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Association between CNS-active drugs and risk of Alzheimer's and age-related neurodegenerative diseases

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Objective: As neuropsychiatric conditions can increase the risk of age-related neurodegenerative diseases (NDDs), the impact of CNS-active drugs on the risk of developing Alzheimer's Disease (AD), non-AD dementia, Multiple Sclerosis (MS), Parkinson's Disease (PD) and Amyotrophic Lateral Sclerosis (ALS) was investigated.

Research design and methods: A retrospective cohort analysis of a medical claims dataset over a 10 year span was conducted in patients aged 60 years or older. Participants were propensity score matched for comorbidity severity and demographic parameters. Relative risk (RR) ratios and 95% confidence intervals (CI) were determined for age-related NDDs. Cumulative hazard ratios and treatment duration were determined to assess the association between CNS-active drugs and NDDs at different ages and treatment duration intervals.

Results: In 309,128 patients who met inclusion criteria, exposure to CNS-active drugs was associated with a decreased risk of AD (0.86% vs 1.73%, RR: 0.50; 95% CI: 0.47-0.53; $p < .0001$) and all NDDs (3.13% vs 5.76%, RR: 0.54; 95% CI: 0.53-0.56; $p < .0001$). Analysis of impact of drug class on risk of AD indicated that antidepressant, sedative, anticonvulsant, and stimulant medications were associated with significantly reduced risk of AD whereas atypical antipsychotics were associated with increased AD risk. The greatest risk reduction for AD and NDDs occurred in patients aged 70 years or older with a protective effect only in patients with long-term therapy (>3 years). Furthermore, responders to these therapeutics were characterized by diagnosed obesity and higher prescriptions of anti-inflammatory drugs and menopausal hormonal therapy, compared to patients with a diagnosis of AD (non-responders). Addition of a second CNS-active drug was associated with greater reduction in AD risk compared to monotherapy, with the combination of a Z-drug and an SNRI associated with greatest AD risk reduction.

Conclusion: Collectively, these findings indicate that CNS-active drugs were associated with reduced risk of developing AD and other age-related NDDs. The exception was atypical antipsychotics, which increased risk. Potential use of

combination therapy with atypical antipsychotics could mitigate the risk conferred by these drugs. Evidence from these analyses advance precision prevention strategies to reduce the risk of age-related NDDs in persons with neuropsychiatric disorders.

KEYWORDS

CNS-active drugs, Alzheimer's disease, retrospective analysis, neurodegenerative diseases, responder analysis

1 Introduction

Neuropsychiatric disorders, while common among age-associated neurodegenerative diseases (NDDs), can be a harbinger of the disease and emerge during the prodromal phase of Alzheimer's disease (AD) (1–3), Parkinson's disease (PD) (4, 5), Multiple Sclerosis (MS) (6, 7) and Amyotrophic Lateral Sclerosis (ALS) (8). Their emergence during the prodromal phase is suggestive of shared pathological drivers of neuropsychiatric and neurodegenerative diseases.

Neuropsychiatric disorders share common features of NDDs, particularly with AD, including increased oxidative stress, inflammation, disruption of the excitatory/inhibitory balance, and protein aggregation (9–21). Chief among these features are beta amyloid deposition and tau hyperphosphorylation and accumulation, which have been observed in depression, insomnia, and epilepsy (13, 22–26).

Signature pathological hallmarks of AD are seen in depression patients including beta amyloid deposition, tau accumulation, chronic inflammation, and deficits in nerve growth factors, particularly brain-derived neurotrophic factor (BDNF) (22, 23, 14, 11, 16, 27, 28). The serotonergic system, implicated in both conditions, influences non-amyloidogenic amyloid precursor protein (APP) release and neuroplasticity processes, while disruption of the noradrenergic system affects inflammation, amyloid deposition, and neuroprotection (29, 30, 31, 27, 32, 33). Long-term poor sleep quality and AD share common features including chronic inflammation, a reduction of neurotrophic factors including BDNF, alterations in blood-brain barrier (BBB) permeability, and accumulation of amyloid beta in the brain (12, 34, 35, 13, 36). Epileptic patients exhibit elevated tau and amyloid beta levels, possibly linked to disturbances in the excitatory/inhibitory balance (24, 25, 21, 37, 38). Schizophrenia, though not directly linked to amyloid beta pathology, shares a reduction in white matter tract integrity with AD, and patients face higher exposure to risk factors for cognitive decline (39, 40). Attention-Deficit and Hyperactivity Disorder (ADHD) has been associated with increased AD risk in epidemiological and genetic studies (41, 42), yet the underlying mechanisms remain unclear and require further investigation.

The retrospective cohort study reported herein investigated the association between CNS-active drugs, including antidepressants, sedatives, anticonvulsants, antipsychotics, and stimulants, and the incidence of AD and other NDDs including non-AD dementia, PD, MS, and ALS in patients 60 years of age or older. For this analysis, the risk of developing AD or other NDDs starting one year after exposure to CNS-active drugs was assessed using the Mariner US-based population insurance claims dataset. Pharmacologic interventions prescribed to treat neuropsychiatric disorders including antidepressants, sedatives, anticonvulsants, antipsychotics, and stimulants are categorized as CNS-active-drugs. These therapies modulate neurotransmitter signaling through multiple mechanisms that can impact neurodegenerative processes and potentially modulate the risk of developing AD and other NDDs (43–51). Secondary analyses to evaluate the impact of age and duration of treatment were conducted. Moreover, we identified and characterized patients who remained free of AD after drug exposure (responders) and those who developed AD (non-responders).

AD is a progressive disease characterized by impaired cognitive function that ultimately results in loss of autonomy and independent living (52–54). Currently, more than 6 million Americans are affected by AD which, along with other dementias, cost the nation \$321 billion dollars in 2022 (54). Presently, select anti-amyloid therapies can slow progression of the disease at early stages (55, 56) but a cure for AD remains elusive. The preclinical phase of AD can begin two decades prior to diagnosis and represents a pivotal window for implementing preventative strategies that target risk factors.

2 Research design and methods

2.1 Data source

The Mariner dataset used for this analysis contains insurance claims data within the United States, with a population primarily residing in the Southeastern region. The Mariner dataset contains patient demographic characteristics, prescription records, patient diagnosis, and procedure information organized under *Current*

Procedural Terminology, International Classification of Diseases, Ninth Revision (ICD-9), and International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes (Supplementary Tables S1, S2), following the International Classification of Diseases. In September 2022, the Mariner database included 151 million patients with claims that went from 2010 to April 2021.

PearlDiver is a research software that facilitates interaction with individual commercial, state-based Medicaid, Medicare stand-alone prescription drug plan, group Medicare Advantage, and individual Medicare Advantage data sets (57).

This report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. This study was approved by the University of Arizona Institutional Review Board. Requirements for informed consent were waived as the data were deidentified.

2.2 Study design and variables

A subset of patients with non-melanoma skin cancer was selected for medical informatic analysis from the Mariner database as this medical condition is not associated with neurodegenerative disease and treatment for the condition does not require chemotherapy or surgical anesthesia for treatment which can impact risk of Alzheimer's and occurs with sufficient frequency in the general population to enable robust analyses. Patients younger than 60 years of age, with a history of neurosurgery or brain cancer, and with a history of NDD (including AD, dementia, MS, PD, and ALS) prior to the index date were excluded from this analysis. Participants were required to be continuously enrolled in the medical and pharmacy insurance database for a minimum of 6 months before and 3 years after the index date (Figure 1). The index date is described as the first drug prescription record for the treatment group, and a period of 6 months minimum after the first patient claim record for the control group. The treatment group was defined as patients with a medication charge for at least one CNS-active drug, while the control

group included patients without any CNS-active drug medication charge throughout the duration of the study. The primary outcome of the study was defined as the incidence of AD, based on ICD-9 and ICD-10 codes, at least 1 year after the index date. The 1-year period is to remove potential unknown effects on NDDs prior to index date. Additionally, incidence of other NDDs including non-AD dementia, MS, PD and ALS was surveyed as exploratory endpoints. Medications considered in the study include FDA-approved antidepressants, sedatives, anticonvulsants, antipsychotics, and stimulants (Supplementary Table S3). These drugs were identified by drug codes and then grouped under categories according to their mechanism of action (Supplementary Table S1). Age in the treatment group was defined by the age of first CNS-active drug exposure. Following the analysis in (58) and (59) an assessment of comorbidities known to be associated with AD outcomes was conducted. The impact of CNS-active drug duration on the risk of AD was evaluated as described in (60), where analyses were conducted for durations of <1 year, 1 to 3 years, 3 to 6 years, and >6 years. Cumulative hazard ratios were built using the propensity score matched population in the Bellwether-PearlDiver interface. The average follow-up time was 6.6 [2.4] years. The number of patients in each drug class and subclass, and the median adherence rate for each therapeutic are reported in Supplementary Table S3. A responder analysis was conducted including selected comorbidities known to be associated with AD and other age-related NDDs (61–64). Common co-therapies that have been previously identified as potential AD risk modifiers were also assessed (58–60, 65–68). The drug groups included were antidiabetics, antihypertensives, anti-inflammatories, Selective Estrogen Receptor Modulators (SERMs), Androgen Deprivation Treatments (ADTs), statins and Menopausal Hormonal Treatment (MHT) (Supplementary Table S1).

2.3 Statistical analysis

Statistical analyses were conducted between May 1st and July 28th, 2022. Patient demographic statistics and incidence statistics

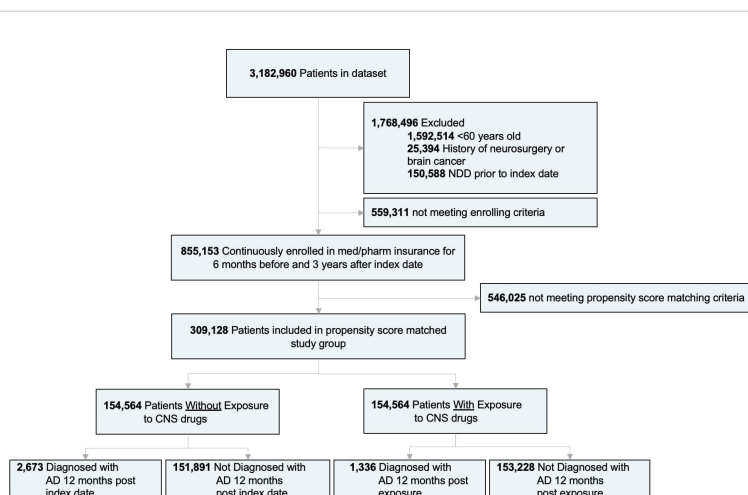


FIGURE 1

Study design and patient stratification. (AD), Alzheimer's disease; (NDDs), neurodegenerative diseases.

were analyzed using unpaired and paired two-tailed t-tests or χ^2 tests, as appropriate, to test the significance of the differences between continuous and categorical variables. In all analyses, a two-sided $p < 0.05$ was considered statistically significant.

To balance demographic and comorbidity characteristics between the treatment and control groups, propensity score matching was conducted as described in (58, 59). A logistic regression was generated prior to propensity score matching to estimate the probability for each patient to receive CNS-active drug therapy given confounding variables like age, sex, region, Charlson Comorbidity Index (CCI) score, and comorbidities of interest. The confounding variables that showed statistically significant differences were used to propensity score match the treatment and control groups; these comprised all the demographic variables as well as comorbidities including Asthma, COPD, Cardiac Arrhythmia, Cerebrovascular Disease, Chronic Artery Disease, Diabetes, Drug Abuse, Hypertension, Hypothyroidism, Liver Disease, Obesity, Osteoarthritis, Rheumatoid Arthritis, Tobacco Use, Acute Kidney Injury, and Capsulitis.

3 Results

Of 3,182,960 patients, a subset of 855,153 met the inclusion and enrollment criteria (Figure 1). After adjusting based on age, sex, region, and selected comorbidities, a population of 309,128 patients was equally divided into treatment (mean age [SD]: 66.1 [4.0] years) and control groups (66.1 [4.0] years) (N:154,564). There were no significant differences ($p > 0.05$) on age, sex, or region between adjusted treatment and control groups (Table 1). Although the CCI was not significantly different, patients on CNS-active drugs had significantly greater incidence of comorbidities ($p < 0.0001$) (Table 1).

The majority of patients in the treated group were exposed to either sedatives (38.86%) or antidepressants (33.28%), where the most prevalent drugs were Selective Serotonin Reuptake Inhibitors (SSRIs) (19.56%) and benzodiazepines (BDZPs) (26.73%), respectively (Supplementary Table S3). The median adherence for all drug subclasses was greater than 60% except for Z-drugs and BDZPs, which had a 43.34% and 15.33% median adherence, respectively (Supplementary Table S3).

Overall, exposure to CNS-active drugs in the propensity score matched population was associated with a significant decrease in the incidence of AD (0.86% vs 1.73%, RR: 0.50; 95% CI: 0.47-0.53; $p < 0.0001$) and other NDDs (3.13% vs 5.76%, RR: 0.54; 95% CI: 0.53-0.56; $p < 0.0001$) compared to untreated patients (Supplementary Figure S1, Supplementary Table S4). The number of patients required to treat to reduce the risk of AD was 115 and for all NDDs combined was 38 (Supplementary Figure S1, Supplementary Table S4). Sex differences analysis revealed that women treated with CNS-active drugs exhibited a significantly greater NDD risk reduction (RR: 0.50; 95% CI: 0.48-0.53; $p < 0.0001$) compared to men (RR: 0.59; 95% CI: 0.56-0.61; $p < 0.0001$), which was driven by non-AD dementia (Supplementary Figure S2).

To evaluate the association between each CNS-active drug class and AD risk, the treated group was subdivided into five drug

classes including antidepressants, sedatives, anticonvulsants, antipsychotics, and stimulants. Stimulants were associated with the greatest risk reduction (0.31% vs 1.73%, RR: 0.18; 95% CI: 0.10-0.32; $p < 0.0001$) followed by anticonvulsants (0.60% vs 1.73%, RR: 0.35; 95% CI: 0.32-0.39; $p < 0.0001$), sedatives (0.66% vs 1.73%, RR: 0.38; 95% CI: 0.35-0.42; $p < 0.0001$), and antidepressants (0.90% vs 1.73%, RR: 0.52; 95% CI: 0.48-0.56; $p < 0.0001$) (Table 2, Figure 2A). Antipsychotics were associated with increased AD risk compared to the non-exposure group (2.15% vs 1.73%, RR: 1.24; 95% CI: 1.07-1.44; $p < 0.005$) (Table 2, Figure 2A). Analysis of sex differences indicated that sedatives were associated with significantly greater AD risk reduction in women (RR: 0.34; 95% CI: 0.30-0.38; $p < 0.0001$) compared to men (RR: 0.44; 95% CI: 0.39-0.50; $p < 0.0001$), whereas antipsychotic association with increased risk of AD was significant only in males (RR: 1.38; 95% CI: 1.12-1.70; $p = 0.003$) (Figure 2B).

To determine the impact of specific drugs within a class on AD risk, each drug category was further divided into subclasses. For antidepressant medications, SSRIs were associated with the lowest risk reduction (1.02% vs 1.73%, RR: 0.59; 95% CI: 0.54-0.65; $p < 0.0001$), followed by tricyclics and tetracyclics (0.82% vs 1.73%, RR: 0.47; 95% CI: 0.41-0.55; $p < 0.0001$), SSRI/Serotonin Partial Agonists (0.84% vs 1.73%, RR: 0.49; 95% CI: 0.27-0.87; $p = 0.010$) and Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs) (0.51% vs 1.73%, RR: 0.30; 95% CI: 0.24-0.36; $p < 0.0001$). Within the sedatives category, Z-drugs (0.43% vs 1.73%, RR: 0.25; 95% CI: 0.21-0.29; $p < 0.0001$) were associated with a significantly greater risk reduction than BDZPs (0.64% vs 1.73%, RR: 0.37; 95% CI: 0.33-0.41; $p < 0.0001$), which corresponded to the greatest risk reduction among all the drug types assessed. First generation anticonvulsants (0.69% vs 1.73%, RR: 0.40; 95% CI: 0.27-0.58; $p < 0.0001$) and second generation anticonvulsants (0.60% vs 1.73%, RR: 0.35, 95% CI: 0.31-0.39; $p < 0.0001$) exhibited a similar risk reduction profile, with the latter inducing slightly greater AD risk reduction as well as reduced variance. Notably, atypical antipsychotics were associated with an increased risk of developing AD (2.37% vs 1.73%, RR: 1.37; 95% CI: 1.18-1.59; $p < 0.0001$) while typical antipsychotics showed no significant change in the association of developing AD (1.27% vs 1.73%, RR: 0.73; 95% CI: 0.49-1.09; $p = 0.13$) (Figure 3).

Cumulative hazard ratios with 95% CI were generated from the propensity score matched population to evaluate the rate of disease conversion for AD and all NDDs combined. In patients aged 60 to 65 years old, there were no differences between patients with exposure to CNS-active drugs and the control group. However, as age increased, divergence between both groups was greater, with the non-exposure group showing increased risk of developing NDDs and AD compared to the treatment group. The greatest divergence occurred in the oldest group, in patients aged 75 to 79 years old (Figure 4). Interestingly, sex differences occurred in patients aged 70 years and older. Females with no exposure to CNS-active drugs had higher risk of developing NDDs and AD compared to males. In contrast, there were no differences in the rate of disease conversion between both sexes in the treated group (Figure 5).

The impact of duration of therapy on risk of developing AD and all NDDs combined was determined for patients with exposure to CNS-active drugs in the propensity score matched population

TABLE 1 Baseline characteristics for unadjusted and propensity score-matched patients with or without exposure to CNS active drugs.

	UNADJUSTED COHORT					PROPENSITY SCORE MATCHED COHORT				
	Without Exposure to CNS drugs		With Exposure to CNS drugs		p value	Without Exposure to CNS drugs		With Exposure to CNS drugs		p value
	n	%	n	%		n	%	n	%	
Number of Patients	252,972		602,181			154,564		154,464		
Age										
60 to 64	64,761	25.60%	287,930	47.81%	0.166	51,147	33.11%	51,147	33.11%	>0.999
65 to 69	57,166	22.60%	108,841	18.07%		34,685	22.46%	34,685	22.46%	
70 to 74	83,434	32.98%	158,592	26.34%		51,071	33.06%	51,071	33.06%	
75 to 79	47,611	18.82%	46,818	7.77%		17,661	11.43%	17,661	11.43%	
Sex										
Female	112,942	44.65%	351,186	58.32%	0.222	75,862	49.08%	75,862	49.11%	>0.999
Male	140,030	55.35%	250,995	41.68%		78,702	50.92%	78,702	50.95%	
Region										
Midwest	56,975	22.52%	126,147	20.95%	0.058	32,880	21.27%	32,880	21.29%	>0.999
Northeast	64,594	25.53%	131,900	21.90%		36,480	23.60%	36,480	23.62%	
South	94,853	37.50%	258,840	42.98%		64,552	41.76%	64,552	41.79%	
West	36,279	14.34%	84,748	14.07%		20,624	13.34%	20,624	13.35%	
Unknown	271	0.11%	546	0.09%		28	0.02%	28	0.02%	
Comorbidities										
Cardiovascular Disease	5,366	2.12%	48,060	7.98%	<.0001	2,255	1.46%	8,048	5.21%	<.0001
Chronic Kidney Disease	5,230	2.07%	50,239	8.34%	<.0001	1,948	1.26%	8,132	5.26%	<.0001
COPD	3,171	1.25%	50,002	8.30%	<.0001	1,170	0.76%	5,812	3.76%	<.0001
Diabetes	7,385	2.92%	54,558	9.06%	<.0001	3,386	2.19%	8,690	5.63%	<.0001
Hypercholesterolemia	11,954	4.73%	80,438	13.36%	<.0001	6,983	4.52%	17,127	11.09%	<.0001
Hypertension	19,982	7.90%	118,033	19.60%	<.0001	12,632	8.17%	29,609	19.17%	<.0001
Obesity	6,835	2.70%	71,387	11.85%	<.0001	6,113	3.95%	10,124	6.55%	<.0001
Stroke	4,738	1.87%	39,117	6.50%	<.0001	2,106	1.36%	6,781	4.39%	<.0001
Tobacco Use	4,914	1.94%	39,442	6.55%	<.0001	2,325	1.50%	5,612	3.63%	<.0001
CCI										
0-4	238,082	94.11%	565,322	93.88%	0.385	152,868	98.97%	152,867	98.97%	>0.999
5-10ASDASD	13,864	5.48%	34,037	5.65%		1,685	1.09%	1,686	1.09%	
11+	1,013	0.40%	2,804	0.47%		11	0.01%	11	0.01%	

(AD), Alzheimer’s disease; (CCI), Charlson Comorbidity Index; chronic (COPD), obstructive pulmonary disease.

(Table 3). Within the exposure group, the majority of patients received treatment for 6 years or longer (44.21%). In patients receiving CNS-active drugs for 3 years or more, CNS-active drugs were associated with a significant reduction in AD and NDD risk. Patients receiving CNS-active drugs for over 6 years exhibited the highest risk reduction in AD (RR: 0.22; 95% CI: 0.20 – 0.25; p <0.0001) and NDD (RR: 0.28; 95% CI: 0.27 - 0.30; p <0.0001). In contrast, when treatment duration was less than 3 years, no

benefit on AD or NDD risk reduction was detected. A significant increase in AD risk occurred in patients exposed to CNS-active drugs for less than 1 year (RR: 1.23; 95% CI: 1.04-1.47; p = 0.02) as well as an increased risk for NDDs in patients receiving treatment from 1 to 3 years (RR: 1.09; 95% CI: 1.03-1.16; p = 0.0025) (Table 3).

A responder analysis was conducted to characterize patients who remained free of AD after CNS-active drug exposure (responders) versus patients who developed AD (non-responders)

TABLE 2 Relative risk of AD development in propensity score matched patients after exposure to different classes of CNS-active drugs.

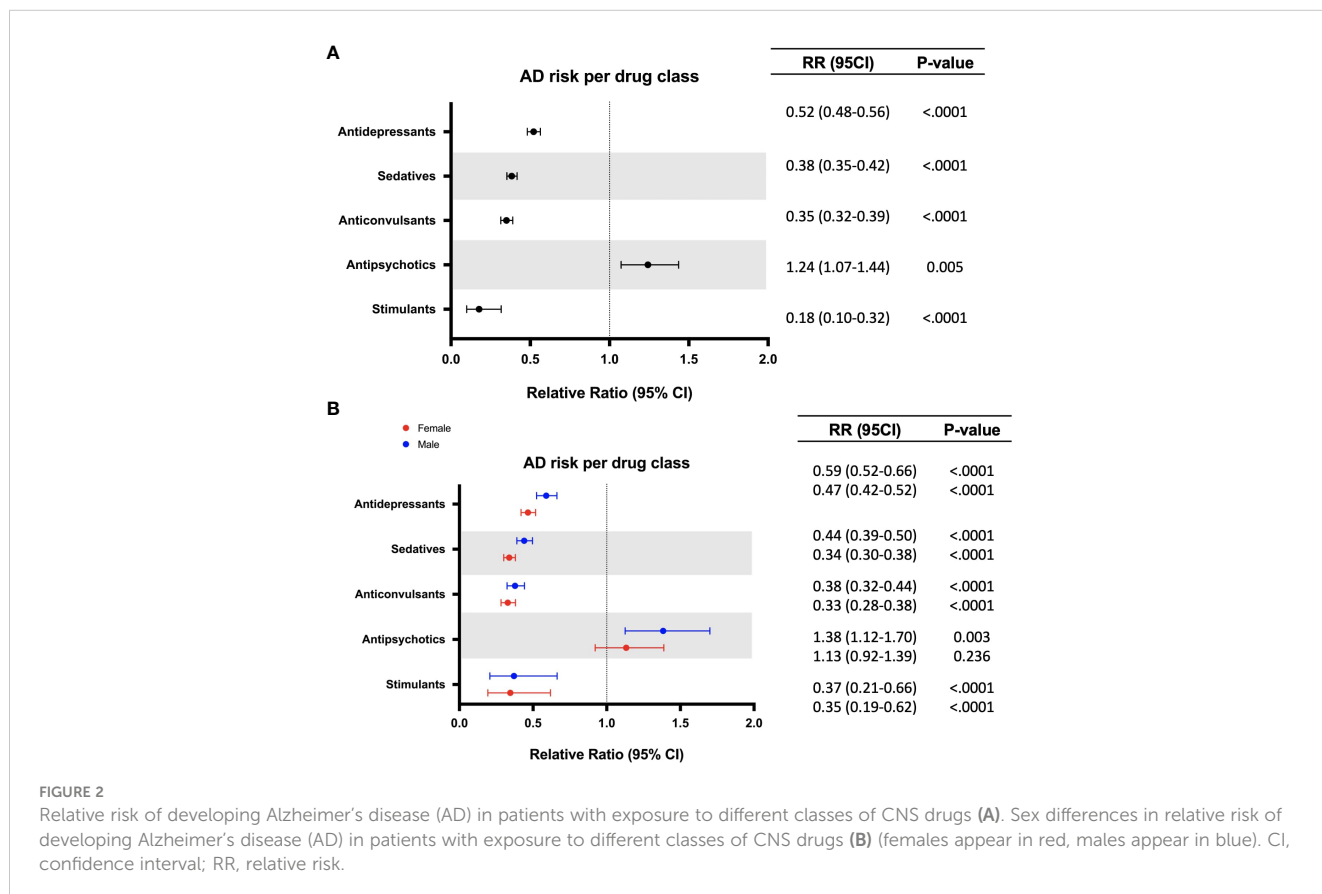
	Patients with AD diagnosis	%	Relative Risk	95%CI	p-value	NNT
No exposure to CNS active drug	2,673	1.73%	–	–	–	–
Antidepressants	800	0.90%	0.52	0.48-0.56	<.0001	121
Sedatives	687	0.66%	0.38	0.35-0.42	<.0001	94
Anticonvulsants	374	0.60%	0.35	0.32-0.39	<.0001	89
Antipsychotics	190	2.15%	1.24	1.07-1.44	0.005	239
Stimulants	11	0.31%	0.18	0.10-0.32	<.0001	70

(AD), Alzheimer’s disease; (CI), confidence interval; (RR), relative risk; (NNT), number needed to treat.

(Table 4). Non-responders were older and predominantly female compared to patients who did not develop AD. Non-responders had a significantly higher prevalence of cardiovascular disease (9.4% vs 5.2%, $p < .0001$), hypertension (26.6% vs 19.1%, $p < 0.0001$), stroke (9.4% vs 4.4%, $p < 0.0001$), chronic kidney disease (10.8% vs 5.3%, $p < 0.0001$), and diabetes (7.3% vs 5.6%, $p = 0.009$). In contrast, responders were significantly more obese (6.6% vs 2.9%, $p < 0.0001$). Further, responders were prescribed significantly more MHT (3.5% vs 2.4%, $p = 0.025$) and anti-inflammatories (30.3% vs 26.1%, $p = 0.0006$) and less antihypertensive medications (21.2% vs 23.6%, $p = 0.037$) compared to non-responders (Table 4).

A risk analysis was conducted to estimate the impact of multiple CNS-active drug combinations on the risk of developing AD (Figure 6). Drug groups with insufficient patient number were excluded from this

analysis. Outcomes of this analysis indicated that addition of a second CNS-active drug was associated with greater reduction in AD risk compared to monotherapy. Specifically, for all antidepressants assessed (tricyclics, SSRIs and SNRIs), the combination of a BDZP, a Z-drug or a second-generation anticonvulsant was associated with greater reduction of AD risk compared to exposure to one antidepressant alone. BDZP and second-generation anticonvulsants exerted greater reduction in AD risk in all drug combinations explored, except when combined with SSRIs. Similarly, Z-drugs showed decreased AD risk in all combinations with the exception of tricyclic antidepressants. Interestingly, atypical antipsychotics were associated with increased AD risk, which was mitigated by the addition of a tricyclic, SNRI, Z-drug or second-generation anticonvulsant, with Z-drugs providing the greatest mitigation of AD risk.



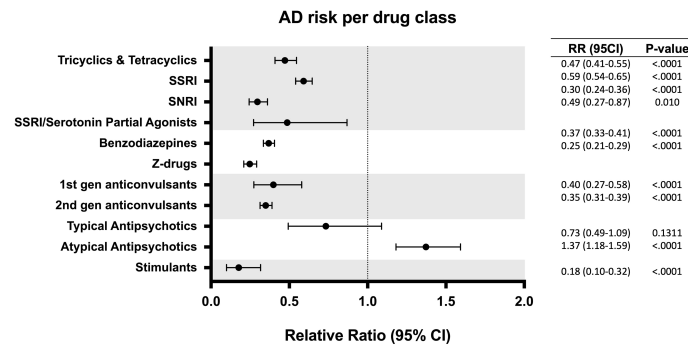


FIGURE 3 Relative risk of developing Alzheimer's disease (AD) in patients with exposure to different subclasses of CNS drugs. CI, confidence interval; RR, relative risk.

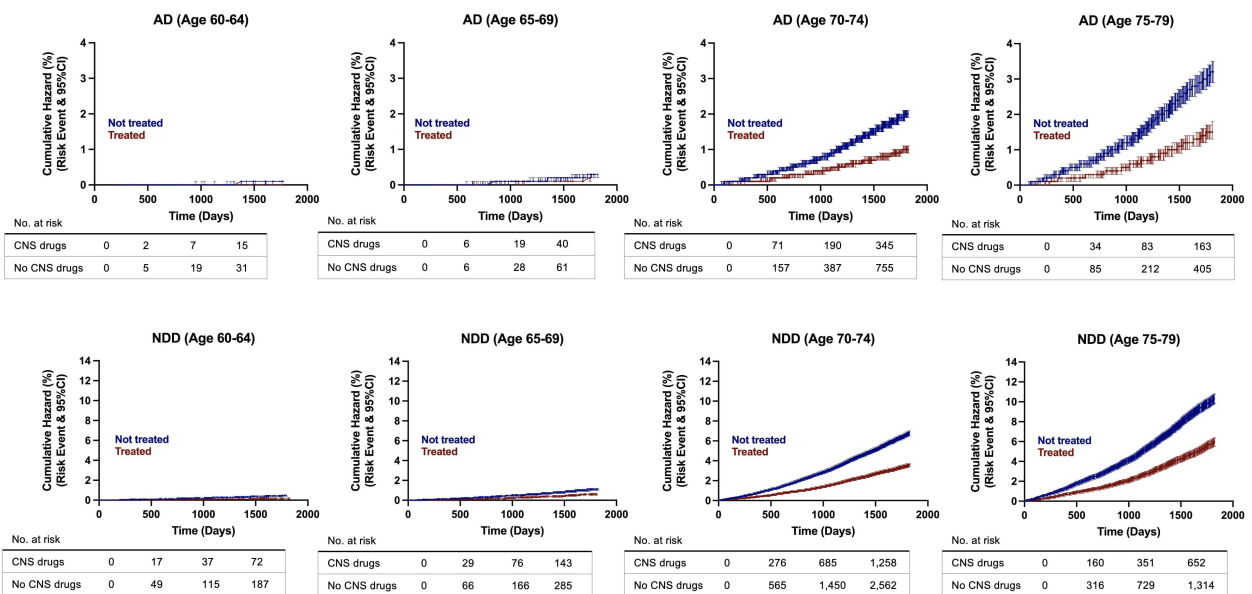


FIGURE 4 Hazard ratio curves for risk of developing Alzheimer's disease (AD) and neurodegenerative diseases (NDDs) combined in propensity score matched patients. AD, Alzheimer's disease; NDD, neurodegenerative disease.

Addition of a Z-drug to any CNS-active drug was associated with the greatest reduction of AD risk for every drug class assessed, with the combination of a Z-drug and an SNRI exerting greatest AD risk reduction (Figure 6).

4 Discussion

This study sought to explore the impact of CNS-active medications in an aging population on the development of AD and other age-related NDDs using health claims records. Outcomes of this retrospective analysis indicated that use of CNS-active drugs was associated with significant risk reduction of AD, non-AD dementia, MS, PD, and ALS. Additional analyses revealed that antidepressant, sedative, anticonvulsant, and stimulant medications were associated with a decreased risk of AD, while antipsychotics,

specifically atypical antipsychotics, were associated with increased risk of developing AD. Additionally, sedatives were associated with a greater reduction in AD risk in women compared to men, and antipsychotic treatment was associated with increased risk of AD only in males.

Age and duration of therapy emerged as two main modulators of AD risk associated with CNS-active drugs, where AD risk reduction was apparent after 3 years of drug exposure and reduction of AD risk was greater with increasing age. During early stages of AD pathology, a misdiagnosis of a neuropsychiatric disorder can occur as a consequence of the common symptomatology of both diseases (69, 70). Thus, the increased AD risk observed in patients receiving CNS-active drugs for less than 3 years may be the result of AD pathology already established in this group of patients, but not yet diagnosed. These findings suggest that accounting for treatment duration and examining patients in the appropriate age range are key elements of the association between

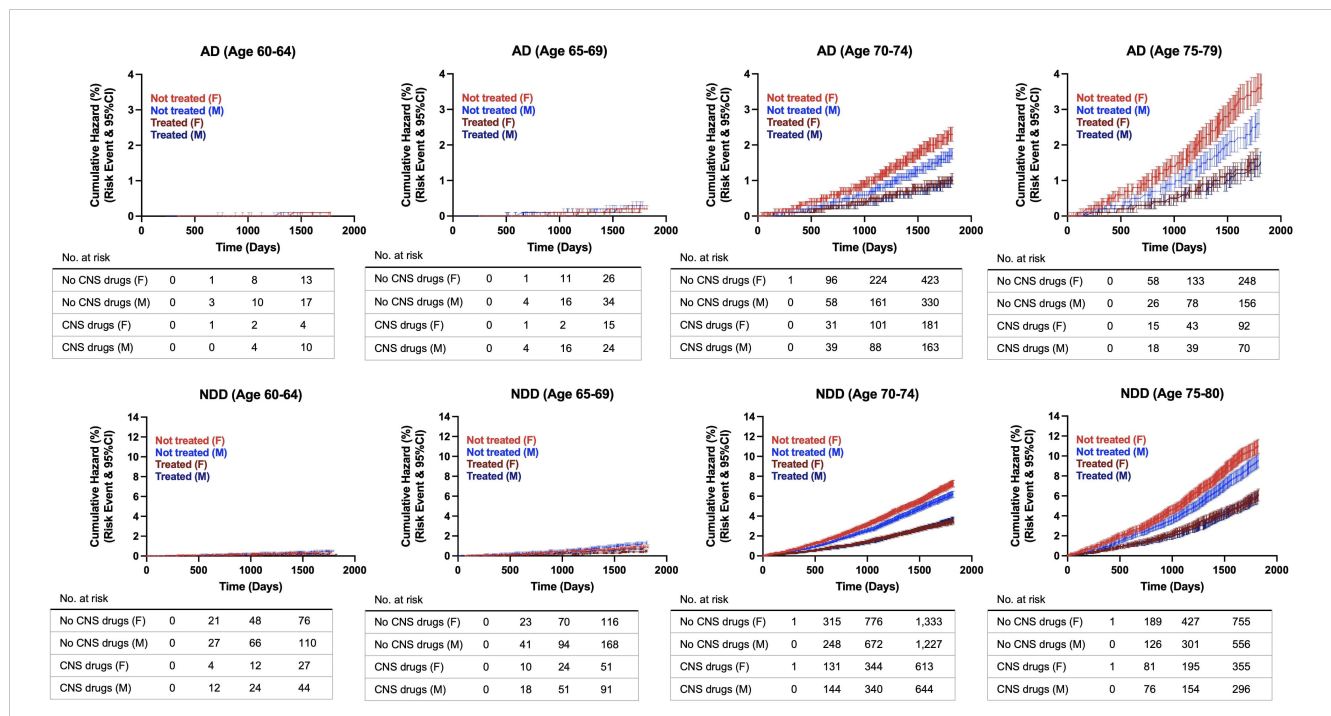


FIGURE 5 Hazard ratio curves for risk of developing Alzheimer's disease (AD) and neurodegenerative diseases (NDDs) combined in propensity score matched patients, females versus males. AD, Alzheimer's disease; NDD, neurodegenerative disease.

TABLE 3 Impact of CNS drug therapy duration on risk of Alzheimer's disease (AD) and neurodegenerative diseases (NDDs) combined.

Duration	AD			NDDs		
	No. (%)	RR (95% CI)	P-value	No. (%)	RR (95% CI)	P-value
1y or less (N = 6,097)	130 (2.13%)	1.23 (1.04-1.47)	0.02	350 (5.74%)	1.00 (0.90-1.11)	0.98
1-3y (N = 19,614)	357 (1.82%)	1.05 (0.94-1.17)	0.35	1,236 (6.30%)	1.09 (1.03-1.16)	0.0025
3-6y (N = 58,143)	582 (1.00%)	0.58 (0.53-0.63)	<.0001	2,125 (3.65%)	0.63 (0.61-0.66)	<.0001
6y and longer (N = 68,338)	265 (0.39%)	0.22 (0.20-0.25)	<.0001	1,113 (1.63%)	0.28 (0.27-0.30)	<.0001

AD, Alzheimer's disease; CI, confidence interval; NDD, neurodegenerative disease; RR, relative risk.

CNS-active drugs and incidence of NDDs. This could also explain disparities in the literature where studies that considered treatment duration indicated that antidepressant and sedative drugs were associated with reduced incidence of dementia (71–73), while studies that did not account for duration of treatment found an increased risk associated with these drugs (74–78).

Risk analysis evaluating sex differences did not reveal significant differences between males and females on AD risk. However, when NDDs were combined a slight but significant difference emerged where females exhibited greater risk reduction compared to males. Consistent with these findings, results from the cumulative hazard analysis indicated a reduction in rate of disease conversion for both sexes in the treated group, with females exhibiting a greater magnitude of divergence between the treated and untreated groups. Within the treated group, females and males exhibited a

comparable trajectory of disease conversion suggesting that CNS-active drugs activate mechanisms that reduce risk of NDD that are independent of biological sex.

Results from these analyses indicated that antidepressants, including tricyclics and tetracyclics, SSRIs, SNRIs and SSRI/Serotonin partial agonists, were associated with a significant risk reduction of developing AD. Mechanistically, antidepressants exert multiple actions in the brain including modifications of synaptic transmission, reduced inflammation, and increased neurogenesis that could ameliorate the pathological changes of depression that could increase the risk of developing AD (43, 45, 79–83). Moreover, antidepressants can impact amyloid plaque development (47, 84). The majority of these beneficial effects are thought to be regulated by increases in serotonin and norepinephrine signaling (85).

TABLE 4 Demographic characteristics, comorbidities and cotreatments in patients who develop Alzheimer's disease (AD) (non-responders) and those who remain free of AD (responders) after treatment with CNS drugs compared to the untreated population.

	Untreated					Treated				
	Develop AD after 12 m		Do not develop AD after 12 m		p value	Develop AD after 12 m		Do not develop AD after 12 m		p value
	n	%	n	%		n	%	n	%	
Number of Patients	2,673		151,891			1,336		153,228		
Age										
60 to 64	78	2.92%	51,069	33.62%	0.017	38	2.84%	51,109	33.35%	0.017
65 to 69	166	6.21%	34,519	22.73%		107	8.01%	34,578	22.57%	
70 to 74	1,838	68.76%	49,233	32.41%		912	68.26%	50,159	32.73%	
75 to 79	591	22.11%	17,070	11.24%		279	20.88%	17,382	11.34%	
Sex										
Female	1,495	55.93%	74,367	48.96%	0.015	687	51.42%	75,175	49.06%	0.012
Male	1,178	44.07%	77,524	51.04%		649	48.58%	78,053	50.94%	
Region										
Midwest	627	23.46%	32,253	21.23%	0.025	287	21.48%	32,593	21.27%	0.043
Northeast	559	20.91%	35,921	23.65%		303	22.68%	36,177	23.61%	
South	1159	43.36%	63,393	41.74%		575	43.04%	63,977	41.75%	
West	328	12.27%	20,296	13.36%		170	12.72%	20,454	13.35%	
Unknown	-	0.00%	28	0.02%		11	0.82%	27	0.02%	
Comorbidities										
Cardiovascular Disease	206	7.71%	2,193	1.44%	<.0001	126	9.43%	7,957	5.19%	<.0001
Chronic Kidney Disease	224	8.38%	1,899	1.25%	<.0001	144	10.78%	8,055	5.26%	<.0001
COPD	120	4.49%	1,151	0.76%	<.0001	57	4.27%	5,781	3.77%	0.3481
Diabetes	119	4.45%	3,318	2.18%	<.0001	98	7.34%	8,612	5.62%	0.0087
Hypercholesterolemia	229	8.57%	6,854	4.51%	<.0001	150	11.23%	17,007	11.10%	0.8612
Hypertension	434	16.24%	12,363	8.14%	<.0001	356	26.65%	29,332	19.14%	<.0001
Obesity	64	2.39%	3,191	2.10%	0.31	39	2.92%	10,094	6.59%	<.0001
Stroke	182	6.81%	2,043	1.35%	<.0001	126	9.43%	6,682	4.36%	<.0001
Tobacco Use	64	2.39%	2,274	1.50%	0.0004	49	3.67%	5,567	3.63%	0.9414
Co-treatments										
Antidiabetics	38	1.42%	1,726	1.14%	0.168	84	6.29%	9,167	5.98%	0.643
Antihypertensives	186	6.96%	7,004	4.61%	<.0001	315	23.58%	32,506	21.21%	0.037
Anti-inflammatories	235	8.79%	11,068	7.29%	0.004	348	26.05%	46,471	30.33%	0.0006
SERMS	17	0.64%	410	0.27%	0.002	19	1.42%	2,640	1.72%	0.451
ADT	55	2.06%	2,718	1.79%	0.303	84	6.29%	11,452	7.47%	0.105
Statins	146	5.46%	6,518	4.29%	0.004	285	21.33%	32,083	20.94%	0.736
MHT	13	0.49%	939	0.62%	0.455	32	2.40%	5,419	3.54%	0.025
CCI										
0-4	2,630	98.39%	150,238	98.91%	0.416	1,310	98.05%	151,557	98.91%	0.416

(Continued)

TABLE 4 Continued

	Untreated				p value	Treated				p value
	Develop AD after 12 m		Do not develop AD after 12 m			Develop AD after 12 m		Do not develop AD after 12 m		
	n	%	n	%		n	%	n	%	
Number of Patients	2,673		151,891			1,336		153,228		
CCI										
5-10	22	0.82%	1,643	1.08%		15	1.12%	1,660	1.08%	
11+	11	0.41%	11	0.01%		11	0.82%	11	0.01%	

(AD), Alzheimer’s disease; (ADT), androgen deprivation therapy; CCI, Charlson comorbidity index; (COPD), chronic obstructive pulmonary disease; (MHT), menopausal hormonal treatment; (SERMS), Selective estrogen receptor modulators.

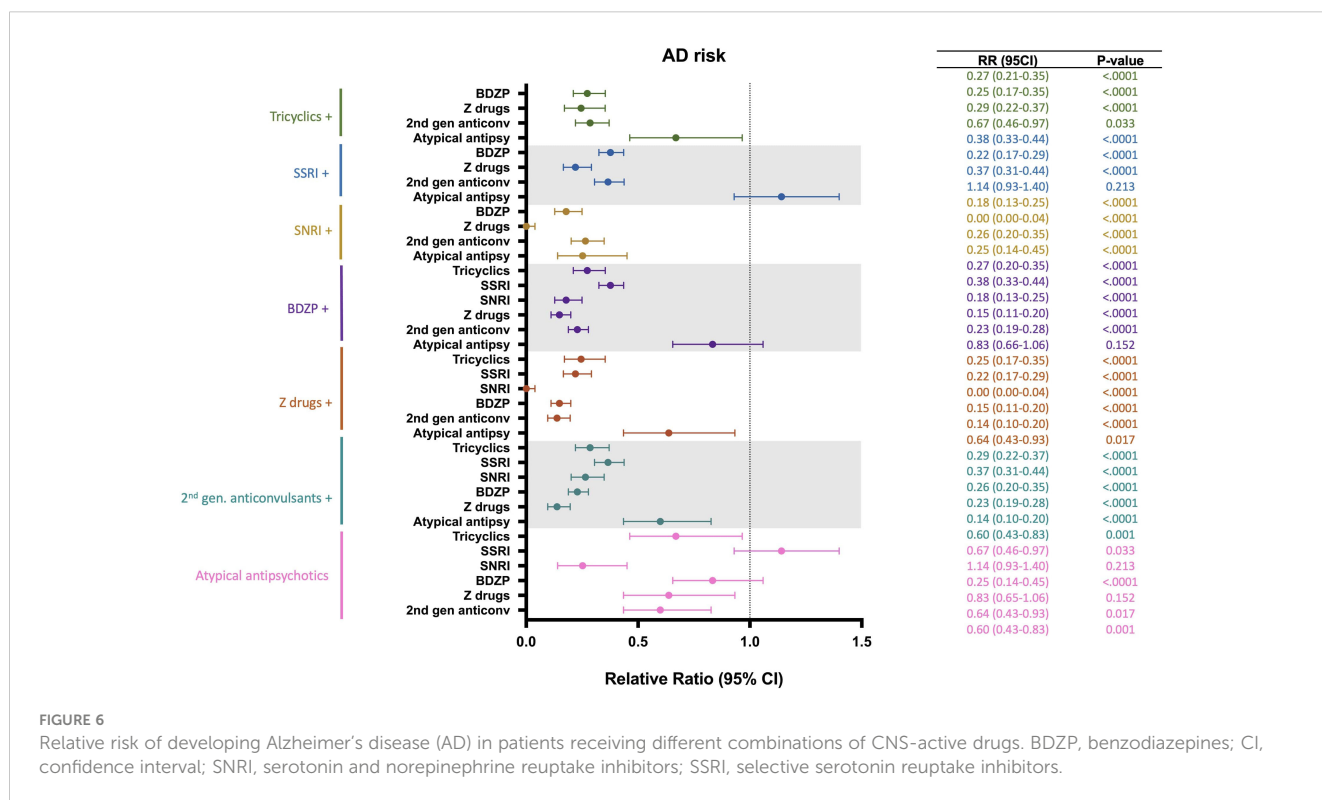


FIGURE 6

Relative risk of developing Alzheimer’s disease (AD) in patients receiving different combinations of CNS-active drugs. BDZP, benzodiazepines; CI, confidence interval; SNRI, serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors.

Sedatives used for the management of insomnia including Z-drugs and BDZPs (86) were associated with reduced risk of developing AD and was greater in females relative to males. Z-drugs were associated with greater risk reduction compared to BDZPs. Both Z-drugs and BDZPs could protect against AD by improving sleep, thereby reducing inflammation, tau aggregation, and amyloid beta accumulation (12, 50, 87). Notably, Z-drugs bind with greater specificity to the GABA-A chloride channel receptor than BDZPs and promote slow-wave sleep, crucial for Aβ clearance and memory consolidation, which could provide an additional benefit in AD risk reduction (88) compared to BDZPs. Interestingly, sedative drugs, especially BDZPs, are highly lipophilic which could induce longer duration of action in women, who have larger volumes of adipose tissue than men (89). Of note, median adherence for both sedative drug classes assessed, specifically for BDZPs, was lower than 50%, which could

impact the results on the association between AD risk and treatment with sedative drugs.

Anticonvulsants were associated with reduced AD risk, despite previous studies reporting contradictory findings on cognition and AD risk (90–93). Data contained herein provide new evidence for potential long-term benefits of anticonvulsants. Neuronal hyperexcitability that occurs in the early stages of AD (94) could potentially be counteracted by anticonvulsants as observed in preclinical studies (46, 48).

Atypical antipsychotics were associated with a significant increase in risk of developing AD. Notably, an association with increased risk of AD was only significant in males. Multiple analyses suggest that certain antipsychotic drugs can impair memory and cognitive function with short-term treatment (44, 95, 96) whereas their long-term impact on AD risk was uncertain (97, 98). Findings reported herein provide evidence for an adverse impact on AD risk.

Antipsychotic antagonistic effects on neurotransmitters like acetylcholine and serotonin, crucial for memory and learning, could contribute to AD vulnerability (99, 100). Interestingly, women's psychotic symptoms respond to lower doses of antipsychotics compared to men (101, 102), which could influence the modulation of AD risk differently in females compared to males.

Interestingly, among all CNS-active drugs stimulants were associated with the greatest AD risk reduction. Although the association between stimulants and AD remains poorly understood, evidence indicates that low-dose methamphetamine may promote neuroprotection via sAPP alpha production (51), neuronal differentiation, and synaptic plasticity (49) that likely involves norepinephrine and dopamine mechanisms.

Responder analyses indicated that non-responders were older and predominantly female compared to patients who did not develop AD which could contribute to the greater incidence of AD in women (54). Additionally, non-responders were characterized by an overall higher incidence of comorbidities than responders, specifically cardiovascular comorbidities, whereas responders had a higher incidence of obesity. Consistent with these findings, previous reports indicate that weight loss at midlife is a risk factor for AD, and that high body mass index in late life could be protective against AD (103–105). Interestingly, responders were also characterized by a greater exposure to anti-inflammatory drugs and MHT which have both been associated with decreased risk of developing AD (60, 65, 106).

5 Limitations

Several limitations of this study are due to the Mariner database which does not include values for laboratory tests or APOE genotype information or socioeconomic factors like race, ethnicity, or level of education or lifestyle modifications or psychological therapies which are recommended for several of the neuropsychiatric disorders assessed. Although the groups were propensity score matched, these factors could have an impact on AD development which is not accounted for in the analyses. Further, there was no information regarding efficacy of CNS-active drugs to control the neuropsychiatric disorder or whether therapies were changed during the course of treatment.

The average median adherence for all drugs considered in the study was 71.88%, which is higher than the estimated adherence to chronic medications in the general population (50%) (107). Because all main analyses were conducted with all drugs grouped together, adherence was sufficient to provide reliable results. However, low adherence rate would specifically impact results derived from drug classes with low median adherence. Both sedative drug classes had an adherence rate lower than 50%, with 15.33% for benzodiazepines and 43.34% for Z-drugs. The low adherence rate would underestimate the magnitude of impact of these drugs on NDD risk.

6 Conclusion

Outcomes of analyses reported herein indicate that CNS-active drugs targeting neuropsychiatric disorders including depression, insomnia, epilepsy, schizophrenia, and ADHD can significantly modify the risk of developing AD. Antidepressants, sedatives, anticonvulsants, and stimulants, were all associated with significant reduction in the risk of AD, especially following long-term treatment. In contrast, antipsychotics, specifically atypical antipsychotics, were associated with a significant increased risk of developing AD, which could be mitigated when combined with other CNS-active drugs such as SNRIs. Women and men exhibited distinct response profiles to sedative and antipsychotic drugs, where sedatives were associated with a greater reduction in AD risk in women compared to men whereas antipsychotic treatment was associated with increased risk in AD only in males. Notably, non-responders to these therapeutics were characterized by a high incidence of cardiovascular disorders. Collectively, the data indicate that long-term management of neuropsychiatric disorders using appropriate pharmacologic treatment can significantly reduce risk of AD and other NDDs.

Data availability statement

The datasets presented in this article are not readily available because restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided. Requests to access the datasets should be directed to info@pearliverinc.com.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

HC-F: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. GT-H: Conceptualization, Supervision, Writing – review & editing. RB: Conceptualization, Funding acquisition, Resources, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpsy.2024.1358568/full#supplementary-material>

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