al., 2014)
	JNJ-10181457	Preclinical	Reversed scopolamine induced-cognitive deficits in rats. Regulated ACh neurotransmission.	(Galici et al., 2009)
Cognitive impairments	ABT-239	Preclinical	Attenuated scopolamine-induced deficits in cognitive tests in rodents. Improvement in social memory.	(Brown et al., 2013)
	A-431404	Preclinical	Ameliorated cognitive impairments induced by ketamine and MK-801.	(Brown et al., 2013)
	DL77	Preclinical	Improvement of cognitive deficits through different memory stages in rats.	(Eissa et al., 2018a)
	GSK189254 GSK207040 GSK334429 Pitolisant	Preclinical	Attenuated scopolamine-induced deficits in cognitive tests in rodents.	(Ligneau et al., 2007; Medhurst et al., 2007a; Medhurst et al., 2007b; Galici et al., 2009)
Epilepsy	DL77	Preclinical	Increased anticonvulsant activity in epilepsy models.	(Sadek et al., 2016c)
Narcolepsy	Pitolisant	Clinical	Reduced excessive daytime sleepiness.	(Baronio et al., 2014)
SCH	ABT-288	Clinical	Failed on providing cognitive improvements to patients.	(Haig et al., 2014a)
	ABT-239	Preclinical	Attenuated cognitive deficits caused by ketamine and MK-801.	(Brown et al., 2013)
	A-431404	Preclinical	Attenuated cognitive deficits caused by ketamine and MK-801.	(Brown et al., 2013)
	Ciproxifan	Preclinical	Enhancement of prepulse inhibition.	(Browman et al., 2004)
	SAR 110894	Preclinical	Normalized impaired social behavior.	(Griebel et al., 2012)
	Thioperamide	Preclinical	Enhancement of prepulse inhibition.	(Browman et al., 2004)
	Pitolisant	Preclinical	Reduced locomotor hyperactivity elicited by methamphetamine or dizolcipine. Abolished the apomorphine-induced deficit in prepulse inhibition.	(Ligneau et al., 2007)

(Baronio et al., 2015) (**Table 2**). The effect of acute administration of ciproxifan (3 mg/kg) 30 min before the behavioral test demonstrated efficacy in improving some social impairments and stereotypies in VPA mice. These results suggested that some of the main clinical alterations displayed in ASD could be improved even in adulthood, as at the stage when the tests were carried out, many changes had already occurred during brain development and have reached equilibrium. Regardless, a single application of ciproxifan was effectively enough to attenuate behavioral deficit (Baronio et al., 2015). Several imidazole-based H3R antagonists, such as ciproxifan, showed potency and selectivity in preclinical animal experiments with oral bioavailability (Ligneau et al., 1998; Stark et al., 2000). However, this class of compounds appeared to have poor CNS penetration and incidences of off-target activity at other receptors including H4R were reported. In addition, imidazole-based agents showed powerful inhibition of CYP450 isoenzymes, rendering them prone to many metabolic interactions with other drugs (Berlin et al., 2011; Panula et al., 2015; Sadek and Stark, 2016). Consequently, medicinal chemistry efforts succeeded in modification of chemical structure to generate various non-imidazole H3R antagonists with higher affinity and selectivity than the imidazole-based H3R antagonist. DL77 ([1-(3-(4-tertpentylphenoxy)propyl) piperidine) is a novel non-imidazole H3R antagonist that strongly resembles the EMA and FDA approved H3R antagonist/inverse agonist pitolisant in structure (Sadek et al., 2016a). In animal studies, DL77 showed improvements in cognitive performance by exerting its action through different memory stages (**Table 2**). A very recent preclinical study demonstrated that DL77 ameliorated cognitive deficits induced by the *N*-methyl-*D*-aspartate (NMDA) receptor antagonist MK-801 in an inhibitory passive avoidance paradigm and in novel object recognition tests in rats (Eissa et al., 2018b). These findings demonstrated the potential role of DL77 for treatment of cognitive symptoms that characterize several neuropsychiatric disorders (Sadek et al., 2016c). As mentioned earlier, social cognitive deficits are hallmark characteristic of ASD (Couture

et al., 2006). Preclinically, it was reported that DL77 had promising effect on sociability deficits and stereotypies in a VPA-induced mice model of ASD (Eissa et al., 2018a). Moreover, and in a recent preclinical study, the dual-active ligand E100 with high H3R antagonist affinity and balanced AChE inhibition demonstrated ameliorative effects on repetitive compulsive behaviors and neuroinflammation in a mouse model of VPA-induced ASD in mice (**Table 2**) (Eissa et al., 2019). In addition, ABT-239 showed improvement in social memory in rodents, an altered parameter in ASD (Fox et al., 2005) (**Table 2**). H3R antagonist DL77 provided promising anticonvulsant activity in experimental epilepsy models (Sadek et al., 2016c) (**Table 2**). It was also reported in a recent population study that 44% of children with ASD were subsequently diagnosed with epilepsy and 54% of children with epilepsy were subsequently diagnosed with ASD (Jokiranta et al., 2014). Several studies demonstrated the effectiveness of H3R antagonists in rescuing behavioral impairment including memory deficit in animal model of SCH (Steele et al., 2007), symptoms diagnosed also in patients of ASD. Preclinically, cognitive ameliorating effect of various non-imidazole-based H3R antagonists, as ABT-239 and A-431404 in experimental rats with cognitive impairments that is induced by ketamine and/or MK-801, demonstrated enhanced results in comparison with reference antipsychotics like risperidone or olanzapine (Brown et al., 2013). In addition to H3R antagonists enhancing effects on different cognitive domains in rodents, H3R antagonists, including ABT-239, GSK189254, GSK207040, GSK334429, and pitolisant, ameliorated scopolamine-induced deficits in cognitive tests in rodents (Fox et al., 2005; Ligneau et al., 2007; Medhurst et al., 2007a; Medhurst et al., 2007b). SAR110894, a potent H3R antagonist also showed efficacy in several animal models addressing certain aspects of cognitive impairments (Griebel et al., 2012) (**Table 2**). This suggests that H3R antagonists may be beneficial in neurological diseases that exhibit abnormalities related to the cognitive symptoms as in ASD. Considering all these evidences, BPSD as heterogeneous range of psychiatric behaviors and symptoms arising from the presence of dementia alongside with progressive decline in cognitive functions, suggests that H3R antagonists may function to improve BPSD through enhancing cognitive performance (Witkin and Nelson, 2004; Dekker et al., 2018) as in related AD, MCI, and ASD. Neurodegeneration in the brain consequently causes dementia, which develops slowly and gradually worsens over years. The cumulative evidences of H3R antagonists cognitive and memory-enhancing effects suggest its potential use in the treatment of neurodegenerative disorders such as AD (Fox et al., 2004; Alachkar et al., 2019). A preclinical research study reported that 3 weeks daily treatment of ciproxifan alleviated the hyperactivity and cognitive deficits observed in a transgenic mouse model (APP_{Tg2576}) of AD. These mice exhibited formation of amyloid plaques with increasing age as well as deficits in spatial learning and memory, that was displayed in significantly greater locomotor activity and longer escape latencies in swim maze test than wild-type mice. Moreover, APP_{Tg2576} mice significant impairment in the object recognition was reversed by acute treatment with ciproxifan (3.0 mg/kg). These data support the theory that H3R antagonism may represent a pathway to cognitive enhancement and memory impairments, signifying the potential of H3R antagonist in treatment of neurodegenerative diseases, including AD (Bardgett et al., 2011; Alachkar et al., 2019) (**Table 2**). Hence, H3R antagonists may serve as a viable therapeutic strategy in the treatment of BPSD. However, the efficacy of the highly selective H3R antagonist ABT-288 across several preclinical cognitive domains was not observed clinically. In a randomized study ABT-288 failed to show efficacy in subjects with mild to moderate AD dementia (Haig et al., 2014a) (**Table 2**). In a randomized, double-blind, placebo-controlled study, investigations of H3R antagonist/inverse agonist GSK239512 to assess cognitive enhancing effects showed positive results on memory, attention (Nathan et al., 2013) and displayed improvement in episodic memory in patients with mild to moderate AD. However, it failed to show any improvements on executive function/working memory or other domains of cognition (**Table 2**) (Grove et al., 2014). On the other hand, administration of JNJ-10181457, a selective non-imidazole histamine H3R antagonist significantly reversed the cognitive deficits induced by scopolamine in rats. JNJ-10181457 also demonstrated normalization of ACh neurotransmission in the rat cortex, which indicates that selective H3R non-imidazole antagonists may be very effective in conditions with decreased levels of ACh release commonly found in cognitive disorders such as AD, dementia, ASD, and SCH. These evidences may suggest promising clinical efficacy of H3R antagonists in cognitive-related disorders, specifically those in which ACh neurotransmission is compromised (Galici et al., 2009). In accordance with this, and as several lines of scientific evidence have implicated cholinergic system abnormalities in ASD, there is substantial support for the suggestion that treatments that modulate the cholinergic system might be effective in ASD (Deutsch et al., 2010; Ghaleiha et al., 2014), including H3R antagonists. The reported H3R antagonist modulation of cholinergic system and consequent ACh release normalization suggest a potential therapeutic efficacy in BPSD, as the cholinergic dysfunction seems to play a major role in contributing to BPSD (Lanari et al., 2006). Hence, among the strategies followed for optimal management of BPSD with respect to neurochemical component, the HS approach with H3R antagonists might be promising.

CONCLUSIONS

Current evidence from clinical and preclinical studies supports the hypothesis that the pathogenesis of ASD is linked to the exposure to inflammation at early developmental stages. The incomplete efficacy of the current therapy for ASD has driven an increased interest in developing of several approaches in searching for new prospective drugs. Clinical studies indicate that ASD children undergo chronic neuroinflammation in different brain regions involving activation of microglia. One of the therapeutic

approaches to control neuroinflammation is to reduce or prevent microglial activation, and to reduce the neuro-destructive effects of chronic neuroinflammatory processes, which contributes to improved developmental outcomes. There is cumulative evidence that HA plays central roles in the CNS, both on different environmental contexts. Since all four HRs are constitutively expressed on microglia, HA has well-established role as neuron-to-glia alarm signal in the brain. Considering the dual role of HA, targeting microglial activation by modulating microglial function and suppressing the deleterious pro-inflammatory neurotoxicity maybe a valid therapeutic strategy for promoting neuroprotection and managing ASD-like behaviors. However, future research efforts are still necessary to study which exact signaling pathways and HRs are involved in this histamine-induced neuroprotective role and for better understanding of the effects of HA and/or HR ligands to inhibit neuroinflammation *in vivo* in inflammatory environments. Evidence suggests that chronic neuroinflammation may be associated with cognitive deficits, and preclinical studies indicated notably that H3R antagonists/inverse agonists have been found to exhibit mitigating effects on several neuroinflammatory processes and, also, to provide cognition-enhancing properties in preclinical animal models of ASD. Further research efforts should be conducted to develop selective H3R antagonists capable of targeting the cognitive symptoms in multifactorial disorders in the field of neuropsychiatric disorders including BPSD and ASD. Identifying neuroanatomic substrates shared between ASD and dementias might accelerate the therapy development for more than one disorder.

AUTHOR CONTRIBUTIONS

NE and BS: Idea, design, writing, and submission. NE, AdS, AsS and BS: Substantial contribution to the conception, formulation, and critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

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Pharmacotherapy of Behavioral and Psychological Symptoms of Dementia: State of the Art and Future Progress

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The core symptoms of different dementia subtypes are the behavioral and psychological symptoms of dementia (BPSD) and its neuropsychiatric symptoms (NPS). BPSD symptoms may occur at any stage in the case of dementia due to Alzheimer's disease (AD), whereas they tend to occur early on in the case of its behavioral variant frontotemporal dementia or dementia with Lewy bodies and are essential for diagnosis. BPSD treatment consists of non-pharmacological as well as pharmacological interventions, with non-pharmacological interactions being suggested as first-line treatment. Agitation, psychotic features, apathy, depression, and anxiety may not respond to acetylcholinesterase inhibitors or memantine in AD cases; therefore, antipsychotics, antidepressants, sedative drugs or anxiolytics, and antiepileptic drugs are typically prescribed. However, such management of BPSD can be complicated by hypersensitivity to antipsychotic drugs, as observed in DLB, and a lack of effective pro-cognitive treatment in the case of frontotemporal dementia. The present paper reviews current knowledge of the management of BPSD and its limitations and discusses on-going clinical trials and future therapeutic options.

Keywords: behavioral and psychological symptoms of dementia, neuropsychiatric symptoms, antipsychotics, antidepressants, non-pharmacological interventions, clinical trial

INTRODUCTION

The commonly-observed core symptoms of dementia are classified as behavioral and psychological symptoms of dementia (BPSD) or as neuropsychiatric symptoms (NPS) (Zhao et al., 2016). NPS are mainly associated with Alzheimer's dementia (AD), but they can occur in various types of dementia, as well as in mild cognitive impairment (MCI) (Siafarikas et al., 2018). NPS have been recognized as a risk factor of dementia among individuals with MCI, especially when co-occuring with affective and psychotic symptoms (Liew, 2019). Moreover, cases characterized by behavioral changes and psychiatric symptoms, but without cognitive impairment in later life, have been described as mild behavioral impairment (Taragano et al., 2009); this has been recognized as an at-risk state for

cognitive decline and dementia, biomarker of cognitive decline, or even a potential manifestation of prodromal dementia (Ismail et al., 2018; Taragano et al., 2018; Creese et al., 2019). While NPSs impair the quality of life of both patient and caregiver, they seem to exert the strongest impact on the latter (Feast et al., 2016; Terum et al., 2017) and may influence the decision regarding nursing home placement (Porter et al., 2016; Vandepitte et al., 2018). In addition, together with the severity of dementia, the presence of NPS contributes to increasing care costs (Rattinger et al., 2015; Wübker et al., 2015; Rattinger et al., 2019).

NPS have a high prevalence index, and different patterns of symptoms are observed depending on the course of the illness, biological factors, diagnosis, age of onset, dementia severity, and place of residence of patients (Lyketsos et al., 2000; Tractenberg et al., 2003; Ryu et al., 2005; Ballard, 2007; Peters et al., 2012; van der Linde et al., 2012; Borsje et al., 2015; Mulders et al., 2016; van der Linde et al., 2016; Bauhuis et al., 2018; Rozum et al., 2019). A good example is AD, in which NPS are extremely common: apathy is the most frequent symptom, followed by depression, aggression, anxiety, and sleep disorder (Zhao et al., 2016). Other symptoms, such as irritability, appetite disorder, aberrant motor behavior, delusion, disinhibition, and hallucination are less common, with their prevalence ranging from 36 to 16% of AD cases. Therefore, it is necessary to implement effective strategies against NPS and their unavoidable serious consequences.

The aim of the paper is to review current knowledge, limitations, and practices regarding the management of BPSD and to discuss on-going clinical trials and future therapeutic options.

REVIEW OF CURRENT KNOWLEDGE ON BPSD MANAGEMENT

Non-Pharmacological Strategies

A number of non-pharmacological techniques are used in medicine, specifically in the late-life population, a number of which have been found to be effective at treating neuropsychiatric symptoms (Gitlin et al., 2009; Abraha et al., 2017); however, the quality of evidence for such interventions is low (Wang G. et al., 2018), and there is limited evidence for recommending their use in general (Cabrera et al., 2015). As recent papers on non-pharmacological interventions have higher reporting quality than older ones, it is likely that our knowledge on the role of non-pharmacological interventions will be steadily improved as more studies are performed (Horr et al., 2015).

Non-pharmacological approaches comprise various types of intervention: sensory stimulation (acupressure, aromatherapy, massage, touch therapy, light therapy, garden activities, music and dance therapy, and snoezelen multisensory stimulation therapy), cognitive and emotion-oriented approaches (cognitive stimulation, reminiscence therapy, validation therapy, and simulated presence therapy), behavior management techniques, multicomponent interventions, and other therapies (education of patients and caregivers, exercise, and animal-assisted therapy involving real or robotic animals) (Abraha et al., 2017). Non-pharmacological strategies were even found to be more effective than pharmacological treatments (Yury and Fisher, 2007; Brodaty and Arasaratnam, 2012; Schneider et al., 2006a) and appear to have fewer adverse effects than pharmacotherapy with antipsychotics (Dyer et al., 2018). Moreover, a meta-analysis found such interventions to prove useful, versatile, and potentially cost-effective in improving outcomes and quality of life in individuals with dementia and their carers (Olazarán et al., 2010).

However, in practice, the widespread use of nonpharmacological strategies is beset by many difficulties, the main ones being lack of trained personnel, limited knowledge on the efficacy of nonpharmacological interventions, staff opinions and preferences, and an expectation of quick resolution of symptoms (Ervin et al., 2014; Jennings et al., 2018). In addition, in the case of severe agitation, or other emergency situations where patients may be endangering themselves or others, pharmacological intervention has priority. In typical situations, current evidence suggests that nonpharmacological techniques should be used as a first-line option for NPS and that many clinical guidelines recommend starting with such management (Dyer et al., 2018).

This part of the review will focus on recent advancements in non-pharmacological management (NPM) and discuss other approaches a reader can find in previous works (see Meyer and O'Keefe, 2018).

As NPM supports mainstream therapy in alleviating symptoms and improving the quality of life of patients, both approaches should be considered as parts of a broader concept of person-centered care (PPC). PPC, by supporting the personhood of patients and understanding their experience, attempts to assist them and their family in reaching the best possible quality of life (Molony et al., 2018).

The well-being of a patient with dementia can be achieved through understanding the individual needs and history of each patient. Similarly, to successfully reduce its occurrence, the underlying cause of the symptom also has to be understood. NPS can stem either from neurocognitive impairment associated with dementia or from the unmet needs of the patient; therefore, the possible interplay between these factors should be addressed while planning intervention.

In cases of dementia where cognitive functions are impaired, patients lose their ability to communicate through language. In such cases, they can sill manifest their needs, such as pain, hunger, boredom, insecurity, or anxiety, through their behavior. However, such behavior may be influenced by their cognitive impairment, which affects the way they perceive, interpret, and react to the environment: patients may have problems with explicit memory, recognition of visual motion or spatial orientation, and topographic disorientation (Zwijsen et al., 2016). A greater understanding of the mechanisms underpinning behavior can serve as a basis for more precise interventions.

Non-pharmacological interventions can be divided into direct ones targeted at patients and indirect ones targeted at their environment (Caspar et al., 2018).

Direct interventions attempt to address the needs of the patient and can include lifestyle modification (e.g., diet, activity programs) or psychological therapy (art therapy, humor, animal, or PARO robotic pets assisted therapy); in contrast, indirect interventions involve either modification of the physical environment such as room temperature, light and noise levels, or familiarity or educating caregivers and reducing the stress and burden placed on them (Marriott et al., 2000; Soril et al., 2014).

One of the most distressing symptoms for caregivers is agitation, or aggression, which also is one of the most common reasons for antipsychotic prescription. However, antipsychotic use is associated with a high risk of adverse effects (Farlow and Shamliyan, 2017), and there is an urgent need to define efficient strategies to reduce their occurrence.

Between 45 and 80% of patients with dementia in nursing homes suffer from chronic pain. Impaired cognitive functions limit the possibility of communicating pain and thereby increase the risk of this pain of being underdiagnosed and untreated (Hadjistavropoulos et al., 2007). Similarly, lack of activity concerns up to 90% of patients with dementia residing in nursing homes: A problem that has been consequently raised by researchers since 1995 (Nolan et al., 1995; Hancock et al., 2006). Pain and boredom are important determinants of agitation (Kolanowski et al., 2017), and interventions directing them have been explored as a potential way to lower the level of agitation. In one study, nursing home residents were visited by a pair of elder-clowns for approximately 10 min, twice a week, for 12 weeks. The clowns interacted with the patients using improvisation, humor, empathy, and expressive modalities such as songs, musical instruments, and dance. At the end of the intervention, the total NPI-NH scores were found to have declined significantly, and a general reduction of agitation was observed (Kontos et al., 2016).

In another study, a group of patients treated with 8 weeks of pain management demonstrated significantly lower agitation and aggression in comparison with controls (Husebo et al., 2011; Husebo et al., 2014).

PARO robotic pets, in use since 2003, have proven successful in lowering stress, depression, and anxiety in patients with dementia. Intervention with a robotic pet three times weekly per 20 min was found to reduce the need for pain medications and psychoactive medication (Petersen et al., 2017).

No significant improvement in total NPI score was observed after 3 months of supplementation with nutraceutical formulation (NF) [folate, alpha-tocopherol, B12, S-adenosyl methionine (SAM) N-acetyl cysteine (NAC), and acetyl-L-carnitine (ALCAR)] as part of the Phase II Randomized Clinical Trial of a Nutritional Formulation for Cognition and Mood in Alzheimer's Disease (Remington et al., 2015).

Another group of interventions are those that directly focus on supporting the identity of the patients with dementia. In 2011, Caddell and Clare reviewed existing interventions and identified 10 studies aimed at promoting the preservation of patient identity. Although all interventions reported benefits to the patients, the considerable heterogeneity of patients and methodologies used in the study do not allow any firm conclusions to be drawn (Caddell and Clare, 2011). A promising area of research attempts to enhance and enrich the strategies used by patients to cope with cognitive impairment to promote well-being in the early stages of dementia. The spectrum of responses to problems with memory has been proposed to range from 'self-maintaining' to 'self-adjusting' (Clare, 2003). While patients following a self-maintaining strategy attempt to maintain the prediagnosis concept of self, those with a self-adjusting stance adapt a self-concept based on the challenges associated with the memory decline. A Preserving Identity and Planning for Advance Care (PIPAC) intervention combines these two components. The self-maintaining (reminiscence-based) component includes documenting an identity-salient role from the life history of the patient with the aim of describing what it meant to patients to "live well" in the past. The self-adjusting component is incorporated into a discussion of advance care planning (ACP), in which the patients focus on what it means for them to 'live well' in the future. They are informed about treatment options and how care decisions are made and rehearse communicating their preferences to relatives. After intervention, authors observed lower depressive symptoms and illness burden and greater quality of life and health-related indicators of well-being (Hilgeman et al., 2014).

Studies suggest that a combination of both direct and indirect non-pharmacological interventions may be essential in order to alleviate BPSD. Moreover, a recent study on health-related quality of life (HRQL) for people with dementia found antipsychotic discontinuation to have a detrimental effect on HRQL. This negative impact was, however, mitigated by social interactions (Ballard et al., 2017).

For intervention to be successful, it should consider the importance of a caring environment, i.e., the physical, built one, and the social environment, as well as care skill development and maintenance, and taking an individualized approach to each patient (Caspar et al., 2018).

Pharmacological Treatments

Currently, non-pharmacological and pharmacological management options exist for treating NPSs. Of the two, pharmacological intervention seems to be the ideal solution, mainly from the perspective of the caregiver. Oral dosage form administration is quick and easier than non-pharmacological interventions; in addition, it does not require professional staff involvement and allows the strength of the effect to be changed by increasing the dose of the drug. Moreover, in real life, some caregivers are interested in the possibility of administering the drug in the form of a solution without informing the patient.

Pharmacological interventions have many limitations in specific populations such as elderly patients with dementia and behavioral symptoms.

A key problem is the relatively small number of randomised clinical trials, most of which have been carried out on a narrowly defined indication, such as apathy, depression, or anxiety: some publications employ general terms such as *psychiatric symptoms*, while others use very detailed ones such as *apathy* in patients

with Huntington's disease. Neuropsychiatric symptoms, on the other hand, occur in the majority of types of dementia, not just Alzheimer's disease (AD). In addition to AD, studies on DLB, PDD and frontotemporal lobe degeneration have also been performed; however, many of the observations on the efficacy of psychotropics in behavioral changes are based on studies conducted in other age groups with different clinical charactristics. Most research focuses on the effectiveness of antipsychotics, mood stabilizers and antidepressants in treating NPSs, and cholinesterase inhibitors and memantine in the case of AD.

Only few drugs are indicated for treating NPSs in dementia. Tiapride is recommended for agitation in cases with dementia in Poland, and pimavanserin for psychosis associated with Parkinson's disease in the USA. In addition, risperidone is recommended for treating persistent aggression in moderate-to-severe cases of AD not responding to non-pharmacological interventions and when there is a risk of harm to the patient; however, treatment should be restricted to 6 weeks (Canada and Europe). Finally, quetiapine is recommended for psychiatric symptoms in patients with dementia; this indication is covered by public insurance in Poland (Lanctôt et al., 2017). Although prescribing psychotropic medications to a patient with dementia appears to be clinically justified, it still remains an off-label order in most countries.

Secondly, a minority of interventions with psychotropic drugs for NPSs in nursing homes is fully appropriate (van der Spek et al., 2016). A difference between correctness of use of antidepressants (used mostly appropriately) and anticonvulsants (used mostly inappropriately) was noticed. Unfortunately, for many (frequently unclear) reasons, the main method of pharmacological treatment of NPSs is based on antipsychotics. Antipsychotics are disproportionately often used in older populations (Colenda et al., 2002; Nijk et al., 2009; Gulla et al., 2016; Maust et al., 2017) for various indications, not only psychosis. Many physicians believe that antipsychotics are multipotential: they may also be effective in other clinical conditions, and their primary activity does not conern psychoses. Therefore, their prescription is reasonable in patients with delusions, hallucinations, or psychotic anxiety (Sultzer et al., 2008). Even if prescribing a neuroleptic to a person with dementia appears to be clinically justified, it still remains an off-label order in most countries (Maglione et al., 2011). In many cases, neuroleptics act mainly *via* a non-specific sedative effect and serve as a form of chemical restraint: efficacy data indicates that for all atypical antipsychotics show at best modest benefit against neuropsychiatric symptoms observed in cases with dementia (Seitz et al., 2013).

Thirdly, antipsychotics have been consistently associated with serious adverse effects and increased mortality in patients with dementia (Schneider et al., 2005; Ma et al., 2014; Schneider et al., 2006a; Kales et al., 2012; Ralph and Espinet, 2018), with the risk being dose-dependent (Maust et al., 2015). Increased mortality is related to a range of interacting factors, and the precise mechanisms of death are still uncertain. Antipsychotic treatment can result in cerebrovascular events (e.g., stroke), cardiovascular effects (e.g., orthostatic hypotension, cardiac arrhythmias, and QTc prolongation), metabolic effects, extrapyramidal symptoms and falls, as well as pneumonia (Steinberg and Lyketsos, 2012).

The growing body of evidence regarding the increased risk related to antipsychotic use among patients with dementia resulted in black box warnings being issued by the FDA for atypical drugs (in 2005) and conventional drugs (in 2008), and as experts' recommendations (Herrmann et al., 2013; Ihl et al., 2015). However, these guidelines have had little impact on prescribing psychotropics in some practices (Desai et al., 2012; Craig et al., 2016) and with positive trends in others, such as Danish residents aged ≥65 years (Nørgaard et al., 2016). The drug may often be prescribed in response to the request of a care giver, family member, or member of staff.

Finally, overuse of antipsychotics has been reported (Rios et al., 2017), and some measures for limiting such practices have been undertaken (Jessop et al., 2017; Kirkham et al., 2017).

However, while long-term antipsychotic treatment is known to be associated with an increased risk of mortality, their use may be justified by circumstances. Even if the decision to implement the treatment may be clinically justified, regular attempts to withdraw these drugs are recommended in guidelines (Azermai et al., 2012), and practical algorithms have been proposed for process of drug discontinuation (Miarons et al., 2017). Even so, withdrawal of these drugs has consequences, especially after long-term use, including the obvious risk of re-aggravation of NPSs. A meta-analysis published by Declercq et al. indicates that AD patients can be withdrawn from chronic antipsychotic medication without demonstrating detrimental effects on their behavior (Declercq et al., 2013); however, the precise effects of withdrawal on patient cognition, adverse events, quality of life, and decrease in mortality remain unknown (Van Leeuwen et al., 2018).

Agitation

Agitation is quite a common problem in patients with Alzheimer-type dementia but may also occur in other types of dementing illnesses. Although non-pharmacological treatments represent first-line options, they are often of limited efficacy. This fact may explain why various categories of psychotropic drugs are used for treatment of agitation in dementia. These include typical (promazine) and atypical antipsychotics, antidepressants, anticonvulsants, antihistaminergic drugs (hydroxyzine), and herbal preparations. Most of these are off-label psychotropic medications, because there is insufficient or no data for their efficacy and safety in patients with dementia, and their prescription is based on tradition and personal opinions of physicians. Most worryingly, their use may entail serious adverse effects (SAEs). For example, a recent Cochrane meta-analysis (Baillon et al., 2018) suggests that valproate preparations, which are widely used for "organic brain disorders", may well be ineffective at treating agitation in people with dementia. The treatment has a high rate of adverse effects, associated with possible SAEs, and hence valproate cannot be recommended for management of agitation in dementia.

Few papers have been published on the efficacy of antidepressants in agitation and psychosis in patients with dementia. A Cochrane meta-analysis concluded that the citalopram and sertraline were more effective in reducing symptoms of agitation compared to placebo in two studies (Seitz et al., 2011). SSRIs and trazodone were also found to be well tolerated when compared to typical and atypical antipsychotics. In addition, no differences were observed between antidepressants and typical or atypical antipsychotics in terms of efficacy.

A recent systematic review and meta-analysis of RCTs performed to determine the most efficacious and acceptable treatments of agitation in dementia found that haloperidol demonstrated little efficacy compared to placebo, despite its relatively widespread use for alleviating agitation (Kongpakwattana et al., 2018). In addition, dextromethorphan/quinidine and risperidone were significantly more efficacious than placebo, as were SSRIs when considered as a class, but not when analyzed individually.

Moreover, some completed randomized controlled trials (RCTs) on treating agitation in dementia of Alzheimer-type with new or repositioned drugs have been published recently (Porsteinsson and Antonsdottir, 2017). Considering the available data on drug efficacy, adverse effects, availability, and novel drug registration procedures, it seems that citalopram may be the most sensible option for many physicians in controlling agitation in AD (Porsteinsson et al., 2014). However, the treatment period should be at least nine weeks long to allow enough time for full response (Weintraub et al., 2015). An alternate algorithm of drug treatment for agitation and aggression associated with AD or mixed dementia was proposed by Davies et al. (2018). The authors recommend starting treatment with risperidone, then aripiprazole or quetiapine, followed by carbamazepine and then citalopram. In the case of citalopram prescription, it is important to be aware of the increased risk of QTc prolongation, which can be problematic in geriatric patients. Promising novel and/or repositioned drugs intended for agitation in dementia are characterized in **Tables 1** and **2**.

An alternative method of treating agitation in dementia is by electroconvulsive therapy (ECT). A recent review of papers investigating the use of ECT for treating agitation in dementia (Glass et al., 2017) identified 11 papers, with a total number of 216 patients. The studies indicate promising results in decreasing agitation in patients with dementia; however, the studies have many methodological limitations regarding the type of study, use of psychotropic medications, choice of scales, lack of control group and numer of patients, among others.

Psychotic Features

Most psychosis symptoms that occur in dementia are hallucinations and delusions, and many patients require antipsychotic treatment to deal with of such distressing psychiatric symptoms. This is especially true when a patient acts on the delusions, experiences significant fear, or if their safety is threatened.

Antipsychotics are still widely prescribed, even in cases of dementia without psychosis. While a decline of first generation antipsychotic drug prescriptions was observed following a UK National Guidance and Drug Safety Warning, by the National Institute for Health and Care Excellence, the decreasing trend in second-generation drug prescriptions has been halted by the increased prescription of risperidone (Stocks et al., 2017).

In 2016, the American Psychiatric Association published a set of Practice Guidelines on the use of antipsychotics to treat agitation or psychosis in dementia (Reus et al., 2016). The guidelines comprise 15 statements on antipsychotic use in dementia, grouped into five sections: assessment of behavioral/psychological symptoms of dementia; development of a comprehensive treatment plan; assessment of benefits and risks of antipsychotic treatment for the patient; dosing, duration, and monitoring of antipsychotic treatment; and use of specific antipsychotic medications depending on clinical context. Although Reus et al. (2016) indicate that "guidelines should not be considered as a statement of the standard of care or inclusive of all proper treatments or methods of care", such guidance regarding the method of assessing the need for antipsychotic treatment and monitoring results may nevertheless be of value to clinicians.

The efficacy and safety of the antipsychotics olanzapine, quetiapine, and risperidone in treating dementia were examined in the CATIE-AD study (Ismail et al., 2007; Sultzer et al., 2008; Schneider et al., 2006b). Other second-generation antipsychotics, such as aripiprazole and ziprasidone, have also demonstrated safety and efficacy in treating AD (De Deyn et al., 2005; Rocha et al., 2006; Mintzer et al., 2007; Streim et al., 2008), as well as in dementia with Lewy Bodies (Lee and Shen, 2017; Sugawara Kikuchi and Shimizu, 2019), where neuroleptic treatment is problematic due to neuroleptic hypersensitivity.

Currently, more data is needed to conclusively determine whether different atypical antipsychotics vary with regard to their effectiveness, or their risk of mortality or cerebrovascular events (Yunusa et al., 2019). Novel drugs such as pimavanserin in synucleinopathies and brexiprazole are undergoing evaluation in various populations of patients with dementia (**Table 1**).

Apathy

Apathy is a non-cognitive symptom and one of the most prevalent behavioral and psychological symptoms of dementia, which can be observed even at the prodromal stage (Sherman et al., 2018). It can be characterized as diminished motivation or even lack of motivation and loss of initiative. Apathy is a longlasting state that is associated with increased mortality and a substantially greater burden for caregivers (Harrison et al., 2016; Camargo et al., 2016; Nijsten et al., 2017; Terum et al., 2017); however, a Japanese study found apathy, anxiety, and depression not to seriously aggravate caregiver burnout. A higher level of burnout was related to agitation/aggression, irritability, aberrant motor behavior, and hallucinations (Hiyoshi-Taniguchi et al., 2018).

Although our understanding of the underlying neuronal basis of apathy has improved in recent years, the effectiveness of treatment is still limited (Huey et al., 2017; Lansdall et al., 2017; Ducharme et al., 2018; Fernández-Matarrubia et al., 2018; Kumfor et al., 2018). The treatment of apathy includes

TABLE 1 | Current studies on pharmacological treatment of agitation and psychosis in dementia with novel drugs [data available at: ClinicalTrials.gov (accessed June 30, 2020); filters used: agitation, psychosis, and dementia; Studies: recruiting; not yet recruiting; active, not recruiting; enrolling by invitation]; PLC, placebo; PD, Parkinson's disease; AD, Alzheimer's disease; FTD, fronto-temporal dementia.

Name	Mechanism of action	Study population	Treatment	Results/status of the study	Study ID (ClinicalTrial.gov) or reference
Pimavanserin	A selective 5-hydroxytryptamine (HT)2A receptor inverse agonist/antagonist	PD psychosis	Pimavanserin 34 mg vs. PLC	Significant improvement with pimavanserin vs. PLC (-5·79 decrease in SAPS-PD scores in pimavanserin group compared with -2·73 for PLC (difference -3·06, 95% CI -4·91 to -1·20; p=0·001; Cohen's d 0·50))	ACP-103-020; (Cummings et al., 2014)
		AD psychosis	Pimavanserin 34 mg vs. PLC	Significant improvement for pimavanserin Primary endpoint (week 6): Mean change in the Neuropsychiatric Inventory-Nursing Home version psychosis score Pimavanserin versus PLC: -3·76 points (SE 0·65) versus -1·93 points (0·63) (mean difference -1·84 [95% CI -3·64 to -0·04], Cohen's d=-0·32; p=0·045); No significant advantage for pimavanserin versus PLC at week 12 (treatment difference -0·51 [95% CI -2·23 to 1·21]; p=0·561);	ACP-103-019; (Ballard et al., 2018)
		AD psychosis	Pimavanserin 34 mg vs. PLC	Significant efficacy in patients with higher baseline severity of psychotic symptoms (delta=-4.43, Cohen's d=-0.73, p=0.011); Pimavanserin vs PLC: ≥30% improvement was 88.9% vs. 43.3% (p<0.001); ≥50% improvement was 77.8% vs. 43.3% (p=0.008);	ACP-103-019; (Ballard et al., 2019)
		Dementia-related psychosis	Pimavanserin (34 mg and 20 mg) vs. PLC	No Study Results Posted on ClinicalTrials.gov for this Study; Study has been completed, results have not been published;	NCT03325556; [ACP-103-045]; 2017-002227-13 (EudraCT Number)
		PD psychosis	A retrospective chart review	Clinical improvement in psychosis documented in 76% of patients (69/91)	(Sellers et al., 2019)
Scyllo-inositol (ELND005)	linhibition of amyloid beta peptide aggregation	Agitation and aggression in AD	A prospective, 12-week, Randomized, Double-Blind, Placebo-Controlled, Phase 2 Efficacy and Safety Study of Oral ELND005 for Treatment of Agitation and Aggression in Patients With Moderate to Severe AD	Study has been completed, results have not been published; Study Results have been posted on ClinicalTrials.gov;	NCT01735630; ELND005-AG201
		agitation and aggression in AD	36-week extension study of Study AG201	Study has been terminated, results have not been published; Study Results have been posted on ClinicalTrials.gov;	NCT01766336
Mibampator (LY-451395)	An amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor potentiator	Agitation and aggression in AD	3 mg of mibampator orally twice daily for 12 weeks (may have been reduced to 1 mg if participant was unable to tolerate) vs PLC	No significant group differences; mibampator was significantly better (p = 0.007) than PLC only on the Frontal Systems Behavior Inventory	NCT00843518; (Trzepacz et al., 2013)

(Continued)

TABLE 1 | Continued

Name	Mechanism of action	Study population	Treatment	Results/status of the study	Study ID (ClinicalTrial.gov) or reference
Lumateperone (ITI-007)	A potent 5-HT2A antagonist, a mesolimbic/mesocortical dopamine phosphoprotein modulator (DPPM) with pre-synaptic partial agonist and post-synaptic antagonist activity at D2, a glutamate GluN2B receptor phosphoprotein modulator with D1-dependent enhancement of both NMDA and AMPA currents *via* the mTOR protein pathway and an inhibitor of serotonin reuptake	Agitation in patients with dementia, wncluding Alzheimer's disease	A phase 3, 4 week, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study (ITI-007 9mg/d vs PLC)	Study terminated; no data published	NCT02817906; (Kumar et al., 2018)
ORM-12741	A potent and selective alpha-2C adrenoceptor (AR)-antagonist	Agitation/ Aggression Symptoms in AD	A randomised, 12-week, Double-blind, Placebo-controlled, Parallel Group, Multicentre Study; ORM-12741 low dose twice a day and ORM-12741 high dose twice a day vs PLC	No study results posted on ClinicalTrials.gov for this Study; study has been completed, results have not been published;	NCT02471196
MP-101 (other names: LY2979165, LY2812223)	LY2979165 is the alanine prodrug of LY2812223, a selective and potent orthosteric mGlu2 receptor agonist	Dementia-related psychosis and/or agitation and aggression	A phase 2, 10-week, double blind, placebo controlled study of MP-101 (escalating dose of MP-101 administered orally once daily, starting at 20 milligrams up to 60 milligrams vs PLC)	Study has been terminated, results have not been published (statistical futility; totality of evidence suggests study unlikely to meet endpoint); study results have not been posted on ClinicalTrials.gov;	NCT03044249

both non-pharmacological and pharmacological strategies and varies according to the type of dementia. A number of non-pharmacological interventions have been employed: music-based interventions, regular individualized one-on-one personal contact, the use of cognitive stimulation therapy, multi-sensory behavior therapy, behavioral and environmental interventions, group art therapy, the use of therapeutic conversation, reminiscent group therapy, and Snoezelen-based care (Goris et al., 2016). However, a review of existing evidence shows it to be an underexplored field (Theleritis et al., 2018).

Cholinesterase inhibitors, memantine, antidepressants, antipsychotics, psychostimulants, and drugs with various mechanisms of action have demonstrated mixed results or no efficacy at all for treating apathy in Alzheimer's disease (Sepehry et al., 2017; Ruthirakuhan et al., 2018). Agomelatine, but not paroxetine, was associated with a significant reduction of apathy in FTD (Deakin et al., 2004; Callegari et al., 2016), while bupropion was ineffective in the treatment of apathy in Huntington's disease (Gelderblom et al., 2017). Apathy is a substantial part of clinical picture of Parkinson's disease (den Brok et al., 2015), Parkinson's disease dementia, and dementia with Lewy bodies, significantly affecting the course of the disease in the case of the latter (Breitve et al., 2018). However, no efficatious treatment currently is known to exist (Santangelo et al., 2013; Holguín Lew et al., 2017).

Depression

Depression is inextricably linked to cognitive disorders and dementia. Over the years, there has been a discussion about the relationship between depression and dementia (Bennett and Thomas, 2014). On the one hand, it was postulated that depression is a risk factor or a causative factor of dementia. On the other hand, depression has been proven to be a typical presentation of the initial phases of dementia or MCI and is in fact part of the clinical picture of dementia. There is also a proposal that antidepressant treatment is responsible for the occurrence of dementia (Lee et al., 2016; Moraros et al., 2017; Wang C. et al., 2018), especially when inappropriate medication is ised (Heser et al., 2018). Regardless of neuropathological and pathophysiological conditions, depression during dementia is a significant clinical and therapeutic problem with serious consequences for the patients and caregivers.

As with all BPSD, the management of clinical depression should start with the optimization of dementia treatment. Unfortunately, while acetylcholinesterase inhibitors and memantine are effective in the symptomatic treatment of AD, current evidence suggests that they have limited efficacy for the treatment of depressive symptoms in dementia. Furthermore, non-pharmacological treatments, which are a preferred initial approach for all NPSs, have limited evidence for depressive symptoms. However, a recent review identified five modifiable relevant factors related to depression in dementia among community-dwelling individuals: pain, neuropsychiatric symptoms, cognitive decline, social isolation, and quality of life; in addition, neuropsychiatric symptoms and quality of life were found to be modifiable factors for patients living in long-term care facilities (Kubo et al., 2019). The authors conclude that

TABLE 2 | Current studies on pharmacological treatment of agitation and psychosis in dementia with repositioned drugs [data available at: ClinicalTrials.gov (accessed June 30, 2020); filters used: agitation, psychosis, and dementia; Studies: recruiting; not yet recruiting; active, not recruiting; enrolling by invitation]; PLC, placebo; PD, Parkinson's disease; AD, Alzheimer's disease; FTD, frontotemporal dementia.

Name	Mechanism of action	Study population	Treatment	Results/status of the study	Study ID (ClinicalTrial.gov) or reference
Deuterated (d6)-dextromethorphan/ quinidine (AVP-786)	Dextromethorphan - a low-affinity N-methyl-D-aspartate receptor antagonist, σ1 receptor agonist, serotonin and norepinephrine reuptake inhibitor, and neuronal nicotinic α3β4 receptor antagonist;	Agitation in patients with Alzheimer's type dementia	A phase 3, 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-design Study (AVP-786 (Dose 1) vs AVP-786 (Dose 1) Vs PLC)	Ongoing (study is recruiting participants)	NCT03393520
	Quinidine - an anti-arrhythmic agent blocking voltage-gated sodium channels, inhibitor of cytochrome P450 2D6; Quinidine increases the bioavailability of dextromethorphan and prolongs its effects	Agitation in patients with Alzheimer's type dementia	A phase 3, multicenter, long-term, extension study for 56 weeks	Ongoing (study is recruiting participants)	NCT02446132
		Agitation in patients with Alzheimer's type dementia	A phase 3, 12-week, multicenter, randomized, double-blind, placebo-controlled Study	Study has been completed, results have not been published;	NCT02442778
Brexpiprazole (OPC-34712)	Second generation antipsychotic	Agitation associated with Alzheimer's type dementia	A phase 3, 12-week, multicenter, randomized, double-blind, placebo-controlled, fixed-dose trial (three arms: Low Dose Brexpiprazole Arm vs. High Dose Brexpiprazole Arm vs PLC)	Ongoing (study is recruiting participants)	NCT03548584
		Agitation associated with Alzheimer's type dementia	A phase 2/3 multicenter, placebo-controlled, randomized, double-blind, parallel-group Comparison Trial (brexpiprazole 1 mg vs. brexpiprazole 2 mg vs. PLC for 10-week treatment regimen)	Ongoing (study is recruiting participants)	NCT03620981
		The long-term safety and tolerability of oral brexpiprazole in agitation associated with Alzheimer's type dementia	A 12-week, multicenter, active-treatment extension trial to evaluate the safety and tolerability of brexpiprazole; brexpiprazole oral tablet 2 mg/day vs. Oral tablet 3 mg/day; taken once daily.	Ongoing (study is recruiting participants)	NCT03594123
		Agitation associated with Alzheimer's type dementia	A multicenter, oncontrolled, open-label trial of brexiprazole 1 mg or 2 mg for a 14 week treatment regimen	Ongoing (study is recruiting participants)	NCT03724942
Prazosin	Postsynaptic alpha-1 adrenoreceptor antagonist	Disruptive agitation in AD	Oral prazosin hydrochloride capsules will be administered twice daily, with individualized doses up to a maximum of 4 mg mid-morning and 6 mg at bedtime, or matching PLC capsules	Ongoing (active, not recruiting)	NCT03710642
		Agitation/aggression in AD	Prazosin (drug was initiated at 1 mg/day and increased up to 6 mg/day using a flexible dosing algorithm) vs. PLC for 8 weeks	Prazosin was well tolerated and improved behavioral symptoms in patients with agitation/aggression in AD	NCT00161473; (Wang et al., 2009)
		Disruptive agitation in AD	Prazosin: 4 mg capsules twice daily for 12 weeks vs. PLC capsules twice daily for 12 weeks	Study has been completed, results have not been published; study results have been posted on ClinicalTrials.gov;	NCT01126099
Cannabinoids	Ligands of cannabinoid receptors CB1 and CB2	Dementia related agitation and aggression	A phase 2, Randomized, Double-blind, Placebo-controlled Trial (cannabis oil containing Δ9-Tetra-Hydrocannabinol (Δ9-THC) and Cannabidiol (CBD) in a 1:20 ratio and at a concentration of 30% CBD and 1.5% Δ9-THC. Each oil drop contains about 12 mg CBD and 0.6 mg Δ9-THC)	Ongoing (study is recruiting participants)	NCT03328676
Mirtazapine	Noradrenergic and specific serotonergic tetracyclic antidepressant (NaSSA)	Agitation in dementia	A Pragmatic, Multi Centre, 12-week, Double-blind, Placebo Controlled Randomised Trial of mirtazapine vs. PLC. Participants will then be followed up for 1 year after	Ongoing (active, not recruiting)	NCT03031184

(Continued)

TABLE 2 | Continued

Name	Mechanism of action	Study population	Treatment	Results/status of the study	Study ID (ClinicalTrial.gov) or reference
Lithium	Mood stabilizer; exact mechanism of action in mood regulation has not been clarified; inhibitor of glycogen synthase kinase 3β (GSK3)	Behavioral symptoms in FTD	A phase 2, 12-week, double blind, placebo controlled study of Lithium (escalating dose of lithium, starting at 150 mg/day, with subsequent dose titration to 300, 450, and 600 mg/day as tolerated according to side effects and blood lithium level)	Ongoing (study is recruiting participants)	NCT02862210
		Psychosis and agitation in AD	A phase 2, randomized, double-blind, placebo-controlled, 12-week trial of lithium (escalating dose of lithium, starting at 150mg/day, with subsequent dose titration to 300mg/day at the 2-week visit, 450mg/day at the 4-week visit, and 600mg/day (maximum daily dose) if tolerated and based on real lithium blood level)	Study has been completed, results have not been published; study results have been posted on ClinicalTrials.gov;	NCT02129348
Escitalopram	Selective serotonin reuptake inhibitor	Agitation in AD	a phase 3, randomized, double-blind, placebo-controlled, 12-week trial (5-15 mg/day (target: 15mg/day if tolerated) of escitalopram vs. PLC)	Ongoing (study is recruiting participants)	NCT03108846; S-CitAD

non-pharmacological interventions improving identified relevant factors may improve symptoms of depression in patients with dementia. Moreover, symptoms of depression and anxiety can be reduced by psychological interventions added to usual care (Orgeta et al., 2014; Orgeta et al., 2015).

While planning to implement non-pharmacological interventions for depression in patients with dementia, it should be considered that the presence of depression may be an important barrier to engagement in therapy, for example, physical activity (Watts et al., 2018).

In the majority of patients, however, pharmacological treatment is the basis of therapy.

A practical question arises whether there is sufficient evidence for recommending the use of pharmacotherapy in treating depression in patients with dementia (Farina et al., 2017; Ford and Almeida, 2017). Serotonergic drugs are a basic option in the treatment of mood disorders in the general population. It seems that they are also a good option for mood disorders in people with cognitive impairment and dementia (Magierski and Sobow, 2016). However, a recent Cochrane meta-analysis found little support for the efficacy of antidepressants for treating depression in dementia (Dudas et al., 2018).

Sleep Problems

Sleep disorders in patients with dementia are frequent, affecting between 25 and 80% of patients; these figures are higher than those associated with healthy aging and are believed to result from neurodegenerative processes (Ohayon et al., 2004; Bombois et al., 2010). The consequences of abnormal sleep in general population are increased risk of cognitive impairment and dementia (Bubu et al., 2017; Shi et al., 2018), but in patients with dementia, consequences include comorbidity, risk of falling, poorer quality of life, and increased psychological, physical, and financial burdens in the caregiver. In addition, sleep disorders are the primary risk factor for nursing home placement, even more so than cognitive impairment. Finally, they often aggravate the course of dementia through drowsiness during the day, thus impairing cognitive performance, driving, and social activities (Tractenberg et al., 2005).

Different sleep disorders are observed depending on the type of dementia (Roth, 2012). Alzheimer's disease is characterized by an irregular sleep-wake rhythm, sundowning, wandering, and obstructive sleep apnea. PDD is characterized by REM sleep behavior disorder, sleep maintance insomnia, hypersomnia, restless leg syndrome/periodic limb movements in sleep, while DLB patients demonstrate REM sleep behavior disorder, hypersomnia, periodic limb movements in sleep, and irregular sleep-wake rhythms. Similarly, those observed in FTDs include insomnia, excessive daytime sleepiness, sleep disordered breathing, and less frequent restless leg syndrome (McCarter et al., 2016).

It is difficult, or even impossible, to propose a universal method of treating sleep disorders in dementia due to this significant variation in clinical picture and neuropathology. Popular drugs for sleep disturbances in dementia include melatonin, trazodone, benzodiazepines, Z-drugs (zolpidem, zopiclone, and zaleplon), and recently registred ramelteon. At this point, it is necessary to recall that elderly benzodiazepine users became more sensitive to their medications. Paradoxical

excitement (increased anxiety, acute excitement, and hyperactivity) can be observed in some cases. Moreover, the Z-drugs have documented night time unrecalled events, which may endanger other residents, and ramelteon may have a delayed onset for therapeutic effects of days. Other treatment modlaities include antihistaminergic drugs, herbal preaprations, or antidepresants (for example, mianserine and mirtazapine). A Cochrane meta-analysis examining the efficacy of pharmacotherapies for sleep disturbances in dementia found a lack of evidence regarding the issue of sleep problems in dementia (McCleery et al., 2016).

NETWORK META-ANALYSES FOR PHARMACOLOGICAL AND NON-PHARMACOLOGICAL TREATMENTS OF BPSD

A sizable numer of papers have been published on the effectiveness of different strategies targeting BPSD. As a result, both pharmacological and non-pharmacological methods are recommended through guidelines. Due to the diversity and extensiveness of interventions (exercise versus reminiscence therapy versus antipsychotic use) and the lack of head-to-head trials, it is difficult or even impossible to synthesize and objectify present data. This applies especially to descriptive literature reviews. Network meta-analysis solves this problem, because it allows findings to be analyzed quantitatively and for direct and indirect evidence to be evaluated simultaneously.

Several systematic reviews and network meta-analyses on the efficacy of different strategies for BPSD treatment were published recently. These publications examine the effectiveness of various therapeutic options and make head-to-head comparisons of the effectiveness of the tested drugs (Kongpakwattana et al., 2018).

A comparison of pharmacological and nonpharmacological interventions for treating aggression and agitation in adults with dementia (Watt et al., 2019) found showed that multidisciplinary care, massage and touch therapy, and music combined with massage and touch therapy were clinically more efficacious than usual care. Despite the study limitations, including high risk of bias related to outcome missing data, it was found that nonpharmacological interventions seemed to be more efficacious than pharmacological interventions for reducing aggression and agitation in adults with dementia. However, the study did not evaluate the harm and costs of the analyzed therapies. The effectiveness of non-pharmacological methods in managing of agitation in patients with dementia has also been confirmed elsewhere (Leng et al., 2020).

Another assessment of the comparative efficacy and safety of pharmacological and non-pharmacological therapies for treating BPSD (Jin and Liu, 2019) based on data from 146 randomized trials comprising 44,873 patients found that the antipsychotics aripiprazole, haloperidol, quetiapine, and risperidone demonstrated significant efficacy compared to placebo, while memantine, galantine, and donepezil have had the least. Importantly, all drugs were found to demonstrate acceptable safety, and the authors conclude that drug therapy should be the first option in the treatment of BPSD.

Similar results were obtained from a Bayesian network meta-analysis on the efficacy of cholinesterase inhibitors in patients with mild-to-moderate AD by Kobayashi et al. (2016) who conclude that ChEIs should have significant efficacy for cognition and global change assessment, but the efficacy on BPSD is questionable.

PROMISING THERAPEUTIC OPTIONS OF BPSD

As current strategies for the management of NPSs often lack effectifveness, there is a need to identify other treatment options. Although most studies focus on pharmacological interventions, some involve techniques known for their efficacy in a other clinical field. Noninvasive brain stimulation methods such as repetitive transcranial magnetic stimulation, (rTMS) and transcranial direct current stimulation (tDCS) have been tested in depression, schizophrenia, autism, and cognitive deficits in AD and MCI (Wei et al., 2017; Barahona-Corrêa et al., 2018; Cruz Gonzalez et al., 2018; Osoegawa et al., 2018). A meta-analysis of randomized controlled trials found rTMS protocols to demonstrate efficacy but not tDCS (Vacas et al., 2018); however, both were found to demonstrate safety and tolerability in the studied population.

SUMMARY

BPSD are a significant problem in everyday clinical practice due to the prevalence, severity of symptoms, burden on the caregiver, and difficulties in treatment. Many existing clinical guides recommend the use of non-pharmacological methods as the first course of action, and that pharmacotherapy should be used as a secondary option or when there is severe presentation of symptoms. In practice, a range of drugs are used, although most are antipsychotics. Unfortunately, many of the pharmacological options lack strong evidence from clinical trials confirming their effectiveness, and many others are used as off-label treatments.

AUTHOR CONTRIBUTIONS

RM and TS determined the outline. RM, ES, and DR reviewed the literature and wrote the manuscript. TS and DR reviewed and approved the manuscript.

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