# NOVEL ANTIPSYCHOTICS WITHIN AND BEYOND CLINICAL TRIALS: THE TREATMENT OF OVERLAPPING PSYCHIATRIC DISORDERS WITH D3-D2 PARTIAL AGONISTS

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# Editorial: Novel antipsychotics within and beyond clinical trials: The treatment of overlapping psychiatric disorders with D3-D2 partial agonists

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Editorial on the Research Topic
Novel antipsychotics within and beyond clinical trials: The treatment of overlapping psychiatric disorders with D3-D2 partial agonists

The main taxonomies, the Diagnostic and Statistical Manual of Mental Disorders (currently in 5th ed.) and the International Classification of Diseases (currently in 11th ed.), have an immense impact on how we interpret, appraise and manage psychiatric disorders (1, 2). In these categorical systems, each disease is distinct and appear only once in a clearly defined place (3). However, there seems to be clusters of dimensional symptoms (i.e., differing in severity) that are characteristic of different disorders (3). Therefore, most psychiatric disorders cannot be conceptualized as distinct entities, but rather as complex combinations of dimensional symptoms.

To counter the limitations of the current classification systems, the "transdiagnostic" approach is gaining momentum, capturing the overlap between psychiatric disorders better, therefore enabling novel ways of conceptualizing the underlying theories and mechanisms contributing to mental ill health (4). The goal of the transdiagnostic approach is to allow for the testing, recognition, and utilization of a general theory of psychopathology by aiming to understand the shared, overarching processes that cut across the classification systems. Despite several limitations and unsolved issues, the transdiagnostic research identified groups or patterns of symptoms that cluster together in clinically meaningful ways. This may reflect a common etiological process, course and treatment response, as well as suggests that the co-occurrence of mental disorders might not reflect the co-occurrence of genuinely distinct syndromes—rather, it could be an artifact that emerged from the format of the currently used categorical classification system (3, 5, 6).

Taking on the transdiagnostic approach, the aim of this Research Topic is to examine the role of dopamine partial agonists in the treatment of overlapping psychiatric disorders within and beyond clinical trials. Given the fact that many of the major psychiatric disorders have shared genetic, pathophysiological, as well as environmental elements, there is a high probability that there are common medical solutions too. Based both on the results of several phase II and III clinical trials that have shown efficacy across several neuropsychiatric disorders, as well as the real-world data available investigating the extent to which an intervention influence the clinical picture when provided under usual circumstances of health care practice, there is a high possibility that dopamine partial agonists, such as cariprazine, can be safe and efficacious in a wide variety of symptom clusters.

In this Research Topic, 27 articles were published touching on a broad spectrum of indications, symptoms, and the consequences of dopamine D3 receptor dysfunction at a pathophysiological level.

Despite the benefits of randomized controlled trials, the generation of real-world data, like electronic/medical health records or clinical case reports, is recommended to complement the knowledge gained from clinical trials (7, 8). This way, data can be collected from more heterogenous populations with a wider range of comorbid disorders or adjunctive treatments, therefore increasing the external validity. Firstly, Csehi et al. conducted the first systematic review of cariprazine case reports, showing that cariprazine is effective across many symptoms and many disorders, like schizophrenia, bipolar disorder, adjunctive MDD, borderline personality disorder, obsessive-compulsive disorder or Wernicke-Korsakoff syndrome. Bogren et al. present the case of a patient with long-standing treatment-resistant schizoaffective disorder, where cariprazine in combination with clozapine yielded a near-complete remission of persistent negative and psychosocial issues, therefore improving the patient's quality of life. Vannucchi et al. describe three cases: the first patient had bipolar disorder with cocaine use disorder, the second patient experienced positive and cognitive symptoms, while the third patient suffered from psychosis. In all three cases, cariprazine treatment successfully improved patients' condition. Then, Taube presents a case where the patient with schizophrenia experienced severe side effects of first-generation antipsychotics and was therefore switched to cariprazine. The side-effects subsided and cariprazine provided effective control over the symptoms. The article by Coentre et al. highlights the efficacy and safety of cariprazine in early psychosis. Three cases—including two with comorbid cannabis use—are presented, where patients showed improvements in negative and psychotic symptoms. The case series by Vasiliu describe how cariprazine yielded improvements in negative symptoms and patient functionality in patients with predominant negative symptoms, without causing severe adverse events. Finally, the case report by Cruz et al. shows how cariprazine in combination with quetiapine improved cognitive functioning and negative symptoms, as well as yielded substance abstinence in a patient with comorbid schizophrenia and substance use disorder (SUD). These case reports further support how heterogenic symptoms are within the same diagnosis and show the overlap between symptoms across different diagnoses.

Given the importance of right dosing in achieving effective treatment outcome while minimizing the risk of side-effects, Rancans et al. synthesized data from real-world experience and clinical trials in order to shed light on the appropriate dosing strategies of cariprazine in schizophrenia from treatment initiation through switching strategies to concomitant medications.

Some of the articles cover the topic of schizophrenia with a special focus on negative and cognitive symptoms, as they remain one of the greatest unmet medical needs in its treatment. Mosolov and Yaltonskaya's article offers a comprehensive review of the history and the state-of-the-art of understanding negative symptoms. It strongly raises awareness on the importance of differential diagnosis of primary and secondary negative symptoms, and its methodological and therapeutic implications that involve D2/D3 partial agonism. Demyttenaere et al. conducted a network analysis to better understand the relationship and interactions between different symptoms of a psychiatric disorder by analyzing data from patients with predominant negative symptoms from the cariprazine-risperidone trial (9). According to the findings, depressive and anxious symptoms were the most central symptoms in this patient population, therefore providing important clinical insight. Ivanov et al. present the findings of their observational study, where cariprazine significantly improved predominant negative symptoms in the majority of patients in 4 weeks. In their perspective article, Morozov et al. argue that cariprazine is an adequate pharmacological treatment option for improving social functioning in schizophrenia by reducing negative, cognitive and affective symptoms. Therefore, cariprazine can be viewed as a "socializing drug" that can positively impact on patients' functionality and quality of life. Another aspect for the evaluation of treatment, finding the minimum clinically important difference can be helpful for physicians. Therefore, Czobor et al. aimed at finding this difference at its earliest occurrence in a patient population with predominant negative symptoms, with results suggesting an even lower threshold than previously thought.

In addition, Peris and Szerman review the current advances and future directions in the use of partial agonists in patients with comorbid schizophrenia and SUD, based on the involvement of the dopamine D3 receptors in both disorders.

Bipolar disorder was the focus of three manuscripts. Do et al. provide a comprehensive review of cariprazine in terms of its pharmacological properties, efficacy, and tolerability profile, based on data from clinical trials, including *post-hoc* analyses. The narrative review of Grunze et al. evaluates the

potential role of partial agonists in the treatment of addiction in patients with comorbid bipolar disorder given the important role of the dopaminergic system in both disorders: current evidence suggests that partial agonists, especially cariprazine, can indeed improve symptoms associated with substance use and bipolar disorder. Finally, Palacios-Garrán et al. conducted an observational study in which cariprazine in combination with a mood stabilizer (lithium or divalproex) proved to be safe and effective in the treatment of first-episode mania patients, therefore providing the first-ever findings about cariprazine in this patient population.

Further indications have been investigated as well: Mandic-Maravic et al. highlight the unmet need in the treatment of autism spectrum disorder (ASD), with a specific focus on the dopamine theory of the disorder and its potential treatment with dopamine receptor partial agonists. Cariprazine, based on animal model studies and its unique affinity to D3 receptor, may theoretically represent a future opportunity in the treatment of ASD, especially social withdrawal and cognitive symptoms. Molnar et al. summarize the findings from the first-ever study evaluating cariprazine's safety and efficacy on mood and cognitive symptoms in Huntington's disease. They concluded that it is an effective treatment option for this patient population, showing the importance of transdiagnostic approach even in the field of neurology and challenging the terminological discrepancies across the diseases and suggesting common D3 receptor related underlying cross-disease neuropharmacological alterations.

Strengthening this pathophysiological approach, Batinic et al. summarize cariprazine's current therapeutic uses and potential advantages for treating the main symptoms of schizophrenia, bipolar I disorder and MDD and showed that cariprazine may be a drug of choice in patients with predominant negative and cognitive symptoms of schizophrenia, as well as those with metabolic syndrome. Next, in their systematic review and meta-analysis, Dombi et al. provide an updated overview of the evidence behind reduced peripheral levels of BDNF in patients on the schizophrenia-bipolar spectrum as well as evaluate its connection to cognitive symptoms in these disorders.

Although no head-to-head comparisons were conducted for the three partial agonists (cariprazine, aripiprazole and brexpiprazole), using data from controlled studies, meta-analyses and systematic reviews, Mohr et al. evaluated whether the clinical efficacy of these three compounds differs, concluding that these drugs form a heterogenous group, each with its own therapeutic benefit. Milanova et al. present a more detailed and science-based account of the beneficial effect of music therapy on the general wellbeing of patients with schizophrenia by discussing evidence from modern neuroimaging research.

Finally, four articles focus on pharmacology, with an emphasis on the dopamine D3 receptors. In their review, Kiss et al. summarize preclinical and clinical evidence demonstrating that despite many antipsychotics displaying substantial activity for both D2 and D3 receptors *in vitro*, only cariprazine and blonanserin can significantly occupy the D3 receptors *in vivo* and therefore achieve the outcomes associated with D3 activity—although only cariprazine exerts partial agonist effect at these receptors among the two drugs. Hart et al. review the available molecular imaging (PET) studies on the three partial agonists (cariprazine, aripiprazole, brexpiprazole) in order to establish the relationship between plasma concentration of a substance and its binding to the molecular target in the brain. This way, by determining the plasma concentration in individual patients, treatment can be tailored individually. Kehr et al. provide behavioral and *in vivo* neurochemical evidence for the preferential D3 receptor action of cariprazine in rats by comparing the abilities of cariprazine, aripiprazole, and ABT-925 (a selective dopamine D3 antagonist). Moving onto polypharmacy, given its widespread use in clinical practice, the article of Hjorth provides a basis with great visual tools for understanding which antipsychotic combinations are the most optimal based on the drugs' receptor profile.

Overall, the articles of this Research Topic are in line with the view of the transdiagnostic approach whereby there is a substantial overlap between psychiatric illnesses, supporting the notion that these neuropsychiatric disorders should not be conceptualized as separate entities due to the fluidity of diagnostic boundaries. The integration of these data might provide an insight into different indications by showing common underlying neuropharmacological alterations.

The results of these articles are supported by genetic studies that shed light on the polygenic nature of psychiatric illnesses, whereby several common variants with small effects as well as many genetic variants impact on more than one phenotype, implying the existence of the shared genetic etiology of psychiatric disorders (10). In fact, studies have shown that there is a high transcriptome correlation between many disorders, especially schizophrenia, bipolar disorder, ASD and MDD (11).

Dopaminergic dysfunction is well-established in many neurological and psychiatric disorders, including schizophrenia, bipolar disorder, SUD, ASD, addiction and Huntington's disease (12), as demonstrated by the articles of this Research Topic as well. The different dopamine pathways are all involved in neuropsychiatric disorders, and depending on which pathway in what extent is dysregulated, different psychiatric symptoms may arise: hypoactivity in the mesocortical pathway (stemming from the ventral tegmental area, innervating the prefrontal cortex) can mediate negative, cognitive and depressive symptoms; under-activation of dopamine in the mesolimbic pathway (stemming from the ventral tegmental area, innervating the ventral striatum, olfactory tubercule and parts of the limbic system) has been associated with negative symptoms; while overactivation in the associative striatum (nigrostriatal pathway I; originating from the substantia nigra and innervating the

associative striatum) has been implied in the development of psychosis (13).

Among the five dopamine receptor types, D2 and D3 receptors play a key role in mediating different psychiatric symptoms. Overactivation of D2 receptors is associated with psychotic and manic symptoms, therefore all antipsychotics target these receptors. On the other hand, D3 receptors have received particular attention due to their anatomical localization: they are prevalently distributed in limbic areas, the hypothalamus, and the ventral tegmental area/substantia nigra and even in prefrontal cortical regions—areas that play a critical role in the regulation of cognition, mood, motivation and negative symptoms (14). Therefore, antipsychotics targeting D3 receptors more potently than the D2 receptors might have potentially favorable effects on these symptoms (15).

Regarding receptor occupancy, for partial agonists to achieve an antipsychotic effect, higher D2 occupancy is required compared to other antipsychotics. In this regard, cariprazine behaves similarly to the other two partial agonists, aripiprazole and brexpiprazole: high D2 receptor occupancy is achieved within a short period of time (16). However, what differentiates cariprazine is that it has the highest affinity to D3 receptors among antipsychotics—even higher than the binding of endogenous dopamine (16). It makes cariprazine the only antipsychotic that is proven to occupy the D3 receptors in the presence of dopamine *in vivo*, exert partial agonist activity here and therefore achieve benefits that might be associated with D3 activity, i.e., improvements in cognitive, affective, and negative symptoms. As these symptoms are characteristic of most mental illnesses and cause the greatest impairment in patient functionality and quality of life, cariprazine is a promising treatment option for a wide variety of neuropsychiatric illnesses, as shown by the articles of this Research Topic as well, offering symptom improvement potentially through restoring altered D3 receptors activity.

## Author contributions

Conceptualization: GN. Both authors participated in the writing, editing, and approved the final version of this manuscript.

## Conflict of interest

Authors GN and RC were employed by Gedeon Richter Plc.

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CASE REPORT
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# Case Report: Cariprazine in a Patient With Schizophrenia, Substance Abuse, and Cognitive Dysfunction

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This case report describes a 30-year old male diagnosed with schizophrenia at the age of 23, and with a long history of drug abuse. He had previously received a wide range of antipsychotic drug treatment regimens, all with some degree of effect, but never with complete symptom relief. He was also suffering from persistent cognitive and negative symptoms. At the time of admission in our clinic, he was on Quetiapine (QUE) and Haloperidol (HAL). It was therefore decided to substitute HAL for Cariprazine (CAR)—an agent with a novel pharmacological and clinical profile—in the hope of gaining increased efficacy, particularly in the cognitive and negative symptom domains. Within 3 weeks of the switch from HAL to CAR the patient clearly improved, and notably so in the aforementioned symptom areas. A number of subsequent adjustments of antipsychotic dosages and adjunct medications during the ensuing months resulted in an apparently more stable alleviation of positive as well as negative and cognitive symptoms, including markedly improved personal and social capabilities. Interestingly, some time after initiating CAR treatment the patient also reported that from being a heavy smoker (60 cig/d) he had cut down and eventually ceased smoking entirely; furthermore, he has remained clean of other substance abuse since his first admission in 2020. The joint treatment with CAR in combination with QUE thus seems to have improved the patient's cognitive functioning as well as possibly his susceptibility to substance abuse.

**Keywords: cariprazine, quetiapine, antipsychotics, drug abuse, cognitive dysfunction, negative symptoms schizophrenia**

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## INTRODUCTION

Schizophrenia is a chronic disorder with variable clinical features and changes in numerous aspects of mental processing. It causes significant and long-lasting impairments, makes heavy demands for hospital care and requires extensive efforts from the healthcare system and other actors. Substance abuse is also common in individuals with schizophrenia, the association of which links to symptom exacerbation, poorer medication compliance, deterioration of functioning, higher risk of hospitalization and overall increased costs to the individual and society (1–3). In this regard, very frequent drug comorbidities are marijuana, and psychostimulant agents like amphetamine and cocaine (1, 4).

Cognitive impairments are also common in patients suffering from schizophrenia, especially in the domains of attention, executive function and memory. As these are considered a better predictor of level of function in outpatients than is the severity of psychotic symptoms, cognitive impairments have become the target of many pharmacological and psychosocial treatment trials (5).

Cariprazine (CAR) is a third-generation antipsychotic, approved in Europe 2017 for the treatment of schizophrenia. Several studies suggest that CAR may be of particular interest with regard to treatment of negative and cognitive symptoms in patients with schizophrenia (6–8). Intriguingly, some reports additionally suggest its usefulness to improve symptoms of substance use disorder (9, 10), although prospective randomized studies are necessary to evaluate this further.

We present a case of a patient with concomitant schizophrenia and substance abuse disorder admitted to an in-patient psychiatric unit due to increasing psychotic symptoms. He had previously been treated with a wide range of antipsychotic drugs. While all of these regimens had had some effect, none had led to complete symptom remission and the patient was suffering from persistent negative and cognitive symptom manifestations.

## CASE PRESENTATION

A 30-year old male was admitted to an in-patient psychiatric unit for treatment, after at least 3 weeks of escalating psychotic symptoms, consumption of amphetamine and treatment compliance failure (Quetiapine 900 mg/d, Lithium 168 mg/d, Mirtazapine 45 mg/d). The months prior to the hospitalization there was a slow decline in function [described in detail under section Current episode (overview in **Table 2**), below] and increase in psychotic symptoms seen correlating with social stressors, and finally with drug intake.

### Background History

He reached 12th grade of education (∼senior high school). Since childhood this patient had shown difficulties in his social interactions. According to caregiver interviews, there were premorbid symptoms, including early behavioral and social deviation. At the age of 18 he started consuming cannabis daily, with breaks no longer than a month. He intermittently used alcohol, opioids, LSD, and benzodiazepines but he tended to prefer cannabis and psychostimulants such as amphetamines.

The first psychotic episode was seen in proximity to drug intake. At this time, he was 23 years old, he had been using cannabis and amphetamines daily during 5 and 3 years, respectively, and sought healthcare for affective symptoms: depression and anxiety. His age of onset of psychosis is thus within the typical range for schizophrenia debut. As he was already advanced in his disease, investigations were made from a neuropsychiatric perspective, and a clinical picture of Attention Deficit Disorder (ADD) and Autism-Spectrum Disorder (ASD) was recognized.

He was described as easily distractible and sensitive to stress. Negative symptoms were also a central source of his general dysfunction. His way of interacting and the lower than expected level of self-care often had a quality that could be mistaken for autism. He expressed satisfaction in taking part in social/rehabilitation training/work, but he had a limited capacity to absorb instruction/new information.

Prior to the current admission the patient had had several admissions to psychiatry inpatient units. His first episode at the age of 23 was deemed to be an amphetamine-induced psychosis, but the diagnosis was later reconsidered and re-labeled schizophrenia. At that time the patient was suffering terrifying auditory hallucinations and religious delusions, even intolerable anxiety and fear that caused self-harm. He had occasional psychomotor agitation and aggressive behavior but mainly marked motor inhibition, inhibited facial expression, alogia and flattened affect, anhedonia, hypobulia, and isolation. He suffered extended periods of catatonia.

Over a period of ∼7 years prior to the present admission he had been prescribed several different antipsychotic treatments with good compliance, but simultaneously continued to consume drugs and got variable efficacy and side effects. He showed persistent psychosis symptoms despite periods of abstaining from dependence-producing agents that could extend to 8 months; this according to the patient's own information, since current urine drug screen methods (UTox) may not catch all types of illicit agents (e.g., "spice," and net-drug variants). **Table 1** summarizes previous treatment regimens.

Benzodiazepines (Diazepam, Clonazepam, Oxazepam, or Lorazepam) as well as antihistamine compounds (Levomepromazine and Alimemazine) were periodically used for the treatment of anxiety, self-harm and agitation in addition to the antipsychotics. Electroconvulsive therapy (ECT) was effective during prior episodes of catatonia.

### Current Episode

An overview of events, medications, and associated comments is found in **Table 2**. By the time of our contact in June 2020, at the age of 30, this patient also used drugs, mainly marijuana and amphetamines. He showed cognitive dysfunction (attention, working memory, cognitive flexibility and spontaneity), as well as worsened social skills and emotional responses that had previously been interpreted as ASD. He also complained about facial tics and tremors. As evident from the above, our patient had previously been treated with a wide range of antipsychotic drugs, none of which was more than partly effective. He was also suffering from persistent cognitive and negative symptoms.

After weeks (possibly months) of progressive deterioration with increasing paranoia and hallucinations he was subject to forced psychiatric clinical admission. At this time there had for 2–3 months been a looming notice of losing his apartment, and there was a suspicion of probable compliance failure. During the last house call, he wore dirty clothes, was verbally aggressive, openly hallucinating and expressed feeling threatened to his life

**Abbreviations:** UKU, Udvalg før Kliniske Undersøgelser; CAR, Cariprazine; QUE, Quetiapine; HAL, Haloperidol; OLA, Olanzapine; EPS, Extrapyramidal Side Effects.

**TABLE 1 |** Medication history overview (in- as well as outpatient periods).

| Agent | Dose/s | Period | Comment |
|---|---|---|---|
| Haloperidol (HAL) | Up to 10 mg/d | 2015 (4 mths)<br>2018 (1 mth)<br>2020 (2 wks)* | Combined with diazepam improved the most distressing hallucinations but caused intolerable extrapyramidal side effects (EPS). |
| Risperidone (RIS) | 6 mg/d | 2015–2016 (∼1 year) | Partially relieved the positive symptoms despite suspected concomitant drug use, but caused EPS and ejaculatory dysfunction. It was replaced by Clozapine, and after a second attempt (4 mths in 2017 during a later admission event) by Quetiapine. |
| Olanzapine (OLA) | Up to 30 mg/d<br>prn 7.5–15 mg<br>during exacerbations | 2018 (2 mths) | Good sedative effect and transiently improved hallucinations and delusions. |
| Clozapine | Up to 700 mg/d | 2015–2018 (∼3 yrs) | The most effective medication according to the medical staff. The patient reported asymptomatic periods alternating with periods of controllable symptoms, though never a permanent relief. |
| Quetiapine (QUE) | 900 mg/d | Current | The most effective medication according to the patient, particularly against hallucinations and anxiety, but still without a permanent relief as monotherapy. |
| Aripiprazole | Up to 30 mg/d | 2017 (3 wks, October) | The patient refused to continue with it and stated that "it was not good" for him, without further explanation. |
| Lithium | Up to 210 mg/d | 2018 (October) - current | Used as a calming agent. |

**Discussed in the current report.*

by the medical staff. He showed alogia and aggressive speech with flattened affect. The patient had no disease insight.

In the inpatient unit he was reinstated on previous treatment and dosages: QUE (900 mg/d), Lithium (168 mg/d) and Mirtazapine (45 mg/d). On week 4 he showed worsening symptoms of psychosis, including bursts of agitation and violence toward his environment and himself, as well as disorganized behavior, e.g., collecting garbage in his room. It was handled with an add-on with RIS (6 mg/d). On week 5 we had to switch from RIS to HAL, to afford an intramuscular alternative due to non-compliance with oral administration.

On week 7 after admission, the decision was taken to switch from HAL to CAR (with a target dose of 6 mg/d on day 9). At the start of this switch his HAL dose was 7.5 mg/d and QUE 900 mg/d. Tapering of HAL was initiated on day 9 after starting CAR. HAL was down-titrated and stopped over 2 weeks. The patient responded well both in terms of alleviation of auditory hallucinations and paranoid delusions, he also markedly improved in negative symptoms. Coinciding with the expected time for 90% of steady-state levels of CAR [∼3 weeks; (11)], he rather suddenly started to pay attention to his personal care and appearance and displayed a significant positive shift in the quality of his social interactions. The patient improved in terms of eye-contact, conveying more spontaneous and meaningful speech as well as a progressive development of self-reflecting capacity.

Three weeks after the start of CAR the patient complained of EPS and akathisia. The dose was therefore reduced 4.5 mg/d and Propranolol 90 mg/d and Biperiden 4 mg/d concurrently added. Four weeks into the treatment with CAR we started down-titrating QUE to 300 mg, applying a plateau-switch strategy (12). During this time, he had access to both antihistamines and benzodiazepines to alleviate possible rebound issues.

He was discharged on week 10 after admission with significant improvements in both negative and positive symptoms. At this time the concentration of total CAR was 84 nmol/L (S-CAR 10 + S-Desmethyl-CAR 4 + S-Di-desmethyl-CAR 70 nmol/L), which is well within the expected range [20–150 nmol/L with doses 1.5–6 mg/d; (11)].

At home he returned to work rehabilitation and leisure activities, like playing the guitar. Auditory hallucinations returned 1–2 weeks after discharge in September 2020. A week later the patient was given an add-on with OLA 10–20 mg/d. The following week his dose of CAR was increased from 4.5 to 6 mg. His QUE was still at 300 mg. However, the symptoms did not abate, and he was readmitted.

It was noted that he retained emotional contact qualities, and at least partial disease insight as compared to prior the initiation of CAR 6 weeks earlier (July 2020). As the previous combination of QUE 900 mg/d and CAR 4.5–6 mg/d apparently was used successfully during the last hospitalization, our first step was to return to that regime.

OLA was down-titrated and eventually stopped completely on day 14, while QUE was increased to reach a full dose of 900 mg/d on day 14. He slowly stabilized regarding his positive symptoms but was suffering from akathisia and anxiety. These symptoms appeared closely related and both were therefore managed by decreasing the dose of CAR from 6 to 4.5 mg/d and adding Clonazepam 2 mg/d (the patient was still on beta-blockade).

His auditory hallucination experiences were evaluated with the use of a "Voice-evaluation scale" (13), 2 days after his release from 10 weeks of in-patient care (June–September 2020) and 2 weeks after readmission October 2020. He scored the same total points both times using this assessment instrument. At the time of discharge on 4th of November, after 4 weeks of in-patient care, the auditory hallucinations are described as much attenuated, lesser in frequency and intensity. Overall the patient describes heightened well-being and plans for the future.

**TABLE 2 |** Timeline summary of patient events and medication across the current admission history.

| Date | Event | Medication/s | Comment |
|---|---|---|---|
| Wk 23, 2020 | **ADMISSION** | QUE (900 mg/d), Lithium (168 mg/d), Mirtazapine (45 mg/d) | Severe positive and negative symptoms Cognitive dysfunction and social/emotional impairment |
| Wk 27, 2020 | Psychotic worsening, agitation, disorganized behavior | RIS (6 mg/d) add-on | |
| Wk 28, 2020 | | Switch from RIS to HAL (7,5 mg/d) | Non-compliance oral RIS → intramuscular HAL |
| Wk 30, 2020 | Decision to switch to from HAL to CAR | QUE (900 mg/d) + HAL (7.5 mg/d) Start CAR (1.5 mg/d → 6 mg/d @ d9) Begin taper HAL on d9 of CAR | |
| Wk 32, 2020 | | QUE (900 mg/d) + CAR (6 mg/d) | Alleviation of paranoid delusions and auditory hallucinations - marked improvement in negative symptoms |
| Wk 33, 2020 | End tapering of HAL | QUE (900 mg/d) + CAR (6 mg/d) | Sudden significant improvement in social interaction, self-care |
| Wk 33, 2020 | EPS and akathisia | QUE (900 mg/d) + CAR (6 mg/d) Reduction of CAR dose (to 4.5 mg/d) Add-on w Propranolol (90 mg/d) + Biperiden (4 mg/d) | |
| Wk 34, 2020 | Start down-titrating QUE to 300 mg/d | QUE (900 mg/d) + CAR (4.5 mg/d) Antihistamines and benzodiazepines available prn for possible QUE rebound symptoms | Antihistamines and benzodiazepines available prn |
| Wk 40, 2020 | Patient **DISCHARGE** | QUE (300 mg/d) + CAR (4.5 mg/d) | Plasma $CAR_{tot}$ in expected therapeutic range Start part-time work rehabilitation |
| Wk 41-42, 2020 | Return of auditory hallucinations | QUE (300 mg/d) + CAR (4.5 mg/d) | |
| Wk 43, 2020 | Persistent auditory hallucinations | QUE (300 mg/d) + CAR (4.5 mg/d) Add-on w OLA (10–20 mg/d) | |
| Wk 44, 2020 | Add-on w OLA, increase CAR (4.5 → 6 mg/d) | QUE (300 mg/d) + CAR (4.5 mg/d) Add-on w OLA (10–20 mg/d) | |
| Wk 45, 2020 | Persistent auditory hallucinations → **READMISSION** | QUE (300 mg/d) + CAR (6 mg/d) Add-on w OLA (10–20 mg/d) | Retained emotional/social improvement, partial disease insight vs. 6 wks earlier; marked reduction of tobacco use |
| Wk 46, 2020 | Return to previously successful treatment regime | QUE (300 mg/d) + CAR (6 mg/d) QUE up-titration and OLA down-titration | |
| Wk 47, 2020 | Voice-evaluation scale scoring | QUE (300 mg/d) + CAR (6 mg/d) QUE up-titration and OLA down-titration | Auditory hallucinations alleviated |
| Wk 48, 2020 | Reduce CAR dose Medication adjustment done | QUE (900 mg/d) + CAR (4,5 mg/d) | Stabilized positive symptoms, but suffering from akathisia and anxiety |
| Wk 49, 2020 | Patient **DISCHARGE** | QUE (900 mg/d) + CAR (4.5 mg/d) Add-on w Clonazepam (2 mg/d) + still on Propranolol | Returned home, restarted work rehabilitation (2 h, 3 times/wk), started going to gym |
| Wk 9, 2021 | | QUE (900 mg/d) + CAR (4.5 mg/d) Add-on w Clonazepam (2 mg/d) + still on Propranolol | Quit smoking |
| Wk 11, 2021 | | QUE (900 mg/d) + CAR (4.5 mg/d) Add-on w Clonazepam (2 mg/d) + still on Propranolol | Increased work rehabilitation to 10 h/wk; shortly thereafter reported stress and voices |
| Wk 13, 2021 | | QUE (900 mg/d) + CAR (4.5 mg/d) Add-on w Clonazepam (2 mg/d) + still on Propranolol | Returned to 6 h/wk work rehabilitation scheme; no drugs of abuse found in regular testing since last discharge |

After another 4 weeks he was discharged and returned to work rehabilitation. The subsequent 2 months the patient attended his work-training 2 h, 3 times/week. He reported finding it stimulating and enjoyed being around other people. He started visiting the gym frequently. He increased his work-training attendance to 10 h a week. Shortly after this increase he reported a sense of stress and increased voices. Two weeks later he returned to the previous 6 h per week schedule (but the possibility of increasing the number of hours daily is kept open).

The patient was at this time regularly tested for any substance use but remained clean of such since the first hospitalization in 2020 (verified by regular UTox testing). When he returned for the second inpatient period in October 2020, a month after

discharge, it was also noticed that he had spontaneously cut down on tobacco use. He had been a regular smoker since the age of 18 (now 30) with a consumption of about 60 cigarettes per day. Two months after the end of his second inpatient stay, he quit smoking cigarettes entirely and now uses only tobacco- and nicotine-free e-cigarettes.

According to the UKU-scale ("Udvalg for Kliniske Undersøgelser" Side Effect Rating Scale) February 2021, 6 months after the first discharge, there is an improvement as compared to half a year ago (September 2020) with respect to quality of sleep, less emotional numbness, less EPS (stiffness, myalgia and bradykinesia). He has an easier time sitting still and relaxing. No more facial tics are evident, and there is less tremor of the hands.

## DISCUSSION

As is often the case, there aren't clear cut diagnostic features for a patient with longstanding psychosis. In the current account, the neuropsychological evaluation was made in adult age, and only after a while it became known that the patient had engaged in frequent recreational substance abuse on and off from late adolescence. The possible contributory aspects from drug consumption makes the precision of a neuropsychiatric diagnosis less reliable. We thus believe that besides the obvious and independent positive symptoms of schizophrenia, the overall profile in this case should be interpreted as a combination of schizophrenia with its premorbid symptoms and negative symptoms, as well as superimposed harmful effects of substance abuse. It is difficult to say whether our patient would have developed a primary psychosis in the absence of substance use, but it seems certain that substance use relapses have driven the relapse in psychosis more than once since his debut. It has also been a hindrance for effective treatment.

At the time when it was decided to add CAR to our patient's treatment he had previously been treated with a wide range of antipsychotic drugs. All of these had shown some effect, but none had led to complete symptom relief, and the suffering from negative and cognitive symptoms persisted. For example, the D2 receptor blocking agents (RIS or HAL) previously used to handle intense positive symptoms were not satisfactory, neither from a negative and cognitive symptom nor a side effect perspective. A Clozapine treatment course earlier in his illness history had been accompanied with some effect also on negative symptoms, but we speculate that this was related to increased abuse of stimulating substances during this period in time. We thus decided to try QUE as an add-on, an agent known to be pharmacologically different and with less D2 receptor impact than the former two high-affinity antagonists. The choice of antipsychotic agent in this case was also based on the express notion that trying a medicine from a different antipsychotic drug class should be attempted if the prior compound has not had the desired effect (5, 12).

The history of severe positive symptoms as well as clear cognitive and negative dysfunction, indicated to us that our patient needed strong support to improve all of these issues. Accordingly, and with the lack of any marked success with previous treatment regimens in mind, our ambition was to test an antipsychotic drug not previously tried; this in order to simultaneously address his positive as well as the prominent cognitive and negative symptoms. The basic pharmacological and clinical profile of CAR points to significant beneficial impact in particular with regard to the negative and cognitive symptom domains, in addition to its efficacy *vs*. positive symptoms (6–8, 14, 15). CAR therefore appeared to provide us with an option with a particularly good fit regarding our patient's symptom expressions, and hence worthwhile to try.

When CAR treatment was initiated he was on a regimen of QUE (900 mg/d) and HAL (7.5 mg/d). The latter agent was used during the intense acute phase of the hospitalization. According to the deliberations above, we choose to switch from HAL to CAR, applying a relatively fast up-titration of the latter, reaching 6 mg/d in 7 days; QUE was retained throughout. HAL was tapered beginning on the 8th day after initiating CAR, and an alleviation of both negative and positive symptoms were evident 2–3 weeks after starting CAR. Incidentally, this time-scale coincides with the predicted reach of steady-state levels of CAR and its main active metabolite [di-desmethyl-CAR; (11)]. The patient then exhibited a sense of increased awareness of disease that could even be described as an increase of insight. Similar changes had been seen before with this patient and it is hard to tell whether it was a new development or an even deeper insight than earlier. Regardless, clinically he engaged clearly more collaboratively around his treatment than the typical schizophrenia patient who needs to be persuaded to agree to treatment. The impression thus was that the effect of the CAR + QUE combination treatment was superior to any of his previous medication trials. During late 2020, adjustments of the doses of both agents were done to find the optimal regimen for our patient, eventually ending in CAR (4.5 mg/d) and QUE (900 mg/d) that appeared to be the best choice for him (see, **Table 2**).

To add to the overall equation, our patient had previously had repeated relapses that seemed at least partly related to substance use. He had tried a number of antipsychotic drugs before, all moderately effective but never leading to complete remission; at some point, even accompanied by relapse in substance use. We therefore speculate that he may have used classified drugs at the end of a deteriorating course in his disorder as a "self-medication" substitute to healthier, better functioning coping strategies. Notably, 2 months after initiating CAR treatment, our patient spontaneously reported that he had decreased cigarette smoking (from 60 cigarettes/d). About 5 months later he stopped altogether and now instead uses e-cigarettes. Interestingly, during this period, all of the urine screen tests (UTox) run for illicit drugs in this patient were negative. We believe that if the CAR treatment contributed to help him stay off substances it may increase his chances of continuous remission. Preclinical theory and findings along with recent clinical case reports are consistent with the idea that partial D3 receptor agonism by CAR may indeed be helpful in the treatment of drug dependence conditions (9, 10, 16–18). In a best-case scenario, his concomitant sudden and unexpected smoking cessation and lack of indication of continuing use of recreational substances could

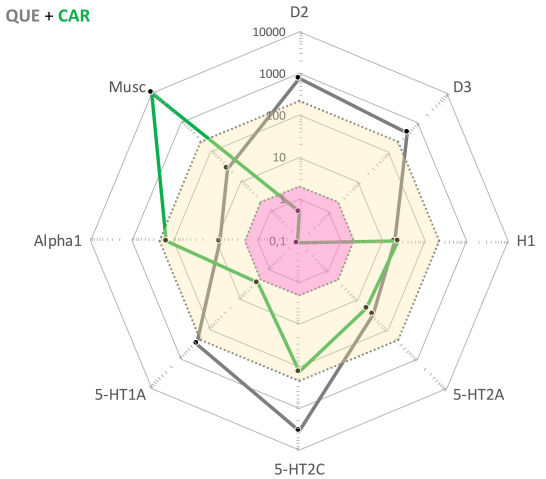


**FIGURE 1 |** Cobweb depiction of Quetiapine (QUE) and Cariprazine (CAR) target profiles overlaid on the free steady-state plasma concentrations of these antipsychotics at average clinical dosage (QUE: yellow area; CAR: pink area). Black dots correspond to drug affinities reported in the literature (in nM) for the targets labeled on the edges of the cobweb; the closer to the center, the higher affinity for the target in question.

signify a dampened drive for substances of abuse. If so, CAR may increase his chances of continuously abstaining from drugs, and by doing so also improve his chances to sustain prolonged remission. In support of this speculation, a recent paper reported the successful remission from persistent methamphetamine psychosis by CAR treatment (19). Interestingly, in another study the abuse of alcohol and cannabis in three bipolar I patients was also attenuated following treatment with CAR—one case of which in fact achieved markedly reduced alcohol craving and sustained stability upon combined CAR and QUE treatment (10).

In summary, for this particular patient the most effective treatment to date was a combination of QUE and CAR. Both of these drugs had been tried and deemed insufficient in monotherapy, but apparently synergized with regard to clinical efficacy once combined. To the best of our knowledge, this is not a treatment combination specifically recommended in any guidelines. This said, the complementary drug target profiles make sense from a pharmacodynamic perspective (see, **Figure 1**). While QUE shows rather poor D2 receptor antagonist properties along with intermediate affinities for, i.a., histamine H1 and 5-HT2A receptor sites, CAR has very high affinity and partial agonist properties at D3, D2, and 5-HT1A receptor sites. Furthermore, the combination of one antipsychotic with short (QUE) and one with extended half-life (CAR) is potentially favorable from a compliance point-of-view as it may provide a "buffering" capacity *vs*. therapeutic target occupancy fluctuation. This complementarity in pharmacodynamic, and also pharmacokinetic, features may tentatively underlie the beneficial clinical outcome in the current patient case.

## Strengths and Limitations

Needless to say, a limitation of the work is that it is based on the description of a single patient case, thus limiting generalizations to a wider patient population. However, the comprehensive and detailed account of the diagnosis and close management follow-up from the clinical and pharmacological perspective is a clearcut strength, particularly as one of the authors (JRC) has been able to follow the disease and treatment course of this patient over several years.

## CONCLUSION

It seems that CAR add-on to QUE treatment improved cognitive functioning and desire for addictive substance use in our patient. From an antipsychotic polypharmacy perspective, the CAR + QUE combination also appears to provide a pharmacodynamically as well as pharmacokinetically attractive treatment option with complementarity across several clinically relevant medication aspects. Prospective randomized studies are necessary to extrapolate the predictability of our findings to the broader population of individuals with schizophrenia, including patients using addictive substances.

## DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the data are extracted from a patient medical journal, and is thus personally confidential within the framework of the medical professionals involved in his treatment. Requests to access the datasets should be directed to José Rodriguez Cruz, jose.rodriguez_cruz@vgregion.se.

## ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## AUTHOR CONTRIBUTIONS

JR and JS were in charge of the patient's clinical management and wrote the original draft. JR, JS, and SH conceptualized and researched the subject, conceptualized, reviewed, and edited the manuscript. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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# Case Report: Cariprazine Efficacy in Young Patients Diagnosed With Schizophrenia With Predominantly Negative Symptoms

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Negative symptoms of schizophrenia are among the most invalidating clinical manifestations of this disorder, and they are correlated with poorer prognosis, lower quality of life, and fewer chances for successful social reintegration and professional rehabilitation. Although atypical antipsychotics have been associated with higher efficacy on negative symptoms than typical agents, not all of them are equally effective. Cariprazine is a new D3 and D2 receptor partial agonist, and its high D3 affinity may be useful for decreasing several adverse events (e.g., extrapyramidal symptoms or hyperprolactinemia), and also for increasing this drug's efficacy over negative symptoms. This case series presents three young adults with predominantly negative symptoms during treatment with an atypical antipsychotic, administered in stable dose within the therapeutic range, and for at least 4 weeks prior to the cariprazine switch. These patients (two male and one female, mean age 35.7 years) were diagnosed with schizophrenia, according to the DSM-5 criteria. They were evaluated using Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression-Severity (CGI-S), and Global Assessment of Functioning (GAF). Their mean initial values were 80.3 on PANSS, 4.3 on CGI-S, and 48 on GAF. All these patients were already on a treatment with stable doses of atypical antipsychotics (olanzapine 10 mg/day, $n = 1$, risperidone 6 mg/day, $n = 1$, and quetiapine 600 mg/day, $n = 1$). Cross-titration to cariprazine was initiated, from 1.5 mg qd up to 6 mg qd, during a mean period of 2.7 weeks. After 12 weeks of cariprazine 6 mg/day, the positive scale of PANSS was relatively stable compared to baseline, while the negative mean score decreased by 22%. Also, the mean CGI-S improvement was 15.4% and the GAF mean score increased by 17%. The overall tolerability was good, without severe adverse events being reported. Conclusions: Cariprazine is well tolerated and efficient for patients diagnosed with schizophrenia who have significant negative symptoms that impair daily functioning. After 12 weeks cariprazine succeeded in improving negative symptoms, global functioning, and clinical global impression.

**Keywords: novel atypical antipsychotics, negative symptoms, schizophrenia, cariprazine, tolerability, quality of life, social reintegration**

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## INTRODUCTION

Negative symptoms of schizophrenia are among the most invalidating clinical manifestations of this disorder, and they are correlated with poorer prognosis, lower quality of life, and fewer chances for successful social reintegration and professional rehabilitation (1–3). Targeting negative symptoms (e.g., apathy, alogia, flat affect) can lead to significant improvements of daily functional and quality of life (4). Although atypical antipsychotics have been associated with higher efficacy over the negative symptoms than typical agents, not all the atypicals are equally effective. According to a meta-analysis of placebo-controlled and head-to-head randomized controlled trials ($n$ = 402 studies, $N$ = 53,463 participants) that compared 32 antipsychotics, only clozapine, amisulpride, olanzapine, and, to a lesser degree, zotepine and risperidone decreased negative symptoms severity more than other agents, while the differences between the remaining drugs were less supported by evidence (5). An important problem that may lead to uncertainty in the interpretation of negative symptoms improvement in clinical trials is represented by lack of discrimination using standard measurements between primary and secondary negative symptoms (6). Therefore, the clinician should address this problem during the psychiatric interview, and to take into account any other sources of information available (medical personnel, family members or other caregivers), in order to differentiate between primary and secondary negative symptoms. This is not of scholastic importance, but it has practical utility, due to the different treatment approaches for the two groups of symptoms.

Cariprazine is a new D3 and D2 receptor partial agonist, and its high D3 affinity may be useful for decreasing several dopamine-related adverse events, and, in the same time, for increasing this drug's efficacy over negative symptoms (7). The efficacy and safety of cariprazine have been demonstrated in adults with schizophrenia during four short-term randomized, double-blind, placebo-controlled trials, two long-term open-label studies, one relapse prevention study, and one prospective negative symptom study vs. the active comparator risperidone (8). *Post-hoc* analyses supported efficacy of cariprazine across individual symptoms and domains of schizophrenia, and in areas like cognition, functioning, negative symptoms, hostility, and global well-being (8).

Cariprazine was generally well tolerated in clinical trials in patients with schizophrenia, and the most frequently reported adverse events were of mild to moderate severity (7). Cariprazine may reduce side effects when switching a patient from other antipsychotic because of its lower anticholinergic, anti-adrenergic, antihistaminergic, and metabolic effects, with a better cardiovascular safety profile (9, 10).

In a multicentric, randomized, double-blind, phase 3b trial ($N$ = 533 patients with predominant negative symptoms), cariprazine (3–6 mg/day) was superior to risperidone (3–6 mg/day) in leading to significant greater least squares mean change in Positive and Negative Syndrome Scale- factor score for negative symptoms (PANSS-FSNS) after 26 weeks of treatment (11). This trial was well-controlled for secondary negative symptoms, but it was sponsored by the manufacturer of cariprazine (6, 11).

According to the recommendations from an International Panel for the management of schizophrenia, cariprazine is useful in patients with first episode of psychosis, predominant negative symptoms (maintenance/acute phase) and significant side effects (e.g., metabolic syndrome, sedation, hyperprolactinemia) with onset during the administration of other antipsychotics (9). If the weight is placed on the long-term efficacy and tolerability, cariprazine may become one of the first-line medications in schizophrenia, not only for prominent negative symptoms, but also for relatively severe positive symptoms (9). An overlap of at least 2–3 weeks is usually recommended in clinical practice when switching from other antipsychotics to cariprazine, in order to avoid a dopaminergic, antihistaminergic and/or muscarinic rebound (9).

This case series presents three young adults with persistent negative symptoms during treatment with an atypical antipsychotic, administered in stable doses within the therapeutic range and for at least 4 weeks, prior to the cariprazine switch.

## CASE PRESENTATION

The first patient was a male, diagnosed with schizophrenia according to the DSM-5 criteria, age 37.5, who received treatment for the last 6 weeks prior to baseline with risperidone 6 mg daily. He was evaluated because of persistent negative symptoms, consisting mainly of anhedonia, alogia and avolition. This patient had a history of schizophrenia of more than 5 years, and received in the past olanzapine (10 mg qd, for almost 2 years) and amisulpride (800 mg daily, for 2 years), to which he responded partially, because several negative symptoms were still present. The patient accused tolerability issues, namely sedation to olanzapine, and extrapyramidal symptoms to amisulpride. The initial psychiatric examination detected residual positive symptoms- ideas of reference, mild suspiciousness and conceptual disorganization, as well as general symptoms- anxiety, insomnia, social withdrawal, poor attention and low memory performances. This patient had no family history of psychiatric disorder and no somatic comorbidity could be identified during the initial visit.

The first evaluation detected a total PANSS score of 80, with a negative scale score of 32, a CGI-S (Clinical Global Impression- Severity) value of 4 and a GAF (Global Assessment of Functioning) score of 52. Cariprazine was initiated based on this antipsychotic pharmacodynamics profile and its presumed efficacy over the negative symptoms. Risperidone was gradually tapered off, while cariprazine was initiated with 1.5 mg and titrated up to 6 mg qd, during a period of 15 days. No incident was reported during the cross-over period.

After 12 weeks of stable dose, the PANSS total score decreased to 66, with the negative scale showing a value of 26, the CGI-S score remained stable, and the GAF score increased to 60. The positive PANSS score decreased minimally, from 21 to 19. This patient reported no adverse events during the 12 weeks of the 6 mg qd cariprazine regimen.

The second patient was a male, age 33.5, diagnosed with schizophrenia for 11 years, who received treatment with olanzapine 10 mg qd for the last 8 weeks. He was previously on treatment with risperidone 8 mg/day for multiple periods of 6–12 months, interrupted by lack of adherence. Also, the patient received treatment with risperidone microspheres, up to 50 mg every 2 weeks, but after more than 1 year he declined the need for any injectable treatment and was switched back on oral medication. This patient had a family history of psychiatric disorder, as his father also had schizophrenia. No somatic comorbidity could be identified during the initial visit.

During the initial psychiatric evaluation this patient presented with fragmentary persecutory delusions without significant behavioral impact and prominent negative symptoms, especially flat affect, avolition, and anhedonia. His baseline PANSS total score was 78, with negative subscale score of 29, positive subscale score of 18, CGI-S score of 4, and GAF score=44. Olanzapine was gradually tapered off, while cariprazine was slowly titrated up to 6 mg qd, during 20 days. No clinical signs of positive or negative symptoms worsening was reported during the titration period.

After 12 weeks of cariprazine administered 6 mg qd, the PANSS total score decreased to 62, with the negative scale showing a value of 22, and the positive scale a value of 16. The CGI-S score decreased to three, while the GAF score improved by eight points, reaching a value of 52.

The third patient was a female, age 36, diagnosed with schizophrenia for 6 years, and she received treatment with quetiapine 600 mg qd for the last month. This patient had no family history of psychiatric disorder and no somatic disease could be identified during the initial visit. She had a personal history of multiple antipsychotics prior to the baseline treatment, including typical (haloperidol, zuclopentixol) and atypical (olanzapine, ziprasidone) agents. Her response to quetiapine was initially good, because it alleviated insomnia and anxiety, but the impact over the negative symptoms was less significant. Therefore, she was switched on cariprazine, starting from 1.5 mg, up to 6 mg qd, during a period of 22 days.

The initial psychiatric evaluation detected mainly negative symptoms, consisting of anhedonia, flat affect, avolition, low attention and memory performances. Her baseline PANSS total score was 83, with negative subscale score of 35 and positive subscale score of 23, CGI-S=5, and GAF=57. After 12 weeks of cariprazine stable dose treatment, PANSS total score decreased to 65, with negative score reaching a value of 27, while the positive score was relatively stable (22, final visit score). The CGI-S score at endpoint was 4, and the GAF improved to 60.

All these patients were screened for psychiatric comorbidities at baseline using Mini-International Neuropsychiatric Interview (MINI), but no specific diagnoses were detected except for schizophrenia. None of them required hospitalization during their switch and up to the final visit. Cross-titration to cariprazine was well tolerated in all cases, and all the other antipsychotics were tapered slowly in order to avoid antihistaminergic/antidopaminergic rebound. After 12 weeks of cariprazine 6 mg/day, the positive subscale of PANSS showed a relatively stable level, but the negative subscale mean score decreased with 22% (**Figure 1**). The overall PANSS mean score decreased by 19.5% (**Figure 2**), the CGI-S mean scores improved by 15.4% (**Figure 3**), while the mean GAF scores increased by 17%. The overall results are presented in

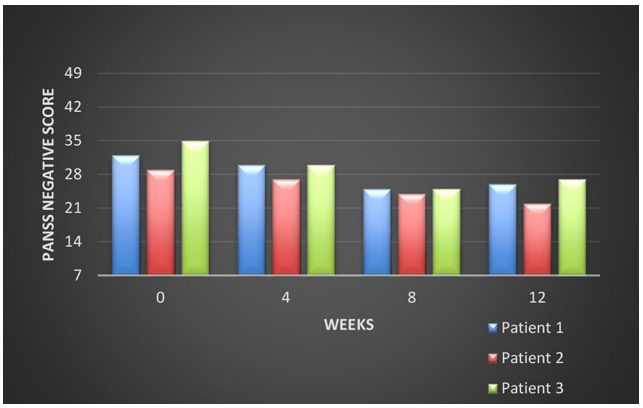


**FIGURE 1 |** Evolution of the PANSS negative subscale scores during cariprazine treatment.

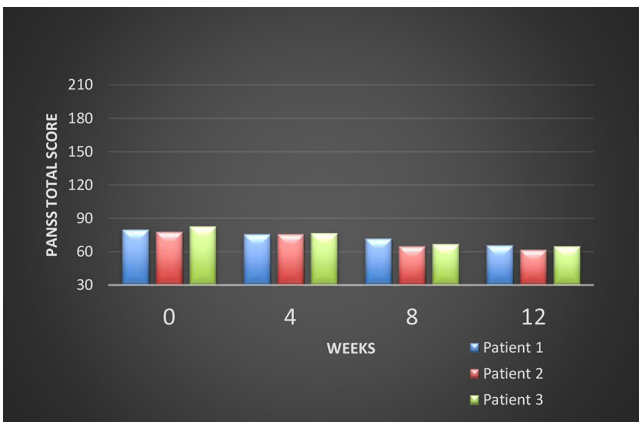


**FIGURE 2 |** Evolution of the PANSS total scores during cariprazine treatment.

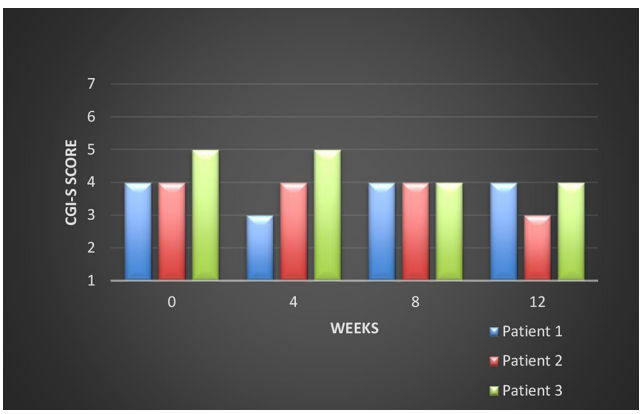


**FIGURE 3 |** Evolution of the CGI-S scores during cariprazine treatment.

**TABLE 1 |** The results of the cariprazine switch during 12 weeks of monitoring.

| | Patient 1 | Patient 2 | Patient 3 |
|---|---|---|---|
| Previous medication, dosage, and duration of its administration | Risperidone, 6 mg/day, 6 weeks | Olanzapine, 10 mg/day, 8 weeks | Quetiapine 600 mg/day, 4 weeks |
| Switch to cariprazine duration | 15 days | 20 days | 22 days |
| PANSS total score- initial visit | 80 | 78 | 83 |
| PANSS total score- final visit | 66 | 62 | 65 |
| PANSS Negative scale score- initial visit | 32 | 29 | 35 |
| PANSS Negative scale score- final visit | 26 | 22 | 27 |
| PANSS Positive scale score- initial visit | 21 | 18 | 23 |
| PANSS positive scale score- final visit | 19 | 16 | 22 |
| CGI-S initial score | 4 | 4 | 5 |
| CGI-S final score | 4 | 3 | 4 |
| GAF initial score | 52 | 44 | 57 |
| GAF final score | 60 | 52 | 60 |
| Self-reported/clinician-detected severe adverse events throughout the monitoring period | None | None | None |

**Table 1**. No severe adverse events was reported throughout the monitoring period.

## DISCUSSION

These patients presented a relatively long history of schizophrenia, between 2 and 11 years (mean value 6.3 years), although their mean age was 35.7 years. They all received multiple treatments before the initiation of cariprazine and presented negative symptoms under their current antipsychotic (olanzapine, quetiapine, or risperidone). Cariprazine is a distinctive antipsychotic agent due to its D3-preferential dopamine partial agonism, which make it preferable for patients with prominent negative symptoms. Patients tolerated well the antipsychotic switch from various antipsychotics to cariprazine. In this case series, after 12 weeks cariprazine succeeded in improving negative symptoms, global functioning, and clinical global impression. The positive symptoms were quite stable, but their low level of severity at baseline may have precluded the observation of a therapeutic effect.

Regarding the limitations of this case series, it must be taken into account the short period of monitoring, which may have prevented the observation of other, long-term, treament effects. Also, variables related to the antipsychotic's adverse events were not monitored in a structured manner, as we only collected patients' reports about tolerability and data from clinical exams during each visit. It is also important to mention that patients included in this case series were relatively stable, based on their initial PANSS, GAF, and CGI-S scores, without severe positive or behavioral symptoms and they did not require hospitalization.

## PATIENT PERSPECTIVE

"I was unable to take care of myself because I had no energy. No interest, either. And I was feeling scared or even frightened. I feel now I can go outside if I have to do something. I feel less blocked from within" (Patient number 1).

"I feel less tension inside me now than before. My thoughts are more synchronized with what I do… I can watch a TV movie, which I couldn't do before because I was sort of numb" (Patient number 2).

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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**Conflict of Interest:** The author declares 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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REVIEW
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# Treatment of Symptom Clusters in Schizophrenia, Bipolar Disorder and Major Depressive Disorder With the Dopamine D3/D2 Preferring Partial Agonist Cariprazine

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Cariprazine is currently approved for the treatment of patients with schizophrenia (USA and EU), and for manic, depressive, and episodes with mixed features in bipolar I disorder (USA): several randomized controlled studies have also explored its efficacy in patients with major depressive disorder. This review summarizes its current therapeutic uses and potential advantages for treating the main symptoms of schizophrenia, bipolar I and major depressive disorder, considering its pharmacodynamic properties, efficacy, and tolerability. Its predominantly D3 receptor preferring affinity, with functional selectivity according to the prevailing neuronal environment, contributes to its efficacy across a wide array of psychopathological symptoms (including reality distortion, disorganized thought, negative symptoms, mood disturbance, anhedonia, and cognitive impairment), and to a favorable side effect profile. Cariprazine may be a "drug of choice" in patients with predominant negative and cognitive symptoms of schizophrenia, as well as those with metabolic syndrome. Further investigation of its relative efficacy when compared to aripiprazole or other active comparators is warranted. Its effectiveness in the treatment of bipolar mania, bipolar I depression and bipolar I episodes with mixed features, with minimal accompanying metabolic changes is well-established. The longer half-life and delayed time to relapse in patients diagnosed with schizophrenia when compared to other second-generation antipsychotics represent other advantages, given the high rates of non-adherence and frequent relapses seen in clinical practice. Its efficacy in overlapping symptom domains in other major psychiatric disorders appears promising.

**Keywords: cariprazine, D3/D2 partial agonist, schizophrenia, bipolar I disorder, major depressive disorder**

## INTRODUCTION

Schizophrenia, bipolar disorder, and major depression are common major mental disorders which make a substantial contribution toward total disability adjusted life years. Despite nosological specificity, these disorders can share mood disturbance (depression, euphoria, irritability, anhedonia, etc.), reality distortion (hallucinations, delusions), and cognitive impairment may be present even during periods of remission, exerting negative effects on social functioning, basic life skills and quality of life (1–3). This overlap differs according to the severity of individual symptoms and may be due to varying degrees of genetic contributions, as indicated by twin, family, and molecular genetic studies (4–8).

Due to the known actions of available psychotropic medicines on individual neuronal and biochemical mechanisms within the central nervous system, and to growing awareness of their effects across a wide range of overlapping symptoms, a current imperative for developing innovative treatments for patients with mental disorders is focused on compounds that combine multimodal activity with greater efficiency on different symptom profiles, potential neuroprotective effects, and modulatory effects on the course of the disorder.

With the advent of aripiprazole, a new class of antipsychotic drugs emerged that exhibit partial agonism at dopamine (DA) receptors, thus allowing adaptation to the prevailing transmitter environment, e.g., to act as either a functional antagonist or agonist (9–14). This modulation of dopaminergic transmission decreases DA levels when they are high or increases levels when they are low (9–14). In the case of schizophrenia, functional antagonism in mesolimbic pathways reduces positive symptoms of psychosis, whereas functional agonism in the nigrostriatal pathways reduces the possible development of iatrogenic extrapyramidal side effects (13, 14). Dopamine D3 receptors have a high affinity for DA and are localized predominantly in the ventral striatum and other parts of the limbic system, whereas their distribution is low in the dorsal (motor) striatum and cortical region (15). This distribution allows dopamine D3/D2 preferring partial agonist cariprazine to exert antipsychotic activity, with a low propensity for unwanted extrapyramidal side effects, hyperprolactinemia, metabolic syndrome, and anhedonia (12, 16).

## CARIPRAZINE

Cariprazine is a "dopamine stabilizer", with higher affinity toward D3 receptors than dopamine, thus increasing dopaminergic neurotransmission in the nucleus accumbens and hippocampus. It binds to D3 receptors with a 10-fold higher affinity than for D2 receptors, exerts antagonist effects at 5-$HT_{2B}$ receptors and partial agonism at 5-$HT_{1A}$ receptors, and has moderate and low activity for histamine H1 and 5-$HT_{2C}$ receptors, respectively (12). Cariprazine was granted approval from the Food and Drug Administration (FDA) in the United States for the treatment of schizophrenia in adults as well as for patients with bipolar I disorder experiencing symptoms of acute mania, mania with mixed features, or depression (17). Furthermore, randomized controlled trials (RCTs) are currently exploring its efficacy as add-on therapy in patients with major depressive disorder (18).

### Metabolism and Interactions

Cariprazine is metabolized via P450 3A4 (CYP3A4) and to a lesser extent by cytochrome P450 2D6 (CYP2D6) into two major active metabolites, desmethyl-cariprazine (DCAR) and didesmethyl-cariprazine (DDCAR) with broadly similar pharmacological activity (19). Time to reach steady state based on half-life is 2–4 days for cariprazine, and 1–2 days and 1–3 weeks for DCAR and DDCAR, respectively (20). This contrasts with the half-life parameters of other oral second-generation antipsychotics, with shorter half-lives between 3 and 91 h (e.g., risperidone, paliperidone, aripiprazole, asenapine, brexpiprazole, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, and ziprasidone) (21, 22).

In patients undergoing treatment with concomitant carbamazepine and oxcarbazepine, the effect of cariprazine will be decreased due to carbamazepine and oxcarbazepine induction of cytochrome P450 CYP3A4 enzyme, and this combination is contraindicated, as well as combination with other P450 CYP3A4 inducers (e.g., phenobarbital, phenytoin, rifampicin, St. John's Wort, and glucocorticoids) (23). When a patient is taking strong inhibitors of P450 CYP3A4 (e.g., clarithromycin, erythromycin, diltiazem, itraconazole, ketoconazole, ritonavir, verapamil, goldenseal, and grapefruit) the dose of cariprazine should be reduced by half. No dosage adjustment is necessary if patient is concomitantly taking CYP2D6 inhibitors (23).

## CARIPRAZINE EFFICACY ACROSS THE WIDE RANGE OF SYMPTOMS OF SCHIZOPHRENIA

The principal clinical features of schizophrenia comprise positive and negative symptoms, mood symptoms, disorganization symptoms and cognitive impairments, with different underlying pathophysiological mechanisms and different responses to pharmacological treatments (24, 25). First- and second-generation antipsychotics can both successfully attenuate the positive symptoms of schizophrenia, however the negative symptom domain (dominated by the "5As"- apathy, amotivation, anhedonia, alogia, asociality) still represents an unmet clinical need as many currently available antipsychotics fail to improve these (26).

Cariprazine has shown efficacy in reducing the total Positive and Negative Syndrome Scale (PANSS) as well the Clinical Global Impression-Severity (CGI-S) scale scores in several double-blind, placebo-controlled clinical trials involving patients with acute exacerbation of schizophrenia (27–29). No clinically significant changes compared to placebo were observed regarding metabolic parameters, ECG abnormalities (including QT prolongation), laboratory results or prolactin levels (27–29). The most common side effects throughout the studies were akathisia, extrapyramidal disorder, tremor, insomnia, sedation, dizziness, and gastrointestinal side effects

(27–29). The pooled-analysis reported by Marder et al. (30) which investigated data from three positive, 6-week duration, double-blind, placebo-controlled, phase 2/3 trials of cariprazine in patients with acute exacerbation of schizophrenia has shown its efficacy in doses of 1.5, 3, 4.5 and 6 mg in treating a wide array of symptoms (positive symptoms, negative symptoms, disorganized thought, uncontrolled hostility/excitement, and anxiety/depression). Furthermore, when compared to placebo, cariprazine in daily doses of 1.5, 3 and 6 mg a day has shown efficacy in relapse prevention (31), as well as in doses of 3, 6 and 9 mg (32). Although clinical studies have examined doses above 6 mg per day, the manufacturer's recommendation is a maximum of 6 mg per day due to the dose-dependent occurrence of adverse events and insufficiently increased efficacy to justify higher dosage (23).

Cariprazine was also found to be uniquely effective in treating primary negative symptoms of schizophrenia, due to its predominant preference for D3 receptors, as well as its considerable affinity for 5-$HT_{1A}$ receptors (33–37). In a randomized, double-blind multicenter study which compared the efficacy of cariprazine and risperidone in patients with schizophrenia with predominantly negative symptoms, cariprazine in the mean dose of 4.2 mg/d showed a superiority over risperidone (mean dose 3.8 mg/d) at Week 14, which was continued until Week 26 (end of trial) (33). Significant improvement over risperidone was evident on a wide array of negative symptoms of schizophrenia (35). In therapeutic doses of 4.5 mg−6 mg/d, cariprazine has shown greater efficacy when compared to aripiprazole in reducing moderate to severe negative symptoms of schizophrenia (36). An observational study by Rancans et al. (34) showed the effectiveness of cariprazine in 'real-life' clinical settings when treating negative symptoms. In a *post-hoc* analysis of long-term treatment, studies have shown that cariprazine also improved everyday functioning and social skills which influence quality of life (37). This is a potentially significant advantage, considering that recovery should include not only symptom reduction but also functional improvement across various aspects of life (38, 39).

## One Day Dosing of Cariprazine

Due to the long half-life of cariprazine once daily administration is possible, which facilitates dosing and treatment adherence (40). The long half-life of cariprazine and its active metabolites, especially (DDCAR) with its 1–3-week half-life (20) distinguish cariprazine from other second-generation antipsychotics whose half-life, including their metabolites, is <4 days. It may be an important factor in the delayed relapse rate when compared to other second-generation antipsychotics (placebo relapse rate after last dose of cariprazine at week four was estimated to be 5%, compared to other oral antipsychotics ranging from 8–34% (22). Treatment with cariprazine can thus bridge the problem of emerging non-adherence after hospital discharge and first outpatients' appointments, as non-adherence and partial adherence is still a substantial problem which threaten patients' recovery (41).

## Cariprazine as an Add-on Therapy to Other Antipsychotics in Patients With Schizophrenia, and Switching Recommendations

Early and late non-response is common in schizophrenia, and several potential management strategies are proposed, among them the adding-on of another medication. Two case reports by de Berardis et al. (42) have shown that adding cariprazine to 400 and 300 mg of clozapine (in an initial dose of 1.5 mg and after 7 days titration 3 mg a day) resulted in an improvement in total PANSS score, positive and negative sub-scores, and general symptoms score: the combination was well-tolerated, with no side effects, and reduction in some of the weight gained during clozapine therapy.

According to the recommendation from an International Panel reported by Fagiolini et al. (43) when switching from other antipsychotic drugs to cariprazine, a cross-titration is recommended with the need to reach an effective dose ("plateau" in plasma concentration) of cariprazine before tapering or stopping the first medication; furthermore, adding benzodiazepines (e.g., lorazepam) for a short period may also help in reducing rebound of symptoms; the length of the titration depends on the type of other antipsychotic, which in the case of aripiprazole is one week or less, 2–3 weeks if the main antipsychotic was risperidone or haloperidol, and longer (3–4 weeks) in the cases of olanzapine and quetiapine.

# EFFECTS OF CARIPRAZINE ON NEUROCOGNITIVE DEFICITS IN PATIENTS WITH SEVERE MENTAL DISORDERS

Patients with severe mental disorders such as schizophrenia, bipolar disorder and major depression often have impairments across many cognitive domains, such as memory, motor speed, verbal fluency, executive function, attention, speed of information processing, and affective memory (3, 44–47), These neurocognitive impairments can limit work performance and social adjustment, reduce overall quality of life as well as are the best predictors for long-term psychosocial outcomes (2, 48). Given that neurocognitive deficits are often also present during periods of remission (3, 49, 50) the importance of addressing neurocognitive function is clear, especially in the early stages of the illness. While DA antagonists regulate DA excess and attenuate positive psychotic symptoms, they may also increase negative symptoms, cognitive problems, and extrapyramidal side effects by blocking activity in the regions characterized by dopaminergic underactivity (51, 52). Animal studies have demonstrated the effects of cariprazine as D3 preferring D3/D2 partial agonists in striatum, nucleus accumbens and ventral hippocampus, parts of the brain important in linking memory of the surrounding and motor behavior when recalling information about reward-seeking behavior (16). Furthermore, cariprazine significantly diminishes phencyclidine (PCP)-induced cognitive deficits in *in vivo* animal studies, via a D3 receptor activity (53, 54). Importantly, it is suggested that compounds which have

partial agonism at D3 receptors function as functional agonists in brain regions with a relative deficit in dopamine, hence causing pro-cognitive effects (53, 55). Therefore, drugs with such mechanism of action can be an important driver for functional recovery in patients with schizophrenia, bipolar I disorder or even major depressive disorder (55–58).

## CARIPRAZINE EFFICACY ACROSS THE WIDE RANGE OF SYMPTOMS OF BIPOLAR DISORDER

Bipolar I disorder is a chronic mental illness presenting with episodes of manic, depressive mood and episodes with mixed features (24), with a significantly negative impact on main domains of quality of life (59), which is lower compared to healthy controls even in the period of euthymia (60). The Diagnostic and Statistical Manual of Mental Disorders-5th edition (24) specifies episodes with mixed features in both Bipolar I and Bipolar II disorder, in which at least three symptoms of opposite polarity are present at the same time with major mood disturbance. This specifier promises recognition and treatment of patients with mixed features, characterized with an unfavorable course with more severe symptomatology, more frequent mood swings, higher rates of comorbidity (61), and suicidal behavior (62).

Double-blind, placebo-controlled studies have demonstrated the efficacy of cariprazine in low doses (3–6 mg/day) and high doses (6–12 mg/day) in the treatment of manic and mixed episodes of bipolar I disorder (63–66). Importantly, cariprazine was well-tolerated with non-significant changes in prolactin levels, QT intervals and metabolic parameters [with the exception for fasting glucose in the study by Durgam et al. (64)]. Akathisia and other extrapyramidal symptoms were the only prominent side effects when compared to placebo (63–65). In a *post-hoc* pooled analysis of three studies by McIntyre et al. (66) cariprazine was efficacious in significantly reducing manic and depressive symptoms in Bipolar I mania with mixed features. The dose range recommended in the treatment of acute manic or acute mixed episodes is 3–6 mg a day, with a starting dose of 1.5 mg a day and increase to 3 mg on Day 2 (23).

In bipolar I disorder patients are spend much of their time in depressive states (67). Antidepressant monotherapy in the treatment of bipolar depression is not recommended as it can induce mania or hypomania as well as increase mood cycling (68). Double-blind, placebo-controlled studies have shown efficacy of cariprazine in reducing depressive symptoms in bipolar I depression (69, 70). Cariprazine in a dosage of 1.5 mg/d had the most robust efficacy and good safety for the treatment of patients with Bipolar I depression (69). Maximum recommended dose is 3 mg a day, increased on Day 15 (23). In a *post-hoc* analysis of pooled data from three randomized, double-blind, placebo-controlled studies, cariprazine was found to be effective across an array of symptoms of bipolar I depression such as sadness, fatigue, and anhedonia (expect inner tension) in the doses of 1.5 and 3 mg in adult patients (71). In addition, cariprazine might be also effective in improving anhedonia and cognitive dysfunction (72). In terms of safety, findings from a pooled analysis of four studies in patients with bipolar depression (73) showed that cariprazine in doses of 1.5 and 3.0 mg is well-tolerated with little weight gain and minimal metabolic changes when compared to placebo. The most common side effects experienced by patients were akathisia, restlessness, nausea, and fatigue. Importantly, cariprazine did not destabilize mood or induce manic switch. Furthermore, incidence of suicidality was low in cariprazine group (73). Finally, a *post-hoc* analysis of three randomized, placebo-controlled studies showed that cariprazine is effective in treating bipolar I depression with mixed features in the doses of 1.5 and 3.0 mg per day (74).

Particular challenges when treating patients with bipolar disorder occur in patients with rapid cycling conditions, background dysregulated affective temperaments, a history of suicidality, as well as elderly patients (75–78). Another problem resides in the frequent need for polypharmacy (79). Cariprazine can be combined with the mood stabilizer lithium carbonate but combination with carbamazepine is contraindicated, as carbamazepine is a strong inducer of cytochrome P450 CYP3A4 (23). Further research can answer whether cariprazine treatment is beneficial in addressing these pressing challenges.

Other than quetiapine, cariprazine is the only drug to receive FDA approval for both acute treatment of mania and acute depressive episodes associated with Bipolar I disorder. The dosage approved for use in bipolar depression ranges from 1.5–3 mg/day. However, the European Medicines Agency (EMA) has not currently approved cariprazine for this indication.

## EFFICACY OF CARIPRAZINE AS AN AUGMENTATION APPROACH IN MAJOR DEPRESSIVE DISORDER

Despite the availability of multiple classes of antidepressants, treatment of patients with major depression is often a challenge, and a significant proportion of patients have an inadequate acute and long-term response to antidepressant treatment, with much "room for improvement" (80). The sub-optimal efficacy of current antidepressant treatment and high rates of treatment resistant cases underlie the need for frequent alternative solutions, such as adding a second-generation antipsychotic with antidepressant effects.

Although not approved by the FDA for the treatment of major depression, some double-blind placebo-controlled studies have indicated the efficacy of cariprazine as an adjunctive therapy to antidepressants in treatment-resistant major depressive disorder (81, 82). By contrast, the randomized-controlled, double-blind study reported by Earley et al. (83) did not find significant improvement with adjunct cariprazine in patients diagnosed with major depressive disorder with previously inadequate response to antidepressant treatment. The meta-analysis undertaken by Vázquez et al. (84) found that cariprazine is more effective than placebo, but less effective than aripiprazole [olanzapine + fluoxetine] combination, risperidone, and ziprasidone in attaining additional antidepressant response in patients diagnosed with major depressive disorder with

inadequate response: akathisia was the most frequent side effect. When combining cariprazine with SSRIs or SNRIs clinicians should be aware of side effects such as akathisia, insomnia, and nausea, especially in doses of cariprazine higher than 2 mg/d (81). Further research is needed to fully clarify the role of cariprazine as an augmentation in the treatment of patients with unipolar depression who previously failed to respond to antidepressants.

## DISCUSSION

Seventy-two years have passed since the appearance of haloperidol as the main representative of the "first generation" or "typical" group of antipsychotics characterized by activity through antagonism of dopamine D2 receptors. Some progress has been made with "second generation" or "atypical" drugs which achieved their effectiveness through potent binding to 5-$HT_{2A}$ receptors as well as to D2 receptors. Current "dopamine modulators" (e.g., aripiprazole, brexpiprazole, blonaserin) differ depending on their predominant site of action at dopamine and serotonin receptors, with consequent differences in the spectrum of psychopathology they reduce and their side effect profile (55). Among them, cariprazine has a D3 receptor preferring affinity, with functional selectivity according to the prevailing neuronal environment, thus contributing to its efficacy across an array of symptoms of schizophrenia, bipolar disorder, and major depressive disorder (27–37, 63–66). Importantly, cariprazine also exhibits a favorable side effect profile with no higher incidence on metabolic parameters, ECG abnormalities, vital sign and prolactin levels changes compared to placebo (27–37, 63, 65, 66). Its efficacy in long term use in schizophrenia is also confirmed (31, 32, 37).

Cariprazine may be a "drug of choice" in patients with predominant negative and cognitive symptoms of schizophrenia, as well those with metabolic syndrome. Its effects as an add-on approach to potentially reverse side effects caused by other medications should be further investigated. Due to the long half-life of cariprazine and its active metabolites, the time to relapse in patients diagnosed with schizophrenia is delayed when compared to other neuroleptics, which represents a useful advantage in clinical practice. Its effectiveness in treatment of bipolar mania, bipolar depression, and bipolar episodes with mixed features with minimal metabolic changes is well-established, and core symptoms of bipolar depression -sadness, fatigue, and anhedonia, as well as cognitive deficit have been strongly reduced by cariprazine, without switching to mania.

Given the efficacy of cariprazine in the treatment of core behavioral, mood and cognitive symptoms of severe mental disorders, it is reasonable to anticipate potential benefits in the treatment of at least some symptoms in autism spectrum disorder and addictions. Preliminary pre-clinical and clinical studies have shown beneficial effects of cariprazine in reversing core behavioral deficits and behavioral disturbances—aggression, irritability, self-injurious behavior, and impulsivity—in autism-spectrum disorder, as well as in "relapse prevention" in cocaine-seeking rats (85–87).

## CONCLUSIONS

The dopamine D3/D2 preferring partial agonist cariprazine has shown efficacy across the wide array of symptoms in schizophrenia and bipolar disorder (reality distortion, disorganized thought, mood disturbance, anhedonia, and cognitive impairment), and a favorable side effect profile. Its efficacy in overlapping symptom domains in patients with other major psychiatric disorders (major depression, autism spectrum disorder, addictions, etc.) is worthy of further exploration.

## AUTHOR CONTRIBUTIONS

BB wrote the first and subsequent drafts of the manuscript. IR and MZ assisted in literature research and writing the manuscript. DB supervised and revised all later drafts of the paper. All authors reviewed the paper and approved the final version.

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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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# The More, the Merrier…? Antipsychotic Polypharmacy Treatment Strategies in Schizophrenia From a Pharmacology Perspective

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Antipsychotic polypharmacy/drug combination treatment (APP) is a remarkably common practice in the schizophrenia context, given the lack of general support in treatment Guidelines. There is also a vast literature on APP outcomes, but a paucity of high-quality evidence-based data to guide and optimize adequate use of APP. This seems particularly true regarding many pharmacology-based considerations involved in APP treatment strategies. This paper first briefly summarizes clinical literature related to the use of APP. Against this backdrop, the pharmacological target profile features are then described of frequently used antipsychotic agents, in relation to estimated free plasma exposure levels at clinically efficacious dosing. APP strategies based on the properties of these drugs are then scrutinized and gauged within the background literature framework. The anticipated usefulness of APP from the pharmacological standpoint is detailed regarding efficacy, adverse effect (AE)/tolerability, and safety perspective, including why, when, and how it may be used to its advantage. For the purpose, a number of theoretically beneficial combinations as well as instances with suboptimal—and even futile—APP approaches are exemplified and discussed from the rational pharmacodynamic and pharmacokinetic pros and cons point-of-view. In this exposé, particular attention is paid to the utility and features of 3rd Generation Antipsychotic dopamine (DA) D2-D3 agonists within an APP setting.

**Keywords: antipsychotics, polypharmacy, schizophrenia, pharmacodynamic profiles, efficacy, adverse events, drug combinations, pros and cons**

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## INTRODUCTION

In an ideal pharmacotherapy setting, schizophrenia treatment with a single antipsychotic agent would be preferable. The treatment drug should additionally be broadly efficacious across symptom domains, while devoid of patient tolerability, safety, and adverse effect issues—thereby overall promoting medication adherence and quality of life. Needless to say, this is however far from the real-world experience with pharmacological treatment approaches to schizophrenia.

**Figure 1** illustrates some general background impressions from the—vast—Antipsychotic PolyPharmacy (APP) literature. Notwithstanding that the practice is not generally encouraged by

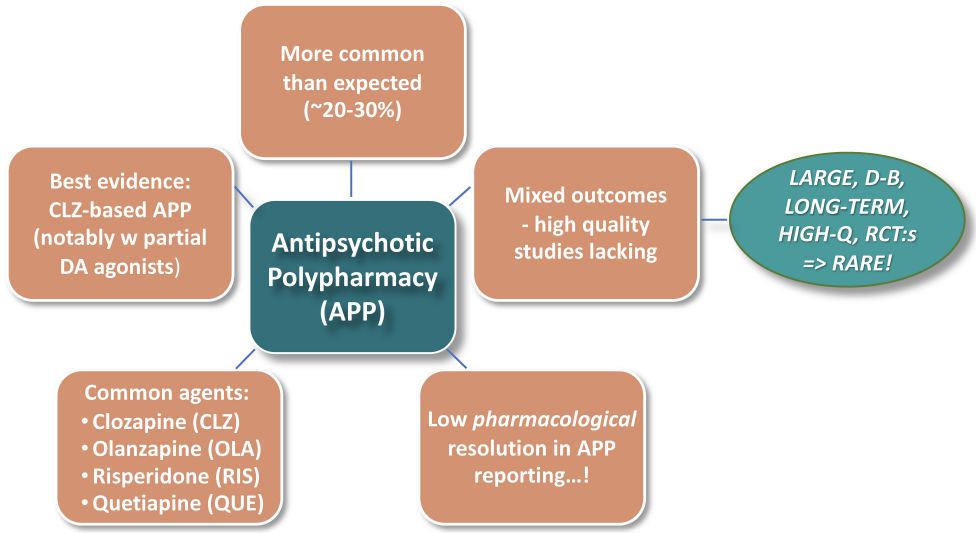


**FIGURE 1 |** Antipsychotic polypharmacy (APP)—broad literature background impressions.

treatment Guidelines, APP is remarkably common in the schizophrenia context. Reported rates also vary substantially across geographies, timeframes, and treatment conditions, with recent median prevalence figures, at least in Western societies, ranging typically between 20 and 30% (1–3). However, there is a paucity of evidence-based data to guide and optimize adequate use of APP. This seems particularly true regarding many pharmacology-based considerations involved in APP strategies.

A comprehensive formal review of the practice of APP *per se* is beyond the scope of the current paper, where the prime focus is upon pharmacological underpinnings in relation to the diverging outcome of combinations of different antipsychotic agents. With a view to nonetheless set a relevant framework for the discussions, the current account attempts to assess and synthesize background knowledge from the APP literature, with particular attention paid to pharmacological aspects involved. This framework is to a large extent based on meta-analysis studies and authoritative systematic reviews (1–4) but also includes information extracted from searches on single agents in the polypharmacy-in-schizophrenia context.

## APP: WHY, WHEN, AND TO WHOM?

Clearly, APP is not for every single antipsychotic therapy situation. The directions described in the NICE, UK, Clinical Guidelines (5) may be viewed as a prototypical example on when to—potentially—introduce APP. Briefly, this represents a stepwise transition from 2 or more failed antipsychotic monotherapy (APM) trials, through clozapine (CLZ; monotherapy) treatment, and then onwards to third-line APP therapy approaches (with proper control assessment stations on the way), and the explicit recommendation to take pharmacological differences in antipsychotic drug profiles into account (see, **Figure 2**).

A variety of reasons for instigating APP have been given. These include general desires to enhance, broaden, and sustain treatment efficacy—but also to attenuate adverse events (AE; e.g., weight gain, metabolic issues, and prolactin rise) and as a preventive measure vs. relapse and rehospitalization—relative to the outcome from APM alone. The aforementioned ambitions apply in particular concerning the management of negative and cognitive symptoms, in patients with greater illness severity and complexity, longer duration of illness and hospitalization, and treatment refractoriness (1, 6, 7). Other associations of APP, e.g., with younger age and male sex may stem from more severe (negative) symptoms already at early age in males than in females (7). Observed variations across geographies possibly reflect an impact of local therapy tradition and inherited prescriptions (1).

### Commonly Given Pharmacodynamic (PD) Reasons

Several pharmacodynamically-based—and inter-related—reasons for initiation of APP have been cited in the literature [**Figure 3**; (1, 8)]. Among these, unsurprisingly, an aim to enhance efficacy and broaden clinical effect into less responsive symptom domains is commonplace, as is the intent to adjust antipsychotic dose vs. adverse event issues (AE). The more direct target-focused reasons include a desire to optimize D2 receptor occupancy, and/or to achieve an overall more favorable treatment response (efficacy and/or AE) outcome by pharmacologically accessing other receptor categories and/or subtypes.

### Concerns, Questions, and Considerations

A number of concerns with APP have also been raised (1, 9). Some of the more common actually contrast with

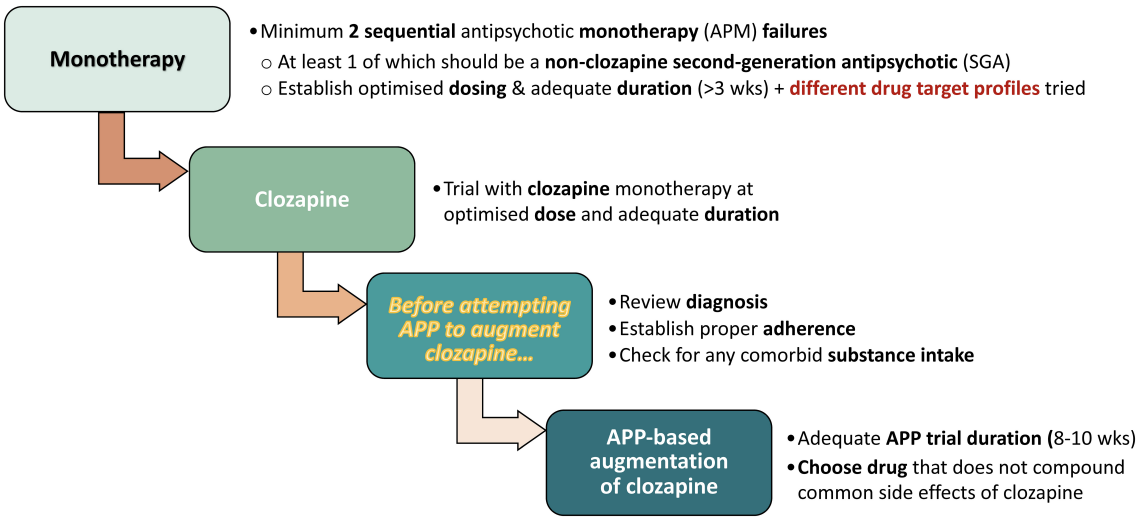


**FIGURE 2 |** Stepwise transition to APP, based on NICE, UK, Clinical Guidelines (5).

the stated intentions for APP. For example, published data suggest that APP often implies higher (instead of lower) total dosages of antipsychotics and increased (rather than attenuated) risks for AE (1, 10, 11)—tentatively related to increased *total* antipsychotic dosage. With more than one drug on board, there might also be a greater risk of drug-drug interaction events, and difficulties attributing a beneficial or undesired response to the individual antipsychotic agent in an APP treatment combination.

Against the above backdrop it appears reasonable to ask whether APP is

- *Effective...?*
- *Tolerable...?*
- *Safe...?*
- *Useful for relapse, re-hospitalization, and prevention purposes?*
- *Based on clear pharmacological rationale…?*

## APP: Commonly Used Agents?

Which antipsychotics are common in APP contexts then? In the literature [e.g., (12, 13)], recurrently emerging drug choices for APP are first- and second-generation (FGA and SGA, respectively) antipsychotic agents like haloperidol (HAL), olanzapine (OLA), risperidone (RIS), quetiapine (QUE), and clozapine (CLZ). In addition, the earliest of the third generation antipsychotics (TGA), aripiprazole (ARI), appears to be a common APP add-on choice to many of the above FGA and SGA class drugs [see, e.g., (14)]. A number of recent case reports likewise suggest that cariprazine (CAR) may emerge as a beneficial option in the APP context [(15–18); *vide infra*], whereas so far there does not seem to be any reports of the use of the latest TGA brexpiprazole in APP combination approaches. A brief overview of antipsychotic target profiles toward APP is shown in **Table 1** below.

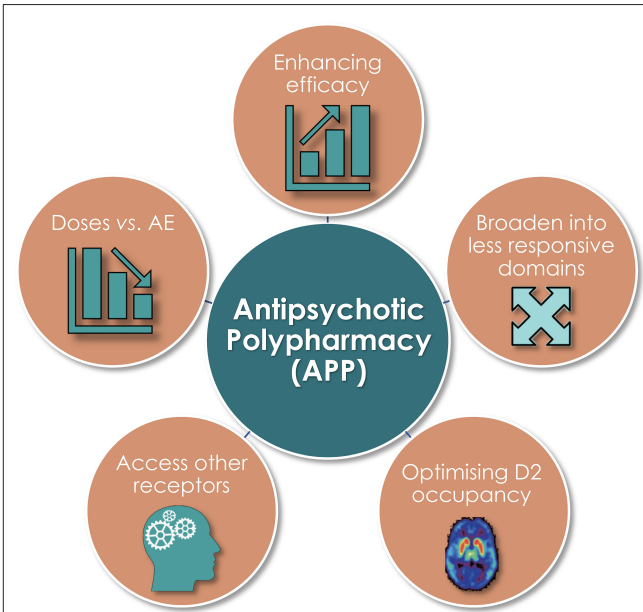


**FIGURE 3 |** Commonly given pharmacodynamically (PD)-based reasons to initiate APP.

## Efficacy of APP vs. Monotherapy?

A recent review and meta-analysis of the literature (4) found superiority of APP vs. monotherapy in open-label, low-quality studies. However, method-related factors and confounders limited the generalizability of interpretations and conclusions, and in corresponding high-quality, double-blind, randomized studies there was support for enhanced efficacy only for selected APP strategies *vs.* monotherapy. Specifically, while no superiority was found for combinations of two FGA/SGA D2 antagonists,

**TABLE 1 |** Examples of antipsychotics considered in the APP context.

| Drug | Desired target/s and affinity | Adverse effect (AE) target/s | Key property |
|---|---|---|---|
| Haloperidol (HAL) | Strong D2 | D2 | Antagonist |
| Olanzapine (OLA) | 5-HT2A/modest D2 | H1, 5-HT2C, cholinergic, D2 | Antagonist |
| Risperidone (RIS) | 5-HT2A/D2 | H1, D2, alpha1 | Antagonist |
| Quetiapine (QUE) | 5-HT2A/poor D2 | alpha1, H1, cholinergic | Antagonist |
| Clozapine (CLZ) | 5-HT2A/poor D2 | H1, 5-HT2C, alpha1, cholinergic | Antagonist |
| Aripiprazole (ARI) | Strong D2/D3 | D2? | Partial agonist |
| Cariprazine (CAR) | Strong D3/D2 | D2? | Partial agonist |

**TABLE 2 |** Key antipsychotic targets + associated drug benefit and AE impact examples.

| Target | Clinical effects associated with antagonism or partial agonism | |
|---|---|---|
| | **Desired** | **Adverse effects (AE)** |
| D2(*) | Antipsychotic *(positive symptoms)* | EPS, prolactin ↑, sexual dysfunction and cognition ↓ |
| D3* | Antipsychotic *(negative symptoms)* | |
| 5-HT1A* | Anxiolytic, antidepressant, anti-EPS(?) | |
| 5-HT2A | Anti-EPS and –akathisia | |
| 5-HT2C | | Appetite/weight ↑ and metabolic effects |
| H1 | Sedation | Sedation, cognition ↓, appetite/ weight ↑ |
| Alpha1 | | Hypotension, sexual dysfunction |
| Muscarinic | Anti-EPS | Dry mouth, constipation, blurry vision, cognition ↓ |

** Partial agonism*

*(*) Antagonism (Desired and Adverse Effects) or partial agonism (only Desired).*

addition of the partial DA agonist antipsychotic ARI to CLZ medication significantly improved negative symptoms compared to CLZ alone. Given the basic pharmacology profile of CAR it appears reasonable to assume that this agent would work at least equally well to ARI as adjunct to CLZ. Actually, recent case reports concurs with this suggestion [(16, 17); *vide infra*], although larger, high-quality, double-blind, randomized studies will be needed for further substantiation.

This said, in schizophrenia the identification of factors at the *individual patient level* will be particularly important to increase the chance of success with an APP approach, thereby promoting personalized treatment in this very heterogeneous patient population. *In short:* finding the "right drug combination" to the "right patient" is key!

## Tolerability and Safety of APP?

While tolerability and safety concerns may cause some hesitancy to start APP, it should be noted that "*…not all antipsychotic combinations are created equal*" (8). In addition, it is not the APP approach *per se* that is the issue, but rather *the composition of the specific agents and doses comprised therein* that matter. In this regard, a systematic review and meta-analysis of randomized controlled trials comparing APP and monotherapy found no differences regarding intolerability-related treatment discontinuation (4). Moreover, again attesting to the above, it is more likely that APP strategies involving a greater total antipsychotic dose, and thus net target (e.g., D2 receptor) occupancy (8)—at least by antagonist agents [see, e.g., (19)]—would be more liable to increase the AE burden. Conversely, therapeutically useful effects on AE outcome may be achieved by partial DA agonist add-on to CLZ, RIS, OLA, or HAL, to relieve metabolic- and prolactin (PRL)-derived issues (*vide infra*). Although so far available data are insufficient to allow definitive conclusions it would appear that—contrary to what may be widely presumed—there is *a priori no general* tolerability, AE, or safety [including mortality; e.g., (20, 21)] *reason* to discard APP as a possible strategy for a patient in need thereof.

## Which Targets Are Key for Antipsychotic Drug Benefit and AE?

The action of agents in the antipsychotic class must be gauged against their individual pharmacologic target profiles, as many carry multiple receptor affinities and activities.

The dopamine (DA) D2 receptor is a pharmacological target shared by all antipsychotics in current use. However, the affinity for the target varies considerably among drugs in the class—from very high in, e.g., HAL, to pretty poor in, e.g., CLZ and QUE. Moreover, mechanistically the TGA agents ARI and CAR act as *partial agonists* rather than full antagonists at the D2, D3, and 5 HT1A receptor sites.

In addition to the above, the majority of FGA and SGA also act as blockers of several other neuroreceptor sites with clinical bearing. **Table 2** lists key antipsychotic targets and clinically observed outcomes (desired and AE) associated with antagonism or partial agonist drug action at the corresponding sites.

# PHARMACOLOGICAL PROFILES OF ANTIPSYCHOTICS IN APP ENDEAVORS

In an aim to provide an easily and rapidly accessible overview of overall target profile patterns of the various antipsychotics discussed "cobweb" diagrams were generated by means of the polar chart diagram function in Microsoft Excel. The "cobweb"

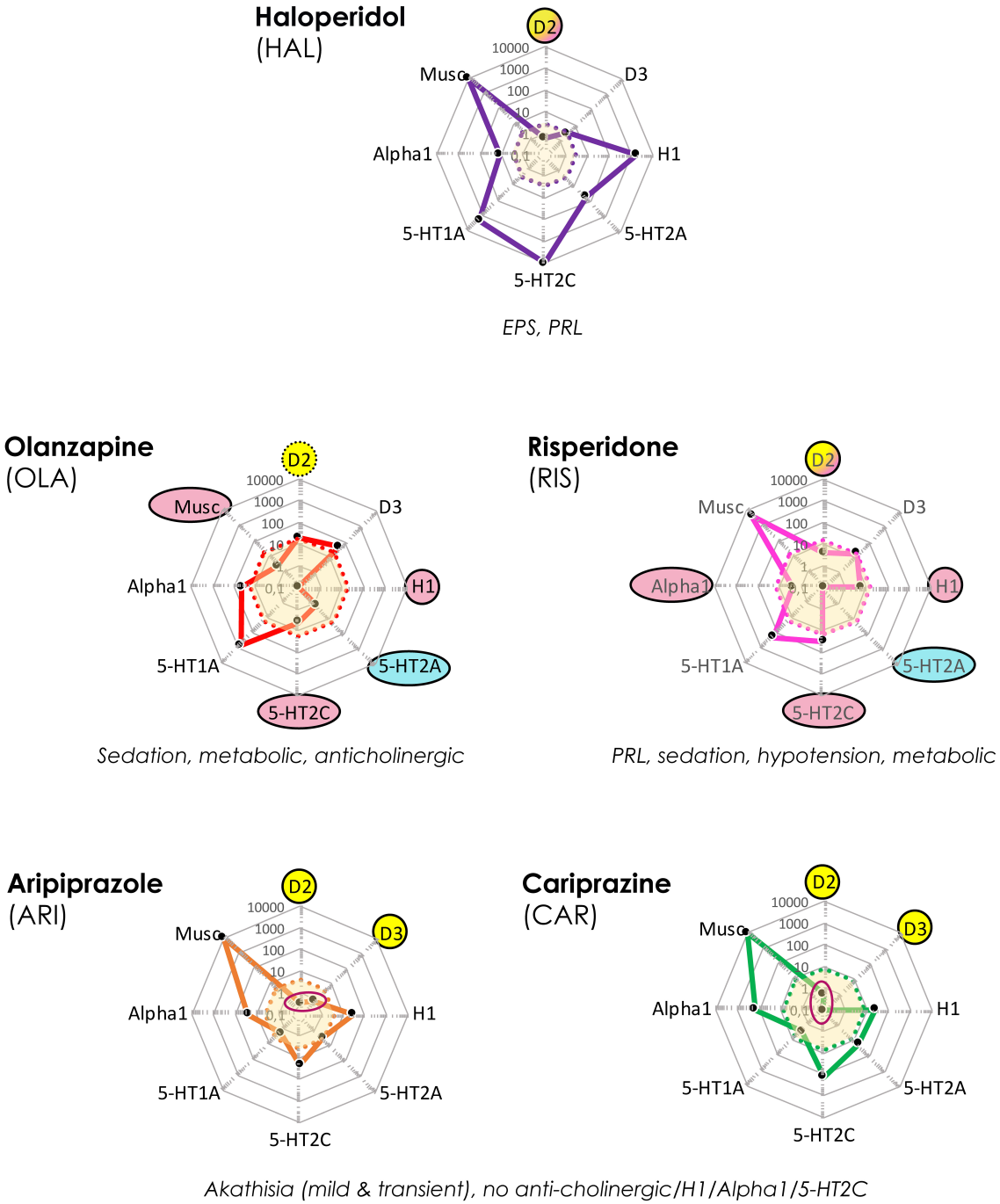


**FIGURE 4 |** Target and associated AE profiles of HAL, OLA, RIS, ARI, and CAR. Colored lines and dots represent drug profiles based on the 8 different targets depicted at the edges of the cobweb; affinity is highest at the center, lowest at the edges (0.1–10,000 nM log scale). Dot line-enclosed shaded areas in the center represent unbound plasma levels of the compounds at efficacious therapeutic dosing. Circles and ovals depict targets likely to be affected at these levels, with colors indicating desired (yellow), accessory beneficial (light blue), and unwanted effects (red; + text below graphs). Red ovals in ARI and CAR graphs pinpoint D2 and D3 affinities. EPS, Extrapyramidal side effects; PRL, prolactin (rise). The drug cobweb profiles in this figure and **Figures 5**, **6** were compiled from data in public web databases and complementary literature, including drug SPC's; *viz*. human (cloned or native tissue) receptor affinities (22–24); therapeutic steady-state exposures[1] (25); free fraction of drug plasma concentrations (26). Therapeutic steady-state exposure areas shown were obtained by converting ng/mL (25) to nM, and multiplying by the free fraction in plasma (26) for the corresponding drug.

approach was employed also as a means to graphically illustrate the array of differences and similarities among antipsychotics commonly used in APP combinations and to further enhance the relevance by integrating into the graphs, depictions of corresponding clinically efficacious unbound drug exposures (further details, see Figure legends). These diagrams thus show the pharmacological fingerprint (drug affinities) vs. approximate free plasma exposures at steady-state and clinically efficacious dosing of the antipsychotics discussed in further detail below.

The cobweb displays in **Figure 4** reveal the markedly different pharmacological target profile patterns and accompanying clinical effect differences of HAL, OLA, RIS, ARI, and CAR. Clearly, while the "enriched" pharmacology in some antipsychotics may sometimes be an advantage [such as 5-HT2A receptors vs. motor AE; e.g., (27)], AE may also arise [such as 5-HT2C and H1 receptors vs. metabolic dysfunction; e.g., (28, 29)]. In addition, even the key D2 receptor target may bring desirable as well as unwanted clinical effects [antipsychotic action vs. EPS and hyperprolactinemia; e.g., (30, 31)]. It follows that selecting an appropriate antipsychotic medication for any individual patient should take into account not only efficacy, but the *total pharmacodynamic (PD) profile in relation to dosage and potential complementarity of neuroreceptor* action in a tentative APP approach.

## Options for Improved Clinical Outcome?

When antipsychotic drug monotherapy responding is an issue—be it for efficacy, AE/tolerability, safety, adherence, and/or other reasons—the treating physician is faced with a number of options and decisions. These may include to adjust the dose, to switch to another antipsychotic agent, and/or to consider augmentation approaches. Irrespective of which tactic is ultimately selected, apart from other clinically-based reflections there are some common basic aspects that require consideration in this situation:

*Is the reason for failure insufficient drug exposure (e.g., poor adherence, PK factors)?*

- Verify adequate antipsychotic plasma levels by therapeutic drug monitoring (TDM).

*Is the reason inadequate efficacy, intolerable AE, and/or safety issues?*

- Improve by dose adjustment, or, improve by switching to another antipsychotic.

If none of the above seem to handle the issue at hand, is APP a worthwhile approach? If so, and similarly to deliberations in a switch situation, thorough attention is recommended to (i) establish the intended therapeutic goal/s (e.g., efficacy domains, AE), (ii) select suitable antipsychotic(s) to use from the PD as well as PK perspective, taking desirable as well as unwanted outcomes into account, and (iii) work out a well-planned strategy to accomplish the goal in mind—*with patient buy-in*!

[1]*Disclaimer*: Needless to say, the size of the exposure area will vary depending on the actual dose, but also individual variation. The area limit shown is created from population-based therapeutic steady-state exposures, defined as *"upper limit above which tolerability decreases or above which it is relatively unlikely that therapeutic improvement may be still enhanced (25)"*.

# PHARMACODYNAMIC (PD) CONSIDERATIONS FOR APP

## The Good, the Bad, and the…Futile…? Some APP Examples

In patients for whom APP is deemed to be a fruitful treatment strategy a thorough scrutiny of available options from a pharmacological perspective is advisable. To this end, a selection of APP options is presented below, and examined from a basic PD *vs.* predicted clinical action perspective. Keep in mind though, that the relative dose/exposure of the selected antipsychotic drugs in an APP combination determines the global response, and hence that the relative clinical benefit/AE outcome in the individual patient may vary.

## Complementary Profiles, Recommendable APP From a PD and PK Point-of-View

Refractoriness and persistent prominent negative symptomatology is a frequently mentioned basis for initiation of APP. To this end, administration of a partial DA agonist TGA together with, e.g., CLZ appears to be a particularly appealing option, as it fulfills the criteria of combining two agents with complementary pharmacodynamic (PD) as well as pharmacokinetic (PK) profiles (see, e.g., **Figure 5**). Indeed, ARI + CLZ is the best documented APP by far, with several studies reporting favorable outcomes both regarding efficacy (not least vs. negative symptoms), tolerability and AE [e.g., (4, 32)].

In addition, Tiihonen (33) recently reported on various APP vs. monotherapy variants with regard to risk for psychiatric rehospitalization in a nationwide Finnish historical cohort (>62,000 patients) of adult schizophrenia. They found that the CLZ + ARI combination conferred the strongest protection against rehospitalization (hazard ratio, HR = 0.42). Interestingly, among the 10 top options (lowest HR) in this regard nine were APP, seven of the APP included CLZ, and the only monotherapy was CLZ—attesting to APP usefulness, as well as to the distinctive position of CLZ in schizophrenia treatment.

Interestingly, as seen in **Figure 5**, the complementarity in neuroreceptor target profile patterns accomplished with a CLZ + ARI APP may be mimicked to a great extent also by CLZ + CAR, OLA + CAR, and QUE + CAR combinations. From the PD standpoint it would appear reasonable to assume that the potent D2 and D3 (and possibly also 5-HT1A) partial agonist properties of CAR will—similarly to ARI (see, above)—result in a therapeutically advantageous APP *via* complementation of a relative lack of strong interactions with these targets in CLZ, OLA, and QUE. In fact, CAR may provide a particularly interesting choice, given its prominent D3 affinity and proven clinical effect against primary negative (34) and cognitive (35) symptoms, as well as extended PK half-life (36). Although only limited clinical data with CAR in APP are hitherto available (*vide infra*), it may be hypothesized that augmentation with

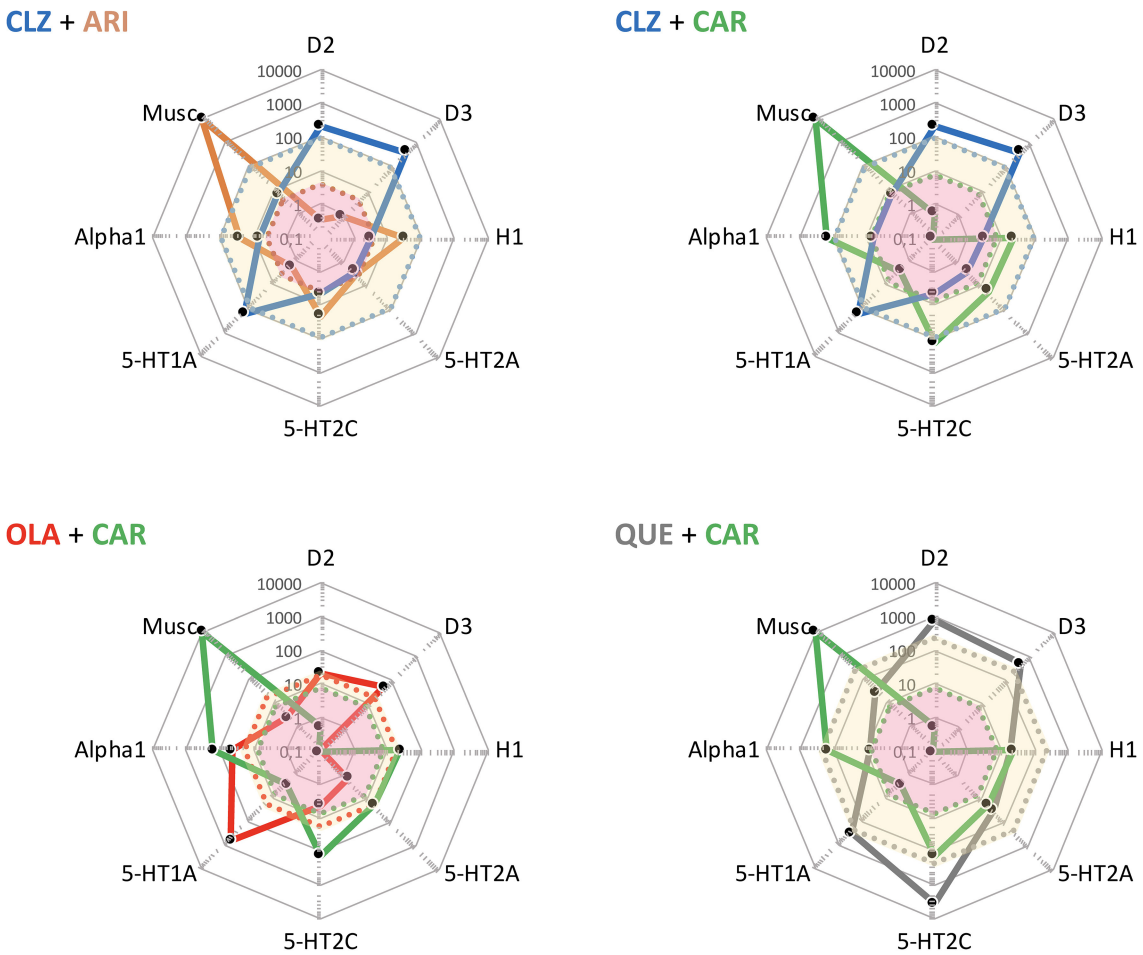


**FIGURE 5 |** Some potentially useful APP target combinations based on FGA, SGA, and TGA. Shown are target profiles of APP combination examples based on CLZ, OLA, QUE, ARI, and CAR, displayed in a cobweb design. The colored lines joining the dots represent the target profile of the agent with corresponding color coding; e.g., blue is CLZ, and green is CAR. The dot line-enclosed shaded areas represent unbound plasma concentrations of the compounds at therapeutic dosing. For example, in the OLA + CAR case, the yellow and pink areas show unbound OLA and CAR plasma concentrations, respectively. For further explanations, see legend to **Figure 4**.

this agent might improve efficacy, counterbalance sedative and metabolic AE issues while maintaining the low EPS propensity of CLZ, OLA, and QUE, but also potentially elicit (typically mild, transient) akathisia. It has been suggested that 5-HT2A antagonist may be a valuable option to the β-adrenoceptor blocker propranolol against antipsychotic-induced akathisia (37). Whether or not such a component in CLZ, OLA, and QUE may serve to attenuate any akathisia triggered by CAR however remains to be established.

## Conceivable, but Theoretically Less Attractive—or Even Futile?—APP Combinations

The RIS + CAR- and HAL + CAR-based APP options are possible, though pharmacologically more complex possibilities (**Figure 6**). Firstly, the D3 receptor partiality of CAR adds a complementary target effect, presumably advantageous from the negative and cognitive symptomatology viewpoint [e.g., (34, 38, 39)]. However, like CAR both RIS and—in particular—HAL possess appreciable D2 receptor affinities, thereby significantly occupying such sites at therapeutic dosing. In turn, this means that the overall clinical outcome of such combinations with CAR will depend on the relative dose (/concentration) ratio between RIS or HAL and CAR, and thus be more difficult to generalize and forecast. It is possible that the high affinity and partiality of CAR at the D2 (and 5-HT1A) sites may contribute to a lower risk for RIS- and HAL-induced EPS and hyperprolactinemia [see, e.g., (27, 30, 31)]. On the other hand, it is also conceivable that because of their moderate-to-high affinity D2 receptor blockade RIS or HAL may partially counter (even obliterate?) the partial D2 receptor agonism-mediated therapeutic benefits of CAR. The differences in drug half-lives among RIS and HAL vs. CAR (*vide infra*) may also add to these complexities, thereby contributing to variability in the therapeutic outcome across the 24 h cycle [see, e.g., (14)]. Taken together, it would appear that finding the optimal dosing for these combinations may be challenging, and

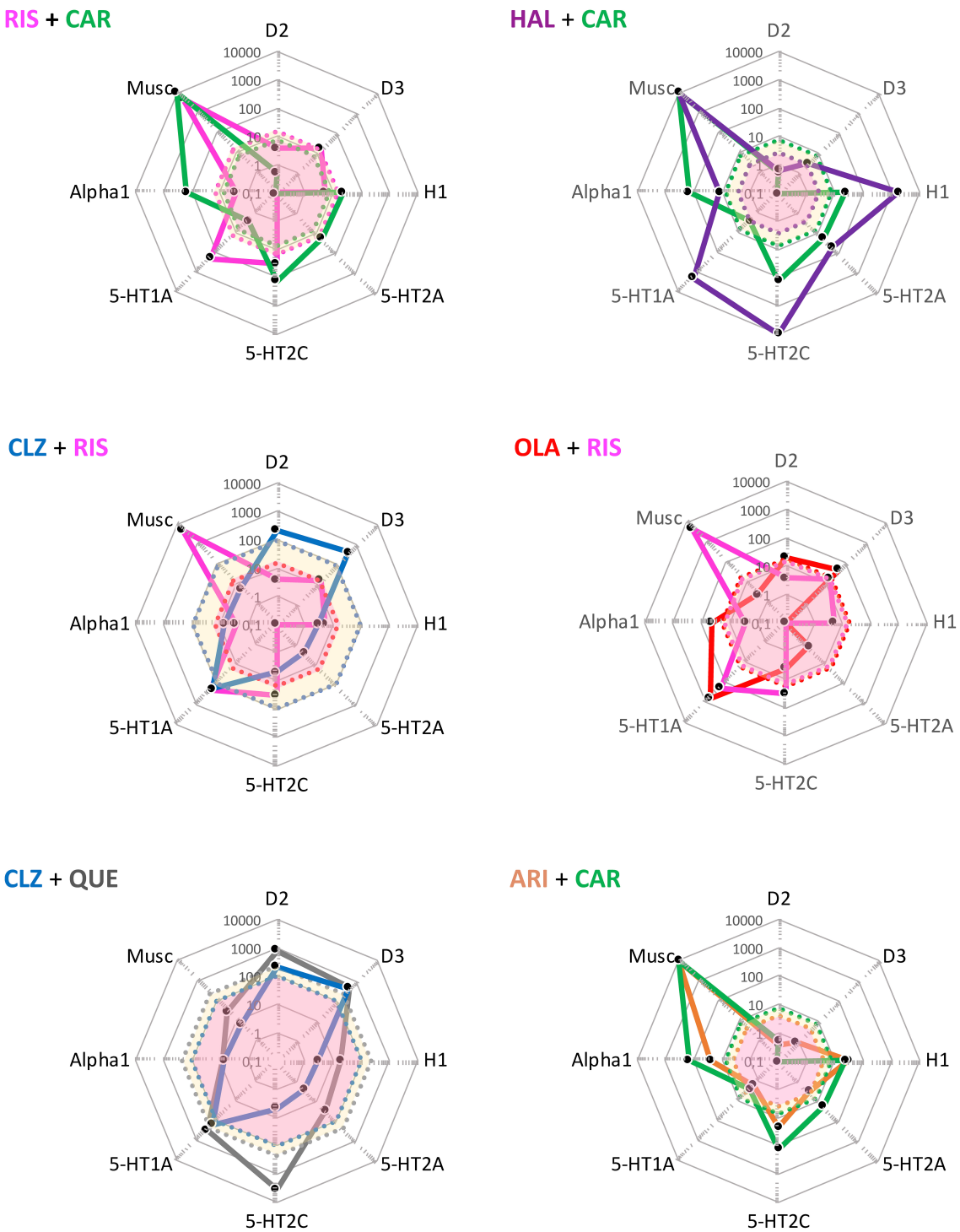


**FIGURE 6 |** Some theoretically suboptimal, less preferable—or even futile—APP target combination examples based on FGA, SGA, and TGA. Shown are target profiles of APP combination examples based on CLZ, RIS, HAL, CAR, QUE, OLA, and ARI displayed in a cobweb design. For further explanations, see legend to **Figures 4**, **5**.

thus it is likely that a switch from RIS or HAL to CAR would in fact be more preferable.

APP combinations like CLZ + RIS, and OLA + RIS appear pharmacologically less desirable. Thus, whereas the poor D2 affinity of CLZ may be complemented by the higher D2 affinity of RIS, the latter agent (together with its active metabolite paliperidone; PAL) is more liable to cause EPS and hyperprolactinemia. Moreover, as both agents possess significant

alpha1-adrenoceptor and H1-receptor antagonism, a CLZ + RIS APP intervention may result in an enhanced acute (orthostatic) hypotensive action as well as risk for accentuated sedation [see, e.g., (40)]. A similar reasoning may apply to the OLA + RIS combination, where any possible benefits of supplemented D2 receptor blockade may be potentially outweighed by an increased AE liability mediated by the very same site (e.g., prolactin rise, increased EPS risk), but also by other targets—as in the CLZ + RIS discussion above. It would appear that within the limitations of available reports (mostly from open, small, short-term, unblinded, non-RCT studies, or case series), clinical outcome data (efficacy and AE) with the aforementioned APP approaches do not generally demonstrate enhanced efficacy but largely concur with the pharmacology-derived reasoning above (41–47).

Among even more *questionable* (or from a pharmacological perspective, even futile) APP combinations are CLZ + QUE, and ARI + CAR. CLZ and QUE are both rather poor D2 receptor antagonists, and share many other target properties as well (e.g., antagonism of alpha1, muscarinic, H1 sites; see, **Figure 6**). Thus, the pharmacology-based likely lack of potential for efficacy improvement, together with a possible/probable accentuation of AE liabilities (e.g., sedation, CV, and QTc risks) renders this a pointless APP combination exercise. Only limited clinical data with the CLZ + QUE combination are found in the literature, but appear consistent with the pharmacology-based considerations given (48). The pharmacological profiles of CAR and ARI are by and large overlapping, with the exception that CAR has the decidedly higher D3 receptor affinity of the two [e.g., (22)]. It follows that an ARI + CAR-based APP combination would be futile, whereas when the D3 receptor partiality of CAR is a desired therapeutic property a switch from ARI (to CAR) might be a feasible option. To the best of my knowledge, there are no clinical reports from trials with this latter APP combination.

Taken together, for the reasons discussed above neither of the aforementioned APP combinations (illustrated in **Figure 6**) are ideal choices from a pharmacological perspective.

## PHARMACOKINETIC (PK) CONSIDERATIONS IN APP

Antipsychotics discussed in this account are metabolized by CYP1A2, CYP3A4, CYP2D6, and/ or CYP2C19 (see, **Table 3**). With regard to drug-drug metabolism interactions (DDI), such issues appear relatively rare with agents commonly found on the APP scene. However, notable metabolism-derived examples include changes in plasma concentrations as a result of altered smoking habits in a patient. Smoking is an inducer of CYP1A2, and may as a result thereof lead to lower-than-expected plasma levels of CLZ and OLA, in turn calling for dose adjustment of these antipsychotics (49). Conversely, (involuntary) cessation from smoking, e.g., when a patient is hospitalized, could lead to too high exposure from agents like these, if the dosage is not correspondingly amended (*NB:* it is components in the smoke—not the nicotine—that mediates the induction of the CYP1A2 enzyme; thus, nicotine substitution approaches like patches/chewing gums may lessen abstinence issues from cigarette smoking).

**TABLE 3 |** Examples of commonly used antipsychotics, their $t_{1/2}$, and main metabolic enzymes.

| Drug | Approximate $t_{1/2}$, h | CYP subtype |
|---|---|---|
| Haloperidol (HAL) | 21 | 3A4 (2D6) |
| Olanzapine (OLA) | 33 | 1A2 (2D6) |
| Clozapine (CLZ) | 12 | 1A2, 3A4, 2C19, (2D6) |
| Risperidone (RIS) | 3 (∼20; 9-OH)* | 2D6, 3A4 |
| Quetiapine (QUE) | 6-7 | 3A4 (2D6) |
| Aripiprazole (ARI) | 70 | 3A4, 2D6 |
| Cariprazine (CAR) | 70 (∼400; DDC)† | 3A4 (2D6) |

*Data extracted from corresponding drug SPC's and the literature [see, i.a., (25)].*
**$t_{1/2}$ of active metabolite to RIS; 9-OH-RIS = paliperidone (PAL).*
*† $t_{1/2}$ of active metabolite to CAR; DDC = di-desmethyl-CAR.*

Inhibition of drug metabolism enzymes (CYP1A2: e.g., fluvoxamine; CYP3A4: e.g., carbamazepine, ketoconazole, and grapefruit juice; CYP2D6: e.g., fluoxetine; CYP2C19: e.g., paroxetine) may result in significant DDI through an impact on the elimination—and thereby plasma concentrations—of antipsychotics metabolized *via* the corresponding pathways (see, **Table 3**). Dose (or drug) adjustments may therefore be necessary. Many antipsychotics are also substrates and inhibitors of the P-glycoprotein (P-gp) drug transporter [e.g., OLA, RIS, and ARI, but not CLZ and QUE; (50)]. While a P-gp-derived DDI between agents in an APP combination may thus theoretically alter plasma and brain concentrations of other substrates, actual patient outcomes are less clear (50); this conceivable DDI risk should nonetheless be kept in mind (For further details on putative PK-derived DDI, please consult relevant drug SPC's).

When choosing antipsychotics to combine in an APP regimen, it is prudent from the PK view to combine antipsychotics that differ in half-life (i.e., a short-acting plus a long-acting agent), time to peak concentration, and ideally also elimination pathway. Hence a better control of fluctuations in DA receptor occupancy may be attained, and some "buffer" capacity provided to promote compliance and prevent relapse in a situation with outpatients that may show erratic medication adherence.

The use of long-acting formulation injection antipsychotics (LAI) is common in schizophrenia treatment, and while LAI-based APP appeared more prevalent before the 1990's than in the 2000's (2), it is still in frequent use (51). The main reason for LAI use overall appears to be maintained compliance, particularly in difficult-to-treat patients (2). Needless to say, whereas the PK properties are distinctly different in oral and LAI formulations of the same drug, the PD target profiles remain identical. LAI is intended to produce a more flat, stable, PK profile vs. the drug targets involved. In APP approaches, the stable target occupancy advantage may be lessened when LAI treatment is accompanied by concomitant oral dosing, either by another antipsychotic, or by the same agent as given by LAI tentatively, i.a., to obtain a more fine-tuned dosing regimen; (1), which may in turn also have implications toward the strength of PD effects across time [discussed, e.g., by (14)]. This said, the variability in target

**TABLE 4 |** Summary of theoretical pharmacological usefulness of APP examples discussed.

| Overall rating | APP combination | Comments |
|---|---|---|
| Fine | CLZ + CAR<br>CLZ + ARI<br>OLA + CAR<br>QUE + CAR | Complementary PD and PK profiles—potential for improved efficacy as well as AE outcome + short- and long-acting agent combination (contributing to compliance) |
| Conceivable, but possible issues | RIS + CAR<br>HAL + CAR | Some potential for improvement, but complex PD interaction—challenging to optimize doses for efficacy and AE benefits |
| | CLZ + RIS<br>OLA + RIS | Doubtful efficacy improvement; increased AE burden |
| Futile | CLZ + QUE<br>ARI + CAR | PK as well as PD profile overlap |

occupancy introduced by LAI-based combinations with oral antipsychotics would appear less significant using agents with complementary target profiles (see, Discussion above), like, e.g., combining QUE or CLZ with TGA like ARI or CAR. Taken together, the very same pharmacological principles would thus appear to be valid regardless of whether oral + oral or LAI + oral APP treatments are considered.

Notably in this context, CAR gives rise to a very long-acting active metabolite (DDCAR, **Table 3**; (36) with essentially matching target affinities and profile to its parent compound (52). At steady-state, CAR may thus be viewed as a "long-acting oral" treatment for schizophrenia, valuable also from a compliance and relapse perspective (53).

## THEORETICAL USEFULNESS OF THE APP EXAMPLES DISCUSSED

**Table 4** summarizes the APP examples illustrated and discussed above in **Figures 5**, **6**, with brief pharmacology-based overview comments and recommendations.

### APP: Reduction of AE?

Antipsychotics clearly differ in AE liabilities and severity, with TGA being generally more benign than FGA and SGA [e.g., (54)]. This also applies regarding the propensity to induce weight gain and accompanying metabolic AE, with the SGA OLA and CLZ displaying the most, and TGA agents like ARI and CAR the least, harmful profiles (55). Additionally, marked antipsychotic drug heterogeneity in prolactin-raising and sedation-inducing properties occur (40, 56). From the APP perspective it is notable that add-on treatment with TGA can significantly attenuate OLA- and CLZ-induced AE like the aforementioned (57–60).

### Case Reports—CAR Add-On to CLZ or QUE

So far, only very limited data on APP involving CAR is available. However, De Berardis et al. (16) recently reported on CAR add-on in two patients, with comparable illness and medication backgrounds, but only partially responding to CLZ treatment. In both of these cases the CAR addition within 6–8 months brought about a marked remission across symptom domains as scored by PANSS (**Figure 7**). Interestingly—and in line with the above predictions—body mass index (BMI) dropped an impressive ∼3 units from baseline over the same period for both patients. These findings thus support the view that the APP combination of an antagonist and a partial DA agonist antipsychotic agent with complementary PD profiles and short- vs. long-acting PK properties may result in an advantageous outcome both with regard to the desired efficacy and unwanted AE features of the treatment.

Interestingly, a recent single-patient case report suggests that CAR plus QUE may also be an attractive APP option (18). The combined treatment with these two antipsychotics resulted in successful alleviation of cognitive and negative impairments in a young male patient, whom previously had been through a variety of but partially efficacious FGA and SGA regimens. Intriguingly, and in line with other recent case studies, the CAR + QUE APP was associated with an abrupt cessation of smoking, and curbed use of recreational drugs, tentatively indicative of anti-craving effects. In support of this speculation, combined CAR + QUE treatment was reported to markedly attenuate alcohol craving and bring about lasting symptom stability in a bipolar I patient (61). Further, CAR monotherapy has also been reported to result in abrupt remission from persistent methamphetamine psychosis and improved positive as well as negative symptomatology in a treatment-naïve male patient (62), and to benefit two cases of schizophrenic patients with other substance use disorders (63). These clinical observations are consistent with preclinical literature and theory suggesting that D3 receptors may be implicated in drug dependence issues (64–66).

### Partial Agonist Effects on Symptoms and (Antagonist-Derived) AE in APP Approaches

What would be the potential PD mechanistic substrate/s underlying partial agonist-induced improvements of core symptoms and AE when incorporated into an APP approach? From a theoretical viewpoint it appears plausible that the effects on positive and negative symptomatology involve partial agonism at the DA D2 and D3 receptor sites (**Table 5**). A direct D2 receptor interaction is also highly likely to explain the normalization of antagonist-induced hyperprolactinemia. However, the reported beneficial effects on anthropometric and metabolic issues, as well as the offsetting of sedation is hypothesized to be the result of counterbalancing neuronal circuits rather than direct competition between drugs at a particular target (**Table 5**). That is, the blockade of, i.a., H1 and 5-HT2C receptors in some brain regions/neurocircuitries drives the weight, metabolic parameters, and sleepiness in one direction, whereas partial D2 agonism drives them the opposite way. Indeed, generally, agents in the TGA partial DA agonist class are considered

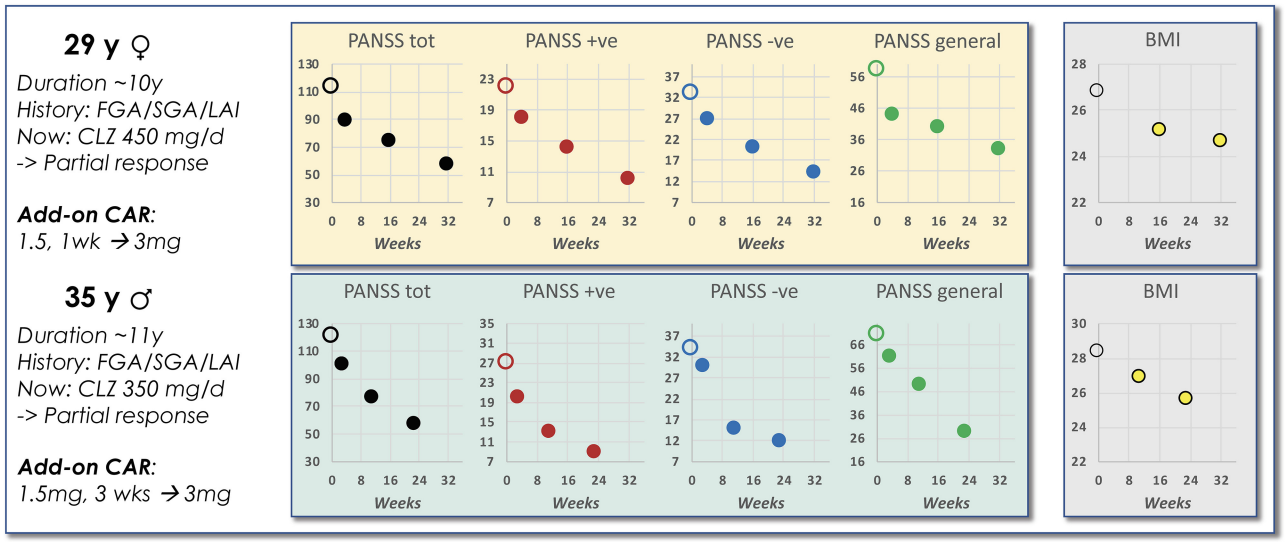


**FIGURE 7 |** Data from a case report of CAR add-on to CLZ treatment. Shown is a brief schizophrenia treatment history of a female and a male patient prior to APP add-on with CAR to ongoing CLZ treatment. The accompanying graphs illustrate PANSS scoring and BMI observations evolving over time following start of the CAR add-on intervention [data extracted from De Berardis et al. (16)].

**TABLE 5 |** Summary of putative clinical impact of APP treatment involving partial agonists.

| Issue | Type | Putative clinical impact (target/s) |
|---|---|---|
| Positive symptoms | Desired | Improvement (partial D2) |
| Negative symptoms | Desired | Improvement (partial D3) |
| Hyperprolactinaemia *(RIS, HAL, PAL)* | AE | Attenuation (partial D2) |
| Weight/metabolic *(e.g., OLA, CLZ)* | AE | Improvement *(interaction partial D2 vs. H1/5-HT2C?)* |
| Sedation *(e.g., OLA, RIS)* | AE | Improvement *(interaction partial D2 vs. H1?)* |

less metabolically adverse [see, e.g., (55)], and also more "activating" and less "sedating" as compared to FGA and SGA (67).

## APP: SOME BRIEF PRACTICAL POINTS

Clearly, many aspects deserve attention when considering initiation of APP. Pae (9) discussed some practical points and tips in a recent review; some of these points are extracted and briefly summarized below:

- Make it clear (to self and patient) why you wish to use APP
- Use measurement-based APP (PANSS, CGI, other scale/s) to monitor effects over time, and increase the ability to link desired/adverse effects to the drug/s in question
- Consider APP for patients with ≥2 failed monotherapy trials, including a trial with CLZ
- Apply rational pharmacological APP reasoning; paying attention to both PD target and mechanism of action complementarity
- Closely monitor *total* AP dose levels, and aim to keep total dosage down
- CLZ is the best documented agent in these contexts, and should thus be one of the first antipsychotic drug options toward APP
- Consider long- plus short-acting agents in the planned APP regimen, hence also applying PK complementarity in the drug treatment

## APP: Overall Theoretical Considerations

In patients for whom APP is deemed to be a worthwhile treatment strategy, it is evident from the above that a thorough scrutiny of available options is advisable. By and large, whereas combinations of (FGA and SGA) D2 receptor antagonists may be challenging, available data discussed in this account indicate that from the pharmacological perspective selected APP, in particular based on SGA + TGA, may indeed be efficacious, tolerable, safe, as well as useful in a preventive, relapse/re-hospitalization context.

Within this APP framework, a PD comparison between the TGA:s CAR and ARI suggests that while both display high affinity partial agonist activity at the D2 receptors, CAR displays even higher affinity for the D3 than the D2 sites and is nearly 10-fold more potent than ARI at D3 receptors [e.g., (22)]. It may be hypothesized that, although similar in their efficacy against positive symptoms the appreciably stronger D3 action of CAR vs. ARI may translate to an improved profile toward primary negative symptoms—and, speculatively, also when dependence issues may be involved (see, above). Further, while both agents

may elicit mild and typically transient akathisia, neither appears burdened by marked EPS, metabolic issues, prolactin rises, or sedation (68). As both agents have long $t_{1/2}$ (CAR > ARI; see, **Table 3**), an SGA + TGA combination in an APP strategy setting thus also fulfills the PK aim to match a short-acting with a long-acting agent.

From an efficacy point-of-view it appears probable that APP will be prescribed for (i) patients with predominant and persistent negative symptoms, and (ii) patients with residual positive symptoms; e.g., patients with chronic auditory verbal hallucinations, only partly alleviated by antipsychotic monotherapies. Unfortunately, available literature does not seem to shed very much light on whether a particular type of APP would be preferred for one vs. the other of these forms of enduring issues. However, as a recommended Guideline sequel to ≥ 2 failed monotherapy trials, it appears logical that CLZ would be highly prevalent in any strategies to deal with persistent residual symptoms—irrespective of domain. While agents with high affinity and antagonism or partial agonism at the D2 receptors are commonly used to attenuate positive symptoms the negative/cognitive domains appear overall less susceptible and more difficult to reach, even with CLZ. From a pharmacological standpoint partial agonist TGAs like ARI or CAR should be useful to boost efficacy of CLZ, although so far high-quality data are supportive only for ARI with respect to negative symptoms [discussed above, see (4)]. The notable efficacy of CAR monotherapy in this latter indication (34, 35) may possibly suggest a further edge of this agent in APP when negative/cognitive issues dominate the clinical picture. Until further studies to assess this prediction, it however must remain purely speculative.

## STRENGTHS AND LIMITATIONS

While the above pharmacology-derived assessments are based on an extensive appraisal of antipsychotic literature data, it should be pointed out that the profile comparisons and associated APP recommendations are based on free drug concentrations in *plasma*—used as a proxy estimate for CNS (and, in part, peripheral) target interactions. This said, there does not seem to be any clinical data that directly contradict the interpretations put forward. On the contrary, APP studies reported in the literature do in fact seem quite aligned with the pharmacodynamic target-based analysis offered.

## SUMMARY AND CONCLUSIONS

In conclusion, APP treatment may be useful in selected patients when switch is not desired or feasible, but is NOT to be applied for ROUTINE use. High-quality studies, with proper pharmacological resolution, are needed toward the generation of evidence-based strategy guidelines for APP treatment of schizophrenia when required in clinical practice [see, (69)]. If an APP combination intervention is considered and initiated, it should

- only be used after ≥2 failed monotherapy trials (adequate dose and duration)
- be based on agents with *complementary* neuroreceptor profiles
- take PK, safety (regular health checks) and tolerability into proper consideration
- always allow sufficient time to establish post-combination treatment outcome

In closing: any APP regimen should be based on drugs that are complementary, beneficial from an efficacy/AE outcome perspective, and follow a clear therapeutic rationale, avoiding PK as well as PD risks. The chosen antipsychotic combination should also focus on the prioritized symptom domains, while avoiding dispensing unnecessary, ineffective or redundant psychotropic agent exposure to individuals with schizophrenia. Against this backdrop it would appear that APP based on add-on with Third Generation Antipsychotics, TGA (e.g., CAR or ARI) may be particularly useful, together, e.g., with CLZ. It should be kept in mind though, that although APP may be both feasible and beneficial, monotherapy is still the preferred state. Consequently, if possible, switching options should always be thoroughly considered before embarking on a combination treatment intervention.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

## AUTHOR CONTRIBUTIONS

SH was solely responsible for the conceptualization, subject research and interpretations, writing, editing, and approval of the submitted version of the article.

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CASE REPORT
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# Case Report: Severe Side Effects Following Treatment With First Generation Antipsychotics While Cariprazine Leads to Full Recovery

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Schizophrenia is a psychiatric disorder characterized by positive, negative, cognitive and affective symptoms. Patient cooperation with health care professionals, compliance with the treatment regime, and regular use of medications are some of the preconditions that need to be met for a favorable disease course. A negative experience following the use of a first-generation antipsychotic to treat first-episode psychosis can negatively affect a patient's motivation for further medication use. In the clinical case reported here, cariprazine was able to restore one such patient's confidence in therapy and facilitated their cooperation with the physician, thereby ensuring effective control of negative and positive symptoms and good functioning for a period of 1 year. Cariprazine may be a good option for maintenance therapy following first-episode psychosis, especially in situations in which a patient has had a negative first experience associated with antipsychotic medication use.

**Keywords: cariprazine, full recovery, psychosis, neuroleptics, side effects, compliance, monotherapy**

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## INTRODUCTION

Schizophrenia is a serious psychiatric disorder with a prevalence of ∼1% in the population (1, 2). Positive symptoms of schizophrenia include delusions, hallucinations, abnormalities in how thoughts are linked together, thought insertion, withdrawal, thought broadcasting, and the belief that actions, feelings, or emotions are being controlled by external forces. Negative symptoms can include affective flattening, lack of motivation, loss of drive, lack of pleasure in any activities, poverty of speech, and diminished capacity to express feelings. Cognitive deficits may also be present with attention, language, and memory impairment. Affective symptoms may include depression and anxiety.

Throughout the course of schizophrenia, it is important to treat exacerbations of the positive, negative, and cognitive symptoms of the disease. Antipsychotics are effective in treating positive symptoms; however, treatment options for negative and cognitive symptoms are limited (3). Currently, most medications have not demonstrated sufficient efficacy in the treatment of negative and cognitive symptoms of schizophrenia; although, cariprazine shows promise for the treatment of negative symptoms (4–6).

Premature termination of therapy leading to repeated psychotic episode is a serious issue when treating schizophrenia. More than 50% of patients with schizophrenia terminate their treatment following hospital discharge (7). Each subsequent psychotic episode adversely affects the overall course of the disease and reduces the patient's functional abilities. However, patients with

schizophrenia are less frequently rehospitalized if they receive maintenance therapy and outpatient treatment (8). Unfortunately, a patient's initial experience with a psychiatric service (e.g., admission to a psychiatric hospital, receiving first-generation antipsychotics, and experiencing the side effects of antipsychotics) may disincentivize them to continue with their treatment (9). While it is difficult to determine a patient's non-adherence to treatment early on; medication adjustment and the minimization of side effects could increase treatment adherence (10).

## CASE PRESENTATION

A 50-year-old male underwent emergency treatment for acute psychosis (delusions and hallucinations) in a psychiatric hospital and received haloperidol. The patient experienced the following side effects in the post hospital phase: acute dystonia, parkinsonism, dysarthria, and akathisia. The medication therapy was changed to a cariprazine-clozapine combination and was then continued with only cariprazine. A dose of 3 mg of cariprazine in monotherapy achieved stable improvement and full patient functionality for a period of at least 1 year.

### Background History

A family history uncovered mental health problems in a sister, which was likely depression. The patient was born in a difficult labor, and presented fetal macrosomia. At an early age, the patient experienced difficulty pronouncing words and had attended speech therapy. He had average grades in school and was a loner. He continued his education at the university and attained a doctoral degree. For the past 20 years he has worked at a public institution at a senior level position.

The patient divorced 15 years ago and has two children. He currently lives with his father and sister and has had a girlfriend for several years with whom he shares common interests in astrology and the occultism.

The patient had rarely been ill during his lifetime and indicated only a gastric ulcer as a problem. Approximately 5 years ago, he suffered a concussion, but did not incur permanent damage. He does not consume alcohol or other addictive substances.

### Diagnostic Assessment

An overview of events, medications, evaluation, and associated comments about first hospital treatment episode is found in **Table 1**. The patient was initially admitted to an acute psychiatric inpatient unit at the instigation of the family as he had rapidly—within a period of 1 week—developed acute psychosis, psychomotor agitation, and thoughts of being cursed.

Using the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD 10) (11), a diagnosis of paranoid schizophrenia (F20.0) was made. Organic causes such as drug-induced psychosis, delirium, and metabolic disturbances were excluded. Differentiation from acute schizophrenia-like psychotic disorder (F23.2) was made based on detailed information from the patient and relatives concerning the duration of the psychosis. At the inpatient unit, the patient received haloperidol up to 15 mg/day (which was initially given intramuscularly in a dose 7.5 mg/day and then perorally 15 mg/day), 6 mg/day of trihexyphenidyl, and 5 mg of olanzapine in the evenings. The patient remained hospitalized for 31 days. Throughout this period, his acute psychotic symptoms lessened, although they were not eliminated. Some delusions remained, and the patient was suspicious.

The patient underwent a psychodiagnostic examination, and it was noted that his thinking was distinctly peculiar, atypical, and characterized by making judgments on the basis of assumptions understandable to himself but difficult for others to understand. The personality profile reflected fatigue, an apathetic state, a low energy level, and difficulty in motivating himself with purposeful actions. Interpersonal relations showed a tendency toward social introversion with avoidance and distancing behavior, a limited ability to express feelings and experiences, sensitivity to other people's attitudes toward him, cautiousness, and slight suspiciousness.

The patient was discharged from the hospital with recommendations to take 15 mg/day of haloperidol, 6 mg/day of trihexyphenidyl, and 5 mg of olanzapine in the evenings. The patient had planned to return to work. However, his condition deteriorated within ∼2 weeks following hospital discharge. An overview of events, medications, evaluations, and comments about second hospitalization and outpatient treatment is available in **Table 2**. The patient began to exhibit side effects from the neuroleptics including parkinsonism, akathisia, dysarthria, and acute dystonia. This was partially the result of the patient reducing the dosage of trihexyphenidyl. In addition, without full understanding about the role of medications, he had little fluid intake due to a fear of sweating. He sought help from the outpatient service because of the pronounced neuroleptic side effects. His treatment was subsequently adjusted, and he was rehospitalized.

Hospital treatment consisted of intravenously administered diazepam to alleviate the side effects, stopping the administration of haloperidol and olanzapine and, instead, introducing 6 mg/day of cariprazine with 37.5 mg of clozapine in the evenings, and 6 mg/day of trihexyphenidyl. Clozapine was added to avoid psychosis as result of the rapid changing of medicines from first generation antipsychotics to cariprazine. Given a treatment history that included an acute psychotic episode, possible future monotherapy appeared to be unlikely. A more likely option was a combination of cariprazine and clozapine. However, the patient received complex therapy during his hospital stay, including psychological counseling, drama, music, and visual art therapy (12), as well as ergotherapy sessions. The medication side effects resolved, and the patient regained confidence in therapy. Therefore, 6 mg/day of cariprazine was recommended following hospital discharge.

### Current Status

After discharge, the patient returned to work. He currently sees a psychiatrist on a regular basis, and the dose of cariprazine has been gradually reduced to 3 mg/day in monotherapy. To

**TABLE 1 |** Timeline of patient events, medications and scoring (CGI-S, CGI-I) across the first inpatient treatment episode.

| Date | Event | Medication/s | CGI-S | CGI-I | Comment |
|---|---|---|---|---|---|
| 14/03/2020 | Admission to psychiatric hospital observation unit | Diazepam (DZP) 10 milligrams daily (mg/d) intramuscularly (i/m) | 6 | 4 | Acute psychotic state; initial observation, blood, alcohol, COVID-19 test |
| 16/03/2020 | Transfer to acute psychiatric inpatient unit | Haloperidol (HAL) 7.5 mg/d i/m, trihexyphenidyl (THP) 6 mg/d orally (p/o), DZP 10 mg/d i/m | 6 | 4 | Acute psychotic state, working diagnosis: Paranoid schizophrenia according ICD 10 (delusion of influence). Differential diagnosis: Acute schizophrenia-like psychotic disorder (no enough information about duration of psychosis). Psychomotor agitation and acute exacerbation of psychosis were reasons for use of first generation antipsychotics |
| 19/03/2020 | Treatment in acute inpatient unit | DZP 5 mg/d p/o instead of i/m | 5 | 3 | Improvement, less psychomotor agitation |
| 24/03/2020 | Treatment in acute inpatient unit | Olanzapine (OLA) 5 mg/d p/o added, DZP canceled | 5 | 3 | Improvement, less psychomotor agitation |
| 6/04/2020 | Treatment in acute inpatient unit | HAL 15 mg/d p/o instead of i/m | 4 | 3 | Improvement, less psychomotor agitation |
| 14/04/2020 | Discharge from psychiatric inpatient unit | Recommendation to take HAL 15 mg/d p/o, THP 6 mg/d p/o and OLA 5 mg/d p/o | 3 | 2 | Final (discharge) diagnosis: schizophrenia according ICD 10 (delusion of influence, time criteria: more than 1 month) |

date, his condition is stable. He has been fully functional for a year, with no positive or negative symptoms such as a loss of drive. However, a diminished capacity to express feelings are mildly pronounced. No additional psychological and social therapies have been needed. The patient is positive about his future treatment course; although, no final decision has been made concerning future medication use. While the patient is interested in quitting medication, there is the risk of future psychotic episodes or, in the case of a worsening mental health status, he might avoid treatment based on his negative experience.

## DISCUSSION

After analyzing the patient's disease course, there is evidence that, while the psychotic episode developed rapidly, there were premorbid signs suggestive of negative symptoms. His acute psychosis and agitation did not allow for a treatment method other than the use of first-generation neuroleptics (13). However, during the treatment process, the administration of olanzapine (14) was initiated with the aim of further transitioning to the use of second-generation antipsychotics.

Cooperation with a psychiatric patient is crucial for a successful treatment outcome. A patient's confidence in therapy is also important, and medication side effects do not facilitate trust in treatments regiments. However, negative, initial hospital treatment experiences can be avoided if proper information and psychoeducation is provided to the patient. It is possible that other atypical, antipsychotic medications would yield results that are similar to cariprazine in regard to negative side effects. However, the choice of cariprazine in this case was based on the patient's negative symptoms.

The patient was at high risk for avoiding further treatment given his negative experience following his first-episode psychosis. Therefore, further treatment needed to result in significantly fewer (and less severe) side effects, but with sufficient efficacy in addressing both his positive and negative symptoms. One important therapy goal is preventing recurrent psychotic episodes that can lead to deterioration in the overall course of the disease. In this case, the patient had a number of preconditions which suggested a sufficiently favorable disease course was possible. This included a late onset of psychosis, a high level of educational attainment, employment, and acute psychosis development (15). It was also extremely important for the patient to have confidence in further treatment and to trust the health care professionals. The choice of cariprazine proved to be effective as the patient's mental health and social functioning have been adequate for a year and continues to be stable.

There are several limitations concerning the approach taken toward this case. First no other clinical scales were used for patient assessment other than the Clinical Global Impressions Scale-Severity (CGI-S) and the Clinical Global Impressions Scale- Improvement (CGI-I). Second, during the first inpatient treatment course not enough information was provided to the patient. There was a low level of psychoeducation and not enough information was given regarding the role of each medication and his future treatment. Providing this information must play role for successful treatment. Finally, the patient did not receive any antipsychotic medications other than cariprazine, haloperidol and, periodically, olanzapine and clozapine. Therefore, we cannot know the possible results of medications other than cariprazine.

Cariprazine should be considered an antipsychotic of choice for maintenance therapy in patients who have experienced

**TABLE 2 |** Timeline of patient events, medications and scoring (CGI-S, CGI-I) across the outpatient treatment and second inpatient treatment episode.

| Date | Event | Medication/s | CGI-S | CGI-I | Comment |
|---|---|---|---|---|---|
| 30/04/2020 | Outpatient visit | HAL 15 mg/d p/o, OLA 5 mg/d p/o and THP 2 mg/d p/o | 3 | 4 | The patient reduced the dosage of THP, reduced fluid intake<br>Extrapyramidal side effects: parkinsonism, akathisia, dysarthria and acute dystonia are presented |
| 5/05/2020 | Admission in psychiatric nonacute inpatient unit | Cariprazine (CAR) 3 mg/d p/o, clozapine (CLO) 6.25 mg/d p/o, THP 6 mg/d p/o, DZP 10 mg/d intravenously (i/v) and DZP 5 mg/d p/o | 3 | 4 | CLO was added to avoid psychosis as result of rapid changing of medicines from first generation antipsychotics to CAR |
| 8/05/2020 | Treatment in psychiatric non-acute inpatient unit | CAR 4.5 mg/d p/o, CLO 6.25 mg/d p/o, THP 3 mg/d p/o, DZP 10 mg/d i/v and DZP 5 mg/d p/o | 3 | 4 | Psychological counseling, drama, music and visual art therapy, ergotherapy were added to the treatment plane, less extrapyramidal side effects, downsizing of THP |
| 12/05/2020 | Treatment in psychiatric non-acute inpatient unit | CAR 4.5 mg/d p/o, CLO 6.25 mg/d p/o, THP canceled, DZP 10 mg/d i/v and DZP p/o canceled | 3 | 3 | Improvement, reduced extrapyramidal side effects |
| 15/05/2020 | Treatment in psychiatric nonacute inpatient unit | CAR 6 mg/d p/o, CLO 12.5 mg/d p/o, DZP i/v canceled | 3 | 3 | Improvement, reduced extrapyramidal side effects |
| 18/05/2020 | Treatment in psychiatric nonacute inpatient unit | CAR 6 mg/d p/o, CLO 25 mg/d p/o | 3 | 3 | Improvement, reduced extrapyramidal side effects |
| 20/05/2020 | Treatment in psychiatric nonacute inpatient unit | CAR 6 mg/d p/o, CLO 37.5 mg/d p/o, THP 2 mg/d p/o | 3 | 4 | The patient complained about tremor |
| 29/05/2020 | Discharge from psychiatric nonacute inpatient unit | CAR 6 mg/d p/o, CLO 37.5 mg/d p/o | 2 | 2 | Loss of drive and diminished capacity to express feelings are mildly pronounced |
| 30/06/2020 | Outpatient visit | CAR 6 mg/d p/o, CLO 25 mg/d p/o, THP 2 mg/d p/o | 2 | 2 | |
| 12/08/2020 | Outpatient visit | CAR 6 mg/d p/o, CLO 25 mg/d p/o, THP canceled | 2 | 2 | No tremor or other extrapyramidal side effects |
| 13/10/2020 | Outpatient visit | CAR 6 mg/d p/o, CLO 25 mg/d p/o | 2 | 2 | |
| 15/12/2020 | Outpatient visit | CAR 6 mg/d p/o, CLO canceled | 2 | 2 | No risk for psychotic episodes, CLO canceled |
| 16/02/2021 | Outpatient visit | CAR 6 mg/d p/o | 2 | 2 | |
| 8/04/2021 | Outpatient visit | CAR 4.5 mg/d p/o | 2 | 2 | |
| 3/06/2021 | Outpatient visit | CAR 3 mg/d p/o | 2 | 2 | |
| 6/08/2021 | Outpatient visit | CAR 3 mg/d p/o | 2 | 2 | |
| 15/10/2021 | Outpatient visit | CAR 3 mg/d p/o | 2 | 2 | Partly diminished capacity to express feelings and reduced ability to persist in goal-directed behavioral (e.g., rent a new flat) still exist. Possibility to cancel medicines was discussed with the patient |

first-episode psychosis, especially if the patient has had a negative experience associated with medication side effects.

## PATIENT PERSPECTIVE

The patient is fully satisfied about current treatment, but also remember side effects from first generation antipsychotics. He is still cautious about treatment and hope quitting medication in a near future. The patient is positive about future, employment, relationship.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## ETHICS STATEMENT

The patient provided written informed consent. Institutional approval was not necessary for publication.

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MINI REVIEW
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# Reducing Addiction in Bipolar Disorder via Hacking the Dopaminergic System

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The dopaminergic system plays a central and decisive role in substance use disorder (SUD), bipolar disorder (BD), and possibly in a subgroup of patients with refractory depression. Common genetic markers and underlying cellular processes, such as kindling, support the close link between these disorders, which is also expressed by the high rate of comorbidity. Although partial dopamine agonists/antagonists acting on $D_2$ and $D_3$ receptors have an established role in treating BD, their usefulness in SUD is less clear. However, dopamine $D_3$ receptors were shown to play a central role in SUD and BD, making $D_2/D_3$ partial agonists/antagonists a potential target for both disorders. This narrative review examines whether these substances bear the promise of a future therapeutic approach especially in patients with comorbid BD and SUD.

**Keywords: substance use disorder (SUD), cariprazine, psychopharmacotherapy, partial agonist, antipsychotic, bipolar disorder**

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## INTRODUCTION

Bipolar disorder (BD) is a complex and serious psychiatric disorder characterized by recurrent mood episodes. Its prevalence is estimated to be at least around 1% in the general population, and it is associated with premature death with a loss of 10–20 years of life attributable to both physical and psychiatric comorbidities (1). Its co-occurrence with other mental illnesses is the norm rather than the exception, especially with substance use disorder (SUD) (2).

## PREVALENCE

The prevalence of SUD in BD population was extensively explored by Hunt et al. (3, 4) who gathered data from clinical settings and national surveys conducted between 1990 and 2015. The prevalence of SUD was found to be more than 30% in community-, and more than 40% in clinical settings. Alcohol use disorder (AUD) was the most prevalent SUD with 20–30% prevalence rates in both community and clinical settings. Among illicit drugs, cannabis was the most commonly abused drug (around 20%), followed by cocaine (around 10%). The findings of these meta-analyses are in line with those of other studies with cannabis use ranking second after AUD (2, 5, 6).

## SIGNIFICANCE AND CONSEQUENCES OF COMORBIDITY

Both BD and SUD have been associated with detrimental consequences on their own, but the co-occurrence of SUD further complicates the already heterogenous clinical presentation of BD,

often masking BD diagnosis and predicting an even worse prognostic outcome for patients (3, 7). Such patients experience more frequent and severe mood destabilizations, increased hospital admissions, accentuated depressive symptoms, an increased likelihood of suicidal behavior and suicide attempts as well as interference with the efficacy of therapeutic medications—either by lowering their mood stabilizing effects or requiring higher doses of the medication to achieve the therapeutic dose (3, 8, 9). Furthermore, earlier mean age of onset was observed for comorbid SUD in BD patients (20.7 years), compared to BD individuals without a lifetime prevalence of SUD (24.0 years), reflecting a significant difference in age of onset in these groups (3). Earlier onset of BD was found to result in a more severe course of illness (10).

## SHARED UNDERLYING MECHANISMS AND THE ROLE OF THE DOPAMINERGIC SYSTEM AND THE D3 RECEPTORS

As patients with comorbid SUD and BD present with accentuated severity of symptoms and have worse prognostic outcomes, shared underlying physiological mechanisms of these disorders are implied and several hypotheses were proposed in support of this notion (11).

One mechanism proposed to underlie SUD and BD comorbidity involves "kindling" which refers to the concept that neurons become increasingly sensitized due to repeated disruptions—and increased sensitization makes them more susceptible to interruption (12). Sensitization is observable in both SUD, where individuals progress from occasional to frequent substance use, and BD, where mood becomes increasingly unstable, depressive, and manic episodes alternate with greater frequency and intensity and periods of remission become briefer (13). Thus, the notion of kindling holds that some individuals might be more vulnerable to neuron sensitization, increasing their risk for developing both SUD and BD.

Furthermore, genetic risk factors are known to play a role in the development of both SUD and BD. Individuals with SUD have a greater chance of having a family member with mood disorder than individuals without such family members—and vice versa—suggesting that SUD and BD might share common gene variants that increase the risk for developing both disorders (12).

The "disorder fostering disorder" concept suggests that the pathological effects of BD and SUD might increase the risk for developing the other (12). Patients with BD might look to self-medicate in order to alleviate their symptoms by taking drugs or consuming alcohol. This view implies that having BD increases the risk for developing SUD. However, the reverse is also true, as substance use exacerbates pathophysiological changes in the already dysfunctional neurotransmitter systems or signaling pathways (14).

The concept of allostasis (the process of maintaining homeostasis through the adaptive change of the organism's internal environment) may provide further insights in the understanding of the pathogenetic mechanisms underlying the comorbidity of BD and SUD (15): if BD is assumed to be a disease involving the cumulative build-up of allostatic states, which as a progressive dysregulation of reward circuits is expressed as negative affective states, it may leave BD patients more vulnerable to drug addiction (16). Furthermore, functional neuroimaging studies identified abnormalities of brain networks—the Default Mode Network—in BD and SUD that are possibly involved in the pathophysiology of both disorders and therefore provide evidence for the shared underlying mechanisms (15).

Yet another mechanism proposed to underlie SUD and BD comorbidity concerns the role of the dopaminergic system, which was recognized a long time ago in both BD and SUD. In BD, bipolar depression is characterized by increased striatal dopamine transporter levels, resulting in attenuated dopaminergic function (17). In contrast, increased $D_2/D_3$ receptor availability as well as hyper-responsive reward system in the ventral striatum is observed in bipolar mania, leading to heightened dopaminergic neurotransmission (17). In SUD, nearly all neurochemical systems in the brain are involved in the pathophysiology, including the dopaminergic system which has been extensively examined due to its involvement in reward and reinforcement (18). Particularly the $D_3$ receptor system and its significance in addiction sparked interest: firstly, due to its anatomical localization, as $D_3$ receptors are highly expressed in limbic areas that form the "reward" circuitry, therefore implying that they mediate motivation, emotions, and by extension, may be involved in addiction (19). The other pivotal feature of $D_3$ receptors is that they have the highest overall affinity to endogenous dopamine ($Ki = 30$ nM) among the five dopamine-subtypes (20, 21). Thus, they are the most sensitive to basal concentration (19), indicating greater occupancy of $D_3$ receptors after dopamine-elevating drug administration (most drugs of abuse) in comparison with $D_1$ or $D_2$ receptors (estimated to be 96% vs. 25–27%) (22).

Human positron emission tomography (PET) studies have contributed greatly to bringing light to the dopaminergic abnormalities in addictions, especially related to the $D_2$-like dopamine receptors ($D_2$ and $D_3$), by allowing measurement of receptor occupancy (18). Reduced striatal $D_2$ receptor availability was found in individuals with SUD [including cocaine (23), alcohol (24), and methamphetamine (25)] compared to healthy controls (18). These abnormalities have been linked to behavioral traits relevant to addiction, such as emotional and behavioral impulsivity (26)—which is also a common feature in BD—, but also in response inhibition (27) and relapse after clinical intervention (28). PET studies further discovered blunted dopamine release at $D_2$ receptors in subjects with addiction [including cocaine (29), alcohol (24), and methamphetamine (25)], assumed to be associated with hypoactive dopaminergic state that bolsters drug-seeking behavior (18).

Recent findings, however, have found that unlike $D_2$ receptors, $D_3$ receptors have actually shown an upregulation in human *post-mortem* (30) and animal studies (18, 31). Despite these *in vitro* findings, the examination of $D_3$ receptors in humans *in vivo* was restricted due to the lack of a selective PET ligand. The relatively recent introduction of [$^{11}$C]-(+)-PHNO—a $D_3$ preferring PET radioligand—has, however, enabled the

investigation of $D_3$ receptors in addiction in the human brain *in vivo* (19, 32). Indeed, PET studies using [$^{11}$C]-(+)-PHNO confirmed the findings of *in vitro* studies: $D_3$ receptor availability is heightened in individuals with SUD, and they were shown to be associated with impulsivity (23), drug craving (33), cognitive dysfunction (34), and symptom severity (18).

Thus, evidence suggests that both SUD and BD share similar dopaminergic dysfunctions especially at the $D_2$ and $D_3$ receptors, which shifts the attention toward dopamine modulating agents such as partial agonists acting at the $D_2/D_3$ dopamine receptors.

## TREATMENT OF BD AND SUD

Traditionally, comorbid SUD in BD or other psychiatric illnesses have usually been treated either in parallel, i.e., patients were receiving concurrent treatment for both disorders, but in different programs, or in sequence, i.e., SUD first, BD second (9). Despite extensive evidence highlighting the frequency of the occurrence of SUD in BD, as well as its detrimental impact on the prognosis and treatment outcomes of BD, only a few studies aimed at exploring appropriate treatment options for this subgroup of BD patients, especially in terms of pharmacotherapies (9). Instead, BD has been traditionally treated with mood stabilizers and anticonvulsant agents, or with second-generation antipsychotics (35). For SUD, the need for pharmacological therapy has long been acknowledged, yet adequate therapeutic options are lacking (36). Current medications include (depending on the substance of abuse) buprenorphine, naltrexone, topiramate, varenicline, bupropion, clonidine, and methadone (37). Given antipsychotics' dopamine-stabilizing effects, they were anticipated to reduce craving in SUD, leading researchers to investigate this notion (2). According to a meta-analysis, the antipsychotics investigated in the study (amisulpride, aripiprazole, olanzapine, and quetiapine) did not produce significant reductions in alcohol craving or drinking behavior in patients with primary AUD without comorbidities (38). Aripiprazole, however, was significantly associated with a decrease in the number of drinks as well as heavy drinking days (39). Furthermore, a study involved patients with comorbid BD/schizoaffective disorder and SUD who were switched to aripiprazole (40). Patients with comorbid AUD showed reduced alcohol craving and spent less dollars on alcohol, while patients with cocaine use disorder showed a decrease in cocaine craving, but not cocaine use (40). Quetiapine, an atypical antipsychotic with a very low affinity for $D_{2/3}$ receptors (41), was further investigated whether it relieves alcohol craving similarly to aripiprazole (42). Results, however, did not demonstrate efficacy in a randomized controlled trial for alcohol use measures in patients with comorbid BD and AUD (42).

In light of the shared underlying mechanisms, integrated treatment options—addressing both disorders by the same team at the same time—need to be established for this patient population (9), and the most likely drug candidates to treat with seem to be partial agonists acting at $D_2/D_3$ dopamine receptors.

## DOPAMINE $D_2/D_3$ PARTIAL AGONISTS IN THE TREATMENT OF BD AND SUD

The currently known and markedly available dopamine $D_2/D_3$ partial agonists are aripiprazole, cariprazine, and brexpiprazole

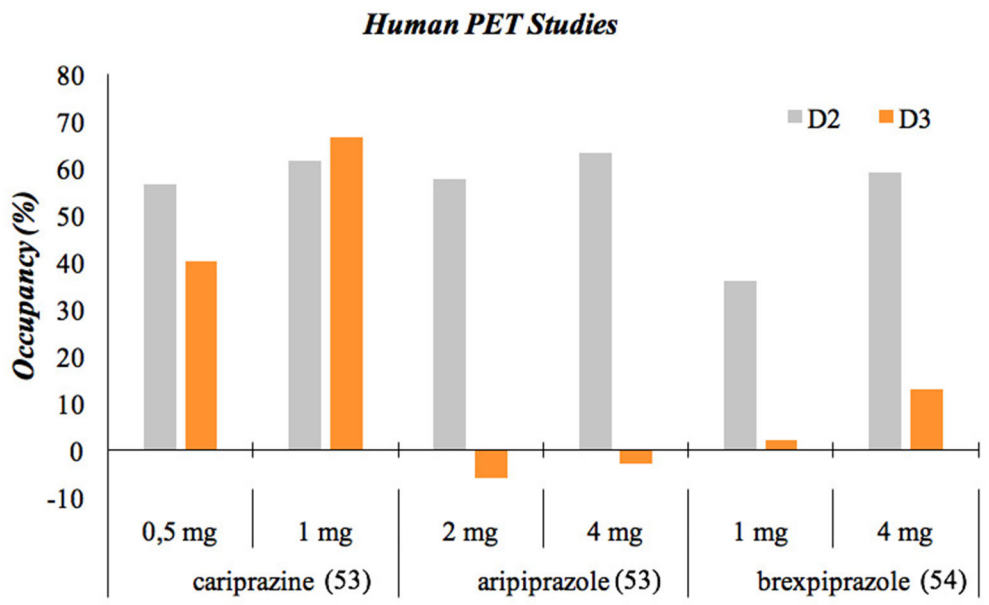


**FIGURE 1 |** Occupancy of $D_2$ and $D_3$ receptors of antipsychotics. The cariprazine and aripiprazole data come from a PET study involving healthy volunteers that aimed to assess the D3 receptor occupancy of cariprazine and aripiprazole at doses that attain similar D2 receptor occupancy by both drugs. This was assessed using two different methods, and the data presented here is the average of the outcome of these methods. The brexpiprazole data comes from a PET study involving schizophrenia patients.

**TABLE 1 |** Cariprazine case reports.

| | |
|---|---|
| Sanders and Miller (65) | |
| Age | 51 |
| Gender | Male |
| Problem | Bipolar I disorder with alcohol use and cocaine craving |
| Cariprazine's effect | Reduced substance use, craving, and improved mood symptoms |
| Short description | The patient had failed multiple medication trials (including risperidone, paliperidone, aripiprazole, bupropion SR, carbamazepine, lamotrigine, and lithium) for treatment of bipolar I disorder symptoms. When he got enrolled in a cariprazine (monotherapy) trial, he was suffering from alcohol abuse and craving cocaine. The transformation of his appearance and presentation was remarkable. He seemed well-groomed unlike during the previous appointments, as well as he reported a lowered urge to drink excessively or use drugs and he was in a stable mood. He stopped using illicit drugs and his drinking behavior has continuously declined, he is now abstinent |
| Age | 20 |
| Gender | Female |
| Problem | Bipolar I disorder, ADHD, alcohol, and cannabis use |
| Cariprazine's effect | Improved mood and behavior symptoms, reduced substance use, enhanced overall functioning |
| Short description | Besides the bipolar I disorder diagnosis, the patient suffered from ADHD, alcohol, and cannabis use as well. Several medications had been tried to mitigate her symptoms of depression, irritability, distractibility, and agitation with little success<br>Cariprazine was started as an add-on treatment at 1.5 mg/day for 3 weeks without improvement; then it was increased to 3 mg/day. Her medication regimen at that time included quetiapine 25 mg/day at bedtime, clonazepam 0.5 mg twice daily at bedtime, and methylphenidate XR 72 mg daily. After 3 weeks on 3 mg cariprazine, she presented with significant improvement—no restlessness, good eye contact, organized thought processes, respectful of her mother's input, and most remarkably she was substance-free. She agreed to random urine toxicology screens, both of which were negative. Following several months of substance abstinence and respectful behavior toward her family, her parents allowed her to return to live at their home. She has been free of substance abuse for 27 months, she continues to function well, her symptoms remain improved, and she recently graduated at the top of her class in an aesthetician training program and has passed all of her state boards |
| Age | 54 |
| Gender | Male |
| Problem | Bipolar I disorder, alcohol use |
| Cariprazine's effect | Improved mood and behavior symptoms, reduced substance use, and enhanced overall functioning |
| Short description | Although the patient and his wife run their own business, he was functionally disabled by his comorbid bipolar I disorder and alcohol use disorder. At the time of his initial presentation, he was taking quetiapine, lithium, lamotrigine, bupropion, duloxetine, omega-3 fatty acids, and gabapentin. Subsequent medication trials included various combinations of lurasidone, olanzapine, methylphenidate, and asenapine. Although there was some benefit for his depression, his excessive alcohol use persisted. After the initiation of cariprazine as add-on treatment to his current regimen, he reported a dramatic decline in alcohol-craving and eventually restricted his alcohol intake to 1–2 drinks on holidays or special occasions only. He was then tapered off his previous medications, and he is now stable and functioning well on cariprazine and quetiapine |
| Ricci et al. (66) | |
| Age | 21 |
| Gender | Male |
| Problem | Methamphetamine-induced psychosis |
| Cariprazine's effect | Improved mood and behavior symptoms, reduced substance use, and enhanced overall functioning |
| Short description | The patient progressed from occasional methamphetamine use at the age of 23 to daily use by the age of 24. He was admitted to the hospital after presenting with persistent visual and auditory hallucination, suspiciousness and social withdrawal, with symptoms remaining after ceasing methamphetamine use. He developed depressive, negative, and cognitive symptoms and suicidal thoughts. After his hospital admission, he received olanzapine with no improvement, followed by risperidone which improved depressive symptoms. He then received cariprazine (starting dose of 1.5 mg/day for 3 days, then 3 mg/day between day 4 and 12, then 4.5 mg/day from day 13 onwards) and benzodiazepines for insomnia. Two weeks of cariprazine treatment yielded an improvement in paranoid and hallucinatory symptoms, and in social functioning, resulting in his discharge. At week 16 of his treatment, his scores on the negative and positive subscales of the Positive and Negative Syndrome Scale (PANSS) were reduced by 61.7 and 69.9%. The patient regained his baseline level of social and occupational functioning, and reported a decrease in methamphetamine use and craving. Cariprazine dose was then reduced to 3 mg/day, and the improvement in symptoms was maintained during the treatment period. The patient remains on cariprazine monotherapy and during the treatment period, he remained free of psychotic symptoms and abstinent from methamphetamine |

(43). Some older compounds (such as bifeprunox), as well as some newer compounds in development (e.g., OSU-6162) also exist and provide valuable information to the understanding of the efficacy of partial agonists in BD and SUD (44, 45).

The efficacy of $D_2/D_3$ partial agonists in SUD is not well-examined and much of the data comes from animal studies. As such, one animal model has investigated the anti-abuse effects of cariprazine, aripiprazole, and bifeprunox in cocaine addiction in rats (44). All compounds succeeded at reducing

the rewarding effects of cocaine—as indicated by enhanced self-administration of the drug—as well as prevented relapse to cocaine seeking following a period of complete withdrawal from cocaine and its related cues (44). Equipotent effects of cariprazine and bifeprunox were observed, 20 times more potent than that of aripiprazole (44). The beneficial effects of partial agonists in animal studies were also observed in alcohol abuse: the compound OSU-6162 effectively reduced self-administration, withdrawal and reinstatement in rats (45), and aripiprazole lessened the acute stimulant effects of alcohol in mice (46, 47). Furthermore, one study investigated the effect of a D3 partial agonist, CJB090, in methamphetamine addiction in rats, where the investigational drug yielded reductions in methamphetamine self-administration (fixed ratio schedule) and its excessive intake in a group of rats with extended access to methamphetamine (48). Human data in SUD is scarce, and little information is available.

The efficacy of $D_2/D_3$ partial agonists in BD has been well-examined for the currently available compounds with different findings. While cariprazine proved to be efficacious in both bipolar mania and bipolar depression (49) [3–6 mg in bipolar mania (50) and 1.5–3 mg in bipolar depression (51)], studies of aripiprazole confirmed efficacy in bipolar mania only (52). Brexpiprazole studies in bipolar mania were unsuccessful (53), and, following a positive pilot trial (54), a RCT in bipolar depression is ongoing (55). Human PET studies with cariprazine (56, 57), aripiprazole (58), and brexpiprazole (58) have pointed to the difference potentially explaining these findings: while all three compounds were able to occupy the $D_2$ receptors in the brain, only cariprazine was able to sufficiently occupy the $D_3$ receptors as well [(59); **Figure 1**]. Additionally, a clinical trial has been initiated to further study the dopamine D3 receptor occupancy of cariprazine (1.5 vs. 3 mg/day) in patients with unmedicated bipolar depression (60).

Cariprazine has in fact a preferential binding to $D_3$ receptors, and its binding is stronger than that of any other antipsychotics and even dopamine itself (61). Given dopamine's very high affinity for the $D_3$ receptors, the low affinities of antipsychotics, with the exception of cariprazine, make them unable to block the $D_3$ receptors in the presence of dopamine in the living brain (62). This means that only cariprazine is able to exhibit the effects usually associated with $D_3$ partial agonism, which are improvements in negative, cognitive and depressive symptoms as well as in motivation and reward (49). Given the increasingly acknowledged role of $D_3$ in SUD along with BD, cariprazine's high affinity for $D_3$ receptors makes it an appropriate candidate for the treatment of comorbid BD with SUD.

Two clinical trials have been initiated to investigate cariprazine's efficacy in SUD, although results are not available yet. An investigator-initiated trial aims to explore cariprazine's effects on the brain and behavior in cocaine use disorder in a phase II, randomized, single-blind, placebo-controlled study using fMRI (1.5 vs. 3 mg/day) (63). Furthermore, a phase IIa, randomized, placebo-controlled pilot study was designed to explore how low-dose cariprazine (1.5 mg/day) affects cocaine use in medically stable patients with comorbid opioid use disorder who have already been taking buprenorphine/naloxone at a stable dose (64). Additionally, scarce data is available from case reports as summarised in **Table 1**. Evidence for the effects of several partial agonists in SUD, BD, and BD or related psychotic disorders and comorbid SUD is depicted in the **Supplementary Table 1**, which also includes two additional recent case reports on cariprazine treatment in major psychiatric disorders with comorbid SUD (67).

## CONCLUSION

So far, pharmacological treatment concepts hardly considered the joint treatment of SUD and BD, which seem to share a common action on dopamine $D_2$ and $D_3$ receptors. An ideal integrated pharmacological treatment would therefore address both disorders through the $D_2$ and $D_3$ receptors, in addition to other therapeutic interventions, such as psychotherapy. Since cariprazine has shown to exert effects on both $D_2$ and $D_3$ receptors (partial agonist effect) next to serotonin receptors, as well as has well-established efficacy in bipolar I disorder, it is believed to be a potential treatment option for this patient population. Data for this assumption comes from animal studies and case reports, however, further studies are needed to validate this rationale-based assumption.

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HG, RC, CB, and ÁB contributed to developing the concept of the manuscript. RC wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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REVIEW
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# Cariprazine in the Treatment of Bipolar Disorder: Within and Beyond Clinical Trials

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Bipolar disorder (BD) is chronic psychiatric disorder associated with significant impairment in psychosocial functioning and quality of life. Although current pharmacological treatments for BD have improved its clinical management, many patients do not achieve remission, particularly those suffering from bipolar depression. In addition, available treatments are associated with a myriad of potential adverse effects, which highlights the need for novel therapeutic agents that can be effective for both phases of the illness with a reduced side effect burden. Cariprazine is a novel antipsychotic that is a dopamine D2/D3 partial agonist with a preference for D3 receptors. In this review, we examine the pharmacological properties, clinical efficacy and tolerability profile of cariprazine in patients with BD, taking into account the latest clinical trials data. We also review *post hoc* analyses addressing clinically relevant subgroups and symptom domains in BD. Current evidence suggests efficacy for cariprazine 3–12 mg/day in the treatment of acute manic and mixed episodes; for bipolar depression, the efficacy of cariprazine appears to be dose-related, with doses of 1.5–3 mg/day beneficial as monotherapy. Cariprazine is overall well-tolerated by patients in both manic and depressive episodes. Its most common side effects relative to placebo include akathisia, extrapyramidal symptoms and nausea. There are no metabolic concerns reported with cariprazine use. In summary, the latest evidence suggests that cariprazine is an effective and safe treatment option for BD.

**Keywords: cariprazine, treatment, bipolar disorder, clinical trial, *post hoc* analyses**

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## INTRODUCTION

Bipolar disorder (BD) is chronic and recurrent psychiatric disorder with a lifetime prevalence of 2.1% (1). It is associated with significant impairment in psychosocial functioning and quality of life, even during periods of euthymia (2). Patients with BD spend up to 50% of their time being ill, with depressive predominating over manic or mixed symptoms (3). The mainstay treatment of BD consists of pharmacotherapy, and specific options depend on the phase of illness (4). Generally, both manic and depressive episodes are managed with mood stabilizers and atypical antipsychotics, either as monotherapy or combination therapy. Although current pharmacological treatments for BD have improved its clinical outlook, many patients do not achieve remission, particularly those suffering from bipolar depression (5). Bipolar depression is often difficult to treat and is linked to worse interpersonal and occupational functional outcomes (6). In addition, available treatments for BD are associated with a myriad of potential adverse effects, such as cardiovascular changes,

extrapyramidal symptoms, metabolic abnormalities and weight gain, which often leads to poor adherence (7, 8). This highlights the need for novel therapeutic agents that can be effective for both phases of the illness with a reduced side effect burden.

The objective of this paper is to review the pharmacological properties and clinical efficacy as well as tolerability profile of the novel therapeutic agent cariprazine in the management of patients with BD, taking into account the latest clinical trials data across all phases of the illness. We also included *post hoc* analyses addressing clinically relevant subgroups and symptom domains in BD.

## OVERVIEW OF CARIPRAZINE

Cariprazine is a piperazine derivative and works primarily as a partial agonist at the dopamine D2 and D3 receptors (9). Compared to aripiprazole and brexpiprazole, which are also partial agonists at the D2 and D3 receptors, cariprazine displays greater selectivity for D3 receptors (10). Cariprazine has been approved by the US Food and Drug Administration (FDA) for the treatment of schizophrenia as well as for the management of manic, mixed and depressive episodes associated with bipolar I disorder in adults. The only other medication with FDA-approval for both mania and bipolar depression is quetiapine. The 2018 Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) guidelines recommend cariprazine as a first-line treatment for acute mania, and a second-line treatment for bipolar I depression (11). However, there was insufficient evidence to recommend its use as a maintenance treatment in bipolar I disorder. A recent meta-analysis found that cariprazine was efficacious and safe for the treatment of acute manic, mixed and depressive episodes associated with BD, but that the effect sizes were smaller for bipolar depression (12).

### Pharmacodynamics

Cariprazine is a partial agonist at D2 and D3 receptors, with a 10-fold higher affinity for D3 compared to D2 receptors *in vitro* (13). The activity of cariprazine *in vivo* depends on the functional status of the dopaminergic system; when dopamine activity is normal, it acts as an antagonist and when dopamine tone is low, it becomes a partial agonist (9). Since it has a higher potency for D3 receptors than dopamine, cariprazine administration results in a net effect of D3 antagonism (14). This property differentiates cariprazine from other atypical antipsychotics and may explain its unique pharmacological profile. D3 receptors are primarily located in the ventral tegmental area (VTA), substantia nigra, hypothalamus and limbic areas (15). Due to its lower potential for inhibiting dopaminergic neurotransmission in the striatum, cariprazine may cause less extrapyramidal symptoms (EPS) than other antipsychotics (13). D3 receptors are believed to be involved in locomotor control, cognition and drug abuse (16, 17). As a result, cariprazine has been associated with pro-cognitive effects and improvement in negative symptoms in patients with schizophrenia (18, 19). Cariprazine also demonstrated anti-abuse potential by reducing the rewarding effect of cocaine in rats (20). Since BD is frequently linked to substance use disorders (21), this finding warrants further investigation in clinical trials. Animal models have suggested a role of D3 receptors in mood regulation, and that partial agonism at D3 receptors may have antidepressant effects (22). A possible mechanism of action is that partial agonism/antagonism at D3 receptors inhibit the activity of somatodendritic D3 receptors in the VTA, resulting in increased dopamine release in the prefrontal cortex and subsequent mood improvement (23).

In addition to being a D2 and D3 partial agonist, cariprazine is a strong antagonist at the serotonin 5-$HT_{2B}$ receptors (24), although the clinical relevance of this effect remains unclear. It also has high affinity for the $\alpha$-$_{1B}$ receptor, which has been associated with reduced EPS and akathisia (25). Cariprazine is a partial agonist at the 5-$HT_{1A}$ receptors and binds to them with moderate affinity; this property may contribute to its antidepressant effects (26). Furthermore, at higher doses of cariprazine, 5-$HT_{1A}$ partial agonism is hypothetically linked to reduced EPS (13). Cariprazine has low to moderate affinity for the 5-$HT_{2A}$, 5-$HT_{2C}$ and $H_1$ receptors (9). Due to its relatively weak antagonism at the 5-$HT_{2C}$ and $H_1$ receptors, cariprazine may be associated with less sedation, weight gain and metabolic abnormalities compared to other atypical antipsychotics, such as olanzapine and quetiapine. It has negligible activity on cholinergic muscarinic receptors and thus, does not cause anticholinergic side effects (13).

### Pharmacokinetics

Cariprazine is an oral medication that is dosed once-daily, with or without food (27). Following oral administration, cariprazine is rapidly absorbed and reaches peak concentrations within 3–5 h (28). It has a large volume of distribution and is extensively distributed in tissues (29). Cariprazine is primarily metabolized by the CYP3A4 isoenzyme and to a lesser extent, by CYP2D6 into two major active metabolites, desmethylcariprazine (DCAR) and didesmethylcariprazine (DDCAR) (30). Both metabolites are pharmacologically equipotent to cariprazine and appear to mediate its therapeutic effect (31). The mean half-lives of cariprazine and its metabolites are 2–4 days and 1–3 weeks, respectively (32). The long half-life of cariprazine and its metabolites has important clinical implications. After initiating cariprazine, the effective dose may be increasing for many weeks even if the daily dose remains constant, since it takes longer for cariprazine to achieve a steady-state (14). For the same reason, occasionally missing a dose of cariprazine will probably not lead to symptomatic relapse or discontinuation symptoms, as opposed to compounds with shorter half-lives (14). According to a 12-week study, steady-state plasma concentrations were reached within 1–2 weeks for cariprazine and DCAR, and within 4 weeks for DDCAR due to its slow elimination (33). Cariprazine and its metabolites are minimally excreted in urine (29). Cariprazine itself is a weak inhibitor of CYP3A4 and CYP2D6 with no significant induction effects in human hepatocytes (30). The pharmacokinetics properties of cariprazine and its metabolites are not altered by age, sex, race, smoking status, and in patients with mild to moderate hepatic or renal impairment.

**TABLE 1 |** Summary of Mania RCTs.

| Reference | Intervention | Dosing | Sample Size[a] | YMRS LSMD (95% CI) | Response[b] (%) | Remission[c] (%) |
|---|---|---|---|---|---|---|
| Durgam et al. (35) | Cariprazine 3–12 mg/day | Flexible | 118 | −6.1 (−8.9 to −3.3) | 48 | 42 |
| | | | | $p < 0.0001$ | $p < 0.001$ | $p = 0.002$ |
| | Placebo | | 117 | – | 25 | 23 |
| Calabrese et al. (36) | Cariprazine 3–6 mg/day | Fixed/flexible | 165 | −6.1 (−8.4 to −3.8) | 60.6 | 44.8 |
| | | | | $p < 0.001$ | $p < 0.001$ | $p = 0.003$ |
| | Cariprazine 6–12 mg/day | | 167 | −5.9 (−8.2 to −3.6) | 59.3 | 44.3 |
| | | | | $p < 0.001$ | $p < 0.001$ | $p = 0.005$ |
| | Placebo | | 160 | – | 37.5 | 29.4 |
| Sachs et al. (37) | Cariprazine 3–12 mg/day | Flexible | 158 | −4.3 (−6.7 to −1.9) | 58.9 | 51.9 |
| | | | | $p = 0.0004$ | $p = 0.0097$ | $p = 0.0025$ |
| | Placebo | | 152 | – | 44.1 | 34.9 |

[a] *Intention-to-treat population.*
[b] *≥50% YMRS score reduction from baseline.*
[c] *YMRS total score ≤12.*
*YMRS, Young Mania Rating Scale; LSMD, least square mean difference; CI, confidence interval.*

## Dosing

For acute mania, the recommended dose range of cariprazine is 3–6 mg/day (34). The recommendation is to start at 1.5 mg/day on day 1 and increase to 3 mg/day as early as on day 2. The dose can be further increased by 1.5–3 mg increments depending on clinical response and tolerability, up to a maximum of 6 mg/day. For bipolar depression, the recommended dose range is 1.5–3 mg/day. The starting dose is 1.5 mg/day, which is the therapeutic dose for the majority of patients. The dose can be increased to 3 mg/day in those that have had a partial response with response plateaued for 2 weeks or longer depending on the tolerability.

Although cariprazine has been studied as a monotherapy agent in bipolar disorder, it can be administered concurrently with lithium, valproic acid or lamotrigine with no dose adjustment required. If cariprazine is used in conjunction with carbamazepine, clinicians need to be aware of the potential reduction in cariprazine levels given that carbamazepine is a potent CYP3A4 inducer; hence, the dose of cariprazine may need to be adjusted accordingly to achieve the desired clinical outcomes. The dose of cariprazine should be reduced by 50% when administered concurrently with strong CYP3A4 inhibitors (27).

# OVERVIEW OF CLINICAL TRIALS AND *POST HOC* ANALYSES

The authors searched for clinical trials and *post hoc* analyses published in the PubMed, Web of Science, Embase, PsychInfo and ClinicalTrials.gov electronic databases. The search strategy contained the following terms: cariprazine, bipolar disorder, bipolar affective disorder, mania, bipolar depression and mixed episode. Randomized, double-blind, placebo controlled (RCTs) trials and *post hoc* analyses were included. To look for additional studies that may have not been captured by the original database search, we performed backwards reference chaining by searching through bibliographies of relevant articles.

At the time of this writing, there were three ongoing clinical trials on the efficacy and/or safety of cariprazine in BD registered on ClinicalTrials.gov; one RCT on the efficacy and safety of cariprazine in bipolar I depression in pediatric participants (NCT04777357), one open-label study on the long-term (26-weeks) safety and tolerability of cariprazine in pediatric participants with schizophrenia or bipolar I disorder (NCT04578756), and one RCT on relapse prevention in bipolar I patients with manic or depressive episodes, with or without mixed features (NCT03573297). However, the preliminary results of these trials are currently not available.

The efficacy and safety of cariprazine in treating bipolar I disorder in adults have been examined in seven RCTs. Their results are summarized below.

# CLINICAL EFFICACY

## Efficacy in Mania

Three RCTs (one phase II and two phase III studies) have assessed the efficacy of cariprazine in patients with mania (35–37) (see **Table 1**).

The Durgam et al. trial was a phase 2, multinational, flexible-dose RCT comprising of 235 patients in the intention-to-treat (ITT) population (35). Participants were randomized to receive cariprazine 3–12 mg/day, or placebo for 3 weeks. The mean daily dose of cariprazine was 8.8 mg/day. For the primary parameter, the change in Young Mania Rating Scale (YMRS) total score from baseline to week 3 was significantly greater for the cariprazine group compared to the placebo group [least square mean differences [LSMD]: −7.0 (95% confidence interval [CI]: −10.0 to −4.0; $p < 0.0001$)] using a mixed-effects model for repeated measures (MMRM) approach. The improvement in YMRS score was observed on day 7, and was maintained through the end of the trial. Cariprazine-treated patients had significantly higher response and remission rates compared to placebo-treated patients, with number needed to treat (NNT) estimates of 5 for response and 6 for remission.

**TABLE 2 |** Summary of Bipolar Depression RCTs.

| Reference | Intervention | Dosing | Sample size[a] | MADRS LSMD (95% CI) | HAMD-17 LSMD (95% CI) | Response[b] (%) | Remission[c] (%) |
|---|---|---|---|---|---|---|---|
| Yatham et al. (38) | Cariprazine 0.25–0.75 mg/day | Fixed/flexible | 64 | −0.7 (−4.6 to 3.3) | −0.2 (−2.9 to 2.5) | 56.0 | 48.0 |
| | | | | $p = 0.7408$ | $p = 0.8936$ | $p = 0.4026$ | $p = 0.2298$ |
| | Cariprazine 1.5-3 mg/day | | 54 | 0.0 (−4.1 to 4.1) | 0.2 (−2.6 to 3.0) | 54.1 | 43.2 |
| | | | | $p = 0.9961$ | $p = 0.8891$ | $p = 0.5066$ | $p = 0.4512$ |
| | Placebo | | 60 | – | – | 49.3 | 38.7 |
| Durgam et al. (39) | Cariprazine 0.75 mg/day | Fixed | 140 | −1.9 (−4.3 to −0.5) | −1.1 (−2.9 to 0.6) | 38.6 | 23.6 |
| | | | | $p = 0.129$ | $p = 0.199$ | $p = 0.227$ | $p = 0.340$ |
| | Cariprazine 1.5 mg/day | | 145 | −4.0 (−6.3 to −1.6) | −2.7 (−4.4 to −1.0) | 49.7 | 36.6 |
| | | | | $p = 0.003$ | $p = 0.002$ | $p = 0.002$ | $p = 0.002$ |
| | Cariprazine 3 mg/day | | 145 | −2.5 (−4.9 to −0.1) | −2.2 (−3.9 to −0.5) | 44.8 | 27.6 |
| | | | | $p = 0.112$ | $p = 0.013$ | $p = 0.024$ | $p = 0.105$ |
| | Placebo | | 141 | – | – | 31.9 | 19.9 |
| Earley et al. (40) | Cariprazine 1.5 mg/day | Fixed | 162 | −2.5 (−4.6 to −0.4) | −1.6 (−3.2 to 0.1) | 40.7 | 25.9 |
| | | | | $p = 0.0417$ | $p = 0.0590$ | $p = 0.3383$ | $p = 0.1648$ |
| | Cariprazine 3 mg/day | | 153 | −1.8 (−3.9 to 0.4) | −0.5 (−2.1 to 1.2) | 42.5 | 26.1 |
| | | | | $p = 0.1051$ | $p = 0.5599$ | $p = 0.2088$ | $p = 0.1625$ |
| | Placebo | | 163 | – | – | 35.6 | 19.6 |
| Earley et al. (41) | Cariprazine 1.5 mg/day | Fixed | 154 | −2.5 (−4.6 to −0.4) | −2.4 (−4.0 to −0.8) | 48.1 | 33.1 |
| | | | | $p = 0.0331$ | $p = 0.0042$ | $p = 0.1300$ | $p = 0.0374$ |
| | Cariprazine 3 mg/day | | 164 | −3.0 (−5.1 to −0.9) | −1.3 (−3.0 to 0.3) | 51.8 | 32.3 |
| | | | | $p = 0.0103$ | $p = 0.0996$ | $p = 0.0243$ | $p = 0.0391$ |
| | Placebo | | 156 | – | – | 39.7 | 23.1 |

[a] *Intention-to-treat population.*
[b] *≥50% MADRS score reduction from baseline.*
[c] *MADRS total score ≤10.*
*MADRS, Montgomery-Åsberg Depression Rating Scale; HAMD-17, 17-item Hamilton Depression Rating Scale; LSMD, least square mean difference; CI, confidence interval.*

Calabrese et al. conducted a phase 3, multicenter, fixed/flexible-dose RCT, which included 492 patients in the ITT population (36). Participants were randomly assigned to cariprazine 3–6 mg/day (low dose), cariprazine 6–12 mg/day (high dose), or placebo for 3 weeks. The mean daily doses were 4.8 mg for the 3–6 mg/day group, and 9.1 mg for the 6–12 mg/day group. For the primary efficacy measure, the YMRS total change score from baseline to week 3 was significantly greater for both cariprazine groups compared to placebo [LSMD for the 3–6 mg/day group: −6.1 (95% CI: −8.4 to −3.8; $p < 0.001$); LSMD for the 6–12 mg/day group: −5.9 (95% CI: −8.2 to −3.6; $p < 0.001$)]. *Post hoc* analyses of the primary outcome resulted in effect sizes of 0.62 for the 3–6 mg/day group, and 0.60 for the 6–12 mg/day group using a MMRM approach. In addition, both cariprazine groups were associated with significantly higher response and remission rates compared to placebo, with NNT estimates of 5 for response and 7 for remission in both groups.

The Sachs et al. study was a phase 3, flexible-dose RCT involving 310 participants in the ITT population (37). Similar to the Durgam et al. trial, patients were randomized to receive cariprazine 3–12 mg/day, or placebo for 3 weeks. For the primary outcome, the cariprazine group had a significantly greater reduction in YMRS total score from baseline to week 3 compared to placebo [LSMD: −4.3 (95% CI: −6.7 to −1.9; $p = 0.0004$)]. The improvement in YMRS score was observed as early as 4 days after the baseline assessment, and was maintained until the end of the trial. The effect size for cariprazine on YMRS change score was 0.45 using a MMRM approach. Response (58.9 vs. 44.1%) and remission (51.9 vs. 34.9%) rates were significantly higher in the cariprazine-treated patients vs. placebo-treated patients.

## Efficacy in Bipolar Depression

Four RCTs (two phase II and two phase III studies) have evaluated the efficacy of cariprazine in participants with bipolar depression (38–41) (see **Table 2**).

Yatham et al. led a phase 2, fixed/flexible-dose RCT, which included 224 participants in the ITT population (38). This trial recruited patients with both bipolar I and bipolar II disorder, who were randomly allocated to cariprazine 0.25–0.5 mg/day (low dose), cariprazine 1.5–3.0 mg/day (high dose), or placebo for 8 weeks. Neither cariprazine group significantly separated from placebo for the primary (change in Montgomery-Åsberg Depression Rating Scale [MADRS] total score from baseline to week 8) and secondary (change in Clinical Global Impressions—Severity/Improvement [CGI-S, CGI-I], 17-item Hamilton Depression Rating Scale [HAMD-17] and 24-item HAMD [HAMD-24] scores) efficacy measures. In addition, there was no significant difference in response and remission rates between both cariprazine groups and placebo.

Durgam and colleagues conducted a phase 2, multicenter, fixed-dose trial which included 571 patients in the ITT population (39). Participants were randomized to receive cariprazine 0.75 mg/day, cariprazine 1.5 mg/day, cariprazine 3.0 mg/day, or placebo. For the primary efficacy outcome, the MADRS score change from baseline to week 6 was statistically significant only for the cariprazine 1.5 mg/day group [LSMD: −4.0 (95% CI: −6.3 to −1.6; adjusted $p = 0.003$)]. The cariprazine 0.75 and 3.0 mg/day groups failed to separate from placebo, although the 3.0 mg/day group demonstrated a greater MADRS score reduction than placebo (adjusted $p = 0.112$). The MADRS effect sizes were 0.20, 0.42, and 0.26 for the cariprazine 0.75, 1.5, and 3.0 mg/day groups, respectively. Only the cariprazine 1.5 mg/day group had significantly higher rates of MADRS response (NNT = 6, $p < 0.05$) and remission (NNT = 6, $p < 0.01$) compared to placebo. The cariprazine 3.0 mg/day group was significantly superior to placebo only for the MADRS response rate (NNT = 8, $p < 0.05$).

Earley et al. conducted a phase 3, fixed-dose RCT involving 478 participants in the ITT population (40). Patients were randomized to cariprazine 1.5 mg/day, cariprazine 3.0 mg/day, or placebo for 6 weeks. For the primary efficacy outcome, only the cariprazine 1.5 mg/day group demonstrated a statistically significant reduction in MADRS total score from baseline to week 6 compared to placebo [LSMD: −2.5 (95% CI: −4.6 to −0.4; adjusted $p = 0.0417$)]. Although patients who received cariprazine 3.0 mg/day had a lower MADRS total score at week 6 vs. placebo, the difference did not reach statistical significance ($p = 0.1051$). The effect sizes for cariprazine at week 6 were 0.28 for the cariprazine 1.5 mg/day group, and 0.20 for the 3.0 mg/day group. Both cariprazine groups failed to achieve higher response and remission rates compared to placebo using the MADRS criteria. However, a significantly greater percentage of patients in the cariprazine 1.5 mg/day group met criteria for HAMD-17 remission (30.6 vs. 16.4%, $p = 0.0051$), which was not the case for the cariprazine 3.0 mg/day group.

Finally, in a phase 3, fixed-dose RCT comprising of 475 patients in the ITT population, participants were randomly assigned to receive cariprazine 1.5 mg/day, cariprazine 3.0 mg/day, or placebo (41). For the primary efficacy parameter, both cariprazine groups showed a significant reduction in MADRS total scores from baseline to week 6 [LSMD for the 1.5 mg/day group: −2.5 (95% CI: −4.6 to −0.4; adjusted $p = 0.033$); LSMD for the 3.0 mg/day group: −3.0 (95% CI: −5.1 to −0.9; $p = 0.010$)]. The effect sizes were 0.28 and 0.34 for the cariprazine 1.5 and 3.0 mg/day groups, respectively. MADRS response rates only reached statistical significance for the cariprazine 3.0 mg/day group (51.8%, NNT = 8, $p = 0.024$). However, MADRS remission rates were significantly higher in both cariprazine groups (33.1%, NNT = 10, $p = 0.037$ for the 1.5 mg/day group; and 32.3%, NNT=11, $p = 0.039$ for the 3.0 mg/day group).

## SAFETY AND TOLERABILITY

Cariprazine was shown to be generally well-tolerated in the RCTs for BD. The majority of treatment-emergent adverse events (TEAEs; defined as ≥5% in the cariprazine group(s) and twice the rate of placebo) were mild or moderate in intensity.

Two *post hoc* analyses have assessed the safety and tolerability of cariprazine by pooling the data from the above RCTs; one *post hoc* analysis was carried out in patients with acute manic/mixed episodes (42), while the other was performed in participants with bipolar depression (43). For the *post hoc* analysis of mania, cariprazine was associated with more TEAEs compared to placebo, but the majority of adverse events were mild to moderate in severity (42). The most common cariprazine TEAEs were akathisia, extrapyramidal symptoms, restlessness and vomiting. The incidence of adverse events leading to study discontinuation was higher in cariprazine compared to placebo, with akathisia being the most common reason. Overall, there were no significant differences for clinically meaningful weight gain (≥7% increase in body weight) or mean change from baseline in metabolic parameters between cariprazine and placebo. Clinically significant weight gain occurred at a similar rate between cariprazine (1.9%) and placebo (1.6%). The mean increases in fasting glucose levels were higher in cariprazine (7.0 mg/dL) than placebo-treated patients (1.7 mg/dL). Cariprazine was not associated with any clinically meaningful changes in electrocardiogram parameters or prolactin levels.

For the *post hoc* analysis of bipolar depression, TEAEs occurred at a similar rate between cariprazine (60%) and placebo-treated (55%) patients (43). The most common TEAEs associated with cariprazine use were akathisia and nausea. Treatment-emergent akathisia occurred in 9.9% of cariprazine and 4.3% in placebo-treated patients. Adverse events leading to discontinuation were slightly higher in the cariprazine group, and the most common side effect leading to discontinuation was akathisia. Similar to the *post hoc* analysis of mania, cariprazine did not lead to clinically significant weight gain or changes in metabolic parameters compared to placebo. The mean weight gain was <1 kg for cariprazine-treated patients. The mean increase in fasting glucose levels was similar for cariprazine (3.1 mg/dL) and placebo (2.6 mg/dL). Cariprazine did not led to any significant changes in electrocardiogram parameters or prolactin levels relative to placebo.

A separate *post hoc* analysis of treatment-emergent akathisia in patients with bipolar I depression showed that the overall incidence of akathisia in cariprazine-treated patients was 7.6% (compared to 2.1% for placebo), which was dose-dependent (44). Akathisia occurred during the first 3 weeks, and was generally mild to moderate in severity, rarely leading to treatment discontinuation. Akathisia associated with cariprazine use can be managed by adding a beta-blocking agent, such as propranolol. In the same *post hoc* analysis, 23.5% of cariprazine-treated patients who achieved akathisia resolution during treatment received a beta-blocking medication (44)".

## *POST HOC* ANALYSES

### Broad Spectrum Efficacy of Cariprazine

The broad spectrum efficacy of cariprazine has been assessed in two *post hoc* analyses. Vieta et al. pooled data from three positive RCTs (35–37) to assess the efficacy of cariprazine 3–12

mg/day on manic symptoms in adult patients with bipolar I disorder (45). Cariprazine was associated with a significant improvement on all 11 individual YMRS symptom items ($p < 0.001$), with the largest effect sizes for irritability (0.55) and disruptive-aggressive behavior (0.49). In addition, significantly more cariprazine-treated patients had mild or no symptoms on all YMRS items at the end of the double-blind phase ($p < 0.001$).

In another *post hoc* analysis, data from three bipolar depression RCTs (39–41) were pooled to explore the efficacy of cariprazine in bipolar depression (46). The data was analyzed in combined cariprazine (pooled 1.5 and 3 mg/day) and individual dose groups (1.5 or 3 mg/day). The cariprazine 1.5–3, 1.5, and 3 mg/day groups were all associated with a significant reduction in MADRS total score from baseline to week 6 (LSMD = −2.6 for 1.5–3 mg/day; −2.8 for 1.5 mg/day; −2.4 for 3 mg/day; $p < 0.001$ for all dose groups). The combined cariprazine 1.5–3 mg/day group showed a significant improvement on all individual MADRS items, except for inner tension. In addition, the combined and 3 mg/day groups had significantly lower scores on the suicidal thoughts item at the end of treatment, but the mean changes were overall small.

## Mania With Mixed Features

In this *post hoc* analysis pooling data from the three mania RCTs (35–37), McIntyre et al. used three criteria to define mania with mixed features: ≥3 depressive symptoms (DS) using the DSM-5, ≥2 DS and MADRS total score ≥10 (47). Overall, cariprazine was associated with significant improvement in mean YMRS scores compared to placebo for each criterion (LSMD = −3.79, $p = 0.0248$ for ≥3 DS; −2.91, $p = 0.0207$ for ≥2 DS; −5.49, $p < 0.0001$ for MADRS ≥10). In addition, more cariprazine- than placebo-treated patients met YMRS response and remission criteria, reaching statistical significance in the ≥2 DS and MADRS ≥10 subgroups.

## Bipolar Depression With Mixed Features

This *post hoc* analysis by McIntyre et al., which pooled data from three bipolar depression RCTs (39–41), used a baseline YMRS total score ≥4 to characterize depressed patients with concurrent manic symptoms (48). In that subgroup, both cariprazine 1.5 and 3.0 mg/day groups had significant reductions in MADRS total score from baseline to week 6 relative to placebo (LSMD = −2.5, $p = 0.0033$ for 1.5 mg/day; −2.9, $p = 0.0010$ for 3.0 mg/day).

## Cognition in Mania

McIntyre et al. pooled data from the three mania RCTs (35–37) in this *post hoc* analysis to assess its effects on cognition (49). Cognitive symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS) Cognitive subscale, with a baseline score ≥15 indicating cognitive symptoms. In patients with baseline cognitive symptoms, cariprazine-treated patients showed significantly greater mean improvement on PANSS cognitive subscale scores compared to placebo (−4.0 vs. −1.9, $p = 0.0002$).

## Functioning in Bipolar Depression

Vieta et al. carried out a *post hoc* analysis of a cariprazine RCT (39) to assess its efficacy on function in bipolar I depression (50). The authors used the mean changes from baseline to week 8 in Functional Assessment Short Test (FAST) total score as a measure of functioning. The FAST is a 24-item scale which assesses functioning in the following areas: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time. The FAST total score ranges from 0 to 72, with a higher score indicating worse functioning. The cariprazine 1.5 mg/day group had a statistically significant reduction in FAST total score from baseline to week 8 compared to placebo (LSMD = −5.3, $p = 0.0051$), but not the 3.0 mg/day group (LSMD = −3.2, $p = 0.0575$). In addition, the LSMD favored cariprazine 1.5 mg/day on all the FAST subscales except financial issues ($p < 0.05$). Rates of functional remission (FAST total score ≤20) and recovery (FAST total score ≤11) at week 8 were significantly greater for cariprazine 1.5 mg/day relative to placebo.

# DISCUSSION

Cariprazine is a partial agonist at the D2 and D3 receptors with a greater selectivity for D3 receptors, which makes it unique among atypical antipsychotics. At doses ranging from 3 to 12 mg/day, cariprazine was effective in the treatment of manic episodes. It was associated with a significant reduction in YMRS total scores with a moderate effect size. In addition, cariprazine-treated patients achieved significantly higher response and remission rates compared to placebo, with NNT estimates of 5–7. However, doses above 6 mg/day did not appear to confer any additional benefit, except in the Calabrese et al. study, where the cariprazine 6–12 mg/day group did better when the cutoff for remission was set at YMRS ≤8 (a stricter cutoff than the usual definition of YMRS ≤12) (36). Cariprazine was also effective in mania with mixed features according to a recent *post hoc* analysis (47).

For bipolar depression with or without mixed features, cariprazine also demonstrated clinical efficacy at doses of 1.5–3.0 mg/day, while doses below 1.5 mg/day were clearly ineffective as shown by the Durgam et al. trial (39). Although both cariprazine 1.5 and 3.0 mg/day doses were associated with significant reduction in MADRS total scores, the effect sizes were small and lower than in the trials for mania. Response and remission rates were overall higher in cariprazine-treated patients compared to placebo, with NNT estimates of 6–10. Interestingly, the 3 mg/day dose did not provide much additional clinical efficacy compared to 1.5 mg/day, and was associated with higher discontinuation rates.

Cariprazine was overall well-tolerated, and the majority of TEAEs were mild or moderate in intensity. The incidence of TEAEs appeared to be dose-dependent. In both mania and depression trials, cariprazine was associated with more adverse events than placebo, with the most common side effects being akathisia, extrapyramidal symptoms and nausea. Akathisia was the main adverse event leading to discontinuation

in cariprazine-treated patients. However, cariprazine was not associated with clinically meaningful changes in body weight, metabolic parameters or prolactin levels.

Although there are no head-to-head trials comparing cariprazine to other atypical antipsychotics, cariprazine appears to be equally effective as other antipsychotics for the treatment of mania, with a better tolerability profile. The NNT estimates of 5–7 for cariprazine response are in keeping with the results of a comparative analysis which assessed the efficacy of antipsychotics commonly used in the treatment of mania, such as aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone (pooled NNTs of 6 for reduction in YRMS scores) (51). For bipolar I depression, the only atypical antipsychotics recommended as first-line treatments by the CANMAT and ISBD guidelines are quetiapine and lurasidone (11). The NNT estimate of 10 for cariprazine remission is higher than the NNTs for quetiapine (NNT of 6) and lurasidone (NNT of 5), but compares favorably to adjunctive antidepressants (NNT of 14) (12). However, the criteria used for defining remission in cariprazine studies was more stringent (i.e., MADRS score $\leq$10) compared with quetiapine and lurasidone studies which used a cut off score of $\leq$12; thus, direct comparisons of remission rates are not appropriate. Since up to 54% of patients with BD meet criteria for metabolic syndrome (52), the need for metabolic-neutral agents for the management of BD is of paramount importance. Lurasidone, despite its efficacy in bipolar I depression, has not been studied in mania and is associated with extrapyramidal symptoms like akathisia (53). In contrast, aripiprazole monotherapy is effective for the treatment of manic episodes, but not for bipolar depression (54). Considering its broad spectrum efficacy for both phases of the illness and favorable tolerability profile, cariprazine has the potential to provide an important new option among atypical antipsychotics in the treatment of BD.

Preclinical studies have suggested that cariprazine may enhance cognition in mice by improving attention and memory (55). Although no study to date has assessed the efficacy of cariprazine in improving cognitive function in bipolar patients, there is some evidence from a *post hoc* analysis that cariprazine is associated with an improvement in cognitive symptoms in patients with mania (49). In addition, there is preliminary evidence that lurasidone adjunctive therapy is more effective than treatment as usual in improving global cognition in euthymic patients with bipolar I disorder (56). This has important clinical implications since patients with BD display broad cognitive impairments that persist even during periods of euthymia (57). Our group is currently recruiting participants for a proof of concept, double blind RCT to assess the efficacy of cariprazine in improving cognition in euthymic patients with bipolar I disorder (NCT04771299).

## CONCLUSION

In conclusion, cariprazine monotherapy has shown efficacy as well as a good tolerability and safety profile for the acute treatment for manic, mixed and depressive episodes associated with BD. *Post hoc* analyses also support its efficacy for mania and bipolar depression with mixed features. Cariprazine appears to have procognitive effects in preclinical studies, but this needs to be examined in larger clinical trials. Future research directions should include studies on relapse prevention, as well as head-to-head trials comparing cariprazine to other atypical antipsychotics with established efficacy in bipolar disorder.

## AUTHOR CONTRIBUTIONS

AD conducted a review of the literature and drafted the manuscript. KK, AS, and LY reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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# Cariprazine Use in Early Psychosis: Three Case Reports

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**Objective:** Cariprazine is a new atypical antipsychotic approved for the acute and maintenance treatment of schizophrenia (1, 2) and for the treatment of manic or mixed episodes associated with bipolar I disorder (1). Recently, cariprazine also got extended FDA-approval for the treatment of depressive episodes in adults with bipolar I disorder (3). The use of low doses of atypical antipsychotics is an essential component of early intervention in psychosis. For its particular performance and tolerability, cariprazine is becoming an important option for the treatment of first-episode psychosis.

**Method:** Three patients experiencing first-episode psychosis (FEP) were successfully treated with cariprazine. Two patients were in their first months of the disease, and the third patient was in his third year after the FEP.

**Results:** The three patients had a diagnosis of non-affective FEP, which includes schizophrenia, delusional disorder, and schizoaffective disorder. One of them was in their third year after the FEP with a predominance of negative symptoms at this stage of the disorder. All the patients were treated with cariprazine with a target dose of 3–4.5 mg/day. The three patients showed improvements in their psychosis, including a decrease in negative symptoms. No significant side effects were reported.

**Conclusion:** Our three case reports indicate that cariprazine is an atypical antipsychotic beneficial in the treatment of early psychosis. Treatment with low doses of cariprazine could be effective and tolerable in this phase of the disorder. Future studies with longer follow-up of FEP patients are recommended to confirm these positive results of cariprazine in the early phases of psychosis.

**Keywords: cariprazine, early intervention, first-episode psychosis, schizophrenia, early psychosis, case report**

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## INTRODUCTION

Psychotic disorders are severe mental illnesses that affect about 3% of the general population (4). Incidences of psychosis are highest in young, male, and ethnic minority patients (5–7). Also, patients with non-affective psychosis have higher incidence rates of psychosis compared to patients who experience affective psychosis (8). Psychosis has a significant impact on patients, families, and society. In Europe, expenses associated with psychotic disorders were over ninety-four billion euros in 2010, covering 5 million affected patients. The cost per patient per year was approximately €19,000 (9).

In previous decades, early intervention in psychosis has been adopted as a best practice by mental health specialists worldwide, as it has the most effective clinical and social results in the treatment of early psychosis, including first-episode psychosis (FEP) (10). Results of early intervention include reductions in the duration of untreated psychosis, hospitalization rates and duration of hospital stays, recurrence rate, and suicidal behavior. Patients saw improvement in quality of life, social functioning, and adherence to treatment (11). Early intervention in psychosis includes multidisciplinary teams utilizing several methods, including antipsychotic treatment and psychosocial interventions (12).

Low doses of atypical antipsychotics are an essential component of early intervention in FEP. Current guidelines indicate that antipsychotic medication should be administered with great care to individuals who are drug naïve (13–16). The classic approach "start low, go slow" is the fundamental attitude for dealing with antipsychotics in FEP. Antipsychotics should first be administered at a low dose, which is then increased depending on clinical results and the patient's tolerability, until reaching the patient's lowest effective dose. Atypical antipsychotics are chosen in FEP based on their side effects profile and comorbidity. Because of its negative metabolic profile, olanzapine and clozapine are indicated for second- and third-line treatment, respectively, in FEP (16).

As new oral atypical antipsychotics have become available over the past decade, monitoring clinical day-to-day experiences in various groups of psychotic patients is useful for clinicians. Cariprazine was approved for the acute and maintenance treatment of schizophrenia (1, 2) and for the acute treatment of manic or mixed episodes associated with bipolar I disorder (FDA, 2015). Recently, cariprazine also got extended FDA-approval for the treatment of major depressive episodes in adults with bipolar I disorder (3).

Cariprazine is similar to other atypical antipsychotics in exhibiting antagonistic activity at serotonin type 2A receptors (17). Cariprazine also acts as a partial agonist at the dopamine D3 and D2 receptors with high binding affinity and at the serotonin 5-HT1A receptor. Cariprazine has a similar profile to aripiprazole, except for D3, which has tenfold greater affinity than for D2, so high that extremely small doses are sufficient to get maximal D3 occupancy (18). This particular D3 receptor blockage could theoretically have pro-cognitive effects, antidepressant effects, and reduce the negative symptoms of schizophrenia (19). Cariprazine has other receptor properties, including moderate histamine antagonism, low α-1a antagonism, and no significant affinity for muscarinic cholinergic receptors (20).

Cariprazine metabolites, desmethyl-cariprazine and didesmethyl-cariprazine, have pharmacological properties similar to their parental drug, but the half-life of didesmethyl-cariprazine is considerably longer (1–3 weeks). Exposure to didesmethyl-cariprazine is several times higher than that for cariprazine. This long half-life of didesmethyl-cariprazine is important because it allows the development of a once-a-day oral formulation, which improves medication adherence. A missed dose of cariprazine may be associated with a lower risk of sub-optimal receptor binding compared to a drug with a shorter half-life. However, the longer half-life may also imply a prolonged duration of hypothetical adverse events after discontinuing the treatment (20).

Cariprazine's clinical profile is described in **Table 1**.

The clinical use of cariprazine was studied in three patients with early psychosis. The data is still scarce, but as more patients use cariprazine during the first years of psychosis, the amount of data continues to increase. These case reports could improve the understanding of the use of the recent antipsychotic cariprazine in the early stages of psychosis.

## CASE REPORTS

### Case 1

Case 1 focuses on a 26-year-old male university student with a history of 8 weeks of clinical picture, characterized by disorganized thoughts and behavior, hypochondriac delusions, reference delusions, and insomnia. This clinical picture progressively worsened. He reported no history of medical comorbidities and had not previously experienced an acute psychiatric episode. He had a family history of alcohol use disorder from both parents. The patient had a history of cannabis use from when he was 19 years old. Initially, he used cannabis once a week, and within the last two years, this increased to daily use. He presented with the described psychotic symptoms to the emergency department of a university hospital in Lisbon, Portugal, where he was seen by a psychiatrist. He voluntarily stayed in the ward of the Department of Psychiatry with the diagnosis of non-affective FEP. During his stay in the ward, several tests were performed on him, including blood analysis with thyroid function, hepatitis B and C, syphilis and HIV serologies, vitamin B12 dosing, prolactin and cortisol levels, metabolic profile, and urine drug screening (cannabis, amphetamines, cocaine, and heroin). The results produced no abnormalities except for the urine screening for cannabis being positive. A cranial MRI, electrocardiogram, and electroencephalogram were also performed, and the results were in normal ranges. The patient was treated with cariprazine 1.5 mg/day during days 1 and 2, and afterwards titrated to 3 mg/day. Within the first 4 days, he took flurazepam 15 mg/day at bedtime, which was then tapered off. After 12 days, the patient showed significant improvement in disorganized thoughts and delusions, and his insomnia ameliorated after 2 days of being in the ward. He had no side effects with psychopharmacology. The patient was discharged while maintaining cariprazine 3 mg/day, which he has been adherent to. The total score of the Positive and Negative Syndrome Scale (PANSS) dropped from 78 (admission) to 41 (hospital discharge). The patient is currently stable on this treatment regimen with a follow-up of approximately 5 months and with good adherence to pharmacological treatment. Besides psychiatric follow-up, the patient has also been followed-up by a psychologist doing individual psychoeducation for psychosis. He did not use cannabis after discharge from the hospital. He returned to his studies at the university, and he is living with his girlfriend.

**TABLE 1 |** Cariprazine clinical profile.

| | Target dose | Common side effects | Pharmacokinetics | Pharmacodynamics | |
|---|---|---|---|---|---|
| | | | | Receptor subtypes | Activity |
| • Acute and maintenance treatment of schizophrenia (FDA, EMA) | • 1.5–6 mg/day | • Extrapyramidal symptoms<br>• Insomnia<br>• Akathisia | • *Route of administration*: Oral<br>• *Bioavailability*: protein binding ∼96%; half-life ∼1 week for the combined drug | *Dopamine* | |
| | | | | • $D_{2S}$ | Partial agonist |
| | | | | • $D_{2L}$ | Partial agonist |
| | | | | • $D_3$ | Partial agonist |
| • Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults (FDA) | • 3–6 mg/day | | • *Metabolism*: hydroxylation and demethylation (via CYP3A4 CYP2D6)<br>• *Elimination*: urine (21% of dose) | *Serotonin* | |
| | | | | • 5-$HT_{1A}$ | Partial agonist |
| | | | | • 5-$HT_{2A}$ | Antagonist |
| • Depressive episodes in adults with bipolar I disorder (FDA) | • 1.5–3 mg/day | | • *Metabolism*: hydroxylation and demethylation (via CYP3A4 CYP2D6)<br>• *Elimination*: urine (21% of dose)<br>• *Main metabolites:*<br>• Desmethyl-cariprazine and Didesmethyl-cariprazine | • 5-$HT_{2B}$ | Antagonist |
| | | | | • 5-$HT_{2C}$ | Antagonist |
| | | | | • 5-$HT_7$ | Antagonist |
| | | | | *Histamine* | |
| | | | | • $H_1$ | Antagonist |
| | | | | *Adrenergic* | |
| | | | | • $\alpha_1$ | Antagonist |

*FDA, U.S. Food and Drug Administration; EMA, European Medicines Agency; D, dopamine; 5-HT, serotonin; H, histamine; α, alpha.*

## Case 2

This is an unemployed 28-year-old man with a history of non-affective FEP, diagnosed three years prior. His previous psychosis was characterized by persecutory and reference delusions and auditory hallucinations. Prior to FEP, he had about one year of social withdrawal and a sudden interest in philosophy and psychology. The patient had a history of cannabis use since he was 21 years old. He had no family history of psychiatric disorders. He also had no significant medical history. During the FEP, the patient was hospitalized in the Department of Psychiatry for about 4 weeks. Several exams were performed consisting of blood analysis (including thyroid function, hepatitis B and C, syphilis and HIV serologies, vitamin B12 dosing, prolactin and cortisol levels), metabolic profile and urine drug screening, cranial MRI, electrocardiogram, and electroencephalogram. The test results produced no significant changes except for the cannabis screening being positive. During his stay in the hospital, he was medicated with aripiprazole 15 mg/day, which produced signs of improvement. Following his discharge from the hospital, he experienced about two years of negative symptoms with exuberant blunting affect and social withdrawal and no other symptoms or relapses. The patient continued to use cannabis, however, less frequently. At this time, the antipsychotic medication was switched to paliperidone 6 mg/day trying to improve these significative negative symptoms. This change in antipsychotic treatment produced no significant repercussions on the clinical picture of negative symptoms of the patient. After 6 months of treatment with paliperidone, the psychopharmacological treatment was again switched to cariprazine. Cariprazine was titrated to 4.5 mg/day (1.5 mg/day on days 1 and 2, 3.0 mg/day on days 4 and 5, and 4.5 mg/day after day 5). After 1 week, he started to feel better, saying, "It feels like I am not on medication." The patient continued improving from the described negative symptoms over the following 6 months. He is now at about 3 years of follow-up after FEP, complying with medication and with no side effects. The PANSS negative subscale score diminished from 38 before starting treatment with cariprazine to 12 at 6 months of treatment. The patient is still using cannabis with a sporadic frequency (approximately once every six months). He started a new relationship and is working at a shop.

## Case 3

This patient is a 32-year-old female. She was an old-age caregiver with a history of about 12 weeks of a clinical picture characterized by persecutory delusions and auditory hallucinations. These psychotic symptoms were accompanied by psychotic anguish and emotional lability. This clinical picture started shortly after her divorce. The symptoms worsened, and the patient refused to leave her home because she felt insecure outside of it. Her sister, understanding the declining mental health of the patient, convinced her to go to a hospital. The patient was seen in the emergency department by a psychiatrist who advised her to stay in the hospital. She accepted, understanding it was a safe place for her. The patient had a history of hypercholesterolemia and had been medicated with simvastatin 20 mg/day. No other medical diseases were known, though the mother of the patient had been diagnosed with schizophrenia. Thus, she was hospitalized in the Department of Psychiatry with non-affective FEP. During her stay in the hospital, several exams were performed on her consisting of a complete blood analysis (including thyroid function, hepatitis B and C, syphilis and HIV serologies, vitamin B12 dosing, prolactin and cortisol levels and urine drug screening), cranial CT, and electrocardiogram. None of the exams showed significant abnormalities. The patient's metabolic profile revealed that her dyslipidemia was controlled with statin treatment (total cholesterol: 176 mg/dL; LDL: 97 mg/dL; HDL: 55 mg/dL; triglycerides: 142 mg/dL). During the hospital stay, the patient was medicated with cariprazine 1.5 mg/day that was then titrated to 3.0 mg/day (1.5 mg/day on days 1 and 2, 3.0 mg/day afterward). In the first three days of treatment, the patient complained of sleepiness during the day, which was

overcome by changing the timing of her cariprazine dosage (1.5–3.0 mg/day) from breakfast to bedtime. She experienced a progressive remission of the described psychotic clinical picture. The patient was discharged after spending 15 days in the hospital. The PANSS total score reduced from 74 (admission) to 34 (hospital discharge). The patient had been followed-up in a psychiatric outpatient clinic at a secondary hospital. After 12 months, she showed improvement with complete remission of psychotic symptoms with no significant side effects and adhering to antipsychotic treatment. She also returned to her job.

## DISCUSSION

The three case reports seem to demonstrate the efficacy of cariprazine in early psychosis, which is new, although expected. In all three patients, there was an improvement in the clinical picture of psychosis. Patients 1 and 3 experienced a remission of psychotic positive symptoms, and patient 2 experienced improvement of negative symptoms while maintaining remission of positive symptoms. The recovery of the three patients was positive, not only with the remission of positive and negative symptoms, but also with the return of functioning.

The results were similar to other trials that demonstrated the efficacy of cariprazine in acute schizophrenia (21–24). In addition, reviews and meta-analysis proved the efficacy of cariprazine in acute schizophrenia (25–27). These studies showed the superiority of administering cariprazine vs. placebo, showing an improvement of the PANSS total score, positive and negative subscale scores, and of the Clinical Global Impression score. For example, a phase III study evaluated the efficacy and safety of cariprazine in acute exacerbation of schizophrenia (23). This was a 6-week double-blind trial, where patients were randomized to three groups: placebo, cariprazine 3 to 6 mg/d, or cariprazine 6 to 9 mg/d. The primary outcome was a change from baseline to week six in the PANSS score. Common adverse effects in the cariprazine groups included mild to moderate akathisia, extrapyramidal disorder, and tremor, with no or very low changes in metabolic measures and decrease of prolactin in all groups. These results show that cariprazine is effective and well tolerated. A recent published systematic review and meta-analysis compared the efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia (28). The results must take into consideration the relatively small number of participants assigned to the treatment with cariprazine and the existence of few trials with direct comparison with cariprazine, almost all with placebo. The results show very low changes in positive and negative symptoms and moderate changes in depressive symptoms. For all causes of discontinuation, the results also show that cariprazine has a low rate compared with placebo.

Cariprazine was also approved for maintenance treatment in schizophrenia. A multinational, randomized, double-blind, and placebo-controlled study evaluated the role of cariprazine for relapse prevention in adults with schizophrenia (29). Stable patients who completed open-label treatment with cariprazine 3–9 mg/day were placed in randomized groups to continue taking cariprazine (3, 6, or 9 mg/day) or a placebo for double-blind treatment for up to 72 weeks. Long-term cariprazine treatment was significantly more effective than the placebo for relapse prevention in patients with schizophrenia. Interestingly, there are reports of using cariprazine as an add-on treatment for treatment-resistant schizophrenia with partial response to clozapine (30). In this case series, cariprazine add-on to clozapine showed excellent efficacy and rapid effect in the treatment of patients with a partial response to clozapine. The tolerability of this association was excellent without reported significant adverse effects.

Cariprazine is one of the newest antipsychotics available to treat FEP. The results presented from the three case reports were positive when using cariprazine in early psychosis. Besides its efficacy in treating positive psychotic symptoms, the case studies showed that cariprazine produced good efficacy on negative symptoms, as with patient 2. Therefore, negative cluster symptoms are important actions of cariprazine (31–34). Pre-clinical studies have proven that cariprazine is effective in the treatment of anhedonia, depressive, and anxiety behaviors (35, 36). Clinical trials also showed efficacy on negative symptoms in patients with schizophrenia. Post-hoc analysis of data from acute schizophrenic patients, with a high score of negative symptoms and a low or moderate score of positive symptoms on the PANSS scale, reported improvement in the PANSS factor score for negative symptoms with cariprazine vs. placebo (37). A randomized, double-blind trial comparing the efficacy of risperidone (4 mg/day) and cariprazine (4.5 mg/day) showed that cariprazine helped to reduce the PANSS factor score for negative symptoms from the baseline to week 26 compared to risperidone (32). This result supported the increased efficacy on negative symptoms while taking cariprazine.

The three case reports showed positive tolerability and safety of cariprazine. Even in FEP patients who usually are sensitive to antipsychotic side effects, cariprazine seemed to be well tolerated (38). In the three cases, no significant side effects were reported. Only one patient reported sleepiness during the day in the first days of cariprazine, which was easily resolved by changing its delivery to the end of the day. Other studies show that the overall possibility of adverse effects is similar for cariprazine and placebo at doses of 1.5–3 mg/day, while higher for doses of 4.5–6 mg/day (39). A higher risk of EPS-related symptoms (akathisia, tremor, and restlessness) and a slight increase in overall body weight can be seen with cariprazine (25, 40). A recently published paper made a pooled analysis of eight phase II/III studies to analyze the safety profile of cariprazine. It includes four short-term (6-week) and four long-term ($\geq$6 months) studies that used the recommended 1.5–6 mg/d dose range for schizophrenia (41). The results showed that cariprazine was safe and well tolerated in the recommended dose. Mild and moderate akathisia was the most common adverse effect seen, but it resulted in few discontinuations. None of these adverse effects were seen in our patients. There are no significant impacts on the prolactin level, metabolic parameters, QT interval, and cardiovascular health (39, 40, 42). Cariprazine also showed a low chance of causing sleepiness and drowsiness, which is vital in terms of compliance with antipsychotic medication, namely in young people (40, 42,

43). Due to its low affinity to cholinergic receptors, there is no impairment in colon transit with cariprazine (42).

Cariprazine also seems useful in other clinically relevant situations frequently associated with schizophrenia. This is the case of obsessive-compulsive symptoms, frequently seen associated with schizophrenia in different phases of the disorder. There are published case reports where the add-on treatment with low-dosage cariprazine showed remission of these symptoms (44).

Some limitations exist regarding these three case reports, most notably some heterogeneities. First, we present here three different case reports regrading the time of cariprazine use: two reports initiated cariprazine immediately in the acute phase of FEP (cases 1 and 3) and the other one after three years of the FEP for the treatment of exuberant negative symptoms (case 2). Second, the follow-up of the three cases varies between the three case reports. The follow-up times are 5, 36, and 12 months, respectively, for case reports 1, 2, and 3. However, these differences between the three case reports presented also improve the knowledge and experience of the clinical use of cariprazine in different time phases of early psychosis.

## CONCLUSION

These case reports seem to indicate that cariprazine is effective and well tolerated in patients experiencing early phases of psychosis, namely those with non-affective FEP. Cariprazine seems particularly useful in patients where negative symptoms are evident. The safety and positive tolerability profile of cariprazine made it especially useful in young and active patients. Future studies should be performed to confirm the long-term positive results of using cariprazine in this type of patient.

## DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

## ETHICS STATEMENT

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants.

## AUTHOR CONTRIBUTIONS

RC, RS, CS, and PL collaborated on the clinical work. RC, RS, and CS completed the literature review. PL oversaw the process and contributed to content and editing. All authors contributed to manuscript revision and read and approved the submitted version.

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# Partial Agonists and Dual Disorders: Focus on Dual Schizophrenia

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Dual disorder is a term applied to patients with an addictive disorder and other mental disorder. Epidemiological studies have established that dual disorders are an expectation rather than an exception. They are difficult to diagnose and treat and constitute a huge burden for both patients and their relatives and society. Current treatments are a combination of those needed to treat the addictive disorder with those focused on the co-occurring psychiatric disorder. Focusing specifically on schizophrenia, growing scientific evidence supports the existence of a shared vulnerability for substance use in these patients and those at risk. Various antipsychotics have been found to be useful in the treatment of psychotic symptoms and disorders; however, few effective treatments have been identified until now for substance use disorders in patients with dual schizophrenia. Partial agonism stands as a new pharmacological option available in recent years. Molecules with this kind of action may act as functional agonists or as antagonists, depending on the surrounding levels of the neurotransmitter. Studies have found their efficacy in schizophrenia, addiction, anxiety and depression. Certain partial agonist antipsychotics seem to have a role in the treatment of dual schizophrenia. That could be the case with cariprazine. Because of its higher affinity for dopaminergic D3 receptors compared to D2, a potential to prevent relapse to addiction, added to its antipsychotic efficacy, has been suggested. Here we briefly review current advances and future directions and introduce some personal insights into the role of partial agonists in co-occurring schizophrenia and substance use.

**Keywords: dual disorders, addiction, partial agonists, schizophrenia, antipsychotics**

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## INTRODUCTION

Research estimates that up to 75% of patients with severe mental illness also have a substance use disorder (SUD) (1). When mental disorders occur with addictive disorders, this clinical condition is referred to as a dual disorder (2).

Dual disorders (DD) are a phenomenon associated with increases in emergency department admissions and psychiatric hospitalizations, higher risk of relapse to drug use and increased likelihood of premature deaths, including those resulting from suicide. The individual, social and public health impact of DD is extremely high, and a comprehensive multidisciplinary and scientific response to the needs of those with these disorders is required. Unfortunately, there are many gaps in the global system, which is ill prepared to meet this challenge (2).

In many countries, the lack of attention to DD is partly driven by the structural differentiation and insufficient coordination between programs to treat SUD and those to treat other mental

illnesses. Other contributing factors include the limited psychiatric training on how to diagnose and treat DD, and misinformation about the potential role of psychiatric drugs and their mechanisms of action when choosing the most appropriate treatment. Present treatments include a combination of those needed to treat addictive disorders together with those focused on other psychiatric disorders. Finding more specific treatments would undoubtedly help to improve the evolution of DD patients.

The aim of this perspective paper is to highlight the potential role of the dopaminergic partial agonists in patients with dual schizophrenia.

## ADVANCES IN NEUROSCIENCE AND TREATMENT CHALLENGES

Epidemiological studies have established that DD are an expectation rather than an exception (3). The symptomatic high co-occurrence supports the fact that both conditions are in some way causally linked (4).

Advances in genetics and precision psychiatry suggest that the co-occurrence of substance use and other mental disorders arises, in part, from a shared genetic etiology (5). Large genome-wide association studies are providing the information needed to investigate genetic research on schizophrenia plus SUD and have yielded increasing evidence of a blurred boundary between schizophrenia and substance use disorder. Significant genetic correlations were found with the majority of analyzed substance use, including smoking, alcohol use, schizophrenia, and risk-taking (6–8).

Neuroscience has revealed that addiction and other mental disorders involve a set of interconnected processes that can be targeted strategically, rather than being a disorder primarily defined by a single behavior (as uncontrollable excessive drug use). It is related to interacting neurobiological and environmental factors involved in behaviors of substance and non-substance related disorders (9). Focusing specifically on psychosis and schizophrenia, we should wonder the underlying reasons for the patient's use of substances. As usual, we can find the answers in neuroscience. Growing scientific evidence supports the existence of a shared vulnerability for substance use in these patients and those at risk (10, 11). An increasing number of researchers claim that, if schizophrenia and SUD share genetic underpinnings, this will strongly challenge the rigid diagnostic boundaries that separate these psychiatric disorders, which may have clinical implications. Understanding the pathogenesis of DD as one entity should finally have the potential to improve clinical outcomes and treatments (6).

When treating a patient with dual psychosis, a psychiatrist might wonder whether all antipsychotics are equally effective. From a neuroscience perspective, it currently seems clear that there are many phenotypes of schizophrenia and many antipsychotics with different mechanisms of action. Dual schizophrenia appears to have a different phenotype that requires a new approach.

Most studies indicate that antipsychotics produce a clear improvement in psychotic symptoms, with a more controversial effect on SUD. The possibility that conventional D2 antagonist antipsychotics increase substance craving has been described, suggesting the need for a new approach to improve SUD in patients with schizophrenia. Conversely, treatment retention is generally low, due in part to the intrinsic characteristics of the addiction itself but also to the lack of efficacy and/or potential adverse events.

Interestingly, clozapine has previously been considered the most effective antipsychotic for these dual psychotic patients, and preliminary but consistent data suggest that it limits substance use in them (12). Given the multireceptorial action of this drug, there is no clear explanation for this clinical effect; however, its use is less frequent than expected, which may be related to specific side effects that require monitoring.

Neuroscience based Nomenclature (NbN) is a new system for classifying psychotropic drugs based on their pharmacological profile. The NbN was developed to replace the current indication-based nomenclature and to provide an up-to-date and more useful framework to better inform pharmacological decisions (13). Not all antipsychotics have the same mechanism of action and therefore should have different clinical effects; in the field of SUD, medications are frequently labeled according to their main symptomatic effect (e.g., "anticraving drugs") or according to imprecise and sometimes old concepts related to treatment strategies (e.g., "replacement therapies, ""antabuse drugs," or "substitution treatments"). In contrast, the NbN offers a clearer and more consistent rationale, according to which the main element of classification is based on the pharmacological mechanism of action (14). In addition, pharmacologically driven nomenclature, by highlighting pharmacological domains and mechanisms of action, may increase drug adherence, as it clarifies the rationale for selecting a specific psychotropic agent.

Moreover, from a precision psychiatry perspective, it is important to consider not only the mechanism of action of different drugs but also their effect on brain functional organization, which varies between individuals and changes according to the psychopathological context. From this perspective, psychoactive drugs, including antipsychotics, may have distinct effects depending on individual brain differences (4).

## PARTIAL AGONISTS IN SCHIZOPHRENIA AND SUD

Drugs approved for the treatment of psychiatric disorders often elicit side effects that may limit their use and their acceptance by patients. Partial agonists (PA) used to treat troubles as hypertension, have demonstrated a better profile regarding adverse events. This has fueled research of potential PA for psychiatric treatment, with a good profile of efficacy and limited adverse events. These molecules may act as functional agonists or as antagonists depending on surrounding neurotransmitter levels, and their use appears to result in fewer side effects than full agonists or antagonists without compromising clinical efficacy

(15). They stand now as a new pharmacological option and, while their number is still scarce, they have already shown their efficacy in several psychiatric disorders, such as schizophrenia, addiction, anxiety, and depression. They are safe, well-tolerated, and may give rise to a stabilization of the systems. It has been suggested that PA constitute in some way a novel approach to the treatment of mental disturbances.

There are various drugs of established use or interest in the field of DD whose mechanism of action is partial agonism; they include buprenorphine, varenicline, nalmefene, aripiprazole, brexpiprazole, and cariprazine. Although the first three drugs are implicated in the treatment of opioids, tobacco and alcohol addiction and the last three in schizophrenia, from the perspective of neuroscience, their clinical action is projected beyond their current indication. Being focused on dopaminergic partial agonists and dual schizophrenia, it is beyond the scope of this review to cover all these drugs in detail.

The recent development of these antipsychotics with new mechanisms of action are promising prospects for dual schizophrenia treatment. Antipsychotics acting as PA behave as functional antagonists in areas with high levels of dopamine (e.g., mesolimbic pathway) but not in areas where dopamine levels are normal (e.g., nigrostriatal and tuberoinfundibular pathways). They are then expected to reduce positive symptoms without producing movement disorders or prolactin alterations (16). By normalizing and stabilizing dopaminergic tone, PA, unlike full dopamine receptor agonists and antagonists, may have reduced abuse liability or disruptive effects on motivated behavior (17).

The involvement of dopaminergic dysfunction in addiction is well-known. While potent dopamine D2 receptor antagonist antipsychotics have been linked to elevated incidence of SUD (e.g., nicotine addiction in smokers with schizophrenia) (18), PA produce substantially less functional antagonism of D2 receptor-mediated neurotransmission than full antagonists (19). Furthermore, the capacity of PA to increase dopamine activity in the mesolimbic dopaminergic pathway and modulate the dopaminergic system might be beneficial for reducing craving, rewarding effects and relapse. The first published reports suggest that specific PA antipsychotics have a potential role in the treatment of dual schizophrenia, which may be the case with long-acting injectable aripiprazole, that showed efficacy against psychotic symptoms as much as addictive ones in patients with schizophrenia and coexisting SUDs in a first multicenter observational study (20).

Cariprazine, a new PA drug, was introduced recently for the treatment of schizophrenia. It is a dopamine D3-preferring D3/D2 receptor PA, serotonin 5HT1A receptor PA and serotonin 5-HT2B and 5-HT2A antagonist. While other atypical antipsychotics may have significant activity at the D3 receptor (D3R), its high potency as an antagonist/PA at the D3 highlights its unique pharmacological profile among other antipsychotics (21).

Outside its non-psychiatric clinical implications, D3R is known to be involved in schizophrenia, depression, anxiety, and addiction and is found mainly in brain areas regulating cognitive and emotional functions, and reward-related behaviors (22). Preclinical evidence from several animal models of human addiction supports the D3R as a viable target for SUD treatment development and predict that D3R selective antagonists and PA may be effective in addiction treatment by regulating the motivation to self-administer drugs and disrupting drug-associated cue-induced craving (23, 24).

Although the role of D3R in addiction is well-recognized today and it has long been a target in addiction pharmacotherapy, translation to clinical medication development has been challenging until recently, especially in relation to the absence of clinically available D3R preferential compounds. Researchers have discovered highly selective D3R antagonists, PA and full agonists that have worked as crucial tools for pharmacological investigations, including at the behavioral level; however, suggestions have been made to reconsider animal models to achieve translation of preclinical findings to clinical success, or the need to explore additional behavioral models of addiction (25).

One arising issue refers to the optimal timing of administration of treatments; for instance, D3R antagonism may not affect the primary reinforcing effects of the drugs but will reduce the motivation for self-administration. D3R PA may possibly become more effective when drugs are not available, and their behavioral pharmacology appears to be different depending on whether the subjects are drug-naive or have a drug history (25).

## DISCUSSION

There has been extensive research on the psychopharmacological treatment of patients with psychosis and co-occurring SUD, but without significant results until now with the exception of clozapine, although its use is still controversial. This perspective paper describes current trends in the treatment of dual psychosis/schizophrenia with a focus on PA drugs to optimize outcomes and foster the development of new dual schizophrenia treatments. The heterogeneity of the pathophysiology of the various domains of dual schizophrenia requires a diversity of treatments that may currently be best met by the use of PA by expert clinicians. In this respect and beyond some evidence regarding aripiprazole, cariprazine, with a stronger D3R-preferential activity, has shown to be potentially useful in preclinical models of drug use.

Although there has been interest in D3R in addiction treatment for over 20 years, there is a lack of positive results to translate to the clinical field. In recent years, reports and reflections regarding the models used in research in the addiction pharmacotherapy field, as well as the findings about the actions of different types of compounds on the receptors, optimal time of administration and relevance of the patient's consumption trajectory in terms of the efficacy of treatments, will undoubtedly modify this situation. New compounds being tested today or in the near future will likely follow a different pathway to unravel their true potential in the field of addiction and DD treatment.

We can't ignore the fact that the Food and Drug Administration and other health authorities have issued a warning regarding the use of one PA such as aripiprazole and

the development of rare impulse control problems, including pathological gambling, binge-eating disorder, and hypersexuality (26). This effect could be a consequence of the increased availability of dopamine (DA) in the brain's reward system. Nevertheless, this is insufficient to explain these effects, and research studies indicate that some clinical phenotypes affected with specific frontal dysfunctions are more vulnerable to develop impulse control disorders when taking dopaminergic agonists (27).

It is conceivable that the benefits of enhancing DA activity to counteract psychopathological symptoms outweigh the risk of such an exceptional side effect in these dual schizophrenia patients. Therefore, the use of PA could be a strength instead of a weakness in dual psychosis, since they may protect against psychotic symptoms and improve addictive ones. It is possible that new PA as cariprazine, with its high antagonist/partial agonist potency at the D3 receptors, minimize these risks while becoming a potential new treatment preventing addiction relapse added to its antipsychotic efficacy, as suggested in previous studies.

Clinical trials, intended to explore the interesting potential of PA in dual schizophrenia and considering recent preclinical findings are warranted.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## AUTHOR CONTRIBUTIONS

LP and NS contributed equally to the conception, drafting and critical revision of the work, and provided approved for the publication of the content. All authors contributed to the article and approved the submitted version.

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# Primary and Secondary Negative Symptoms in Schizophrenia

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The negative symptoms of schizophrenia include volitional (motivational) impairment manifesting as avolition, anhedonia, social withdrawal, and emotional disorders such as alogia and affective flattening. Negative symptoms worsen patients' quality of life and functioning. From the diagnostic point of view, it is important to differentiate between primary negative symptoms, which are regarded as an integral dimension of schizophrenia, and secondary negative symptoms occurring as a result of positive symptoms, comorbid depression, side effects of antipsychotics, substance abuse, or social isolation. If secondary negative symptoms overlap with primary negative symptoms, it can create a false clinical impression of worsening deficit symptoms and disease progression, which leads to the choice of incorrect therapeutic strategy with excessive dopamine blocker loading. Different longitudinal trajectories of primary and secondary negative symptoms in different schizophrenia stages are proposed as an important additional discriminating factor. This review and position paper focuses primarily on clinical aspects of negative symptoms in schizophrenia, their definition, phenomenology, factor structure, and classification. It covers the historical and modern concepts of the paradigm of positive and negative symptoms in schizophrenia, as well as a detailed comparison of the assessment tools and psychometric tests used for the evaluation of negative symptoms.

**Keywords: schizophrenia, course trajectory, secondary negative symptoms, primary negative symptoms, depression, extrapyramidal symptoms**

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## INTRODUCTION

Negative symptoms are a core component of the schizophrenia syndrome. Negative symptoms can be primary symptoms, which are intrinsic to the underlying pathophysiology of schizophrenia, or secondary symptoms that are related to psychiatric or medical comorbidities, adverse effects of treatment, or environmental factors. Although negative symptoms are diverse and difficult to differentiate, careful assessment, timely identification, and provision of adequate therapy are required. More than half of patients with chronic schizophrenia exhibit at least one negative symptom (1), and the prevalence of persistent negative symptoms following the first psychotic episode is reaching 11–37% (2). In a multicenter retrospective study ($n$ = 1,452), the majority of the patients (57.6%) diagnosed with schizophrenia spectrum disorders had at least one or more negative symptoms, while primary negative symptoms were reported in 12.9% of the patients; in another study ($n$ = 7,678), 41% of the patients had at least two negative symptoms (3).

In a 15-year prospective study in patients with schizophrenia and schizoaffective and affective disorders, the prevalence of negative symptoms was found to be high: 75, 68, and 44%, respectively (4). In the course of the disease, negative symptoms occur very early, often in ultrahigh risk state, and this very likely predicts the transition to schizophrenia (5). In a retrospective study of the onset of schizophrenia in 4,707 patients seeking psychiatric assistance, negative symptoms were observed in 95% of the examined subjects. Furthermore, at the pre-manifest stage of the disease, 32.7% of the subjects demonstrated social withdrawal with increasing self-isolation, 25.8% developed asthenoneurotic and asthenodepressive symptoms, and only 7% showed apatho-abulic manifestations (6). Apart from decreasing patients' quality of life, negative symptoms are associated with impaired daily life functioning, social relationships, and the professional activity of such patients (7–9), as well as with rarer achievement and poorer quality of remissions in the course of the disease (10, 11). As compared to positive symptoms, negative symptoms show no tendency toward spontaneous improvement in the course of the disease and respond poorly to treatment with currently used antipsychotics (12–14).

## HISTORICAL EVOLUTION OF THE CONCEPT OF NEGATIVE SYMPTOMS IN SCHIZOPHRENIA

The first theories regarding negative symptoms in schizophrenia date back to the beginning of the 19th century, when J. Haslam, a British physician, described a mental disease in young people that was characterized by a long-lasting "depressed sensitivity and emotional indifference" (15). However, the first conceptual justification for differences between positive and negative symptoms was given by the British neurologist J. R. Reynolds, who proposed to distinguish plus-symptoms associated with distortion or superfluity of natural functions (delusions, hallucinations, convulsions, pathological movements, etc.) and minus-symptoms associated with loss or deficit of natural functions or misbehavior. This referred first of all to motivation and interest, although it was indicated that any function could be lost, e.g., memory, sensitivity, motor activity, etc. (16). That said, negative and positive symptoms were not mutually exclusive and could coexist. Another British neurologist J. H. Jackson considered negative symptoms as a stable impairment of higher cortical functions, whereas periodic positive symptoms were regarded as a phenomenon of excessive functioning (17). He considered the relationship between positive and negative symptoms within the framework of the evolutionary theory of stratification applied to mental disorders ("dissolution of the nervous system") and believed that loosening of control of higher cortical functions (negative symptoms) leads to disinhibition of the activity of phylogenetically more ancient and primitive lower subcortical structures. This manifests as a pathological response (positive symptoms, primarily affective and psychotic symptoms) that is effectively the secondary compensatory phenomenon.

The German psychiatrist Emil Kraepelin was the first to point out the significance of negative symptoms (restricted emotional expression and avolition, cognitive impairment, and social withdrawal) in patients with dementia praecox and to set them against productive symptoms, such as hallucinatory-delusional and catatonic-hebephrenic symptoms (18). Furthermore, if the latter was considered as reversible (relapsing), then negative symptoms were regarded as irreversible, progressive, and leading to dementia, i.e., as a residual deficit or "defect."

Unlike Kraepelin, who, despite the acknowledgment of a simple form of schizophrenia later on, still did not consider negative symptoms obligatory for dementia praecox, E. Bleuler, who introduced the term "schizophrenia" meaning "schisis" or "splitting of antagonistic functions" in 1911, immediately tried to define its basic manifestations with the emphasis on negative symptoms. According to Bleuler, negative symptoms comprised weakening of the association process, inadequacy or affective flattening, and volitional disorders, including ambivalence and autism (19). The irregular development and known reversibility of the main (negative) and primary (somatic) symptoms were assumed. Interestingly, speech and written language disorders, memory impairment, and personality changes were also referred by the author to secondary accessory symptoms, along with affective, catatonic, and psychotic symptoms. Bleuler was mostly interested in psychological and even psychodynamic mechanisms of schizophrenia development, viewing those as losing associations, rather than in the course and prognosis of the disease. This understanding, relying on the detection of obligatory (basic) negative symptoms, led to a significant expansion of the diagnostic spectrum of schizophrenia to include early, mild, and latent forms of the disease with insignificant intensity or even complete absence of any given positive psychopathological symptoms.

In the 1970s, the German psychiatrist J. Strauss asserted the primary and chronic nature of negative symptoms, while considering positive symptoms as a non-specific transient reaction to stress (20). Another of his compatriots, G. Huber, and his followers developed the concept of "basic symptoms" in schizophrenia, by which they meant primary subjective experiences of patients directly related to a pathological process in the brain and forming the basis for the development of complex secondary symptoms (21, 22). In this context, basic symptoms were regarded as deficit symptoms, which are subjectively evaluated by patients as insufficiency or defect at the so-called basic stages of the disease, namely, in the pre-psychotic (prodromal), reversible post-psychotic, or irreversible state of "pure" defect. In turn, productive psychotic symptoms were deemed as psychoreactive, adaptive, and personality-mediated "epiphenomena of schizophrenia." All basic stages can be reversed, and, therefore, the progression of the disease does not lead to the inevitable formation of a defect. Only a non-specific reduction in the overall level of mental energy is irreversible (the so-called pure asthenic defect) if it lasts for more than 2 years (21).

A 20-year follow-up study of patients with schizophrenia has shown that persistent basic symptoms occurred more frequently than characteristic personality changes. This stance of focusing

on non-specific asthenic and pseudo-organic (somatic) deficit disorders and leveling the significance of peculiar (specific) personal, cognitive, and emotional disorders in schizophrenia significantly distinguishes the concept of G. Huber from the dominant views in Russian psychiatry. Following the ideas of Janzarik (23), the author uses a taxonomic multilevel model of basic symptoms and identifies the following: (1) "substrate-active" disorders with hyperfunction of dopaminergic structures, when negative symptoms are the consequence of active functional inhibition (e.g., inability to concentrate, deautomatization of motor actions, apatho-adynamic disorders, and poor speech production); (2) "substrate-negative" disorders accompanied by exhaustion and hypofunction of dopaminergic structures, when a persistent torpid to traditional antipsychotic therapy reduction of affective and energy levels is developed; (3) "substrate-deficient" disorders associated with final structural changes in the brain and loss of functions (e.g., persistent asthenic symptoms—"pure defect") (24).

An important role in the development of the concept of negative (deficit) symptoms in schizophrenia was played by the Russian school of psychiatry headed by A. V. Snezhnevsky, who paid a lot of attention to specific autistic personality changes and described an entire range (continuum) of deficiency symptoms—from hardly noticeable for the patient's immediate circle, social withdrawal with the prevalence of frailty and excessive vulnerability, to a pronounced decrease in energy potential, lack of initiative, and emotional impoverishment to the extent of outright apatho-abulic dementia with regression of the earliest acquired automatic daily activity skills (25). Negative or deficit symptoms in schizophrenia include many reversible or persistent impairments—from asthenization of mental activity to pronounced state of mental marasmus, including personality changes, amnestic syndrome, and dementia, which could be ranked according to their severity (**Figure 1**). Each circle of a higher level includes all the underlying and less specific syndromes—from mental exhaustion and reduced energetic potential to personality regression and total dementia. For a better understanding of the terminology of this model, we added a small glossary of terms in the addendum (**Appendix 1**). Following J. H. Jackson, A. V. Snezhnevsky and most Russian psychiatrists interpret negative symptoms as a loss or reduction of mental function (minus-symptoms), i.e., loss of any mental ability due to the damage of the central nervous system. Since the deficit of mental functions is understood as irreversible damage caused by the disease, so-called "scar" by Kraepelin, negative symptoms are often associated with a notion of the deficit or "defect." This negative or deficit syndrome is considered nosospecific for schizophrenia (26). The most common deficit symptoms are falling intellectual activity, autism or social withdrawal, willful decline or avolition, impoverishment of emotional reactions or blunted affect, reduction of mental activity, or apathy. Personality changes ("personality shift") and "specific" thought disturbances (loosening of associations, derailments, tangential thinking, etc.) are also included in the definition of "schizophrenic defect." The originality of Snezhnevsky's clinical approach primarily lied in the dynamic analysis of the disease course, within which progression of negative symptoms was considered in close relation to syndrome kinetic pattern of different psychotic symptoms. For A. B. Smulevich, the pupil and the most consistent follower of Snezhnevsky, the concept of "schizophrenic defect" also includes persistent positive residual symptoms and some personality (pseudopsychopathic) deviations like "Verschrobener" or bizarre/eccentric behavior with dysbulia (weakness and uncertainty of volition) without necessarily premorbid evidence of personality disorder (27). The intertwining and dynamic of all these residual symptoms are very important for determining a more accurate definition of remission in schizophrenia and for the prognosis of long-term therapeutic effect (28). We believe that the severity, frequency, and presentation of various negative symptoms are different in specific forms and stages of schizophrenia (29).

In the 1980s, the British researcher T. Crow formulated a dichotomous hypothesis of schizophrenia highlighting two independent pathological processes: (1) type I schizophrenia with a predominance of negative symptoms and (2) type II schizophrenia with a predominance of positive symptoms. Positive schizophrenia was characterized by a nearly normal premorbid period, relatively acute onset of the disease, prevalence of psychotic symptoms, clear episodic course (exacerbations and attenuation of symptoms), relatively good social and working adaptation, nearly normal performance on cognitive tests, and absence of structural changes in the brain evaluated using different scanning techniques. Negative schizophrenia was characterized by the presence of cognitive and negative symptoms in the premorbid period, low level of education, gradual or latent onset of the disease, predominant negative symptoms (emotional blunting, poor speech, anhedonia, attention deficit, lack of motivation, and volitional impulses), chronic or malignant course, social and working disadaptation, poor performance on cognitive tests, and different structural changes in the brain including signs of cerebral atrophy. The subtypes also differed in their response to dopamine-blocking antipsychotic therapy. In negative schizophrenia, unlike positive one, low response to antipsychotics was observed. Post-mortem and neuroimaging studies have revealed that in positive schizophrenia, different cerebral structures demonstrate predominant dopaminergic activity and increased density (hypersensitivity) of $D_2$-receptors, while negative schizophrenia is characterized by hypodopaminergic activity (mostly in the pre-frontal cortex), normal or reduced density of $D_2$-receptors, reduced glucose metabolism, neuronal loss, and their decreased functional activity (reduced gray matter volume and number of spikes in the frontal cortex). In a factor analysis of psychopathological symptoms, T. Crow had found no relationship between positive and negative symptoms; however, negative symptoms correlated with cognitive impairment, low social functioning, and residual neurological symptoms (30).

## POSITION OF AMERICAN RESEARCHERS

At the end of the 1970's, American researchers criticized the existing criteria for diagnosis of schizophrenia based on the

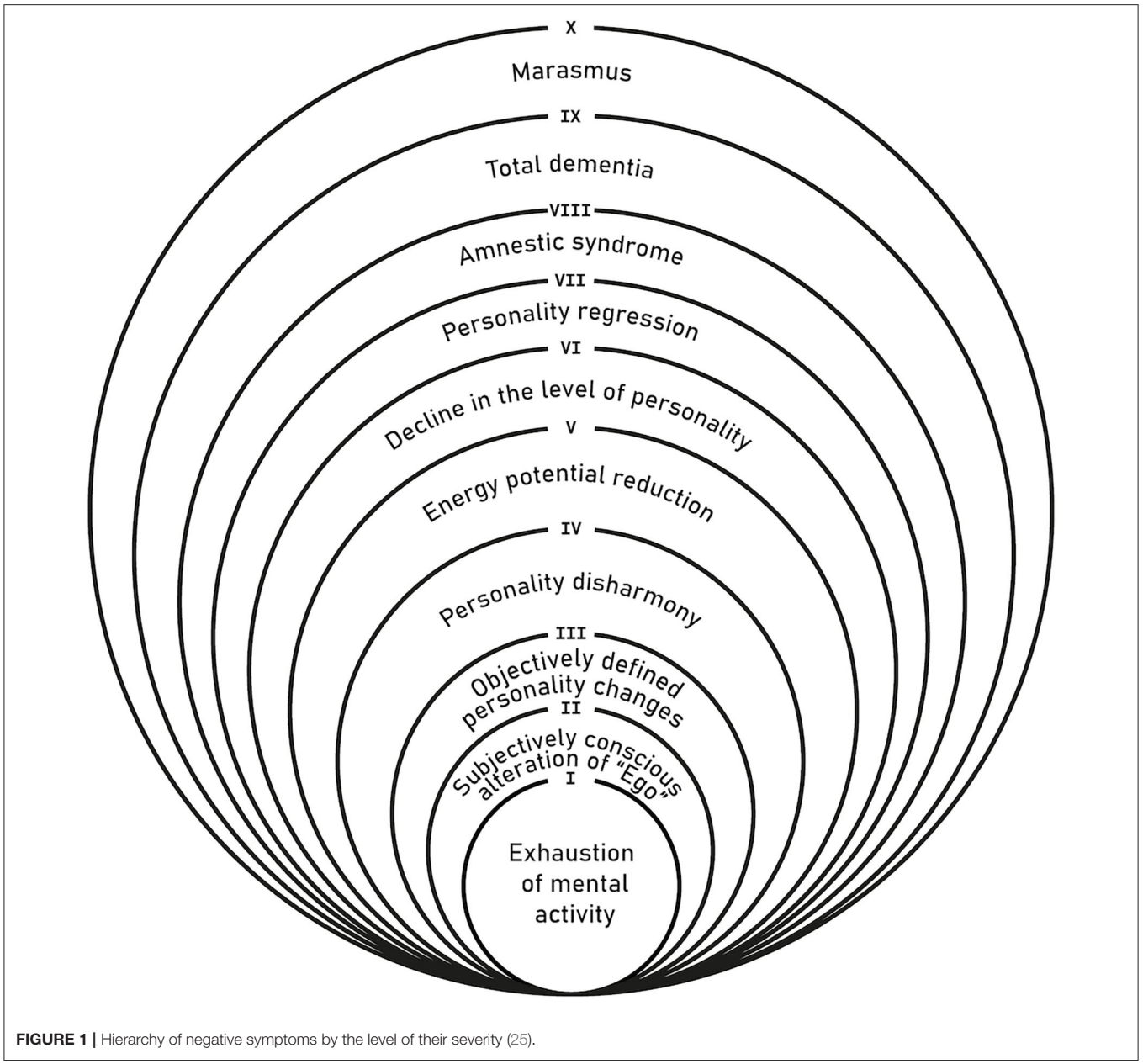


**FIGURE 1 |** Hierarchy of negative symptoms by the level of their severity (25).

first-rank symptoms of K. Schneider and associative cognitive dysfunction of E. Bleuler due to their lack of specificity (20, 31–33). Based on the old concept of J. R. Reynolds and J. H. Jackson, they proposed to allocate two main pathological syndromes of schizophrenia, i.e., positive and negative syndromes. A particular credit for describing and quantifying the symptoms comprising these syndromes goes to the psychologist from Iowa, Nancy Andreasen, who had developed special scales for psychometric assessment of positive (SAPS) and negative (SANS) symptoms. The SANS scale includes the following five domains of negative symptoms:

1) affective flattening or blunting, unchanging facial expression, amimia, decreased spontaneous movements, paucity of expressive gestures, poor eye contact, affective non-responsivity, inappropriate affect, lack of vocal inflections (monotone voice);
2) alogia (poverty of speech): reduction in the quantity of speech, poverty of content of speech, blocking, breaks in thought, increased latency of response;
3) avolition—apathy: poor grooming and hygiene (including personal hygiene), impersistence at work or school, physical anergia;
4) anhedonia—asociality: reduced interest in recreational activities, reduced sexual interest and activity, inability to feel intimacy and closeness, difficulties with relationships with friends and peers;

5) attention impairment: social inattentiveness, inattentiveness during mental status testing.

Eventually, N. Andreasen concluded that there were two fundamentally different forms of schizophrenia, with the prevalence of positive or negative symptoms. However, unlike T. Crow, she admitted the existence of a continuum of intermediate forms with mixed symptoms (33). Patients with predominant negative symptoms were characterized by a lower level of premorbid adaptation and social functioning, more pronounced cognitive impairment, and signs of cerebral atrophy.

Factor analysis of symptoms using the SANS scale revealed three main factors: (1) affective flattening (reduced expressiveness); (2) disturbed attention—alogia (poverty of speech); (3) reduced social motivation (abulia, apathy, anhedonia, asociality). In different studies, the most frequently observed symptom was reduced social motivation; somewhat rarely seen are symptoms of decreased emotional expressiveness (34–36).

These and other new studies conducted over the last decade have shown the necessity to exclude negative symptoms that are not directly associated with emotional and motivational deficits (e.g., attention disturbance, poverty of content of speech, increased latency of response, inappropriate affect), as well as those overlapping the other dimensions of schizophrenia, such as cognitive disorganization, cognitive impairment, and depressive symptoms. The consensus had been reached regarding the inclusion of the following five major factors in the concept of negative symptoms (37):

1) anhedonia—inability to feel pleasure;
2) avolition (apathy)—lack of energy and initiative, loss of interest for usual activity;
3) social withdrawal—disturbed social activity and avoidance of interpersonal contacts;
4) alogia—negative cognitive disorder, narrowing of speech range, and poverty of content of speech;
5) emotional (affective) flattening or blunting, reduced emotional response to stimuli.

This five-factor model of negative symptoms in schizophrenia has recently been also confirmed with independent network analysis (38).

Volitional impairment and, above all, goal-oriented behavior seem likely to be core negative symptoms in schizophrenia, as in this disease, the reward system, and goal-directing planning are disturbed (39). Patients can experience pleasure from a particular moment in the present but do not extrapolate it to the future, suffering from so-called anhedonia paradox (40). Avolition, abulia, apathy, anhedonia, and social withdrawal apparently have a single underlying mechanism based on disturbances in motivational sphere, including a decrease in motivation for social activity. The other component is associated with impairment of emotional expression and includes poverty of speech (alogia) with a paucity of spontaneous speech and affective flattening (decreased facial expressiveness, voice intonations, and gesticulation).

A two-factor structure of negative symptoms (motivational–volitional and emotional–expressive disorders) has been confirmed in several studies (37, 41, 42). Besides, such division is also confirmed by the trajectory of their development in the course of the disease, including their long-term stability and relationship with functional outcomes (10). It cannot be ruled out that they have different neurophysiological and neurochemical mechanisms and different responses to drug therapy (43). However, recent cohort studies have again shown a number of advantages and validity of a five-factor model of negative symptoms in schizophrenia (44, 45).

Another clinical approach to studying schizophrenia in patients with predominant negative symptoms was proposed by W. Carpenter, who designated schizophrenia with deficit syndrome as a particular subtype of the disease called "deficit schizophrenia" (46, 47). The authors proposed the following diagnostic criteria for a given subtype:

1) presence of at least two of the following negative symptoms is required:
   - restricted affect;
   - diminished emotional range and reduced variability of emotional reactions;
   - poverty of speech;
   - curbing of interests;
   - diminished sense of purpose;
   - diminished social drive;
2) symptoms have been present for the preceding 12 months and during periods of clinical stability;
3) symptoms are of primary nature with regard to the disease.

The deficit syndrome occurs in approximately 15% of patients experiencing the first episode of schizophrenia, in 20–25% of inpatients, and in 15–20% of all cases of schizophrenia (48). It is also found throughout the long-term follow-up period and remains stable in the course of the disease (49, 50). In contrast to all other variants of the disease, patients with deficit schizophrenia consistently demonstrate the worst therapeutic and social prognosis (51). For instance, comparison of the efficacy of haloperidol and clozapine in a small randomized clinical trial (RCT) did not reveal any differences in the effect of drug therapies on negative symptoms, although clozapine reduced positive symptoms to a greater extent (52). Notwithstanding several studies that emphasized the clinical uniqueness of deficit schizophrenia (53), its identification as a separate form can be hampered primarily because of practical difficulties of differentiating primary and secondary negative symptoms.

In the RCTs evaluating the effect of new treatments on negative symptoms in order to faster identify a homogeneous group of patients with predominant negative symptoms, the more pragmatic concepts of dominant and persistent negative symptoms have gained widespread use.

Persistent negative symptoms (PNSs) include pronounced negative symptoms that persist for at least 6 months with no and/or minimal depressive symptoms and pseudoparkinsonism; they persist during the period of clinical stability (remission)

on the background of low intensity or absence of positive symptoms and interfere with everyday functioning and social activities (54). The diagnosis of PNS rests on three criteria: (1) presence of a clinically stable negative syndrome for at least 3 months before psychiatric evaluation; (2) negative symptoms positive and negative syndrome scale (PANSS) score >24; (3) mild intensity (<4 points) of such symptoms as psychomotor agitation, hyperactivity, hostility, suspiciousness, negativism, and deficits in control of motivation as evaluated by PANSS. PNSs present a broader concept as compared to deficit syndrome. Although there is no clear distinction between primary and secondary negative symptoms, the criteria for PNS have been used in several RCTs (1, 55, 56). The prevalence of PNS depending on the severity of positive symptoms and duration of follow-up is 3.8–31.5% (54). In 23.7% of patients with first episode of schizophrenia, stable PNSs have been observed for 3 years (57). PNSs are more common in men, unemployed, subjects with a longer period of untreated psychosis, lack of insight, and a more significant, as compared to other forms of schizophrenia, decrease in the premorbid progress in studies and in social and cognitive functioning (2). However, as compared to patients with deficit schizophrenia, subjects with PNSs demonstrate, as a rule, less pronounced premorbid deficit and cognitive impairment. The concept of PNSs is now widely recommended both in practice and in clinical studies because it takes into account the parameter of symptom stability and allows to differentiate primary and secondary negative symptoms (58).

Notwithstanding the necessity of reaching a consensus on the definition of negative symptoms in RCTs, the inclusion criteria for patients with negative symptoms differ significantly (37, 54). Apart from PNSs, there are also dominant or predominant negative symptoms (DNSs). The latter is usually seen in patients with a negative PANSS composite index. However, in RCTs, these criteria are often modified, and additional conditions are added, e.g., intensity of three negative symptoms of not <4 points or of two negative symptoms of not <5 points amid low (below 4 points) intensity of two or more positive symptoms (59, 60). According to Riedel et al. (61), the DNS criteria include the following: (1) mandatory presence of three negative symptoms of moderate severity (at least 4 points) or two severe negative symptoms (at least 5 points); (2) PANSS total negative subscale score of at least 6 points higher than that on the positive symptom subscale (negative composite index); (3) negative symptom PANSS total score is equal to or >21 (61); (4) severity of the symptoms described in items 1 and 2 is determined by the total score on the PANSS positive symptom subscale and should be not more than 19 points (62).

Differences in the definition of DNS are in part associated with disagreement among regulatory agencies on their use in RCTs. The US Food and Drug Administration insists that negative symptoms recognized as pronounced should be used only for patients with high severity of negative symptoms, whereas the European Medicines Agency has introduced an additional criterion of "no-to-little positive symptoms," which brings this group of negative symptoms closer to PNS (63). In the large-scale CATIE trial that enrolled 1,447 patients with schizophrenia, two-thirds of the patients had clinically significant negative symptoms, and in 18.9% of them, these symptoms were predominant (64).

## DIAGNOSIS AND PSYCHOMETRIC ASSESSMENT OF NEGATIVE SYMPTOMS

The clinical diagnosis of negative symptoms is a rather difficult task. It is much easier to detect and evaluate positive symptoms owing to their intensity and direct response to antipsychotic therapy. The diagnosis of negative symptoms requires objective information and careful observation of the patient's behavior including their ability to express emotions, motivation in different spheres of personal and social activity, and interest in receiving treatment. Special scales for differential diagnosis of negative symptoms have been developed, including SANS (33) and PANSS (65). Although the PANSS includes a subscale consisting of seven negative symptoms, a subsequent factor analysis with independent evaluation has shown that four symptoms from the general psychopathological subscale are also related to the PANSS (mannerism and posturing, motor retardation, disturbance of volition, and active social withdrawal). This new cluster consisting of 11 symptoms forms the so-called Marder factor (66), which has recently been used mostly in the assessment of the negative dimension in schizophrenia using the PANSS scale. Interestingly, in the CATIE trial conducted in 1,447 schizophrenic patients to comparatively evaluate the efficacy of atypical antipsychotics without the involvement of pharmaceutical companies, the Marder factor appeared to be the strongest predictor of global patient functioning as compared to any other PANSS factors or symptoms both at baseline and after 18 months of any therapy. New scales and structured interviews for evaluation of negative symptoms include the Negative Symptom Assessment Scale (NSA-16 and NSA-4) (67, 68), Brief Negative Symptom Scale (BNSS) (69), and Clinical Assessment Interview for Negative Symptoms (CAINS) (42). The last two scales contain 13 items, take 15–30 min for evaluation, and allow to differentiate between the emotional and motivational negative symptom clusters.

**TABLE 1** | Differential diagnosis of negative symptoms.

| Negative symptoms | Depression | Parkinsonism |
|---|---|---|
| Emotional blunting | Anhedonia, indifference, anesthesia | Indifference, amimia |
| Apatho-abulic disorders (reduced psychic energy potential) | Motor retardation | Akinesia, increased muscle tone |
| Cognitive impairment, poverty of speech and associative thinking | Mental retardation, difficulties with concentration | Bradypsychia, cognitive impairment, decreased vigilance, difficulties with concentration, impaired speech production |
| Autism | Social withdrawal | Forced restriction of social contacts |

In addition to physician-rated scales, there are questionnaires for Self-evaluation of Negative Symptoms (SNS) and Motivation and Pleasure Scale–Self-Report (MAP-SR), which seem to be promising tools for routine clinical screening (70, 71). An important aid in diagnosis, particularly in complex cases that require the differentiation between depressive and negative symptoms, special psychometric scales such as the Calgary Depression Scale for Schizophrenia (CDSS) enable the evaluation of the severity of depression in schizophrenic patients (72). The Maryland Trait and State Depression scale (MTSD) enables the identification of depressive symptoms in the clinical picture of schizophrenia (73). The CDSS seems to be a more accurate tool for differential diagnosis; the uniqueness of CDSS compared to HAMD is that CDSS factors are stable over the course of the disease and appear independent of positive and negative symptoms.

A detailed analysis of the advantages and disadvantages of the various scales for assessing negative symptoms was recently provided by Lincoln et al. (74). In addition to clinical observation and structured interviews used for detection of negative symptoms, new registration methods, such as actigraphy or examination using a smartphone, provide an opportunity to detect symptoms and increase the level of activity of patients in their natural environment (75).

## DIFFERENTIAL DIAGNOSIS OF PRIMARY AND SECONDARY NEGATIVE SYMPTOMS

The distinction between primary and secondary negative symptoms has important diagnostic and therapeutic significance. Primary negative symptoms are an integral part of the phenomenon of schizophrenia and are characterized by a longer manifestation throughout the disease (13). Secondary negative symptoms may result from positive symptoms (e.g., social withdrawal based on suspicion in persecutory delusions), comorbid depression, side effects of antipsychotics, side effect of antidepressants, or use of psychoactive substances (e.g., cannabis) or can be caused by social deprivation resulting from long-term hospitalizations and loss of close relatives.

Some neuropsychological disorders, especially depression and parkinsonism, have phenomenological similarities with negative symptoms in schizophrenia (**Table 1**). Therefore, in clinical practice, it can be very difficult to distinguish emotional blunting from depressive anhedonia, anesthesia, apathy, and mental indifference or amimia in parkinsonism. Apatho-abulic disorders can be easily mixed up with depressive motor retardation and parkinsonian akinesia, and cognitive impairment, and disturbance of associative thinking—with depressive retardation often accompanied by difficulties with concentration or bradypsychia, cognitive dysfunction, and impaired speech production in parkinsonism. Schizophrenic autism may be difficult to differentiate from social withdrawal in depression or forced restriction of social contacts in parkinsonism. Many foreign and Russian authors have paid attention to difficulties in diagnosing such disorders (76–78).

The following differential diagnostic considerations can be suggested for secondary negative symptoms, even though a definitive distinction is often impossible.

1. Common Psychopathological Aspects of Negative Symptoms and Depression Include Anhedonia, Apathy, Suppression of Affective Sphere, Social Isolation, and Asthenia. Depressed Mood and Sleep Disorders Are More Often Observed During Depression. Besides, in Depression, the Leading Symptoms Include low Self-Esteem, Feelings of Despair, and Ideas of Guilt. Autonomic Symptoms, Circadian Rhythm Disruption, and Suicidal Ideation Are Also Common (79). In a special study, it has been found that the most important differentiating features for depression in schizophrenia

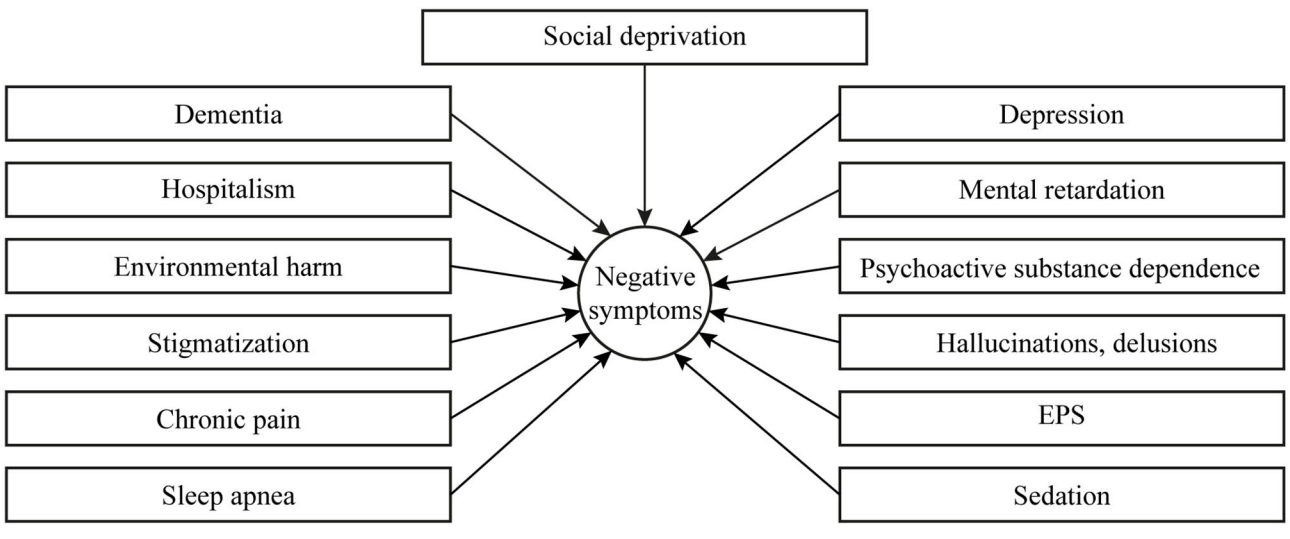


**FIGURE 2 |** Secondary negative symptoms in schizophrenia. EPS, extrapyramidal symptom.

patients are low mood and pessimistic and suicidal ideation and for negative syndrome are alogia, flattened affect, and social withdrawal (80).

2. Positive symptoms are often accompanied by daily life restrictions, for instance, delusions of persecution or hallucinations can lead to social isolation and anhedonia. Such negative symptoms become less intense as the hallucinations and delusions are reduced with antipsychotic therapy (81).
3. The other cause of secondary negative symptoms can be the inadequate use of antipsychotic therapy. Excessive sedation or extrapyramidal symptoms (EPSs) can lead to flattening of affect and motor impairments like stiffness and reduced activity (82). In such cases, differential diagnosis is made by establishing links between the onset of symptoms and the start of antipsychotic therapy or the addition of a new antipsychotic with strong dopamine-blocking properties.
4. Chronic substance abuse, e.g., cannabis, is associated with the so-called amotivational syndrome, which can clinically overlap with the existing negative symptoms imitating the latter (83). In such cases, differential diagnosis is made by collecting a detailed history of substance use, performing laboratory tests for their presence in the blood or urine, and following up symptoms during the abstinence period.
5. Less frequently, the development of secondary negative symptoms is related to environmental conditions, for instance, social deprivation during long-term hospitalization (81, 82). In this case, the issue of differential diagnosis is solved through obtaining detailed anamnestic and follow-up data of symptoms when a patient changes his/her type of activity or place of residence.

The above listed secondary negative symptoms are seen most frequently in clinical practice; however, their possible variants are much more diverse and have a broader spectrum of causes (neurological, somatic, social, or environmental) (**Figure 2**). Nonetheless, their careful detection and identification of their causes are of enormous practical importance, as it determines further therapeutic strategy. Unfortunately, in Russia, patients with severe stable negative symptoms rarely seek help from a psychiatrist, and they are usually pushing back against the idea of treatment. At the same time, physicians are seldom able to distinguish between primary and secondary negative symptoms and do not always attempt to treat negative symptoms because they consider them irreversible. To a certain degree, such therapeutic negativism in Russia is related to the prevalence of the "defect" concept of E. Kraepelin and A. V. Snezhnevsky. In a recent online survey of 807 members of the Russian Soci ety of Psychiatrists, only 51% of physicians specifically inquired about the presence of negative symptoms for diagnostic purposes, and 58% of those analyzed whether these symptoms were primary or secondary (84).

Another critical parameter for differentiating primary and secondary negative symptoms is the dynamics or trajectory of

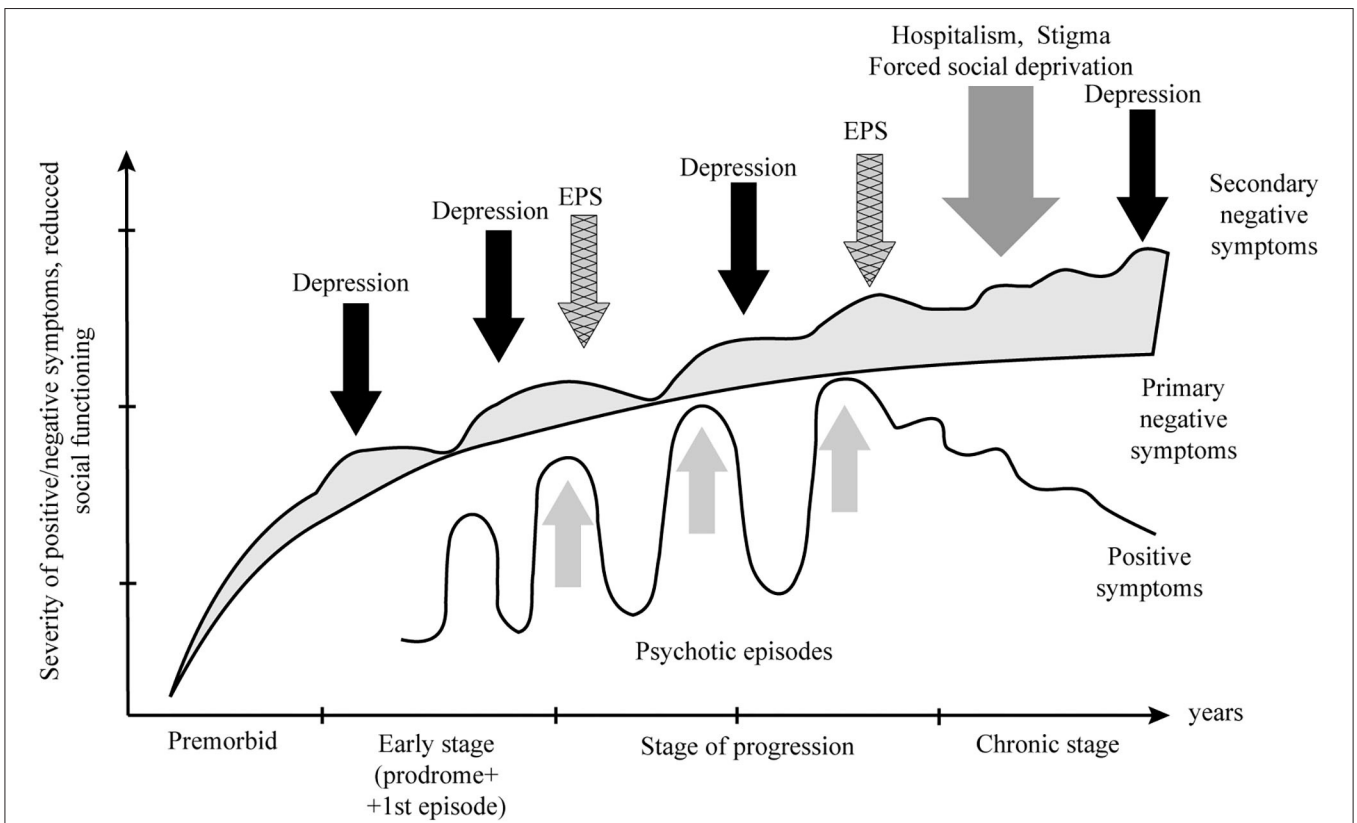


**FIGURE 3 |** Trajectory of the development of primary and secondary negative symptoms in schizophrenia. EPS, extrapyramidal symptom.

negative symptom development (**Figure 3**). The matter is that primary or deficit negative symptoms are fairly stable, hardly change in the course of the disease, and are often detected at the premorbid stage. Their structure and, specifically, the ratio of motivational-volitional and emotional domains, as a rule, remain unchanged. The severity of negative symptoms either increases or remains unchanged and directly correlates with the level of the patient's functional and social disability. At the same time, the intensity of secondary negative symptoms constantly undulates depending on the patient's condition, for instance, due to the development of depression, EPS, or psychotic symptoms. In this case, secondary negative symptoms overlap with primary negative symptoms, and this can create a false clinical impression of worsening deficit symptoms and disease progression, which frequently leads to the choice of incorrect therapeutic strategy and, namely, the intensification of antipsychotic dopamine-blocking treatment.

## CONCLUSION

Negative symptoms lead to a significant burden and deterioration of the quality of life in patients with schizophrenia. In everyday clinical practice, negative symptoms cannot be easily recognized, and this requires focused research and the use of special psychometric scales. While the mechanisms of secondary negative symptoms are related to external causes, the pathophysiological mechanisms of primary negative symptoms are unknown and the subject of intensive research. Their understanding will help to improve pharmacotherapy and, perhaps, facilitate a better understanding of the pathogenesis of schizophrenia in general.

Managing negative symptoms in schizophrenia is a major challenge for psychiatric services. It is important to differentiate between primary and secondary negative symptoms to select the correct therapeutic tactics. When secondary negative symptoms are present, it is recommended to manage their cause, primarily comorbid depressive symptoms, and extrapyramidal disorders. When dealing with primary negative symptoms, therapeutic options should include changes in treatment regimen by adding some atypical antipsychotics with a proven "anti-negative symptom effect" (partial D2/D3 agonists may have selective benefit), specific psychotherapy [cognitive behavioral therapy (CBT), cognitive rehabilitation, Metacognitive Reflection and Insight Therapy (MERIT)], exercise physical activity, transcranial magnetic stimulation, and possibly other alternative therapies (58, 85, 86). Considering promising studies in this field, it is worth highlighting a focus on primary negative symptom specificity in different stages, forms, and subpopulations of schizophrenia patients in future development and validation of novel highly sensitive psychometric scales and identification of genetic and neurochemical markers, which should aim to establish the pathogenesis of negative symptoms, and develop more effective targeted therapy for negative symptoms.

## LIMITATIONS

Due to the limited number of journal articles on this subject, the authors focused only on the historical and conceptual aspects of negative symptomatology in schizophrenia, especially on the clinical distinction between primary and secondary negative symptoms, and did not consider cognitive, genetic, or other neurobiological aspects and pharmacological and non-pharmacological therapies. The latter includes psychotherapeutic interventions targeting cognitive deficit, which is an important predictor for the worse social functioning and therapeutic response of negative symptoms (85).

## AUTHOR CONTRIBUTIONS

SM: study design, conceptualization, methodology, and writing and reviewing. PY: data collection, drafting the article, and figures and tables. All authors critically reviewed the article content and approved the final version.

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The remaining author declares 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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# APPENDIX 1

Glossary of terms to the **Figure 1**

*Amnestic syndrome* - prominent impairment of recent and remote memory while immediate recall is preserved, reduced ability to learn new material, and disorientation in time. Confabulation may be a marked feature, but perception and other cognitive functions, including the intellect, are usually intact.

*Decline in the level of personality* - persistent drop in activity and efficiency, in a narrowing of the circle of interests, paling of the features inherent in the individual, increased fatigue, irritable weakness, indistinctly expressed dysmnestic disorders. Further personality changes lead to its regression, and to more severe degree of various clinical manifestations like extreme explosiveness, brutality, affective lability, sudden decrease in adaptation, manipulative behavior; or complacency, stupidity, lack of insight, inability to solve simple personal tasks.

*Energy potential reduction* - decrease in mental energy potential, which expressed by a reduction in mental activity, productivity, inability to actively use the available volume of knowledge, inability to learn new information while retaining a reserve of professional and other knowledge.

*Exhaustion of mental activity* - increased mental exhaustion, signs of irritability, weakness, hyperesthesia. Mental asthenia is the mildest form of negative syndrome.

*Marasmus* - fragmentation of the personality to such an extent that the individual no longer presents a unified, predictable set of beliefs, attitudes, traits, and behavioral responses; profound dementia with loss of contact with the environment and complete disappearance of interests and desires. The food and sexual instincts are preserved, but severe physical exhaustion, trophic changes in the skin, dystrophy of the internal organs, increased bone fragility could be observed. Marasmus with a full disintegration of the personality is the most severe type of negative syndrome.

*Objectively defined personality changes* – unexpected shift in patient personality obvious to the others. In mild cases, it's a hypertrophy or accentuation of existed personal traits, in more severe ones – it's a change of temperament, the entire warehouse of the personality changes with appearance of psychasthenic, hysterical, hypochondriacal and paranoid features, that were not typical of the patient before.

*Personality disharmony* – discordance and contradictoriness in personality traits. It can appear in acquired autism (schizoidism), manifested by detachment from environment, egocentrism, reflexivity, introversion, paradoxical emotional reactions and behavior, impoverished emotionality combined with fragile feelings ("wood and glass"), loss of emotional resonance, inability to react adequately to events around, and schematic thinking detached from reality. In such cases, monotonous behavior, paradoxical pedantry, absence of flexibility, a drop in activity and passive submissiveness are noted. Sometimes an unusual combination of inactivity and passivity with remarkable achievements in any professional areas due to the originality of the patient's technical, scientific or artistic positions is observed. Signs of personality disharmony can be a constant feeling of dissatisfaction with others, irritability, excessive exhaustion, decreased productive thinking, easy and superficial judgments, egocentrism, narrowing of interests. Minor life difficulties cause patients to experience prolonged states of confusion, helplessness and hopelessness.

*Personality regression* - regress in behavior and social or labor activities. It can be manifested by the persistent drop in activity, lack of spontaneity, sharp narrowing of interests, indifference to the others, mild memory problems.

*Subjectively conscious alteration of "Ego"* - subjectively perceived by patients changes in the pattern of their personality, which manifested by mild deviations in internal attitudes, emotional reactions, assessment of current events, and attitudes toward peers. Such changes are quite often not stated and not noticed by others.

*Total dementia* – global impairments of multiple higher cortical brain functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement, usually of a chronic or progressive nature. The cognitive dysfunction is commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behavior or motivation, leveling of individual personality traits. Patients are usually euphoric, prone to frivolous, often ridiculous acts, and flat humor; their behavior is inadequate to the situation.

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# Dosing Cariprazine Within and Beyond Clinical Trials: Recommendations for the Treatment of Schizophrenia

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Although the optimal dosing of an antipsychotic medication is known to be essential in the long-term management of schizophrenia, in case of novel drugs such as cariprazine, determining the right dosing strategy is not that simple. Without decades of experience with a particular compound, evidence regarding dosing and titration comes primarily from double-blind, placebo controlled clinical trials that are not necessarily mirroring the real-life experiences of doctors. Via summarizing data from both clinical data ($n = 3275$) and real-world evidence (observational study $n = 116$, case studies $n = 29$), this perspective paper aims to shed a light on the appropriate dosing strategies of cariprazine from treatment initiation through switching strategies to concomitant medications.

**Keywords: cariprazine, schizophrenia, antipsychotic, dosing, psychopharmacotherapy**

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## INTRODUCTION

Antipsychotic medication, has been prescribed as the first line of treatment in schizophrenia since the 1950s (1, 2). While the so-called typical or first-generation antipsychotics (FGAs) such as haloperidol have been associated with considerable side effects, atypical or second-generation antipsychotics (SGAs) changed the view of psychosis treatment by offering similar level of efficacy as FGAs but with much lower rates and severity of adverse events (3). Throughout the past few decades however, third-generation antipsychotics (TGAs), have been in the spotlight given their ability to improve not only positive but potentially negative and cognitive symptoms as well (4–7). Many of these atypical antipsychotics are characterized by dopamine partial agonism (8), which explains their improved efficacy and safety profile (9) but also the fact why practitioners feel challenging to find the right strategy to dose them (10, 11).

The optimal dosing of antipsychotics is known to be essential in the long-term management of schizophrenia (12). The general rule is that one should aim for a treatment initiation and titration strategy that promotes quick and adequate response without the introduction of side effects that are too bothersome for the patient (12). Indeed, discontinuation and frequent switching between different antipsychotics due to adverse events or insufficient therapeutic response are highly common in schizophrenia patients (13, 14)—many practitioners switch or start polypharmacy before optimizing the current medication dose in order to address the patients' complains and to avoid non-adherence (12).

In case of novel drugs however, determining the right dosing strategy is not that simple. Without decades of experience with a particular compound, evidence regarding dosing and titration comes primarily from clinical trials (12). Aiming to determine efficacy against placebo with the lowest

possible side effects, in such studies manufacturers utilize doses that are often much lower than what is actually needed in real life (12, 15). In addition, patients involved in clinical trials are required to fit into a highly rigorous criteria and hence can be immensely different from those seen by doctors in their everyday clinical practice (16). Thus, in this paper, we aim to summarize the clinical data of cariprazine dosing within and beyond clinical trials.

## METHODS

Trials, studies, and cases for this perspective were identified by searching Embase and Medline databases for English language articles published in peer-reviewed journals between 1 January 2000 and 1 June with search terms "(cariprazin* OR "rgh-188" OR rgh188) AND ("case report*" OR "case stud*" OR "case series*" OR "trial*" OR "stud*")." Searches by hand were also conducted to identify additional relevant articles. Articles were included if they: (1) were an original research conducted with human subjects; (2) involved patients with diagnosis of schizophrenia; (3) provided adequate information regarding the dosing of cariprazine. Out of the 186 findings, 6 clinical trials, 1 observational study and 29 cases met the inclusion criteria.

## CARIPRAZINE, A THIRD-GENERATION ANTIPSYCHOTIC AGENT

Cariprazine is a TGA that is approved for the treatment of schizophrenia by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). It is a dopamine D3 receptor preferring partial agonist at the D3/D2 and at the serotonin 5-HT1A receptors and an antagonist at the 5-HT2B receptors (17). Compared to other antipsychotics, cariprazine's uniqueness is based in its high potency for the D3 receptor that is higher than what is exhibited by dopamine itself, resulting in full D3 receptor occupancy at clinically relevant doses (17). There are two major active metabolites of cariprazine, namely desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR) (18, 19). Both are pharmacologically equipotent to cariprazine and are known to be jointly responsible for the overall therapeutic effect (18, 19).

Throughout the clinical development programme for the treatment of schizophrenia, the efficacy and safety of cariprazine were established in 8 clinical trials; 4 short-term, randomized, double-blind, placebo-controlled studies with acute patients and 4 long-term studies of various design. In the short-term (6-week) studies patients who had current exacerbation of schizophrenia for <2 weeks in duration and were at least moderately ill were included (20–23). Within the 4 long-term studies, there were two 48-week open-label, flexible-dose safety trials, which served as extensions to the short-term studies (24, 25). The efficacy of cariprazine for the prevention of relapse in patients with acute schizophrenia was also evaluated in a long-term (up to 97 weeks) trial with a randomized, double-blind, placebo-controlled design (26). Finally, the last clinical trial, a 26-week, double-blind, active-controlled study, measured the efficacy of cariprazine in predominant negative symptoms (7).

Additionally to the clinical trials, there was one observational study in Latvia involving patients who were experiencing predominant negative symptoms despite receiving antipsychotic medication (27). Furthermore, several cases have been published that discuss cariprazine's effectiveness and safety in various schizophrenia patients.

### Treatment Initiation With Cariprazine

Cariprazine is currently approved in four doses: 1.5, 3.0, 4.5, and 6.0 mg/day (28). According to the Summary of Product Characteristics (SmPC) the recommended starting dose for cariprazine is the lowest available dose, 1.5 mg/day (28, 29). Indeed, as summarized in **Table 1**, in the majority of cases cariprazine treatment was initiated with this dose. Exceptions were three patient cases where cariprazine was prescribed in the dose of 3.0 mg/day (40), as well as the Latvian observational study where 7.7% of patients received 3.0 mg/day, 3.4% 6.0 mg/day and 1.7% 4.5 mg/day as their starting dose (27). Importantly, as reported in the cases, the higher starting dose was well-tolerated and quick improvement in behavior was detected (40).

After initiation of treatment, cariprazine doses are recommended to be increased in 1.5 mg increments up to a maximum of 6.0 mg/day, if necessary (28, 29). In general, there are two main titration strategies—a fast and a slow one. Fast titration involves an increase of 1.5 mg/day each day or every second day until the target dose is achieved, as seen in the short-term clinical trials (20, 21, 23). This or similar strategy was utilized in several cases (31, 33–35, 37, 40, 41, 43), where 3.0 mg/day dose was introduced within less than a week after the beginning of the treatment. In these cases, most of the patients exhibited considerable psychotic symptoms with or without negative symptoms and weight gain problems caused by previous medication. The other—slow—titration strategy has been described in one of the long-term studies, where patients with predominant negative symptoms received cariprazine in a dose of 1.5 mg/day until week 1 and then doses were increased in 1.5 mg increments weekly up until 6.0 mg/day, if it was needed (7). It is also worth to note however, that in this study cross-titration with previous antipsychotic medication was performed in the first two weeks of treatment, whereas in the short-term studies a 7-day wash-out period before cariprazine monotherapy was introduced (20–23). Slow titration strategy was also performed in cases where patients were less psychotic (30, 39) or received cariprazine as add-on treatment (32, 36). As expected, in the Latvian observational study both strategies were present (27); in 34% of the patients, dose was increased every 3rd day, in 28% every 4th day, in 6% every 6th day and in 32% every 7th day.

### Switching From Another Antipsychotic to Cariprazine

In case of cariprazine, switching from another antipsychotic can be beneficial if there has been no or only partial response to positive or negative symptoms (27, 31, 32, 35, 37, 41, 43), if the patient suffers from side effects (27, 34–36, 42)

**TABLE 1 |** Dosing strategies with cariprazine.

| Author | Study type (patient number) | Dosing scheme | Switching strategy | Starting dose | Dosing strategy | Maintenance dose | Concomitant medication |
|---|---|---|---|---|---|---|---|
| Amore et al. (30) | Case study (1) | Flexible 1.5–6.0 mg/day | Full-dose overlap from risperidone | 1.5 mg/day | 3.0 mg/day on day 15 | 3.0 mg/day | Risperidone gradually discontinued |
| Aubel (31) | Case study (1) | Flexible 1.5–6.0 mg/day | Risperidone was tapered to 2 × 0.5 mg daily | 1.5 mg/day | 3.0 mg/day on day 4 and 4.5 mg on day 14 | 4.5 mg/day | Risperidone gradually discontinued |
| Aubel (31) | Case study (1) | Flexible 1.5–6.0 mg/day | Cross-titration from clozapine and amisulpride | 1.5 mg/day | 3.0 mg/day on day 4 | 4.5 mg/day | - |
| Aubel (31) | Case study (1) | Flexible 1.5–6.0 mg/day | Aripiprazole 10 mg and risperidone 0.5 mg were discontinued | 1.5 mg/day | 3.0 mg/day on day 2 and 4.5 mg/day on day 3 | 4.5 mg/day | - |
| De Berardis et al. (32) | Case study (1) | Flexible 1.5–6.0 mg/day | Cariprazine as add-on | 1.5 mg/day | 3.0 mg/day on day 8 | 3.0 mg/day | Clozapine |
| De Berardis et al. (32) | Case study (1) | Flexible 1.5–6.0 mg/day | Cariprazine as add-on | 1.5 mg/day | 3.0 mg/day on day 22 | 3.0 mg/day | Clozapine |
| De Berardis et al. (33) | Case study (1) | Flexible 1.5–6.0 mg/day | No previous treatment | 1.5 mg/day | 3.0 mg/day on day 4, 4.5 mg/day on day 30 | 4.5 mg/day | - |
| De Berardis et al. (33) | Case study (1) | Flexible 1.5–6.0 mg/day | No previous treatment | 1.5 mg/day | 3.0 mg/day after a few days, 4.5 mg/day and then 6.0 mg/day after 14 days | 6.0 mg/day | Alprazolam |
| Di Sciascio et al. (34) | Case study (1) | Flexible 1.5–6.0 mg/day | Cross-titration from risperidone over 2 days | 1.5 mg/day | 3.0 mg/day on day 2 | 3.0 mg/day | Risperidone discontinued |
| Di Sciascio et al. (34) | Case study (1) | Flexible 1.5–6.0 mg/day | Cross-titration from olanzapine over 2 weeks | 1.5 mg/day | 6.0 mg/day | 6.0 mg/day | Olanzapine gradually discontinued by day 15 |
| Durgam et al. (23) | Phase II/III clinical study (390) | Flexible 1.5–4.5 mg/day or 6.0–12.0 mg/day | 7-day wash-out | 1.5 mg/day | 1.5–4.5 mg/day group: 3.0 mg/day on day 3, maximum 4.5 mg/day on day 5 6.0–12.0 mg/day group: 3.0 mg/day on day 3, 6.0 mg/day on day 5, maximum 9.0 mg/day on day 7 or 12.0 mg/day by day 9 | - | Lorazepam Zolpidem, zaleplon, chloral hydrate, eszopiclone, diphenhydramine, benztropine, propranolol |
| Durgam et al. (21) | Phase II/III clinical study (675) | Fixed 1.5 mg/day, 3.0 mg/day, 4.5 mg/day | 7-day wash-out | 1.5 mg/day | If target dose higher than 1.5 mg/day then 3.0 mg/day on day 2, 4.5 mg/day on day 3 | 1.5 mg/day, 3.0 mg/day, 4.5 mg/day | Lorazepam Zolpidem, zaleplon, chloral hydrate, eszopiclone, diphenhydramine, benztropine, propranolol |
| Durgam et al. (20) | Phase II/III clinical study (600) | Fixed 3.0 mg/day, 6.0 mg/day | 7-day wash-out | 1.5 mg/day | 3.0 mg/day on day 2, if target dose higher, then 4.5 mg/day on day 3 and 6.0 mg/day on day 4 | 3.0 mg/day, 6.0 mg/day | Lorazepam Zolpidem, zaleplon, chloral hydrate, eszopiclone, diphenhydramine, benztropine, propranolol |
| Durgam et al. (26) | Phase II/III clinical study (700) | Flexible: 3.0–9.0 mg/day Fixed: 3.0, 6.0, or 9.0 mg/day | 7-day wash-out | 1.5 mg/day | Flexible dose: 3.0 mg/day on day 2, 6.0 mg/day on day 6, 9.0 mg/day on day 10 until day 63 Fixed dose: 3.0, 6.0 or 9.0 mg | 3.0 mg/day, 6.0 mg/day, 9.0 mg/day | Lorazepam Zolpidem, zaleplon, chloral hydrate, eszopiclone, |

*(Continued)*

**TABLE 1 |** Continued

| Author | Study type (patient number) | Dosing scheme | Switching strategy | Starting dose | Dosing strategy | Maintenance dose | Concomitant medication |
|---|---|---|---|---|---|---|---|
| | | | | | between day 63 to 147 Fixed-dose double blind: randomized to 3.0. 6.0 or 9.0 mg between day 147 to 644 | | diphenhydramine, benztropine, propranolol |
| Carmassi et al. (35) | Case study (1) | Flexible 1.5–6.0 mg/day | Cross-titration from aripiprazole over 10 days | 1.5 mg/day | 3.0 mg/day on day 5, 4.5 mg/day on day 9, and 6.0 mg/day on day 13 | 6.0 mg/day, | Aripiprazole gradually discontinued, benzodiazepine |
| Heck et al. (36) | Case study (1) | Flexible 1.5–6.0 mg/day | Discontinuation of quetiapine before start of cariprazine, then adding quetiapine again | 1.5 mg/day | 3.0 mg/day on day 5 | Cariprazine was reduced to 1.5 mg/day 3 days after the onset of akathisia. Another 2 days later, cariprazine was stopped. | Quetiapine |
| Heck et al. (36) | Case study (1) | Flexible 1.5–6.0 mg/day | Cariprazine as add-on | 1.5 mg/day | 3.0 mg/day on day 15 | Developed severe Parkinsonism, risperidone treatment was fully stopped, 1.5 mg/day cariprazine was maintained | Risperidone and biperiden |
| Heck et al. (36) | Case study (1) | Flexible 1.5–6.0 mg/day | No previous treatment | 1.5 mg/day | 3.0 mg/day on day 8, 4.5 mg/day on day 13 | 4.5 mg/day | Pipamperone, then olanzapine |
| Heck et al. (36) | Case study (1) | Flexible 1.5–6.0 mg/day | Cross-titration from amisulpride | 1.5 mg/day | 3.0 mg/day on day 15, 4.5 mg/day on day 29, and 6.0 mg/day on day 85 | 6.0 mg/day | - |
| Kane at al. (22) | Phase II/III clinical study (450) | Fixed/flexible 3.0–6.0 mg/day, 6.0–9.0 mg/day | 7-day wash-out | 1.5 mg/day | 3.0–6.0 mg/day group: 3 mg/day until day 14 if inadequate response 4.5 mg/day on days 14 to 15 and 6.0 mg/day thereafter 6.0–12.0 mg/day group: 3.0 mg/day on days 2–3, 6.0 mg until day 14, if inadequate response 7.5 mg/day on days 14 to 15 and 9.0 mg/day thereafter | - | Lorazepam Zolpidem, zaleplon, chloral hydrate, eszopiclone, diphenhydramine, benztropine, propranolol |
| Kapulsky et al. (37) | Case study (1) | Flexible 1.5–6.0 mg/day | Abrupt discontinuation of clozapine and gradual titration of cariprazine | - | 6.0 mg/day by day 7 | Discontinued due to urinary retention | - |
| Mencacci et al. (38) | Case study (1) | Flexible 1.5–6.0 mg/day | Cross-titration from haloperidol and risperidone over 1 month | - | up to 4.5 mg/day | 4.5 mg/day | Haloperidol and risperidone gradually discontinued |
| Mencacci et al. (38) | Case study (1) | Flexible 1.5–6.0 mg/day | Cross-titration from olanzapine over 3 weeks | - | up to 4.5 mg/day until day 21 | 4.5 mg/day | Olanzapine gradually discontinued, biperiden, lorazepam, antihistamine |
| Molnar et al. (39) | Case study (1) | Flexible 1.5–6.0 mg/day | No previous treatment | 1.5 mg/day | up to 4.5 mg/day until day 14 | 3.0 mg/day | - |

*(Continued)*

**TABLE 1** | Continued

| Author | Study type (patient number) | Dosing scheme | Switching strategy | Starting dose | Dosing strategy | Maintenance dose | Concomitant medication |
|---|---|---|---|---|---|---|---|
| Montes et al. (40) | Case study (1) | Flexible 1.5–6.0 mg/day | No previous treatment | 3.0 mg/day | - | 3.0 mg/day | - |
| Montes et al. (40) | Case study (1) | Flexible 1.5–6.0 mg/day | No previous treatment | 3.0 mg/day | 6.0 mg/day on day 3 | 6.0 mg/day | Diazepam |
| Montes et al. (40) | Case study (1) | Flexible 1.5–6.0 mg/day | Abrupt discontinuation of aripiprazole | 3.0 mg/day | 6.0 mg/day on day 3 | 6.0 mg/day | Quetiapine |
| Müller et al. (41) | Case study (1) | Flexible 1.5–6.0 mg/day | Quetiapine and amisulpride wash-out phase over 4 days | 1.5 mg/day | 3.0 mg/day on day 5, 4.5 mg/day on day 13 | 4.5 mg/day | - |
| Müller et al. (41) | Case study (1) | Flexible 1.5–6.0 mg/day | Cross-titration from olanzapine over 3 days and risperidone over 10 days | 1.5 mg/day | 3.0 mg/day on day 3, 4.5 mg/day on day 24 | 4.5 mg/day | Risperidone until 4.5 mg cariprazine |
| Németh et al. (7) | Phase II/III clinical study (460) | Flexible: 3.0–6.0 mg/day | Cross-titration over 2 weeks | 1.5 mg/day | 3.0 mg/day on day 7–13, 4.5 mg/day on day 14 | 3.0 mg/day, 4·5 mg/day, 6.0 mg/day | Trihexyphenidyl Hydrochloride, biperiden, propranolol |
| Rancans et al. (27) | Observational study (116) | Flexible 1.5–6.0 mg/day | Cross-titration over 2 weeks | 1.5, 3.0, 4.5, 6.0 mg/day | Cross-titration until day 14 | 1.5 mg/day, 3.0 mg/day, 4.5 mg/day, 6.0 mg/day 7.5 mg/day | Anti-EPS medication, antidepressants, benzodiazepines, mood stabilizers |
| Riedesser et al. (42) | Case study (1) | Flexible 1.5–6.0 mg/day | Cariprazine as add-on | 1.5 mg/day | Discontinued after 6 days | - | Clozapine, escitalopram |
| Riedesser et al. (42) | Case study (1) | Flexible 1.5–6.0 mg/day | Cariprazine as add-on | 1.5 mg/day | 4.5 mg/day | 3.0 mg/day | Amisulpride, hydro-chlorothiazide, amlodipine and ramipril |
| Riedesser et al. (42) | Case study (1) | Flexible 1.5–6.0 mg/day | Abrupt discontinuation of risperidone and olanzapine 4 days later | 1.5 mg/day | 3.0 mg/day | Discontinued after 14 days | Pantoprazole |
| Vita et al. (43) | Case study (1) | Flexible 1.5–6.0 mg/day | Cross-titration from risperidone over 9 day | 1.5 mg/day | 3.0 mg/day on day 4, 4.5 mg/day on day 8 | 4.5 mg/day | Risperidone discontinued |
| Vita et al. (43) | Case study (1) | Flexible 1.5–6.0 mg/day | Abrupt-gradual from paliperidone long-acting | 1.5 mg/day | 3.0 mg/day on day 4, 4.5 mg/day on day 8, 6.0 mg/day on day 12 | 6.0 mg/day | Paliperidone discontinued |

that are less common with cariprazine such as weight gain, hyperprolactinemia, sexual disturbance or sedation (44) or if the patients has been prone to non-adherence or substance abuse (29, 35).

In general, there are four possible ways of switching antipsychotics; abrupt, abrupt-gradual, gradual-gradual (i.e., cross-tapering) and gradual-abrupt (12, 29). In case of abrupt switching, the previous antipsychotics medication is promptly discontinued, while the new one is immediately started (12, 29). The second option is to immediately discontinue the current medication and gradually introducing the new one (abrupt-gradual) (12, 29). In contrast to this option, gradual-abrupt switching involves the gradual dose reduction of the previous medication and the immediate start of the new one (12, 29). Finally, in cross-tapering the new antipsychotic is gradually introduced while the previous is gradually tapered down (12, 29). This can be achieved in two ways as well, either at the same time, or delayed; first, reaching a plateau where the target dose of the new antipsychotic is achieved and only then starting to decrease the dose of the previous medication (full-dose overlap) (12).

The most recommended strategy for switching to cariprazine is gradual cross-titration with different timeframes depending on the mechanism of action of the previous medication as seen in **Figure 1** (29, 48). In case of antipsychotics that have

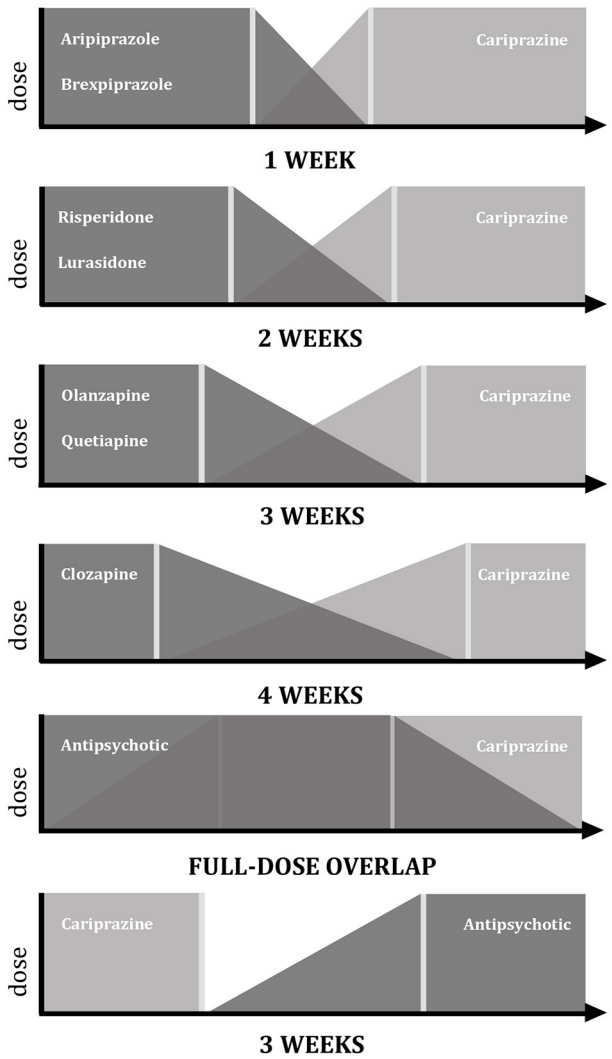


**FIGURE 1 |** Switching strategies with cariprazine. Graphic representation of data according to Németh et al. (7), Fagiolini et al. (45), Sullivan et al. (46), Stephen (47).

a similar profile to cariprazine i.e., partial agonism at the D2 receptor with comparable histaminergic and cholinergic affinity (e.g., aripiprazole), a 1-week cross-titration is recommended where the previous drug is tapered off within 7 days while at the same time cariprazine dose is escalated to the target dose (29, 48). In contrast, about 2 weeks is necessary if switching from a second-generation antipsychotic that has D2 antagonism (e.g., risperidone) in order to avoid dopaminergic rebound causing increased psychotic symptoms, agitation and dyskinesia (29, 48). Finally, most time (3-4 weeks) should be given when switching from antipsychotics with completely different receptor profiles i.e., those with stronger antihistaminic and/or anticholinergic affinity (e.g., olanzapine, quetiapine or clozapine) so that histaminergic and cholinergic rebound is avoided hence reducing the risk of insomnia, nausea and vomiting (29, 48). At last, various panels emphasize the advantages of a full-dose overlap when switching to cariprazine regardless of the type of antipsychotic drug that has been taken by the patient (45, 46). In such case, a period of overlap for about 2 weeks is recommended before the tapering down of the previous medication hence ensuring that there will be no relapse of symptoms (45, 46).

When analyzing data from clinical cases however, the picture regarding switching strategies is much more mixed. In case of switching from risperidone, some chose abrupt switching (42), while others discontinued it over 2, 9 or 10 days period while gradually increasing the dose of cariprazine (34, 41, 43). Similarly, abrupt stop as well as cross-titration over a 3-day, 2- or 3-week period was described when switching from olanzapine to cariprazine (34, 38, 41). Interestingly, abrupt switching was frequently described in case of quetiapine (36, 41) and clozapine as well (37). In case of making the clinical decision to switch from cariprazine to another antipsychotic, the abrupt-gradual strategy is recommended due to the long half-life of cariprazine (28).

Even if carefully planned and executed however, complications throughout switching can still emerge. In case of a dopaminergic rebound, the re-initiation or dose increase of the previous antipsychotic is recommended (29). If appropriate, this strategy can also be applied to cholinergic and histaminergic rebounds, however in general, the adding of an anticholinergic (e.g., biperiden) or antihistamine (e.g., hydroxyzine) medication can also solve the complications (29). One of the most common side effects of antipsychotic medications is akathisia which can also emerge during a switching period and is recommended to be managed with beta-blockers (e.g., propranolol), benzodiazepines or anticholinergics (29).

## Maintenance Treatment and Concomitant Medications

Maintenance treatment involves the stabilization of the patient on a certain dose that has the ability to control the patient's symptoms without causing any side effects that are intolerable for the patient. Among the four available doses of cariprazine, all doses can be utilized as maintenance dose—depending on the patient's symptom and side effect profile. For instance, although the 1.5 mg/day is most often prescribed in the treatment initiation phase, 11% of the patients in the Latvian study and 4% of the reviewed cases remained on it long-term. Importantly, the rest of the doses were used as maintenance dose equally in these real-life settings; about one fourth of the patients were on 3.0 mg/day, one fourth on 4.5 mg/day and another one fourth on 6.0 mg/day. These data also shows that patients stabilizing on 6.0 mg/day are more usually psychotic and hence require higher D2 activity, while the lower doses found to be more adequate for improving negative and cognitive symptoms. If looking at the pooled data of the fixed-dose studies, based on the effect sizes for the PANSS total and positive symptom factor scores, the optimal dose for most schizophrenia patients is the 4.5 mg/day (49). Thus, prescribing this dose for an adequate time is recommended before switching from cariprazine to another antipsychotic medication due to insufficient effectiveness.

Additionally, the final dose of cariprazine is often related to the maintenance dose of the previous antipsychotic medication

(29). Equivalent doses of different antipsychotics are clearly described in The Maudsley Prescribing Guidelines in Psychiatry (50) where it has been stated that 3 mg cariprazine is approximately the same dose as 3 mg risperidone, 10 mg olanzapine, 80 mg lurasidone, 2 mg brexpiprazole, 300 mg quetiapine and 400 mg amisulpride. Indeed, in the negative symptom study, patients were randomized to receive fixed doses of cariprazine (3 mg, 4.5 mg or 6 mg per day) or the equivalent in risperidone (3 mg, 4.0 mg or 6 mg per day) (7). Additionally, the same principle was applied in a case by Di Sciascio et al. that reported a successful switch and maintenance from risperidone 3 mg to cariprazine 3 mg per day (34).

Even though cariprazine is approved for mono-therapeutic use, polypharmacy—essentially the use of more medications—is quite common in real-life settings (51, 52). In fact, in 5 out of the 29 cases was cariprazine used as an add-on treatment (32, 36, 42). To give an example, De Berardis and colleagues utilized cariprazine successfully in combination with clozapine in two patients and reported the effects of cariprazine combination to be remarkable not only regarding symptom control but also concerning the management of side effects caused by clozapine (32). Moreover, in the Latvian observational study, 27% of patients were taking quetiapine, 10% olanzapine and 9% clozapine at their last visit, mostly for non-specific sedation or control of anxiety (27). Importantly, in a *post-hoc* analysis of the cross-titration period of the negative symptom study (7), the co-administration of cariprazine with other antipsychotic medications did not show an unexpected safety profile nor overlapping toxicities, suggesting that it is unlikely that safety will be compromised if polypharmacy with cariprazine is unavoidable (53). This shows that in certain cases patients can benefit from cariprazine combination treatment, nonetheless only if the second antipsychotic is well-chosen with careful consideration regarding the compatibility of the two medications (54).

Concomitant medications other than antipsychotics are well-described in the cariprazine literature. In the clinical trials zolpidem, zaleplon, chloral hydrate, or eszopiclone for insomnia, diphenhydramine, benztropine, or propranolol as rescue medication for extrapyramidal (EPS) symptoms, and lorazepam for agitation, restlessness, irritability, and hostility were permitted (20, 21, 23, 26). Similarly, in the Latvian observational study anti-EPS medication, benzodiazepines, mood stabilizers and antidepressants were allowed (27). Nonetheless, it is important to note that fewer patients needed concomitant medication with cariprazine compared to the antipsychotic they were previously on; 14% of the patients stopped taking anti-EPS medication, 5% antidepressants and mood stabilizers and 3% benzodiazepines (27). In the reviewed cases, most concomitant medications were benzodiazepines (alprazolam, lorazepam and diazepam) (33, 35, 38, 40) and biperiden (36, 38).

## DISCUSSION

The success of antipsychotic treatment depends not only on the mechanism of action of a compound but also on the physician's ability to find the right dosing strategy in which the medication is introduced to the patient. This is especially important, as high levels of non-adherence is caused by issues with ineffectiveness and adverse drug reactions which in turn can increase the risk of relapse (55, 56). With years of practice with a certain antipsychotic medication, clinicians can make confident decisions on how to switch from one medication to another, but this is more complicated with a novel compound such as cariprazine where most data is coming from clinical trials where the conditions are often different from what is seen in real-life practice.

Based on the reviewed literature, it can be stated that evidence regarding dosing, titration and switching strategies with cariprazine is not that different from trials compared to real-life settings. Almost all patients outside of clinical trials received 1.5 mg/day as their first dose of cariprazine, as recommended by the SmPC, however those who started with higher doses tolerated cariprazine just as well and reported effectiveness soon after the beginning of treatment. Higher initial doses might work if they are the corresponding dose of the previous medication or if they are at least half of the target dose.

More variance was found in how cariprazine was up-titrated; compared to the 1.5 mg increase a day or every second day, the dose of cariprazine was increased every third or fourth day, depending on the down-titration of the outgoing antipsychotic medication. Importantly, quicker up-titration was utilized when patients were not switching from another medication but were drug-free or acutely ill with mostly psychotic symptoms. In contrast, slower titration strategies seem to work for patients with more negative symptoms better.

Cross-titration strategies from antipsychotics with different receptor profiles and mechanism of action were also reviewed in detail and evidence shows that gradual switching where the dose of the outgoing antipsychotic is continuously decreased while cariprazine dose is increased is the safest option, as with this strategy the risk of rebounds and adverse reaction are the lowest. The timeframe of the cross-titration should depend on the previous medication; the more similar to cariprazine, the less time is needed. In case of the emergence of any side effects such as anxiety or agitation during the cross-titration period, three options are present—decreasing the dose of cariprazine, slowing down the titration process or control with additional medication such as benzodiazepines or quetiapine.

After the cross-titration period, maintenance treatment follows where patients were found to receive 3.0 mg, 4.5 mg, and 6.0 mg per day equally often in real-life settings. However, when analyzing the clinical data, 4.5 mg/day was reported as the most appropriate dose. Although recommended as monotherapy, cariprazine was also found to be effective in combination with other medications such as clozapine. If polypharmacy is unavoidable however, the compatibility of the drugs in terms of receptor affinity and mechanism of action should be evaluated.

## DATA AVAILABILITY STATEMENT

Data presented in the article can be found in already published materials that are cited accordingly.

Further questions should be directed to the corresponding author.

## AUTHOR CONTRIBUTIONS

ER, ZBD, and ÁB contributed to the conception of the manuscript. ZBD wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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# Preferential Effects of Cariprazine on Counteracting the Disruption of Social Interaction and Decrease in Extracellular Dopamine Levels Induced by the Dopamine $D_3$ Receptor Agonist, PD-128907 in Rats: Implications for the Treatment of Negative and Depressive Symptoms of Psychiatric Disorders

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The negative and cognitive symptoms of schizophrenia and related disorders may be due to reduced dopaminergic tone in cortical brain areas. Alteration in the function of dopamine (DA) $D_3$ receptors may play a role in this cortical hypofunctionality and underlie the deficits in social behaviors and cognitive functions in schizophrenia. Cariprazine is a potent DA $D_3$-preferring $D_3/D_2$ receptor partial agonist that is approved for the treatment of schizophrenia and bipolar disorder. The objective of the study was to compare the abilities of cariprazine, aripiprazole (another DA receptor partial agonist with more $D_2$ receptor preference), and ABT-925 (a selective DA $D_3$ antagonist) to counteract the social deficit and neurochemical alterations induced by the $D_3$ receptor-preferring agonist (+)-PD 128907 (PD) in rats. Administration of PD (0.16 mg/kg; s.c.) induced a marked (−72%) but short-lasting disruption of the defensive social aggregation behavior (huddling) in the first 10-min period. Cariprazine at all doses (0.1, 0.3, 1 mg/kg; p.o.) almost completely abolished the PD-induced disruption of huddling. Likewise, ABT-925 (3 mg/kg; p.o.) and to a lesser extent aripiprazole (20 mg/kg; p.o.) were effective in blocking the PD-induced disruption of huddling. As measured by microdialysis, the highest dose of cariprazine prevented a PD-induced decrease in DA levels (40–80 min post PD dose) in the medial prefrontal cortex (mPFC), whereas aripiprazole did not have a significant effect. ABT-925 significantly counteracted the effect of PD at 80 min post-dose. In the nucleus accumbens (nAcc) shell, the highest dose of cariprazine, as well as ABT-925 and aripiprazole, significantly reversed the PD-induced decrease in DA levels.

Taken together, these data provide behavioral and *in vivo* neurochemical evidence for the preferential DA $D_3$ receptor action of cariprazine in the rat. This property of cariprazine may offer therapeutic benefits against the cognitive deficits and negative/depressive symptoms of schizophrenia and related disorders.

**Keywords: cariprazine, schizophrenia, dopamine $D_3$ receptor, huddling, microdialysis**

## INTRODUCTION

Cariprazine (Vraylar® in USA; Reagila® in Europe) is approved in the USA for the acute and maintenance treatment of schizophrenia, as well as the acute treatment of manic or mixed episodes associated with bipolar I disorder and bipolar depression in adults. It is also approved by the EMA for the treatment of schizophrenia in adults and is in clinical development as an adjunctive treatment for major depressive disorder. Cariprazine acts as a potent dopamine (DA) $D_3$ receptor-preferring $D_3/D_2$ receptor partial agonist, as well as a partial agonist of serotonin 5-$HT_{1A}$ receptors (1). Cariprazine can be distinguished from currently used atypical antipsychotics by its higher *in vitro* binding affinity ($K_i$) and selectivity for human $D_3$ receptors (0.085 nM) compared to $D_{2L}$ (0.49 nM) and $D_{2S}$ (0.69 nM) receptors (1, 2). In addition, cariprazine displays subnanomolar affinity for serotonin 5-$HT_{2B}$ receptors; nanomolar affinity for serotonin 5-$HT_{1A}$, 5-$HT_{2A}$, and histamine $H_1$ receptors; and low affinity for serotonin 5-$HT_7$, 5-$HT_{2C}$, and adrenergic alpha receptors (1).

The $D_3$ receptor is thought to play a role in mood (3) and cognition (4). Cariprazine was developed based on the hypothesis that a compound with high affinity for $D_3$ and $D_2$ receptors may provide benefits for treating the affective and cognitive deficits associated with schizophrenia and bipolar disorder (5, 6). *In vivo*, cariprazine achieves high occupancy of both $D_3$ and $D_2$ receptors at doses that produce antipsychotic-like effects in rats (7) and at clinically active dose ranges in patients with schizophrenia (8). Cariprazine's pharmacological profile differs from that of other atypical antipsychotics such as aripiprazole, clozapine, olanzapine, and risperidone, which have varying levels of *in vitro* affinity for $D_3$ receptors but fail to show significant $D_3$ receptor occupancy at doses that produce antipsychotic-like effects in rats (9) and/or at clinically relevant doses in patients with schizophrenia (10, 11). These data indicate that cariprazine can modulate the activity of $D_3$ receptors *in vivo* to a greater extent than other atypical antipsychotics in clinical use.

In animal models of schizophrenia, cariprazine reversed PCP- or MK-801-induced behavioral effects such as hyperlocomotion (7), demonstrating putative efficacy for treating the positive symptoms of schizophrenia. In a follow-up study in mice, cariprazine significantly diminished PCP-induced cognitive deficits in wild-type mice, but not in $D_3$ receptor knockout mice (12). In addition, two recent studies provide further support for cariprazine's ability to ameliorate PCP-induced cognitive and social deficits in adult rats (13) and in a PCP-neurodevelopmental model of schizophrenia in rats (14). Together, these results from PCP models of schizophrenia suggest that cariprazine may exert beneficial effects on the cognitive and social/affective functions disrupted by PCP, at least in part through its high affinity for and occupancy of $D_3$ receptors.

Indeed, in addition to cariprazine's efficacy (vs. placebo) in patients with acute exacerbation of schizophrenia (15–17), cariprazine has also demonstrated enhanced efficacy (vs. risperidone) for treating the negative symptoms of schizophrenia in patients with predominantly negative symptoms (18, 19). These data suggest that cariprazine displays a differentiated clinical profile compared to other atypical antipsychotic medications, which may be driven by its unique $D_3$ receptor mechanism.

It has been demonstrated that dopamine $D_3$ receptor-preferring agonists such as 7-OH-DPAT (20), (+)-PD 129807 (PD) (21, 22), and pramipexole (23) cause biphasic behavioral changes in rats: at low doses they cause yawning, whereas at high doses they cause increased penile grooming, sniffing, hypothermia, locomotor stimulation, and stereotypy (22–27). It has been proposed that induction of yawning elicited by these agonists at low doses is mediated through the activation of dopamine $D_3$ receptors (22, 26, 27). At low doses, similar to those that induce yawning, (±)-7-OH-DPAT and (+)-PD 128907 also caused a dose-dependent disruption of huddling, a normal social behavior involving direct body contact in rats. Thus, the alteration of huddling elicited by low, $D_3$ receptor-selective doses of (+)-PD 128907 and (±)-7-OH-DPAT are considered a useful behavioral model for dopamine $D_3$ receptors (28–30). (+)-PD 128907-induced disruption of huddling can be reversed by selective dopamine $D_3$ receptor antagonists such as A-437203 (ABT-925) or A-690304 (30, 31) or partially reversed by antipsychotics (29).

The objective of this study was to evaluate the ability of acute cariprazine administration to counteract the disruptive effect of the $D_3$ receptor-preferring dopamine agonist, (+)-PD 128907, on huddling behavior in rats compared to the $D_2/D_3$ receptor partial agonist antipsychotic aripiprazole (32) and the selective $D_3$ receptor antagonist ABT-925 (31). This study also aimed to determine the role of $D_3$ receptors in dopaminergic neurotransmission. To this end, we used dual-probe microdialysis in the prefrontal cortex (mPFC) and nucleus accumbens (nAcc) shell of awake rats to measure the extracellular levels of DA and its metabolites, dihydroxy-phenylacetic acid (DOPAC) and homovanillic acid (HVA), in response to cariprazine, ABT-925, and aripiprazole before a (+)-PD 128907 challenge.

# MATERIALS AND METHODS

## Animals

Male Sprague-Dawley rats (8–10 weeks of age, weighing 300–350 g on the day of the experiment) were used in the study. The rats weighed 250–275 g upon reception from Janvier Labs, France, and were allowed a minimum acclimatization period of 1 week prior to any experiments. No prophylactic or therapeutic treatments were administered during the acclimatization period. Animals were kept in a controlled environment (22 ± 1°C; 45–50% rel. humidity) on a 12 h dark/12 h light cycle (40 Lux, lights on at 6:00 AM). The rats had free access to standard laboratory chow (RM1A(P), SDS, Scanbur, Sweden) and tap water until the time of the experiments. The rats were housed in groups of five in Eurostandard type IV cages (595 × 380 × 200 mm, LWH, floor area 1,820 $cm^2$) with wire lids (Tecniplast, Buguggiate, Varese, Italy) and aspen bedding (Tapvei, Estonia). Aspen gnawing bricks, aspen arcades, or tunnels (Tapvei) were placed in each cage as environmental enrichment. All rats were examined and weighed prior to study initiation to assure adequate health and suitability. Rats were randomly assigned to treatment groups.

## Test Compounds

Cariprazine hydrochloride salt, aripiprazole free base, and ABT-925 were provided by Allergan, NJ, USA. (+)-PD 128907 hydrochloride was purchased from Tocris Bioscience, UK. All other chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA).

## Groups and Doses

### Huddling Study

The huddling study included 10 groups of eight rats each. The test compounds cariprazine, aripiprazole, or ABT-925 (3 ml/kg total volume) were administered orally (p.o.) 30 min prior to administration of either (+)-PD 128907 or saline. (+)-PD 128907 or saline (1 ml/kg total volume) were administered subcutaneously (s.c.). The vehicle for the p.o. administrations consisted of 0.4% (v/v) acetic acid in saline (20 µl acetic acid in 5 ml saline). The vehicle for the s.c. injections was saline. Fresh formulations of the test compounds were prepared on the day of each experiment. The doses and treatments for each group are summarized in **Table 1** below.

**TABLE 1** | The doses and the order of the test compounds for the huddling study.

| Group | Treatment 1 ($t = -30$ min) | Treatment 2 ($t = 0$ min) |
|---|---|---|
| 1 | Vehicle p.o. | Vehicle s.c. |
| 2 | Vehicle p.o. | (+)-PD 128907 (0.16 mg/kg s.c.) |
| 3 | ABT-925 (3 mg/kg p.o.) | Vehicle s.c. |
| 4 | Cariprazine (1.0 mg/kg p.o.) | Vehicle s.c. |
| 5 | Aripiprazole (20 mg/kg p.o.) | Vehicle s.c. |
| 6 | ABT-925 (3 mg/kg p.o.) | (+)-PD 128907 (0.16 mg/kg s.c.) |
| 7 | Cariprazine (0.3 mg/kg p.o.) | (+)-PD 128907 (0.16 mg/kg s.c.) |
| 8 | Cariprazine (0.1 mg/kg p.o.) | (+)-PD 128907 (0.16 mg/kg s.c.) |
| 9 | Cariprazine (1.0 mg/kg p.o.) | (+)-PD 128907 (0.16 mg/kg s.c.) |
| 10 | Aripiprazole (20 mg/kg p.o.) | (+)-PD 128907 (0.16 mg/kg s.c.) |

*The doses refer to free bases.*

### Microdialysis Study

The microdialysis study included six groups of seven rats each. The test compounds cariprazine (0.1, 0.3, and 1 mg/kg), aripiprazole (20 mg/kg), or ABT-925 (3 mg/kg) were administered p.o. at the same doses and volumes as in the huddling study, 20 min prior to administration of (+)-PD 128907 (0.16 mg/kg) or saline (s.c.). Fresh formulations of the test compounds were prepared on the day of each experiment.

## Experimental Procedures

### Social Behavior (Huddling)

The protocol for the huddling study was modified from that described by Kagaya and colleagues (28). Examination of huddling behavior can be automated (by video recording) and then visually evaluated afterwards. Four rats (one from each housing cage) were randomly selected and placed in the housing room. Two rats were randomly selected to be scored for huddling behavior and distinctly marked with a non-toxic permanent marker. All four rats were then placed in a new cage (2154F; floor area 940 $cm^2$, height 21 mm; Tecniplast, Italy) with aspen bedding and left to habituate for 24 h. Water and food pellets were available *ad libitum*. On the day of the experiment, the cage was transferred to the examination room for video recordings. Following 10 min of acclimatization in the examination room, the marked rats were administered the vehicle or the test substance (p.o.) and placed back into the home cage. After 30 min, the two marked rats were administered (+)-PD 128907 (0.16 mg/kg) or vehicle (s.c.) and placed back into the cage with the remaining two naïve rats. The motor behavior of all rats was recorded on video for 90 min using the Smart 3.0 Video Tracking System (Panlab, Harvard Apparatus, USA). Huddling was defined as the total time each of the marked rats spent in direct body contact with a group of two or three other rats. The video recordings were examined and the total huddling time for each marked rat was determined by a blinded experimenter.

### Surgical Procedure

The microdialysis experiments were carried out in awake rats following a previously described protocol (33, 34). The initial stereotaxic surgery was performed under aseptic conditions. The rats were anesthetized with isoflurane using a Univentor 400 anesthesia unit (AgnThos, Lidingö, Sweden) and placed in a stereotaxic frame (David Kopf Instruments, Tujunga, CA, USA) in a flat skull position with the incisor bar set to −3.2 mm. After the induction of anesthesia but before the surgery, each animal received 5 mg/kg (s.c.) carprofen ("Rimadyl", Pfizer). An ocular lubricant gel (Viscotears, Novartis) was applied to both eyes to prevent drying of the cornea during the surgical procedure. During the operation, the body temperature of the animal was controlled using a thermometer and a heating pad maintained at 37°C by a CMA/105 temperature controller (CMA/Microdialysis, Stockholm, Sweden). The site of the surgical incision was clipped of hair, disinfected with chlorhexidine solution (1%), and injected s.c. with the local

anesthetic Marcain (bupivacaine). A midline scalp incision 1.5–2 cm in length was made and the incision was kept open using homeostatic forceps. After exposing the skull, two small holes were drilled on each side of the brain for the implantation of the guide cannulae using a fine trephine drill. Two more holes were drilled for the anchor screws. Two micro screws were then placed into the skull. One guide cannula (Eicom Corp., Kyoto, Japan) was implanted into the mPFC at the following coordinates: AP +3.2 mm; L −1.5 mm; DV −2.1 mm, at a 10° angle, such that the final DV coordinate was−5.0 mm for the tip of the microdialysis probe. The second guide cannula was implanted into the nAcc shell in the contralateral hemisphere: AP +2.2 mm; L +0.8 mm; DV −5.5 mm, such that the final DV coordinate was −7.5 mm for the tip of the microdialysis probe. This arrangement allowed both brain structures to be targeted in the same rat. The coordinates were made in reference to bregma and the dural brain surface and were determined using the Paxinos and Watson stereotaxic atlas (35). The final placement of the probes is shown in **Figure 1**.

The guide cannulae were fixed firmly to the skull surface using dental cement (Dentalon Plus, Heraeus, Germany). After completing the surgery, the animals were closely supervised and allowed to recover over the following 7 days. After surgery, the rats were housed individually in their home cages (Eurostandard III H, Tecniplast, Italy) until the day of the microdialysis experiment. During this period, the general health status of the animals was monitored regularly.

## Microdialysis Sampling

On the day of the microdialysis experiment, the microdialysis probes (Eicom A-I: 0.22 mm o.d., 50 kDa cut-off, mPFC: 3 mm membrane length, nAcc: 2 mm membrane length) were inserted into each respective guide cannula of the awake rat. The probes were perfused with artificial cerebrospinal fluid (aCSF) solution (148 mM NaCl, 4 mM KCl, 0.8 mM $MgCl_2$, 1.4 $CaCl_2$, 1.2 mM $Na_2HPO_4$, 0.3 mM $NaH_2PO_4$, pH 7.2) at a constant flow-rate of 1 µl/min. The rat was placed into a microdialysis system (CMA/Microdialysis, Stockholm, Sweden) equipped with a 2-channel swivel (TCS2-23; ALS, Tokyo, Japan), which allowed the rat to move freely within its home cage during microdialysis. The rat was allowed to habituate to the new environment for 120–150 min. Following this stabilization period, the microdialysis samples were collected in 20-min intervals. The first 3 samples were collected to determine the basal extracellular levels of neurotransmitters and their metabolites. The test compound or vehicle was then administered, followed 20 min later by a s.c. injection of (+)-PD 128907. Samples were then collected for an additional 3 h. All microdialysis experiments were performed between 9 AM and 6 PM. After the experiment, the animals were sacrificed by isoflurane overdose and dislocation of the neck. Terminal blood was collected intracardially. The brains were rapidly removed, frozen on dry ice, and stored at −80°C for additional analysis of tissue biomarkers or histological verification of the microdialysis probe placement.

## Locomotor Activity Test

The locomotor activity of rats undergoing microdialysis sampling was monitored using a single-beam activity frame (44 x 30 cm; ACTIMO 10, Shintechno, Japan) placed around the lower part of the Macrolon III cage in order to control for the effects of stress induced by handling and drug administration. This arrangement allowed for simultaneous locomotor activity recording and microdialysis sampling. The data were collected by counting and summarizing the overall activity (number of beam crossings) in 5-min intervals, which if necessary were further pooled into 20-min bins to match the frequency of microdialysis sampling.

## HPLC Analysis

The monoamines DA and 5-HT were measured by ion-exchange narrow bore column liquid chromatography with electrochemical detection as described previously (34). The HPLC system (HTEC-500, Eicom, Japan) included a pulse-free microflow pump, a degasser, and an amperometric detector equipped with a graphite electrode operating at +0.45 V vs. an Ag/AgCl reference electrode. Samples were injected using a CMA/200 Refrigerated Microsampler (CMA/Microdialysis) and the chromatograms were recorded and integrated using a computerized data acquisition system (DataApex, Prague, Czech Republic). DA and 5-HT were separated using a 200 x 2.0 I.D. mm column (CAX, Eicom, Japan). The mobile phase consisted of 0.1 M phosphate buffer at pH 6.0, 30 mM potassium chloride, and 28% (v/v) methanol. The detection limit (signal-to-noise ratio = 3) for DA and 5-HT was 0.5 fmol per 10 µl injected onto the column. The concentration of the acidic metabolites, DOPAC and HVA, in 3–5 µl microdialysis samples was determined using a second HPLC system with electrochemical detection (33, 34). Briefly, the HPLC system (HTEC-500, Eicom Corp., Kyoto, Japan) included a pulse-free microflow pump, a degasser, and an amperometric detector equipped with a glassy-carbon electrode operating at +0.45 V vs. an Ag/AgCl reference electrode. Samples were injected using a CMA/200 Refrigerated Microsampler (CMA/Microdialysis). The chromatograms were recorded and integrated using a computerized data acquisition system (DataApex, Prague, Czech Republic). DOPAC and HVA were separated using a 150 x 2.1 I.D. mm column (CA5-ODS, Eicom Corp., Kyoto, Japan). The mobile phase consisted of 0.1 M phosphate buffer at pH 6.0, 0.13 mM EDTA, 2.3 mM sodium-1-octanesulfonate, and 20% (v/v) methanol.

## Data Presentation and Analysis

Raw data were entered into data files using a standard spreadsheet program (Microsoft Excel) and statistical analysis was performed using Prism 9 statistical software (GraphPad Software, USA) and differences are considered to be statistically significant at the $P < 0.05$ level. Values for figures showing the time courses of behavioral and microdialysis variables are presented as mean ± standard error of mean (SEM). The huddling behavior was counted in seconds and summarized in 10-min bins during 90 min post-treatment with (+)-PD 128907. The interaction of time and treatment between the (+)-PD 128907-treated group and the drug-treated groups were

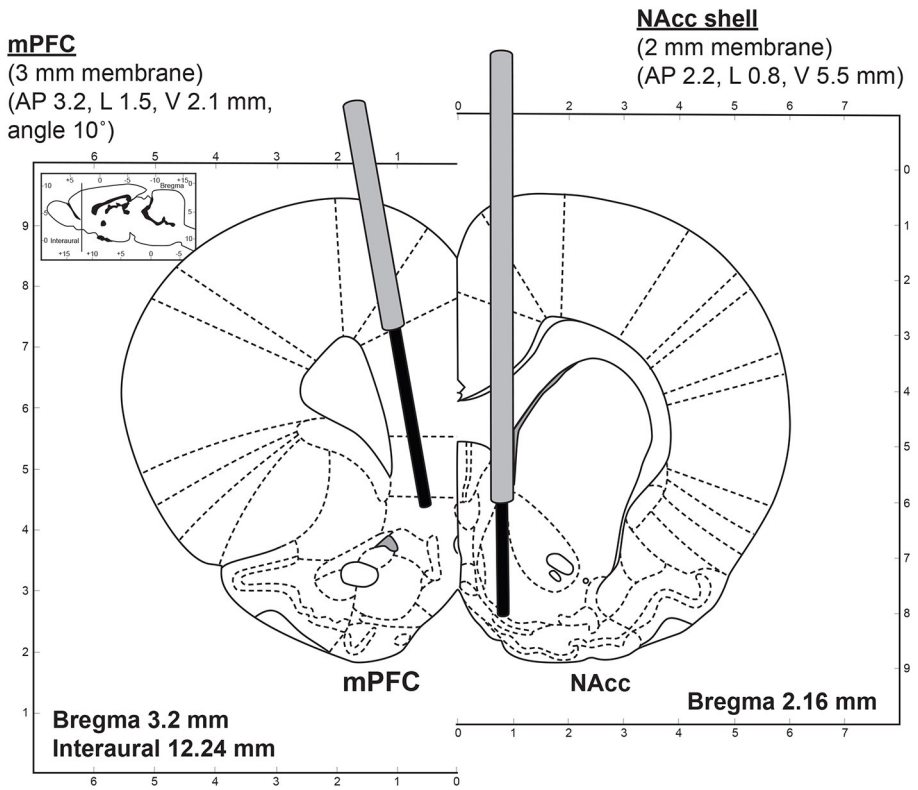


**FIGURE 1 |** Dual-probe microdialysis—an illustration of the stereotaxic placement of the microdialysis probes into the mPFC (3 mm membrane length) and nAcc shell (2 mm membrane length) at coordinates determined using the rat brain atlas (35).

compared by the two-way RP ANOVA followed by Bonferroni's multiple comparison test. Differences between the saline and drug-treated groups, as well as the (+)-PD 128907-treated group and the (+)-PD 128907+drug-treated groups in 10 and 20 min bins, respectively, were analyzed by one-way ANOVA followed by Šidák's multiple comparison test. The figures are presented as box-and-whiskers including the median values, 25 and 75% values (boxes), and minimum and maximum values (whiskers). The normal distribution of data was evaluated by D'Agostino & Pearson test.

For graphic presentation of the microdialysis data, concentrations of monoamines and metabolites over time were expressed as the percentage of the basal concentrations at time 0 min. The mean (±SEM) basal levels were calculated from the three samples collected before drug treatment. The basal levels were compared using a Kruskal-Wallis test followed by Dunn's multiple comparison test. Differences between the treatments and the interaction of time and treatment were analyzed by repeated measures two-way ANOVA followed by Bonferroni's post-test and using the Geisser-Greenhouse correction for non sphericity of variables. The overall effects of the treatments were expressed as the differences in relative $AUC_{(0-180\,min)}$ for each treated group compared to the theoretical 100% control values. The differences between the relative $AUC_{(0-180\,min)}$ for the groups were analyzed by Kruskal-Wallis followed by Dunn's multiple comparison test. The figures are presented as box-and-whiskers with median, 25 and 75% and minimum-maximum values.

# RESULTS

## Huddling Behavior

The effect over time of the DA $D_3$ receptor-preferring agonist (+)-PD 128907 (0.16 mg/kg, s.c.) on the disruption of huddling behavior of two drug-treated rats, compared to two naïve rats habituated in the same cage, is shown in **Figure 2**.

The control, saline-treated rats showed a typical pattern of being tightly attached to each other in a clump, typically in one corner of the cage, during the entire recording period (600 s). Treatment with (+)-PD 128907 induced an immediate and significant ($P < 0.001$) reduction of huddling behavior during the first 10- and 20-min periods, as shown in **Figure 2A**. Thereafter, the treated rats returned to socializing with the naïve group. The time spent huddling between the groups was significantly different for both the treatment [$F_{(1, 14)} = 28.98$; $P < 0.001$] and the interaction of time and treatment [$F_{(8, 112)} = 37.84$; $P < 0.001$] as revealed by two-way repeated measures ANOVA followed by Bonferroni's post-test. Pre-treatment with cariprazine attenuated the disrupted huddling induced by (+)-PD 128907 during the first 10 min post-treatment, as shown in **Figures 2B**, **3A**. The overall time spent huddling during the 90-min recording period between the groups was significantly

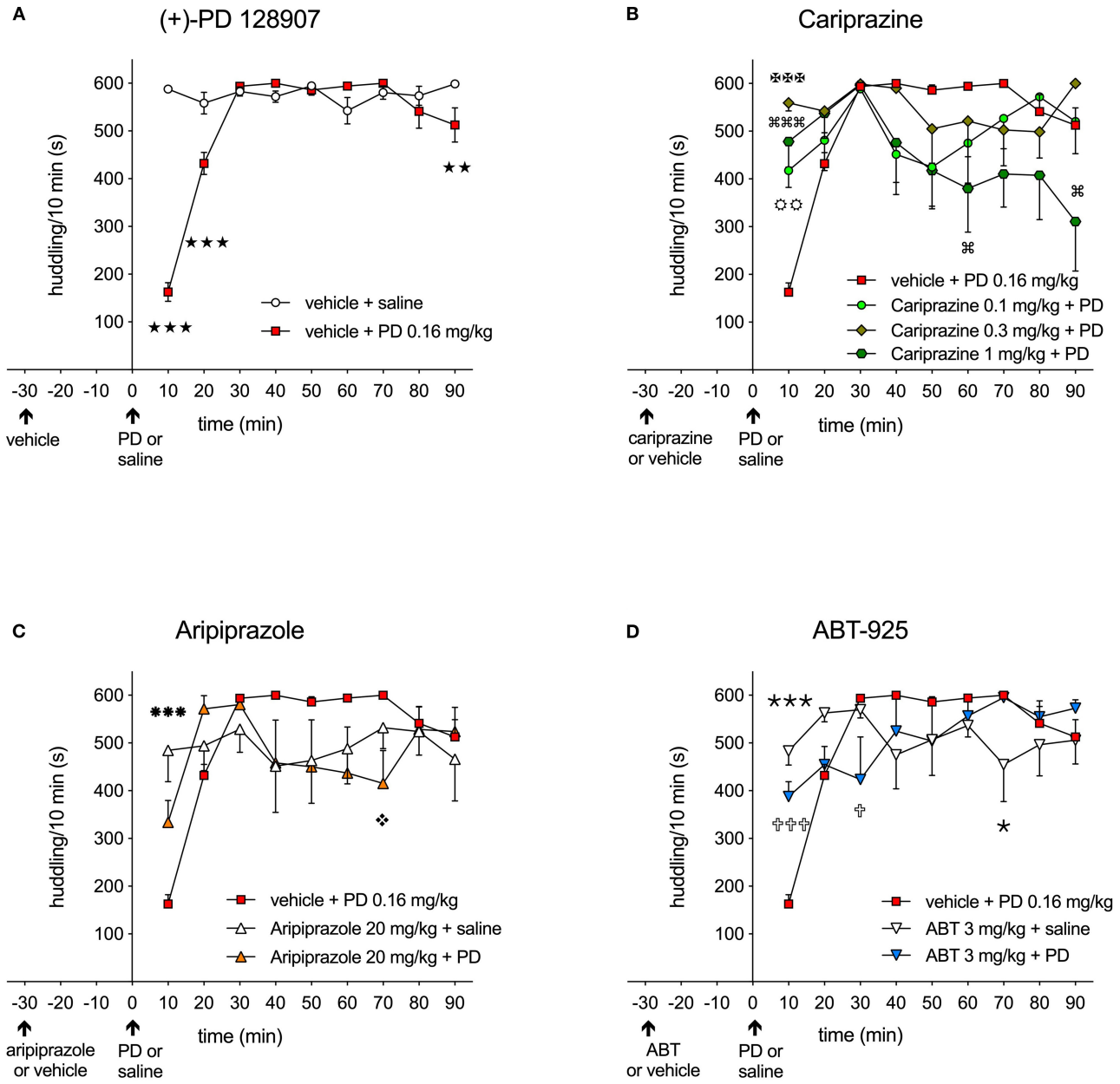


**FIGURE 2 | (A)** Effect of the $D_3/D_2$ receptor agonist (+)-PD 128907 (0.16 mg/kg s.c.) on disruption of huddling behavior in rats over 10-minute intervals compared to the saline-injected group (stars); (★★★) $P < 0.001$, (★★) $P < 0.01$; **(B)** The effect of cariprazine on attenuating the disruption of huddling induced by (+)-PD 128907; (☼☼) $P < 0.01$ for the 0.1 mg/kg dose (circles), (✠✠✠) $P < 0.001$ for the 0.3 mg/kg dose (Maltese crosses), (⌘⌘⌘) $P < 0.001$, (⌘) $P < 0.05$ for the 1 mg/kg dose (square loops); **(C)** The effect of aripiprazole (20 mg/kg, p.o.) on attenuating the disrupted huddling induced by (+)-PD 128907; (✱✱✱) $P < 0.001$ for aripiprazole + saline (snowflakes) vs. PD, (❖) $P < 0.05$ for aripiprazole + PD (diamonds); **(D)** The effect of ABT-925 (3 mg/kg p.o.) on attenuating the disrupted huddling induced by (+)-PD 128907; (★★★) $P < 0.001$, (★) $P < 0.05$ for ABT + saline (thin stars) vs. PD; (✝✝✝) $P < 0.001$,(✝) $P < 0.05$ for ABT + PD (crosses); mean ± SEM, $n = 8$; two-way repeated measures ANOVA followed by Bonferroni's multiple comparison test. ABT, ABT-925; PD, (+)-PD 128907.

different for the interaction of time and treatment [$F_{(24, 224)} = 3.105$; $P < 0.001$] but not for the treatment [$F_{(3, 28)} = 1.99$; P = 0.139]. However, for the first 10-min period, there was a marked and significant attenuation of disrupted huddling for both the higher doses of cariprazine ($P < 0.001$) as well as the lowest tested dose ($P < 0.01$). In addition, the highest dose of cariprazine tended to disrupt huddling at the end of the recording period (between 60 and 90 min) compared to the group treated with (+)-PD 128907 alone (**Figure 2B**).

The effects of aripiprazole and the selective DA $D_3$ receptor antagonist ABT-925 on disrupted huddling induced by (+)-PD 128907 are shown in **Figures 2C,D**, respectively. Aripiprazole

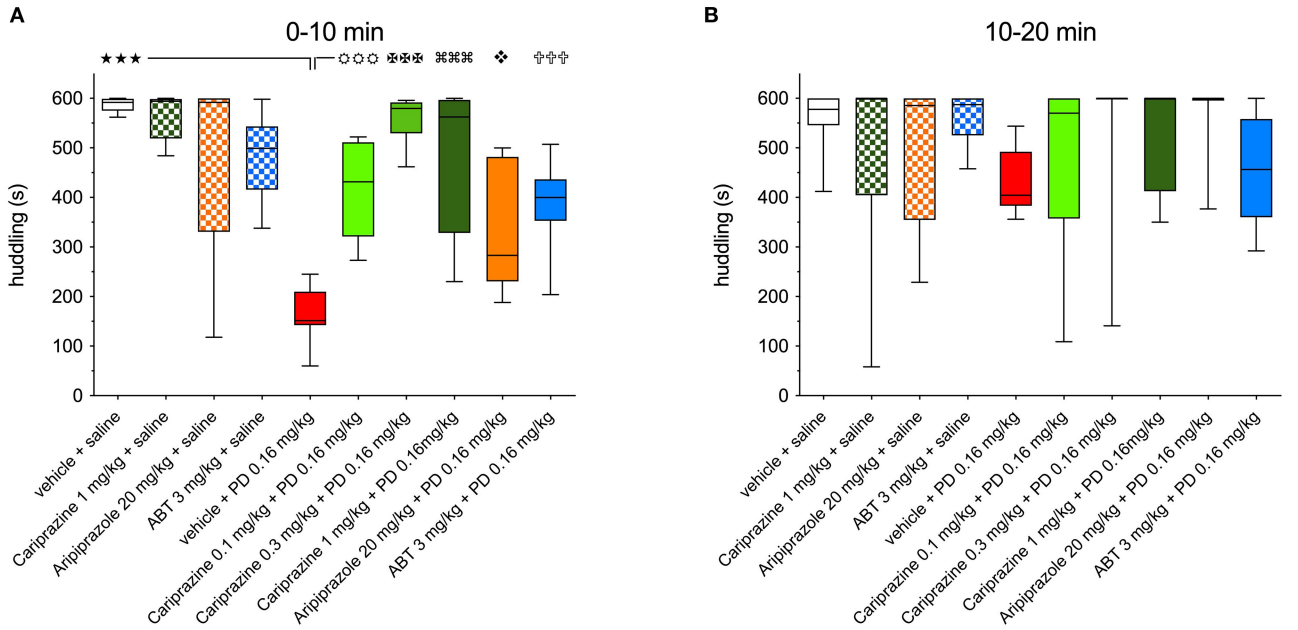


**FIGURE 3 |** The effects of cariprazine, aripiprazole and ABT-925 on the (+)-PD 128907-induced disrupted huddling during **(A)** the first 0-10-minute period and **(B)** the second 10–20 min period post-treatment; mean ± SEM, $n = 8$; (★★★) $P < 0.001$; (☼☼☼) $P < 0.001$, (✠✠✠) $P < 0.001$, (⌘⌘⌘) $P < 0.001$ (❖) $P < 0.05$, (✞✞✞) $P < 0.001$, one-way ANOVA followed by Šidak's multiple comparison test.

tended to attenuate the effect of (+)-PD 128907 during the first 10-min period, but this effect was not statistically significant (**Figure 2C**). Notably, aripiprazole showed a tendency to disrupt the huddling at the end of the recording period at 70 min ($P < 0.05$) compared to the group treated with (+)-PD 128907 alone, similarly to the highest dose of cariprazine. The time spent huddling was significantly different for the interaction of time and treatment [$F_{(16, 168)} = 4.391$; $P < 0.001$] but not for treatment with aripiprazole [$F_{(2, 21)} = 0.012$; $P = 0.834$]. However, the effect of aripiprazole was statistically significant when comparing the mean levels of huddling at 10-min intervals for all tested compounds by one-way ANOVA followed by a Šidak's multiple comparison test (**Figure 3A**). ABT-925 significantly ($P < 0.001$) but not completely attenuated (+)-PD 128907-induced disruption of huddling during the first 10 min post-treatment (**Figure 2D**). The overall time spent huddling during the 90-min recording period between groups was significantly different for the interaction of time and treatment [$F_{(16, 168)} = 4.488$; $P < 0.001$] but not for the treatment [$F_{(2, 21)} = 0.012$; $P = 0.988$].

Comparisons of the ability of all three test compounds to attenuate the (+)-PD 128907-induced disruption of huddling during the first and second 10-min post-dose intervals are shown in **Figures 3A,B**, respectively.

(+)-PD 128907 induced a marked and significant ($P < 0.001$) disruption of huddling during the first 10-min period. This can be compared to pretreatment with cariprazine, ABT-925 or aripiprazole before s.c. saline, which did not significantly impact time spent huddling compared to the vehicle + saline group. However, pretreatment with cariprazine or ABT-925 before (+)-PD 128907 administration markedly ($P < 0.001$) attenuated the (+)-PD 128907-induced disruption of huddling. Aripiprazole produced a similar but slightly weaker ($P < 0.01$) effect. Finally, as already shown in **Figure 2**, (+)-PD 128907-induced disruption of huddling was short lasting, as the rats returned to their social behavior and formed a clump (huddle) during the second 10-min period (**Figure 3B**). ABT, ABT-925; PD, (+)-PD 128907.

## Dual-Probe Microdialysis

### Basal Levels of DA, DOPAC and HVA in the Rat mPFC and nAcc Shell

The basal concentrations of DA and its metabolites were calculated from the mean values of three fractions collected from each individual animal during the pre-drug period (−60 to 0 min) and then calculated as a mean ± standard error of the mean (SEM) for each treated group, $n = 7$ rats. The basal extracellular levels of DA, DOPAC, and HVA (expressed in fmol/10 μl) in the microdialysates from vehicle and drug-treated rats are presented in **Supplementary Table S1**.

The mean basal extracellular levels of DA, DOPAC, and HVA of vehicle and drug-treated groups were compared using Kruskal-Wallis test followed by Dunn's multiple comparison test. There were no significant differences between the groups when each group was compared to all other groups.

### Effects of Cariprazine, Aripiprazole, and ABT-925 on DA Levels in the Rat mPFC and nAcc Shell Following (+)-PD 128907 Challenge

Administration of (+)-PD 128907 in rats pretreated with vehicle decreased DA levels (**Figures 4**, **5A,B**) in both regions. The most prominent effect was observed 40 min after (+)-PD 128907

injection, when the DA levels decreased to 57 and 45% in the mPFC and nAcc shell, respectively. In addition, the DA levels in the mPFC remained low until the end of the sampling period, whereas accumbal DA levels tended to return to pre-drug levels. The slight increases in DA levels in fractions collected at 0 and 20 min (compared to the basal samples collected at −60 to −20 min) were most likely caused by the handling stress and administration of drugs at these time intervals (arrows) as also confirmed by recordings of locomotor activity (see **Supplementary Material**).

Administration of cariprazine 20 min before (+)-PD 128907 administration caused a dose-dependent attenuation of (+)-PD 128907-induced decreases in DA levels in the mPFC (**Figure 4A**) and nAcc shell (**Figure 4B**).

While the lowest dose of 0.1 mg/kg had no effect, the intermediate dose of 0.3 mg/kg tended to attenuate the DA decrease in the mPFC at 40 min ($P < 0.05$) and a had minor effect in the nAcc shell at 180 min ($P < 0.01$). The highest dose of 1 mg/kg significantly ($P < 0.01$) prevented the (+)-PD 128907-induced DA decrease in the mPFC and completely abolished ($P < 0.001$) the effect of (+)-PD 128907 in the nAcc shell during the first 40-60 minutes and the end of the sampling period (140–180 min). In the mPFC, there was no significant difference between the groups for the treatment [$F_{(3, 24)} = 2.275$; P = 0.1056], but the interaction of time and treatment was significant [$F_{(36, 288)} = 2.914$; $P < 0.001$]. In the nAcc shell, there was a significant difference between the groups for both the treatment [$F_{(3, 24)} = 6.082$; $P < 0.01$] and the interaction of time and treatment [$F_{(36, 288)} = 3.743$; $p < 0.001$].

In the mPFC, ABT-925 tended to diminish the effect of (+)-PD 128907, particularly in the later stages of recording. However, the effect was only significant ($P < 0.05$) at 80 and 160 min post (+)-PD 128907 injection. Aripiprazole had no significant effects (**Figure 4C**). In the mPFC, there was no significant difference between the groups for the treatment [$F_{(2.18)} = 2.648$; P= 0.0981] or the interaction between time and treatment [$F_{(264, 216)} = 1.059$; $P < 0.3929$]. In the nAcc shell, there was a significant difference between groups for both treatments [$F_{(2.18)} = 13.69$] but not for the interaction between time and treatment [$F_{(24, 216)} = 1.183$; P = 0.259].

The overall effects of pretreatment with cariprazine, aripiprazole, and ABT-925 on (+)-PD 128907-induced changes in the extracellular DA levels in the mPFC and nAcc shell are shown in **Figures 5A,B**, respectively.

The decreased DA levels were expressed as the relative area under the curve ($AUC_{(0-180\,min)}$) for each treated group subtracted from the theoretical $AUC_{(0-180\,min)}$ value (900%), which corresponds to nine 20-min basal samples from each group. The DA $D_3$-receptor-preferring agonist (+)-PD 128907 decreased DA levels by 37.3 and 23.4% in the mPFC and nAcc shell, respectively. In the mPFC (**Figure 5A**), only the highest dose of cariprazine significantly ($P < 0.05$) diminished the effect of (+)-PD 128907, whereas aripiprazole had no significant effect. ABT-925 trended toward reversing the effect of (+)-PD 128907 on DA levels, although this was not statistically significant. In the nAcc shell (**Figure 5B**), all three compounds effectively counteracted the effect of (+)-PD 128907 on DA, with the highest dose of cariprazine having the most potent effect ($P < 0.001$), followed by ABT-925 ($P < 0.01$) and aripiprazole ($P < 0.05$).

### Effects of (+)-PD 128907 and the Pretreatment With Cariprazine, Aripiprazole and ABT-925 on Levels of DOPAC and HVA in the mPFC and nAcc Shell of Awake Rats

Administration of (+)-PD 128907 in rats pretreated with vehicle did not induce long-lasting effects on DOPAC or HVA levels in either the mPFC or nAcc. As with DA, the most prominent effects were observed in the nAcc shell at 40 min after (+)-PD 128907 administration, with a 28% decrease for DOPAC and a 15% decrease for HVA. DOPAC and HVA returned to the basal levels within the following 60 min (data not shown).

The overall effects of pretreatment with cariprazine, ABT-925, and aripiprazole in combination with (+)-PD 128907 on DOPAC and HVA levels in the mPFC and nAcc shell are shown in **Figure 6**.

In the mPFC, the relative $AUC_{(0-180\,min)}$ values for DOPAC and HVA were significantly ($P < 0.001$) different for the highest dose of cariprazine relative to (+)-PD 128907 alone (**Figures 6A,C**). In the nAcc shell, significant increases in the $AUC_{(0-180\,min)}$ values for DOPAC and HVA were observed for two higher doses of cariprazine ($P < 0.05$ for 0.3 mg/kg, $P < 0.001$ for 1 mg/kg), as well as for aripiprazole ($P < 0.01$ for DOPAC; $P < 0.001$ for HVA) relative to (+)-PD 128907 alone (**Figures 6B,D**).

### Effects of (+)-PD 128907 and Pretreatment With Cariprazine, Aripiprazole, and ABT-925 on Locomotor Activity of Rats Undergoing Microdialysis Sampling

The locomotor activity of rats was recorded simultaneously with microdialysis sampling in order to assess the effects of handling during drug administration and to identify other sources of stress potentially affecting the microdialysis data. The effects of cariprazine, aripiprazole, or ABT-925 pretreatment in combination with (+)-PD 128907 on the locomotor activity of rats undergoing microdialysis are shown in the supplementary data (**Supplementary Figure S1A** for cariprazine, **Supplementary Figure S1B** for aripiprazole and ABT-925). Following administration of the test compounds followed by (+)-PD 128907, there was an initial increase in motor activity during the first 20-min period, followed by a slowing of motor activity until it reached similar levels as shown by habituated rats at the start of the microdialysis sampling.

The forward movement of rats in their home cages was recorded in 5-min bins. Temporal increases in locomotor activity were observed between −20 to 0 min and 0 to 20 min. The differences between the drug-treated groups compared to the (+)-PD 128907 group during these periods are most likely caused by the stress induced by handling and administration of the test compounds per orally followed by subcutaneous (+)-PD 128907.

## DISCUSSION

Dysregulated dopamine signaling is central to many models describing the pathophysiology of schizophrenia (36). In line with the corticolimbic distribution of $D_3$ receptors, their role has

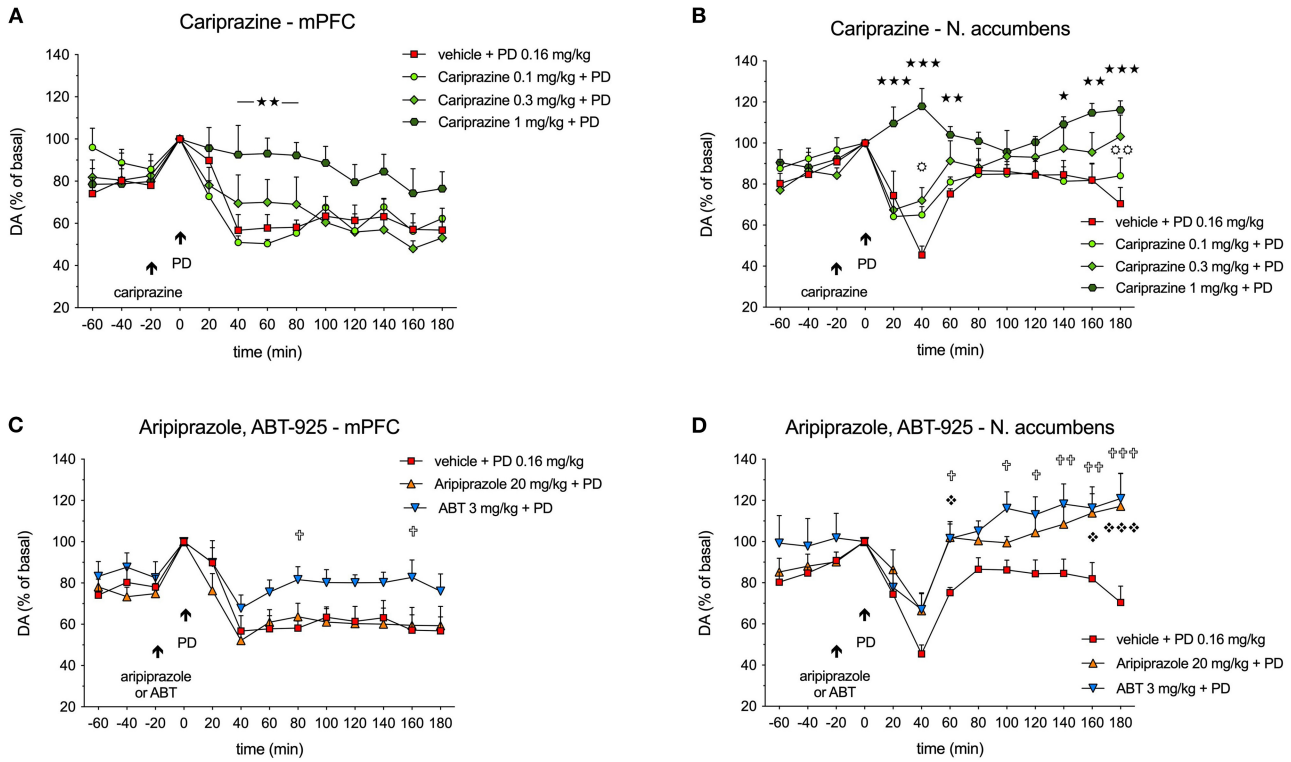


**FIGURE 4 |** Effects of **(A,B)** cariprazine, and **(C,D)** aripiprazole and ABT-925 on (+)-PD 128907-induced decreases in extracellular DA levels in the mPFC and nAcc shell regions of awake rats; (★★★) $P < 0.001$, (★★) $P < 0.01$, (★) $P < 0.05$ for cariprazine (1 mg/kg) + PD vs. PD alone (stars); (☼☼) $P < 0.01$, (☼) $P < 0.05$ for cariprazine (0.3 mg/kg) + PD vs. PD alone group (circles); (❖❖❖) $P < 0.001$, (❖) $P < 0.05$ for aripiprazole + PD vs. PD alone (diamonds); (✝✝✝) $P < 0.001$, (✝✝) $P < 0.01$, (✝) $P < 0.05$ for ABT + PD vs. PD alone (crosses); mean ± SEM, $n = 7$; two-way repeated measures ANOVA followed by Bonferroni's multiple comparison test. ABT, ABT-925; PD, (+)-PD 128907.

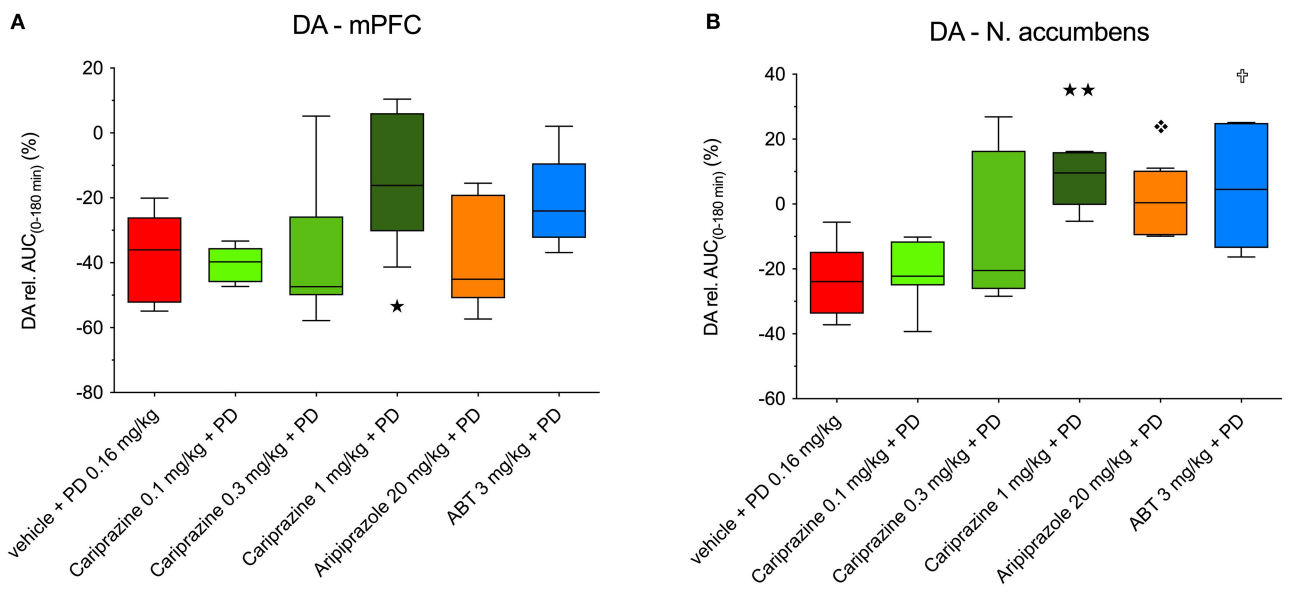


**FIGURE 5 |** The overall propensity of cariprazine, aripiprazole and ABT-925 to counteract the (+)-PD 128907-induced decrease in basal extracellular levels of DA in the **(A)** mPFC and **(B)** nAcc shell of awake rats. (★★) $P < 0.01$, (★) $P < 0.05$ for cariprazine (1 mg/kg) + PD; (❖) $P < 0.05$ for aripiprazole + PD; (✝) $P < 0.05$ for ABT-925 + PD; Kruskal-Wallis test followed by Dunn's multiple comparison test. ABT, ABT-925; PD, (+)-PD 128907.

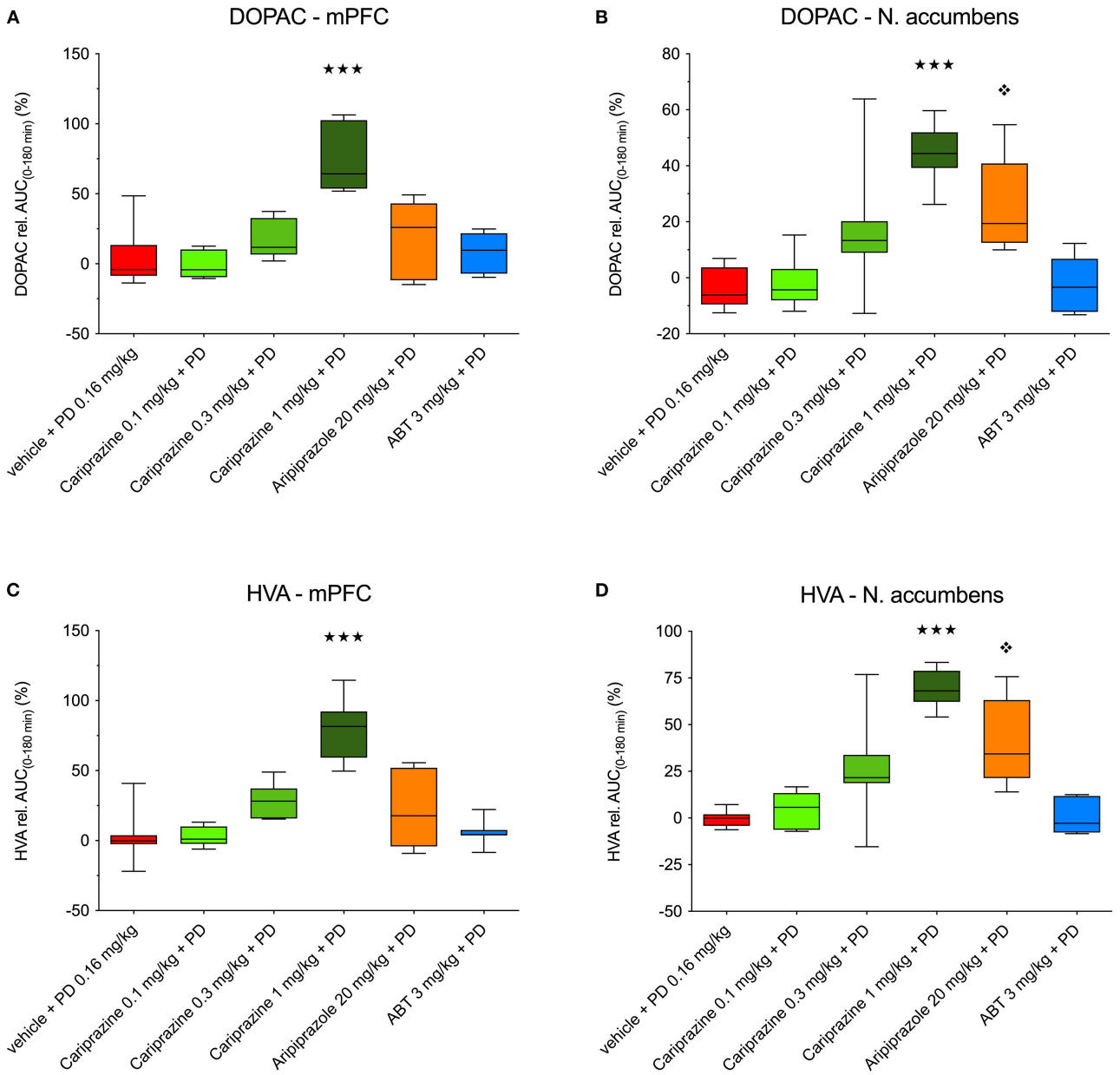


**FIGURE 6 |** The overall effects of (+)-PD 128907 and the combined treatment with (+)-PD 128907 and cariprazine, aripiprazole or ABT-925 on DOPAC **(A,B)** and HVA **(C,D)** levels in the mPFC and nAcc shell of the awake rats. (★★★) $P < 0.001$, for cariprazine (1 mg/kg) + PD; (❖) $P < 0.05$ for aripiprazole + PD; Kruskal–Wallis test followed by Dunn's multiple comparison test. ABT, ABT-925; PD, (+)-PD 128907.

long been studied in brain areas modulating cognitive functions or emotions. Interestingly, the extracellular DA level is twice as high in the nucleus accumbens of mice lacking the $D_3$ receptor than in wild type animals (37), and pharmacological blockade of $D_3$ receptors by selective antagonists increases extracellular levels of DA in the prefrontal cortex (38), a major regulator of the midbrain dopamine system. Distribution of the dopamine $D_3$ receptors is mainly restricted to the limbic areas (Islands of Calleja, nucleus accumbens and ventral part of caudate nucleus) of the human and rodent brain, though low level of $D_3$ receptor expression has also been described for cortical regions, particularly in the frontal cortex (20, 39–42). Here we report the first study of on dopamine $D_3$ receptor associated behavior (i.e., huddling) with concurrent monitoring of extracellular dopamine in the mPFC and nAcc by dual microdialysis in freely moving rats.

In the huddling study, the $D_3$ receptor-preferring agonist (+)-PD 128907 induced a marked (−72%) disruption of huddling behavior in the first 10 min after administration. Even the lowest dose of cariprazine (0.1 mg/kg) was more potent than

aripiprazole at counteracting the disruption of huddling induced by (+)-PD 128907. Disruption of huddling behavior was almost completely abolished at a cariprazine dose of 0.3 mg/kg. Likewise, ABT-925, and to a lesser extent aripiprazole, were effective in blocking the (+)-PD 128907-induced effect. Pretreatment with cariprazine, ABT-925, and aripiprazole in the absence of (+)-PD 128907 had no effects on huddling duration compared to the vehicle-treated group. Because huddling behavior is believed to be mediated via DA $D_3$ receptors (28–30), these behavioral results provide further evidence for cariprazine's preferential action at DA $D_3$ receptors over $D_2$ receptors *in vivo*.

Microdialysis sampling showed that cariprazine antagonized the effects of (+)-PD 128907 on basal extracellular levels of DA in both the mPFC and nAcc shell of awake rats. Pretreatment with cariprazine at the highest dose prevented the (+)-PD 128907-induced decrease in DA levels in the mPFC at various time points, as did ABT-925. Aripiprazole had no significant effect at any time point tested in this brain region. In the nAcc shell, all three compounds significantly reduced the (+)-PD 128907-induced decrease in DA levels. Levels of the DA metabolites DOPAC and HVA were not affected by (+)-PD 128907; however, levels of DOPAC and HVA were markedly elevated in the mPFC of rats treated with cariprazine (1 mg/kg) in (+)-PD 128907-treated rats. In the nAcc shell, DOPAC and HVA levels were also increased in rats treated with the lower 0.3 mg/kg dose of cariprazine, as well as in rats treated with aripiprazole in (+)-PD 128907-treated groups. These data suggest that $D_3$ receptors may have a predominant role in regulating DA neurotransmission in the mPFC relative to $D_2$ receptors, with $D_3$ preferring agents having a greater impact in this region as compared to $D_2$ receptor-preferring compounds. On the other hand, in the nAcc $D_2$ and $D_3$ receptors could both be involved as $D_3$ receptor-preferring as well as $D_2$ receptor-preferring agents affected DA neurotransmission.

The different involvement of dopamine $D_2$ and $D_3$ receptors in mediating neuronal responses has been suggested for the mPFC based on behavioral, as well as electrophysiology findings. Hodge et al. investigated the role of dopamine receptors in a reinforced response paradigm upon direct bilateral mPFC drug injection and found that the $D_2$ antagonist raclopride did not modify the delayed response onset when co-administered with the $D_{2/3}$ agonist quinpirole (43). Consistently, direct bilateral infusion of the $D_3$ antagonists S33084 and SB277011 into the frontal cortex dose-dependently reversed the deficit in recognition induced by a delay, while the $D_2$ antagonist, L741,626 had no effect. Moreover, such social recognition improving action of S33084 was specific to cortex as its injection into the nucleus accumbens was ineffective (44). Further, a bilateral injection of S33084 into the PFC prefrontal cortex increased the social novelty discrimination and novel object recognition (NOR) in rats, whereas no such effect was seen after intranigral injection, whereas the injection of L741626, a preferential dopamine $D_2$ antagonist into the PFC (but not striatum) caused impairment in the NOR (45). Also, a distinct subset of pyramidal cells expressing dopamine $D_3$ receptors has been described recently for the mPFC that may indirectly contribute to the predominant $D_3$ receptor mediated DA neurotransmission in this cortical area. Within these neurons, dopamine $D_3$ receptors via low-voltage-activated $Ca_V3.2$ calcium channels localized on the axon initial segment regulate the ability of glutamatergic cells to generate high-frequency action potential bursts. Since neither $D_2$, nor other dopamine receptors apart from the $D_3$ are involved in regulating the excitability of this mPFC neuronal population, the $D_3$ receptors seem to have unique actions in the mPFC (42).

The time courses of the behavioral and neurochemical effects of cariprazine were somewhat disparate in this study. The reasons for this disparity remain elusive. Disruption of huddling by (+)-PD 128907 occurred only during the first 10–20 min of the observational period, which is in agreement with the results of Kagaya et al. (28), while the extracellular DA level lowering effect of (+)-PD 128907 reached its maximum between 20–40 min after administration, in agreement with the results of Pugsley et al. (21) who described the short acting duration of (+)-PD 128907 for midbrain dopaminergic cells. Systemic dosing with the $D_3$ agonist compound robustly, but transiently, suppressed the firing and bursting activity of dopamine neurons in the ventral tegmental area and pars compacta region of the substantia nigra and the spontaneous firing of dopamine neurons is restored within 5–10 min to 70–80% of the baseline firing (46, 47). These electrophysiology results are in line with the time-course of the behavioral effect of the current study as well as the data of former studies describing the effect of (+)-PD 128907 in induction of yawning or disruption of huddling as the latter also take place within 20–30 min (26, 28).

Data on locomotor activity from freely moving animals during microdialysis were collected that might have provided some hints on this discrepancy. However, the temporal increases in locomotor activity observed from −20 to 0 min and from 0 to 20 min were most likely due to the stress induced by handling and test compound administration. These stressors may have masked the effect of (+)-PD 128907 on social behavior observed in habituated rats. Nevertheless, the neurochemical changes by (+)-PD 128907 were evident in the microdialysis experiments and provided a solid basis for studying the effects of dopamine $D_3$ receptor partial agonist and antagonist compounds for restoring or even further increasing DA levels in the mPFC and nAcc, respectively.

## CONCLUSION

Taken together, these data provide further evidence for cariprazine's preferential action *via* DA $D_3$ receptors over $D_2$ receptors in the rat brain *in vivo*. Cariprazine showed greater efficacy and potency than did aripiprazole at restoring a $D_3$ receptor-mediated behavior (huddling). Further evidence for cariprazine's DA $D_3$ receptor mechanism was its ability to counteract the effects of the $D_3$ receptor-preferring agonist (+)-PD 128907 on decreased DA levels in both the rat mPFC and nAcc areas (unlike aripiprazole, which was only effective in the nAcc). These findings suggest that under conditions of cortical dopaminergic hypofunctionality, cariprazine can reverse this deficit. Cariprazine may therefore offer therapeutic benefits against a broad range of symptoms in schizophrenia and related disorders associated with reduced

cortical DA neurotransmission, including cognitive deficits and negative/depressive symptoms.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

All animal experiments and protocols were approved by the Regional Ethical Committee at the Stockholm County court, following the directives of the Swedish Animal Welfare Act 1988:534 and complying with the Directive 2010/ 63/ EU (Council of the European parliament) The Guide for the Care and Use of Laboratory Animals and the Principles of Laboratory Animal Care (NIH publication No. 85-23).

## AUTHOR CONTRIBUTIONS

NA, BK, BF, and JK were involved in the study design, analysis, and interpretation of data, the decision to present the results, and contributed to writing the manuscript. JK, F-HW, FI, and SY were involved in all experiments. All authors contributed to the article 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/fpsyt.2021.801641/full#supplementary-material

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**Conflict of Interest:** JK, F-HW, FI, and SY are employees of Pronexus Analytical AB. NA is an employee of Allergan (AbbVie). BK and BF are employees of Gedeon Richter Plc.

frontiers in Psychiatry

ORIGINAL RESEARCH
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# Early Clinical Effects of Novel Partial D3/D2 Agonist Cariprazine in Schizophrenia Patients With Predominantly Negative Symptoms (Open-Label, Non-controlled Study)

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**Background:** Because of limited efficacy of antipsychotics against negative symptoms in schizophrenia new drugs with wider spectrums of clinical efficacy are very desirable. The newer 3rd generation antipsychotic cariprazine presents the unique mode of action acting as partial agonist predominantly for dopamine D3- and in lesser extent D2-receptors. Cariprazine is found to be effective in the treatment of negative symptoms in schizophrenia comparing to second generation antipsychotic risperidone.

**Objectives:** To evaluate initial effects of cariprazine in schizophrenia patients with predominantly negative symptoms.

**Design and Patients:** Open-label, non-controlled study included 60 adult schizophrenia patients (F20 on ICD-10, 49% males) with predominantly negative symptoms (Positive and Negative Syndrome Scale, S factor score for negative and positive symptoms, PANSS-FSNS $\geq$ 15 and PANSS-FSPS $<$ 19) treated with cariprazine (starting daily dose 1.5 mg followed by upward titration by 1.5 mg weekly up to 6 mg if needed) were assessed with PANSS, CAINS (The Clinical Assessment Interview for Negative Symptoms), CDSS (Calgary Depression Scale for Schizophrenia), and SAS (Simpson-Angus Scale for Extrapyramidal Symptoms) scales at baseline and on week 1, 2, and 4.

**Results:** Most patients (75%) improved during 28 days of cariprazine treatment. At the end of assessment (day 28) mean starting total scores for negative symptoms on PANSS-NS and CAINS scales significantly ($p < 0.05$) reduced by 4.3 and 4.9, respectively, with no significant changes in depression symptoms (CDSS). Cariprazine tolerability was very good, only four patients discontinued because of TEAEs (akathisia, insomnia).

**Conclusions:** The results of this study suggest early effect of cariprazine on negative symptoms at least in some schizophrenia patients with predominantly negative symptoms starting from 1 to 2 weeks of treatment and could be useful for determination of early clinical predictors for efficacy. Considering limitations of open-label design with no control groups these data need to be confirmed.

**Keywords: schizophrenia, negative symptoms, pharmacotherapy, clinical effects, cariprazine**

## INTRODUCTION

Negative symptoms are regarded as a key factor affecting both the clinical and social prognosis of the schizophrenia, more important than positive symptoms (1, 2). Despite certain achievements in improving the efficacy and safety of treatments for schizophrenia driven by the development of atypical antipsychotics, pharmacological management of negative symptoms remains a challenge that, in contrast to treating positive and affective disturbances, is beyond the capacity of most available methods of pharmacotherapy (3, 4).

To date, the most convincing and promising data in the context of pharmacological management of negative symptoms have been obtained in clinical trials of a novel third-generation antipsychotic cariprazine. Cariprazine belongs to the class of partial dopamine agonists and has a unique 10-fold greater affinity for D3 receptors than for D2 receptors (unlike other third-generation drugs aripiprazole and brexpiprazole) (5, 6). Cariprazine is approved in Europe and the Russian Federation as an acute and maintenance treatment for schizophrenia in adult patients when given at a daily dose of 1.5–6 mg.

According to available publications, cariprazine is the only antipsychotic drug with a proven effect on primary negative symptoms that is verified according to the current methodological requirements (4, 7). The evidence for the efficacy of cariprazine in the treatment of negative symptoms was obtained in a 26-week, randomized, double-blind, comparative (with no placebo control) study of cariprazine 4.5 mg/day and risperidone 4 mg/day in 460 adult patients with predominant and persistent negative symptoms (8). The statistically significant superiority of cariprazine over risperidone in reducing negative symptoms (PANSS negative symptom factor score) was observed from week 14 of therapy, and it increased steadily until the end of treatment. Cariprazine has been shown to have a superior effect on the majority (five out of seven) of negative symptoms according to the PANSS scale score, including blunted affect, emotional withdrawal, passive/apathetic social withdrawal, poor rapport, difficulty in abstract thinking (9).

However, according to published data, differences between cariprazine and risperidone in terms of the change from baseline in PANSS negative symptom subscale scores over time were observed as early as at week 1 of therapy. Moreover the differences between the two treatments showed further steady growth, although not being statistically significant up to week 14 of therapy (8, 9). Hence, it may be assumed that cariprazine exerts its initial therapeutic effect on negative symptoms from the first 1-2 weeks of therapy. If this hypothesis is confirmed, this opens up perspectives for further identification of significant early clinical predictors of the efficacy of cariprazine in the first weeks of treatment that correlate with the long-term treatment prognosis in patients with schizophrenia with predominantly negative symptoms.

To confirm this assumption, this study was conducted to assess the initial effect of cariprazine at standard doses (1.5–6 mg/day) during the first 4 weeks of treatment in patients with schizophrenia with predominantly negative symptoms.

## STUDY DESIGN AND PATIENTS

The study was conducted at the clinic of Department of Borderline Mental Pathology and Psychosomatic Disorders of the Federal State Budgetary Scientific Institution "Mental Health Research Center (director—professor T. P. Klyushnik) and by employees of the Department of Psychiatry of FSBEI HE "Kazan State Medical University" of the Ministry of Health of the Russian Federation (head of the department—prof. K. K. Yakhin) at clinical departments of the National Autonomous Healthcare Institution "Bekhterev Republican Clinical Psychiatric Hospital" of the Ministry of Health of the Russian Federation (chief medical officer—F. G. Ziganshin)[1]. In accordance with the objective of the study, the sample included 60 inpatients (31 females, 29 males; average age 35.6 ± 9.1 years) with a confirmed ICD-10 diagnosis of schizophrenia; socio-demographic characteristics of the sample are presented in **Table 1**.

The study sample included patients diagnosed with schizophrenia (F20). The reported duration of the disease ranged from to 2 to 26 years and the number of episodes in the medical history was 2 to over 10.

Patients were sequentially and continuously enrolled in the study upon their admission to the clinical departments in accordance with the inclusion criteria, either immediately or after stabilization if hospitalization was associated with disease exacerbation. The study required four visits to the clinic: 1 day before the start of treatment with cariprazine, on day 7 of cariprazine treatment, on day 14 of cariprazine treatment, and on day 28 of cariprazine treatment.

During the study, psychopathological and psychometric methods were used: PANSS (Positive and Negative Syndrome Scale) (10); CAINS (The Clinical Assessment Interview for Negative Symptoms) (11), CDSS (Calgary Depression Scale

[1]The study was conducted in accordance with legal and ethical regulations of the Declaration of Helsinki, the current legislation of the Russian Federation and principles of Good Clinical Practice (GCP).

**TABLE 1 |** Socio-demographic characteristics of the study sample ($n = 60$).

| Parameter | No. of patients Abs. (%) |
|---|---|
| **Gender** | |
| Males | 29 (49%) |
| Females | 31 (51%) |
| **Education** | |
| Higher/incomplete higher | 40 (66%) |
| Secondary specialized | 11(18.3%) |
| **Social status** | |
| Unemployed | 47 (78.3%) |
| Receiving disability assistance | 35 (58%) |
| **Family status** | |
| Married | 10 (16%) |
| Divorced | 5 (9%) |
| Single | 45 (35%) |

for Schizophrenia) (12), CGI-I (Clinical Global Impression—Improvement) (13). To assess the tolerability throughout study treatment, adverse events leading to dose modification or discontinuation of cariprazine were recorded, as well as the change of the SAS score (Simpson-Angus Scale for Extrapyramidal Symptoms) over time (14).

Inclusion criteria were as follows: disease duration $\geq$ 2 years; stable state with no psychotic episodes during $\geq$6 months before enrollment; prevalence of negative symptoms with minimal/no positive symptoms during $\geq$6 months as per the clinician's assessment and in line with the following PANSS criteria: PANSS negative symptom factor score (PANSS-FSNS) $\geq$ 15; score $\geq$ 4 for at least two negative symptoms (blunted affect, passive or apathetic social withdrawal, lack of spontaneity and flow of conversation); informed consent obtained.

Exclusion criteria were as follows: pronounced positive symptoms as per the clinician's assessment and in line with the following PANSS criteria: PANSS positive symptom factor score (PANSS-FSPS) $\geq$ 19; moderate/severe depressive disorders as per the clinician's assessment and the CDSS criterion: total score $>$ 6; clinically significant parkinsonism as per the clinician's assessment and the SAS criterion: total score for the first eight items $>$ 3; organic CNS disorders; alcohol and/or psychoactive substances abuse/dependence.

After initial screening and eligibility assessment against the inclusion criteria, patients received cariprazine (Reagila) once daily, with or without food, for 28 days at the following daily doses: starting dose of 1.5 mg once daily with up-titration by 1.5 mg per week up to 6 mg once daily according to criteria as follows: (1) no changes in negative symptoms according to investigator's assessment and PANSS negative and CAINS scores; (2) no clinically significant adverse events (investigator's assessment and SAS scores).

A patient's state over time was assessed based on the change from baseline in PANSS negative symptom subscale scores as well as CAINS scores (total score and scores for individual items of the scale).

**TABLE 2 |** Patient disposition by cariprazine daily dose at each of 4 weeks of treatment.

| Cariprazine dose (mg/day) | Treatment week | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| 1.5 | 60 | 5 | 0 | 0 |
| 3 | 0 | 55 | 28 | 22 |
| 4.5 | 0 | 0 | 26 | 20 |
| 6 | 0 | 0 | 0 | 7 |
| Total* | 60 | 60 | 53 | 49 |

**A decrease in the number of patients by week 4 is associated with premature treatment discontinuation in several cases.*

Given the resistance of negative symptoms and short duration of the assessment period, a reduction in baseline total scores on each of the specified scales at least of 3 points after 4 weeks of treatment plus $\leq$ 3 points (minimal or more pronounced improvement) on the CGI-improvement scale was chosen as an outcome measure.

Patients were withdrawn from the study in case of the following: individual drug intolerance or severe side effects, patient's refusal to continue treatment.

The statistical analysis was performed using the Microsoft Excel and STATISTICA v.12.5 software with the Wilcoxon *T*-test. A $p \leq 0.05$ value was taken as the threshold level of statistical significance for comparisons between initial and each subsequent weekly assessment.

## RESULTS

Of 60 patients enrolled in this study, 49 (81.7%) completed the planned 28-day treatment period. Hence, 11 (18.3%) patients prematurely dropped out from the study at week 2–3 of treatment. None of these premature discontinuations was related to safety concerns, i.e., the occurrence of potentially life-threatening adverse effects. All 11 patients discontinued treatment based on their own initiative; 4 (6.7 %) due to poor tolerability (see details in the discussion of treatment tolerability) while the remaining 7 (11.6 %) motivated their refusal to continue treatment with cariprazine by anxiety and agitation (week 1–2 of treatment, doses of 1.5–3 mg/day), yet not accompanied by exacerbation or relapse of psychotic disorders. Even though in all of these seven cases the clinician deemed the exacerbation of the mentioned symptoms to be mild/moderate, acceptable at the initial stage of therapy with a non-sedative antipsychotic and manageable with the use of anxiolytics and sedatives, cariprazine treatment was discontinued.

According to the method of therapy, all patients started treatment with cariprazine at a recommended initial dose of 1.5 mg/day followed by up-titration or down-titration due to lack of efficacy or side effects, respectively. Administration at the initial dose of 1.5 mg/day did not lead to a desirable effect. By week 4 of follow-up, the majority of patients (42 out of 49) had the optimal balance between therapeutic effect and tolerability in the dose range of 3 to 4.5 mg/day (**Table 2**).

**TABLE 3 |** Changes in baseline scores for positive, negative, and extrapyramidal symptoms during 28 days of treatment with cariprazine (1.5–6 mg/day).

| Scale | Days of therapy | | | |
|---|---|---|---|---|
| | 0 | 7 | 14 | 28 |
| PANSS negative | 24.8 | 23.9 | 22.6 | 20.5* |
| PANSS positive | 12.5 | 12.4 | 11.8 | 10.2 |
| CAINS total | 41.8 | 39.6 | 38.3 | 36.9** |
| SAS total | 1.3 | 1.8 | 2.4 | 2.1 |

*PANSS, Positive and Negative Syndrome Scale; CAINS, The Clinical Assessment Interview for Negative Symptoms; SAS, Simpson-Angus Scale for Extrapyramidal Symptoms; Significant changes from baseline values: *p < 0.05; **p < 0.01.*

**TABLE 4 |** Change from baseline in negative symptom scores for separate items of the Positive and Negative Syndrome Scale (PANSS) during the first four weeks of treatment with cariprazine.

| PANSS items for negative symptoms | Days of therapy | | | | D0 vs. D28 difference |
|---|---|---|---|---|---|
| | 0 | 7 | 14 | 28 | |
| Blunted affect | 4.08 | 3.6 | 3.1 | 3.25 | −0.83 |
| Emotional withdrawal | 4.5 | 3.1 | 2.8 | 2.9* | −1.6 |
| Poor rapport | 3.8 | 2.9 | 2.6 | 2.5 | −1.3 |
| Passive/apathetic social withdrawal | 4.25 | 3.5 | 3.0 | 3.1 | −1.15 |
| Difficulty in abstract thinking | 4.5 | 4.08 | 3.75 | 3.0* | −1.5 |
| Lack of spontaneity and flow of conversation | 3.75 | 3.8 | 3.6 | 3.25 | −0.5 |
| Stereotyped thinking | 4.0 | 3.75 | 3.3 | 3.25 | −0.75 |

**Significant changes from baseline values: *p < 0.05.*

The prevalence of negative symptoms is supported by the ratio of mean baseline total scores on PANSS positive and negative syndromes subscales: 12.5 and 24.8, respectively, composite index minus 12.2 (**Table 3**). The mean baseline total CAINS score of 41.8 also reflects quite pronounced negative symptoms (given that the maximum score on this scale is 52) (**Table 3**).

According to the accepted outcome measure (a reduction in baseline total scores for negative symptoms on the PANSS and CAINS scales by ≥3 points plus ≤3 points on the CGI-S scale), in a subgroup of 49 patients who completed 28 days of treatment with cariprazine, the therapy was considered effective in 45 patients and ineffective in 4 patients. Thus, 75% of patients from the overall sample (60 patients) met the efficacy criterion.

During treatment, there was a progressive weekly improvement in baseline PANSS scores at all stages of the assessment with concurrent reduction of positive and negative symptoms. However, it should be noted that at the end of week 4 the decrease in the baseline total negative symptom subscale score was more pronounced—by 4.3 points (from 24.8 to 20.5; $p < 0.01$), whereas the baseline score for positive symptoms showed only a minimum change from 12.5 to 10.2.

Starting from day 7 of therapy, there was a gradual decrease in the scores for all seven negative symptom PANSS items; the most pronounced changes over time were observed for such parameters as "emotional withdrawal" and "difficulty in abstract thinking," for which the mean baseline scores decreased by 1.6 and 1.5 points, respectively (**Table 4**).

Changes from baseline in PANSS negative symptom subscale scores over time are consistent with changes in the CAINS scores (**Table 3**). There was also a significant and continuous decrease in the severity of negative symptoms across all stages of the assessment, with a reduction in the baseline score of 4.9 points ($p < 0.01$).

Patients with depressive symptoms were not included in the study in accordance with the inclusion criteria; this was verified using the Depression Scale for Schizophrenia (CDSS). Correspondingly, baseline CDSS scores were minimal, and the mean total score at cariprazine initiation in the study sample was close to zero and was equal to 2.3, well below the six-point threshold for depression (maximum total score on this scale is 27). However, there was a decrease in the baseline score to 1.2. after 4 weeks of therapy.

Cariprazine was well-tolerated. Only 4 out of 60 treatment discontinuations were associated with side effects. The main causes were severe akathisia and persistent insomnia, anxiety with a feeling of tension and irritability, which were reported in 3 patients during the first days of treatment at the initial dose of 1.5 mg/day and then got worse, and in another patient—at week 2 following up-titration to 3 mg/day. These events could not be adequately managed by dose reduction or use of anticholinergic and hypnotic drugs.

Extrapyramidal symptoms (EPS) were reported in 27 patients, mostly ($n = 25$) in the dose interval from 4.5 to 6 mg/day, including 2 of 4 patients who received 6 mg/day at week 4. Extrapyramidal symptoms were mild or moderate, did not require drug discontinuation, and were quickly resolved with minimal doses of anticholinergic drugs without reducing the daily dose of cariprazine.

The favorable tolerability profile is confirmed by a positive change over time in the SAS scores for abnormal movements (**Table 3**). The mean baseline score was 1.3, reflecting minimal movement disorders at the beginning of treatment with cariprazine. During therapy, there was only a slight increase in the baseline score of <2.5 points, and in the last week there was even a downward trend. Taking into account an up-titration of the dose at each subsequent week, and maximum daily dose of the drug (up to 6 mg/day) received by most patients at week 4, the values and changes over time in the SAS scores confirm low severity and ease of correction of the side effects of the drug.

## Clinical Case

A male patient, 37 years of age, single, incomplete higher education, 2nd degree disability due to a mental disorder. Diagnosis: shift-like schizophrenia. No family history of mental disorders. Pregnancy, delivery and early development with no particulars. The patient did not stand out among the other

children, completed elementary school and 3 years (out of 5) at the university. He was anxious, impressionable, prone to avoidance behaviors, had several friends and was conform in companies. At the age of 19 (being a sophomore), he experienced the first psychotic episode with hallucinations and delusions and was treated at a residential psychiatric clinic, which resulted in the reduction of positive symptoms. Following the episode, he became passive, reserved and failed to study well. He left the university and worked irregularly, taking low-qualified jobs (delivery and cleaning services). Consequently, he had three more episodes with similar symptoms that required in-patient treatment; the last one was 6 years ago (at the age of 31). At that time the patient was given a disability group. No delusions or hallucinations have been noted during the last 5 years and the patient has remained stable. The patient was observed by a residential psychiatrist and received regular maintenance treatment with antipsychotic drugs (most recently olanzapine at the dose of 10 mg/day for 13 months). Due to the lack of positive dynamics and persistent functional decline, on relatives' advice the patient applied for hospitalization at the Federal State Budgetary Scientific institution "Mental Health Research Center." The patient was eligible for this study of cariprazine and so took part in it. As the result of treatment, positive response was achieved at cariprazine dose 4.5 mg at week 3. The reduction in the baseline total negative symptom score on the PANSS scale was four points (from 22 to 18), and in the CAINS scores—four points. The patient became more active, did household chores without a reminder from his family, and did shopping on his own. He became more sociable, but only with his family. He began to show interest toward his old hobbies, started coin collecting again, attempted to play chess. With regard to side effects, the patient experienced insomnia at 3 mg/day, but when the dose was increased to 4.5 mg such events reduced.

## DISCUSSION

According to currently available publications, this was the first study of initial effects of cariprazine in the treatment of patients with predominantly negative symptoms. Clearly, the open-label design, relatively short duration of treatment considering low sensitivity of negative symptoms to pharmacological therapy and a small number of observations do not provide sufficient validity and reliability of the obtained data. Hence, the results of the study should be interpreted with caution and may only be regarded as preliminary, with future verification needed.

However, the results of this study indicate a possible early response to treatment with cariprazine when given at standard doses (1.5–6 mg/day) starting from the first weeks of treatment in terms of positive dynamics of one's negative symptoms. Despite a relatively small change in the PANSS and CAINS negative symptom scores, which is understandable given the known resistance of negative symptoms to antipsychotics, the stable and progressive improvement in these scores and the achievement of statistical significance at the time of the final assessment is striking. It is also important to highlight the minimal severity and small changes in positive symptoms as well as the absence of clinically significant signs of depressive disorders and mild severity of Parkinsonism phenomena. Hence, it may be assumed that, as in a long-term comparative study of cariprazine and risperidone in the treatment of schizophrenia with predominantly negative symptoms, these data reflect a direct effect of therapy on primary negative symptoms already at the initiation of treatment and may be regarded as potential evidence of early effect.

These findings also suggest an activating effect of the drug when given at 1.5 mg/day (initial dose) and greater doses. This suggestion is supported by improved general and social activity, enhanced speech production and better social connection that were observed during treatment and confirmed by the change in the corresponding psychometric parameters over time. Insomnia, increased anxiety and tension may be indirect signs of activation. These observations are consistent with the tolerability profile of cariprazine established in clinical trials, in which insomnia is one of the most common side effects, no signs of severe sedation, and only minimal (rated as the best among antipsychotics) indicators of sleepiness are present (15).

The favorable tolerability profile with only mild EPS and akathisia being the most common and, apparently, problematic effect of the drug, is also consistent with the data of clinical studies (16).

Thus, the results of this 28-week open-label study suggest that a rapid initial treatment effect of cariprazine at doses of 3–6 mg/day with respect to deficit disorders in schizophrenic patients with predominantly negative symptoms is possible. The presented results require further verification and may be taken into account in the design of future studies, including those aimed at identifying early predictors of the therapeutic effect of cariprazine in reducing negative symptoms in schizophrenia.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Federal State Budgetary Scientific Institution Mental Health Research Center, Moscow, Russia. The patients/participants provided their written informed consent to participate in this study.

## 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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REVIEW
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# Dopamine Receptor Partial Agonists: Do They Differ in Their Clinical Efficacy?

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Dopamine receptor partial agonists (DRPAs; aripiprazole, brexpiprazole, and cariprazine) constitute a novel class of antipsychotics. Although they share a similar mechanism of action, DRPAs differ in their pharmacodynamics, pharmacokinetics, drug interactions, or safety and tolerability. The antipsychotic efficacy of all three drugs was established in several placebo-controlled randomized trials (RCTs) in schizophrenia, both acute phase and relapse prevention. In addition, each of the DRPA agents has been tested in other psychiatric disorders, including bipolar disorder or major depression. However, a few studies have examined their comparative clinical efficacy. There are no head-to-head comparisons between aripiprazole, brexpiprazole, or cariprazine. In two acute schizophrenia RCTs of cariprazine and brexpiprazole, aripiprazole was used as an indirect comparator to control for study sensitivity. To assess potential differences in the efficacy of DRPAs, we reviewed data from controlled trials, systematic reviews, and meta-analyses. Our results showed that the acute antipsychotic effects of DRPAs, as measured by the number needed to treat, are comparable. The three agents were superior to placebo in acute treatment, and cariprazine was found to be effective in the reduction of primary negative symptoms of schizophrenia. In the therapy of bipolar disorder, aripiprazole and cariprazine showed antimanic efficacy, cariprazine was also effective in the management of bipolar depression, and aripiprazole was effective for relapse prevention. The addon administration of aripiprazole or brexpiprazole reduced symptoms of major depression. Aripiprazole can control acute agitation associated with psychosis or bipolar disorder; brexpiprazole showed the potential to manage agitation in dementia patients. Aripiprazole has also established evidence of efficacy in children and adolescents and other conditions: OCD, tic disorders, and autism spectrum disorder. Our review of published data suggests that in terms of clinical efficacy, DRPAs are a heterogeneous group, with each drug possessing its own therapeutic benefits.

**Keywords: antipsychotics, dopamine partial agonists, aripiprazole, brexpiprazole, cariprazine, clinical efficacy**

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## INTRODUCTION

Antipsychotic drugs represent the mainstay of schizophrenia treatment (1). They all share a common mechanism of action: antagonism at postsynaptic dopamine $D_2$ receptors (2). However, one group of antipsychotics, dopamine receptor partial agonists (DRPAs), differs in its effects on the dopamine system. Unlike most of the other antipsychotic agents, DRPAs also possess intrinsic dopamine $D_2/D_3$ agonist activity and act differently (either as agonists or antagonists) in various parts of the brain (3).

At present, three DRPAs have been approved for clinical use: aripiprazole, brexpiprazole, and cariprazine. Comparing their pharmacodynamics, aripiprazole has the highest intrinsic $D_2$ activity, and cariprazine has the highest $D_3$ activity (**Table 1**) (4, 5). High intrinsic $D_2$ activity can explain activating effects of aripiprazole; high selective affinity for $D_3$ receptors of cariprazine is effective on positive, negative, and cognitive symptoms. Moreover, hyperstimulation of $D_2$ or $D_3$ receptors can cause restlessness, akathisia, agitation, insomnia, nausea, dyspepsia, or rarely compulsive or impulsive behavior (e.g., hypersexuality, compulsive shopping, pathological gambling, and overeating) (4, 6). Brexpiprazole with a lower intrinsic $D_2$ and $D_3$ has less activating effects and lower risk for akathisia, insomnia, nausea, and dyspepsia.

DRPAs also vary in their relative affinity for other neurotransmitter systems: Brexpiprazole has the highest occupancy of the serotonin 5-$HT_{1a}$ and 5-$HT_{2a}$ receptors, and adrenergic alpha$_{1a}$, alpha$_{1b}$, and alpha$_{2c}$ receptors (4). High affinity for the 5-$HT_{1a}$ and 5-$HT_{2a}$ receptors reduces the risk of extrapyramidal symptoms (EPS) and improves anxiety and depression symptoms. Blockade of the adrenergic alpha$_{1a}$ and alpha$_{1b}$ receptors increases the risk of sedation and hypotension; alpha$_{2c}$ antagonism has antidepressant and prosexual effects. All three drugs have low affinity for serotonin 5-$HT_{2c}$, histamine, and muscarinic receptors, and thus, possess low risk of metabolic side effects, weight gain, and anticholinergic effects (4).

Following oral administration, DRPAs reach maximum serum concentrations within 3–6 h (4). Their respective bioavailability is 87% (oral aripiprazole), 95% (brexpiprazole), 97% (intramuscular aripiprazole), and 52–80% (cariprazine). The elimination half-life is 75 h for aripiprazole (active metabolite dehydro-aripiprazole has 94 h), 91 h for brexpiprazole, and 48–96 h for cariprazine; its active metabolites have half-lives of 30–38 h (desmethyl-cariprazine) and 168–504 h (didesmethyl-cariprazine). DRPAs are mainly metabolized via the hepatic cytochrome isoenzymes CYPD6 and CYP3A4.

Pharmacodynamics and pharmacokinetics predict clinical effects and tolerability (**Table 1**). Thus, given their variances in pharmacology, it is reasonable to assume that DRPAs differ in their efficacy. There is a paucity of data comparing their antipsychotic effects between each other, the only available (indirect) comparison is based on the number needed to treat (NNT) (4, 7). To assess potential differences in the efficacy of DRPAs further, we reexamined data from randomized controlled trials, systematic reviews, and meta-analyses.

## METHODS

All publicly available records on PubMed, Cochrane Library, and ClinicalTrials.gov were searched using the key words "aripiprazole," "brexpiprazole," or "cariprazine." Included were randomized, double-blind trials with neuropsychiatric patients that examined clinical efficacy. Additional entries were obtained

**TABLE 1 |** Human receptor affinity of dopamine receptor partial agonists (DRPAs) and potential clinical effects (modified from 4, 5).

| Receptor | Type of activity | Affinity *K*i (nM) *in vitro* | | | Potential clinical effects |
|---|---|---|---|---|---|
| | | Aripiprazole | Brexpiprazole | Cariprazine | |
| Dopamine $D_2$ | Partial agonist | 0.34 | 0.30 | 0.49 | Antipsychotic effect, extrapyramidal syndrome (EPS), prolactin elevation, |
| | *Intrinsic activity* | *60%* | *45%* | *30%* | akathisia, nausea, insomnia, subjective response to treatment |
| Dopamine $D_3$ | Partial agonist | 0.8 | 1.1 | 0.08 | Effects on positive and negative symptoms, procognitive effect, EPS, |
| | *Intrinsic activity* | *28%* | *15%* | *71%* | akathisia |
| Serotonin 5-$HT_{1A}$ | Partial agonist | 1.7 | 0.12 | 2.6 | Antidepressant and anxiolytic effects, procognitive effect, reduction of EPS |
| | *Intrinsic activity* | *73%* | *60%* | *39%* | |
| Serotonin 5-$HT_{2A}$ | Antagonist | 3.4 | 0.47 | 19 | Reduction of EPS, weight gain |
| Serotonin 5-$HT_{2B}$ | Antagonist | 0.36 | 1.9 | 0.58 | ? (unknown) |
| Serotonin 5-$HT_{2C}$ | Antagonist | 15 | 34 | 134 | Weight gain |
| Serotonin 5-$HT_7$ | Antagonist | 10.3 | 3.7 | 111 | Antidepressant and procognitive effects |
| Histamine $H_1$ | Antagonist | 28 | 19 | 23 | Sedation and weight gain, hypnotic and anxiolytic effects |
| Adrenergic alpha$_{1A}$ | Antagonist | 26 | 3.8 | 155 | Vasodilatation, hypotension, sedation, antihypertensive effects, improvement of prostate hypertrophy, effect on nightmares |
| Adrenergic alpha$_{1B}$ | Antagonist | 35 | 0.17 | >155 | ? (unknown) |
| Adrenergic alpha$_{2C}$ | Antagonist | 38 | 0.59 | >155 | Antidepressant and prosexual effects |
| Muscarinic $M_1$ | Antagonist | >1,000 | >1,000 | >1,000 | Dry mouth, blurred vision, constipation, urinary retention, tachycardia, cognitive impairments, delirium |

through appropriate references; retrieved records were checked for duplicity. In addition to the randomized controlled trials (RCTs) as the primary data source, meta-analyses of DRPAs assessing comparative efficacy (between DRPAs, DRPAs vs. placebo or standard treatment) or generalizing efficacy data were included, where available. If there was more than one meta-analysis examining the same subject, the most inclusive and/or methodologically sound one was used. The results were reviewed by the authors narratively according to the conditions in which the drugs were tested.

# RESULTS

## Clinical Efficacy

A total of 143 randomized, double-blind, placebo- or active-comparator controlled trials of DRPAs were identified as of August 31, 2021. The therapeutic efficacy of aripiprazole, brexpiprazole, and cariprazine was tested in 68 RCTs with schizophrenia (**Table 2**), 26 RCTs with bipolar disorder, 19 RCTs with major depression (**Table 3**), and 30 RCTs in other neuropsychiatric disorders (**Table 4**).

### Schizophrenia—Acute Treatment

Aripiprazole was found to be superior to placebo in numerous short-term studies of adult patients with acute schizophrenia. A recent comprehensive meta-analysis comparing the antipsychotic efficacy of 32 oral drugs analyzed a total of 27 placebo- or active-comparator-controlled RCTs with aripiprazole (8). The oral formulation of aripiprazole was significantly more efficacious than placebo in the overall change of symptoms ($n$ = 1,926 patients; standardized mean difference (SMD) = −0.41, 95% CI −0.50, −0.32), positive symptoms ($n$ = 1,451; SMD = −0.38, 95% CI −0.48, −0.28), negative symptoms ($n$ = 1,353; SMD = −0.33, 95% CI −0.41, −0.24), and depressive symptoms ($n$ = 150; SMD = −0.40, 95% CI −0.69, −0.10), but not in social functioning ($n$ = 50; SMD = −0.23, 95% CI −0.55, 0.09).

Moreover, the antipsychotic efficacy of aripiprazole was compared with risperidone in four RCTs (in two of them, it was used to control for study sensitivity). It was compared with olanzapine in four RCTs, with haloperidol in three placebo-controlled RCTs, and with ziprasidone in one RCT (8). In the pairwise comparisons, aripiprazole was as effective as all active comparators (**Table 2**).

Aripiprazole was found to be more effective than placebo in the treatment of children and adolescents with schizophrenia (9). The results of a 6-week RCT showed that 10 or 30 mg/day of aripiprazole in patients 13–17 years old improved schizophrenia symptoms, as measured by the PANSS, Clinical Global Improvement (CGI), and Children's Global Assessment Scale. The difference from placebo in the total PANSS score at study end was significant for both doses, 10 mg ($p$ = 0.05) and 30 mg ($p$ = 0.007).

The efficacy of brexpiprazole 2 and 4 mg in the treatment of acute schizophrenia was established in six RCTs (8). Brexpiprazole was more effective than placebo in overall symptom reduction ($n$ = 1.180; SMD = −0.26, 95% CI −0.39, −0.12), improvement of positive symptoms ($n$ = 1,180; SMD = −0.17, 95% CI −0.31, −0.04), negative symptoms ($n$ = 1,180; SMD = −0.25, 95% CI −0.36, −0.14), depressive symptoms ($n$ = 1,090; SMD = −0.16, 95% CI −0.29, −0.03), and social functioning ($n$ = 918; SMD = −0.25, 95% CI −0.38, −0.12).

The antipsychotic efficacy of cariprazine has been proven by the results of four, 6-week RCTs in acute schizophrenia (8). Compared with placebo, cariprazine improved significantly more overall symptoms ($n$ = 999; SMD = −0.34, 95% CI −0.49, −0.20), positive symptoms ($n$ = 999; SMD = −0.30, 95% CI −0.45, −0.16), negative symptoms ($n$ = 999; SMD = −0.34, 95% CI −0.44, −0.20), and depressive symptoms ($n$ = 305, SMD = −0.36, 95% CI −0.63, −0.09). No data on social functioning of cariprazine were obtainable from acute trials.

### Schizophrenia—Relapse Prevention

For maintenance treatment and prevention of schizophrenia relapse, oral aripiprazole outperformed the placebo or haloperidol in three long-term trials. In a 26-week study, 310 patients were randomized to aripiprazole 15 mg/day or placebo (10). The time to relapse was significantly longer for aripiprazole than for placebo ($p < 0.001$), and more patients relapsed on placebo (57%) than on aripiprazole (34%). The relative risk of relapse for the aripiprazole group was 0.59 (95% CI 0.35, 0.71; $p < 0.001$), the risk was reduced by 41%. Additionally, 30 mg of aripiprazole daily was as effective as 10 mg/day of haloperidol in two, 1-year RCTs with similar protocols, and the total study sample consisted of 1,294 patients (11). Based on a 30% improvement in the Positive and Negative Syndrome Scale (PANSS) total score maintained for at least 28 days, aripiprazole produced a significantly higher response rate than haloperidol (52 vs. 44%; $p < 0.003$). Time to discontinuation for any reason was significantly greater with aripiprazole than with haloperidol ($p$ = 0.0001), more relapses or treatment failures were reported for haloperidol (21%) than aripiprazole (17%). Compared with haloperidol, aripiprazole reduced the risk of relapse by 19% (hazard ratio HR = 0.81, 95% CI 0.57, 1.14).

The long-term efficacy of brexpiprazole in maintenance treatment of schizophrenia was evaluated in a year-long, double-blind trial (12). Patients with acute psychotic symptoms were switched to open-label treatment with brexpiprazole 1–4 mg/day over a period of 1–4 weeks. Patients completing the conversion phase entered a 12- to 36-week stabilization phase. In this phase, patients were titrated to a dose of brexpiprazole (1–4 mg/d). Those who remained stable ($n$ = 202) were then randomized to continuation treatment with either their stabilization dose of brexpiprazole or placebo. Compared with placebo, brexpiprazole significantly delayed the time to relapse ($p < 0.0001$) and reduced relapse risk by 71% (HR = 0.29, 95% CI 0.16, 0.55). The proportion of patients meeting the criteria for impending relapse was 13.5% with brexpiprazole and 38.5% with placebo ($p < 0.0001$), the relative risk of relapse for the brexpiprazole group was 0.35.

A 97-week, placebo-controlled, multicenter study assessed efficacy of cariprazine in the long-term maintenance treatment of schizophrenia (13). In the first open phase, during an 8-week run-in period, the patients were given a flexible dose of cariprazine 3–9 mg/daily and then kept on a fixed dose over

**TABLE 2 |** Randomized double-blind trials of DRPAs in schizophrenia.

| Indication | Aripiprazole | Brexpiprazole | Cariprazine |
|---|---|---|---|
| Acute treatment (overall symptom change) | **ARI oral**<br>27 RCTs vs. placebo:<br>SMD = −0.41 (95% CI −0.32, −0.50)<br>Registration studies: NNT = 8 (95% CI 6, 13)<br>4 RCTs vs. risperidone:<br>n.s. (SMD = −0.07; 95% CI −0.35, −0.20)<br>4 RCTs vs. olanzapine:<br>n.s. (SMD = −0.15; 95% CI −0,32, 0.02)<br>1 RCT vs. ziprasidone:<br>n.s. (SMD = −0.16; 95% CI 0.50, 0.18)<br>3 RCTs vs. haloperidol:<br>n.s. (SMD = 0.00; 95% CI −0.24, 0.23)<br>**ARI LAI**<br>2 RCTs vs. placebo:<br>ALAI monohydrate: $p < 0.0001$<br>ALAI lauroxil: $p < 0.001$ | 6 RCTs vs. placebo:<br>SMD = −0.26 (95% CI −0.12, −0.39)<br>NNT = 7 (95% CI 5, 12) | 4 RCTs vs. placebo:<br>SMD = −0.34 (95% CI −0.20, −0.49)<br>NNT = 10 (95% CI 7, 18) |
| Relapse prevention | **ARI oral**<br>1 RCT vs. placebo:<br>time to relapse: $p < 0.001$<br>HR: 0.59 (95% CI 0.35. 0.71)<br>relapses: 34% vs. 57% ($p < 0.001$)<br>2 RCTs vs. haloperidol:<br>time to relapse: $p = 0.0001$<br>HR: 0.81 (95% CI 0.57. 1.14)<br>relapses/treatment failures:<br>17% vs. 21%<br>**ARI LAI**<br>1 RCT vs. placebo:<br>time to relapse: $p < 0.0001$<br>HR (PL/ALAI): 5.03 (95% CI 3.15, 8.02)<br>impending relapses: 10.0% vs. 39.6%<br>2 RCTs vs. ARI oral (= noninferiority) | 1 RCT vs. placebo:<br>time to relapse: $p < 0.0001$<br>HR: 0.292 (95% CI 0.156. 0.548)<br>impending relapses: 13.5% vs. 38.5% ($p < 0.0001$) | 1 RCT vs. placebo:<br>time to relapse: $p = 0.001$<br>HR: 0.45 (95% CI 0.28, 0.73), NNT = 5<br>relapses: 24.8% vs. 47.5% |
| Acute agitation | **ARI im**<br>2 RCTs vs. placebo:<br>ARI 5.25 mg: $p \leq 0.05$<br>ARI 9.75 mg: $p < 0.001$<br>responses: 55% vs. 36%. NNT = 5 | n/a | n/a |
| Children and adolescents | 1 RCT vs. placebo:<br>ARI 10 mg: $p = 0.05$;<br>remission NNT = 6 ARI 30 mg: $p = 0.007$;<br>remission NNT = 5 | n/a | |
| Predominant negative symptoms | n/a | n/a | 1 RCT vs. risperidone:<br>LSMD in PANSS-FSNS: −1.46 (95% CI −2.39, −0.53), $p < 0.01$<br>responses: 69% vs. 58%; NNT = 9 |
| Treatment-refractory patients | ***Clozapine augmentation***<br>7 RCTs vs. placebo:<br>total symptoms: SMD = −0.57 (95% CI −1.02, −0.13) | n/a | n/a |

*n/a, no studies available; ARI, aripiprazole; ARI LAI/ALAI, aripiprazole long-acting injectable; ARI im, aripiprazole intramuscular injection; ARI oral, aripiprazole oral formulation; HR, hazard ratio; LSMD, least squares mean difference; NNT, number needed to treat; n.s., no significant difference; PANSS, Positive and Negative Syndrome Scale; PANSS-FSNS, PANSS-factor score for negative symptoms; RCT, randomized controlled trial; PL, placebo; SMD, standardized mean difference.*

the course of a 12-week stabilization period. The patients ($n = 200$) were subsequently randomized to a blinded administration of cariprazine (3, 6, or 9 mg/day) or placebo. Double-blind phase lasted from 26 to 72 weeks. The results demonstrated that maintenance treatment with cariprazine was superior to placebo in terms of time to relapse ($p < 0.001$), and the risk of relapse was reduced by 55% (HR = 0.45, 95% CI 0.28, 0.73). Relapse occurred in 24.8% of cariprazine- and 47.5% of placebo-treated patients; the relative risk of relapse for the cariprazine group was 0.52.

## Schizophrenia—Treatment Resistance and Primary Negative Symptoms

Aripiprazole demonstrated efficacy in augmenting clozapine in treatment-resistant schizophrenia in short- and long-term

**TABLE 3 |** Randomized double-blind trials of DRPAs in mood disorders.

| Indication | Aripiprazole | Brexpiprazole | Cariprazine |
|---|---|---|---|
| Bipolar disorder *manic/mixed episode* | 6 RCTs vs. placebo (monotherapy):<br>responses (3 W): 47.7 vs. 31.4%. NNT = 6<br>remissions (3 W): 39.6 vs. 32.4%. NNT = 14 | 2 RCTs vs. placebo:<br>reduction in YMRS:<br>LSMD = 0.14 (95% CI −1.74, 2.03) (n.s.)<br>LSMD = −1.62 (95% CI −3.56, 0.32) (n.s.) | 3 RCTs vs. placebo:<br>responses: 57% vs. 36%. OR = 2.30 (95% CI 1.78, 2.98), NNT = 5, $p < 0.001$<br>remissions: 46% vs. 30%. NNT = 7. $p < 0.001$ |
| Bipolar disorder *depressive episode* | 2 RCTs vs. placebo: *negative results* | n/a | 4 RCTs vs. placebo: reduction in MADRS:<br>1.5 mg/day SMD = −0.26 (95% CI −0.49, −0.02)<br>3 mg/d SMD = −0.21 (95% CI −041, −0.01)<br>remissions: NNT = 10 (1.5 mg); NNT = 14 (3 mg) |
| Bipolar disorder *maintenance treatment* | **ARI oral**<br>1 RCT monotherapy vs. placebo:<br>26 W time to relapse: $p = 0.020$<br>number of relapses 25 vs. 43% ($p = 0.013$)<br>100 W time to relapse: $p = 0.011$<br>1 RCT adjuvant therapy:<br>time to relapse of mania: $p < 0.01$<br>**ARI LAI**<br>1 RCT vs. placebo:<br>time to relapse: $p < 0.0001$<br>number of relapses: 26.5 vs. 51.1% ($p < 0.0001$) | n/a | 1 RCT vs. placebo:<br>results not available |
| Bipolar disorder *acute agitation* | **ARI im**<br>1 RCT vs. placebo<br>responses: 66 vs. 37%. NNT = 3 | n/a | n/a |
| Bipolar disorder *children and adolescents* | 4 RCTs vs. placebo:<br>response in acute mania: $p < 0.01$ relapse prevention: $p < 0.05$ | n/a | n/a |
| Unipolar depression *adjunctive treatment* | 3 RCTs vs. placebo:<br>reduction in MADRS: −10.3 vs. −6.5; $p < 0.0001$<br>responses: 36 vs. 19%, NNT = 6<br>remissions: 24 vs. 12%, NNT = 8 | 9 RCTs vs. placebo:<br>reduction in MADRS: SMD = −0.20; (95% CI −0.29, −0.11)<br>responses: NNT = 17<br>remissions: NNT = 25 | 5 RCTs vs. placebo:<br>1 positive study (2.5–4/day mg: change in MADRS $p = 0.01$; responses: NNT = 9)<br>2 negative studies<br>2 studies: no results available |
| Unipolar depression *elderly patients* | | 2 RCTs vs. placebo:<br>well tolerated, no efficacy data | |

*n/a, no studies available; ARI, aripiprazole; ARI LAI/ALAI, aripiprazole long-acting injectable; ARI im, aripiprazole intramuscular injection; ARI oral, aripiprazole oral formulation; LSMD, least squares mean difference; MADRS, Montgomery–Asberg Depression Rating Scale; NNT, number needed to treat; n.s., no significant difference; OR, odds ratio; RCT, randomized controlled trial; PL, placebo; SMD, standardized mean difference; W, week; YMRS, Young Mania Rating Scale.*

treatments (14). In a systematic review and meta-analysis of seven placebo-controlled trials (duration from 8 to 24 weeks) with 486 clozapine-refractory patients, addon aripiprazole produced improvement in the total psychotic symptoms (SMD = −0.57, 95% CI −1.02, −0.13) and in negative symptoms in five RCTs ($n = 328$; SMD = −0.33, 95% CI −0.55, −0.11). However, the reduction of positive symptoms was nonsignificant ($n = 328$; SMD = −0.15, 95% CI −0.60, 0.30).

The specific effect of cariprazine on negative symptoms of schizophrenia was investigated in a separate, actively controlled RCT (15). A total of 461 patients with predominant negative symptoms and minimum positive symptoms were randomized to 26 weeks of treatment with either cariprazine (4.5 mg/day) or risperidone (4 mg/day). Cariprazine produced a greater reduction of negative symptoms than risperidone, and the difference was consistently significant from week 14 to the end of the study. The cariprazine-induced change in the PANSS factor score for negative symptoms was −8.90 vs. −7.44 points in the risperidone group; the least squares mean difference (LSMD) was −1.46 (95% CI −2.39, −0.53; $p = 0.0022$), effect size (ES) at 0.31. Cariprazine also outperformed risperidone in the secondary efficacy measure, the Personal and Social Performance Scale, the change of the total score was 14.30 for cariprazine vs. 9.66 for risperidone; (LSMD = 4.63, 95% CI 2.71, 6.56; $p < 0.0001$; ES = 0.48).

## Bipolar Disorder—Manic Episode

Aripiprazole monotherapy in the management of the acute manic phase of bipolar disorder was tested in seven RCTs, four 3-week and three 12-week studies, with a total of 2,303 patients (16). In all but one trial, aripiprazole was compared with placebo, in two it was compared with haloperidol, and in one it was compared with lithium. Across all studies, aripiprazole achieved significantly higher response and remission rates than placebo.

**TABLE 4 |** Randomized double-blind trials of DRPAs in other indications.

| Indication | Aripiprazole | Brexpiprazole | Cariprazine |
|---|---|---|---|
| Alzheimer's dementia | ***Psychosis***<br>3 RCTa vs. placebo:<br>1 study: NPI-NH $p = 0.013$<br>2 negative studies<br>***Agitation***<br>ARI im (10–15 mg) > PL | ***Agitation***<br>2 RCTs vs. placebo: efficacy of 2 mg/d (CMAI)<br>SMD = −3.77 (95% CI −7.38, −0.17), $p = 0.040$<br>SMD = −5.06 (95% CI −8.99, −1.13), $p = 0.012$ | n/a |
| OCD (adjunctive therapy) | 2 RCTs vs. placebo:<br>YBOCS, WMD = 7.32 (95% CI −12.99, −1.66) | n/a | n/a |
| Tic disorder and Tourette syndrome | 17 RCTs vs. active treatment vs. PL:<br>SMD = −4.74 (95% CI −8.67, −1.06) | n/a | n/a |
| Autism spectrum disorder | 3 RCTs vs. placebo:<br>responses: RR = 2.08 (95% CI 1.24, 3.46);<br>NNT = 4 (95% CI 2.8, 5.7) | n/a | n/a |
| Alcohol dependence | 1 RCT vs. placebo:<br>Days abstinent: 58.7 vs. 63.3% (n.s.)<br>1 RCT vs. naltrexone: Number of alcohol-free subjects: 12 vs. 11 (n.s.)<br>number of relapsed subjects: 4 vs. 7 (n.s.) | n/a | n/a |

*n/a, no studies available; ARI im, aripiprazole intramuscular injection; CMAI, Cohen–Mansfield Agitation Inventory; NNT, number needed to treat; NPI-NH, Neuropsychiatric Inventory-Nursing Home; n.s., no significant difference; OCD, obsessive-compulsive disorder; PL, placebo; RCT, randomized controlled trial; RR, response rate; SMD, standardized mean difference; WMD, weighted mean difference; YBOCS, Yale–Brown Obsessive Compulsive Scale.*

Response was defined as ≥50% improvement in the Young Mania Rating Scale (YMRS) total score, remission as the YMRS total score ≤12. At week 3, the average response rate was 47.70% for aripiprazole, 45.99% for the comparator agents, and 31.40% for placebo. At week 12, the response rate was 59.12% for aripiprazole and 50.63% for the controls. A meta-analysis of the effect sizes (aripiprazole vs. placebo) suggested a pooled d-value equal to 0.34 (95% CI 0.24, 0.44) for YMRS (16). In addition to monotherapy, aripiprazole at 15 and 30 mg/day ($n = 1{,}101$) was found to be effective for acute mania as an addon therapy to lithium or valproate compared with placebo or haloperidol (17). Aripiprazole demonstrated similar efficacy for improving manic or mixed episodes, psychotic or non-psychotic manic episodes, or rapid cycling.

Two 3-week, placebo-controlled RCTs with brexpiprazole for acute mania were negative (18). In the total sample of 654 patients, brexpiprazole (flexible dosing of 2–4 mg/day, titrated to a maximum of 4 mg/day) failed to separate from the placebo in the reduction of the YMRS score. Response or remission rates were not reported. A gradual improvement of manic symptoms was observed only in a 26-week, open-label extension in the subjects who completed acute studies ($n = 381$): the mean decrease of the YMRS total score was −14.0 (SD 8.9).

A summary analysis of three placebo-controlled studies with cariprazine in the treatment of acute manic or mixed episode included 1,037 patients (19). Trial designs were similar; after a week-long washout period, patients received a 3-week, double-blind treatment. Two studies used a flexible dosing schedule of cariprazine, 3–12 mg daily, and the third included two active groups of 3–6 mg/daily and 6–12 mg daily. The results at week 3, measured by the YMRS score reduction, demonstrated significant efficacy of cariprazine in the management of acute mania compared with placebo in response (57 vs. 36%; NNT = 5) and remission (46 vs. 30%; NNT = 7) rates. Cariprazine was superior to placebo in the effect size for both response rate (ES = 2.31, 95% CI 1.35, 3.95; $p = 0.021$) and remission rate (ES = 2.05, 95% CI 1.61, 2.61; $p = 0.006$) (20). The risk difference (RD) of response rates was 0.204 (95% 0.090, 0.317; $p = 0.0163$; NNT = 5), the RD of remission rates was 0.165 (95% 0.125, 0.206; $p = 0.003$; NNT = 6).

## Bipolar Disorder—Depressive Episode

Neither aripiprazole monotherapy (5–30 mg/day) nor adjunctive therapy was found to be effective in the treatment of depressive episode of bipolar disorder. Although aripiprazole in two 8-week RCTs ($n = 749$) reduced the severity of depressive symptoms, its efficacy did not separate it from placebo (21). No double-blind controlled studies of brexpiprazole in bipolar depression have been reported.

Cariprazine monotherapy dosed within the range of 0.25 to 3 mg daily was tested in two 6-week and two 8-week, placebo-controlled studies with 1,799 patients (20). The primary results of one 8-week study were negative. In all others, cariprazine at 1.5 or 3.0 mg/day improved symptoms of acute bipolar depression. The effect size of cariprazine at 1.5 mg in the reduction of the Montgomery–Asberg Depression Rating Scale (MADRS) scores was −0.26 (95% CI −0.49, −0.02; $p = 0.040$), and the ES for 3 mg cariprazine was −0.21 (95% CI −0.41, −0.01; $p = 0.045$).

Cariprazine at 1.5 mg/day produced non-significant response rates on MADRS (≥50% reduction of the MADRS score) with an ES of 1.53 (95% CI 0.78, 2.99; $p = 0.113$) and a trend for higher remission rates on MADRS (MADRS score ≤10) with an ES of 1.75 (95% CI 0.96, 3.22; $p = 0.057$). The RD of response rates on MADRS was 0.10 (95% −0.06, 0.26; $p = 0.112$; NNT = 10, the RD of remission rates was 0.10 (95% −0.02, 0.23; $p = 0.072$; NNT = 10). The 3 mg/day of cariprazine yielded a statistically significant

ES for response rate according to the MADRS, with an odds ratio (OR) of 1.55 (95% CI 1.11, 2.17; $p = 0.030$) and a remission rate with an OR of 1.53 (95% CI 1.36, 1.72; $p = 0.043$). The RD of response rates according to MADRS was 0.10 (95% 0.02, 0.18; $p = 0.030$; NNT = 10). The RD of remission rates was 0.07 (95% 0.04, 0.11; $p = 0.01$; NNT = 14) (20).

## Bipolar Disorder—Maintenance Therapy

No DRPA has established efficacy in the prophylaxis of both symptom domains of bipolar disorder. Only aripiprazole was found to be effective in preventing relapse to mania in both monotherapy and in combination with mood stabilizers. Moreover, there is an ongoing trial with cariprazine in the relapse prevention of bipolar disorder, but the results are not available yet (22). No study of brexpiprazole in the maintenance treatment is registered.

In a placebo-controlled trial of 161 patients, aripiprazole doses of 15 and 30 mg daily were effective in delaying the time to manic relapse after 26 and 100 weeks but not in preventing relapse to depression (23, 24). At week 26, aripiprazole-treated patients had significantly fewer relapses (25%) than patients on placebo (43%; $p = 0.013$).

A 52-week study of addon aripiprazole 10–30 mg/day in combination with lithium or valproate demonstrated significantly better efficacy over placebo in the prevention of relapses in patients with mania ($p < 0.01$) but not in subjects with mixed episodes (25). In a randomized sample of 337 patients, there was a significantly greater reduction in the YMRS total score from baseline with aripiprazole in both manic (treatment difference = −3.32, $p < 0.01$) and mixed episode populations (treatment difference = −2.56, $p = 0.02$).

## Bipolar Disorder—Children and Adolescents

Aripiprazole was tested in several RCTs in children and adolescents with acute bipolar mania and in maintenance therapy. In a 4-week study with 296 patients 10–17 years old, aripiprazole doses of 10 or 30 mg daily reduced the symptoms of mania significantly more than placebo (26). The response (≥50% reduction in the YMRS total score) was achieved in 44.8, 63.6, and 26.1% of subjects in the aripiprazole 10 mg, aripiprazole 30 mg, and placebo groups, respectively ($p < 0.01$ for both doses vs. placebo). The acute phase was followed by a 26-week blinded maintenance phase with 210 study subjects (27). The overall time to all-cause discontinuation was longer for 10 mg/day aripiprazole (15.6 weeks) and 30 mg/day aripiprazole (9.5 weeks) than for placebo (5.3 weeks; both $p < 0.05$ versus placebo). The two aripiprazole doses were significantly superior to placebo in response rates, as well as on all other measures.

Aripiprazole also significantly delayed the time to a new episode (hypomania, mania, mixed state, or continued cycling) in a 72-week, placebo-controlled study of maintenance treatment with 96 bipolar outpatients aged 4–9 years (28). There was a high attrition rate over the first four study weeks: 50% in the aripiprazole group and 90% in the placebo group.

A small 6-week study with 43 patients aged 8–17 years old who suffered from mania comorbid with ADHD found that aripiprazole (mean dose 13.6 ± 5.4 mg daily) was effective at reducing YMRS score vs. placebo ($p = 0.02$; ES = 0.80) (29). Aripiprazole also achieved higher rates of response ($p = 0.02$) and remission ($p = 0.01$).

More recently, a placebo-controlled trial investigated the efficacy of aripiprazole (mean dose 7.1 ± 3.7 mg daily) in a study sample of 59 symptomatic patients aged 5–17 years diagnosed with cyclothymia or bipolar disorder not otherwise specified, with high genetic risk for bipolar disorder (30). At week 12, the subjects responded more to aripiprazole than to placebo (reduction of the YMRS total score: $p < 0.005$).

## Depressive Disorder—Adjunctive Treatment

The clinical efficacy of addon aripiprazole in the treatment of unipolar depression with insufficient response to antidepressant therapy was established in three, 6-week RCTs with identical designs (31). Patients who failed to improve during the initial 8 weeks of open-label treatment with antidepressants were randomly assigned to adjunctive aripiprazole (2–20 mg/day, based on tolerability) or placebo. The total study sample comprised 746 patients, and in patients with minimal response to previous antidepressant therapy, adjuvant aripiprazole yielded greater improvement in the MADRS total score than placebo ($p < 0.0001$), as well as in response rates (36 vs. 19%; $p < 0.0001$; NNT = 6) and remission rates (24% vs. 12%; $p < 0.0001$; NNT = 8).

A meta-analysis of nine 6- to 24-week RCTs of brexpiprazole for augmentation of antidepressant therapy (total $n = 3673$) showed that brexpiprazole was more effective than placebo for all outcome measures (32). Brexpiprazole was administered in fixed or flexible doses within a range of 0.5–3 mg/day, and one study used quetiapine XR as an active comparator. Treatment with brexpiprazole resulted in a higher response rate (risk ratio RR = 0.93, 95% CI 0.89, 0.97; NNT = 17), remission rate (RR = 0.95, 95% CI 0.93, 0.98; NNT = 25), and reduction of the MADRS total score (SMD = −0.20, 95% CI −0.29, −0.11). Doses beyond 2 mg/day produced a significantly greater RR than doses ≤2 mg/day (RR 0.96 vs. 0.89).

Two small trials (NCT01670279: $n = 18$ and NCT01837797: $n = 15$) evaluated the safety and tolerability of brexpiprazole in elderly patients above 65 years and 70–85 years, respectively (22). Efficacy assessment was planned only for the NCT01837797 study. There were 129 enrolled patients, and only 15 patients were randomized to Period 2 (double-blind addon treatment with brexpiprazole at 1 mg, 3 mg, or placebo) before the study was terminated. Due to the limited number of patients, no efficacy data were collected. Unpublished results of a completed 4-week (plus 2-week follow-up) study of brexpiprazole augmentation (up to 3 mg/day) with intranasal ketamine (40 mg) in 51 depressive patients (NCT03149991) were negative (22).

Published were findings of three 8-week, double-blind trials examining the efficacy of cariprazine as an addon treatment of depression with insufficient response to antidepressants. The first 8-week study with 819 patients who did not respond to a minimum of 6 weeks of antidepressant therapy brought positive results (33). Significant improvement in the MADRS total score vs. placebo was observed for cariprazine doses of 2–4.5 mg/day from week 2 ($p = 0.011$; NNT for response at

the endpoint was 9) but not for doses of 1–2 mg/day. The second study with 530 randomized patients failed to demonstrate significant improvement with cariprazine 1.5–4.5 mg daily vs. placebo (34). Similarly, negative results were found in a study with 231 patients that used two cariprazine dosing schedules, 1–2 mg/day or 2–4.5 mg/day (35). Two additional 6-week placebo-controlled RCTs with cariprazine as an adjunctive treatment (1.5–3 mg) to antidepressant treatment in major depression have been completed, but the results are not yet available (22).

### Other Neuropsychiatric Disorders

The oral formulation of aripiprazole was investigated in three placebo-controlled RCTs in Alzheimer's disease (36). In the management of psychosis, only one of three 10-week studies met the primary efficacy criteria. In a 10-week, placebo-controlled study with 208 outpatients, the mean age was 81.5 years, and aripiprazole (mean end dose of 10.0 mg/day) yielded greater improvement than placebo only in the Brief Psychiatric Rating Scale (BPRS) psychosis ($p < 0.03$) and core ($p < 0.04$) subscales but not in the primary outcome measure, the caregiver assessment Neuropsychiatric Inventory (NPI) psychosis subscale (37). The second study with 256 inpatients used flexible dosing of aripiprazole (2 to 15 mg/day) with a mean aripiprazole dose at the endpoint of 8.6 mg/day (38). There was no significant difference between aripiprazole and placebo in the NPI psychosis subscale, only in several secondary measures, suggesting efficacy on agitation, anxiety, and depression. In the third study, 487 institutionalized nursing home patients were randomized to placebo or fixed doses of aripiprazole at 2, 5, or 10 mg/day (39). Aripiprazole at 10 mg/day produced a statistically significant improvement vs. placebo on the NPI-Nursing Home (NPI-NH) Psychosis subscale score ($-6.87 \pm 8.6$ vs. $-5.13 \pm 10.0$; $p = 0.013$) at week 10, as well as on the secondary measures [BPRS, CGI, Cohen-Mansfield Agitation Inventory (CMAI)].

The clinical efficacy and safety of brexpiprazole in the management of agitation associated with Alzheimer's disease was tested in two placebo-controlled RCTs (40). Both studies were 12-week trials. Study 1 ($n = 433$) used a fixed dose of 2 mg of brexpiprazole daily, and Study 2 ($n = 270$) used a flexible dosing schedule of 0.5–2.0 mg/day. The results showed that agitation, measured by the reduction of CMAI score, was reduced by a dose of 2 mg, but not by lower doses. The dose of 2 mg in Study 1 significantly outperformed placebo (adjusted mean difference $-3.77$, 95% CI $-7.38$, $-0.17$; $p = 0.040$), and *post hoc* analysis of Study 2 also found better efficacy of the maximum dose of 2 mg ($-5.06$, 95% CI $-8.99$, $-1.13$; $p = 0.012$).

Two small double-blind, placebo-controlled studies examined aripiprazole addon to SSRIs in the treatment of obsessive–compulsive disorder (OCD). In the first trial, 40 patients were randomized to 16 weeks of administration of aripiprazole 15 mg/day or placebo (41). Among the 30 completers, adjunctive aripiprazole treatment achieved significantly greater improvement on the Yale–Brown Obsessive Compulsive Scale (Y-BOCS) total score and subscores (obsessions, $p = 0.007$; compulsions, $p = 0.001$; total score, $p < 0.0001$). The second study was a 12-week trial with 39 patients, 32 of whom were evaluable (42). The results were positive, and a fixed aripiprazole dose of 10 mg/daily reduced the Y-BOCS total score significantly more than placebo ($p < 0.0001$). Compared with other antipsychotics in treatment-resistant OCD, addon aripiprazole was less effective than risperidone in a single-blind study (43) and quetiapine in a double-blind RCT (44). However, in a network meta-analysis of 20 RCTs with 790 patients comparing the efficacy and tolerability of antipsychotics in treatment-resistant OCD, aripiprazole did not differ from risperidone, haloperidol, olanzapine, quetiapine, or paliperidone (45). After excluding studies with an overall high risk of bias, only aripiprazole was significantly superior to placebo (mean difference: $-7.32$, 95% CI $-12.99$, $-1.66$).

A meta-analysis of 17 RCTs in the treatment of tic disorders and Tourette syndrome in children and adolescents that comprised 1,305 subjects, found aripiprazole to be as effective as other therapeutics, haloperidol, topiramate, risperidone, or tiapride (46). According to a recent network meta-analysis of 60 RCTs with antipsychotics for tic disorders, aripiprazole was superior to placebo (SMD $= -4.74$, 95% CI $-8.67$, $-1.06$) and tiapride (SMD $= -4.27$, 95% CI $-8.01$, $-0.58$) (47).

The efficacy of aripiprazole in the management of behavioral impairments in children and adolescents with autism spectrum disorders was examined in a meta-analysis of three RCTs that included 408 patients (48). The change in psychiatric symptoms and behavioral disturbances measured by the Aberrant Behavior Checklist showed that compared with placebo, aripiprazole significantly reduced scores across various domains: irritability (weighted mean difference, WMD $-5.41$, 95% CI $-7.58$, $-3.24$), hyperactivity/non-compliance (WMD $= -7.68$, 95% CI $-9.92$, $-5.45$), inappropriate speech impairments (WMD $= -1.23$, 95% CI $-2.08$, 0.38), and stereotypic behavior (WMD$= -2.04$, 95% CI$-3.33$, $-0.74$), but not lethargy/social withdrawal. The overall pooled response rate of the aripiprazole-treated group was significantly higher than that of the placebo-treated group, with an RR of 2.08 (95% CI 1.24, 3.46), and the NNT was 4 (95% CI 2.8, 5.7).

Several controlled trials tested adjuvant aripiprazole in substance use disorders and in patients with comorbid substance use and schizophrenia or depression (49, 50). The findings from studies on cocaine or amphetamine/methamphetamine dependence remain inconclusive.

In addition to human laboratory and neuroimaging studies, aripiprazole monotherapy was investigated in several open and controlled clinical trials of the treatment of alcohol dependence (51). In a 12-week, placebo-controlled study with 295 patients, aripiprazole failed to outperform placebo on the primary outcome measure, percentage of days abstinent, and percentage of subjects without a heavy drinking day and the time to first drinking day (52). Aripiprazole (5–15 mg/day) was as effective as naltrexone (50 mg) in a 16-week study of 75 patients in the number of alcohol-free subjects, the number of subjects who relapsed, the mean number of abstinent days, and heavy drinking days (53). Patients treated with aripiprazole remained abstinent for a longer time than those treated with naltrexone, but naltrexone treatment resulted in a greater reduction in craving scores.

### Other Drug Formulations

Aripiprazole is the only DRPA available in various drug formulations. In addition to oral formulation of tablets, orally disintegrating tablets, oral solution, intramuscular (acute) injections, or long-acting (depot) injections (LAI). In 2017, the US Food and Drug Administration (FDA) approved aripiprazole tablet with ingestible sensor, using a digital ingestion system to monitor whether the medication was taken. Long-acting injectable brexpiprazole is currently under clinical investigation; no efficacy data are accessible (22).

Both formulations of long-acting injectable aripiprazole (ALAI) once-monthly, ALAI monohydrate and ALAI lauroxil, were effective in two 12-week studies of acute schizophrenia exacerbation (54, 55). In a study sample of 340 patients, ALAI monohydrate 400 mg reduced PANSS total score at week 10 significantly more than placebo (mean difference in the least square (LS) change: −15.1, 95% CI −19.4, −10.8; $p < 0.0001$) and the CGI-Severity score (CGI-S) (LS −0.8, 95% CI −1.1, −0.6; $p < 0.0001$) (54). ALAI lauroxil also outperformed placebo in the PANSS total score improvement in a study with 623 patients (55). The difference (LS) in the 441 mg group was $-10.9 \pm 1.8$ ($p < 0.001$) and in the 882 mg group was $-11.9 \pm 1.8$ ($p < 0.001$). The proportion of patients who were very much or much improved on the CGI-Improvement (CGI-I) scale was significantly greater with aripiprazole lauroxil 441 and 882 mg treatments vs. placebo ($p < 0.001$).

Aripiprazole LAI was also tested for schizophrenia relapse prevention. ALAI monohydrate at a dose of 400 mg per 4 weeks was superior to placebo in a 1-year study with 403 patients (56). The trial was terminated prematurely because efficacy was already demonstrated by the preplanned interim analysis. The time to impending relapse was significantly delayed with ALAI treatment compared with placebo in both the interim analysis and the final analysis ($p < 0.0001$). Additionally, ALAI 400 mg once-monthly showed non-inferiority to oral aripiprazole in two long-term trials. In the first study, 662 patients were randomized to 26 weeks of treatment with ALAI or 10–30 mg/day of oral aripiprazole (57), and the second 1-year study with 455 patients used 6–24 mg/day oral aripiprazole (58).

ALAI monohydrate 400 mg once-monthly also showed prophylactic efficacy for bipolar disorder (59, 60). In a 1-year study with 266 patients, ALAI significantly delayed the time to recurrence of any mood episode compared with placebo (hazard ratio HR: 0.45, 95% CI, 0.30, 0.68; $p < 0.0001$) and time to hospitalization ($p = 0.0002$), with a recurrence rate of 2.3% for the ALAI group vs. 13.5% for placebo (HR = 0.14, 95% CI 0.04, 0.47). ALAI primarily reduced the number of manic episodes ($p < 0.0001$).

A randomized, open-label, rater-blinded study compared head-to-head ALAI monohydrate (400 mg once-monthly) with paliperidone palmitate LAI (PP-LAI; 78–234 mg once-monthly) over the course of 28 weeks of treatment (61). The study sample consisted of 295 schizophrenia patients, and the primary outcome measure was the Heinrichs–Carpenter Quality-of-Life Scale (QLS). The results revealed a statistically significant least squares mean difference between the treatments in the change from baseline to week 28 on the QLS total score [4.67 (95% CI 0.32, 9.02), $p = 0.036$] in favor of ALAI over PP-LAI, suggesting superiority of ALAI on clinician-rated quality of life. Moreover, ALAI was also significantly more efficacious for clinical improvement measured by the change in the CGI-S ($p < 0.01$).

The primary goal of a naturalistic, 1-year randomized trial was to compare clinical efficacy, substance craving intensity, and quality of life between aripiprazole LAI (400 mg once-monthly) and paliperidone LAI (100 mg once-monthly) in 101 patients with psychosis (schizophrenia spectrum or bipolar disorder) and comorbid substance use (62). The results showed that both drugs yielded significant improvements, with a comparable effect in the reduction of psychopathology, but aripiprazole was superior in the improvement of quality of life and craving reduction.

A short-acting intramuscular injectable formulation of aripiprazole was effective at reducing acute agitation associated with psychosis in two placebo-controlled studies with an analogous design (63, 64). Aripiprazole (1–15 mg i.m.), haloperidol, or placebo were administered to a total of 805 acutely psychotic patients diagnosed with schizophrenia, schizoaffective disorder, or schizophreniform disorder. The doses of aripiprazole, 5.25 or 9.75 mg, significantly outperformed placebo and were as effective as an active comparator of a haloperidol intramuscular injection (6.5–7.5 mg/day). Compared with placebo, aripiprazole produced a 1.5- to 2-fold greater reduction in mean PANSS-Excited Component scores (PANSS-EC) 2 h after the first dose (primary endpoint).

An intramuscular injectable formulation of aripiprazole significantly reduced acute agitation associated with manic episode in a single, placebo-controlled trial (65). A study sample of 301 acutely agitated bipolar patients was randomized to 9.75 or 15 mg of aripiprazole injection, lorazepam 2 mg i.m., or placebo. Aripiprazole at doses of 5 mg and higher was superior to placebo and as effective as lorazepam. Improvements in the PANSS-EC scores at 2 h were significantly greater with i.m. aripiprazole (9.75 mg, −8.7; 15 mg, −8.7) and i.m. lorazepam (−9.6) vs. i.m. placebo (−5.8; $p \leq 0.001$).

Aripiprazole i.m. injection showed efficacy in the reduction of acute agitation in Alzheimer's, vascular, or mixed dementia in a trial with a primary outcome of tolerability and safety (66). In a 24-h study of 129 inpatients, doses of 10 or 15 mg (but not 5 mg) were superior to placebo in the improvement of PANSS-PEC at 30 min and maintained their superiority throughout the 24-h study.

## Comparative Efficacy

None of the double-blind randomized studies in various indications compared directly, head-to-head, efficacy between the reviewed dopamine receptor partial agonists. Three acute schizophrenia trials, two double-blind and one open-label, used aripiprazole as an indirect comparator of the tested DRPAs to control for study sensitivity (22, 67, 68).

The objective of a placebo-controlled, 6-week Phase II RCT (NCT00905307) was to establish the optimal dose of brexpiprazole in acute schizophrenia based on efficacy, safety, and tolerability (22). The results have not been published yet. In a failed study with a sample of 459 patients, active treatment

**TABLE 5 |** Comparison of clinical efficacy of DRPAs vs. placebo using number needed to treat for therapeutic response (NNT, 95% CI) in schizophrenia, acute mania (7), bipolar depression (71, 72), and major depression (70).

| | Aripiprazole | Brexpiprazole | Cariprazine |
|---|---|---|---|
| Schizophrenia—acute treatment | 8 (6, 13) | 7 (5, 12) | 10 (7, 18) |
| Schizophrenia—relapse prevention | 5* | 4* | 5* |
| Bipolar mania | 7 (5, 11) | n.s. | 5 (4, 18) |
| Bipolar depression | 45 (10, ∞) | – | 10 (7, 21) |
| Major depressive disorder | 9 (5, 24) | 16 (8, 52) | 16 (10, 34) |

**based on a single study; n.s., no significant difference.*

arms (brexpiprazole at doses of 0.25 mg, 1 ± 0.5 mg, 2.5 ± 0.5 mg, 5 ± 0.5 mg, or aripiprazole 15 ± 5 mg daily) did not differ significantly from placebo in any of the efficacy measures.

The acute antipsychotic efficacy of cariprazine (3 or 6 mg/day) and aripiprazole (10 mg/day) was comparable in a randomized trial with 617 schizophrenia patients (67). A statistically significant reduction in the PANSS total score vs. placebo was similar across all three active arms: cariprazine 3 mg (LSMD −6.9, 95% CI −10.1, −1.9), cariprazine 6 mg (LSMD −8.8, 95% CI −12.9, −4.7), and aripiprazole 10 mg (LSMD −7.0, 95% CI −11.0, −2.9).

Aripiprazole as a positive control to confirm assay sensitivity was also included in an open-label randomized study of brexpiprazole in acute schizophrenia (68). The study aim was to explore changes in efficacy, cognitive functioning, and safety over the course of 6 weeks of treatment with flexibly dosed brexpiprazole (target dose 3 mg/day) or aripiprazole (target dose 15 mg/day) monotherapy. A total of 97 schizophrenia patients were randomly (2:1) assigned to a 6-week open treatment. Improvement observed in the PANSS total score was comparable in both treatment arms: the least squares mean improvement observed at week 6 was −22.9 points for brexpiprazole ($p <$ 0.0001 vs. baseline) and −19.4 points for aripiprazole ($p < 0.0001$ vs. baseline).

In clinical practice, the number needed to treat (NNT) represents a useful tool for indirect comparison of therapeutic effects measured by categorical outcomes. NNT indicates how many patients need to be treated with a new treatment to see an additional improvement over a comparator, with lower numbers, single digits, indicating clinically relevant differences. Citrome comprehensively analyzed NNT and the number needed to harm for adverse events and likelihood to be helped or harmed of the DRPAs vs. placebo in registration studies (7, 69). The comparative efficacy of DRPAs in adjuvant treatment of major depression measured by NNT can be extracted from a recent meta-analysis (70). NNT for treatment response from pivotal trials in schizophrenia, bipolar disorder, and major depression are summarized in **Table 5**.

The greatest NNT for therapeutic response in acute schizophrenia (30% or greater reduction in the PANSS total score) compared with placebo was 7 (95% CI 5, 12) in brexpiprazole (2–4 mg/day), followed by 8 (95% CI 6, 13) in aripiprazole (10–30 mg/day), and 10 (95% CI 7, 18) in cariprazine (1.5–6 mg/day) (7). Nevertheless, due to the overlap of 95% confidence intervals (**Table 5**), the differences cannot be considered significant. In the maintenance treatment of schizophrenia, NNT for the number of relapses vs. placebo is based on a single trial of each DRPA (10, 12, 13). No difference was observed between the drugs: NNT for aripiprazole was 5 (4.3), NNT of impending relapses for brexpiprazole was 4, and the cariprazine NNT was 5 (4.4).

Likewise, no statistically significant differences between the DRPAs in treatment responses can be detected for acute mania or adjunctive treatment of major depression. The NNT for response in bipolar mania (≥50% decrease in the YMRS total score) was 5 (95% CI 4, 18) for cariprazine 3–6 mg/day and 7 (95% CI 5, 11) for aripiprazole 15–30 mg/day (7). In bipolar depression, only cariprazine demonstrated a positive effect, studies with aripiprazole produced negative results, and no studies with brexpiprazole have been reported. The NNT for cariprazine in bipolar depression was 10 (95% CI 7, 12) for response and 11 (95% CI 8, 22) for remission (73). Non-significant NNT (>45) for aripiprazole confirms the superiority of cariprazine for the treatment of bipolar depression (71).

Therapeutic response in major depressive disorder, defined as a ≥50% decrease in the MADRS total score, yielded an NNT of 7 (95% CI 5, 11) for aripiprazole 2–20 mg/day and 11 (95% CI 8, 20) for brexpiprazole (1–3 mg/day) (7). In a meta-analysis where the dose was not specified and the response was not defined, the greatest response was observed for aripiprazole (NNT = 9, 95% CI 5, 24), followed by cariprazine (NNT = 16, 95% CI 8, 52), and brexpiprazole (NNT = 16, 95% CI 10, 34) (70). Despite the numeric differences in NNT, the great variance and overlap of 95% confidence intervals indicate that the DRPAs do not differ significantly in their antidepressant action.

Other options for comparing efficacy provided meta-analyses. A systematic review and network meta-analysis that included 3,925 patients indirectly compared aripiprazole with brexpiprazole in acute schizophrenia therapy (74). The results confirmed that the response rates of both antipsychotics were significantly superior to placebo: aripiprazole RR = 0.84 (95% CI 0.78, 0.92) and brexpiprazole RR = 0.84 (95% CI 0.77, 0.92). There was no statistically significant difference between the drugs in their efficacy: brexpiprazole vs. aripiprazole RR = 1.0 (95% CI 0.88, 1.12).

A large network meta-analysis of 32 oral antipsychotics enabled us to compare the acute antipsychotic efficacy of DRPAs with that of other antipsychotic agents and placebo (8). All three DRPAs were more effective than placebo in the overall change in psychotic symptoms. In a pairwise comparison, aripiprazole vs. placebo SMD = −0.38 (95% CI −0.51, −0.25), brexpiprazole vs. placebo SMD = −0.25 (95% CI −0.39, −0.11), and cariprazine vs. placebo SMD = −0.37 (95% CI −0.53, −0.21), while no analyzable data for mutual pairwise comparison of the DRPAs were available, network meta-analysis did not detect a significant difference between the DRPAs: aripiprazole vs. brexpiprazole SMD = −0.15 (95% CI −0.32, 0.01); aripiprazole vs. cariprazine SMD = −0.07 (95% CI −0.23, 0.10); cariprazine vs. brexpiprazole SMD = −0.09 (95% CI −0.29, 0.11).

For the treatment of acute mania, a network meta-analysis confirmed the superior efficacy of aripiprazole and cariprazine over placebo: aripiprazole SMD = 0.37 (95% CI 0.2, 0.55) and

**TABLE 6 |** Relative risk of the common side effects induced by DRPAs (modified from 4, 76).

| | Aripiprazole | Brexpiprazole | Cariprazine |
|---|---|---|---|
| Akathisia | + | +/– | + |
| EPS | + | + | + |
| Anxiety | ++ | + | + |
| Sedation | + | +/– | +/– |
| Weight gain | + | ++ | + |
| Metabolic effects | + | + | + |
| Hyperprolactinemia | +/– | + | +/– |
| Nausea/vomiting | + | +/– | + |
| Insomnia | + | +/– | +/– |
| Impulse control symptoms/compulsive behaviors | + | +/– | +/– |
| QTc prolongation | + | + | + |
| Postural hypotension | + | + | + |

*EPS, extrapyramidal symptoms; +/-, very low; +, low; ++, moderate.*

**TABLE 7 |** Overview of the clinical efficacy of dopamine receptor partial agonists (DRPA).

- All DRPAs have evidence of acute antipsychotic efficacy that is comparable: it is lower than in some other AP2G (clozapine, amisulpride, olanzapine, and risperidone)
- All DRPAs have comparable evidence of preventing relapse of schizophrenia
- Aripiprazole (≥15 mg/day) and cariprazine (≥3 mg/day) are effective in acute mania
- Cariprazine (1.5–3 mg/day) is effective in bipolar depression
- Aripiprazole in monotherapy (15–30 mg/day), as addon (10–30 mg/day), or LAI (400 mg/4 weeks) is effective in maintenance treatment of bipolar disorder and for preventing relapse to mania
- Aripiprazole (5–15 mg/day) and brexpiprazole (≥2 mg/day) are effective as adjunctive treatment for major depression with insufficient response
- Cariprazine (4.5 mg/day) is effective in treatment of primary, predominant negative symptoms of schizophrenia
- Aripiprazole i.m. injection (9.75 mg/day) is effective for acute agitation in psychosis or bipolar disorder
- Brexpiprazole (2 mg/day) has potential efficacy in the management of acute agitation in Alzheimer's dementia
- Aripiprazole has evidence of efficacy in other indications: treatment of schizophrenia and bipolar disorder in children and adolescents (10–17 years), clozapine augmentation in refractory schizophrenia, adjunctive treatment of obsessive–compulsive disorder (OCD), tic disorders, and autism spectrum disorders

cariprazine SMD = 0.47 (95% CI 0.22, 0.73) (75). There was no difference between the two drugs in the improvement of manic symptoms measured by YMRS reduction (SMD = 0.1, 95% CI −0.21, 0.41).

In a network meta-analysis of the efficacy and tolerability of second-generation antipsychotic monotherapy in acute bipolar depression, the only DRPA more efficacious than placebo was cariprazine; aripiprazole was not separated from placebo (72). The mean change in the MADRS total score for cariprazine was −2.29 (95% CI −3.47, −1.09), and the odds ratio for response (≥50% improvement in the MADRS) was 1.47 (95% CI 1.17, 1.82). However, the difference in response between cariprazine and aripiprazole failed to reach statistical significance on both outcome measures, change in the MADRS score (SMD = −1.21, 95% CI −3.70, −1.29), and the response rate (OR = 1.35, 95% CI 0.90, 1.95).

## Tolerability

DRPAs are generally well tolerated with a favorable safety profile (**Table 6**) (4, 76). The highest risk of akathisia, dose-dependent, is reported in cariprazine, and the lowest incidence is reported in brexpiprazole. High doses of cariprazine can also induce extrapyramidal symptoms. Brexpiprazole is associated with a medium risk of weight gain. Aripiprazole treatment can cause nausea, less frequent sedation, or pathological gambling or compulsive behavior. A recent review of EudraVigilance data found a higher reporting odds ratio of impulse control symptoms for aripiprazole than for brexpiprazole or cariprazine (77). All DRPAs have a low risk of metabolic and cardiovascular side effects and are considered as prolactin-sparing drugs.

The relationship between efficacy and safety can be assessed indirectly with the measure of likelihood to be helped or harmed (LLH) (78). LLH values of >1.0 signify that benefit (response) is more likely than harm (adverse event). LLH values of ≥10 mean that the response is at least 10 times more likely to occur than the evaluated side effect. In schizophrenia treatment, LLH ≥ 10 was found for akathisia in brexpiprazole (LLH = 16) and for somnolence in cariprazine (LLH = 10) (69). LLH for response vs. akathisia was 3.1 for aripiprazole and 1.5 for cariprazine. The LLH for response vs. somnolence was 2.5 for aripiprazole and 7.1 for brexpiprazole.

# DISCUSSION

In the absence of direct head-to-head studies between DRPAs, their comparative efficacy can only be estimated from a synthesis of available preclinical and clinical data (79). The reviewed results from controlled trials and meta-analyses clearly indicate that DRPAs do not represent a fully homogeneous group and possess different therapeutic benefits. This finding only corroborates the fact that the clinical effects of pharmacological agents are directly linked to their pharmacological profiles (4).

Our review did not reveal any significant differences between DRPAs in their antipsychotic efficacy, treatment of acute schizophrenia, or relapse prevention. For acute mania, aripiprazole doses above 15 mg/day and cariprazine doses greater than 3 mg/day are clinically effective. Data analysis suggested that cariprazine in the treatment of manic episode may have a particular effect on irritability (**Table 7**). The lack of antimanic efficacy of brexpiprazole in two RCTs can be attributed to the high placebo response, slow titration schedule, or regional differences (significant separation from placebo was observed in the EU but not the US study sites). Thus, more studies are needed (18).

In the treatment of bipolar depression, only cariprazine (1.5–3 mg/day) yielded positive results, aripiprazole studies were negative, and no data for brexpiprazole were available. Aripiprazole monotherapy or adjuvant treatment is effective as

maintenance treatment of bipolar disorder, only in preventing relapse to mania. The results of a cariprazine trial in the relapse prevention of bipolar disorder are not available yet; no studies have examined the prophylactic efficacy of brexpiprazole.

Aripiprazole (5–15 mg/day) and brexpiprazole (≥2 mg/day) were found to be effective in augmenting treatment-resistant major depression. *Post hoc* analysis suggested that adjuvant brexpiprazole in depressive disorder produces more anxiolytic and sedative effects. The potential therapeutic benefit of addon cariprazine in unipolar depression reported in a meta-analysis (with equivocal results from individual trials) needs to be further corroborated (70).

Additionally, published data suggest that brexpiprazole is expected to have better efficacy than aripiprazole on cognitive deficit in schizophrenia; cariprazine may specifically improve negative symptoms of schizophrenia. Enhancement of higher cerebral functions by partial dopamine agonism can be explained by the increased dopaminergic transmission in the prefrontal cortex. Analogously, the reduction of negative symptoms by lower doses (100–200 mg/day) of the $D_2/D_3$ receptor antagonist amisulpride is ascribed to the fact that at lower concentrations, presynaptic actions prevail and ensure that dopamine is more released at the synapse (80). Efficacy of amisulpride and cariprazine for predominant negative symptoms was also confirmed in a meta-analysis (81).

The first approved DRPA was aripiprazole (launched in the United States in 2002), and it has been used for the longest time period with extensive clinical experience available. Unlike brexpiprazole or cariprazine, aripiprazole was also tested in numerous other indications and special populations: children and adolescents, dementia patients, OCD patients, patients with tic disorders, patients with autism spectrum disorder, clozapine augmentation, and patients with substance use disorders. There are currently several ongoing trials with brexpiprazole and cariprazine in the treatment of other psychiatric conditions (e.g., attention deficit hyperactivity disorder, generalized anxiety disorder, post-traumatic stress disorder, borderline personality disorder, autism spectrum disorder, Alzheimer's dementia, alcohol use, etc.) and more studies in different indications and populations can be expected. Besides long-term availability, more data are available for aripiprazole due to the studies with various drug formulations. Thus, a reliable comparison between DRPAs can be made only for their oral formulas in few indications: schizophrenia, bipolar disorder, and major depression.

It should be noted that the evidence from clinical trials is not fully reflected in approved indications listed in the summary of product characteristics. Moreover, US and EU regulations differ. The European Medical Agency approved all three DRPAs for the treatment of schizophrenia in adults, aripiprazole for schizophrenia in adolescents 15 years of age and older, treatment of bipolar disorder, manic and mixed episodes (adults and adolescents above 13 years), monotherapy or adjuvant treatment in the maintenance treatment of bipolar disorder, and prevention of relapse to mania. The FDA additionally approved aripiprazole as an adjunctive therapy of major depressive disorder in adults, treatment of children and adolescents with acute mania, either as monotherapy or addon therapy to lithium or valproate, treatment of Tourette syndrome in children, irritability associated with autism spectrum disorder, brexpiprazole as an adjunctive therapy of major depression, and cariprazine for acute treatment of adults with manic, mixed, and depressive episodes of bipolar disorder.

Our review is the first comprehensive comparison of the clinical efficacy of partial dopamine agonists across various psychiatric disorders. All available studies, reviews, and meta-analyses, including unpublished records, were analyzed. The findings, summarized in **Table 7**, can provide useful guidance for clinicians in psychiatric practice. The results were reviewed qualitatively; heterogeneity of the data and the lack of studies in some indications did not allow more detailed statistics beyond NNT. Moreover, due to the primary focus on efficacy and space limitations, we provide only a brief overview and a general comparison of side effects, without specific details for different conditions or patient populations.

While our review focused solely on double-blind, controlled studies, we should be aware of their shortcomings, especially the limited generalizability of the results. Subject selection for RCTs, especially placebo-controlled RCTs, is biased and not representative of the general psychiatric population (82). To fully assess the efficacy and safety of any treatment, real-world data are needed. Finally, efficacy is just one of the factors in the selection of treatment. Although we exclusively examined differences in the therapeutic effects, choosing a drug for a specific patient should always be individualized, balancing risks vs. benefits, considering not only efficacy but also drug tolerability, safety profile, and preferences of the patients.

## CONCLUSIONS

The clinical efficacy of aripiprazole, brexpiprazole, and cariprazine in the treatment of various psychiatric disorders has been confirmed in numerous RCTs. Although there are no direct head-to-head comparisons between them, indirect appraisals indicate that there are clinically meaningful differences in their effects that can be attributed to their specific pharmacological profiles. More RCTs with brexpiprazole and cariprazine for various indications are needed, as well as head-to-head studies examining the variances of DRPAs in their efficacy and safety.

## AUTHOR CONTRIBUTIONS

PM, JM, and MK contributed equally to the study design, data collection, and interpretation of the findings. PM drafted the original manuscript. JM and MK reviewed and edited the paper. All authors contributed to the article and approved the submitted version.

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REVIEW
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# Dopamine in Autism Spectrum Disorders—Focus on D2/D3 Partial Agonists and Their Possible Use in Treatment

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Autism spectrum disorders (ASD) are a group of disorders characterized by impairment in social communication and repetitive and stereotyped behaviors. ASD etiology is very complex, including the effect of both genetic and environmental factors. So far, no specific treatment for the core symptoms of ASD has been developed, although attempts have been made for the treatment of repetitive behavior. The pharmacological treatment is aimed at treating non-specific symptoms such as irritability and aggression. Recent studies pointed out to the possible role of altered dopamine signaling in mesocorticolimbic and nigrostriatal circuits in ASD. In addition, several research pointed out to the association of dopamine receptors polymorphism and ASD, specifically repetitive and stereotyped behavior. In this paper, we will provide a review of the studies regarding dopamine signaling in ASD, existing data on the effects of D2/D3 partial agonists in ASD, possible implications regarding their individual receptor profiles, and future perspectives of their possible use in ASD treatment.

**Keywords: autism, D2 receptors, D3 receptors, dopamine, autism spectrum disorders**

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## INTRODUCTION

Autism spectrum disorders (ASDs) are a heterogeneous group of disorders with primary characteristics being impairment in social development and communication, associated with the presence of repetitive behaviors and restricted interests (1). ASD have been in the focus of research in the past decades, predominantly due to the rise in their prevalence. Namely, recent studies have shown that about 16.8 per 1,000 (one in 59) children aged 8 years are diagnosed with ASD (2).

Despite the increasing clinical and scientific interest in ASD, it is still a group of disorders defined only by clinical manifestations, without defined etiopathogenetic causes (1, 3).

The recommendation for ASD treatment, especially in children, are educational and behavioral interventions (4). However, recent studies show that 27–50% of persons with ASD are treated with medication (5–7). The prevalence of medication use in ASD rises with age and comorbidities (7). Without a known and well-defined underlying cause, pharmacotherapy of ASD is mostly oriented toward the controlling of associated symptoms of ASD, while there is still no evidence-based pharmacological intervention that can be used for the core symptoms of this group of disorders (8). A well-defined group of maladaptive behaviors, which includes aggression, self-injury, stereotypies. and tantrums, usually requires pharmacotherapy (1). These symptoms are seen in up to 85% of children with ASD (9) and are usually the targeted symptoms in ASD treatment with medication (10, 11).

The mostly used treatment so far was oriented toward using serotonin and dopamine-related medication. For selective serotonin reuptake inhibitor (SSRI) antidepressants, there were some positive, but conflicting results only for fluoxetine and fluvoxamine (studies with adults), while there could not be enough data to support recommendation of SSRI in the treatment of repetitive behavior in children and adults with ASD (12).

When it comes to antipsychotics, however, the benefit is somewhat more documented. The first studies from the 1980's showed benefit from the use of first generation antipsychotics (FGA), such as haloperidol, mostly on decreasing hyperactivity, stereotypic behaviors, aggressiveness, and tantrums, without the beneficial effect on learning (13). A much larger body of evidence can be found regarding the efficacy of risperidone in the treatment of both aggression/impulsivity and stereotyped behavior (14, 15). It was Food and Drug Administration (FDA) approved in 2005, for the treatment of irritability in ASD, including tantrums, aggression, and self-injury (16)—but not for stereotyped behavior.

For olanzapine, there has only been one pilot randomized controlled trial (RCT) in children with ASD (17). In this study, the Clinical Global Impression—Improvement scale (CGI-I) was improved 50% in the olanzapine group vs. 20% in the placebo group; although it showed promising results for the overall functioning in ASD, a significant weight gain remained a limiting factor for its use (17). Quetiapine has not been examined in an RCT so far, but an open-label study showed significant reduction in aggression and improvement of sleep in children and adolescents with ASD (18). No RCTs were done for clozapine and ziprasidone, as well (16), although in open label studies, these medications were found to be effective in treatment of aggression and irritability (16). One study compared the clinical efficacy of amisulpride and bromocriptine in a randomized, double-blind, crossover trial in nine children with ASD. Amisulpride had no effect on the overall autistic behavior but was effective in treating negative symptomatology, such as inhibition and withdrawal (19).

In spite of some positive effects in the reduction in maladaptive behaviors, the adverse effects of the regularly used pharmacotherapy are significant and limit their use in children and adults with ASD. A study done in 202 subjects with ASD showed that treatment with risperidone, aripiprazole, and olanzapine resulted in statistically significant increase in body mass index (BMI) z-score, while this was not the case with ziprasidone and quetiapine. The greatest increase in BMI was shown for olanzapine (20).

We will review the current state regarding the role of D2/D3 partial agonists in the treatment of ASD and further explore the future possibilities of their use in ASD treatment—in general and on specific symptoms of this group of disorders, specifically considering their better adverse effects profile in comparison to other FGA and second generation antipsychotics (SGA). Before that, we will briefly present the dopamine theory of ASD, with a specific focus on D2/D3 receptors.

## THE DOPAMINE THEORY OF AUTISM SPECTRUM DISORDERS

Although there has been an abundance of research related to the etiology and pathophysiology of ASD in the last two decades, the researchers are still in the dark when it comes to the mechanisms that take part in the pathogenesis of ASD (1).

The two modulatory centers of the brain that mainly modulate core traits of ASD through their rich projections are the ventral tegmental area (VTA) and substantia nigra (SN), respectively (21). The similarities in the clinical presentation of ASD to other psychiatric conditions (e.g., schizophrenia) lead to the hypothesis that the basic pathogenic process is related to the dysfunction of the dopaminergic signaling system in certain brain areas (22).

Dopamine (DA) is indeed one of the main neurotransmitters in charge of social behavior and social cognition and of control of movement (23, 24). Several researchers in this area proposed a framework that clarifies the role of the dopaminergic system in ASD (22, 25, 26).

A network of brain regions (amygdala, ventral striatum, and prefrontal cortex) works in synergy to produce different aspects of social motivation and social behavior (27). The fine alterations in this network correlate with individual differences in social motivation; e.g., anti-social personality traits in certain individuals are associated with the lesser activity in these areas (28). These processes are controlled mainly through the mesocorticolimbic (MCL) pathway, a pathway known to guide reward and motivation-related behavior (29). Research has shown that MCL connections regulate this behavior mainly through the dopaminergic projections from VTA to the nucleus accumbens and the prefrontal cortex. More specifically, the research performed on animal models confirmed that the activation of VTA leads to the activation of D1 receptors, which consequently stimulates the social interaction in animals. In contrast, the inhibition of the same area had the opposite effect—social inhibition (29).

Dichter et al. first summarized all current evidence related to the DA pathway changes in ASD and provided a new perspective in approach to ASD, mainly through the "reward-circuitry" dysfunction (25). More specifically, individuals with ASD have functional alterations in the DA mesocorticolimbic signaling pathway. These alterations include the reduction in DA release in the prefrontal cortical area and diminished responsiveness of nucleus accumbens (30). Additionally, there is evidence that ASD is related to the general hypoactivation of the reward system (31). New genetic research has discovered genetic variants and mutations of dopamine transporter (DAT) that alter dopamine transmission and consequently lead to ASD-like behavior patterns (32, 33). However, as in the majority of neurodevelopmental conditions, the susceptible genotype is not always enough to explain the occurrence of ASD. The interaction between genes and environment has proven to be the model that explains the abnormal dopamine transmission and ASD-like behavior in animal models (34, 35).

According to some authors, the alterations in dopaminergic transmission could be the cause of reduced motivation

to pursue social interactions, since the brain of autistic individuals could register these activities as "not rewarding." The reduced motivation also leads to reduced social experience and consequently to deficits in the development of social cognition.

The other important dopaminergic circuit that supports the dopaminergic theory of ASD is the nigrostriatal circuit (NS). This circuit arises from the neural projections from the substantia nigra toward the dorsal striatum. The NS modulates the motor aspects of goal-directed behavior to produce suitable actions for a specific outcome (27). Considering this crucial role of NS, it is not surprising that the dysfunction of this neural circuit could result in loops of purposeless, stereotyped patterns of behavior typical for ASD. Moreover, animal studies have proven that drug-induced dysfunction of this circuit caused stereotyped autistic-like behavior in mice (26). The treatment of these behaviors using D1/D2 dopaminergic receptor blockers leads to their reduction (36). This finding has opened a new treatment possibility in individuals with ASD.

Recently, immune alterations in ASD have been demonstrated in multiple studies, and a link between this alteration and brain maturation, and dopaminergic pathways is currently being intensively studied. A few molecular signaling pathways have been recognized linking immune activation to ASD phenotypes, including cytokine pathways. It was recently shown that children with ASD had increased interleukin (IL)-31 messenger RNA (mRNA) and protein expression levels, and elevated interleukin 16 expression compared to typically developing children (37, 38). Not only cytokines play an important role, but also CD45 cells have a key role in the pathogenesis of several autoimmune disorders (39). Ahmad and coworkers have shown that children with ASD exhibited significantly higher numbers of $CD45^+GM\text{-}CSF^+$, and other proinflammatory mediators such as $CD45^+IFN\text{-}\gamma^+$, $CD45^+IL\text{-}6^+$, $CD45^+IL\text{-}9^+$, $CD45^+IL\text{-}22^+$, $CD45^+T\text{-}bet^+$, and $CD45^+pStat3^+$ cells, compared with the control group (40).

On the other hand, research on animal models of ASD also correlated immunological alteration with alteration in transcription factor signaling pathways (41–43). It was shown in animal models that immune activation at late stages of the embryonic brain development initiates the activation and alteration in expression of multiple receptors in different signaling pathways (including immunological) that causes changes in neuronal migration and production of interneurons. For example, maternal immune activation at late gestation day in animal models altered the expression of neuregulin 1 (NRG1), its receptor tyrosine-protein kinase (ErbB4), and NRG1-ErbB4 pathway and also consequently or inherently lead to alteration in dopamine D2 receptor with further resulting in cognitive dysfunction (44). Other data suggest that early prenatal stress induces both alteration in expression of dopamine D1 and D2 receptors and increased levels of immune response genes, including the proinflammatory cytokines IL-6 and IL-1β (45).

As it was shown, several studies pointed out to the possibility of a link between immune alteration, dopaminergic pathways and ASD (44, 45), adding to the complexity and the potential significance of the dopamine theory of ASD.

## THE ROLE OF D2 AND D3 RECEPTORS AND THEIR POSSIBLE IMPLICATIONS IN ASD

D2 receptor (D2R) and D3 receptor (D3R) belong to the class-2 dopamine receptors (DRD2, DRD3 and DRD4). Their mechanism of action is manifested *via* inhibition of the cAMP production by coupling to Gi/o G proteins (46).

D2Rs are expressed throughout the brain and are localized both on presynaptic dopaminergic neurons and postsynaptic neurons targeted by dopaminergic afferences (47). That way, D2Rs have a function of modulating the DA release, while as heteroreceptors, they modulate neurotransmitter release from postsynaptic neurons, as well.

D2Rs are densely present in the striatum, while extrastriatal D2R are also detected in the cortex, mostly in the temporal, frontal, occipital, prefrontal, and anterior cingulate cortices (46, 48). The cortical density of D2Rs is 2–8% of the density found in the putamen (49).

Interestingly, D2Rs are expressed mostly in cortical areas involved in the processing of emotional and sensory-motor modalities. Variations in expression of D2Rs in different brain regions might be associated with various symptoms in psychiatric disorders (46).

A recent study was done on postmortem basal ganglia (BG) of persons with ASD comparing to neurotypical controls (50). The basal ganglia (BG) are important in action selection, learned habits, action sequences, and repetitive behaviors (50). The study showed significant elevation in D2Rs mRNA within the medium spiny neurons (MSNs) of the caudate and putamen of persons with ASD, implicating the indirect BG pathway. The indirect BG pathway enables the performing of an action chosen by the direct way, by inhibiting competing motor actions. Therefore, its disturbance might lead to motor dysfunction, stereotypy, and other repetitive behaviors in individuals with ASD (50). Besides this translation to clinical manifestations of ASD, the authors of the study point out to the fact that the BG has also been implicated in the cognitive control of language processing, therefore showing the possible link between DR2s alterations and language impairment in ASD (50).

In addition, it is important to note that D2 receptors in the prefrontal cortex PFC favor fast flexible switching between representations, meaning D2Rs have an important role in cognitive flexibility (51). This function of D2R might, therefore, be impaired in the typical ASD symptom of insistence on sameness.

The localization of D3 receptors is mostly in the limbic system (including nucleus accumbens), which is, as it is already mentioned, important in motivation and reward and also social interaction (52). The important fact is that dopamine D3R are also autoreceptors—presynaptic receptors, with inhibitory effects on dopamine impulse flow, dopamine synthesis, and dopamine release (53). The D3 system is involved in the regulation of cognitive, social, emotional, motivational, and locomotor processes (54).

It was shown that D3 receptors play an important role in cognition and learning (54). The basic rule is that D3R agonism reduces cognition, while D3 antagonism improves cognitive functioning (54). A study by Lemercier et al. showed that the basis of D3R agonism effect lies in the decreased synchronized electrophysiological activities necessary for proper cognitive functioning (55). At the level of neurotransmitters, D3 antagonists promote the release of ACh in the frontal cortex and may potentiate D-serine gating of N-methyl-D-aspartate (NMDA) receptors, making D3 antagonists even a possible choice for treatment of Alzheimer's disease (56).

D3R, more than D2R, are implicated in social interaction and play a significant role in social behavior, with D3R agonists reducing manifestations of social interaction in animals (54, 57). Cariprazine, the D3R partial agonist, has been proven to improve social interactions in animal studies (58).

The role of D3 receptors in locomotor activity has been explored in studies with D3 agonists, showing a biphasic response after their application—hypomotility at low doses and hypermotility at higher doses (54).

Therefore, besides the elements of impaired social functioning, D3 receptor might also be important in terms of repetitive behavior in ASD. The rigid, repetitive actions and stereotypies are affecting individuals with ASD greatly. As already mentioned, these kinds of behavior are often the reason to use pharmacological interventions in children with ASD (59). A study done in 2009 showed that the specific part of repetitive behavior—the insistence on sameness [derived from the Autism Diagnostic Interview (ADI-R)] is associated with polymorphism of the D3 receptor gene (DRD3) in ASD (60). It was also proven to be associated with ASD in a later study (61). These findings are important in terms of possible subphenotyping of persons with ASD. Specific clinical manifestations might have a genetic basis underlying the specific symptoms, not the ASD itself. Besides etiological importance, the subphenotyping might be of great value in terms of pharmacotherapy specifically oriented toward the symptoms (59). If we translate that notion into clinical practice, it might mean that already available drugs acting on D3 receptors might be effective in treating repetitive and stereotyped behavior.

The localization and function of D2 and D3 receptors are presented in **Table 1**.

## THE USE OF D2/D3 PARTIAL AGONISTS IN ASD

The most important compounds in this group of antipsychotics are aripiprazole, cariprazine, and brexpiprazole (64). D2/D3 partial agonists show different levels of D2 and D3 intrinsic activity, making every compound specific regarding clinical efficacy and safety (65). All of the three compounds have high affinity for the dopamine D2 receptor with brexpiprazole having the highest affinity, followed by aripiprazole and cariprazine (64). D2/D3 partial agonists have intrinsic D2 receptor activity lower than that of dopamine, leading to functional dopamine antagonism (64). Aripiprazole has intrinsic activity of about 20% that of dopamine, while brexpiprazole and cariprazine both have lower intrinsic dopamine activity than aripiprazole, similar to one another [see in (64)].

Studies have shown differences in binding kinetics of aripiprazole and cariprazine (66). Specifically, both aripiprazole and cariprazine show slow dissociation kinetics at the D2 receptor. On the other hand, a significant difference was found regarding D3 receptors. Namely, while aripiprazole shows a slow, monophasic dissociation, cariprazine exhibits a biphasic binding behavior (66). This finding might be translated into cariprazine's *in vivo* action—it might mean that it can react rapidly to variations in the dopamine level (66), which may be important for the reduction of negative symptoms (64). In addition, cariprazine is a D3 preferring D2/D3 partial agonist. This property is unique of cariprazine (67).

In the next section, we will give a short review of the specific D2/D3 partial agonists and their possible use in ASD.

Aripiprazole is an atypical antipsychotic that is FDA approved and predominantly used for management of psychosis in patients with schizophrenia and monotherapy or adjunctive therapy for acute manic episodes associated with bipolar disorder. The oral tablet and solution are also FDA approved for the treatment of ASD. The FDA approved aripiprazole in 2009 for the treatment of irritability in children (ages 6–17 years) with ASD (68). It is considered to be a stabilizer of dopamine and serotonin within the nucleus accumbens, ventral tegmental area, and frontal cortex (69).

A review of three studies suggested that aripiprazole can be effective as a short-term medication intervention for some behavioral aspects of ASD in children/adolescents (70). After a short-term medication intervention with aripiprazole, children/adolescents showed less irritability and hyperactivity and fewer stereotypies. However, notable side effects, such as weight gain, sedation, drooling, and tremor, must be considered. Relapse rates did not differ between children/adolescents randomized to continue aripiprazole vs. children/adolescents randomized to receive placebo, suggesting that re-evaluation of aripiprazole use after a period of stabilization in irritability symptoms is warranted (70).

A 2018 meta-analysis concluded that aripiprazole is efficacious in the acute treatment of irritability, hyperactivity/noncompliance, inappropriate speech, and stereotypic behavior in children and adolescents with ASD (71). On the other hand, it was shown that treatment with aripiprazole did not improve the social withdrawal in such patients. However, it is reasonably safe, more acceptable, and well tolerable in such treatments. In addition to its efficacy in ASD children and adolescents, aripiprazole has shown low risk of adverse events, particularly in cardiovascular, metabolic, and hyperprolactinemic side effects (71). A recent post-marketing surveillance study suggested that aripiprazole was well tolerated and effective in the long-term treatment of irritability associated with ASD in Japanese children and adolescents in the real-world clinical practice (72). Initially, there was an opinion that aripiprazole was safer than risperidone (73). More recent studies stated that there was not much difference in safety and efficacy between the two drugs (74). Another study compared efficacy

**TABLE 1 |** The localization and function of D2 and D3 receptors.

| Type of receptor | $D_2$ Receptors | $D_3$ Receptors |
|---|---|---|
| Localization | Presynaptic and postsynaptic neurones of striatum, cerebral cortex (temporal, prefrontal, frontal, occipital and anterior cingulate cortices), putamen (46, 48) | Presynaptic receptors in limbic system (ventral striatum including nucleus accumbens), thalamus, hippocampus, cerebral cortex, putamen (52, 53) |
| Mechanism of action | Inhibition in production of cAMP and negative modulation of PKA activity by coupling to Gi/o G proteins and negatively coupling to adenylyl cyclase (AC) (46) | |
| Function | Aspects of motor function and behavior, language processing, cognition, control of prolactin secretion and alpha MSH secretion from pituitary gland, cardiovascular system function (50, 62). | Aspects of motor function, cognition, emotional processing, social interaction (54, 63) |

and tolerability of aripiprazole and risperidone and came to a conclusion that the benefit of aripiprazole treatment seemed significantly greater at 12 weeks but that this difference did not persist at 24 weeks. This could indicate a faster positive effect of aripiprazole compared to risperidone. In this study, aripiprazole and risperidone appeared to have similar benefits in terms of efficacy and tolerability, since both drugs were well tolerated with no serious adverse events detected (75).

Brexpiprazole acts as a partial agonist at 5-HT1A and D2 receptors at similar potencies and as an antagonist at 5-HT2A and adrenergic alpha1B/2C receptors. As it was already mentioned, brexpiprazole has less intrinsic agonist activity at D2 receptor than aripiprazole, suggesting a relatively lower tendency to cause D2 partial agonist-mediated side effects, such as akathisia and restlessness (67). The affinity of brexpiprazole for the 5-HT1A receptor is over 14 times higher than that of aripiprazole and about 22 times higher than that of cariprazine (64). Therefore, the specificity of brexpiprazole might be acting on serotonin 5-HT1A receptor. That way, it might increase dopamine and acetylcholine release in the prefrontal cortex and may be beneficial for improving cognitive dysfunction, negative symptoms, and depression (76). Clinical studies in patients with schizophrenia showed a good profile of adverse effects—the only common adverse event was weight gain (67). Akathisia was not significantly associated with brexpiprazole in comparison to placebo. Most cases were mild or moderate in severity and did not lead to treatment discontinuation (67). There were no head-to-head comparisons with aripiprazole, but given the mechanism of action and recent data, brexpiprazole might be related to less akathisia and more weight gain than the two compounds (67).

To our knowledge, there were no studies of brexpiprazole in ASD, nor in specific age-groups (children or adolescents). A preclinical study showed that brexpiprazole significantly ameliorated dizocilpine-induced social recognition deficits, which was not shown for risperidone or olanzapine in this study. This mechanism might be related to brexpiprazole effect on the $5\text{-HT}_{1A}$ receptor (77). The fact that brexpiprazole might have beneficial effects on social recognition possibly might be explored in future studies in ASD.

When it comes to cariprazine, to our knowledge, there are no studies regarding its efficacy in persons with ASD. Recently, a study on an animal model of ASD was published (60). Namely, a study was done in the rat prenatal valproic acid (VPA) exposure model, and it explored the effects of cariprazine on behavioral endpoints representing the core and associated symptoms of ASD, in comparison to aripiprazole and risperidone (60). Behavioral tests such as employing social play, open field, social approach avoidance, and social recognition memory tests were done in male offspring of rat dams treated with valproates during pregnancy. Cariprazine showed dose-dependent efficacy on all behavioral endpoints and was the only test compound effective in the social play paradigm. In other behavioral measures, cariprazine was equally effective as aripiprazole and risperidone (60). Cariprazine has also been shown to facilitate social interactions in animal models of schizophrenia (58). The beneficial effect on social interactions might be explained by the findings of studies that proved that cariprazine increases dopamine release in the nucleus accumbens and ventral hippocampus (61).

Since this is a finding from an animal study, it is important to understand the implications of the results. The social play has rewarding properties; therefore, dopamine might modulate social play behavior (62). An optimal level of dopamine is required for the expression of social play behavior, while both stimulating and reducing dopaminergic neurotransmission can disrupt social play (62). It was also found that the effect of dopamine on social play is manifested mostly in the nucleus accumbens as the site of action. Blockade of either D1 or D2 NAc dopamine receptors reduced social play in animals highly motivated to play as a result of longer social isolation before testing (52). The authors conclude that the functional activity in the mesolimbic dopamine pathway plays an important role in adaptive social development, whereas abnormal NAc dopamine function may underlie the social impairments observed in developmental psychiatric disorders such as ASD (52).

The specificity of cariprazine's pharmacological profile is its affinity to D3 receptors. In addition, it is important to emphasize that cariprazine's binding affinity is not only higher for the D3 than for the D2 receptor, but also it is even higher than dopamine's affinity for the D3 receptor. That way, with dopamine at physiological doses, cariprazine acts as a D3 receptor blocker, which is not the case with other dopamine partial agonists (63). A PET study done in patients with schizophrenia showed that at dose of 1 mg/day, mean D3R and D2R occupancy was 76 and 45%, respectively, while at the 3 mg/day dose, it was 92 and 79%, respectively (64). These occupancy data first

provided evidence that cariprazine is an antipsychotic that dose dependently occupies both the D2R and D3R receptors not only *in vitro* but also *in vivo* with a 3.5–5.5-fold selectivity toward the D3R over the D2R (64).

Taken altogether, with cariprazine expressing high affinity to D3 receptors, it might be a promising medication for intensive repetitive and stereotyped behavior in ASD.

It is hypothesized that cariprazine improves mood, anhedonia in affective disorders, and negative symptoms in schizophrenia specifically with its partial agonist actions at presynaptic D3 autoreceptors in the ventral tegmental area and substantia nigra, causing the disinhibition of dopamine release in the prefrontal cortex, leading to positive dopamine tone (63).

A study done in 2017 by Nemeth et al. compared the effect of cariprazine vs. risperidone in patients with schizophrenia and predominant negative symptoms (78). Patients treated with cariprazine had a greater improvement in predominant negative symptoms of schizophrenia than did patients given risperidone. Additionally, greater improvement for patients given cariprazine vs. risperidone was seen in self-care, personal and social relationships, and socially useful activities (78).

In line with this finding, it is important to note that schizophrenia and ASD share common genetic risk factors and symptom presentations (79, 80) and that there is a significant clinical and biological overlap between the negative symptoms in schizophrenia and ASD. Negative symptoms in schizophrenia include symptoms such as reduced affective sharing and eye contact and lack of social recreational interest, while similarly, one of the core features of ASD includes deficits in social interaction (such as reduced sharing of emotion or lack of social initiation, reduced eye contact, and limited range of facial expressions) (79, 81). Hence, there is a suggested overlap between ASD and schizophrenia, in terms of impairment of social and communicative functioning. The clinical overlap has been suggested in studies showing the same patterns of social cognition between negative schizophrenia and ASD, possibly implying the same neural basis of specific social presentation (79, 82).

Having said that, the documented beneficial effect of cariprazine on negative symptoms in schizophrenia might be translated to the potential beneficial effect of cariprazine on the social impairment of ASD as well.

There are only few studies regarding the tolerability and safety of cariprazine in children and adolescents, in a population with bipolar disorder (65) and schizophrenia (66). In a retrospective study, cariprazine was proven to be well tolerable and effective, but it was done on a small sample (16 patients). There were no serious adverse events, and the main side effect was weight gain. BMI before and after treatment did not change significantly, and weight gain was greater in patients receiving higher doses of cariprazine ($\geq$4.5 mg/day) (65). In another study on 49 adolescents (13–18 years) with the diagnosis of schizophrenia, cariprazine was proven to be well tolerated during the 28-day period. There were no reported changes in the vital signs, laboratory findings, or ECG. Cariprazine did not cause parkinsonism in this study, while akathisia was shown, regardless of the dosing regimen (66).

## CONCLUSION

As it was shown, there is no pharmacotherapy oriented toward the core symptoms of ASD. Most pharmacological treatment is oriented toward maladaptive behaviors, such as aggression, self-injury, stereotypies, and tantrums. Two core groups of symptoms of ASD—impairment of social interaction and repetitive and stereotyped behaviors—might be, at least partially, explained through the dopamine hypothesis of ASD. When taking into account their localization and function, D2 and D3 receptors might be connected to these symptoms.

The D2R might be connected to stereotypy, and other repetitive behaviors, and language impairment in ASD. This hypothesis might already have a confirmation, since the FDA-approved agents, namely, aripiprazole and risperidone, show action on D2 receptors and improvement in stereotypies in persons with ASD (11, 55).

D3Rs more than D2Rs are implicated in social interaction (57) and cognition and learning (44). Clinically, polymorphism in D3R gene was also connected to insistence on sameness in persons with ASD (60).

Having said that, the group of D2/D3 partial agonists might be a potentially promising therapeutic option, not only for associated but also some of the core symptoms in ASD.

To our knowledge, there are no studies exploring the therapeutic effect of brexpiprazole or cariprazine in persons with ASD.

When everything is taken into account, having in mind the specific receptor profile of cariprazine, and its rather safe adverse events profile, one of the next steps could be directed toward the further exploration of its treatment potential in children and adults with ASD. RCT studies are needed to explore whether the specific pharmacological profile leads to specific clinical changes in this group of disorders.

Future studies might show whether pharmacological agents acting as dopamine "stabilizers" on these receptors have more therapeutic possibilities than those that are currently available and affecting only on non-core symptoms of ASD.

## AUTHOR CONTRIBUTIONS

VM-M and MP-M designed the study, contributed with their expertise in the process of literature research, and reviewing process. RG, LM, and AM-J contributed with literature research, shaping up the article, and technical work. VM-M, RG, LM, AM-J, and MP-M interpretation and writing the article. All authors contributed to the article and approved the submitted version.

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# Improving Mood and Cognitive Symptoms in Huntington's Disease With Cariprazine Treatment

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In Huntington's disease (HD), the main clinical symptoms include depression, apathy, cognitive deficits, motor deficiencies and involuntary movements. Cognitive, mood and behavioral changes may precede motor symptoms by up to 15 years. The treatment of these diverse symptoms is challenging. Tetrabenazine and deutetrabenazine are the only medications specifically approved for Huntington's chorea, but they do not affect the non-motor symptoms. For these, antidepressants, antipsychotics, and benzodiazepines have demonstrated benefit in some cases and can be used off-label. These drugs, due to sedative side effects, may negatively influence cognition. Sixteen patients having HD received a 12-week off-label cariprazine (CAR) treatment (1.5–3 mg/day). Cognitive performance and behavioral changes were measured by the Addenbrooke Cognitive Examination (ACE) test, the Cognitive and Behavioral part of the Unified Huntington's Disease Rating Scale (UHDRS), and the Beck Depression Inventory (BDI). Mixed model for repeated measures was fitted to the data, with terms of visit, baseline (BL) and their interaction. Cariprazine treatment resulted in the following changes from BL to week 12, respectively: the mean score of BDI decreased from 17.7 ± 10.7 to 10.0 ± 10.7 ($p < 0.0097$), while the Behavioral Assessment score of the UHDRS decreased from 54.9 ± 11.3 to 32.5 ± 15.4 ($p < 0.0001$); ACE score increased from 75.1 ± 11.0 to 89.0 ± 9.3 ($p < 0.0001$); Cognitive Verbal Fluency score from 6.2 ± 2.5 to 7.7 ± 2.7 ($p < 0.0103$); Symbol Digit Test from 9.2 ± 6.9 to 12.3 ± 8.9 ($p < 0.0009$). Mild akathisia was the most frequent side effect, presenting in 2 out of 16 patients (12.5%). We conclude that CAR had a positive effect on depressive mood, apathy and cognitive functions in patients with early stage of HD. Based on the neurobiological basis of these symptoms, CAR can improve the dopamine imbalance of the prefrontal cortex. This draws attention to the transdiagnostic approach which supports the further understanding of the similar symptomatology of different neuropsychiatric disorders and helps to identify new indications of pharmaceutical compounds.

**Keywords: Huntington's disease, cariprazine, apathy, cognitive decline, behavioral alteration, mood**

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# INTRODUCTION

## Huntington's Disease

Huntington's disease (HD) is an autosomal dominantly inherited polyglutamate repeat expansion disease causing neurodegeneration in the brain. In the huntingtin (*HTT*) gene the expansion of an unstable polymorphic trinucleotide repeat (CAG) region located within the open reading frame at the 5′ end of the first exon is responsible for the disease. In HD individuals the range of the expanded CAG repeats is between 36 and 250 (1). There is an inverse correlation between the number of repeats with onset, severity and progression of the disease. However, at least 6 genes are known to have a modulating effect on disease manifestation (2). The pathomechanism is related to the CAG repeat expansion in the *HTT* gene, which results in complex pathophysiological changes (3) affecting mitochondrial function, mitophagy and immune system as well (4). The clinical picture is dominated by motor symptoms (chorea, at end stage akinetic-rigorous hypokinesis), and non-motor features, such as cognitive dysfunction (including executive dysfunction, planning difficulties, cognitive decline), depression, apathy, irritability and behavioral disinhibition (e.g., making inappropriate comments, impulsivity, hypersexuality). Non-motor symptoms can appear before the motor symptoms, and are very strong predictors of loss of independence and quality of life.

## Role of Dopamine in Huntington's Disease

Dopamine (DA) as a major neurotransmitter has essential roles regulating motor function, motivation, reward/pleasure, spatial memory function, lactation, and nausea (5). Five subtypes of dopamine receptors are known and classified into two receptor classes, class D1 and class D2. D1 and D5 receptor subtypes belong to class D1, while D2, D3, and D4 subtypes belong to class D2. The two most important dopamine receptors in the pathophysiology of neuropsychiatric disorders are the D2 and D3. The highest expression of D3 receptors is localized in the islands of Calleja, but is expressed throughout the limbic circuits, including the prefrontal cortex (PFC) (6), while the highest expression of D2 is linked to the striatum. Three major dopaminergic pathways are thought to be involved in HD: the mesolimbic pathway, projecting from the ventral tegmental area to the ventral striatum in the forebrain; the mesocortical pathway projecting from the ventral tegmental area to the prefrontal cortex; and the nigrostriatal pathway connecting the substantia nigra and the caudate and putamen. These loops maintain physiological regulation on behavior and voluntary movement.

In HD, the dopamine balance in the striatum and the frontal lobe is altered, leading to changes in motion, cognitive and behavioral performance. In early stages of the disease, the amount of DA is increased while the expression of DA receptors is decreased. In later stages, similar to Parkinson's disease, the amount of DA declines (7, 8). First over- then under-production of DA mirrors the biphasic changes in motor symptoms characteristic of HD patients throughout the disease course (9, 10). Optimal function of the non-motor symptoms depends on the constant level of DA. Both low and high levels of DA lead to behavioral, mood, and cognitive malfunction (11). Increasing evidence suggests the crucial role of the dopaminergic system in the development of HD symptoms, therefore DA-release modulating compounds might be a promising therapeutic option. DA stabilizing compounds, such as dopamine partial agonists, can increase or decrease DA receptor activity depending on the dopamine levels at the synapse.

## Treatment Approaches of HD

There is a definite unmet need for causative therapies in HD. Several approaches have been designed to reduce mutant huntingtin (mHTT) concentrations in the CNS such as (1) non-allele-selective antisense oligonucleotides (ASOs); (2) gene editing strategies, including zinc finger nucleases, transcription activator-like effector nucleases, clustered regularly interspaced short palindromic repeats (CRISPR-Cas 9) techniques; (3) gene therapy, and (4) stem cells reprogramming with single-stranded RNAs, mismatch-containing RNAs, antisense oligonucleotide, and small hairpin RNA (12). However, ultimate treatment solutions are not yet available, therefore the treatment of HD still heavily relies on symptomatic treatment.

Tetrabenazine (TBZ) and deutetrabenazine (deuTBZ) are approved for the treatment of motor symptoms in HD, such as chorea. TBZ is an inhibitor of the vesicular monoamine transporter 2 and its most prevalent dose-limiting side effects include somnolence, insomnia, depressed mood, akathisia, and parkinsonism (13). The deuterated form of hydrogen molecules in deuTBZ has a longer half-life requiring less frequent daily dosing, and likely having a better tolerability profile than TBZ. Thus, far, no study has compared TBZ and deuTBZ directly. A network meta-analysis of FIRST-HD and TETRA-HD studies showed that deuTBZ and TBZ had similar anti-chorea effect and safety profile, while patients receiving TBZ were more prone to experiencing depressive symptoms and somnolence (14). An indirect treatment comparison found a greater association between TBZ-use and neuropsychiatric adverse events, like akathisia and parkinsonism, compared to deuTBZ-use (15).

Clinical trial data is lacking on the management of non-motor symptoms. The clinical trial with buspirone to treat apathy had a negative result (16). Currently, dextromethorphan/quinidine and SRX46, a vasopressin 1A receptor antagonist, are being assessed for irritability (12), while psychiatric symptoms are treated based on expert consensus[1]. Selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI) are recommended for both depression and anxiety, while irritability is managed by sedative antidepressants, antipsychotics, or mood stabilizers. However, the treatment of apathy and cognitive symptoms in HD remains challenging. To improve cognition, two small clinical trials were not able to confirm the efficacy of cholinesterase inhibitors (17). A Phase 2 trial with SAGE-718 (NMDA receptor modulation) will start in the near future[2] and a Phase1b open label trial is ongoing with nilotinib, to increase the dopamine level (NCT03764215).

[1]https://www.gedeonrichter.com/en/news/211029

[2]https://investor.sagerx.com/news-releases/news-releasedetails/sage-therapeutics-receives-fast-track-designation-sage-718

## Cariprazine

Cariprazine (CAR) is a third-generation antipsychotic approved for the treatment of schizophrenia as well as for the depressive and manic and mixed episodes associated with bipolar I disorder in adult patients[3]. Furthermore, two studies had positive results for the adjunctive treatment of major depression disorder (MDD)[1]. Cariprazine is a dopamine D3 receptor preferring partial agonist at the D2/D3 receptors as well as at the serotonin 5-HT1A receptors, and acts as an antagonist at the 5-HT2B receptors (18). In fact, cariprazine's affinity to the D3 receptors is stronger than that of any other antipsychotics or even dopamine itself (19). Due to other antipsychotics' low affinity and dopamine's high affinity for the D3 receptors, antipsychotics (except for cariprazine) cannot occupy the D3 receptors in the presence of dopamine in the living brain (20). Therefore, only cariprazine is known to have the potential to dock to these receptors and exhibit the effects usually associated with D3 receptor blockade, which include improvements in negative, cognitive and depressive symptoms as well as in motivation and reward (21).

## Study Aims

This study aimed to explore the effects of 12-week cariprazine treatment on the mood and cognitive symptoms associated with Huntington's disease.

# MATERIALS AND METHODS

## Patients

All patients had an abnormal expansion in the *HTT* gene (CAG >36) and were clinically diagnosed according to the diagnostic confidence level of the Unified Huntington's Disease Rating Scale (UHDRS). The diagnostic confidence level ranges from 0 (normal) to 4 (unequivocal extrapyramidal signs of HD, ≥99% confidence of the examiner).

The stage of the disease was identified by the Total Functional Capacity (TFC) of the UHDRS. Based on the TFC score, patients were classified into five stages that indicate levels of disease severity based on functional decline. Patients in Stage I had TFC scores of 11–13 (least severe); Stage II for scores 7–10; Stage III for scores 3–6; Stage IV for scores 1–2; and Stage V for a score of 0 (most severe).

All participants received the permission for off-label use of cariprazine issued by the Hungarian National Institute of Pharmacy and Nutrition. The study was conducted in accordance with the Declaration of Helsinki and all patients provided written informed consent.

## Study Design

This is a retrospective study aiming to evaluate the effect and safety of cariprazine in the treatment of non-motor (mood, behavioral, and cognitive) symptoms of Huntington's disease (**Table 1**). Efficacy and safety parameters were evaluated on week 8 and 12.

Cariprazine was indicated if the patient had either mood symptoms (loss of motivation, apathy, anhedonia, depression) or cognitive alterations (executive dysfunction, planning difficulties, cognitive decline). The initial dose of CAR was 1.5 mg/day in the morning, which was increased to 3 mg/day if needed. Co-medications like tetrabenazine, benzodiazepines, antidepressants or antipsychotics were allowed if needed (**Table 1**). During the 12 week observational period of the study as new medication only procyclidine was introduced if akathisia appeared.

## Efficacy Evaluations

The study duration was 12 weeks. All efficacy parameters were evaluated at baseline, on week 8 and 12. Changes from baseline in mood and behavior were measured by the Beck Depression Inventory (BDI) and the Behavioral Assessment in the UHDRS scale. The BDI is a 21-item, self-report rating inventory that measures characteristic attitudes and symptoms of depression (22). The UHDRS scale was developed by the Huntington Study Group in 1996, updated in 1999 and its Cognitive and Behavioral Sections were clarified in 2005 (23).

Changes from baseline in cognitive performance was evaluated using the Addenbrooke Cognitive Examination (ACE) test and the Cognitive part of the UHDRS (computerized Stroop Test, Symbol Digit test, and Cognitive Verbal Fluency). The ACE consists of 19 activities in five cognitive domains: attention, memory, fluency, language and visuospatial processing (24, 25). The computerized Stroop Interference Test of the Vienna Test System (SCHUHFRIED GMBH Austria) was only performed at baseline, as it was highly challenging for the patients due to motor symptoms or cognitive impairment.

## Safety Evaluations

Safety assessments performed at baseline, 8 and week 12 included: body weight, vital signs, neurological examination, ECG, and routine laboratory testing along with assessments of motor functioning and adverse events.

## Statistical Analysis

Efficacy parameters were analyzed by mixed model for repeated measures (MMRM) separately for each parameter, with the terms of visit, baseline parameter value and their interaction, assuming unstructured covariance structure and using Kenward-Roger's approximation of the degrees of freedom. Least square (LS) means of the parameters (changes) by visits were estimated and compared between visits. Results are expressed as arithmetic means (+/- standard error) and statistics are related to the LS means (+/− standard error) of change from baseline (BL). If not otherwise stated, number of patients were 15. Because of the exploratory nature of the study, and since the changes might be correlated between the efficacy parameters, no adjustment for the possible increase of the type I error rate were applied, and differences were considered significant when $p < 0.05$.

# RESULTS

## Patients

Our cohort consisted of four males and twelve female patients with a mean age of 48.13 years (± 26 yrs., SD 10.60) and mean disease duration of 3.78 years (± 6.22, SD 2.88). The average

[3]https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/204370s006lbl.pdf

**TABLE 1 |** Demographic and clinical measures of participants.

| Patient Id | Sex | Age | AOO | Repeats | TFC | Stage | Dose of CAR | Co-medication | Side effect |
|---|---|---|---|---|---|---|---|---|---|
| P1 | M | 44 | 40 | 23/50 | 10 | I | 1.5 mg | Tetrabenazine 2 × 25 mg | None |
| P2 | F | 50 | 49 | 21/50 | 10 | I | 1.5 mg | Tetrabenazine 3 × 25 mg | None |
| P3 | F | 53 | 48 | 22/41 | 10 | I | 1.5 mg | Tetrabenazine 3 × 7.5 mg<br>Paroxetin 1 × 20 mg | Akathisia |
| P4 | F | 56 | 54 | 23/42 | 7 | II | 1.5 mg | Alprazolam 3 × 0.5 mg | None |
| P5 | F | 50 | 45 | 21/48 | 12 | I | 3 mg | Glimepirid 1 × 4 mg | Akathisia |
| P6 | F | 38 | 31 | 19/47 | 10 | I | 1.5 mg | Tetrabenazine 4 × 25 mg<br>Tiapridal 1 × 100 mg | None |
| P7 | F | 42 | 41 | 18/44 | 15 | P | 4.5 mg | None | None |
| P8 | F | 55 | 40 | 17/48 | 5 | II | 1.5 mg | Tetrabenazine 2 × 12.5 mg<br>Clonazepam 3 × 0.5 mg<br>Chlorprotixen 3 × 12.5 mg | None |
| P9 | M | 76 | 46 | 20/41 | 6 | II | 1.5 mg | Tetrabenazine 3 × 25 mg<br>Alprazolam 1 × 0.25 mg | None |
| P10 | F | 45 | 41 | 23/48 | 6 | II | 1.5 mg | Tiapridal 3 × 100 mg<br>Escitalopram 1 × 5 mg | None |
| P11 | M | 57 | 34 | 26/46 | 1 | III | 1.5 mg | Tetrabenazine 4 × 25 mg<br>Sertraline 1 × 50 mg<br>Clopazipne 1 × 25 mg | None |
| P12 | F | 44 | 40 | 15/48 | 10 | I | 1.5 mg | Tetrabenazine 3 × 12.5 mg<br>Procyclidin 2 × 5 mg | Akathisia. Weight loss |
| P13 | F | 68 | 39 | 23/44 | 8 | II | 1.5 mg | Tetrabenazine 3 × 7.5 mg<br>Paroxetin 1 × 20 mg | None |
| P14 | F | 45 | 40 | 16/40 | 5 | II | 1.5 mg | Tetrabenazine 3 × 50 mg<br>Sertraline 1 × 50 mg | None |
| P15 | M | 44 | 42 | 21/48 | 12 | I | 1.5 mg | Tiapridal 3 × 100 mg | None |
| P16 | F | 37 | 36 | 20/48 | 12 | I | 1.5 mg | None | None |

*Clinical stage is calculated on the basis of functional abilities (TFC, total functional capacity Score). Co-medication describes the concomitant pharmacotherapy given for the underlying condition. Side-effect column contains observations about adverse-events recorded to be attributed to administration of cariprazine. AOO, age of onset; CAR, cariprazine.*

size of the CAG repeat expansion on the pathological allele was 46 (± 5, SD 3.28). One patient dropped out due to multiple events of non-compliance; hence, the presented efficacy analyses included data from 15 HD patients, while safety data included all 16 patients. One patient was in pre-symptomatic stage having 15 points in the TFC, eight were in Stage I, six in Stage II, and one in Stage IV (**Table 1**).

## Efficacy Outcomes

### Mood and Behavioral Symptoms

The severity of mood and apathy were evaluated by the Beck Depression Inventory and Behavioral Assessment from the UHDRS. The mean score of the BDI decreased from 17.7 + 10.7 (BL) to 10.0 + 10.7 (LS mean of change −7.7 +/−2.6 $p < 0.0097$) at week 12 (**Figure 1A**).

Baseline scores of on the Behavioral Assessment in the UHDRS showed that irritability, anxiety, depression, low self-estimation, disruptive behavior and apathy were the most severe symptoms (**Figure 2**). The overall Behavioral Assessment score of the UHDRS decreased from 54.9 + 11.3 to 32.5 + 15.4, (LS mean change −22.5 3.4 $p < 0.0001$) after 12 weeks (**Figure 3**).

### Cognitive Symptoms

Neuropsychological investigation detected the following changes regarding the cognitive functions: mean Addenbrooke Cognitive Examination total score increased from 75.1 + 11.0 (baseline) to 86.7 + 9.3 (week 12) (LS mean change 11.5+/−1.4 $p < 0.0001$, **Figure 1B**). The Cognitive Verbal fluency score of the Cognitive part of the UHDRS was 6.2 + 2.5 at the baseline, increased to 7.7 + 2.7 by week 12 (LS mean change 1.5+/−0.5, $p = 0.0103$). The mean baseline score of 9.2 + 6.9 on the Symbol Digit test increased to 12.3 + 8.9 by week 12 (LS mean change 3.1 +/−0.7, $p = 0.0009$, **Table 2**). The data of the baseline Stroop Interference tests are shown in the **Supplementary Table**.

## Safety Outcomes

The routine laboratory results (hematology and clinical chemistry) were within the normal range during the observation: serum glucose levels were slightly elevated in 3 patients at baseline (ranged between 6.3 and 7.1 mmol/l), however remained stable during the observation. Other laboratory parameters were within normal ranges. No significant changes were observed in vital signs, neurological examination, and ECG. Only a few patients reported experiencing side effects. Mild akathisia was the most frequent side effect, presenting in 2 of 16 patients (12.5%). No CAR related safety concerns arouse in motor functions.

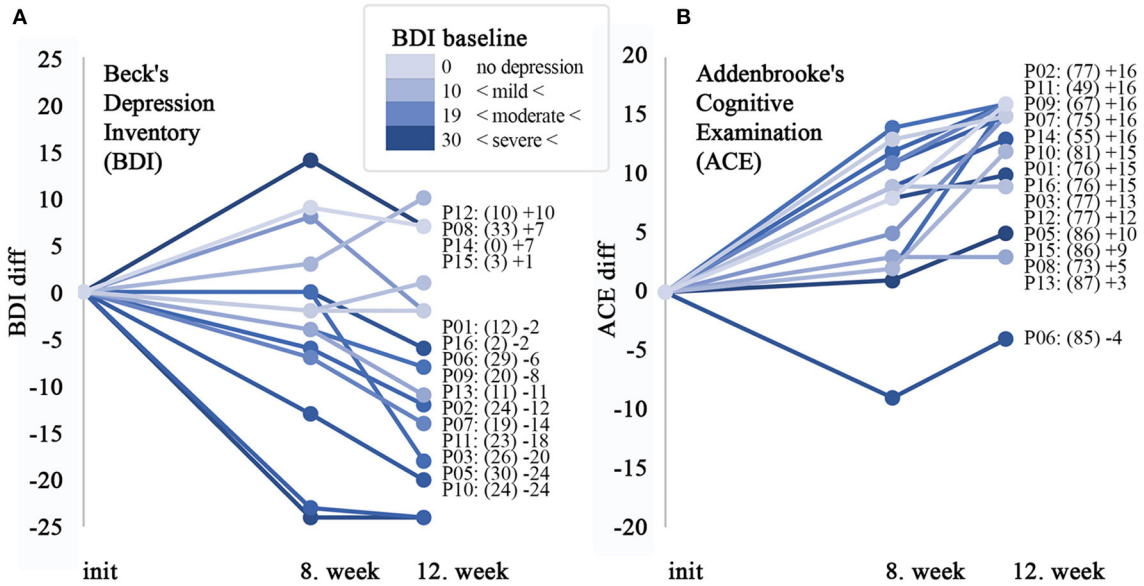


**FIGURE 1 |** Significant improvement in cognitive performance, which can only partly be explained by the effect on depression. Alteration of the cognitive performance and depression status of participants with HD after starting administration of cariprazine. **(A)** Line plot shows the difference in individual points scored by Beck's Depression Inventory (0–63) compared to the baseline and 8 and 12th weeks, respectively. Next to the diagram, all of the participating patients are listed in the order of the largest difference in observed change over the observation period. The baseline points in brackets, followed by change at the 12th week is shown. **(B)** Line plot for Addenbrook's Cognitive Examination (ACE) questionnaire (0–100). On both diagrams, the color intensity of the lines is proportional with the severity on the depression scale in a similar way.

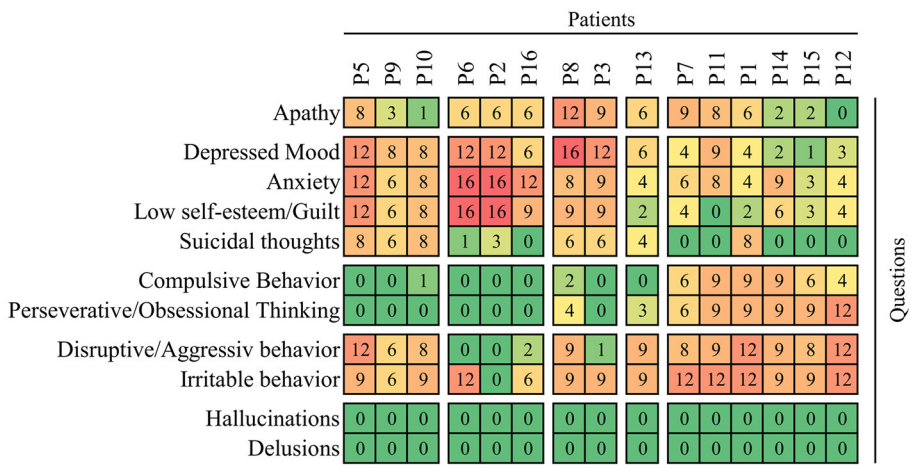


**FIGURE 2 |** Individual profiles of behavioral impairment at baseline of observation before administration of cariprazine. The frequency x severity scores are shown on the heatmap with the maximum 16 points calculated as product of 4 (which means very frequently, most all the time on a 0–4 scale) and 4 (severe, causing a restriction of activities). The rows (questions/items) and columns (patients) are clustered on the basis of average correlation and separated in blocks according to first-order branches of dendrograms.

## DISCUSSION

To our knowledge, this is the first paper providing data on the efficacy of CAR in Huntington's disease. Next to studies proving cariprazine's efficacy in schizophrenia, mania and depression associated with bipolar I disorder recent large-scale studies showed efficacy in adjunctive MDD treatment as well[1] (26, 27). Moreover, CAR is the only antipsychotic with proven superiority over another antipsychotic in the treatment of predominant negative symptoms, including anhedonia, avolition-apathy, and alogia (28). Furthermore, there are *post-hoc* analyses demonstrating improvement of cognitive dysfunction in different psychiatric disorders after CAR treatment (29–32). Positive observations have been reported further in the following

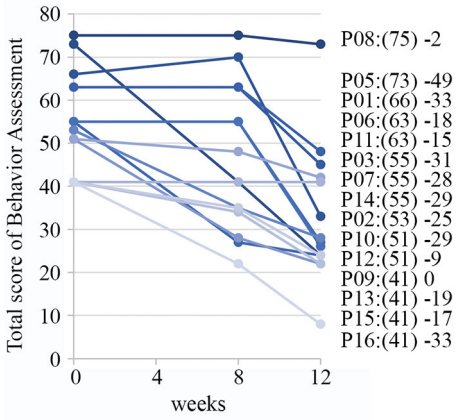


**FIGURE 3 |** Improvement on behavior assessment measures of UHDRS. Individual patient profiles are shown with captions including baseline sum of frequency x severity scores in brackets and difference between baseline and assessed scores at the week 12.

indications: mitochondrial encephalomyopathy and lactic acidosis (MELAS syndrome) due to the mutation m.A3243G where the predominantly negative symptoms and cognitive dysfunction improved (33); substance use disorder (e.g., cocaine, alcohol, methamphetamine) (34, 35); obsessive-compulsive disorder as add-on therapy (36) and borderline personality disorder (37). Our study provides data for cariprazine's efficacy in non-motor symptoms of HD especially in loss of motivation, apathy, anhedonia, depression and cognitive symptoms.

In HD, *apathy* is one of the most common psychiatric symptoms, frequently occurring several years before the onset of motor symptoms. Studies suggest that between 11 and 64% of pre-symptomatic, and 47–76% of symptomatic HD patients have apathy (38–40). Another equally prevalent symptom in HD is depression. McAllister and colleagues (41) analyzed the prevalence, timing, and functional impact of psychiatric, cognitive, and motor abnormalities in HD in more than 6,000 individuals from the European Huntington's Disease Network[4]. They found that the most prevalent symptom after motor symptoms was depression, occurring in 64.5% of individuals with HD. Differentiation between depression and apathy would be important since their pharmaceutical and behavioral therapies may differ. However, the clinical differentiation is challenging since the definition of these entities is overlapping and not constant across diseases (42, 43). Apathy covers different aspects of a loss in motivation, which is commonly observed in many psychiatric and neurological disorders, including MDD, schizophrenia, Alzheimer's disease, Parkinson's disease, HD, ADHD, frontotemporal dementia, traumatic brain injury, post-traumatic stress disorders and stroke (38). The use of this terminology differs across patient groups, although it is now acknowledged that the underlying symptoms overlap greatly (38). In neurological disorders, loss of motivation is typically categorized as the syndrome of apathy, which itself is defined as diminished motivation for physical, cognitive and/or emotional activity (44). In psychiatry—with special reference to schizophrenia—loss of motivation corresponds to negative symptom domains such as avolition (lack of motivation, sense of purpose) and anhedonia (lack/loss of pleasure) (45) (loss of motivation = avolition, anhedonia). In HD many aspects can hinder the accurate diagnosis of apathy, like anergia, hopelessness and others on the negative affect and akinetic spectrum—a deeper understanding of their shared aspects is needed to better define and manage them in HD (40).

*Depression* can either be a disease (major depression or bipolar depression) with several ICD-10 (46) criteria needed to be met, or a symptom of decreased mood. Decreased mood can occur in various neuropsychiatric disorders, such as schizoaffective disorder, schizophrenia, bipolar disorder, MDD, stroke, Parkinson's disease, HD etc. In HD anxiety and irritability is frequently associated to the depression[4].

In our study, apathy symptoms were measured by the Behavioral Assessment of the UHDRS, while depressive symptoms by the BDI. At baseline, irritability, anxiety, depression, low self-estimation, disruptive behavior and apathy dominated the clinical picture based on the Behavioral Assessment of the UHDRS. BDI detected moderate- to severe depression in 9 out of 15 patients. Both symptom domains improved significantly with CAR treatment. International guidelines for the treatment of Huntington's disease recommend the use of SSRIs or SNRIs for the treatment of either depression alone or depression combined with anxiety, suicidal ideation or impulsivity (47). However, there is a lack of evidence on specific antidepressant treatments in HD (48). A phase IIb multicentric, double-blind, placebo-controlled crossover trial with bupropion, a drug blocking the reuptake of dopamine and norepinephrine, failed to show any meaningful improvement targeting apathy in HD (16). In one case report, aripiprazole improved apathy induced by risperidone treatment (49). In our HD cohort, treatment with CAR resulted in significant improvements in both depression and apathy. This finding is crucial in the context of the large unmet need in the treatment of both apathy and depression in HD. Our study suggests that cariprazine might be a favorable therapeutic option for both symptoms.

The dopaminergic abnormalities are well-known in HD (for a comprehensive review, see Schwab et al.) (50). Altered DA signaling contributes not only to different component processes of reward, mainly mediating anticipatory phases, reinforcement processes and hedonic response (51, 52) but to cognitive manifestations of HD as well. The dysfunction of cognitive processing of emotion, similar to apathy, has been described in several CNS disorders such as depression (53), post-traumatic stress disorder (54) and progressive supranuclear palsy (55). In another dopamine associated disease, Parkinson's disease (PD) the cognitive deterioration was observed commonly in association with apathy (56, 57): apathetic PD patients had a significant decline in memory compared with non-apathetic patients (58). In Huntington's disease, cognitive deficit is also an important non-motor hallmark of the disease. Mild

[4]http://www.ehdn.org/

**TABLE 2 |** Differences during the observation period in cognitive and behavioral dimensions.

| | ACE | | | Symbol digit test | | | Verbal fluency | | | BDI | | | Behavioral assessment | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **BL** | **BL-W8** | **BL-W12** | **BL** | **BL-W8** | **BL-W12** | **BL** | **BL-W8** | **BL-W12** | **BL** | **BL-W8** | **BL-W12** | **BL** | **BL-W8** | **BL-W12** |
| P1 | **76** | 5 | 15 | **20** | 0 | 1 | **6** | 1 | 2 | **12** | 8 | −2 | **66** | 4 | −33 |
| P2 | **77** | 12 | 16 | **6** | 0 | 3 | **5** | 1 | 3 | **24** | −6 | −12 | **53** | −18 | −25 |
| P3 | **77** | 9 | 13 | **6** | 4 | 4 | **7** | 2 | 1 | **26** | −13 | −20 | **55** | −28 | −31 |
| P5 | **86** | 8 | 10 | **18** | 5 | 9 | **10** | 2 | 4 | **30** | −24 | −24 | **73** | −32 | −49 |
| P6 | **85** | −9 | −4 | **8** | 0 | 0 | **8** | −2 | −1 | **29** | 0 | −6 | **63** | 0 | −18 |
| P7 | **75** | 11 | 16 | **8** | 0 | 2 | **8** | 0 | 1 | **19** | −7 | −14 | **55** | 0 | −28 |
| P8 | **73** | 1 | 5 | **8** | 0 | −2 | **8** | 0 | −3 | **33** | 14 | 7 | **75** | 0 | −2 |
| P9 | **67** | 14 | 16 | **3** | 0 | 2 | **2** | 1 | 3 | **20** | −4 | −8 | **41** | 0 | 0 |
| P10 | **81** | 11 | 15 | **4** | 3 | 4 | **6** | 3 | 4 | **24** | −23 | −24 | **51** | −23 | −29 |
| P11 | **49** | 2 | 16 | **0** | 0 | 1 | **2** | 0 | 1 | **23** | 0 | −18 | **63** | 0 | −15 |
| P12 | **77** | 2 | 12 | **6** | 0 | 3 | **7** | −1 | 1 | **10** | 3 | 10 | **51** | −3 | −9 |
| P13 | **87** | 3 | 3 | **20** | 5 | 10 | **6** | 1 | 1 | **11** | −4 | −11 | **41** | −7 | −19 |
| P14 | **55** | 8 | 16 | **0** | 0 | 2 | **2** | 0 | 2 | **0** | 9 | 7 | **55** | 0 | −29 |
| P15 | **86** | 9 | 9 | **15** | 2 | 2 | **9** | 2 | 0 | **3** | −2 | 1 | **41** | −6 | −17 |
| P16 | **76** | 13 | 15 | **16** | 4 | 6 | **7** | 2 | 3 | **2** | −2 | −2 | **41** | −19 | −33 |

*Individual baseline values (BL, in bold) are shown following by the differences between BL values at the baseline and week 8 or 12, respectively. Scores and in case of symbol digit test and verbal fluency correct answers within the specified time are indicated.*

cognitive impairments as prefrontal symptoms are present prior to diagnosis in over half of the patients in early stages of HD (59). In many cases, similarly to psychiatric symptoms, cognitive deficits precede the onset of motor symptoms by years or even decades (41). A large multicentric study revealed that cognitive impairment is a very common feature besides depression, apathy and irritability (38). Patients with cognitive or behavioral symptoms had lower Total Functional Capacity (TFC) score of the UHDRS scale (41). In a longitudinal study of HD patients, half of those patients who were not affected by cognitive impairment at baseline experienced cognitive decline over time (60). There is a definite unmet need to improve the cognitive symptoms of HD especially in the early stage of the disease (61). In this study, treatment with cariprazine resulted in a significant improvement in the cognitive functions based on all test which was performed: the scores of the Addenbrooke Cognitive Examination, the Single Digit Modality and Verbal Fluency test significantly increased during the 12-week observational period. In our cohort, the cognitive scores improved in parallel with the BDI and UHDRS Behavioral Assessment Scores. It supports the hypothesis that by influencing the dopaminergic system, especially through the D3 receptors, the motivation and the cognitive functions can be improved (6).

Our present knowledge about the neurobiology of apathy, depression, and cognitive deficits suggests that there might be some shared mechanisms between these syndromes which are present in brain disorders associated with different etiology (38). Regarding apathy, the dysfunction of circuits connecting the PFC, basal ganglia and limbic system is believed to form the neurobiological basis (62, 63). The contributor effect of DA as a neurotransmitter in apathy besides its known involvement in the physiology of reward and hedonic response (51) is supported by the observations that in Parkinson's disease (64), and in patients with prefrontal or basal ganglia lesions, dopaminergic medication improved apathy (65), while ceasing dopaminergic medication after deep brain stimulation for PD increased apathy (64, 66).

In neurodegenerative disorders, neuropathological and neuroimaging studies revealed that apathy is strongly associated with lesion or functional impairment of the anterior cingulate cortex, ventromedial and dorsolateral PFC or ventral striatum and ventral tegmental area, as well as brain regions connected to these areas (67). Studies showed that compared to controls, there was a largely convergent network of brain regions with blunted activation during appetitive and decision-making tasks, as well as consummatory or learning phases of reward processing in patients with depression who have apathy (38). It is described that the same regions involved in the higher cognitive functions and the lesions of these areas are causing cognitive dysfunction (e.g., attention disturbances). Furthermore, in depression, activation is reduced in the above-mentioned regions, although contradictory results were reported in other studies (38). Martinez-Horta et al. (68) detected by PET that deterioration in apathy (as measured by the short version of the Problem Behaviors Assessment) significantly correlated with hypometabolism in the PFC, while the changes in depressive scores were correlated with hypometabolism in parietal-temporal regions in patients with pre-symptomatic Huntington's disease. In HD, decreases in the volume of the caudate, putamen, and the globus pallidus had the strongest correlations with clinical outcome measures for both motor and cognitive functions (69), however there is increasing evidence supporting the potential involvement of frontal lobe volume loss (68, 70).

Furthermore, the cognitive and mood symptoms (apathy and depression) might share common aetiological causes at

neurotransmitter level: the dysfunction of the DA mesocortical pathway (71). In different psychiatric disorders, negative symptoms, like apathy, depression and cognitive impairment, have been associated with hypodopaminergic states in the prefrontal cortex (72). D3 partial agonist drugs, like CAR, increase dopamine levels in the PFC, normalizing the hypodopaminergic state. D3 receptors have been shown to play a distinct role in regulating excitability in layer 5 pyramidal cells in the PFC (73). Regional selective layer 5 pyramidal neuron degeneration correlates with clinical heterogeneity in HD symptom profiles (74). Also, the higher executive functions are linked to the PFC, which is partially damaged in HD. Given that the layer 5 pyramidal cells in the PFC contain D3 receptors, it can explain how HD causes impairments in motivation and how CAR is effective in restoring it.

There were some limitations to our study. Firstly, the present version of the Behavioral Assessment of the UHDRS has its limitations concerning the measurement of apathy, anhedonia and depression, since the questionnaire includes only one item intended to capture apathy and no item specifically focusing on anhedonia. Secondly, we only examined a small sample size and patient numbers were limited. Data should be confirmed by a study including a large sample size. Finally, longer follow-up time in a larger cohort is needed to validate our data.

In conclusion, our observations provide data about the positive effect of CAR on some psychiatric symptoms such as depressive mood, apathy and cognitive functions in patients with early stage of HD. We indicated that based on the neurobiological basis of these symptoms, CAR can improve the dopamine imbalance of the prefrontal cortex and thereby the symptoms themselves. This draws attention to a symptom-based transdiagnostic approach which supports the understanding of similar symptomatology in different neuropsychiatric disorders and helps identifying new indications of pharmaceutical compounds.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Regional and Institutional Research and Ethical Committee of Semmelweis University. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

MM and ZG: study design, patient management, neurological investigation, data interpretation, and writing the manuscript. VM: data collection, data interpretation, and writing manuscript. MF: neuropsychological testing. RC: data interpretation and writing the manuscript. KA: statistical analysis. BB: neurological investigation and writing the manuscript. All authors contributed to the article and approved the submitted version.

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The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.825532/full#supplementary-material

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REVIEW
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# A Complex Combination Therapy for a Complex Disease–Neuroimaging Evidence for the Effect of Music Therapy in Schizophrenia

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Schizophrenia is a disease characterized by clinical polymorphism: a combination of diverse syndromes defined by differences in structure, course and outcome. The etiology and pathogenesis of this mental disorder is still not completely understood, in spite of the achievements in the fields of neuroscience, genetics, neuroimaging and others. Different treatment strategies have been developed for patients with schizophrenia, but the search for new pharmacological agents continues with the mission of achieving a more effective control over the disease manifestations (positive and negative symptoms), improvement of the patients' social functioning and quality of life. The accumulated clinical experience has revealed that drug treatment and the inclusion in various rehabilitation programs and social skills training shows promising results in these patients. In recent years a plethora of evidence has been compiled regarding the role of music therapy as a possible alternative in the combination treatment of patients with mental disorders, schizophrenia included. Thus, the purpose of this review is to present the reader with a more detailed and science-based account of the beneficial effect of music therapy on the general wellbeing of patients diagnosed with schizophrenia. To fulfill our goal, we will focus mainly on the evidence provided by modern neuroimaging research.

**Keywords: schizophrenia, music therapy, combination therapy, neuroimaging, negative symptoms, cognitive deficits**

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## INTRODUCTION

Schizophrenia is a devastating psychiatric disorder, characterized by a variety of different symptoms that are organized in several different clusters. The positive symptoms cluster is composed of delusions, hallucinations and disorganized speech and behavior. Conversely, the negative symptoms cluster encompasses deficits in the normal daily and social functioning of the patient–lack of motivation, anhedonia, social isolation and poverty of speech (1). Currently schizophrenia is diagnosed according to the criteria described in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) or the International Classification of Diseases, 10th edition (ICD-10). However, modern neuroimaging tools may offer a more in-depth understanding of the brain's morphological and pathophysiological abnormalities relating to schizophrenia. This search for biomarkers is an important step in the elaboration of our knowledge about the onset, course and

outcome of the disease (2). Considering the heterogeneous nature of different psychopathologies, the accumulation of data from neuroimaging studies will provide a more complex view of the affected neurocircuitry. The progress that has been made in fields such as machine learning and bioinformatics is already improving the effectiveness of large-datasets analysis (3). These advances are bringing the much needed breakthrough in the elucidation of the genetic, structural and the neuromodulatory basis of schizophrenia.

Currently, the psychopharmacological treatment of schizophrenia is based on the usage of typical and atypical antipsychotics, pharmacological agents with well-established efficacy (4). When used as maintenance treatment, antipsychotic drugs prevent the relapse of the diseases (5). Antipsychotic drugs are capable of reducing the intensity of the symptoms from the positive cluster. However, negative symptoms and cognitive deficits remain the main therapeutic obstacle as antipsychotics show little to no effect on their progression (6) from a clinical standpoint, it is also important to acknowledge the side effects of antipsychotic drugs (7). Adversities include dyskinesia, obesity and greater risk of sudden cardiac death (8–10). These side effects must be considered when analyzing the lack of compliance among some groups of schizophrenic patients (11, 12). Nevertheless, antipsychotic drugs remain essential in the management of acute psychotic states and future research in this area must take into account the possibility of overcoming the burden of the above-mentioned side effects.

Regarding negative symptoms, the introduction of third-generation antipsychotics like Cariprazine gives reason for optimism. Cariprazine is an innovative antipsychotic agent as it acts as a dual D2/D3 partial agonist, with a greater affinity for D3 receptors (13, 14). This noteworthy mechanism of action, differing vastly from that of all previously discovered antipsychotics, has been confirmed through the use of positron emission tomography (PET) scans (15). Clinical trials and observational studies have shown that Cariprazine is especially effective in the treatment of patients with predominant negative symptoms (16, 17). Negative symptoms are often viewed as multidimensional and heterogeneous. In terms of the multidimensional aspects of negative symptomatology, Cariprazine has demonstrated beneficial effects with regard to key constructs underlying negative symptoms (18). Concerning heterogeneity, negative symptoms have been strongly interlinked with, and often secondary to, cognitive, depressive, positive and motor manifestations. That allows for the implication of the unique receptor profile and mechanism of action possessed by Cariprazine in the alleviation of secondary negative symptoms (19–21). These findings complement the published results, revealing improvements in predominant negative symptoms in patients given Cariprazine, independently of the amelioration registered in other symptoms known to affect negative symptoms (16). Additionally, Cariprazine's favorable safety and tolerability aids in further differentiating the psychotherapeutic agent from the older antipsychotics (22). It stands to reason that a future clinical trial, combining the application of Cariprazine with a non-pharmacological treatment strategy and neuropsychological assessment of large patient cohorts may offer new perspective on outpatient treatment strategies for negative symptoms.

One such non-pharmacological treatment strategy is the use of music to improve the information processing capacities of the brain. Music therapy has long been used as a part of combination therapy for various neuropsychiatric disorders, ranging from affective and anxiety disorders to different forms of dementia. Neuroimaging studies provide further evidence for the brain structures and neural circuits corresponding to music processing. The processing of musical stimuli increases the activity within brain structures typically associated with the affective circuits of the brain. This effect is observed in the insula, the cingulate cortex (CC), the prefrontal cortex (PFC), hippocampus, amygdala and hypothalamus (23). Moreover, music can evoke changes in the levels of important neuromodulators like dopamine, endorphins, endogenous cannabinoids and nitric oxide (24). Understanding the beneficial effect of music is impossible if not put in the context of neuroplasticity. Neuroplasticity could be defined as the adaptive structural changes occurring in the sensory, motor and associative circuits of the brain as a response to a salient environmental stimulus. These plastic changes may be related to increased volume of certain brain areas and better connectivity between regions belonging to a particular functional circuit. In the cases of pathological or traumatic alteration in the integrity of the brain tissue, neuroplastic changes may also have compensatory function, helping to reorganize the storage and utilization of sensory information (25). Neuroimaging studies have discovered the higher rates of neuroplastic changes in the brains of musicians (26). This is yet another reason why music therapy may be a suitable choice when considering an effective therapeutic intervention during the course of outpatient treatment of patients suffering from somatic, cognitive, affective or behavioral disorders (27–29). Using innovative imaging techniques like Functional near-infrared spectroscopy (fNIRS) it has been shown that music is beneficial for memory and could modulate the activity of the PFC (30). This is further demonstrated by the utilization of Functional magnetic resonance imaging (fMRI), with studies reporting induction of plasticity and changes in connectivity during the course of music therapy, which leads to improved memory, attention and executive functions (31). Overall, the enhancement of neuroplasticity through music may invigorate various neurophysiological operations of the brain, improve movement and could even positively influence our circadian rhythms (32–34).

Regarding schizophrenia, clinical trials have provided evidence for the efficacy of music therapy as part of complex treatment (35). Music therapy may have a positive influence on the willingness of the patient to cooperate with the medical staff and other mental health professionals (36). There is a lack of general agreement about the effect of music therapy on patients with positive symptoms. Some authors have provided evidence for the beneficial effect of this kind of therapy for both positive and negative symptoms (37–39), white others have failed to replicate these results regarding the positive symptoms (40). Furthemore, the notion that musical therapy may not

be sufficient in providing help for the positive symptoms of schizophrenia is further reinforced by several different meta-analyses (36, 41, 42). Regardless, neuroimaging studies provide additional support for the application of music therapy in the context of schizophrenia. A recent study has compared two groups of patients—a group of participants that was treated only with antipsychotics and another group which received musical intervention regularly for a period of 1 month along with the pharmacological treatment. Using fMRI the researchers were able to demonstrate changes in the levels of connectivity between the striatum and the areas composing the default mode network (DMN) in the patients from the music intervention group (43).

Considering the foregoing evidence, the current review paper will try to provide additional arguments why music therapy is an efficient non-pharmacological strategy for improving the cognitive deficits and the general wellbeing of those who are fighting with schizophrenia. We will summarize some of the important contributions of the field of neuroimaging in order to outline the most prominent pathological features of the diseases. By doing so, we hope to create a conceptual framework for presenting the advantages that musical therapy has offered when being considered as a part of combination treatment.

## THE COMPLEXITY OF SCHIZOPHRENIA–LOOKING THROUGH THE LENSES OF NEUROIMAGING

It is becoming increasingly evident that schizophrenia is associated with deteriorating alteration in normal brain functioning and morphology. For example, the cortex of the frontal and temporal lobes in patients with schizophrenia has been shown to thin progressively (44). These changes correspond to the onset of the disease and its course. Additionally, the thinning of the cortex may be directly related to the outcome of the pharmacological treatment (44). Chronicity in the course of the disease is associated with an increasing hypofunction of the frontal cortical areas, which is in direct correlation to the observed deficiency in attention and memory observed in these patients (45). The deficits in working memory are further confirmed by meta-analysis of neuroimaging data, linking it to the abovementioned frontal hypofunction, while also reporting increased activity in the anterior cingulate cortex (ACC) and the left frontal pole (46). Another meta-analytic study demonstrates that during resting state, in schizophrenic patients, there is decreased activity of the ventromedial prefrontal cortex (vmPFC), the left hippocampus, the posterior cingulate cortex (PCC) and the precuneus is decreased. However, the bilateral lingual gyrus seems to be more active at this state (47). Considering white matter integrity, diffusion tensor imaging (DTI) studies illustrate the reduced fractional anisotropy (FA) of the fiber tracts connecting the PFC with the temporal regions when comparing schizophrenic patients with healthy control group (48, 49). Decreased FA is also observed in the corticothalamic and interhemispheric tracks, including corona radiata and corpus callosum (50).

The pathophysiological nature of schizophrenia has long been considered to be related to dysregulated dopaminergic volume transmission. Increased synthesis and abnormal dopamine release in the striatum has been described in patients with schizophrenia (51). Elevated dopamine levels at the synapses predict good therapeutic response to the pharmacological treatment (52). Neuroimaging studies using Single-photon emission computed tomography (SPECT) and Positron emission tomography (PET) have confirmed the important role of the cortical D2/D3 receptors in the treatment of schizophrenia. However, there is a growing scientific interest in the role of other dopamine receptors, like the D5 receptors located in the prefrontal cortex. It is believed that these receptors may enhance the therapeutic effect in many psychopathologies, schizophrenia included (53).

But schizophrenia is also linked to abnormal synaptic plasticity. Novel neuroimaging approaches may shed light on the pathological processes taking part on the microscopic level. For example, PET imaging using ligands to target the Synaptic vesicle glycoprotein 2A (SV2A) is an exciting new opportunity to measure synaptic density in schizophrenic patients (54). Integrating other innovative neuroimaging methods like the neurite orientation dispersion and density imaging (NODDI) into clinical research will allow for better understanding of the pathological changes in the gray matter in schizophrenia (55).

PET, MRI and fMRI techniques also have great clinical value, as they can provide additional information on the responses of the patient to the different pharmacological treatment strategies Higher levels of striatal dopamine have been detected in patients with first psychotic episode. The observed hyperdopaminergia predicts better response to pharmacological treatment (56, 57). Conversely, alteration in the volume of the gray matter and decrease of glial cells are predictors for poor responses to antipsychotic treatment (58, 59). Neuroimaging methods could also be used to predict the outcome of the application of non-pharmacological treatment. One morphological marker for this is cortical reserve (pre-treatment gray matter volume and surface areas) (60). Cortical surface area parameters and gray matter volume have been used as evidence to explain the better social functioning of patients during the 1 year period after they have participated in Cognitive Enhancement Therapy (60). Other authors have also suggested that there is a positive connection between the greater cortical reserve in the left PFC and the improvement in memory performance after undergoing cognitive strategy training (61). The greater volume of the gray matter in the PFC is linked to the better outcome of cognitive-behavioral therapy and reduction of the symptoms of psychosis (62). Thus, cortical reserve is the prerequisite for improvement in neuroplasticity and information processing. The application of combination therapy—integrating pharmacological treatment with cognitive-behavioral and other approaches—is the most effective way to take advantage of these "hidden" capacities of the brain.

The research work outlined here showcases the complex pathophysiological profile of schizophrenia. The reviewed evidence from these neuroimaging studies demonstrates that schizophrenia is a disease that cannot be explained by a single

etiological concept. The pathological processes are observed on various different levels in various different regions. The fact that multiple neurotransmitter systems are affected may explain the altered functional properties of many neural circuits. Further investigation of these altered properties will be crucial for the establishment of more advanced non-pharmacological approaches to negative symptoms and cognitive deficits characterizing schizophrenia. From the clinical point of view, several important findings were highlighted. First, the considerable release of dopamine in the striatum, the greater gray matter volume, the relatively preserved amount of glial cells and the increased activity in the frontoparietal network are considered to be potential markers for better response to psychopharmacological agents. On the other hand, the conserved volume of the gray matter in the PFC is seen as a possible predictor for the outcome of patients participation in non-pharmacological therapeutic programs.

## MUSIC THERAPY FOR SCHIZOPHRENIA - A SCIENCE-BASED APPROACH AND POSSIBLE THERAPEUTIC TARGETS

Musical therapy utilizes different components like melody, timbre and harmony to promote and improve information processing and the general wellbeing of the participant, putting the focus on the interaction between him and the therapist (63, 64). There is a growing interest toward the role of music therapy in treating different psychopathologies (65, 66). Researchers are providing evidence for the role of different musical interventions in inducing plastical changes (67). Music activates a large-scale bilateral network composed of frontal, temporal, parietal, cerebellar and limbic structures. This network processes various types of information and is involved in such cognitive domains like declarative memory, working memory language, attention, etc. (68). This ability of music to activate simultaneously numerous different brain regions makes it a perfect foundation for the development of rehabilitation strategies that target the cognitive, emotional and motor deficits associated with different neurological and psychiatric diseases. Thus, music therapy appears suitable for patients of various age groups, from children and adolescents with pervasive developmental disorders to adults and seniors suffering from stroke, Parkinson's disease and dementia (68).

Blood and Zetore (69) were the first to use PET to track cerebral activity during the exposure to pleasant music. The researchers were able to detect changes in the Regional cerebral blood flow (rCBF) while the participants were listening to extracts of favorite musical pieces. The exposure to pleasant music led to increased rCBF in the ventral striatum, the orbitofrontal cortex (OFC), the insula and the ACC, while decrease of rCBF was registered in amygdala, hippocampus and the ventromedial prefrontal cortex (vmPFC). The following fMRI studies further confirmed that there is an increase in the activity of the above mentioned limbic and paralimbic structures (32, 70, 71).

Salimpoor et al. (72) have demonstrated that dopamine is associated with the experience of pleasure related to music. Using PET the researchers have revealed that there is an increase in the dopamine released in the dorsal and ventral striatum while listening to pleasant music. This effect was most pronounced in the right caudate and the right nucleus accumbens (NA). Moreover, taking advantage of the better temporal resolution of fMRI the authors were able to observe the temporal dynamics of this reward signal. They demonstrated that while the participants were anticipating the peak of the emotional response the BOLD signal was stronger for the right caudate, in contrast to when they were actually experiencing that peak the signal shifted to the right NA.

Additional evidence for the significance of dopamine for the impact of music listening on reward comes from a recent publication by Ferreri et al. (73). The authors created a double blind within-subject pharmacological design, in which 27 healthy participants were assigned to receive orally levedopa (dopamine antagonist), risperidone (dopamine antagonist) or placebo in the form of lactose. The participants were exposed to self-selected and experimenter-selected musical excerpts. To measure the intensity of the pleasure response of the participants, the researchers examined their electrodermal activity (EDA—a marker for physiological arousal) and ask them to rate their experiences. The motivational responses of the participants were also measured. The attained results report that while levodopa enhanced the ability of the participants to experience pleasure related to music, risperidone had the opposing effect. This was also confirmed by the EDA rates of the two group when compared with placebo. Since risperidone is known to be an antagonist for the D2 receptors, it can be speculated that those receptors are crucial for the positive affective states induces by music. Moreover, the study by Ferrari et al. (73) offers an interesting perspective regarding schizophrenia, as one of the well-established negative symptoms of the disease is anhedonia—the inability to experience pleasure. Future studies should considered the effect of music therapy on anhedonic behavior and neuroimaging studies may provide further evidence for the role D2 receptors in music-evoked reward.

Beside dopamine, endogenous opioids may also be related to reward. According to Berridge and Kringelbach (74) "hedonic hotspots" within the NA contain opioid receptors that are activated when we are experiencing reward. Furthermore, while dopamine may be responsible for the anticipation of the reward, opioids may be related to actual feeling of pleasure (75). The pleasant feelings evoked by music are related to the greater activation of the ventral striatum (32).

It has been shown that some musical stimuli are processed in a laterized fashion—the stimuli that induce the feeling of tenderness activate the right ventral striatum, whereas those inducing happiness activate the left ventral striatum (71). The activation of the ACC and the insula by pleasant music may modulate homeostasis due to the projections these cortical areas send to the nuclei of the hindbrain (76). The ACC and the insula are thought to be part of a circuit responsible for the generations of feelings (77). Thus, these cortical areas are responsible for the interaction between emotional states and

homeostatic control (76). The hippocampus, a structure involved in episodic memory, is responsible for the formation of memories for events associated with a particular musical piece (78). Other studies have reported that there is an increase in hippocampal activity when listening to pleasant music (79). Just like the ACC and the insula, the hippocampus can also influence homeostasis through connections with other subcortical structures (80). The effect of music on these brain areas is particularly relevant to schizophrenia as the disease has been associated with autonomic dysfunctions (**Figure 1**).

A study by Schultz and colleagues (81) was the first one to try to establish existing abnormalities in the interaction between the central nervous system (CNS) and the autonomic nervous system (ANS) in paranoid schizophrenic patients. By analyzing vital parameters like blood pressure, heart rate and electroencephalogram and comparing them to those of a healthy control group, the researchers were able to demonstrate the disturbed central—automatic coupling. One meta-analysis has described that the heart rate variability in schizophrenia may be linked to the dysfunction of the "top-down" control managed by the cortico-subcortical pathways that influences the activity of the brainstem where the automatic responses are initiated (82). This correlates well-with the observed hypofunction of the PFC in schizophrenia (83). All of the above evidence is in accordance with the neurovisceral integration model of Thayer and Lane (84), a model that offers a physiological link between attention, the affective functions of the brain and automatic regulation. Thus music may act to improve the synchronization of the various nodes of the cortical system dedicated to the regulation of the homeostatic states of the body.

The paper by Salimpoor et al. (72) discussed above demonstrates the pivotal role of the striatum (both caudate

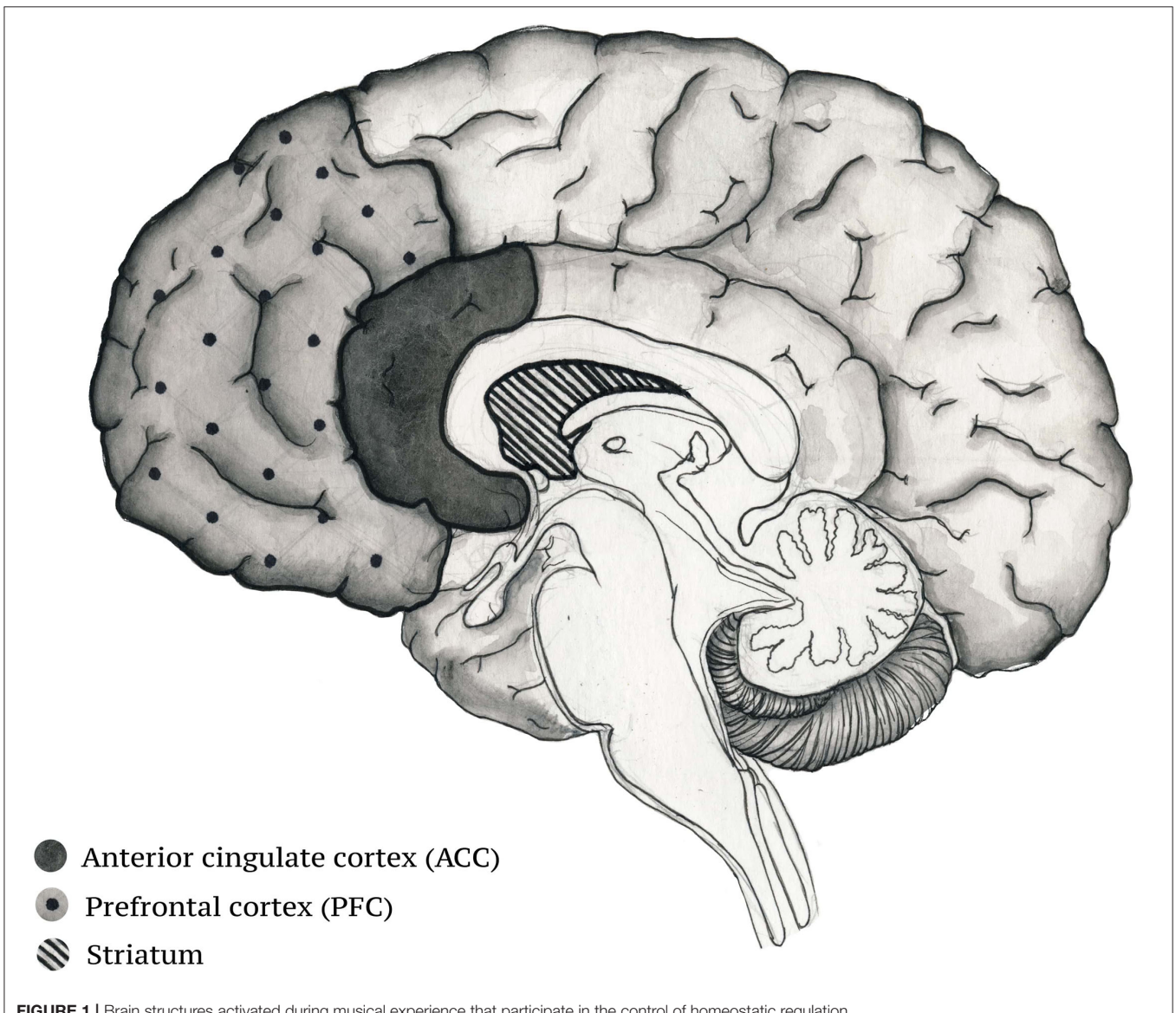


**FIGURE 1 |** Brain structures activated during musical experience that participate in the control of homeostatic regulation.

nucleus and nucleus accumbens) in reward anticipation and positive valence emotions. Beside this role in reward processing and motivation, the striatum has also been found to participate in the processing of temporal information (85) (**Figure 2**). Both animal models and human neuroimaging research have provided substantial evidence for the involvement of the striatum in interval timing (86–88) and have put forward the hypothesis that the structure is a part of a larger cortico-striatal circuit dedicated to temporal processing (89). Interval timing is the processing of temporal information in the milliseconds to seconds range. Interval timing can be further subdivided into explicit and implicit timing. Explicit timing is related to the estimation of duration and can be perceptual—stimulus duration or interstimulus interval—and motor—timing of the motor response based on the time span of the stimulus. Conversely, implicit timing is the utilization of temporal information for constructing a goal-directed behavior. Explicit timing can best be explained in terms of predictions. For example, when we try to estimate the likelihood of something happening in our environment based on the information about the duration of the available stimuli (85).

Nevertheless, interval timing in the cortico-striatal circuit is not the sole form of temporal coding in the brain. Time is an important element of the contextual framework that constitutes our memory for events (episodic memory) (90). As it was already outlined, the hippocampus is the brain structure that is responsible for the formation of episodic memories (**Figure 3**). This requires the binding of different objects and social stimuli with the information about the spatiotemporal context in which they were encountered (91). Recently it has been discovered that groups of cells in the hippocampus fire at particular moments in between successive events to bridge them and create a unifite sequential representation. These cells came to be known as "time cells" (92). Studies using intracranial microelectrode recordings in surgical epilepsy patients have confirmed the existence of cells with similar coding strategy in the human hippocampus (93, 94).

The progression of schizophrenia has been associated with a range of cognitive impairments (95). Unsurprisingly, temporal processing is one of the many affected cognitive domains (96). Ward and colleagues (97) have reviewed the behavioral evidence related to distorted interval timing in schizophrenic patients and have suggested that a greater understanding of this deficit could bring a more detailed perspective about disease-related cognitive dysfunction in general. In addition, the authors have provided a valuable neurobiological framework for the role of D2 receptors of the striatum in abnormal interval timing. Indeed, neuropharmacological studies have advanced the knowledge about the neuromodulatory functions of dopamine in interval timing (98, 99). Considering the fact that the episodic memory system is also damaged in schizophrenia (95), it will

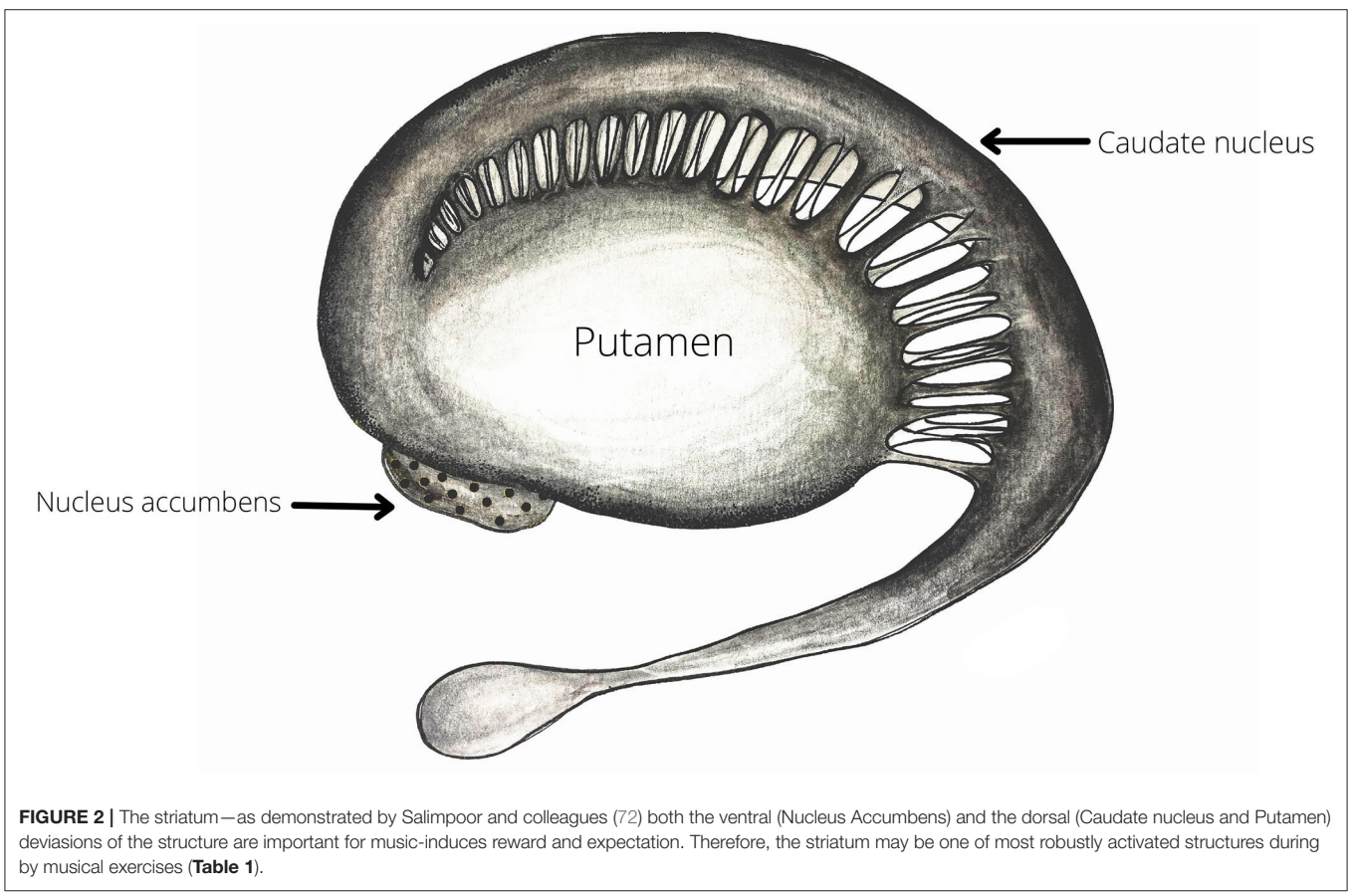


**FIGURE 2 |** The striatum—as demonstrated by Salimpoor and colleagues (72) both the ventral (Nucleus Accumbens) and the dorsal (Caudate nucleus and Putamen) deviasions of the structure are important for music-induces reward and expectation. Therefore, the striatum may be one of most robustly activated structures during by musical exercises (**Table 1**).

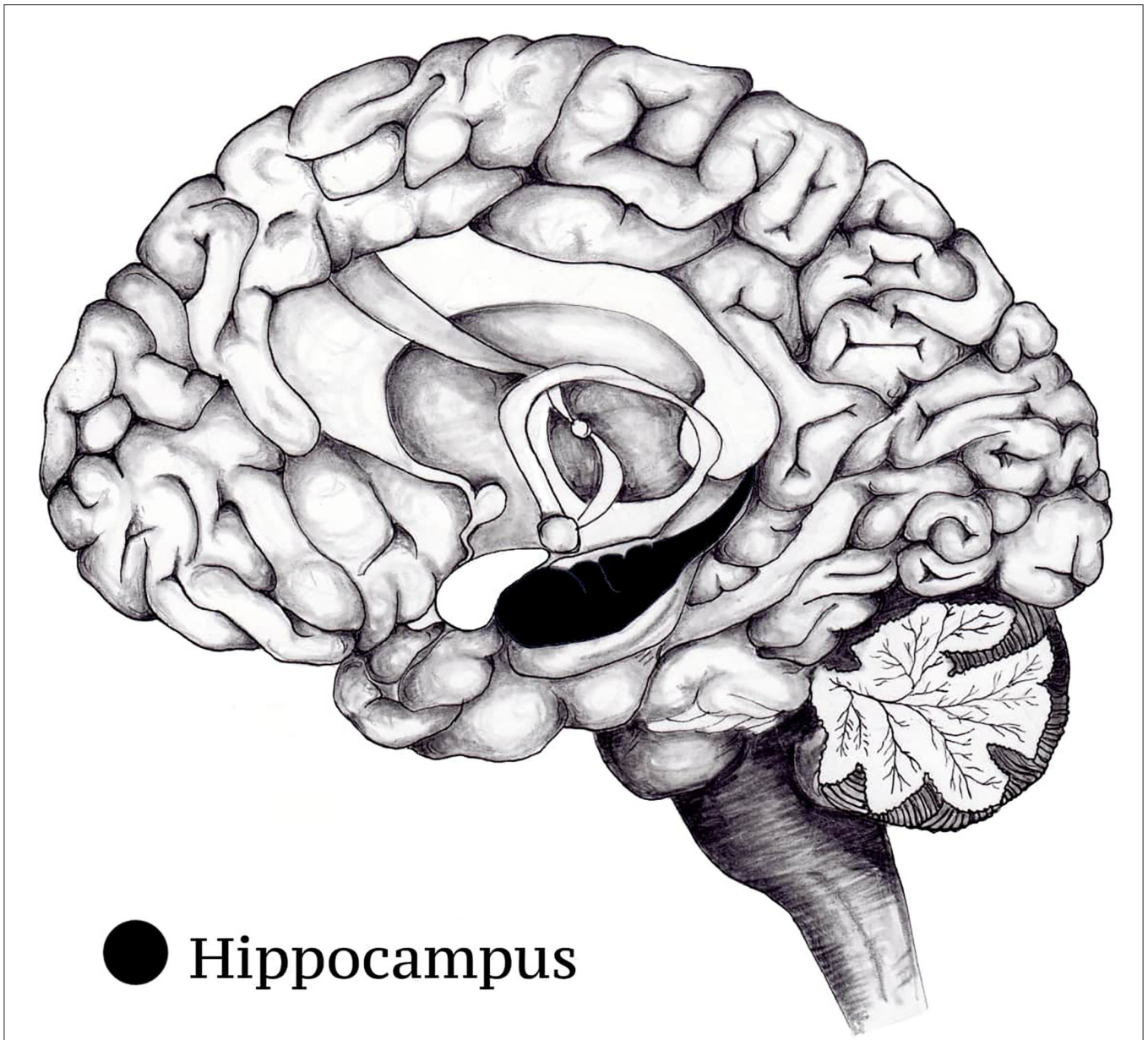


**FIGURE 3 |** Location of the hippocampus.

be interesting to further elucidate how this affects temporal processing. At the current moment, evidence from the field of neuropsychology is scarce, but a recent study by Malek et al. (100) has revealed that patients with schizophrenia have difficulties locating and ordering personal events in time. The processing of temporal information in the hippocampus is drawing great attention in the field of neuroscience (101), but how schizophrenia is altering these mechanisms remains to be established.

Popov (102) has provided a number of empirical observations on how temporal processing is altered in schizophrenia. According to him, people could perceive and analyze time on two different functional levels—the psychological and the biological. Psychological time is defined as the subjective awareness, perception and estimation of physical time and its duration. As such, it does not necessarily reflect an "intrinsic sense" of time, as much as it is merely a function of different psychophysiological and psychological processes. The author further proposes that at the psychological level humans could spontaneously process events from multiple different time points as long as these events carry their own "temporal tags" in the stream of consciousness. Thus, due to the fact that events from multiple different time points are interacting in our minds, we experience changes both sequentially and simultaneously. Additionally, Popov asserts that

**TABLE 1 |** Summary of different forms of exercises that could be applied during musical therapy.

| Active group exercises | Performance techniques | Result–expected (or reported) |
|---|---|---|
| Rhythmic (tactile and body moving type) | Direct finger-and-palm drumming on the surface of a hand drum. The exercise can also include feet tapping. A variety of rhythmic structures are used presenting different levels of gradually increasing complexity and speed. | Attempt to keep in synchron with the rest of the group; achieving better concentration; enhancing short-term memory through learning and reproducing short rhythmic patterns; working on the perception of time and self-awareness. |
| Logical rhythmic patterns overlapping with short individual "turns" | A simple regular rhythmic pulse is given to the group by the therapist to keep with unchanged. A different short rhythmic structure is introduced to a single member of the group (or improvised by him or her) to combine with the regular pulsation. The "solo" pattern is passed from one to another in a pre-set logical order or through eye contact. | Receiving and giving individual attention in a secure (friendly) environment with the active support by the therapist and the rest of the group. The individual turn is meant to take place while keeping secondary concentration into the common regular group pulsation. |
| Mathematical logic patterns | Rhythmic pattern set by the therapist with graded complexity. It is produced mostly using small percussive instruments and/or sound-accompanied body movements—feet and knee tapping. It can also incorporate counting and simple calculation. | Supporting logical (mathematical) thinking; development of reasoning and rationalizing of time and proportions; focus on the present moment (the "here and now"); improving short-term and working memory. |
| Active eye contact-based exercises | Passing of a short randomly-improvised sound signal from one participant to another through eye contact (fully non-verbal communication technique). | Stimulating visual concentration and fast reaction, eye contact and non-verbal communication; fighting eye contact fear in a friendly medium. |
| Simultaneous mirror exercises | Simultaneously, the movement and sound of a musical instrument are used by two –one participant is a "leader" and the other is a "performer," watching for simultaneous performance; the "leader" and the "performer" then change their roles. | Improving visual concentration; stimulating some executive functions; various analyzers are involved. |
| Creative exercises | Discussion and reproduction of feelings and emotions; free conscious choice of instrument, volume and rhythmic structures; group emotional improvisation. | Stimulates personal communication and discussion and expression of feelings in a secure environment; Boosting self-confidence and understanding others' feelings. |
| Improvisation | Choice of instrument, its timbre, pitch and volume usage combined with the type of body movement all based on a pre-set theme to work on. The participant is given complete freedom concerning the choice of expression through sound and rhythmic structures. | Improves the ability to make independent decisions, action plans and putting them to practice. Self-awareness of the result arises by the instant answer through the sound. Improvisation itself is a process of constant decision making with respect to a wide range of details. |
| Emotional self-control | Training for gradual transition from one emotional state to another while improvising on a musical instrument; working with negative emotions through the sound and subsequent relaxing improvisational technique. | Helps to share and deal with negative emotion experiences transferring the awareness of the ability to daily routine. |
| Relaxing techniques | Reproducing relaxing timbre, body movement and breathing exercises. | Mind and body relaxation; muscle tension relief; breath and pulse regulation. |

the same time interval may be interpreted as having different duration depending on whether it concerns a currently occurring event (prospective judgment) or one that has already passed (retrospective judgment). Popov describes the phenomenon of "excessive time retention" associated with schizophrenia—the tendency of schizophrenic patients to display significantly lengthened retrospective judgment (compared to physical time), with a higher ratio of retrospective to prospective judgment, termed the coefficient of retention, showing a positive correlation with onset of schizophrenia—acute schizophrenic patients possess 3 times higher coefficients of retention as compared to subacute patients. The description of such phenomena as "excessive time retention" could allow for the deepening of current knowledge regarding the pathogenesis and diagnosis of schizophrenia, in light of the cognitive deficit observed in patients with the disorder.

By providing a brief summary of the mechanism of temporal processing in the brain and how these mechanisms could be affected by schizophrenia, we are trying to establish a novel possibility for future neuroimaging investigation of the effect of music therapy. As it was outlined already, music can enhance the synchronization between the cortical and subcortical structures that compose the cognitive and affective circuits of the brain. Timing and temporal associations could be seen as just another aspect of this synchronized activity, with structures like the striatum and the hippocampus acting as hubs that coordinate the integration and distribution of the sensory information within the circuit. According to this view, cognitive deficits and negative symptoms will be nothing more than the manifestation of desynchrony. Thus, by taking into account the clinical evaluation of the patient, the music therapist can select from a range of available exercises (summarized in **Table 1**) to indirectly improve the balance between the different regions of the corresponding circuit. Sometimes a more creative approach may be required—improvisation. During improvisation the patient is placed in a situation, where he or she must quickly make a series of decisions regarding timbre, rhythm, sound volume and other characteristics of the musical instrument of his choice.

Conversely, the choice of musical instrument aids the patient in receiving appropriate feed-back through the produced sound. The positive effects of improvisation are associated with an improved capability for independent decision-making by the patient. The music therapist follows and records the "choices" made by the patient, as well as stimulate or "lead" (non-verbally, through improvisation in a duet or specific exercises) the patient, if the therapist finds it necessary to signal the need for making more balanced decisions.

Having outlined the known and the hypothetical effects of music therapy on information processing in the brain, it is of great clinical interest to further assess the possibility of implementing a complex therapy (medication and music therapy) in treating patients with schizophrenia. Adequate assessment of this possibility necessitates the examination of certain relevant factors, such as the selection of an appropriate group of patients, choice of accompanying pharmacotherapy, number and duration of sessions, as well as evaluation of the "dose-response" relationship, when administering music therapy. With respect to inclusion criteria, researchers place emphasis on the following: age between 18 and 65 years; ICD-10 diagnostic criteria for schizophrenia being met; psychiatric examination using Positive and Negative Syndrome Scale (PANSS) with emphasis on negative symptoms, mainly blunted affect, difficulties in establishing rapport and social withdrawal. Similarly, the following exclusion criteria may be used: relatively recent onset of schizophrenia; clinical presentation dominated by positive symptoms; changes in medication in the prior month; recent hospitalization; history of substance abuse; history of significant adverse effects of antipsychotic therapy (extrapyramidal symptoms, sedation, etc.) (103). Meta-analytical results appear to corroborate the proposed idea of a beneficial influence of music therapy on symptom reduction, including negative symptoms, as well as on quality on life (104). Additionally, there is published research that suggests that music therapy may be suitable for patients with chronic schizophrenia, on account of the often coexisting deficits in verbal communication, coupled with the fact that music therapy does not necessarily depend on patient's verbal communication ability (105).

Following the above-noted definition of suitable inclusion/exclusion criteria, the attention turns to the determinants of the appropriate "dose" of music therapy as applied to schizophrenic patients, with the number of sessions varying from 7 to 78. For this reason it is necessary for the effects of music therapy to be evaluated within a short-term and mid-term timeframe (1–4 months). It is the view of the authors that adequate evaluation of the outcome of music therapy entails careful consideration of the following: the initial patient selection; session quality, as opposed to simply the number of sessions; deeper analysis of long-term effects of music therapy; the dose-response relationship (106). Alternatively, other authors have suggested complex therapy consisting of 25 sessions of music therapy, with improvements in general functioning and alleviation of negative symptoms having been reported (103). Still other findings suggest an optimal duration of 3 months for music therapy in order for an effect on negative symptoms to be registered (104). However, a more thorough investigation of the psychophysiological bases of music therapy will bring a more comprehensive view on how to best integrate and apply it as part of a complex treatment for schizophrenia. This could only be achieved by the implementation of the multidisciplinary approach in carefully controlled research settings. The greater deal of the current neuroimaging studies have been conducted with patients who have a chronic course of the disease and have been undergoing a long-term antipsychotic treatment (107–111). This brings certain limitations to the interpretation of data as to whether the obtained results are due to the progression of the disease or due to prolonged intake of antipsychotic medication. In future, it will be interesting to use neuroimaging tools to track the effect of music therapy in patients who are past their first episode of psychosis. This information will allow the music therapists to design more accurate and patient-centered programs for their clients.

## CONCLUSION

Music is a versatile art form, capable of evoking memories, emotions, as well as the corresponding feelings. These effects of music are related to changes in our physiology and behavior. Therefore, music could influence the interaction between our mental and homeostatic states. Here we presented evidence of different natura why music therapy is a good alternative for a non-pharmacological therapy that could be combined with pharmacological treatments to form a more efficient approach toward schizophrenia. It appears that musical therapy is more suitable for the targeting of negative symptoms associated with the disease and that it can improve to a greater extent the quality of life of the patients. This view is strongly supported by a recent meta-analysis (104). It may be that the presence of positive symptoms limits the efficacy of music therapy as the patients are experiencing deficits in attention and motor coordination. It is important to note that music therapy is well-accepted among patients and that it does not demand any prior training (112). Another advantage of music therapy, compared to other psychological interventions, is that it does not involve verbal communication. Considering that one of the negative symptoms of schizophrenia is incoherent speech, music therapy may provide an alternative way for these patients to express their thoughts and emotions (113).

In schizophrenic patients, music therapy may be viewed as complementary to pharmacotherapy (114), with its utilization as part of a complex therapy for patients with negative symptoms still being debated (115). One of the key roles that music therapy may be hypothesized to serve in the alleviation of negative symptoms, might be through synergistic effects, when coupled with psychopharmacological agents with D2/D3 partial agonistic properties, such as Cariprazine. Published research has juxtaposed the effects of stimulating and blocking agents at the D2 receptor site in terms of the resulting influence on the ability of experiencing musical pleasure, with D2 antagonists, such as risperidone, displaying considerable impairment in hedonic and motivational

responses, thus potentially hindering negative symptom reduction (73). The possibility of assessing such synergism between music therapy and D2/D3 partial agonists, as mediated by changes in activity specifically at D3 receptors, is currently severely limited by the scarcity of research on the topic. Further investigation on these D3 receptor specific mechanisms would greatly benefit the understanding of the intricacies of combination therapy use with regard to reducing negative symptomatology.

## 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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# Real-Life Clinical Experience With Cariprazine: A Systematic Review of Case Studies

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**Background:** The hierarchy of evidence coming from evidence-based medicine favors meta-analyses and randomized controlled trials over observational studies and clinical cases. Nonetheless, in the field of psychiatry, where conditions are much more complex, additional evidence coming from real-world clinical practice is necessary to complement data from these gold standards. Thus, in this systematic review, the aim is to summarize the evidence coming from clinical case reports regarding cariprazine, a third-generation antipsychotic drug that has been approved for the treatment of schizophrenia and bipolar I disorder with manic, depressive or mixed features in adults.

**Methods:** A systematic review was performed using Embase and Pubmed databases searching for English-language cases published in peer-reviewed journals between 2000 January and 2021 September with the following search terms: (cariprazin* OR "rgh-188" OR rgh188 OR vraylar OR reagila) AND ("case report*" OR "case report"/de OR "case stud*" OR "case study"/de OR "case seri*").

**Results:** After the removal of duplicates, 49 articles were retrieved via the search, from which 22 were suitable for this review. These 22 articles encompassed 38 cases from which 71% described patients with schizophrenia, 16% patients with psychotic disorders, 5% patients with mood disorder and 8% described patients with other disorders such as Wernicke-Korsakoff syndrome, borderline personality disorder and obsessive-compulsive disorder with paranoid schizophrenia. The median age of patients was 31, and half of them were female. The majority of patients (76%) started cariprazine with 1.5 mg/day, and the most common maintenance dose was 4.5 mg/day (34%) and 3.0 mg/day (29%).

**Conclusion:** Cariprazine was found to be safe and effective in a wide range of psychiatric conditions with different symptom profiles from acute psychotic symptoms through addiction to negative and cognitive symptoms. The results are in-line with the established evidence from clinical trials, however, they also show how cariprazine can be successfully utilized for treating certain symptoms irrespective of the indication.

**Keywords: cariprazine, antipsychotic, case report, systematic review, psychopharmacology, partial agonist**

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# INTRODUCTION

Evidence-based medicine (EBM) is a concept developed for treating patients via the integration of the best research evidence with clinical expertise, and it has gained considerable prominence in the field of psychiatry (1). According to EBM, there is a clear hierarchy of evidence based on the different research methods in which meta-analyses of randomized controlled trials (RCTs) are the highest quality evidence, while case-control and non-controlled observational studies are the least reliable sources (1). Indeed, RCTs are considered to be the gold standard in developing scientific evidence about the efficacy and safety of new interventions such as novel medications (2).

Nonetheless, the direct application of EBM to psychiatry also means to view mental disorders exactly the same way as physical disorders, which would disregard the complexity of psychiatric conditions (1). To give an example, despite the clear advantages of RCTs, one of the biggest downside concerns is generalisability, as populations involved in these trials can significantly diverge from those seen in actual clinical practices (3). Patients enrolled in clinical trials are highly selected: they go through a rigorous screening based on an extensive list of inclusion-exclusion criteria; comorbidities and concomitant medications are usually controlled; and adherence to the therapeutic product is extensively supported which does not seem feasible in real-world settings (2).

Therefore, in the field of psychiatry, it is worth considering other sources of information, such as real-world data in EBM, to complement the knowledge gained from clinical trials (1). These can be electronic health/medical records, product/disease registries, pharmacy data, electronic devices and applications, observational studies, and of particular importance to this paper, clinical case reports (4). The advantages of real-world data over clinical trials lie in that they better represent patients with a broader range of age, illness-severity, comorbidities and usage of concomitant medications, thus they help establish all the potential applications of an intervention (3). For instance, such data can provide further information regarding the effectiveness and tolerability of a drug, which is particularly important in case of new medications, where clinical experience is not yet well-established.

Thus, the focus of this review is to summarize the evidence generated by clinical case reports of cariprazine, an antipsychotic medication that has been approved for the treatment of schizophrenia in adults by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) (5), as well as for the manic/mixed and depressive episodes associated with bipolar I disorder in adult patients by the FDA (6). Furthermore, two Phase III clinical trials found positive results for the adjunctive treatment of major depressive disorder (MDD) (7). Cariprazine is a $D_3$-preferring partial agonist at the dopamine $D_2/D_3$ receptors and at the serotonin 5-$HT_{1A}$ receptors, while acting as an antagonist at the serotonin 5-$HT_{2B}$ receptors (8). There are two major active metabolites of cariprazine, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR), both pharmacologically equipotent to cariprazine and known to be jointly responsible for the overall therapeutic effect (9, 10).

The clinical development programme of cariprazine included eight Phase II/III clinical trials with acute schizophrenia patients (11–18), four Phase II/III clinical trials including patients with bipolar I depression (19–22), three Phase II/III clinical trials (23–25) and one safety study (26) with bipolar mania patients as well as with patients with MDD (27–30). In addition, there was an observational study conducted in Latvia that explored the effectiveness and tolerability of cariprazine in schizophrenia patients with predominant negative symptoms who had inadequate response to previous antipsychotic medications (31). All in all, the findings of these trials suggest that cariprazine is a safe and effective treatment for patients with schizophrenia (1.5–6 mg/day) (32), bipolar disorder (bipolar mania: 3–6 mg/day; bipolar depression: 1.5–3 mg/day) (32) and more recently, MDD as an add-on therapy (7). Of note, cariprazine is the only antipsychotic that has proven efficacy over an active comparator in the treatment of predominant negative symptoms (18).

# METHODS

## Search Strategy

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (33). A literature search was conducted in two databases, Embase and PubMed, looking for English language articles published between January 2000 and September 2021 with the following search terms: (cariprazin* OR "rgh-188" OR rgh188 OR vraylar OR reagila) AND ("case report*" OR "case report"/de OR "case stud*" OR "case study"/de OR "case seri*"). Searches by hand and via the reference section of published case reports and previous review papers were further performed in order to identify relevant studies in addition to the ones identified by the database search.

## Inclusion and Exclusion Criteria

Titles and abstracts of identified articles were screened to determine eligibility for this systematic review; R.C. and Z.B.D. conducted the screening separately and then jointly agreed on which ones to include. During the screening process, the following inclusion criteria were considered: (1) case report involving one or more human subject, (2) treatment with cariprazine. In case cariprazine was only mentioned in the medical history of the patient, or insufficient data was provided regarding the extent of cariprazine treatment i.e., dosing strategy, titration scheme, or timeline, then the article was excluded.

## Data Analysis

Data retrieved from the case reports was summarized in tables and figures. Diagnoses, sex, age, starting dose and maintenance dose were analyzed using descriptive statistics. In the table summarizing the cases, a column titled "Problem" was created to describe the symptoms that led to the switch to/initiation of treatment with cariprazine. Thus, this does not necessary report on all the symptoms the patients experienced. The other table that summarizes outcomes with cariprazine reports on all the effects that were attributed to cariprazine treatment by the authors.

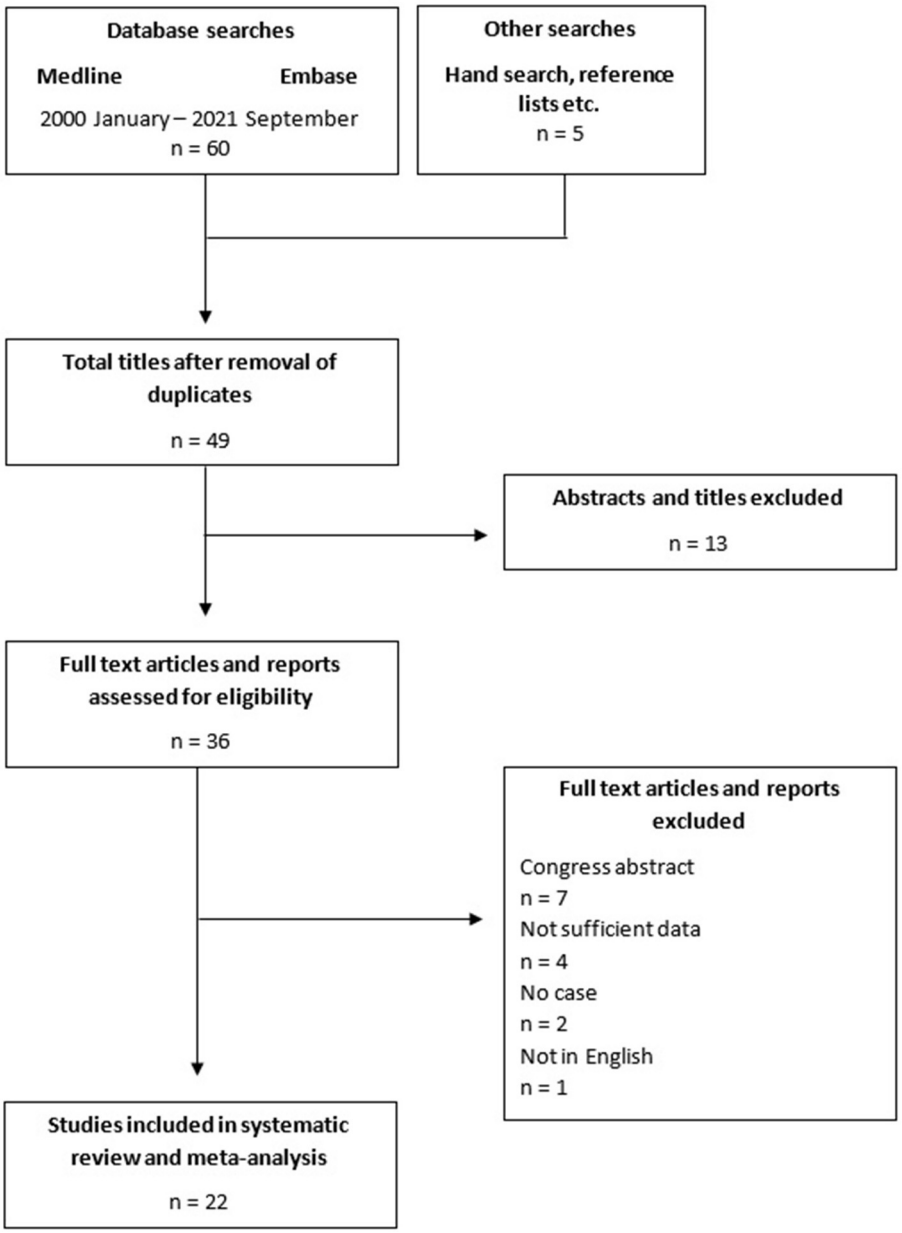


**FIGURE 1 |** PRISMA chart.

# RESULTS

## Search Results

Altogether, 60 articles were retrieved via database search, while 5 articles were found via hand search. After the removal of duplicates, 49 articles remained. Based on the titles and abstracts, 13 articles were excluded, leaving 36 articles for assessment of eligibility. After reading the full text, further 14 articles were excluded due to the following reasons: congress abstract ($n = 7$); insufficient data on cariprazine ($n = 4$); not a case report ($n = 2$); and not written in English language ($n = 1$). In the end, 22 articles were included and analyzed in this systematic review, which encompassed a total of 38 cases (**Figure 1**).

## Overview of Results

Demographics are summarized in **Table 1**. Out of the 38 cases, most patients were diagnosed with schizophrenia ($n = 27$, 71%), followed by psychotic disorders ($n = 6$, 16%), mood disorders ($n = 2$, 5%) and other disorders ($n = 3$, 8%) such as Wernicke-Korsakoff syndrome, borderline personality disorder and obsessive-compulsive disorder. There were 19 female and 18 male cases, and one was not specified (2.6%). The mean age

**TABLE 1 |** Summary of results.

| **Number of cases** | |
|---|---|
| Total, *n* | **38** |
| **Diagnosis, *n* (%)** | |
| **Schizophrenia** | **27 (71.1)** |
| Schizophrenia | 13 (34.2) |
| Paranoid schizophrenia | 8 (21.1) |
| Schizophrenia/schizoaffective with substance abuse | 5 (13.2) |
| Disorganized schizophrenia | 1 (2.6) |
| **Psychotic disorders** | **6 (15.8)** |
| Early psychosis | 3 (7.9) |
| Psychosis | 2 (5.3) |
| Acute polymorphic psychotic disorder | 1 (2.6) |
| **Mood disorders** | **2 (5.3)** |
| Bipolar I disorder | 1 (2.6) |
| Major depression | 1 (2.6) |
| **Other** | **3 (7.9)** |
| Wernicke-Korsakoff syndrome | 1 (2.6) |
| Borderline personality disorder | 1 (2.6) |
| Obsessive-compulsive disorder with paranoid schizophrenia | 1 (2.6) |
| **Sex, *n* (%)** | |
| Male | 18 (47.4) |
| Female | 19 (50.0) |
| Not specified | 1 (2.6) |
| **Age** | |
| Mean | 33.8 |
| Median | 31 |

*The bold values are the values of the category e.g. schizophrenia, which are under this value.*

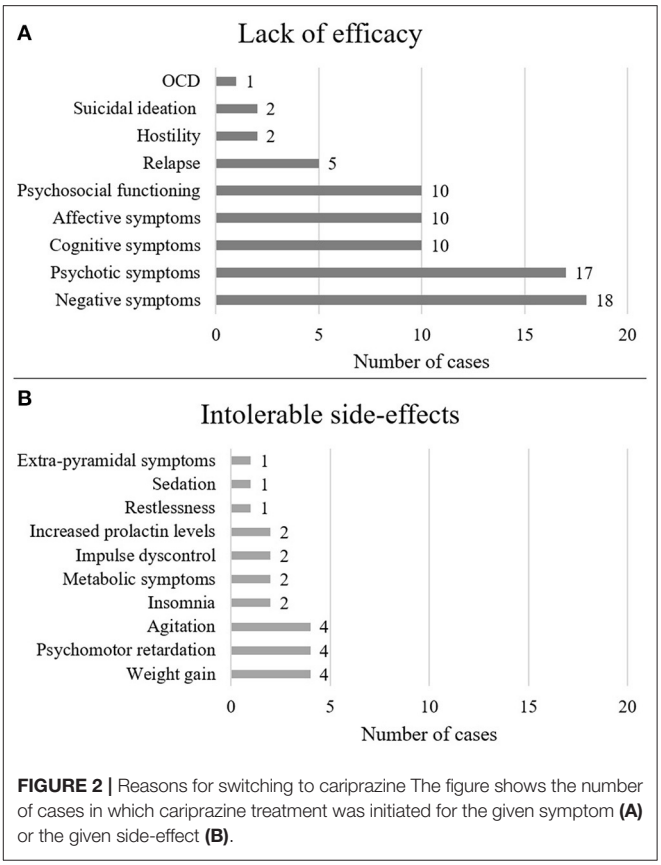


**FIGURE 2 |** Reasons for switching to cariprazine The figure shows the number of cases in which cariprazine treatment was initiated for the given symptom **(A)** or the given side-effect **(B)**.

of patients was 33.8 years, the median was 31 years. Dosing and clinical characteristics and are presented in **Figures 2**, **3**. The starting dose of cariprazine was 1.5 mg/day in the majority of cases ($n = 29$, 76.3%); the rest of the patients started with 3.0 mg/day ($n = 4$, 10.5%) or it was not specified ($n = 5$, 13.5%). Most commonly, the maintenance dose was 4.5 mg/day ($n = 13$, 34.2%), followed by 3.0 mg/day ($n = 11$, 28.9%), 6.0 mg/day ($n = 8$, 21.1%) and 1.5 mg/day ($n = 2$, 5.3%). In 4 cases (10.5%), cariprazine treatment was discontinued. In most cases, patients were experiencing negative ($n = 18$, 47.4%) and psychotic ($n = 17$, 44.7%) symptoms before switching to cariprazine, followed by affective ($n = 10$, 26.3%) and cognitive ($n = 10$, 26.3%) symptoms, as well as relapse ($n = 5$, 13.2%). In terms of tolerability problems, most patients suffered from psychomotor symptoms, weight gain and agitation (all $n = 4$, 10.5%). **Table 2** gives a detailed overview of each case, including sex, age, diagnosis, problem, starting and maintenance dose, titration strategy, concomitant medication, as well as provides the reference of each case. **Table 3** summarizes the outcome of cariprazine treatment of each case, broken down into symptoms.

## Schizophrenia

Out of the 38 cases, 27 had a diagnosis of schizophrenia (71.1%), of whom eight cases had a diagnosis of paranoid schizophrenia (29.6%), five had schizophrenia/schizoaffective disorder with substance abuse (18.5%), one patient had disorganized schizophrenia (3.7%), and in 13 cases, the subtype of schizophrenia was not specified (48.1%).

### Initiation of Cariprazine Treatment

Cariprazine treatment was primarily initiated due to the lack of efficacy of previous medications or drug-induced side-effects. The presence of positive symptoms ($n = 19$) was one of the main reasons for switching to cariprazine. These symptoms usually emerged due to medication non-adherence and therefore relapse. Following positive symptoms, the presence of negative symptoms was the most common reason for initiating cariprazine treatment ($n = 12$), which emerged due to the lack of efficacy or as a result of previous antipsychotic treatments. Patients reported experiencing reductions in motivation, social interactions, and everyday activities. Furthermore, cognitive ($n = 4$) and affective ($n = 4$) symptoms as well as substance abuse ($n = 4$; mainly alcohol and cocaine) indicated a switch to cariprazine treatment.

Many patients experienced intolerable side effects induced by other antipsychotics, therefore cariprazine was initiated due to its favorable safety profile. Three patients experienced psychomotor retardation ($n = 3$), and in case of one patient (*case 2*) (35), it got so severe that she became fully bedridden. Furthermore, weight gain ($n = 3$) and the development of metabolic syndrome ($n = 3$) were problematic for patients; one of them (*case 15*) (42)

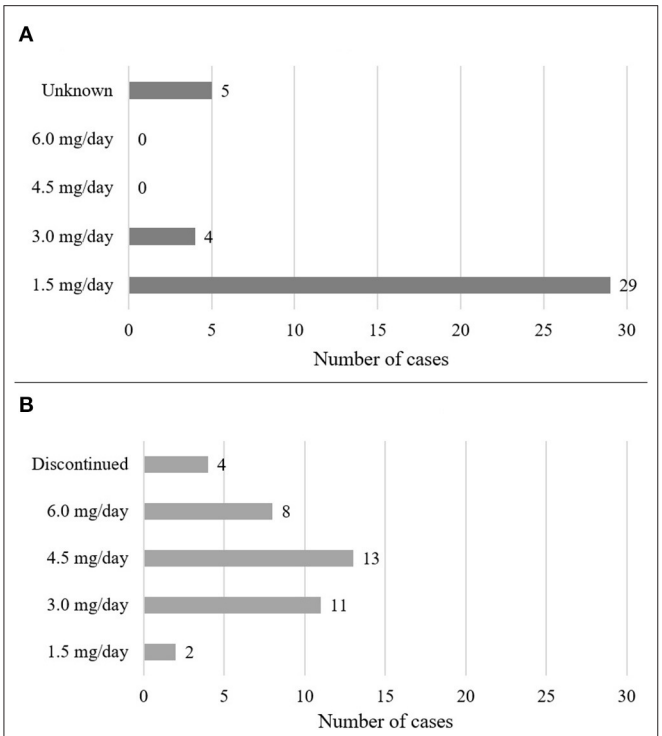


**FIGURE 3 |** Dosing of cariprazine. The figure shows the starting **(A)** and maintenance **(B)** doses of cariprazine.

gained 30 kg after the first year of taking olanzapine, causing increases in triglyceride and cholesterol levels. As a result, she developed social inhibition and stopped practicing her hobbies, thus impacting on her everyday life. Insomnia ($n = 1$), agitation ($n = 2$), restlessness ($n = 1$), and heightened prolactin levels ($n = 1$) were further issues for which cariprazine treatment was initiated.

The starting dose of cariprazine was 1.5 mg/day in most cases ($n = 20$, 74.1%), followed by 3.0 mg/day ($n = 3$, 11.1%), while it was not specified in four cases (14.8%). In most cases, the maintenance dose was 4.5 mg/day ($n = 11$, 40.8%), followed by 6.0 mg/day ($n = 6$, 22.2%), 3.0 mg/day ($n = 6$, 22.2%) and 1.5 mg/day ($n = 1$, 3.7%), while cariprazine was discontinued in three cases (11.1%).

## Outcome of Cariprazine Treatment

Overall, cariprazine proved to be an effective treatment for many symptom domains: it reduced positive ($n = 20$), negative ($n = 15$), cognitive ($n = 8$) and affective symptoms ($n = 8$); reduced hostility ($n = 2$); yielded substance-abstinence ($n = 4$); and improved psychosocial functioning ($n = 14$).

Importantly, there were five patients (*cases 5, 6, 7, 17, 18*) (36, 37, 44, 45) with comorbid substance use disorder, who had several antipsychotic failures previously either due to ineffectiveness in reducing symptoms of schizophrenia and addiction, or due to severe side-effects. The patients had severely impaired psychosocial functioning and quality of life. Cariprazine yielded significant improvements in positive, negative, cognitive, and affective symptoms, it contributed to substance abstinence and had positive effects on sleep regulation, psychomotor symptoms, weight decrease and metabolic symptoms. Although cariprazine induced extrapyramidal symptoms in two cases (*case 6 and 7*) (36, 37), they were well managed by the reduction of dose (from 6 to 4.5 m g/day in *case 7*) (37) and by using concomitant medication (*cases 6 and 7*) (36, 37).

In case of four patients (*cases 14, 15, 18, 38*) (42, 45, 55), cariprazine treatment was initiated due to psychotic relapse. Three patients decided on their own to discontinue previous medication (*cases 14, 15, 18)* (42, 45): two of them (*cases 14, 15*) (42) due to undesired side-effects, such as sexual difficulties, weight gain, sedation, the emergence of negative and affective symptoms, as well as a reduction in psychosocial functioning. One patient (*case 38*) (55) switched to cariprazine due to the inefficacy of the long-acting therapy. In all cases, cariprazine effectively reduced and reversed the side-effects of previous medications without causing any other side-effect. In addition, it proved to be an efficacious medication yielding remission of psychotic, negative, affective, and cognitive symptoms.

Regarding the effects of cariprazine on psychosocial functioning, eight patients (*cases 1, 2, 5, 6, 7, 15, 24, 28)* experienced difficulties with it before cariprazine treatment. Importantly, after the initiation of cariprazine, fifteen patients (*cases 1–9, 14, 15, 17, 24, 28, 37*) experienced a significant improvement in psychosocial functioning and quality of life as a result, including re-entering school or securing a job, and being more involved in family and social activities and events.

As a result of cariprazine treatment, psychomotor retardation resolved in two cases, including the previously described patient (*case 2*) (35) who recovered from being fully bedridden, and at the time of the report, she took care of her household independently. Cariprazine also contributed to the resolution of metabolic syndrome ($n = 1$) and weight reduction of five patients, including the patient who gained 30 kg in a year due to the previous medication (*case 15*) (42). Furthermore, cariprazine demonstrated beneficial effects toward normalizing prolactin levels ($n = 2$, while increased it in one patient), sexual function ($n = 1$), and sleep patterns (insomnia $n = 1$; sedation $n = 2$). Nonetheless, it is also worth noting that cariprazine contributed to the development of agitation in one, and restlessness in two patients.

## Side Effects and Discontinuation

Although cariprazine reduced extrapyramidal symptoms in one patient and led to its complete resolution in another, the most common side-effects induced by cariprazine were extrapyramidal symptoms (EPS), mainly akathisia, reported in six patients.

Cariprazine was discontinued in three cases (11.1%): due to akathisia in two cases (*cases 18 and 33*) and due to urinary retention in one patient (*case 23*) (47). In the latter case, cariprazine was up-titrated to 6.0 mg/day in a week when the patient complained of dysuria. The bladder scan revealed a postvoid residual urine volume of 900 mL (reference: <50–100 mL), therefore cariprazine was discontinued given the proximity of its introduction and the onset of urinary retention. After 3 days, the postvoid residual urine volume decreased

**TABLE 2 |** Summary of cases.

| References | No. | Sex | Age | Diagnosis | Problem | Starting dose | Titration strategy | Maintenance dose | Concomitant medication |
|---|---|---|---|---|---|---|---|---|---|
| Amore and Aguglia (34) | Case 1 | Not specified | 24 | Schizophrenia | Negative, cognitive, and mild psychotic symptoms with risperidone treatment, reduced psychosocial functioning | 1.5 mg/day | 3.0 mg/day on day 15 | 3.0 mg/day | Risperidone gradually discontinued |
| Aubel (35) | Case 2 | Female | 59 | Paranoid schizophrenia | Negative and psychotic symptoms, psychomotor retardation, reduced psychosocial functioning | 1.5 mg/day | 3.0 mg/day on day 4 and 4.5 mg on day 14 | 4.5 mg/day | Risperidone gradually discontinued |
| | Case 3 | Male | 31 | Paranoid schizophrenia | Persistent negative symptoms, psychomotor retardation | 1.5 mg/day | 3.0 mg/day on day 4 | 4.5 mg/day | Amisulpride and then 2 months later clozapine gradually discontinued |
| | Case 4 | Male | 32 | Paranoid schizophrenia | Desired switch to cariprazine due to psychotic symptoms and suicidal ideation | 1.5 mg/day | 3.0 mg/day on day 2 and 4.5 mg/day on day 3 | 4.5 mg/day | Aripiprazole and risperidone gradually discontinued |
| Carmassi et al. (36) | Case 5 | Male | 39 | Schizophrenia with substance abuse (alcohol, cocaine, THC, MDMA) | Negative, cognitive, and psychotic symptoms, reduced psychosocial functioning | 1.5 mg/day | 3.0 mg/day on day 5, 4.5 mg/day on day 9, and 6.0 mg/day on day 13 | 6.0 mg/day | Aripiprazole gradually discontinued, benzodiazepine |
| | Case 6 | Male | 20 | Schizophrenia with substance abuse (cocaine) | Psychotic and affective symptoms, restlessness, insomnia, suicide attempt, reduced psychosocial functioning | 1.5 mg/day | 3.0 mg/day on day 7 | 4.5 mg/day | Quetiapine gradually discontinued, biperiden 4 mg/day |
| Rodriguez Cruz et al. (37) | Case 7 | Male | 30 | Schizophrenia with substance abuse (amphetamine, cannabis) | Psychotic, negative, and cognitive symptoms, reduced psychosocial functioning | 1.5 mg/day | 6.0 mg/day on day 9 | 4.5 mg/day | Gradual down-titration of haloperidol over 2 weeks, quetiapine, add-on clonazepam, propranolol |
| De Berardis et al. (38) | Case 8 | Female | 29 | Schizophrenia | Symptomatic despite clozapine 450 mg/day and amisulpride 800 mg/day treatment with weight gain | 1.5 mg/day | 3.0 mg/day after a week | 3.0 mg/day | Clozapine 400 mg/day |
| | Case 9 | Male | 35 | Schizophrenia | Symptomatic despite clozapine, weight gain | 1.5 mg/day | 3.0 mg/day after three weeks | 3.0 mg/day | Clozapine 350 mg/day, then reduced to 300 mg/day |
| De Berardis et al. (39) | Case 10 | Female | 21 | Early psychosis | Psychotic, negative, and cognitive symptoms, increased sedation, and appetite despite olanzapine treatment | 1.5 mg/day | 3.0 mg/day on day 4, 4.5 mg/day around day 30 | 4.5 mg/day | – |
| | Case 11 | Male | 19 | Early psychosis | Psychotic, negative, cognitive, and affective symptoms, insomnia, and impulse dyscontrol | 1.5 mg/day | 3.0 mg/day after a few days, 4.5 mg/day and then 6.0 mg/day after 14 days | 6.0 mg/day | Alprazolam 1 mg/day |
| De Berardis et al. (40) | Case 12 | Male | 26 | Obsessive-compulsive disorder with paranoid schizophrenia | Persistent OCD symptoms despite paliperidone treatment | 1.5 mg/day | 3.0 mg/day on day 7 | 3.0 mg/day | Paliperidone oral suspended, add-on paliperidone long-acting injectable 100mg |
| Dieci et al. (41) | Case 13 | Male | 54 | Major depression | Affective symptoms | 1.5 mg/day | Not specified | 1.5 mg/every second day | Citalopram 40 mg/day |

*(Continued)*

**TABLE 2** | Continued

| References | No. | Sex | Age | Diagnosis | Problem | Starting dose | Titration strategy | Maintenance dose | Concomitant medication |
|---|---|---|---|---|---|---|---|---|---|
| Di Sciascio and Palumbo (42) | Case 14 | Male | 26 | Schizophrenia | Psychotic relapse, and negative and affective symptoms | 1.5 mg/day | 3.0 mg/day on day 2 | 3.0 mg/day | Risperidone discontinued in 2 days |
| | Case 15 | Female | 22 | Disorganized schizophrenia | Relapse due to discontinuation of previous therapy (weight gain and metabolic syndrome), cognitive and psychotic symptoms, reduced psychosocial functioning | 1.5 mg/day | 6.0 mg/day | 6.0 mg/day | Olanzapine gradually discontinued in 2 weeks |
| Grant and Chamberlain (43) | Case 16 | Male | 42 | Borderline personality disorder | Affective symptoms, hostility, and impulsivity | 3.0 mg/day | 4.5 mg/day after 2 weeks, 6.0 mg/day after 3 weeks | 6.0 mg/day | – |
| Halaris and Wuest (44) | Case 17 | Male | 37 | Schizoaffective disorder with substance abuse (alcohol and tobacco) | Metabolic syndrome with olanzapine | Not specified | 3.0 mg/day and then a year later 4.5 mg/day | 4.5 mg/day | Olanzapine discontinued over 2 months |
| Heck et al. (45) | Case 18 | Female | 30 | Paranoid schizophrenia with substance use disorder | Relapse followed by patient's request to discontinue quetiapine | 1.5 mg/day | 3.0 mg on day 6 | Cariprazine was reduced to 1.5 mg/day 3 days after the onset of akathisia (day 16). Another 2 days later, cariprazine was stopped. | Quetiapine 300 mg reinitiated on day 5 |
| | Case 19 | Male | 22 | Paranoid schizophrenia | Negative symptoms despite risperidone treatment | 1.5 mg/day | 3.0 mg/day after 2 weeks, then 10 days later reduced to 1.5 mg/day | 1.5 mg/day | Risperidone 0.5–3 mg/day, biperiden 4 mg/day (both discontinued) |
| | Case 20 | Male | 52 | Paranoid schizophrenia | Psychotic symptoms due discontinuation of medication and history of severe negative symptoms | 1.5 mg/day | 3.0 mg/day 1 week later, 4.5 mg/day another 5 days later | 4.5 mg/day | Pipamperone 40 mg/day, then olanzapine 10 mg/day added and pipamperone discontinued |
| | Case 21 | Female | 22 | Paranoid schizophrenia | Hyperprolactinemia under aripiprazole 10 mg/d and amisulpride 250 mg/d. | 1.5 mg/day | Increased to 3.0, 4.5, and 6.0 mg/day after 2, 4, and 12 weeks, respectively | 6.0 mg/day | – |
| Jimoh et al. (46) | Case 22 | Female | 32 | Wernicke-Korsakoff syndrome | Psychotic, cognitive, and negative symptoms, psychomotor retardation despite aripiprazole treatment, reduced psychosocial functioning | Not specified | Not specified | 3.0 mg/day | Not specified |
| Kapulsky and Brody (47) | Case 23 | Male | 33 | Schizophrenia | Psychotic and predominantly negative symptoms despite clozapine 225 mg treatment | Not specified | Up to 6.0 mg/day in a week | Discontinued due to urinary retention | – |

*(Continued)*

**TABLE 2 |** Continued

| References | No. | Sex | Age | Diagnosis | Problem | Starting dose | Titration strategy | Maintenance dose | Concomitant medication |
|---|---|---|---|---|---|---|---|---|---|
| Mencacci et al. (48) | Case 24 | Male | 51 | Schizophrenia | Negative symptoms despite ziprasidone, lurasidone and risperidone treatment, reduced psychosocial functioning | Not specified | Up to 4.5 mg/day | 4.5 mg/day | Haloperidol and risperidone gradually discontinued |
| | Case 25 | Female | 49 | Schizophrenia | Metabolic side-effects and negative symptoms despite olanzapine treatment | Not specified | Up to 4.5 mg/day until day 21 | 4.5 mg/day | Olanzapine gradually discontinued, and biperiden, lorazepam, antihistamine gradually reduced |
| Molnar et al. (49) | Case 26 | Female | 23 | Early psychosis | Severe negative, cognitive and psychotic symptoms, agitation, reduced psychosocial functioning | 1.5 mg/day | 3.0 mg/day from day 4 to 12, 4.5 mg/day from day 13 | 3.0 mg/day | – |
| Montes et al. (50) | Case 27 | Male | 31 | Schizophrenia | Psychotic symptoms | 3.0 mg/day | Not specified | 3.0 mg/day | – |
| | Case 28 | Female | 54 | Schizophrenia | Psychotic and affective symptoms, reduced psychosocial functioning | 3.0 mg/day | 6.0 mg/day on day 3 | 6.0 mg/day | Diazepam 10 mg |
| | Case 29 | Female | 36 | Schizophrenia | Psychotic symptoms, agitation, hostility despite aripiprazole treatment | 3.0 mg/day | 6.0 mg/day on day 3 | 6.0 mg/day | Quetiapine 50 mg |
| Müller and Moeller (51) | Case 30 | Female | 38 | Schizophrenia | Extrapyramidal and negative symptoms | 1.5 mg/day | 3.0 mg/day after 4 days, 4.5 mg/day after another week | 4.5 mg/day | – |
| | Case 31 | Female | 34 | Psychosis | Psychotic relapse, negative and cognitive symptoms, and increased weight | 1.5 mg/day | 3.0 mg on day 3 for 3 weeks | 4.5 mg/day | Risperidone until 4.5 mg cariprazine |
| Ricci et al. (52) | Case 32 | Male | 25 | Methamphetamine-induced psychosis | Persistent psychotic, negative and affective symptoms | 1.5 mg/day | 3.0 mg/day on day 4, 4.5 mg/day on day 13 | 3.0 mg/day | Benzodiazepine |
| Riedesser and Gahr (53) | Case 33 | Female | 46 | Paranoid schizophrenia | Psychotic, affective, and psychomotor symptoms and agitation | 1.5 mg/day | 1.5 mg/day | Discontinued after 5 days | Clozapine 12.5 mg/day, escitalopram 10 mg/day |
| | Case 34 | Female | 62 | Paranoid schizophrenia | Haloperidol, then amisulpride without sufficient antipsychotic effect | 1.5 mg/day | Up to 4.5 mg/day | 3.0 mg/day | Amisulpride, biperiden (later phased out), hydro-chlorothiazide, amlodipine and ramipril |
| | Case 35 | Female | 19 | Acute polymorphic psychotic disorder | Hyperprolactinaemia attributed to risperidone and olanzapine | 1.5 mg/day | 3.0 mg/day | Discontinued after 2 weeks | Olanzapine 5 mg/day discontinued after 4 days; pantoprazole initiated |
| Sanders and Miller (54) | Case 36 | Female | 20 | Bipolar I disorder, ADHD, substance use disorder (cannabis and alcohol) | Affective and cognitive symptoms and agitation | 1.5 mg/day | 3.0 mg/day after 3 weeks | 3.0 mg/day | Quetiapine 25 mg/day, clonazepam 2 × 0.5 mg/day, methylphenidate XR 72 mg/day |
| Vita et al. (55) | Case 37 | Female | 31 | Schizophrenia | Negative symptoms despite risperidone treatment | 1.5 mg/day | 3.0 mg/day on day 4, 4.5 mg/day on day 7 | 4.5 mg/day | Risperidone dose decreased by 3 mg every 3 days until full discontinuation |
| | Case 38 | Female | 27 | Schizophrenia | Psychotic relapse 2 weeks after the administration of paliperidone palmitate 1-monthly long-acting therapy | 1.5 mg/day | 3.0 mg/day on day 4, 4.5 mg/day on day 7, 6.0 mg/day on day 10 | 6.0 mg/day | Paliperidone discontinued |

**TABLE 3 |** Clinical outcomes with cariprazine treatment.

| References | No. | Outcome | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Efficacy | | | | | | | | | Safety | | | | | | | | | |
| | | Positive | Negative | Cognitive | Affective | Hostility | Substance abuse | OCD | Impulsivity | Psychosocial functioning | Psychomotor | Insomnia | Sedation | Weight gain | Metabolic syndrome | Increased prolactin levels | Agitation | EPS | Sexual dysfunction | Restlessness |
| Amore and Aguglia (34) | Case 1 | ↓ | ↓ | ↓ | ↓ | | | | | ↑ | | | | | | ↓ | | ↓ | ↓ | |
| Aubel (35) | Case 2 | X | ↓ | | | | | | | ↑ | X | | | | | | | | | |
| | Case 3 | X | X | | X | | | | | ↑ | | | | | | | | | | |
| | Case 4 | X | | ↓ | | | | | | ↑ | | | | | | | | | | |
| Carmassi et al. (36) | Case 5 | ↓ | ↓ | ↓ | | | X | | | ↑ | X | | ↓ | | | | | | | |
| | Case 6 | | ↓ | ↓ | ↓ | | X | | | ↑ | | | | | | | | + | | |
| Cruz et al. (37) | Case 7 | ↓ | ↓ | | | | X | | | ↑ | | | | | | | | + | | |
| De Berardis et al. (38) | Case 8 | ↓ | ↓ | | | | | | | ↑ | | | | ↓ | | | | | | |
| | Case 9 | ↓ | ↓ | ↓ | | | | | | ↑ | | | | ↓ | | | | | | |
| De Berardis et al. (39) | Case 10 | ↓ | ↓ | ↓ | | | | | | | | | ↓ | | | | | | | |
| | Case 11 | ↓ | ↓ | ↓ | ↓ | | | | X | | | ↓ | | | | | | | | |
| De Berardis et al. (40) | Case 12 | | | | | | | X | | | | | | | | | | | | |
| Dieci et al. (41) | Case 13 | | | | ↓ | | | | | | | | | | | | | + | X | |
| Di Sciascio and Palumbo (42) | Case 14 | ↓ | ↓ | | ↓ | | | | | ↑ | | | | | | | | | | |
| | Case 15 | X | X | X | ↓ | | X | | | ↑ | | | ↓ | ↓ | | | | | | |
| Grant and Chamberlain (43) | Case 16 | | | | ↓ | X | | | X | | | | | | | | | | | |
| Halaris and Wuest (44) | Case 17 | X | ↓ | | | | | | | ↑ | | | | ↓ | ↓ | | | | | |
| Heck et al. (45) | Case 18* | ↓ | | | | | | | | | | | | | | | | + | | + |
| | Case 19 | | | | | | | | | | | | | | | | | + | | |
| | Case 20 | ↓ | ↓ | | | | | | | | | ↓ | | | | | | | | + |
| | Case 21 | | | | | | | | | | | | | | | ↑ | | | | |
| Jimoh et al. (46) | Case 22 | ↓ | ↓ | ↓ | | | | | | ↑ | | | | | | | | | | |

*(Continued)*

**TABLE 3 |** Continued

| References | No. | Outcome | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Efficacy | | | | | | | | | Safety | | | | | | | | | |
| | | Positive | Negative | Cognitive | Affective | Hostility | Substance abuse | OCD | Impulsivity | Psychosocial functioning | Psychomotor | Insomnia | Sedation | Weight gain | Metabolic syndrome | Increased prolactin levels | Agitation | EPS | Sexual dysfunction | Restlessness |
| Kapulsky and Brody (47) | Case 23* | | | | | | | | | | | | | | | | | | | |
| Mencacci et al. (48) | Case 24 | | ↓ | ↓ | | | | | | ↑ | | | | | | | | | | |
| | Case 25 | ↓ | | ↓ | | | | | | | | | | ↓ | | ↓ | | | | |
| Molnár et al. (49) | Case 26 | ↓ | ↓ | X | | | | | | ↑ | | | | | | | X | + | | X |
| Montes et al. (50) | Case 27 | ↓ | | | ↓ | | | | | | | | | | | | | | | |
| | Case 28 | ↓ | | | ↓ | ↓ | | | | ↑ | | | | | | | | | | |
| | Case 29 | ↓ | | | ↓ | ↓ | | | | | | | | | | | | | | |
| Müller and Moeller (51) | Case 30 | | ↓ | | | | | | | | | | | | | | | + | | |
| | Case 31 | ↓ | ↓ | ↓ | | | | | | | | | | ↓ | | | | | | |
| Ricci et al. (52) | Case 32 | ↓ | ↓ | | | | X | | | | | + | | | | | | | | |
| Riedesser and Gahr (53) | Case 33* | | | | | | | | | | | | | | | | + | + | | |
| | Case 34 | ↓ | | | | | | | | | | | | | | | | + | | |
| | Case 35 | | | | | | | | | | | | | | | X | | + | | |
| Sanders and Miller (54) | Case 36 | | | X | | | X | | | ↑ | | | | | | | X | | | X |
| Vita et al. (55) | Case 37 | X | ↓ | | | | | | | ↑ | | | | | | | | | | |
| | Case 38 | X | | | | | | | | | | | | | | | | | | |

↑, *Increase;* ↓, *Decrease; X, Absent;* +, *Present.*

**Discontinued due to akathisia (case 18, 33, 35) or urinary retention (case 18).*

to normal range. In the other patient (*case 18*) (45), 6 week after the dose increase of cariprazine from 1.5 to 3.0 mg/day, the patient complained of restlessness of lower extremities, anxiety, and an uncontrollable urge to move around. Despite a significant reduction in psychotic symptoms, cariprazine was reduced to 1.5 mg/day 3 days after the onset of akathisia, and another 2 days later, cariprazine treatment was stopped. The patient started to appear calmer and less distressed 5 weeks after the discontinuation of cariprazine, however, slight akathisia symptoms remained for another 3 weeks until her discharge. Finally, in case 33, cariprazine-treatment was initiated at 1.5 mg/day, but it was discontinued 5 days later due to cariprazine-induced akathisia, agitation, and parkinsonism of extremities. The following day, the symptoms subsided completely.

## Psychotic Disorders

Six cases discussed patients with different psychotic disorders such as early psychosis or acute polymorphic psychotic disorder. The three patients with early psychosis, two females (*case 10 and 26*) and one male (*case 11*), were between 19 and 23 years old, who all suffered from psychotic, negative, and cognitive symptoms (39, 49). In the female patients, self-neglect and social withdrawal were prominent, while the male patient showed signs of impulse dyscontrol (39, 49). All patients started their cariprazine treatment on 1.5 mg/day, which was up-titrated to the necessary dosage of 3.0, 4.5, or 6.0 mg/day (39, 49). Improvement in overall symptoms with maintained effect with cariprazine was reported in all three cases (39, 49). Remarkably, cariprazine was highly effective in eliminating impulse dyscontrol as well as treating severe and predominant negative symptoms in a drug-naïve patient (39, 49). The patients reported that "it is a long time since my thoughts were so clear" and "I feel more alive" (39). Interestingly, one of them was followed-up for 52 weeks, and was reported to be symptom-free with cariprazine (49).

The other three psychotic disorder cases included a patient with methamphetamine-induced psychosis (*case 32*) (52), psychosis (*case 31*) (51), and acute polymorphic psychotic disorder (*case 35*) (53). The latter suffered from hyperprolactinaemia due to treatment with olanzapine and risperidone and was prescribed 1.5 and then 3.0 mg/day cariprazine (53). Although serum prolactin levels normalized, due to the development of severe akathisia, cariprazine was discontinued after 2 weeks (53). The other two patients were experiencing psychotic, negative, cognitive and affective symptoms and received 1.5 mg cariprazine per day (51, 52). Cariprazine dosage was increased up to 3.0 mg/day in the patient with substance-induced psychosis with adjunctive benzodiazepines for insomnia, which resulted in an improvement in both negative and psychotic symptoms (52). Most importantly, the patient remained abstinent from methamphetamine (52). Similar improvement of symptoms on 4.5 mg/day was seen in the other patient who switched from risperidone to cariprazine and who also reported significant weight loss (16 kg) (51).

## Mood Disorders

Altogether, two cases were found that reported on patients with mood disorders. One of these cases (*case 36*) described a young patient with a diagnosis of bipolar I disorder, ADHD and substance abuse disorder (alcohol and cannabis) (54). According to the report, the patient exhibited affective and cognitive symptoms as well as agitation (54). Cariprazine 1.5 mg/day was prescribed for 3 weeks, then up-titrated to 3.0 mg/day, as no improvement was detected with the lower dose. Concomitant medications, quetiapine, clonazepam and methylphenidate XR were also taken by the patient (54). After three additional weeks, the patient improved a lot and more importantly, she remained substance free even after 27 months (54). The other case (*case 13*) reported on a man with MDD who had been taking several different antidepressant medications without significant response (41). Cariprazine 1.5 mg/day was initiated as add-on therapy to his current regimen and led to partial improvements of depressive symptoms and significant improvement of sexual functioning after 30 days (41). Due to mild akathisia, cariprazine dose was reduced to 1.5 mg per every second day, to which akathisia disappeared (41).

## Other Disorders

Finally, three cases outside the approved and clinically studied indications were determined. The first (*case 12*) described a patient with obsessive-compulsive disorder (OCD), a history of paranoid schizophrenia and current treatment of long-acting paliperidone and oral paliperidone 6 mg (40). After suspending oral paliperidone, introducing cariprazine 1.5 mg/day, and then up-titrating it to 3.0 mg/day within a week, the patient's symptoms decreased without any adverse effects (40). The second patient (*case 16*) was diagnosed with borderline personality disorder and reported to suffer from affective symptoms, hostility, and impulsivity (43). Cariprazine dose was continuously increased from 3.0 to 4.5 mg/day, and then to 6.0 mg/day after the improvement of affective symptoms (43). Seven months later, no signs of impulsivity, hostility or adverse events were detected. (43). The third patient (*case 22*) had Wernicke-Korsakoff syndrome with psychotic, cognitive, and negative symptoms as well as psychomotor retardation despite aripiprazole treatment (46). After switching to cariprazine 3.0 mg/day, improvements in both psychotic and negative symptoms were detected without any side-effects, which was followed by cognitive improvement 3 months later (46).

# DISCUSSION

This is the first systematic review that summarizes the real-life effectiveness and tolerability of cariprazine based on published case studies. The results of the review indicate that cariprazine is an effective treatment option for a wide range of symptoms in several psychiatric conditions including schizophrenia, psychotic disorders, mood disorders and even borderline personality disorder. In addition, it has been also shown that cariprazine is well-tolerated by the majority of patients and it has the potential to reverse some of the side effects such as weight gain or hyperprolactinemia that are typically caused by other antipsychotic medications. The relevance of these results in relation to the wider literature is discussed below.

## Treatment Initiation and Dosing

In almost all cases, cariprazine was initiated at 1.5 mg/day dose and then up-titrated to the necessary dosage, most commonly to 4.5 mg/day. This dosing strategy is recommended by the summary of product characteristics (SmPC) (5) and by other expert opinion panels as well (56). Recently, an article by Rancans and colleagues summarized the evidence regarding cariprazine dosing and came to similar conclusions (57).

## Effectiveness in a Wide Range of Symptoms

### Psychotic and Manic Symptoms

Irrespective of the diagnosis, cariprazine was found to reduce or even resolve psychotic symptoms, such as hallucinations, delusions, or disruptive behavior, in many different cases from early psychosis to psychotic relapses. Although most dopamine $D_2/D_3$ partial agonists are perceived as being "weak" in terms of addressing positive symptoms compared to $D_2$ antagonists, such examples show that with adequate doses, a partial agonist can also initiate and maintain the necessary therapeutic effect. Indeed, the pooled results of the three short-term Phase II/III clinical trials reported cariprazine to be significantly better than placebo in reducing positive symptoms in acute patients as measured by mean change form baseline to week 6 in the Positive and Negative Syndrome Scale (PANSS)-derived Marder Positive Symptom factor score (58). Short-term trials demonstrated the efficacy of cariprazine in the treatment of bipolar mania or mixed episodes. Change from baseline to week 3 in the Young Mania Rating Scale (YMRS) scores was significantly greater in the cariprazine group than in the placebo group (23–25). What is more, the efficacy of cariprazine was extended over the longer-term, as shown by a 16-week-long study (26). *Post-hoc* analysis of these studies showed significant improvements on the Young Mania Rating Scale (YMRS) scores (manic symptoms) and numerically greater improvements in the MADRS scores (depressive symptoms) at week 3 in the cariprazine-group, compared to the placebo group (59). This effect is attributed to the high affinity of cariprazine for $D_2$ receptors (60, 61), as overactive dopamine release at the $D_2$ postsynaptic receptors is hypothesized to induce the positive symptoms of schizophrenia (62, 63) as well as the manic symptoms of bipolar I disorder (64).

### Hostility

Similarly to psychotic symptoms, hostility was also reported in a few of the reviewed acute cases (43, 50). In these patients, anger outbursts and other hostile behavior reduced significantly after the initiation of cariprazine treatment (43, 50). Again, the pooled results of three short-term clinical trials with acute schizophrenia patients also showed that cariprazine, compared with placebo, produced significantly greater improvement in hostility in patients with acute exacerbation of schizophrenia, with greatest effect in patients with the highest level of baseline hostility (65). Importantly, based on the results of this review, patients who stayed on cariprazine for a longer period (up to 27 months) did not experience relapse, which is in line with the results of the relapse-prevention study of cariprazine (17). The trial showed that time to relapse was significantly longer in the cariprazine- compared to placebo-treated patients and occurred in <25% of cariprazine- and more than 45% of placebo-treated patients (17). Thus, it can be stated that cariprazine might be a good choice of medication for acute as well as maintenance treatment of several psychiatric conditions.

### Negative Symptoms

Among other antipsychotics, cariprazine has the highest affinity to $D_3$ receptors, even greater than that of dopamine itself (8). Given other antipsychotics' low affinity to $D_3$, in the presence of dopamine, cariprazine is the only antipsychotic that is able to block the $D_3$ receptors in the living brain (66). $D_3$ actions translate into efficacy against negative and cognitive symptoms, improving mood and regulating motivation and reward-related behavior (67). Thus, it is not surprising that cariprazine is currently the only antipsychotic medication that was found to be significantly better in the treatment of predominant negative symptoms than an active comparator, risperidone (18). Indeed, in many cases, cariprazine was prescribed due to residual negative symptoms which were resolved in all cases. The effectiveness of cariprazine in real life was also assessed in an observational study that was conducted in Latvia involving 116 patients with predominant negative symptoms (31). The results also supported the notion that cariprazine is a valid treatment option for those patients who have residual negative symptoms with ongoing antipsychotic treatment (31). Nonetheless, this effect is not exclusive to patients with predominant negative symptoms; in the pooled *post-hoc* analysis of three short-term Phase II/III clinical trials, cariprazine was found to be also significantly better than placebo in reducing negative symptoms in acute patients as measured by the mean change from baseline to week 6 in the PANSS Marder Negative Symptom factor score (58).

### Cognitive Symptoms

Neurocognitive deficits are also a core feature of many neuropsychiatric disorders, including schizophrenia and bipolar disorder, and are associated with reduced psychosocial functioning and worse illness prognosis (68, 69). Evidence suggest that cognitive effects are further mediated by the $D_3$ receptors (67). Indeed, in many of the presented cases, cariprazine effectively enhanced patients' cognition, further contributing to improved quality of life. In support of its potential advantage for treating cognitive symptoms, cariprazine yielded significantly greater improvements in cognition than an active comparator, risperidone, as measured by both the PANSS Meltzer Cognitive subscale and the PANSS-derived Marder factor for Disorganized Thoughts in a 26-week-long Phase IIIb clinical trial (70). However, cariprazine did not only improve cognitive symptoms in the long-term, but also in the short-term studies; pooled data from three 6-week, phase II/III trials demonstrated the superiority of cariprazine over placebo in the reduction of cognitive symptoms, as measured by the PANSS-derived Marder Disorganized Thought factor—this effect was driven by all 7 factor items (58). In bipolar disorder, pooled analysis of three Phase II/III trials showed that 3 weeks of cariprazine treatment significantly enhanced

cognition compared to placebo in patients with manic/mixed episodes, as measured by the PANSS Cognitive subscale (71). Finally, pooled analysis of three Phase II/III trials demonstrated similar improvements in cognition for patients with bipolar I depression at week 6 of cariprazine treatment, as measured by the change in Concentration item score of the Montgomery-Åsberg Depression Rating Scale (MADRS) (72).

### Addiction

The observed effect of cariprazine in the reduction of substance use can also be attributed to the role of $D_3$ receptors (54). $D_3$ receptors are highly expressed in limbic areas forming the "reward circuitry", implying their involvement in the mediation of motivation and emotions—all heavily involved in the pathophysiology of addiction (73). To date, in addition to the presented cases here, evidence for the effectiveness of cariprazine in substance abuse comes from animal studies: in rats, cariprazine reduced the rewarding effects of cocaine and prevented relapse, and its effect was 20 times more potent than that of another partial agonist, aripiprazole (74). Two clinicals trials have been initiated to uncover the effectiveness of cariprazine in substance use disorder, although the results are not yet available. A Phase II, placebo-controlled study is focusing on how cariprazine (1.5 vs. 3.0 mg/day) affects the brain and behavior in cocaine use disorder, using fMRI (75). Furthermore, a Phase IIa, randomized, placebo-controlled pilot study will shed light on how low-dose cariprazine (1.5 mg/day) treatment impacts on cocaine use in patients with comorbid opioid use disorder who are medically stable and have already been on a stable dose of buprenorphine/naloxone treatment (76). Currently, a narrative review has investigated the potential of cariprazine in the treatment of substance use disorder in patients with bipolar disorder and concluded that based on the evidence and the receptor profile of cariprazine, it is a potential pharmacological treatment option for this patient population (77). However, further studies are warranted to validate this rationale-based postulation.

### Affective Symptoms

Although only one case report described the efficacy of cariprazine in bipolar disorder and another in MDD, the positive outcomes of these cases and the potential of cariprazine for the treatment of affective symptoms are further supported by the findings of clinical trials. A *post-hoc* analysis of three pivotal studies in bipolar depression was conducted to evaluate the efficacy of cariprazine in patients with or without manic features (78). For patients with manic symptoms, both 1.5 and 3.0 mg/day cariprazine yielded significant improvements on the MADRS scores, while for patients without manic symptoms, the 1.5 mg/day cariprazine dose was significantly more effective than placebo (78). Furthermore, two Phase III clinical trials found positive results for the efficacy of cariprazine in MDD as adjunctive treatment (7): compared to placebo, patients treated with 1.5 mg/day cariprazine showed significantly greater change from baseline to week 6 in the MADRS total scores. Dopamine $D_3$ and serotonin 5-$HT_{1A}$ receptors have been implicated in mood disorders; given the high affinity of cariprazine to these receptors, its antidepressant efficacy may be mediated by these receptors (67, 79).

### Psychosocial Functioning

Psychosocial functioning remains one of biggest causes of disability in patients with serious mental illness (80). Patients have severe social and occupational dysfunctions, difficulty attending to everyday tasks due to clinical symptoms (especially negative, affective and cognitive) or comorbid conditions, which have detrimental effects on their quality of life—yet, it remains a large unmet need (81). Furthermore, its evaluation is not standardized, as there is no consensus definition of psychosocial functioning (82). This was reflected in the presented cases as well: 10 patients reported reduced psychosocial functioning for which cariprazine treatment was initiated. In clinical trials of schizophrenia patients with predominant negative symptoms, cariprazine significantly improved patient functionality from week 10 onwards compared to risperidone, as measured by the Personal and Social Performance scores, driven by significant changes in all three relevant subdomains (18). In patients with bipolar I depression, despite depressive symptoms being one of the main contributors to reduced functioning, the resolution of depressive symptoms is not enough; impaired psychosocial functioning persists during periods of euthymia (83). Studies of patients with bipolar I depression showed that cariprazine significantly improved psychosocial functioning, as indicated by 5 of 6 subscale scores of the Functioning Assessment Short Test (Autonomy, Occupational Functioning, Cognitive Functioning, Leisure Time, and Interpersonal Relationships). Therefore, cariprazine is a good pharmacological treatment choice, as it does not only improve clinical symptoms, but also contributes to improved patient functioning, which is often more important for patients than the resolution of symptoms. These findings from the clinical trials are in line with the reported cases here, as improved psychosocial functioning and quality of life was reported in 20 patients.

## Cariprazine Is Well-Tolerated Compared to Other Medications

Cariprazine proved to be a safe and tolerable medication based on the results of this review and previous trials as well. Its activity at serotonin 5-$HT_{2B}$ receptors (antagonist), 5-$HT_{1A}$ receptors (partial agonist), and activity with lower affinity for 5-$HT_{2A}$, 5-$HT_{2C}$, histamine $H_1$, and $\alpha_1$ receptors may have implications for the gentle safety profile of cariprazine on metabolic, sedative and hyperprolactinaemia-related side-effects (84).

### Metabolic Symptoms and Weight

Second-generation antipsychotics have been associated with the development of metabolic symptoms and increase in weight (85). Weight gain is among the most concerning side-effects for patients, and metabolic syndrome contributes to a reduction in quality of life and satisfaction with care, and contributes to the premature mortality of patients with serious mental illness, compared to the general population (80). Cariprazine led to a reduction in weight in six patients, sometimes even without dieting or exercising, who all gained weight due to their previous

antipsychotic medication. Although only one case reported an improvement in metabolic symptoms (other than weight loss), safety studies confirm that cariprazine is metabolically neutral in the approved dose-range, and is comparable to placebo (84). Specifically, cariprazine caused only slight changes in weight, hyperlipidaemia, hyperglycaemia and diabetes mellitus and no dose-response relationship was observed in the long-term studies (86).

### Extrapyramidal Symptoms

Akathisia is another common side-effect of antipsychotics, and it is associated with increased risk of suicide or aggressive behavior, treatment discontinuation, and ultimately, lower quality of life (87). In the presented cases, despite reducing EPS symptoms in 2 patients (*cases 1 and 30*) (34, 51), these were the most commonly reported side-effects of cariprazine treatment ($n = 9$). The symptoms were managed either by dose-reduction or the administration anti-akathisia medication. These EPS-management strategies were also applied in clinical trials of patients with schizophrenia, as well as they are recommended by experts (84, 88). Cariprazine was discontinued due to EPS (akathisia) in three cases (*case 18, 33, 35*) (45, 53): 5 days (*cases 18 and 33*) (45, 53) and 2 weeks (*case 35*) (53) after the onset of symptoms. In the discontinuation cases, only one case (*case 18*) (45) adapted one of the above-mentioned strategies (dose reduction), although after 2 days only on the lower dose, cariprazine was stopped. In case of the emergence of akathisia in cariprazine trials, the median time to resolution of akathisia was 17 days when anti-akathisia medication was added, with 85% of events resolving. The median time to resolution in case of down-titration of cariprazine was 15 days with over 90% of event resolving. Therefore, it is recommended to first try one of the above-mentioned strategies and give it some time before deciding to completely withdraw cariprazine. In order to minimize the risk of developing akathisia, it is also recommended to adapt a slower up-titration strategy when introducing cariprazine, as well as stick with lower doses if possible, as higher doses are associated with greater risk of developing akathisia (18, 84).

### Prolactin Level Changes

Five patients experienced increased prolactin levels or hyperprolactinaemia as well as sexual side effects in response to previous antipsychotic treatment (olanzapine and amisulpride) which was reduced after cariprazine was prescribed and taken by the patients (34, 41, 45, 48, 53). This is not surprising given the fact that no treatment-emergent adverse events of prolactin elevation and low rate of sexual dysfunction were found in the pooled analysis of eight schizophrenia studies (84). However, in *case 21* (45), cariprazine was administered to a female patients who experienced high prolactin elevation due to aripiprazole and amisulpride. Since she had a family history of breast cancer, she was given cariprazine as a precautionary measure. Although prolactin levels decreased, 13 months after the start of cariprazine treatment, prolactin levels elevated, however, it was classified as non-serious and cariprazine treatment was continued under regular endocrinological and gynecological surveillance.

### Sleep Disturbances

Next to akathisia, insomnia was the second most frequently occurring side-effect of cariprazine with a dose-response effect observed in the pooled safety studies (84). Since cariprazine is rather an activating substance, it is not surprising that it improved sedation in three of the reviewed cases.

### Agitation

Agitation and restlessness were also common symptoms in patients before cariprazine treatment, however, a reduction was experienced in most of them in response to cariprazine (49, 54). Yet, in three cases, agitation was induced by cariprazine, which resulted in withdrawing cariprazine treatment (45, 53). Throughout the clinical development program of cariprazine, restlessness was described as an adverse event that can as a result of cariprazine treatment in a dose-response manner (84).

## Limitations

The biggest limitation of the present systematic review is publication bias. It is well-known that successful case reports are much more likely to be submitted by authors than unsuccessful ones, except those cases where the patient develops a serious side effect (89). Indeed, in the present review, only four articles (10.5%) reported cariprazine to be unsuccessful compared to 34 cases (89.5%) where cariprazine was effective and well-tolerated. Nonetheless, the aim of this systematic review is not to determine the efficacy and safety of cariprazine, but to provide additional information on its use in clinical practice.

# CONCLUSIONS

Cariprazine was found to be safe and effective in a wide range of psychiatric conditions with different symptom profiles from acute psychotic symptoms through addiction to negative and cognitive symptoms. The results are in-line with the established evidence from clinical trials, however, it also shows how cariprazine can be successfully utilized for the treatment of many symptoms, irrespective of the indication. Although according to evidence-based psychiatry, case reports are lower quality evidence, this systematic review shows that they can contribute to the overall scientific knowledge and support what has been established in clinical trials.

# DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material,

further inquiries can be directed to the corresponding author/s.

## AUTHOR CONTRIBUTIONS

RC, ZBD, BS, and MM contributed to conception of the manuscript. RC and ZBD wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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REVIEW
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# Potential Mechanisms for Why Not All Antipsychotics Are Able to Occupy Dopamine $D_3$ Receptors in the Brain *in vivo*

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Dysfunctions of the dopaminergic system are believed to play a major role in the core symptoms of schizophrenia such as positive, negative, and cognitive symptoms. The first line of treatment of schizophrenia are antipsychotics, a class of medications that targets several neurotransmitter receptors in the brain, including dopaminergic, serotonergic, adrenergic and/or muscarinic receptors, depending on the given agent. Although the currently used antipsychotics display *in vitro* activity at several receptors, majority of them share the common property of having high/moderate *in vitro* affinity for dopamine $D_2$ receptors ($D_2$Rs) and $D_3$ receptors ($D_3$Rs). In terms of mode of action, these antipsychotics are either antagonist or partial agonist at the above-mentioned receptors. Although $D_2$Rs and $D_3$Rs possess high degree of homology in their molecular structure, have common signaling pathways and similar *in vitro* pharmacology, they have different *in vivo* pharmacology and therefore behavioral roles. The aim of this review, with summarizing preclinical and clinical evidence is to demonstrate that while currently used antipsychotics display substantial *in vitro* affinity for both $D_3$Rs and $D_2$Rs, only very few can significantly occupy $D_3$Rs *in vivo*. The relative importance of the level of endogenous extracellular dopamine in the brain and the degree of *in vitro* $D_3$Rs receptor affinity and selectivity as determinant factors for *in vivo* $D_3$Rs occupancy by antipsychotics, are also discussed.

**Keywords: schizophrenia, antipsychotics, $D_3$ receptor, $D_2$ receptor, dopamine, brain occupancy**

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## INTRODUCTION

It is widely accepted that dysfunction of the dopaminergic neurotransmitter system plays a major role in the pathophysiology of schizophrenia. The primary pharmacotherapy of schizophrenia involves the use of antipsychotics, a group of drugs representing great heterogeneity in their chemical structure, pharmacological and functional profile, as well as clinical efficacy. At present, all available antipsychotics display affinity for $D_2$Rs, and it is widely accepted that $D_2$R antagonism or partial agonism is essential for their antipsychotic efficacy. Currently used antipsychotics display medium-to-high *in vitro* affinity for $D_2$R as well as $D_3$R, and high correlation can be demonstrated between their affinities for these receptors. This is not surprising considering the high structural homology, and the *in vitro* functional and pharmacological similarities of the two receptors. On

the other hand, significant differences have been demonstrated in their *in vivo* pharmacology and behavioral roles. All currently used antipsychotics, in agreement with their *in vitro* $D_2R$ affinity, show significant *in vivo* brain $D_2R$ occupancy at their antipsychotic effective doses. However, despite their substantial *in vitro* $D_3R$ affinity, not all antipsychotics demonstrated *in vivo* $D_3R$ occupancy in animals or in humans. Here, a review is given on the data available for the *in vitro* affinity for $D_2Rs$ and $D_3Rs$ and a hypothesis is provided as to why a group of antipsychotics do not show significant *in vivo* brain $D_3R$ occupancy despite their notable *in vitro* $D_3R$ affinity.

## SCHIZOPHRENIA

Schizophrenia is one of the most serious and debilitating psychiatric disorder affecting about 1% of the population disregarding economic, social, or cultural background of the society (1). Schizophrenia is characterized by positive symptoms (delusions, hallucinations) negative symptoms (social and emotional withdrawal, anhedonia, lack of motivation) and cognitive dysfunction, as well. All these symptoms may be mixed with aggressive behavior, depression, or anxiety (2–4).

The early, so called "dopamine hypothesis" stated that low prefrontal dopamine activity would cause "deficit symptoms" whereas enhanced activity in mesolimbic dopamine system would be in the background of the positive symptoms (5). In fact, the increased dopamine transmission has been demonstrated by positron emission tomography (PET) (6, 7). Further, presynaptically increased synthesis of dopamine in the basal ganglia has been found [(8, 9), see for review]. Loss of glutamatergic functions is also hypothesized and is thought to explain negative symptoms (9–11).

## ANTIPSYCHOTICS

Recognition of the neuroleptic action of chlorpromazine in 1952 represented a breakthrough in the drug treatment of schizophrenia (12). Chlorpromazine was soon followed by introduction of several other "neuroleptics" such as haloperidol, fluphenazine, pimozide, sulpiride, thioridazine etc. (Interestingly enough, this group of drugs was named/categorized by their side effect profile).

At the time of their discovery, the main mechanism of action of the first-generation antipsychotics was believed to be mediated by their actions on the monoaminergic system. Carlsson and Lindquist demonstrated that haloperidol and chlorpromazine increased monoamine turnover in the rat brain and these changes were attributed to the monoamine receptor antagonism action of these compounds (13). Van Rossum was the first describing that antipsychotics exert their therapeutic effects through the blockade of dopamine receptors (14). For the history of antipsychotics' discovery see the recent review by Seeman (15).

Some antipsychotics, such as clozapine, fluperlapine and melperone were found to produce weak catalepsy in rodents, with minimal extrapyramidal symptoms and serum prolactin elevation in humans, compared to the earlier typical antipsychotic drugs, such as haloperidol. Meltzer and Matsubara explored the basis of these differences by testing the affinity of 38 antipsychotics for the rat striatal dopamine $D_1$ receptors ($D_1Rs$), $D_2R$ and serotonin 5-$HT_2$ receptors (5-$HT_2R$). They found that the 5-$HT_2R/D_2R$ affinity ratio was the most useful means of differentiation from the typical antipsychotics. They demonstrated that compounds displaying 5-$HT_2R/D_2R$ affinity ratio of 1.12 or higher were the ones showing the atypical characteristics (16). These findings had significant impact on the antipsychotic drug research: the primary aim was to find antipsychotics possessing a significant serotonin 5-$HT_{2A}$ receptor (5-$HT_{2A}R$) affinity that would be similar or higher than that for the $D_2R$. The quest for compounds with $D_2R/5$-$HT_{2A}R$ affinity led to discovery of risperidone, asenapine, olanzapine, quetiapine, ziprasidone, blonanserin and lurasidone, collectively classified as atypical or second-generation antipsychotics.

Atypical antipsychotics, like to the typical antipsychotics, are efficacious in the treatment of positive symptoms of schizophrenia but display relatively lower propensity to cause extrapyramidal side effects. However, it was claimed that the label of "atypical" is not fully justified as they are different from first-generation antipsychotics only in their side effect profile (e.g., weight gain, alteration in metabolic parameters, cardiovascular complications) (17–19). In fact, neither group represented major step forward in the treatment of other symptoms of schizophrenia, such as negative or cognitive symptoms.

Distinct category of second-generation antipsychotics with partial agonism at dopamine $D_2R$, $D_3R$ and serotonin 5-$HT_{1A}$ receptors (5-$HT_{1A}R$) as well as antagonism at serotonin 5-$HT_{2A}R$ and 5-$HT_{2B}$ receptors (5-$HT_{2B}Rs$) is represented by aripiprazole, cariprazine and brexpiprazole. Amongst these three partial agonist antipsychotics, aripiprazole and brexpiprazole display preferential binding affinity for dopamine $D_2R$ (20, 21), whereas cariprazine has higher affinity for dopamine $D_3R$ over $D_2R$ receptors (22). These dopamine receptor partial agonists may be referred to as third generation antipsychotics (23). These dopamine-serotonin partial agonists were originally approved for acute schizophrenia, schizophrenia maintenance, later, however, they were found to be useful in treatment of mania, bipolar disorder, and as adjunct in unipolar depression (24).

## DOPAMINE RECEPTORS

Effects of dopamine are mediated through five receptors subtypes, namely $D_1$-, $D_2$-, $D_3$-, $D_4$-, and $D_5$-receptors. All dopamine receptors belong to G-protein coupled receptor (GPCR) family: $D_1$ and $D_5$ receptors ($D_1$-receptor family) stimulate cAMP signaling pathway through a $G_{\alpha s}$ G-proteins, whereas $D_2$-, $D_3$- and $D_4$-receptors ($D_2$-receptor family) inhibit cAMP signaling through a $G_{\alpha i/o}$ G-proteins (25–29).

Expression of dopamine $D_1$ receptors ($D_1R$) is the highest in basal ganglia (caudate nucleus, putamen and globus pallidus), accumbens nuclei, substantia nigra, amygdala and the frontal cortex. The cortex, substantia nigra, hypothalamus and the hippocampus express low level of dopamine $D_5$ receptors ($D_5Rs$).

High levels of $D_2$Rs are found in the basal ganglia, while cortical regions express low level of these receptors. $D_2$Rs are the primary drug targets in schizophrenia, Parkinson's disease, restless leg syndrome and neuroendocrine tumors. Highest expression of dopamine $D_3$Rs are found mainly in the limbic system (islands of Calleja, nucleus accumbens, ventral part of caudate nucleus), with minor/low levels of expression in cortical regions. Dopamine $D_4$ receptors ($D_4$Rs) are found with relatively low level of expression in the amygdala, hippocampus, hypothalamus, cortex and, in the substantia nigra (25–28, 30–34).

# $D_2$Rs AS KEY TARGETS FOR THE THERAPEUTIC ACTION OF APs

## *In vitro* Affinity and Selectivity of Antipsychotics for Dopamine Receptors of $D_2$R-Subtype

First and second-generation antipsychotics possess diverse structural, pharmacological (*in vitro* receptor profile, functional activity, e.g., antagonism, partial agonism, inverse agonism) and behavioral effects and side-effect profiles. However, their common property is that all display medium-to-high affinity for dopamine receptors of $D_2$R-subtype (i.e., $D_2$R, $D_3$R, and/or $D_4$R) under *in vitro* conditions (18, 35–40). The *in vitro* affinities of currently used antipsychotics for dopamine $D_2$R-like (i.e., $D_2$R, $D_3$R, and $D_4$R subtypes) and their degree of $D_3$R selectivity are summarized in **Table 1**.

**TABLE 1** | *In vitro* affinity of major first-, second-, and third-generation antipsychotics at human dopamine receptors of $D_2$R-type and their degree of their $D_3$R selectivity.

| Compound | Ki (nM) | | | $D_3$ selectivity | |
|---|---|---|---|---|---|
| | $D_2$R | $D_3$R | $D_4$R | vs. $D_2$R | vs. $D_4$R |
| Amisulpride | 3.0 | 2.4 | 2,369 | 1.3 | 984 |
| Aripiprazole | 0.9 | 1.6 | 514 | 0.56 | 321 |
| Asenapine | 1.4 | 1.8 | 1.8 | 0.78 | 1 |
| Blonanserin[I] | 0.28 | 0.28 | n/a | 1 | – |
| Brexpiprazole[II] | 0.3 | 1.1 | 6.3 | 0.27 | 5.7 |
| Cariprazine[III] | 0.49 | 0.09 | >1,000 | 5.8 | >1,000 |
| Chlorpromazine | 2 | 3 | 24 | 0.67 | 8 |
| Clozapine | 431 | 283 | 39 | 1.5 | 0.14 |
| F17464[IV] | 12.5 | 0.12 | >1,000 | 104 | >1,000 |
| Fluphenazine | 0.5 | 0.7 | 36 | 0.71 | 51 |
| Haloperidol | 2.0 | 5.8 | 15 | 0.34 | 2.6 |
| Iloperidone | 0.4 | 11 | 13.5 | 0.04 | 1.2 |
| Loxapine | 10.0 | 23.3 | 12 | 0.43 | 0.52 |
| Lurasidone[V] | 1.0 | 15.7 | 29.7 | 0.06 | 1.9 |
| Lumateperone[VI] | 32 | n/a | n/a | n/a | – |
| Olanzapine[VII] | 21 | 34.7 | 19 | 0.6 | 0.50 |
| Paliperidone | 9.4 | 3.2 | 54.3 | 2.9 | 17 |
| Quetiapine[VII] | 417 | 383 | 1,202 | 1.1 | 3 |
| Risperidone[VII] | 6.2 | 9.9 | 18.6 | 0.6 | 0.33 |
| Ziprasidone | 4.0 | 7.4 | 105 | 0.54 | 14 |
| Zotepine | 25 | 6.4 | 18 | 3.9 | 2.8 |

*I: (41); II: (21); III: (22); IV: (42); V: (43); VI: (44); VII: (39).*
*n/a, no data available.*
*A part of affinity data were taken from Ellenbroek an Cesura (37), and the PDSP data base (https://pdsp.unc.edu/pdspweb). The same data base-derived data for major antipsychotics are given in Gross and Drescher (38) and Kaar et al. (40), however, the affinities were somewhat different even though they were taken from the same data base. Receptor affinity data for major antipsychotics generated by Tadori et al. (20), Seeman (35), and Shahid et al. (39) also differed from the above data-based sources.*

## Daily Dose and Plasma Levels of Antipsychotics Correlates With Their *in vitro* Affinity for Dopamine $D_2$Rs

Seeman demonstrated a close correlation between the therapeutic doses of antipsychotics and their *in vitro* $D_2$R receptor affinity, but no correlation was found with $D_1$R affinity (45, 46). Correlation between $D_2$R affinities, optimal occupancy of brain $D_2$R for antipsychotic efficacy (i.e., 60–70%) and the free plasma levels of antipsychotics were also demonstrated (47).

## Antipsychotics Occupy $D_2$Rs in Brain

At present, it is broadly accepted that $D_2$R affinity is the primary mechanism for antipsychotic efficacy (18, 36, 48, 49). Positron emission tomography (PET) studies demonstrated that for the clinical efficacy of $D_2$R antagonist antipsychotics, a 60–75% occupancy of brain $D_2$R is essential (50). In case of partial agonist antipsychotics, such as aripiprazole or cariprazine $D_2$R occupancy can be as high as 95% at dose levels with established clinical efficacy (51–53), whereas brexpiprazole produced only 80% occupancy at the highest dose applied (54).

At present, despite the great efforts to develop non-dopamine antipsychotics, no such compounds are approved for the treatment of positive, negative, or cognitive symptoms of schizophrenia (55).

# $D_3$R, A POTENTIAL NOVEL TARGET IN THE THERAPY OF CENTRAL NERVOUS SYSTEM DISORDERS: COMPARISON WITH $D_2$R

## Similarities and Differences of $D_2$Rs and $D_3$Rs

### Structural

The $D_3$R is a member of the largest phylogenetic class of GPCRs, known as class A, which contains the transmembrane domain without a large extracellular domain. Native ligands of aminergic GPCRs bind directly to the transmembrane domain, which is composed of seven transmembrane (TM) helices embedded in the cell membrane connected by three extracellular (EL) and three intracellular (IL) loops (56). The C-terminus of the protein is the eighth small α-helix (H8).

Analysis of amino acid sequence of human and rat dopamine $D_2$R and $D_3$R exhibits a high level of general sequence identity which is increased in the transmembrane helices forming a highly

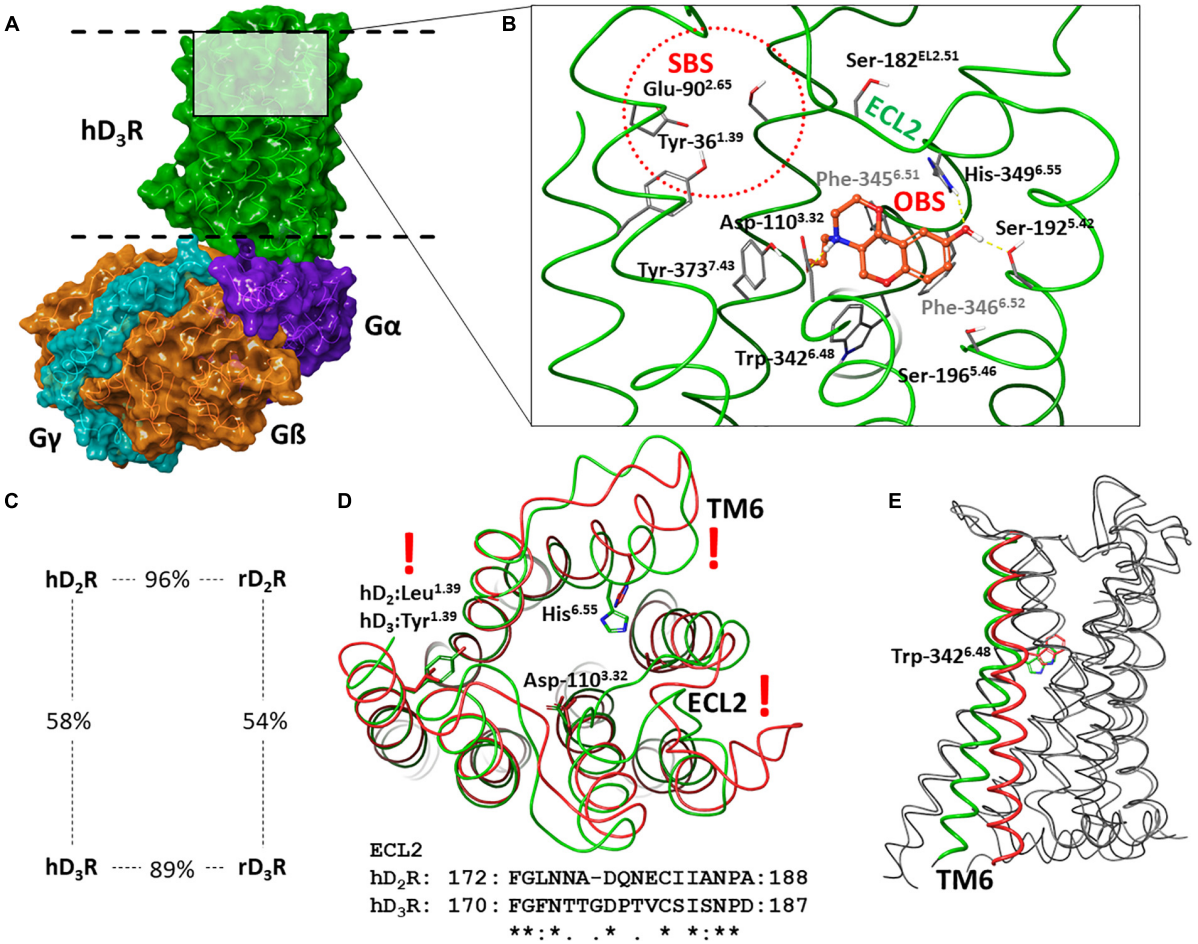


**FIGURE 1 |** Structure of $hD_3R$: **(A)** $hD_3R$-$G_i$ complex; **(B)** binding of the selective agonist PD128907 in the orthosteric binding site (Secondary binding site and ECL2 are also depicted); **(C)** percent identity of human and rat $D_2R$ and $D_3R$ sequences; **(D)** comparison of $hD_2R$ (red) and $hD_3R$ (green); **(E)** comparison of active (green) and inactive (red) conformation of $hD_3R$*.

conserved orthosteric binding site (OBS) (see **Figures 1A–C**). The most obvious differences in the sequences can be found in the intracellular loop region (ICL3) between transmembrane helices of the TM5 and TM6. However, this region is quite distant from the orthosteric binding site, and thus the differences in the ECL2 (between the TM4 and TM5) and in the secondary binding site (SBS) are more relevant for the discovery of selective $D_3R$ vs. $D_2R$ ligands (57, 58). Moreover, targeting SBS may be a tool for fine tuning functional activity and biased agonism (59, 60). The shape and the sequence of the ECL2 is highly different in $D_2R$ and $D_3R$ (see **Figure 1D**). The SBS is the most probable binding site for the tail group of several elongated $D_3R$ ligands, where for instance the amino acid at the position 1.39 [Ballesteros-Weinstein numbering; (61)] is leucine in the $D_2R$ and tyrosine in the $D_3R$. The amino acids forming the OBS are identical, but comparison of $D_2R$ and $D_3R$ structures suggest a slightly different shape of OBS because of the slightly different TM6 orientation (62).

Recently published experimental structures of $D_2R$ and $D_3R$ (62–68) provide extensive information sources on ligand binding and receptor function. Like other GPCRs, the most conspicuous change during activation is the movement of the TM6, which enables the G-protein to connect to the receptor (see **Figure 1E**). The Trp in the position 6.48 may have a key role in the activation since it is close to the OBS and its position is related to the TM6 orientation (62).

## Intracellular Signaling Pathways

All dopamine receptors belong to GPCR family: $D_1R$ and $D_5R$ receptors ($D_1$-receptors family) stimulate cAMP signaling pathway through $G_{\alpha s}$ G-proteins whereas $D_2R$, $D_3R$, and $D_4R$ ($D_2R$ family) inhibit this pathway through $G_{\alpha i/o}$ G-proteins. There exists cAMP- independent pathways such as the recently recognized ß-arrestin pathway which is thought to be involved in several physiological functions and drugs' effects (25–29).

Upon activation, both isoforms of $D_2R$ (i.e., $D_2$Short and $D_2$Long) and $D_3R$ inhibit the enzyme adenylyl cyclase (AC) through $G_{\alpha i/o}$ subtype of G-protein leading to inhibition of cAMP-PKA-pDARPP32-PPI pathway. However, differences may

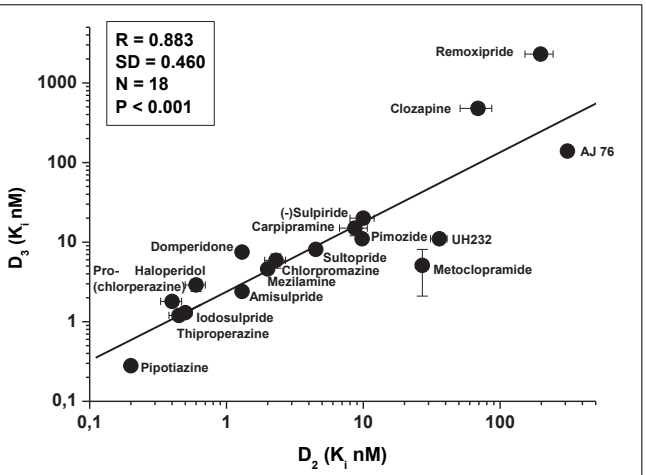


**FIGURE 2 |** Correlation between *in vitro* affinity of various dopaminergic antagonists for human recombinant $D_3$Rs and $D_2$Rs [data taken from Sokoloff et al. (80)]; ligand: [$^{125}$I]sulpiride.

exist in the coupling efficiency of the two receptors and AC (or its subtypes).

In different cell lines, both $D_2$R and $D_3$R can activate ERK/MAPK signaling albeit with different mechanisms: $D_2$Rs are coupled to and activate through α-subunit of $G_{i/o}$ protein following agonist stimulation whereas, $D_3$R functions through $G_o$ or $G_ß$ subunit depending on the signaling machinery of the given cell line. Both $D_2$Rs and $D_3$Rs are positively coupled to ß-arrestin-Akt-GSK3 pathway. GSK3ß is expressed in several brain regions and plays important role in neuronal development, neurovegetative and psychiatric diseases such as schizophrenia or bipolar disorder (26, 29, 70–79).

## *In vitro* Pharmacological Profile of Dopaminergic Agents at $D_3$Rs vs. $D_2$Rs

It has been demonstrated that significant correlation exists between the *in vitro* affinities of various dopaminergic agents (agonists, antagonists, partial agonists) for $D_2$Rs and $D_3$Rs (80) (**Figure 2**).

Further results, using additional compounds, have confirmed earlier evidence showing close correlation between affinities of antipsychotics for human recombinant $D_2$Rs and $D_3$Rs (**Figure 3A**). However, no such correlation was found between $D_1$R vs. $D_3$R or $D_3$R vs. $D_4$R (data not shown). Similarly, high level of correlation was found between the affinity of antipsychotics for the rat $D_2$R and $D_3$Rs using [$^3$H](+)-PHNO radioligand (81, 82) (**Figure 3B**).

Based on recognition that $D_3$Rs are mainly expressed in the limbic system (*vide supra*), the region is involved in schizophrenia pathology, and that significant correlation existed between the affinity of antipsychotics for $D_2$Rs and $D_3$Rs, it was thought that $D_3$R affinity may play a role in the therapeutic efficacy of antipsychotics and led to propose development of selective $D_3$R antagonists as novel antipsychotics (30, 80, 83–85).

## Predicted Binding Mode of Antipsychotics in the $D_3$R

One of the available experimental structure studies of $D_3$R has been carried out with the antagonist eticlopride (63), and the other two with the agonists, pramipexole and PD128907 (62). All these agents bind to the orthosteric binding site (see **Figure 1B**). The most important interactions are the salt bridge with the Asp-110$^{3.32}$ as well as the π-π interactions with the aromatic residues (e.g., Trp-342$^{6.48}$, Phe-345$^{6.51}$, Phe-346$^{6.52}$), which form a lipophilic cavity. Hydrogen bond interaction with the serines in the 5.42 and 5.46 positions is typical for agonist binding state in $D_3$R (62), and also in $D_2$R structures (64, 65).

Non-selective ligands most probably bind to both the $D_2$R and $D_3$R in the same binding mode, forming a very similar interaction pattern. Thus, the $D_2$R structural binding results obtained for non-selective $D_2$R/$D_3$R antagonists, such as risperidone, haloperidol or spiperone can be predictive of their binding mode at the $D_3$R. It should be noted that distinct inactive conformations of $D_3$R exists, and ligands may have different preferences which lead to different functional behaviors of antagonists (antagonism vs. inverse agonism, sensitivity for sodium ions) (86). These results are in line with the well-known highly dynamic nature of the GPCRs (87).

Based on the available experimental structural information supplemented by computational investigations (60, 88–90) the binding mode of antipsychotics at the $D_3$R can be predicted at a reliable manner. In order to illustrate this, we docked several selected ligands into the $D_3$R structures available in the Protein Data Bank (PDB ID: 7CMV (62) for dopamine and 3PBL (63) for the others) using the Glide, induced-fit-docking and the protein-ligand complex refinement protocols implemented in the Schrödinger software package (Schrödinger Release 2020-2) (**Figure 4**).

## *In vivo* Roles and Behavioral Pharmacology of $D_3$R and $D_2$Rs Is Different

Despite the similarities in the *in vitro* properties of $D_3$Rs and $D_2$Rs described above, the *in vivo* roles and behavioral pharmacology of $D_3$Rs compared to $D_2$Rs are remarkably different. Animal data suggest opposite role of $D_2$R vs. $D_3$R in the control of locomotor activity, and cortical functions such as learning and memory (91, 92). On the other hand, both $D_2$R and $D_3$R receptor agonists were shown to impair certain social functions and cognitions (93–95). Enhanced expression of striatal dopamine $D_3$R receptors impairs motivation (96). Antagonists of dopamine $D_2$R receptors stimulate prolactin secretion (18), whereas $D_3$R antagonism does not produce such effect either in rats or in human (97, 98). Majority of $D_2$R antagonist antipsychotics (e.g., haloperidol, risperidone, and olanzapine) elicit catalepsy at higher doses (99). In contrast, $D_3$R antagonists do not cause catalepsy (97), they rather inhibit haloperidol-induced catalepsy (100, 101).

Microdialysis studies demonstrated that $D_2$R antagonist antipsychotics enhance, whereas selective $D_3$R antagonists (such as SB-277011) (97, 102) or $D_3$R-preferring $D_3$R/$D_2$R (such as S33138) antagonists (84, 103) exert no or minimal effects on cortical or striatal dopamine release (104).

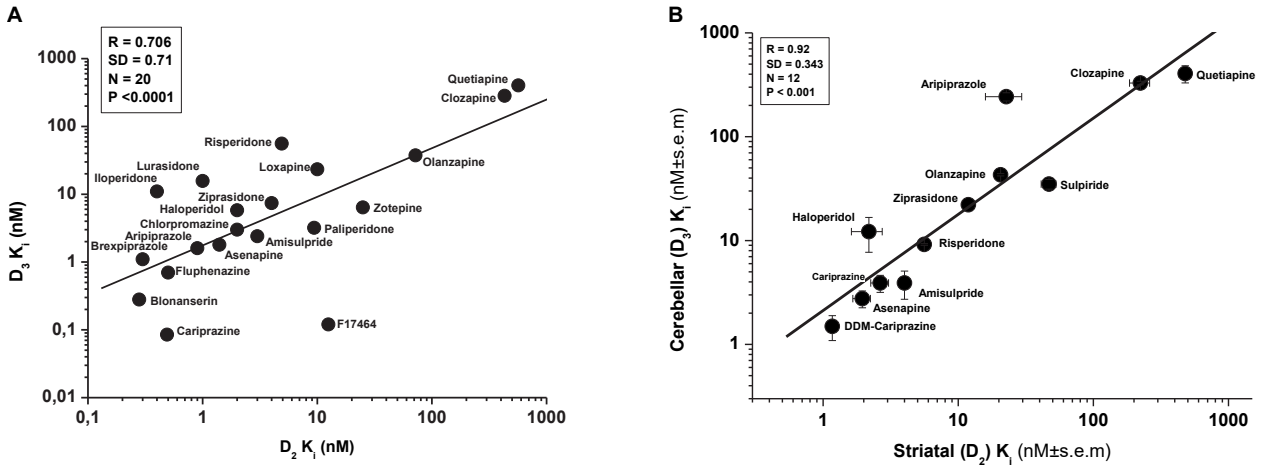


**FIGURE 3 |** Correlation between *in vitro* affinity of antipsychotics for human $D_2$Rs and $D_3$Rs (**A**, data taken from **Table 1**; various radioligands) and for rat striatal $D_2$Rs (striatal membrane) and cerebellar $D_3$Rs (CB L9,10 membrane) **(B)**; rat $D_2$R and $D_3$R affinity data derive from the extension of the study of Kiss et al. (81) and Kiss et al. (82). Determination of $D_2$R and $D_3$R affinity in membranes from CHO cells expressing human $D_3$R or cerebellar L9,10 membranes (ligand: [$^3$H]-(+)-PHNO) is described in Kiss et al. (81).

Little is known on the functions of dopamine $D_3$R receptors in humans although their involvement is assumed in central nervous system (CNS) diseases such as schizophrenia, Parkinson's disease, addiction, anxiety, and depression or in the clinical effects of antipsychotics (26, 38, 70, 75).

## SELECTIVE AGONISTS OR ANTAGONISTS FOR $D_3$R: THE CHALLENGE OF DRUG RESEARCH

The availability of drugs displaying high selectivity and affinity for $D_2$R or $D_3$R receptors are of great importance. Such compounds are useful tools in the exploration of neural mechanisms related to dopamine $D_3$R receptors and may lead to novel agents for the treatment of various CNS disorders. Because of the close similarity in structure and signaling pathways of $D_2$R and $D_3$R, development of highly selective compounds for either subtype has been very challenging (34, 105).

Amongst agonists, the *in vitro* $D_3$R affinity and selectivity of 7-OH-DPAT, PD128907 and pramipexole demonstrated great variability depending on the assay conditions used (105). Nevertheless, their degree of $D_3$R vs. $D_2$R selectivity seems adequate for use as tools for *in vitro* studies and their *in vivo* $D_3$R selectivity may not be optimal, as they may also stimulate $D_2$Rs within a narrow dose range (38, 106–109). For example, all three compounds produce biphasic behavioral effects in rats, some of which can be inhibited by either $D_3$R and/or $D_2$R selective antagonists, depending on the exposure levels of these agonists (95, 110–114).

The quest for high affinity, selective antagonists for $D_3$R receptors (i.e., low-nanomolar $K_i$ with $D_2$R/$D_3$R selectivity $\geq$100) began soon after the discovery of $D_3$R. Several antagonists fulfilling the selectivity requirements such as SB-277011A (97), ABT-925 (115), GSK598809 (116), compound 74 in Micheli et al. (117) are currently available for experimental purposes. The pharmacological properties of the selective $D_3$R antagonists have been reviewed by Gross et al. (84). L-741626 seems to be relatively selective for $D_2$R reaching 100-fold higher $D_2$R affinity vs. $D_3$R, depending on the assay system used (118).

## SELECTIVE $D_3$R ANTAGONISTS AS ANTIPSYCHOTICS?

Compounds with relatively high selectivity for dopamine $D_3$Rs such as SB-277011A (97), S33084 (119), ABT-925 (115, 120), GSK598809 (116, 117), or the $D_3$R-preferring $D_3$R/$D_2$R antagonist S33138 (103), or the $D_3$R-preferring partial agonist BP-897 (121) demonstrated antipsychotic-like properties in animal models, however none of them reached therapeutic application. The high affinity $D_3$R -preferring antagonist F17464 with partial agonism at serotonin 5-$HT_{1A}$R and antagonism at dopamine $D_2$R (42) showed promising preclinical profile as well as clinical efficacy in schizophrenia patients in a Phase II study. This compound is still under development and (122, 123). Propose the development of selective $D_3$R antagonist for the treatment of negative symptoms of schizophrenia based on the available scientific evidence (84).

## IMAGING THE $D_3$Rs *IN VIVO*

### PHNO for Labeling $D_3$Rs

Number of tracers have been tried to develop for selective imaging of $D_3$Rs in the brain (124–126), however, the only radioligand currently available for labeling of $D_3$R in occupancy studies suitable for separation of $D_3$R and $D_2$R signal is the [$^3$H]- or [$^{11}$C]-labeled (+)-4-propyl-9-hydroxynaphthoxazine

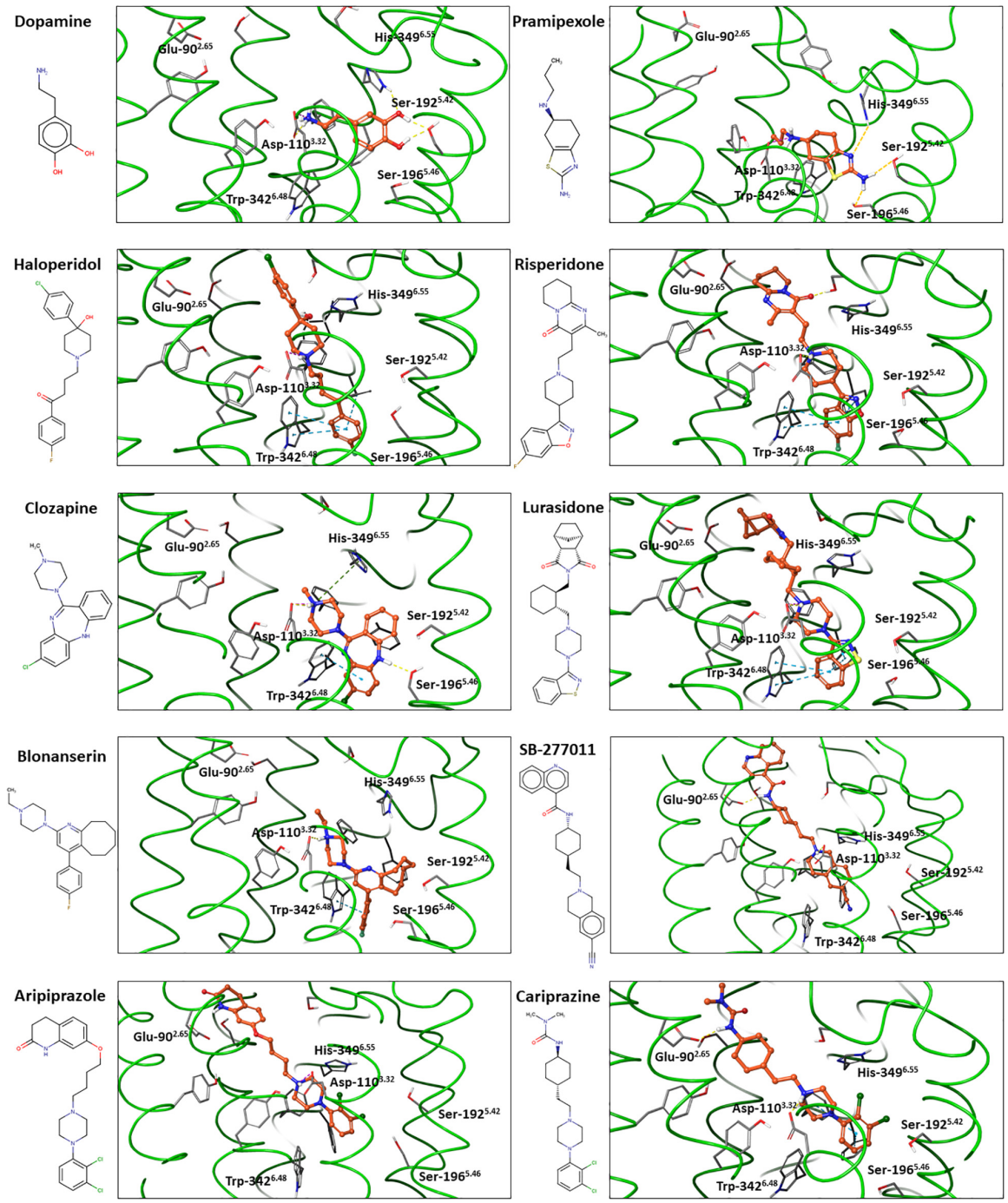


**FIGURE 4 |** Dopamine, pramipexole and selected antipsychotics docked into experimental $D_3R$ structures*.

[(+)-PHNO, naxagolide]. (+)-PHNO was originally described as an orally acting, potent dopamine receptor full agonist (127). (+)-PHNO was shown to possess 50-fold selectivity for human recombinant $D_3R$ ($K_i$: 0.16 nM) vs. $D_2R$ (Ki: 8.5 nM) (128).

[$^{11}$C]-(+)-PHNO was synthesized by Wilson et al. (129) and it was shown that, in contrast with the antagonists such as [$^{11}$C]raclopride, [$^{18}$F]Fallypride, [$^{11}$C]FLB-457 or the agonist [$^{11}$C]N-methyl-norapomorphine, (+)-PHNO highly binds to regions rich in $D_3Rs$. Using selective compounds such as the $D_3R$ antagonists SB-277011A, GSK598809 or the $D_2R$ antagonist SV-156, [$^{11}$C]-PHNO proved to be useful for the separation of $D_3R$ and $D_2R$ binding signal and quantification of $D_3Rs$ in the brain, thus becoming an important tool for the

investigation of the *in vivo* $D_3R$ occupancy by antipsychotics (116, 129–136).

## $D_3R$ Occupancy of Antipsychotics—Animal Studies With [$^3$H](+)PHNO

It was reported that after *intravenous* administration of [$^3$H](+)-PHNO, $D_3Rs$ are labeled in the rat cerebellum L9,10 and $D_2R$ in the striatum. This is based on the finding that the selective $D_3R$ antagonist, SB-277011 inhibited [$^3$H](+)-PHNO binding in CB L9,10 membranes but not in the striatum whereas, the opposite profile was obtained with the $D_2R$ selective antagonist, SV-156 (118) (compound 9); (81).

Using the above approach, olanzapine, risperidone, haloperidol, and clozapine given acutely or chronically, at doses corresponding to human doses, showed nearly full occupancy in the striatum and NAC ($D_2R$ rich regions) with significantly lower level or no occupancy in VP, ICj and substantia nigra (SN) ($D_3R$ rich regions). In contrast, in the *in vitro* autoradiography experiments all these antipsychotics inhibited [$^3$H]-(+)-PHNO binding in the above regions except CB L9,10. It was concluded that under *in vivo* conditions the above-mentioned antipsychotics occupy dopamine $D_2R$ but not $D_3Rs$ despite their significant affinity for $D_3Rs$ *in vitro* (137, 138).

We extended this approach and compared the *in vitro* affinity of several dopamine $D_2R/D_3R$ agonists, partial agonists, and antipsychotics using membranes prepared from rat striatum ($D_2R$-rich) and cerebellar L9,10 region ($D_3R$ rich) to determine their *in vivo* $D_3R$ and $D_2R$ occupancy. The affinity data are given in Kiss et al. (82). We also compared the effects of systemic administration of selected full agonists, partial agonists and antipsychotics on the *in vivo* binding/uptake of intravenously given [$^3$H](+)-PHNO binding/uptake in the rat striatum and cerebellar L,910 regions. The results are summarized in **Table 2**. Among the drugs with subnanomolar or low nanomolar Ki values for $D_3R$, full agonists pramipexole and PHNO potently inhibited [$^3$H](+)-PHNO binding of CB L,910 membranes with marked preference toward CB L9,10 $D_3Rs$. Cariprazine, didesmethyl-cariprazine (DDCAR), asenapine, raclopride and amisulpride, produced dose-dependent inhibition of [$^3$H](+)-PHNO binding/uptake both in the striatal and CB L9,10 regions. Raclopride and asenapine, however demonstrated high striatal vs. cerebellar selectivity (82). The antipsychotics, aripiprazole, olanzapine, risperidone, quetiapine, ziprasidone (all with high nanomolar $K_i$ values) produced inhibition of [$^3$H](+)-PHNO binding/uptake in the striatum and little or modest level of inhibition in the CB L9,10.

Blonanserin, an antipsychotic marketed in Japan, was originally described as $D_2R$ and serotonin 5-$HT_2R$ antagonist (139). It has recently been found that blonanserin displayed high affinity *in vitro* for human $D_2R$ and $D_3Rs$ (Ki: 0.28 nM). Using the *in vivo* [$^3$H](+)-PHNO method it caused dose-dependent, high occupancy of striatal $D_2R$ and $D_3R$ in the rat CB L9,10. In agreement with our data (see above) risperidone, olanzapine and aripiprazole demonstrated high occupancy only in the striatum and moderate or no occupancy was noted in the CB L9,10 region (41).

**TABLE 2 |** Effects of selected antipsychotics, $D_3R$ agonists, antagonists, on the [$^3$H](+)-PHNO uptake in rat striatum and cerebellum L9,10 region*,&.

| | Route | Administered highest dose (mg/kg) | Striatal $ED_{50}$ (mg/kg) | CB L9/10 $ED_{50}$ (mg/kg) | Striatum/ CB L9,10 ratio |
|---|---|---|---|---|---|
| **Agonists** | | | | | |
| (+)-PHNO | p.o. | 1 | >1 (33) | 0.05 (95) | >>20 |
| (−)-Pramipexole (PRP) | s.c. | 1 | >1 (39) | 0.018 (96) | >>55 |
| **Partial agonists** | | | | | |
| Aripiprazole (ARP) | p.o. | 30 | 7.65 (92) | >30 (14) | <<0.26 |
| Cariprazine (CAR) | p.o. | 3 | 0.23 (99) | 0.43 (99) | 0.53 |
| Cariprazine | i.v. | | 0.023 (94) | 0.035 (98) | 0.66 |
| DD-CAR$^+$ | p.o. | 10 | 0.58 (99) | 0.41 (100) | 0.66 |
| **Antagonists** | | | | | |
| Amisulpride (AMS) | i.p. | 30 | >30 (35) | 3.0 (82) | >10 |
| Asenapine (ASN) | s.c. | 1 | 0.037 (95) | 0.177 (74) | 0.21 |
| Clozapine$^\#$ (CLZ) | p.o. | 60 | 60 (34) | 60 (29) | n.c. |
| Haloperidol (HP) | p.o. | 3 | 0.23 (100) | 1.05 (100) | 0.22 |
| Olanzapine (OLZ) | p.o. | 30 | 1.46 (91) | ∼30 (48) | ∼0.05 |
| Quetiapine$^\#$ QUET) | p.o. | 250 | 250 (36) | 250 (36) | n.c. |
| Raclopride (RCP) | s.c. | 1 | 0.013 (98) | 0.072 (97) | 0.18 |
| Risperidone (RSP) | p.o. | 3 | 0.29 (89) | ∼2.3 (53) | ∼0.13 |
| SB-277011A (SB) | p.o. | 30 | >30 (28) | 1.31 (100) | >>23 |
| SV-156 | s.c. | 10 | 0.89 (84) | >12 (20) | <<0.07 |
| Ziprasidone (ZPR) | p.o. | 30 | 1.63 (92) | ∼30 (52) | ∼0.05 |

**The $ED_{50}$ doses were calculated from individual dose response curves consisting of at least 4–5 doses with 3–8 animals in each dose-group. Group means were analyzed by one-way analysis of variance (ANOVA) followed by Tukey-Kramer post-hoc multiple comparison test. The highest inhibition percentage achieved at the highest applied are given in the brackets. Where the highest achieved inhibition at highest applied dose was around 50% percent, approximate $ED_{50}$ values are given and are marked with ∼ sign.*

*$^+$DD-CAR, didesmethyl-cariprazine; one of the major human metabolites of cariprazine.*

*$^\#$In case of clozapine and quetiapine the highest achievable inhibition was less than 50%, thus $ED_{50}$ could not be calculated.*

*$^\&$Kiss et al. (82).*

## $D_3R$ Occupancy of Antipsychotics—Human PET Studies

In patients suffering from schizophrenia, occupancy of $D_2Rs$ and $D_3Rs$ following long-term treatment with risperidone, clozapine or olanzapine was examined using [$^{11}$C]raclopride or [$^{11}$C](+)-PHNO PET. This study demonstrated that these antipsychotics caused high $D_2R$ occupancy in the $D_2R$-rich dorsal striatum, using either [$^{11}$C]raclopride or [$^{11}$C](+)-PHNO. However, they failed to show binding signal in the $D_3R$-rich globus pallidus using [$^{11}$C](+)-PHNO (140). Similar results with [$^{11}$C](+)-PHNO PET were reported by Mizrahi et al. demonstrating that in drug-naive, first episode schizophrenia patients, olanzapine and risperidone resulted in high occupancy in the $D_2R$-rich regions but not in the globus pallidus where even "negative occupancy" was noted (141). On the other hand, blonanserin, ($hD_2R$ Ki: 0.284 nM; $hD_3R$ Ki: 0.277 nM), in agreement with data obtained in rats, achieved significant $D_3R$ occupancy in healthy volunteers (142).

PET studies in healthy volunteers using [$^{11}$C]raclopride (51) as well as in patients with schizophrenia using [$^{18}$F]Fallypride (52) aripiprazole with $D_2R$ preference showed dose-dependent occupancy in the $D_2R$-rich striatum without causing extrapyramidal side effects. A subsequent study with $D_3R$ preferring PET ligand, [$^{11}$C](+)-PHNO confirmed the $D_2R$ occupancy of aripiprazole however, minor levels of $D_3R$ occupancy was detected (143).

Cariprazine, a $D_3R$ preferring $D_3R/D_2R$ partial agonist antipsychotic ($hD_2R$ Ki: 0.49 nM; $hD_3R$ Ki: 0.09 nM) (22) dose-dependently inhibited [$^{11}$C](+)-PHNO binding in brain regions with varying $D_2R$ and $D_3R$ expression. It showed significant occupancy of both $D_2R$ and $D_3R$, albeit with approximately 3–6-fold selectivity for $D_3R$ (53, 143).

Brexpiprazole is also a partial agonist antipsychotic with $D_2R$ preference ($hD_2R$ Ki: 0.3 nM; $D_3R$ Ki: 1.1 nM) (21). Occupancy study in healthy volunteers showed that in the therapeutic dose range (1 and 4 mg/d) it produced only very low levels (i.e., 2–13%) of $D_3R$ occupancy whereas it achieved 36 and 59% $D_2R$ occupancy, respectively, in the applied dose range (54).

F17464 with remarkable affinity for $D_3Rs$ ($D_3R$ Ki: 0.16 nM; $D_2R$ Ki: 12 nM) demonstrated antipsychotic-like activity in animal experiments (42, 144). It was reported that in a double blind, multicenter Phase II study, F17464 (20 mg/bd) improved schizophrenia symptoms (122). In a phase I study, F17464 resulted in 69–95% occupancy of $D_3Rs$ whereas only a 20% occupancy of $D_2Rs$ were noted (145).

# POTENTIAL EXPLANATION FOR WHY SIGNIFICANT *IN VITRO* AFFINITY MAY NOT GUARANTEE SUBSTANTIAL $D_3$ OCCUPANCY *IN VIVO*

## Role of Endogenous Dopamine

### Affinity of Dopamine for $D_3R$

The dopamine displays considerably higher *in vitro* affinities for $D_3Rs$ ($K_i$ values vary from 30 nM to 100 nM) compared with $D_2R$ ($K_i$ values vary from 200 nM to 1000 nM)[1]; (70). The *in vitro* $K_i$ values greatly depend on several *in vitro* binding conditions such as the receptor source, radioligands used for binding assays, and assay methodology.

As to the dopamine $K_i$ values for $D_3Rs$ the picture is further complicated since like $D_2R$, $D_3R$ may also exist in low and high affinity state. Sokoloff et al. did not find differences between affinity of dopamine for $D_3R$ in the absence or presence of Gpp(NH)p (24 vs. 27 nM) (30, 80). However, Gross and Drescher (38) and Seeman et al. (146) reported remarkable difference between the low and high affinity states of $D_3R$. $D_3Rs$ are prone to dimerization and to form heteromers with $D_1Rs$ or $D_2Rs$, or with non-dopaminergic receptors (147). Affinity of dopamine (and the signalization pathway) as well as that of other dopaminergics (including antipsychotics) toward $D_3R$ di- or heteromers may also change.

[1]https://pdsp.unc.edu/databases/pdsp.php

### Endogenous Dopamine Concentrations

As determined by *in vivo* microdialysis in rodents, under physiological conditions the extracellular, (i.e., resting or steady state) dopamine concentrations are in the low nanomolar range in various brain regions, including n. accumbens (∼1.5–4.5 nM), striatum (∼2–5 nM), hippocampus (∼1 nM) and in subnanomolar range in the prefrontal cortex (∼0.3–0.6 nM) (104, 148–154).

Little is known about the endogenous dopamine concentration in the human brain. Using [$^{11}$C]-(+)-PHNO PET Caravaggio et al. estimated that the $K_d$ (dissociation constant) of dopamine is 22–24 nM and they reported that concentration of dopamine is between 8 and 9 nM in the ventral striatum, caudate and putamen and 2.8 nM in the globus pallidus (155).

### Endogenous Dopamine May Compete With Antipsychotics for Occupying $D_3Rs$

Using *ex vivo* autoradiography Schotte et al. (156) demonstrated that endogenous dopamine had greater ability to occupy $D_3Rs$ as compared to $D_2Rs$ and concluded that $D_3Rs$ are preferably occupied by endogenous dopamine which "*limits the binding of antipsychotic drugs to $D_3$ receptors in the rat brain.*"

The alkylating agent, EEDQ (1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline) concentration dependently reduced the *in vitro* [$^3$H]7-OH-DPAT and [$^3$H]spiperone binding in membranes from rat ventral striatum. *In vivo* treatment of rats with EEDQ resulted in reduction of the *ex vivo* [$^3$H]spiperone binding in striatal membranes but did not alter [$^3$H]7-OH-DPAT binding in membranes from ventral striatum. The author concluded [$^3$H]7-OH-DPAT binding sites (i.e., mostly $D_3R$) seem to be resistant to EEDQ-induced inactivation *in vivo* sites (157).

In agreement with these results, Zang et al. using autoradiography, demonstrated that treatment of rats with EEDQ or NIPS (*N- p*-iso-thiocyanatophenethyl-spiperone) did not alkylate $D_3Rs$ receptors in n. accumbens and in the island of Calleja at doses that resulted in blockade of $D_2Rs$ receptors in caudate and n. accumbens. On the other hand, under *in vitro* conditions when slices from the above regions were incubated with EEDQ or NIPS, both inhibited dopamine $D_2Rs$ as well as $D_3Rs$ and inhibition at $D_3R$ sites were prevented by dopamine in nanomolar concentration range whereas only millimolar concentration of dopamine was able to protect $D_2Rs$. The authors concluded that their results *"are consistent with the view that alkylation of $D_3$ receptors in vivo is prevented by its high affinity for even minor concentrations of endogenous dopamine*" (158).

## Modulation of Extracellular Dopamine by $D_2R$ Antipsychotic Treatment

### Microdialysis Studies

The partial agonists antipsychotics such as aripiprazole (159, 160), brexpiprazole (21) and cariprazine (153, 154) caused only moderate or no change of the extracellular dopamine concentration in the rat prefrontal cortex, hippocampus, n.

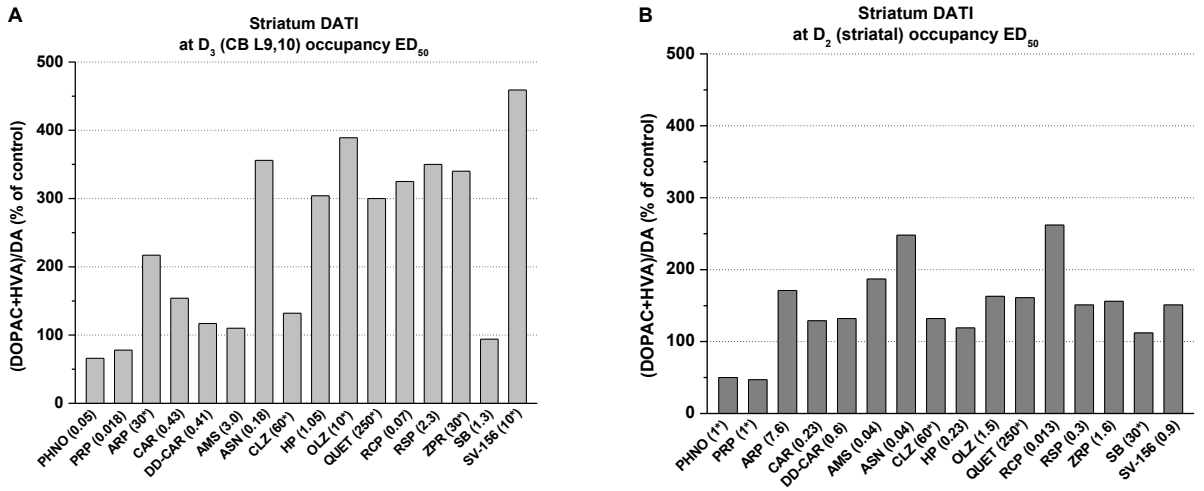


**FIGURE 5 |** Graphical presentation of percent changes in striatal dopamine turnover indices (DATI) at $D_3R$ (i.e., cerebellar L9, 10) occupancy $ED_{50}$ doses **(A)** and at $D_2R$ (i.e., striatal) occupancy $ED_{50}$ doses **(B)** *in vivo**,#. *Doses in brackets denote the occupancy $ED_{50}$ doses (or close to $ED_{50}$) taken from **Table 2**. Dopamine turnover index (DATI) was estimated from turnover dose-response curves (consisting of at least 4–5 doses, with five rats in each dose-group) for individual compounds listed in this figure. In cases where the occupancy $ED_{50}$ values could not be exactly calculated (see **Table 2**) the turnover indices were determined at doses denoted with asterisks. Dopamine turnover index was defined as DA/(DOPAC+HVA). Determination of tissue dopamine, DOPAC and HVA was carried out exactly as described in Kiss et al. (22) (for abbreviations of drugs' names, see **Table 2**). #Dopamine turnover data for cariprazine and DD-CAR were published in Kiss et al. (173). Turnover results of other compounds are unpublished and are on file at G. Richter. Plc.

**TABLE 3 |** Summary of *in vitro* human $D_3R$ affinity, $D_3R$ selectivity and occupancy* of some antipsychotics, partial agonists, highly preferring/selective $D_3R$ agonists, antagonists.

| Compounds | $hD_2R$ $K_i$ (nM) | $hD_3R$ $K_i$ (nM) | $hD_3R$ selectivity | Species | $D_3R$ occupancy | References |
|---|---|---|---|---|---|---|
| **$D_3R$ preferring agonists** | | | | | | |
| (+)-PHNO | 0.35 | 0.17 | 2.2 | Rat | YES | (82, 129) |
| (-)-Pramipexole | 42 | 1.85 | 23 | Rat | YES | (82, 140) |
| **Selective $D_3R$ antagonists** | | | | | | |
| ABT-925 | 600 | 2.9 | 207 | Human | YES | (98, 174) |
| GSK598809 | 740 | 6.2 | 119 | Human | YES | (116) |
| SB-277011A | 1047 | 11 | 95 | Rat | YES | (82, 175, 176) |
| F17464 | 12 | 0.16 | 72 | Human | YES | (145) |
| **Partial agonists** | | | | | | |
| Aripiprazole | 0.9 | 1.6 | 0.56 | Rat, human | Low | (82, 143), |
| Brexpiprazole | 0.3 | 1.1 | 0.27 | Human | Low | (54) |
| BP897 | 61 | 0.92 | 66 | Human | Moderate | (85) |
| Cariprazine | 0.49 | 0.09 | 5.8 | Rat, human | YES | (53, 82) |
| DD-CAR | 1.41 | 0.056 | 25 | Rat | YES | (173) |
| **Antipsychotics** | | | | | | |
| Asenapine | 1.4 | 1.8 | 0.78 | Rat | YES | Table 2 |
| Blonanserin | 0.28 | 0.28 | 1 | Rat, human | YES | (41, 142) |
| Clozapine | 431 | 283 | 1.5 | Rat, human | Low | (82, 140) |
| Haloperidol | 2.0 | 5.8 | 0.34 | Rat | YES | (82, 175) |
| Olanzapine | 21 | 34.7 | 0.6 | Rat, human | Low | (82, 141, 175) |
| Risperidone | 6.2 | 6.9 | 0.9 | Rat, human | Low | (82, 141, 175) |
| Quetiapine | 417 | 389 | 1.1 | Rat | Low | (82) |
| Ziprasidone | 4.0 | 7.4 | 0.54 | Rat | Low | (82) |
| **$D_2R$ antagonist** | | | | | | |
| SV-156** | 4.04 | 250 | 0.02 | Rat | NO | (82) |

**Rat or human brain occupancy determinations were carried out by [$^3$H](+)-PHNO (rat) or [$^{11}$C](+)-PHNO (human).*
***Compound 9 in Vangveravong et al. (118).*

accumbens and in the striatum. It is interesting to note that the high affinity $D_3$R-preferring antagonist antipsychotic, F17464 ($K_i$ for $D_3$R: 0.16 nM; Ki for $D_2$R: 12.1 nM) also did not significantly change extracellular dopamine concentration in the medial prefrontal cortex (42).

Both the typical antipsychotic haloperidol and the atypicals such as such as asenapine, blonanserin, clozapine, risperidone, olanzapine, lurasidone, and ziprasidone dose-dependently and remarkably (by 2- to 4-fold) elevated the extracellular dopamine concentrations in the rat prefrontal cortex, hippocampus, n. accumbens and in the striatum (104, 148–152, 161, 162). It should be mentioned that the above antipsychotics, beside their $D_2$R affinity, display high affinity for adrenergic alpha, dopamine $D_3$, $D_4$, serotonin 5-$HT_{2A}$, 5-$HT_{1A}$, 5-$HT_{2B}$, 5-$HT_6$, and 5-$HT_7$, muscarinic, and histaminergic receptors (37) which may influence the extracellular dopamine levels evoked *via* $D_2$R antagonism. In fact, among atypical antipsychotics risperidone, asenapine, increased extracellular concentration of serotonin in the prefrontal cortex (151, 161), while olanzapine (162), lurasidone (152) blonanserin (137), and clozapine (138) resulted in modest or no effect. Olanzapine, blonanserin, asenapine and haloperidol significantly increased extracellular norepinephrine levels, as well (137, 148, 163).

### $D_2$R Antagonists Directly Inhibit Dopamine Transporter

Former studies showed that $D_2$R antagonists can inhibit dopamine uptake *via* $D_2$Rs (164). Amato et al. have recently proposed that beside $D_2$R antagonism/occupancy, the direct blockade of DAT by antipsychotics, i.e., the modulation of extracellular dopamine, is a likely important factor in the antipsychotic efficacy (165–167).

The involvement of $D_3$Rs in the regulation of DAT or the effects of antipsychotics *via* $D_3$Rs on the DAT is much less known. Zapata et al. found that $D_3$R upregulate DAT (168), whereas Luis-Ravelo et al. demonstrated that the regulation appears to be biphasic, i.e., acute $D_3$R activation increased DAT expression whereas prolonged activations reduced dopamine uptake (169).

### Turnover Studies

Early studies found greatly increased dopamine turnover rate in the rat or cat brain after antipsychotic treatment (170–172).

We compared the effects of selected antipsychotics, $D_3$R or $D_2$R antagonists and $D_3$R preferring dopamine agonists on the dopamine turnover index in the rat striatum (and in olfactory tubercle and n. accumbens, data not shown) with $D_3$R occupancy $ED_{50}$ doses (i.e., doses causing 50% inhibition of [$^3$H](+)PHNO uptake/occupancy, **Table 2**) in the striatum and in CB L9,10.

At cerebellar (i.e., CB L9,10 $D_3$R) occupancy $ED_{50}$ doses, the agonists (+)-PHNO and (-)-pramipexole reduced the striatal dopamine turnover index by about 50%, whereas antipsychotics such as asenapine, haloperidol, olanzapine, risperidone, and ziprasidone and the $D_2$R preferring antagonist SV-156 greatly enhanced (by about 3–4-fold) striatal dopamine turnover index (**Figure 5A**). Blonanserin was not involved in this study, but it is reported that it caused 3–4-fold increase of striatal, frontal and limbic (i.e., olfactory tubercle and n. accumbens) DOPAC and HVA, which are all clearly indicate turnover increasing effect of blonanserin (139). The partial agonist cariprazine, the cariprazine metabolite, DD-CAR did not significantly change the striatal dopamine turnover index as was noted with amisulpride and the $D_3$R antagonist SB-277011A. Interestingly enough, the $D_2$R partial agonist aripiprazole produced effects more like to those seen with $D_2$R antagonist antipsychotics.

On the other hand, at the $D_2$R occupancy $ED_{50}$ doses (i.e., doses causing 50% inhibition of striatal [$^3$H](+)-PHNO uptake) which were much lower than that of necessary for 50% occupancy of CB L9, 10 $D_3$Rs, all antipsychotics (i.e., asenapine, haloperidol, olanzapine, risperidone, and ziprasidone and the $D_2$R preferring antagonist SV-156) caused much less increase in dopamine turnover index (**Figure 5B**). The effects of the partial agonist cariprazine, DD-CAR and the SB-277011A, at their $D_2$R occupancy doses, produced modest turnover changes in the striatum as was seen at their $D_3$R $ED_{50}$ occupancy doses.

The results of dopamine turnover studies, in agreement with microdialysis results, indicate that $D_2$R antagonist antipsychotics greatly increase the dynamics of dopamine metabolism including the increase of extracellular dopamine at doses sufficient to achieve occupancy of $D_3$Rs. Opposite effects were seen with dopamine $D_3$R-preferring agonists (-)-pramipexole and (+)-PHNO (which is probably due to the $D_2$R agonist effects manifested under *in vivo* conditions). At pharmacological doses, neither cariprazine nor its one of the major metabolite, DD-CAR did not seem to alter significant alteration in dopamine metabolism in rat striatum.

## Affinity and/or Selectivity of Compounds for $D_3$Rs *in vitro* vs. $D_3$R Occupancy *in vivo*

In **Table 3**, a summary is given on the $D_2$R and $D_3$R affinity and selectivity of some $D_3$R selective antagonist, agonists, and antipsychotics along with their $D_3$R occupancy determined in rats or in human.

Based solely on the *in vitro* affinity data one may expect compounds with low-or sub-nanomolar affinities for both receptor subtypes, would show $D_2$R as well as $D_3$R occupancy *in vivo*. However, the preclinical and human occupancy studies summarized above do not necessarily support such a correlation.

Both $D_3$R-preferring agonist, (+)-PHNO and pramipexole as well as the antagonists (ABT-925, GSK598890, SB-277011A and the antipsychotic candidate F17464) all display low- or sub-nanomolar $D_3$R affinity and high selectivity for $D_3$Rs *in vitro*. These compounds produced $D_3$R occupancy in rat or human studies. The same (i.e., high $D_3$R affinity, selectivity *in vitro* and high $D_3$R occupancy) is applicable for the partial agonists, cariprazine and its metabolite, DD-CAR. Although aripiprazole and brexpiprazole displayed low nanomolar *in vitro* $D_3$R affinity, their $D_3$R selectivity was below 1, which could explain their lack of $D_3$R occupancy *in vivo*. Among the currently used antipsychotics, only the $D_2$R/$D_3$R antagonist blonanserin, which has low- or sub-nanomolar affinity for these receptors has been shown to have significant *in vivo* occupancy for both receptors in rats. Second generation antipsychotics (i.e., risperidone,

quetiapine, clozapine) with low $D_3R$ affinity ($K_i$: >3–10 nM) and selectivity resulted in negligible $D_3R$ occupancy.

## LIMITATIONS

Our knowledge about the occupancy of $D_3Rs$ in the rat or human brain comes from the use of [$^3$H](+)-PHNO or the [$^{11}$C](+)-PHNO radiotracers. Their use represented a great advance in the *in vivo* imaging of $D_3Rs$ and determination of occupancy of brain $D_3Rs$ by antipsychotics.

[$^3$H](+)-PHNO or the [$^{11}$C](+)-PHNO however, are not ideal ligands/tracers for several reasons. They may not be sensitive enough for more detailed mapping of $D_3Rs$ in regions having low $D_3R$ expression e.g., cerebral cortex. Although both display higher affinity than dopamine for $D_3R$, they are still sensitive to endogenous dopamine (155, 177).

Furthermore, both $D_2Rs$ and $D_3Rs$ may exist in high- or low-affinity states and they are prone to di- or heteromerization (147, 178, 179). It was reported that recombinant human or rat $D_3R$, like $D_2R$, may exist in low- and high-affinity state and the affinity of PHNO shows significant difference for these states (30, 81, 128, 146, 180) which may have implication in drugs' imaging studies (140, 155).

These conditions (i.e., the high/low affinity state and di- or heteromerization, if they exist) may greatly change the affinity of the two receptors toward the agonist tracer and the affinity of drugs to be examined and their occupancy. Thus, the quest for better ligands (agonist or antagonist?) for the demonstration of brain $D_3Rs$ occupancy *in vivo* by therapeutically useful compounds (e.g., antipsychotics among others) continues (109, 125, 126, 177, 181).

Moreover, in contrast with the known therapeutically optimal occupancy of antipsychotics at $D_2Rs$ (i.e., 65–75%) there is no reliable information on the optimal level of $D_3R$ occupancy for manifestation of therapeutic effect.

## SUMMARY AND CONCLUSION

All currently used antipsychotics display high-to-medium affinity for both $D_2R$ and $D_3Rs$ *in vitro*. In agreement with the *in vitro* $D_2R$ affinity they show significant $D_2R$ occupancy in the rat and human brain at their antipsychotic-effective doses. However, as revealed by animal and human occupancy studies, despite the considerable *in vitro* $D_3R$ affinity, not all antipsychotics demonstrated brain $D_3R$ occupancy *in vivo.*

There may exist several possibilities for this dichotomy, as outlined in the following:

First, dopamine displays much higher affinity for $D_3Rs$ than for $D_2Rs$ and thus endogenous dopamine might, at least partly, keeps $D_3Rs$ occupied even under basal conditions.

Second, animal microdialysis and turnover studies revealed that acute treatment with dopamine agonists such as (-)-pramipexole and (+)-PHNO reduced dopamine turnover, i.e., they decrease extracellular dopamine and increase D3R availability. Administration of antipsychotics (e.g., risperidone, olanzapine, haloperidol, ziprasidone, clozapine, quetiapine), due to antagonism of presynaptic and biosynthesis and release regulating $D_2Rs$, leads to several-fold increase of extracellular dopamine. Further, Amato et al. demonstrated that antipsychotics initially suppress dopamine transporter (DAT) activity leading to increase of dopamine in synaptic cleft, a mechanism which represents a further possible alternative way to modulate extracellular dopamine (166). Thus, the increase of extracellular dopamine following antipsychotics with $D_2R$ antagonism seems to be a likely important factor in the lack or low levels of *in vivo* $D_3R$ occupancy; given the higher affinity of dopamine for $D_3R$ vs. $D_2R$. Thus, $D_2R$ antagonist antipsychotics inhibit their own binding at $D_3Rs$ by increasing extracellular dopamine.

Third, beside the effects on the endogenous dopamine levels, the D3R affinity and selectivity appear to be further factors of importance. All three selective $D_3R$ antagonists ($D_3R$ vs. $D_2R$ selectivity $\geq$100) such as ABT-925, GSK595809 and SB-277011 (with the *in vitro* low nanomolar $D_3R$) affinity produced high $D_3R$ occupancy in animal or human studies, indicating primary importance of selectivity to achieve $D_3R$ occupancy *in vivo*.

Example of antipsychotics such as the $D_3R/D_2R$ partial agonist cariprazine and the $D_2R/D_3R$ antagonist blonanserin shows that, in the presence of relatively high affinity for $D_2Rs$, subnanomolar affinity for $D_3Rs$ appears to be necessary for $D_3R$ occupancy *in vivo*. Further, cariprazine and the F17464 (subnanomolar affinity for $D_3R$ with 75-fold $D_3R$ vs. $D_2R$), do not increase extracellular dopamine and hence are able to compete for $D_3Rs$ vs. extracellular dopamine.

The case of $D_2R/D_3R$ partial agonist antipsychotics, aripiprazole and brexpiprazole is somewhat controversial. Both demonstrated low nanomolar affinity for $D_2Rs$ and $D_3Rs$ (with $D_2R$ preference) *in vitro*, with negligible effects on extracellular dopamine *in vivo*. However, both produced no or very low occupancy of $D_3Rs$ for which the likely explanation is the $D_2R$ preference.

In conclusion, data reviewed and discussed here regarding the current antipsychotics' *in vitro* $D_2R/D_3R$ affinity vs. their brain $D_3R$ occupancy *in vivo*, indicate that levels of extracellular dopamine (or its change) in different brain regions is a key factor regarding $D_3R$ occupancy. On the other hand, the compounds' high (i.e., subnanomolar) $D_3R$ affinity and/or high $D_3R$ vs. $D_2R$ selectivity are also important determining factors to achieve significant $D_3R$ occupancy in the brain.

## AUTHOR CONTRIBUTIONS

BKi and BKr drafted the manuscript with several inputs from IL. All authors were participating in the final editing and critical revision of the article and approved the final version to be published.

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REVIEW
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# Molecular Imaging of Dopamine Partial Agonists in Humans: Implications for Clinical Practice

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Positron emission tomography (PET) has been used since the late 1980s for the assessment of relationships between occupancy of $D_{2/3}$ receptors by antipsychotic drugs in the human brain and the clinical effects and side effects of these compounds in patients. It is now well established for most $D_{2/3}$ antagonists, both of the first and the second generation, that the ideal occupancy of their target receptors is between approximately 65 and 80%. If the occupancy is below 65%, the probability of treatment response is reduced, if the occupancy is higher than 80%, the risk for extrapyramidal side-effects increases substantially. However, partial agonist antipsychotics behave different from these rules. It has been shown for all three available drugs of this class (aripiprazole, brexpiprazole, cariprazine) that, due to their special pharmacology, a very high target engagement (>90%) not only is not harmful but represents a prerequisite for antipsychotic efficacy. The available PET studies for these drugs are reviewed in this work. It is demonstrated that optimal plasma levels for partial agonist antipsychotics can be derived from these studies, which can guide individual treatment in routine patient care.

**Keywords: dopamine partial agonists, brexpiprazole, cariprazine, aripiprazole, positron emission tomography, molecular neuroimaging**

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## INTRODUCTION

Determination of clinically useful and rational doses of antipsychotics represents the application of neuroimaging that has had the largest impact on clinical practice in psychiatry (1–3). Molecular imaging with positron emission tomography (PET) is now a routine tool for development of new compounds of this class (3). All antipsychotic agents that are currently in use for the treatment of psychotic disorders, such as schizophrenia, are either antagonists or partial agonists at dopamine $D_{2/3}$ receptors. Assessment of occupancy (target engagement, TE) of these receptors by antipsychotics helped in establishing relationships between TE and antipsychotic doses and their respective plasma concentrations. Studies of the clinical effects and side effects as a function of TE facilitated not only the understanding of antipsychotic drug action, but also the rational dosing of these compounds, which can be further improved when dosing is guided by Therapeutic Drug Monitoring [TDM; (2)]. Assessment of TE with PET or single photon emission computed tomography (SPECT) is based on the concept that the experimental pharmaceutical displaces the radioligand, which binds to the target at trace concentrations. The extent of this displacement is

related to the baseline binding of the radioligand in its unblocked state. Because it is often not feasible to study patients with schizophrenia in medication-free state, patients are usually studied in blocked state only (which means that they are treated with the experimental drug). Unblocked baseline data are taken from healthy volunteers, assuming that patients in the untreated state and controls differ only marginally in receptor availability. The radioactivity in the region of interest in the blocked vs. the unblocked state then. provides the target occupancy (in%) as follows (2):

$$\text{Occupancy}\,[\%] = 100 - [(\text{Tracer binding}_{\text{blocked}}/\text{Tracer Binding}_{\text{unblocked}}) \times 100] \quad (1)$$

Farde et al. in their pioneering early PET studies from the late 1980s demonstrated that clinically effective doses of first-generation antipsychotics (e.g., haloperidol) occupy $D_{2/3}$ dopamine receptors in the striatum of patients with schizophrenia in the range between 65 and 90% (4). These authors also suggested a "therapeutic window" between 65 and 80% striatal dopamine $D_{2/3}$ receptor occupancy for antipsychotic drug action, implying a "ceiling" of about 65% occupancy for sufficient treatment response, although such a high occupancy does not necessarily mean that every patient sufficiently improves. The risk for extrapyramidal side-effects (EPS) increases above a striatal $D_{2/3}$ receptor occupancy of 80%. These relationships also apply to most of the second-generation antipsychotics (5). However, there are certain exceptions to those general rules (6). Antipsychotics with low affinity for $D_2$-like dopamine receptors such as clozapine and quetiapine even at very high doses or plasma concentrations practically never occupy striatal $D_{2/3}$ receptors to an extent that is associated with EPS (7, 8). Partial agonists at $D_{2/3}$ receptors, on the other hand, have a completely different binding pattern at their main targets. At clinically effective doses, they almost completely occupy $D_{2/3}$ receptors, an observation that has been made first for aripiprazole (9). This unique feature is explained by the pharmacological properties of partial agonists with low intrinsic activity (10). **Figure 1** depicts the different prototypic patterns of target engagement of the available antipsychotic drugs at striatal $D_{2/3}$ dopamine receptors as a function of their plasma concentrations.

Here, we summarize the literature on molecular imaging studies with the available partial agonists, aripiprazole, brexpiprazole, and cariprazine. We show that these studies, especially when target engagement is related to plasma concentrations of the respective drug, can guide rational dosing and Therapeutic Drug Monitoring of these compounds.

Aripiprazole was the first $D_{2/3}$ dopamine partial agonist that was approved for the treatment of schizophrenia (United States: 2002). It was later approved for various other indications including mania and major depression (adjunctive treatment). Aripiprazole binds with very high affinity (in the low nanomolar range) to $D_2$ and somewhat lesser affinity to $D_3$ receptors. At both receptors it acts as a partial agonist with low intrinsic activity. Aripiprazole is also a partial agonist at the 5-$HT_{1A}$ and an antagonist at the 5-$HT_{2A}$ serotonin receptor. It has an elimination half-life of 60–80 h. Its main active metabolite, dehydroaripiprazole, has a similar receptor binding profile, and it amounts to up to 40% of the parent concentrations (11).

Brexpiprazole is approved for the treatment of schizophrenia (United States: 2015) and as an adjunctive treatment for major depression. It has a binding profile very similar to the one of its predecessor aripiprazole, with somewhat lower intrinsic activity at $D_2$ and $D_3$ receptors. Brexpiprazole has an elimination half-life of approximately 90 h. Its main metabolite (DM-3411) amounts to 23–48% of the parent compound, but it does not contribute to the pharmacodynamic effects, because it does not pass the blood-brain barrier (12).

Cariprazine received FDA approval for the treatment of schizophrenia in 2015. It has partial agonist activity at dopamine $D_{2/3}$ receptors, with and six- to eightfold higher affinity for human dopamine $D_3$ over $D_2$ receptors. Like aripiprazole and brexpiprazole, cariprazine is a partial agonist at the 5-$HT_{1A}$ and an antagonist at the 5-$HT_{2A}$ serotonin receptor. The elimination half-life of the parent compound is 50–120 h. However, cariprazine has two active metabolites, N-desmethyl cariprazine (DCAR) and NN-didesmethyl cariprazine (DDCAR). DDCAR is eliminated with a half-life of 2–3 weeks. At steady-state, it significantly contributes to the antipsychotic activity of the drug (13, 14).

# METHODS

## Search Strategy

In September 2021 (last updated 08.12.2021), four electronic databases (PsycINFO, Medline via PubMed, Cochrane CENTRAL, Web of Science) were systematically searched for relevant articles without restrictions in language or publication date. Keywords included the respective psychotropic drug (aripiprazole, brexpiprazole or cariprazine) and PET/SPECT. Studies in humans and non-human primates were included. Only full-text articles were taken into consideration, abstracts were excluded.

## Calculation of $EC_{90}$ Values

The available literature was screened for papers that reported $D_{2/3}$ dopamine receptor occupancy values of the respective drug in relation to administered doses. Both studies in healthy volunteers and in patients were acceptable. Special emphasis was put on studies that also reported plasma or serum drug concentrations, because they usually allow the calculation of an "effective concentration 50" ($EC_{50}$), which is the concentration predicted to provide 50% of the maximum attainable receptor occupancy. This is a constant characterizing an individual drug. It is related to the maximum attainable receptor occupancy ($E_{max}$) and the plasma concentration of the drug (C) that is associated with a measured receptor occupancy according to the law of mass action (Michaelis-Menten kinetics):

$$\text{Occupancy}[\%] = (E_{\max} \times [C])/(EC_{50} + [C]) \quad (2)$$

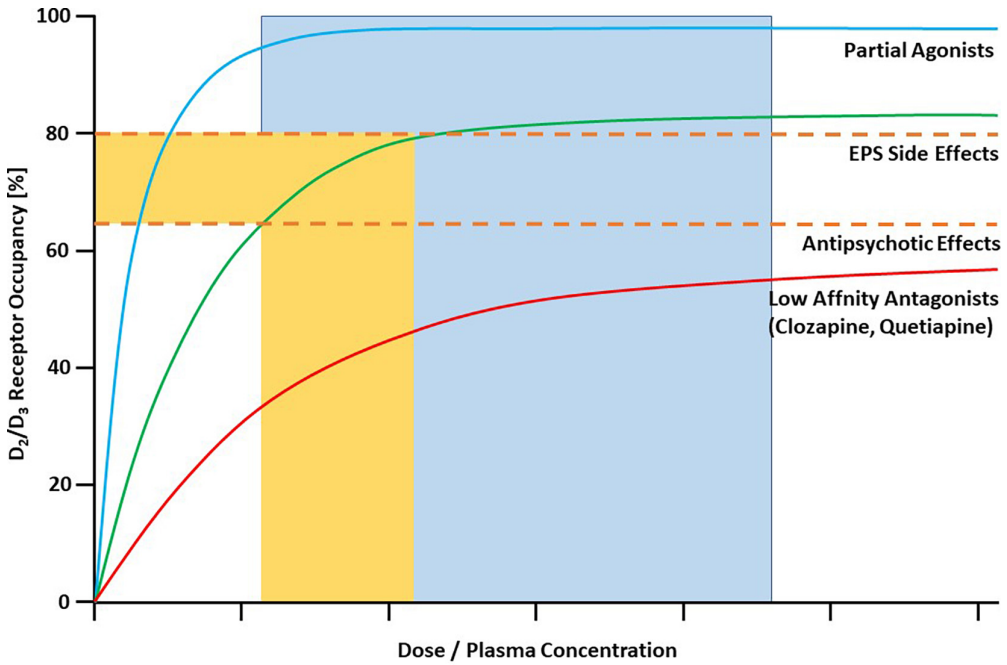


**FIGURE 1 |** Characteristic binding curves of antipsychotic drugs in human striatum as measured with PET. Dashed lines represent threshold occupancy values for EPS (80%) and antipsychotic effects (65%). Most antipsychotics, including most of the SGAs, are characterized by the green line. They reach optimal occupancy (65–80%) in a "therapeutic window" of corresponding plasma concentrations. Antipsychotics with low affinity for $D_2/D_3$ receptors are described by the red line. Even at very high plasma concentrations they usually do not cross the 80% threshold for EPS. They exert antipsychotic effects despite relatively low occupancy in the striatum. All clinically available partial agonist antipsychotics are characterized by the blue binding curve. They have antipsychotic effects only at almost total saturation of $D_2/D_3$ receptors (in the flat part of the curve), represented by the blue area. The upper threshold is not sharply defined. Copyright © 1969, Elsevier. From (1).

From the experimentally determined $EC_{50}$ values, an $EC_{90}$ value can be calculated according to the following equations (maximum attainable receptor occupancy is less than 100%; unconstrained model):

$$90 \times (EC_{50} + [C]) = E_{max} \times [C] \quad (3)$$

$$90 \times EC_{50} + 90[C] = E_{max} \times [C] \quad (4)$$

$$90 \times EC_{50} = E_{max} \times [C] - 90[C] \quad (5)$$

Assuming that the maximum attainable receptor occupancy is 100% (i.e., all available receptors can be occupied by the drug; constrained model), $EC_{90}$ is then:

$$EC_{90} = (90 \times EC_{50})/10 \quad (6)$$

Uchida et al. (15) demonstrated that the relationship between $D_{2/3}$ dopamine receptor occupancy and the respective plasma levels are in some cases better described by an unconstrained model. The constrained model assumes that all dopamine $D_{2/3}$ receptors (100%) can be occupied by the antipsychotic. For most antipsychotics, $E_{max}$ values derived with an unconstrained model are close to 100%, and therefore $EC_{50}$ values estimated from the constrained and the unconstrained model do not substantially differ. For example, for haloperidol the $EC_{50}$ estimated from the unconstrained model was 0.32 and 0.70 ng/ml, when $E_{max}$ was constrained to 100% (15). For olanzapine, the respective values are 7 and 10 ng/ml, and for risperidone 5 and 8 ng/ml. For compounds with a low affinity to $D_{2/3}$ receptors such as clozapine, the situation is more complicated. Here, the experimentally determined $E_{max}$ values are far below 100%. Using an unconstrained model, Uchida et al. (15) calculated a maximum attainable receptor occupancy for clozapine of only 60%, with a respective $EC_{50}$ of 105 ng/ml. The constrained model provided an $EC_{50}$ value of 483 ng/ml. Biologically, it makes no sense to believe that clozapine does not occupy more than 60% of striatal $D_{2/3}$ dopamine receptors. In monkeys, high doses of clozapine occupy more than 80% of $D_{2/3}$ receptors (16). Almost all PET studies that determined $D_{2/3}$ dopamine receptor occupancy by clozapine used [$^{11}$C]raclopride as the radiotracer (15). In our own study with [$^{18}$F]fallypride as the radiotracer, we calculated, using an unconstrained model, an $E_{max}$ close to complete receptor saturation, and respective $EC_{50}$ values of 950 ng/mL for the putamen and 582 ng/ml for the caudate (7). These values seem to be biologically and especially clinically more meaningful, since the therapeutic reference range for clozapine is 350 – 600 ng/ml (17), and even much higher plasma concentrations are tolerated without extrapyramidal side-effects (7).

For the purpose of this paper, it seems feasible to work with $EC_{90}$ values that are derived from a constrained

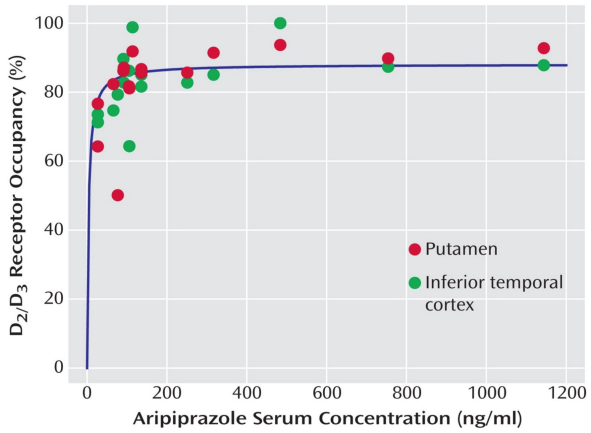


**FIGURE 2 |** Relationship between aripiprazole serum levels and dopamine D2/D3 receptor occupancy in the putamen and the inferior temporal cortex (representative of cortical binding due to high D2/D3 receptor density) in 16 patients with schizophrenia and schizoaffective disorder receiving therapeutic doses of aripiprazole. Copyright © American Psychiatric Association. From (18).

model. All available $D_{2/3}$ partial agonist antipsychotics are high affinity compounds that occupy their main molecular target close to saturation at doses used in clinical practice. Differences in $EC_{90}$ values calculated from constrained versus unconstrained models might therefore be negligible. It is proposed here that the $EC_{90}$ values determined experimentally with molecular (in almost all cases PET) imaging represent the lower threshold of a therapeutic reference range to be used for TDM.

## MOLECULAR IMAGING OF DOPAMINE PARTIAL AGONISTS

### Aripiprazole

For aripiprazole, nine PET studies in human subjects are available that report $D_{2/3}$ receptor occupancy values (9, 18–26) (**Table 1**). However, only two of them report $ED_{50}$ values [or individual plasma concentrations, from which an $ED_{50}$ value was derived: (18, 26); **Figure 2**].

Yokoi et al. (9) published the first PET occupancy study with aripiprazole in 15 healthy volunteers, who were treated with fixed aripiprazole doses for a duration of 14 days. They documented a dose-dependent increase of $D_{2/3}$ dopamine receptor occupancy, with a mean occupancy of 30% (caudate) and 34% (putamen) at a dose as low as 0.5 mg, that increased to 49 and 57% at 1 mg, 74 and 72% at 2 mg, 86 and 85% at 10 mg, and 92 and 86% at 30 mg. These authors measured plasma levels, but they did not calculate $EC_{50}$ values. However, the plasma concentration/occupancy curve reported by Yokoi et al. (9) is very similar to the one published by Gründer et al. (18), indicating that the flat part of the curve begins at around 100 ng/ml.

Mamo et al. (23) quantified aripiprazole binding to three different receptor types in 12 patients with schizophrenia, who were treated with aripiprazole doses between 10 and 30 mg daily: $D_{2/3}$ dopamine (with [$^{11}$C]raclopride), 5-$HT_2$ serotonin (with [$^{18}$F]setoperone), and 5-$HT_{1A}$ (with [$^{11}$C]WAY100635). Even the lowest dose was associated with 85% $D_{2/3}$ dopamine receptor occupancy, and the higher doses led to occupancies above 90%. Extrapyramidal side-effects were documented in two patients (with occupancy > 90%) in whom plasma levels were far above the mean for their dose (442 ng/ml and 663 ng/ml, respectively). 5-$HT_2$ serotonin occupancy was in the medium range (54–60%), while 5-$HT_{1A}$ receptors were occupied by less than 20% (23). The authors measured aripiprazole and dehydroaripiprazole plasma levels, but $EC_{50}$ values were not reported. However, at the (lowest) 10 mg dose the mean aripiprazole level was 126 ng/ml (dehydroaripiprazole 35 ng/ml); later PET studies [(18, 26), see below] have consistently shown that at these plasma levels $D_{2/3}$ dopamine receptor occupancy is close to 90%. Mizrahi et al. (24) described the same patient sample that Mamo et al. (23) have been investigating. These patients with schizophrenia were switched from olanzapine or risperidone to aripiprazole and both $D_{2/3}$ receptor occupancy and subjective well-being (with the Subjective Wellbeing under Neuroleptics Scale, SWN) were measured. Although receptor occupancy was very high under aripiprazole treatment (82–99%), the SWN score increased significantly after switch from an antagonist to the partial agonist antipsychotic. Plasma levels were not reported (24).

$D_{2/3}$ dopamine receptor occupancy was measured in 16 patients with schizophrenia or schizoaffective disorder on steady-state treatment with aripiprazole at doses ranging from 5 to 30 mg daily by Gründer et al. (18). $D_{2/3}$ receptor occupancy was high already at 5 mg/day, and receptors were almost completely occupied above plasma levels of 100–150 ng/ml (**Figure 2**). $EC_{50}$ values for the various brain regions examined ranged from 4 to 10 ng/ml, with 10 ng/ml for the putamen and 9 ng/ml for the caudate. This study is also the only one that reports $EC_{50}$ estimates that are based on active moiety (aripiprazole + dehydroaripiprazole) concentrations of the drug (putamen 20 ng/ml, caudate 18 ng/ml). Aripiprazole's main (active) metabolite, dehydroaripiprazole, also occupies the $D_{2/3}$ receptor. Thus, a not negligible fraction of total occupancy (usually 20–30%) is attributable to dehydroaripiprazole binding. When one calculates $EC_{90}$ values based on an $EC_{50}$ value of 10 ng/ml for aripiprazole alone and 20 ng/ml for the active moiety, these values are 90 and 180 ng/ml, respectively (18).

Kegeles et al. (20) measured $D_{2/3}$ dopamine receptor occupancy in 19 patients with schizophrenia or schizoaffective disorder, who were subchronically (minimum of steady dose: 10 days) treated with aripiprazole doses between 2 and 40 mg daily. Occupancy values were very high, ranging from a mean of 72% at 2 mg/day to 97% at 40 mg/day. Changes in the PANSS positive symptom subscale correlated positively with receptor occupancy in the striatum, but not in extrastriatal brain regions. Unfortunately, since plasma levels were not measured in two patients, these authors related occupancy values to doses rather than plasma levels. Thus, $EC_{50}$ values are not reported. Instead, they calculated $ED_{80}$ values (effective dose 80: the dose, that is associated with 80% occupancy). The mean $ED_{80}$ from striatal regions was 5.6 mg and the mean $ED_{80}$ from extrastriatal

**TABLE 1 |** PET studies reporting $D_2$ receptor occupancy and aripiprazole (ARI) blood concentrations.

| No | Author, year | PET tracer | Design | Subjects | *Mean Dose (range) [mg/day]* | Mean ARI Conc. (range) [ng/ml] | Mean Receptor occupancy (%) | $EC_{50}$ [ng/ml] | $EC_{90}$ (estimated from $EC_{50}$) [ng/ml] | Comment |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | (9) | [$^{11}$C]raclopride | Cohort study, dose response PET scans of fixed doses of ARI taken for 14 days, trough samples analyzed by HPLC with UV detection | *N* = 15; healthy volunteers; age 32 ± 9; 100% males | 10 ± 12.8 (0.5–30) | NA (only in diagram) | $D_{2/3}$: 66.8 ± 25.0 (c); 66.9 ± 21.59 (p) | NA | NA | Hyperbolic relation between peak ARI conc. and $D_2$ occup. (p) |
| 2 | (23); (24) (same cohort) | [$^{11}$C]raclopride, [$^{18}$F]setoperone, [$^{11}$C]WAY100635 | RCT, 3 PET scans after ARI taken for 14 days; diagnosis acc. to DSM-4. Peak levels measured with LC/MS, clinical efficacy assessments | *N* = 12; SCZ or SD; age 31 ± 7; 75% males | 18.8 ± 7.7 (10–30) | 220.8 ± 179.0 | $D_{2/3}$: 86.6 ± 3.7 (p), 92.9 ± 5.7 (c), 91.0 ± 4.0 (cs); 5-$HT_2$: 54.0 ± 15.3 (tc), 59.4 ± 12.9 (fc); 5-$HT_{1A}$: 16.2 ± 14.3 (tc), 16.5 ± 13.8 (fc) | NA | NA | ARI and DARI conc. correlated with $D_2$ occup. (p and s). No corr. between occup. and clinical or well-being scores. EPS in 2 patients with occup. >90% |
| 3 | (18) | [$^{18}$F]fallypride | Cohort study with unmedicated vs. medicated patients, trough serum concentrations in steady-state measured with HPLC | *N* = 16/8 (medicated/ unmedicated); SCZ or SD (DSM-4); age 30; 94% males | 18.8 ± 7.2 (5–30) | 245 ± 307 | $D_{2/3}$: 83 ± 1 (p), 84 ± 1 (c), 85 ± 7 (t) | 10 ± 4 (p) 9 ± 4 (c) | 90 (p), 81 (c) | Complete occup. with ARI conc. >100–150 ng/ml. Lower $EC_{50}$ in thalamus (6 ± 2 ng/mL) |
| 4 | (20) | [$^{18}$F]fallypride | Cohort study, fixed doses of ARI taken for min. 14 days, serum conc. measured with RP LC with UV, clinical efficacy assessments | *N* = 19; SCZ or SD (DSM-4); age 29; 79% males | 13.9 ± 11 (2–40) | NA (excl. in analysis) | $D_{2/3}$: NA 79.8 ± 14.8 (s) in 15 mg | $ED_{80}$ 5.63 ± 1.0 (s) approx. 100 ng/ml | NA | Dose correlated with ARI conc., PANSS positive scale corr. with $D_2$ occup. (s). No EPS. |
| 5 | (19) | [$^{11}$C]raclopride, L-[ß-$^{11}$C]DOPA | Cohort study on dopamine synthesis capacity, PET scans after single dose of ARI, serum conc. measured with LC/MS | *N* = 12; healthy volunteers; age 24.1 ± 3.2; 100% males | 5.3 ± 2.3 (3–9) | 23.8 ± 11.3 | $D_{2/3}$: 67.2 ± 9.7 (c), 64.3 ± 8.9 (p) | NA | NA | No changes in dopamine synthesis capacity. |
| 6 | (21) | [$^{11}$C]raclopride | RCT, single dose of aripiprazole after fasting, sampling up to 120 h | *N* = 18; healthy volunteers; age 22.9 ± 2.4; 100% males | 12.7 ± 11.5 (2–30) | Peak: 3.4 ± 0.9 per mg | $D_{2/3}$: 61.7 ± 21.2 (s) | 11.1 (s) | 99.9 (s) | Values reported for PK model; PK/PD model estimates $EC_{90}$ of 77.4 ng/mL (s) |
| 7 | (26) | [$^{11}$C]raclopride, [$^{11}$C]FLB457 | Cohort single dose study on extrastriatal binding of ARI, peak conc. measured with LC/MS | *N* = 11; healthy volunteers; age 23.7 ± 4.0; 100% males | 6 | 29.4 ± 4.8 | $D_{2/3}$: 74.1 ± 6.7 (c), 70.1 ± 6.3 (p), 57.6 ± 6.7 (t), 51.3 ± 9.2 (fc), 58.4 ± 3.0 (tc) | 9.9 (s), 12.2 (p), 18.9 (t), 24.3 (fc), 18.2 (tc) | 89.1 (s), 109.8 (p) | Concentration reported for raclopride scans; lower in FLB457. No preferential extrastriatal binding of ARI |
| 8 | (22) | [$^{11}$C]raclopride and [$^{18}$F]FDG | RCT, PET and fMRI study with single dose of aripiprazole after fasting, sampling before scans | *N* = 15; healthy volunteers; age 23.1 ± 2.4; 100% males | 12.4 ± 11.4 (2–30) | 15.0 ± 14.3 | $D_{2/3}$: 50.2 ± 22.0 (s) | NA | NA | Reaction times in working memory task and metabolic change in frontal lobe pos. corr. with $D_2$ occup. |
| 9 | (25) | [$^{11}$C]raclopride | Cohort study; PET and fMRI scans performed after flexible ARI; trough samples in the steady-state | *N* = 7; SCZ (DSM-4); age 32; 28.6% males | 14.2 ± 12 (2–30) | 289.9 ± 325.2 | $D_{2/3}$: 65.0 ± 8.6 (s) | NA | NA | Error rates and reaction time in working memory task pos. corr. with $D_2$ occup. |

*c, cortex; fc, frontal cortex; p, putamen; s, striatum; tc, temporal cortex; t, thalamus; NA, no information available; RCT, randomized-controlled trial; SCZ, Schizophrenia; SD, schizoaffective disorder.*

**TABLE 2 |** PET studies reporting $D_2$ receptor occupancy and brexpiprazole (BXP) blood concentrations.

| No | Author, year | PET Tracer | Design | Subjects | *Mean Dose (range) [mg/day]* | Mean BXP Conc. (range) [ng/ml] | Mean Receptor Occupancy (%) | $EC_{50}$ [ng/ml] | $EC_{90}$ (estimated from $EC_{50}$) [ng/ml] | Comment |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | (28) | [$^{11}$C]raclopride | Cohort study with dose response PET of BXP after single doses (phase 1). Plasma samples measured with HPLC | *N* = 15; healthy volunteers; age 33.9 ± 6.8; 93.3% males | 2.68 (0.25–6) | 32.5 ± 25.8 | $D_{2/3}$ (p and c): 0.25 mg: < 20; 2–4 mg: 59–75; 5–6 mg: 77–88 | 7.75 (c), 8.13 (p) | 69.8 (c), 73.2 (p) | BXP AUC and $c_{max}$ increased with dose, no ADR observed in study. |
| 2 | (36) | [$^{11}$C]-(+)-PHNO, [$^{11}$C]CUMI101, [$^{11}$C]MDL100907, [$^{11}$C]DASB | Cohort study comparing patients at baseline (unmedicated) and medicated, trough serum conc. at steady-state measured with HPLC | *N* = 12; SCZ (DSM-4); age 42 ± 8; 58.3% males | 3.0 (1–4), at day 4–10 | 82 ± 59 (*N* = 7 from $D_2$ diagram) | $D_{2/3}$: 47.7 ± 38.5 SERT: −3 ± 15 $5\text{-HT}_{1A}$: 4 ± 6 $5\text{-HT}_{2A}$: 36.5 ± 20.9 | 22 (s) | 198 (s) | Dose dependent binding for $D_2$ and $5\text{-HT}_{2A}$ receptors, not detectable for $D_3$. $EC_{50}$ from non-linear model. Values for other models ranged up to 52 ng/ml. |

*c, cortex; p, putamen; s, striatum; t, thalamus; SCZ, Schizophrenia.*

**TABLE 3 |** PET studies reporting $D_2$ receptor occupancy and cariprazine (CP) blood concentrations (*converted; conversion factor 2.34).

| No | Author, year | PET tracer | Design | Subjects | *Mean Dose (range) [mg/day]* | Mean CP conc. (range) [ng/ml] | Mean receptor Occupancy (%) | $EC_{50}$ [ng/mL] (*converted; conversion factor 2.34) | $EC_{90}$ (estimated from $EC_{50}$) [ng/ml] (*converted; conversion factor 2.34) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | (30) | [$^{11}$C]raclopride, [$^{11}$C]MNPA, [$^{11}$C]WAY-100635 | Animal PET study after single doses of CP, plasma samples measured with HPLC | *N* = 3; healthy monkeys (macaca fascicularis) 3–4 kg weight | (a) 1–5 μg/kg (b) 30–300 μg/kg | (a) < 1.0 (b) 3.1–34.1 | $D_{2/3}$: 5–94% (antagonist); $D_{2/3}$: 45–80% (agonist); $5\text{-HT}_{1A}$: 18–30% | NA | NA | Dose dependent occupancy of 5–90% of $D_2/D_3$ receptors in striatum of monkeys |
| 2 | (13) | [$^{11}$C]-(+)-PHNO | Cohort study after single doses of CP, plasma samples measured with HPLC | *N* = 9; SCZ; age 42 ± 8; 58.3% males | 4.5 (1–12), at day 5–15 | 12.4 ± 13.1 | $D_2$: 0.91; $D_3$: 0.78; (regions accounted for: c, p, vs, t, globus pallidus, substantia nigra/ventral tegmental area) | $D_2$: 4.14 ± 0.91*; $D_3$: 3.32 ± 0.87* | $D_2$: 37.26*; $D_3$: 29.88* | Near complete $D_2$ and $D_3$ occup. after 12 mg for 2 weeks. One patient withdrew due to emesis. PK-PD analysis reports higher $EC_{50}$ values of 9.0 ($D_3$) and 30.5 ($D_2$). |

*c, cortex; p, putamen; t, thalamus; vs, ventral striatum; NA, no information available.*

regions 3.9 mg. While this significant difference indicates a high binding in extrastriatal brain regions, the 1.7 mg difference is clinically meaningless. The study is in line with the one by Gründer et al. (18) insofar as it indicates that $D_{2/3}$ receptors are almost completely occupied by aripiprazole at doses as low as 10 mg/day (20).

Takahata et al. (26) assessed striatal $D_{2/3}$ receptor occupancy with [$^{11}$C]raclopride and extrastriatal occupancy with [$^{11}$C]FLB457. They administered single oral doses of 6 mg aripiprazole to 11 healthy male volunteers 150 min prior to the PET scan. While they could not find differential binding in striatal and extrastriatal regions, $D_{2/3}$ occupancy was 74% in the caudate and 70% in the putamen. The corresponding mean plasma concentrations were 29.4 ng/ml for aripiprazole and 1.4 ng/ml for dehydroaripiprazole. Based on these values, the calculated $EC_{50}$ values were 9.9 ng/ml for the striatum and 12.2 ng/ml for the putamen. However, Takahata et al. (26) based the calculation of their $EC_{50}$ values on plasma concentrations of the parent (aripiprazole) compound only (K. Takahata, personal communication). Because the concentrations of the metabolite were so low in that study (the PET scan was started 150 min after administration of the drug), its contribution to total occupancy was most likely very small. With prolonged treatment, the effect of dehydroaripiprazole on $EC_{50}$ estimates is substantial (18).

Ito et al. (19) administered single oral aripiprazole doses in the range between 3 and 9 mg to twelve healthy men. They measured $D_{2/3}$ receptor occupancy with [$^{11}$C]raclopride PET and dopamine synthesis capacity with L-[β-$^{11}$C]DOPA. The mean striatal $D_{2/3}$ occupancies were 55% (putamen) and 57% (caudate) at 3 mg, 69 and 73% at 6 mg, and 76 and 78% at 9 mg. Plasma concentrations of aripiprazole and dehydroaripiprazole were assessed separately. They were 12 + 0.4 ng/ml at 3 mg, 29 + 0.9 ng/ml at 6 mg, and 40 + 1.4 ng/ml at 9 mg. $EC_{50}$ values are not reported by Ito et al. (19). However, from the reported data a value of approximately 10 ng/ml can be roughly estimated.

Kim et al. (22) assessed $D_{2/3}$ receptor occupancy with [$^{11}$C]raclopride PET in 15 healthy volunteers after administration of single oral aripiprazole doses. In addition, they measured glucose metabolism with [$^{18}$F]FDG and assessed cognitive performance. Mean $D_{2/3}$ receptor occupancy was 16% after 2 mg aripiprazole, 36% after 5 mg, 63% after 10 mg and 73% after 30 mg. The corresponding aripiprazole plasma concentrations (there is no information in the paper on determination of metabolites) were 2.6, 5.8, 13.2, and 35.4 ng/ml. Although these values were determined after single doses in healthy subjects, they are in line with the $EC_{50}$ values of approximately 10 ng/ml determined after chronic treatment in patients with schizophrenia (18, 26). Greater striatal $D_{2/3}$ receptor occupancy was associated with lower frontal glucose metabolism, and greater reduction in frontal metabolism corresponded to longer reaction times (22).

The same authors compared two different analytical approaches on data from 18 healthy subjects (21), who received the same single aripiprazole doses as those applied in Kim et al. (22). It has to be assumed that the subject samples in these two studies are overlapping. The mean $D_{2/3}$ receptor occupancy in this somewhat larger sample was 30% after 2 mg aripiprazole, 54% after 5 mg, 72% after 10 mg and 82% after 30 mg. The authors calculated an $EC_{50}$ of 11.1 ng/ml with the conventional pharmacodynamic model. When they applied a novel PK-PD model, they found a slightly lower $EC_{50}$ of 8.6 ng/ml. This difference might be considered negligible for clinical purposes, and when taking into account that these values are omitting the contribution of the metabolite to total aripiprazole occupancy.

Shin et al. (25) measured $D_{2/3}$ receptor occupancy in seven patients with schizophrenia and related striatal occupancy to cognitive performance. They found that patients with higher occupancy performed better in certain cognitive dimensions such as working memory and reaction time (25). While these authors determined aripiprazole plasma levels at times of the PET scans, they did not report $EC_{50}$ values.

### Conclusion for Clinical Practice

Among the three available partial dopamine agonist antipsychotics, by far the broadest molecular imaging database exists for aripiprazole. Nine PET studies have been conducted over the last 20 years. Although only two of them estimated $EC_{50}$ values (18, 26), the evidence regarding a therapeutic reference range that can be derived from those studies is appealingly consistent. Above a threshold of approximately 100 ng/ml aripiprazole (parent compound only) $D_{2/3}$ receptors are close to being completely occupied. When the active moiety (aripiprazole + dehydroaripiprazole) is considered, this value is 180 ng/ml.

The "Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017" (17) reports a therapeutic reference range of 100 – 350 ng/ml for the parent compound and 150 – 500 ng/ml for the active moiety. The lower thresholds are in good agreement with the imaging-based values. The upper thresholds are somewhat arbitrary in nature, since much higher values are tolerated by many patients in clinical practice. However, there are hints in the literature that point to an increased EPS risk at higher plasma concentrations (20).

## Brexpiprazole

Two PET studies that measured $D_{2/3}$ receptor occupancy are available for brexpiprazole (27, 28) (**Table 2**). One study was conducted in healthy subjects after the administration of single oral brexpiprazole doses (28), the second study assessed $D_2/D_3$ receptor occupancy as well as 5-$HT_{1A}$, 5-$HT_{2A}$ and serotonin transporter (SERT) occupancies in a total of 12 patients with schizophrenia after 10 days treatment (27).

Wong et al. (28) administered single brexpiprazole doses in the range between 0.5 and 6 mg to 15 healthy subjects and determined $D_{2/3}$ receptor occupancy with [$^{11}$C]raclopride at two different time points post-dose (4 h and 23.5 h). The mean $D_{2/3}$ receptor occupancy in putamen and caudate nucleus increased with increasing doses, with less than 20% at the 0.25 mg dose and values above 80% at the 6 mg dose. Receptor occupancy remained in the similar range 23.5 h after drug administration. At the clinically recommended brexpiprazole doses of 2–4 mg/day, $D_{2/3}$ receptor occupancies ranged from 59 to 75% at 4 h and from 53 to 74% at 23.5 h post-dose. When the estimated attainable maximum occupancy $E_{max}$ was unconstrained, it was 89% for the

**TABLE 4 |** Main pharmacokinetic parameters derived from PET studies of aripiprazole, brexpiprazole and cariprazine.

| Partial agonists and active metabolites | Recommendation to use TDM | Half-live ($t_{1/2}$) | Therapeutic reference range | Laboratory alert level |
|---|---|---|---|---|
| **Aripiprazole** | Recommended | 60–80 h | 100–350 ng/mL | 1,000 ng/mL |
| Aripiprazole plus dehydroaripiprazole | | 30–47 days | 150–500 ng/mL | |
| **Brexpiprazole** | Useful | 90 h | 40–140 ng/mL | 280 ng/mL |
| **Cariprazine** | Useful | 50–120 h | 10–20 ng/mL | 40 ng/mL |
| N-desmethyl cariprazine | | | | |
| N,N-didesmethyl cariprazine | | 2–3 weeks | | |

putamen and 95% for the caudate, with the corresponding $EC_{50}$ values being 8.1 and 7.8 ng/ml, respectively (28). When $E_{max}$ was constrained to 100%, $EC_{50}$ was 11.5 and 9.0 ng/ml, respectively.

When the estimation of an $EC_{90}$ value is conducted based on an $EC_{50}$ of 10 ng/ml, $EC_{90}$ is 90 ng/ml, with an $EC_{50}$ of 9 ng/ml the estimated $EC_{90}$ is 81 ng/ml, and with an $EC_{50}$ of 11 ng/ml the estimated $EC_{90}$ is 99 ng/ml. Thus, the study suggests that at brexpiprazole plasma concentrations of 80–100 ng/ml striatal $D_2/D_3$ receptors are almost completely occupied by the drug.

The second PET study with brexpiprazole was a multi-tracer study to characterize the compound's binding to four different molecular targets: dopamine $D_2/D_3$, serotonin 5-$HT_{1A}$ and 5-$HT_{2A}$ receptors, and the serotonin transporter (SERT) (27). While $D_2/D_3$ receptor occupancy is usually measured with antagonist radiotracers like [$^{11}$C]raclopride or [$^{18}$F]fallypride, this study applied the agonist tracer [$^{11}$C]-(+)-PHNO. [$^{11}$C]-(+)-PHNO allows the differentiation of binding to $D_2$ and $D_3$ receptors, but it systematically underestimates $D_2$ occupancy by about 20% compared to assessment with antagonist radiotracers (29). After 10 days of treatment of patients with schizophrenia with brexpiprazole, the mean $D_2$ receptor occupancy was 64% following 1 mg/day and 80% following 4 mg/day. The corresponding estimated $EC_{50}$ values were, depending on the brain region, between 22 and 52 ng/ml (27). From these numbers an $EC_{90}$ value between 198 and 495 ng/ml can be derived. Thus, in this study, at the same plasma concentrations the measured $D_2$ receptor occupancies are substantially lower than in the study published by Wong et al. (28). While brexpiprazole did not significantly occupy the 5-$HT_{1A}$ receptor and the SERT, 5-$HT_{2A}$ receptor occupancy was 28% following 1 mg and 45% following 4 mg brexpiprazole (27).

### Conclusion for Clinical Practice

The two available molecular imaging studies are inconclusive with regard to their clinical implications. One study determined $D_2/D_3$ receptor occupancy after single brexpiprazole doses (28); the second study used an agonist radiotracer that systematically underestimates $D_2$ receptor occupancy (27, 29). Taking this underestimation into account, it seems reasonable to believe that striatal $D_2/D_3$ receptors are almost or completely saturated at 80–100 ng/ml brexpiprazole in plasma, and probably even at lower concentrations. However, this has to be confirmed in a study in patients treated with multiple doses and with an antagonist radiotracer.

The "Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017" (17) reports a therapeutic reference range of 40 – 140 ng/ml for brexpiprazole. Based on the available PET studies, the lower limit value would tend to be too low, while the upper limit value could also be exceeded in clinical practice.

## Cariprazine

Two PET studies quantified $D_2/D_3$ receptor occupancy under treatment with cariprazine, one in monkeys (30) and one in humans (13) (**Table 3**). Seneca et al. (30) studied the occupancy of $D_2$ and $D_3$ dopamine receptors and 5-$HT_{1A}$ serotonin receptors after a single low and a single high cariprazine dose, respectively, in three monkeys. Girgis et al. (13) assessed the occupancy of $D_2/D_3$ receptors by cariprazine in eight patients with schizophrenia at various doses and time-points post-dose.

Seneca et al. (30) in their study in three monkeys applied three different radiotracers: $D_2/D_3$ receptor occupancy was quantified both with an agonist ([$^{11}$C]MNPA) and an antagonist tracer ([$^{11}$C]raclopride), and [$^{11}$C]WAY-100635 was used for assessment of 5-$HT_{1A}$ receptor occupancy. A total of 15 PET examinations were carried out. Each monkey was subjected to a baseline examination and then scanned again after intravenous administration of either a low (1–5 μg/kg body weight) or a high (30–300 μg/kg) dose of cariprazine. Blood samples for determination of the plasma concentrations of cariprazine and its two main metabolites desmethyl- (DCAR) and didesmethyl cariprazine (DDCAR) were taken at prespecified time-points. At doses of 5 and 30 μg/kg cariprazine caused a dose-dependent $D_2/D_3$ receptor occupancy of approximately 45 and 80%, while the highest dose (300 μg/kg) was associated with 94% occupancy. Occupancy values did not differ for agonist and antagonist radiotracers. Occupancy of 5-$HT_{1A}$ receptors was 10–20% at the lower doses, and it plateaued at 30% with the highest dose (30). Although the authors measured plasma levels of cariprazine and its metabolites, they did not calculate $EC_{50}$ values. Therefore, an $EC_{90}$ value cannot be calculated based on that study.

The second study assessed cariprazine's occupancy of $D_2/D_3$ receptors in patients with schizophrenia (13). The radioligand used was the agonist tracer [$^{11}$C]-(+)-PHNO, and the patients were scanned at baseline and on days 1, 4, and 15 of treatment with cariprazine between 1 and 12 mg/day. Plasma (and cerebrospinal fluid) samples were analyzed for concentrations of cariprazine, DCAR, and DDCAR. After treatment with the lowest cariprazine dose (1 mg/day), $D_3$ occupancy was 76% (range 58–89%) and $D_2$ occupancy 45% (range 14–64%). At the dose of 3 mg/day, the mean $D_3$ and $D_2$ receptor occupancies were 92% (range 86–96%) and 79% (range 68–88%), respectively. Thus, at

those lower doses, cariprazine binding was more selective for $D_3$ over $D_2$ receptors. At higher doses, this selectivity is lost. The dose of 12 mg/day led to complete saturation of both receptor subtypes. Since both metabolites are pharmacologically active, estimation of $EC_{50}$ values were carried out with active moiety values (cariprazine + DCAR + DDCAR). Also, $EC_{50}$ estimation was conducted separately for $D_2$ and $D_3$ receptors and for acute (occupancy estimation on days 1 and 4) and for subchronic treatment (occupancy estimation on day 15).

After acute dosing, the $EC_{50}$ was 0.61 ng/ml for the $D_3$ and 0.76 ng/ml for the $D_2$ receptor. After 15 days treatment, when more of the slow-forming active metabolites, especially DDCAR, have accumulated, the $EC_{50}$ values were 1.64 ng/ml for the $D_3$ and 5.56 ng/ml for the $D_2$ receptor. This suggests greater $D_3$ selectivity of cariprazine with longer treatment, which is most likely explained by the grater $D_3$ selectivity of DDCAR. DDCAR, which has a very long half-life, develops very slowly during treatment. While cariprazine is the dominant compound during the first few days of treatment, the active moiety mainly consists of DDCAR and cariprazine during chronic treatment (13). From the $EC_{50}$ values estimated at day 15, the corresponding $EC_{90}$ values are 14.8 ng/ml for the $D_3$ receptor and 50.0 ng/ml for the $D_2$ receptor.

### Conclusion for Clinical Practice

Only one human PET study that provides $EC_{50}$ estimates has been published, and this was conducted with the agonist radiotracer [$^{11}$C]-(+)-PHNO. PET studies with the antagonist radiotracers [$^{11}$C]raclopride and [$^{18}$F]fallypride have been published as abstracts only. While the available PET study in monkeys suggests that $D_{2/3}$ receptor occupancy is similarly high when assessed with the agonist [$^{11}$C]MNPA and the antagonist [$^{11}$C]raclopride, the $D_3$-preferring agonist [$^{11}$C]-(+)-PHNO might still underestimate $D_2$ occupancy (29). The study by Girgis et al. (13) suggests that $D_3$ and $D_2$ receptors are almost completely saturated at approximately 15 and 50 ng/ml. The "Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017" (17) reports a therapeutic reference range of 10 – 20 ng/ml for cariprazine. However, the latter range is based on cariprazine levels only, while the $EC_{50}$ values estimated by Girgis et al. (13) are based on active moiety values. A therapeutic reference range for the active moiety (cariprazine + DCAR + DDCAR) will be necessarily higher than one for the parent compound only (see discussion of aripiprazole above). However, due to a lack of data, such a reference range has not been defined yet.

## DISCUSSION

Molecular imaging, especially with PET, has been used since the late 1980s for determination of rational antipsychotic dosing. These studies did not only demonstrate that the doses of some of the classical antipsychotics such as haloperidol over the first decades of their clinical use were irrationally high (31). They also showed that some of the newer (second-generation) antipsychotics were initially not dosed correctly. The best example is risperidone. This compound was approved and marketed for the treatment of schizophrenia in the United States in 1993 and soon thereafter throughout the world. The highest approved dose was 16 mg, and two-digit doses were quite commonly used during the first several years after market access (32). The first PET study with risperidone was published in the year of market entry (33). Three healthy volunteers were administered a single 1 mg oral dose of risperidone. The determined $D_{2/3}$ receptor occupancy was approximately 50% even at this very low dose. Subsequent studies showed that the incidence of EPS rises at doses above 6 mg risperidone daily, the dose at which $D_{2/3}$ occupancy crosses the 80% threshold in most patients (34). It took years for the results of these PET studies to change clinical practice of excessive doses, years in which many patients suffered unnecessary side effects due to incorrect dosages. Thus, since the mid-1990s at the latest, the characterization of target engagement of new antipsychotics has been part of their development program.

This is also true for the class of dopamine partial agonists. Aripiprazole was the prototype of this class of new drugs, it entered the market in 2002 in the United States. With the publication of the first PET study on this compound (9), it became immediately clear that the magnitude of its target engagement has to be interpreted differently from antagonist antipsychotics, and that it does not follow the "65 – 80% therapeutic window" rule for $D_2$ antagonists (10) (**Figure 1**). Aripiprazole is still by far the most extensively studied partial agonist antipsychotic, and – as demonstrated in this paper – the data are very consistent in showing that more than 90% of all $D_{2/3}$ dopamine receptors are occupied above a plasma concentration of approximately 100 ng/ml of the parent compound. Theoretically, substantially increasing the plasma concentration above this value is probably of no benefit to the patient. This is underlined by a recent dose-response meta-analysis that demonstrated that the 95% effective dose of aripiprazole is 11.5 mg/day and that its antipsychotic efficacy does not increase above this dose (35). The plasma concentration, however, can substantially vary at a given dose (18). Thus, monitoring of the plasma concentration is certainly a better tool for tailoring treatment to the individual patient. Although factors that characterize a patient individually, e.g., his psychopathology, are likely to influence the measurement of receptor availability, these influences are small and negligible compared to the effects of pharmacological treatment *per se*.

The situation is much less clear for the other two available dopamine partial agonist, brexpiprazole and cariprazine. As outlined in this paper, the few PET studies that have been published with these compounds, are somewhat inconclusive with regard to a therapeutic reference range. Specifically, a lower threshold at which almost complete occupancy of $D_{2/3}$ receptors can be assumed, cannot be derived from these studies with sufficient certainty. It would be desirable if at least one PET study that met certain methodological standards were carried out when a new antipsychotic is launched on the market, or even before it is launched. A methodological standard procedure for PET studies aiming at supporting therapeutic concentration ranges has not been specified yet. Certainly, such investigations

should be performed in a minimum number of patients ($n$ = 15 or larger) who have been treated for a sufficient period of time (minimum steady-state) over the entire dose range. An antagonist should be used as the radiotracer ([$^{11}$C]raclopride or [$^{18}$F]fallypride), as extensive reference data are available for these. Studies with agonists as radioligands or those with preferential binding to $D_3$ receptors could supplement the characterization in individual cases. Not only a large variance in reporting the results across studies, but also a considerable heterogeneity in the study populations (i.e., healthy volunteers vs. patients; dose and blood sampling designs; measurement of solely the major analyte vs. the analyte plus active metabolites) impede a comparability of the results. In terms of design, it has to be differentiated between studies that do or do not aim at linking PET findings with clinical effects. In order to be able to report a reliable relationship between receptor occupancy and clinical effects, the study designs have to be far more complex than most of the studies reviewed in this work (i.e., including a randomized, double-blind study phase).

In summary, this overview shows that molecular imaging is an excellent tool for characterizing antipsychotics in general and partial dopamine agonists in particular (**Table 4**). This is not just an academic exercise. Once the relationship between plasma concentrations of a substance and its binding to the molecular target in the brain has been clarified (which can be done with little effort), the determination of the plasma concentration in the individual patient allows for tailor-made treatment at the lowest possible cost.

## AUTHOR CONTRIBUTIONS

GG developed the first draft of the protocol. XH contributed to the writing of the manuscript, to the development of the search strategy, and critical appraisal. CS contributed with writing and critical appraisal. All authors have read and approved the final manuscript.

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# What Is the Minimum Clinically Important Change in Negative Symptoms of Schizophrenia? PANSS Based *Post-hoc* Analyses of a Phase III Clinical Trial

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**Introduction:** Minimum clinically important difference (MCID) is a measure that defines the minimum amount of change in an objective score of a clinical test that must be reached for that change to be clinically noticeable. We aimed to find the MCID for patients with predominantly negative symptoms of schizophrenia at its earliest occurrence.

**Methods:** Data of a 26-week long, double-blind study with 454 patients [Positive and Negative Symptom Scale Negative Factor Score (PANSS-FSNS) ≥24, Positive and Negative Symptom Scale Positive Factor Score (PANSS-FSPS) ≤19] treated with cariprazine 4.5 mg/d or risperidone 4 mg/d were analyzed. The Clinical Global Impression—Improvement scale was used to quantify minimum improvement (CGI-I = 3) and no clinical change (CGI-I = 4) on the PANSS-FSNS, and the MCID was estimated with the following methods: as the mean PANSS-FSNS changes corresponding to the first instance of minimal improvement across all visits ($MCID_1$); as the difference between the PANSS-FSNS change associated with the first instance and the PANSS-FSNS changes associated with the last recorded clinically unchanged status across all visits ($MCID_2$); with the effect size approach ($MCID_3$); as the Youden Index based cut-off value between no clinical change and minimal improvement ($MCID_4$); as the relative likelihood of minimal improvement ($MCID_5$).

**Results:** The $MCID_1$ and $MCID_2$ resulted in, respectively, a 3.8-point (18.5%) and a 1.5-point (7.3%) decrease from baseline severity on the PANSS-FSNS. Greater values were required for the MCID at later evaluation times. The cut-off between minimum improvement and no clinical change defined by the Youden Index was a−3-point (15%) change in the PANSS-FSNS. The effect size approach indicated the 1.5-point difference between minimally improved and unchanged patients to be a medium effect (ES = 0.6).

**Conclusion:** Applying different methods led to different results, ranging between 7.3 and 18.5% improvement from the baseline for the MCID at its earliest occurrence in patients with predominantly negative symptoms of schizophrenia.

**Keywords: minimum clinically important difference, negative symptoms, schizophrenia, MCID, clinical trial, cariprazine**

## INTRODUCTION

The efficacy of various treatment interventions can be assessed in clinical trials by testing for statistical significance, yet a statistically significant change on a symptom scale score does not necessarily indicate a clinically relevant improvement (1). Thus, various approaches have been developed across different diseases to define the smallest beneficial effect for patients. One of the first attempts to obtain the slightest empirically observed, "clinically important" effects of intervention was published in 1989 by Jaeschke et al. (2), who defined the Minimum Clinically Important Difference (MCID) as "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management." It is, therefore, a within-person, "before-after" change and conceptually distinct from minimum between-group differences that can be expected between two different treatments. The latter would be called the smallest worthwhile difference (SWD) (3). While the MCID is scale specific and assumes no substantial adverse effects or costs, the SWD represents the ratio of benefits and negative effects of two alternative treatments (4). Although other reports described the MCID with very similar names, such as the Minimal Clinically Important Difference (5, 6) Minimum Important Difference (7) or Minimal Important Change (6), the intended meaning is the same: MCID is a measure that defines the minimum amount of change in the objective score of a clinical test that must be reached for that change to be clinically noticeable.

Calculations of the MCID are usually divided into two groups: anchor- and distribution-based approaches. In anchor-based methods, an objective outcome measure of change is linked to a clinically meaningful external anchor, largely corresponding to patient perception (3, 6, 7) or in case of impaired insight, e.g., in dementia or schizophrenia, to clinical opinion (8–10). Distribution-based methods use statistical properties of study results, e.g., effect size or standard error of measurement, to calibrate the MCID (11–15).

In schizophrenia, the Positive and Negative Syndrome Scale (PANSS) measuring positive, negative, and general psychopathology, is the gold-standard instrument for assessing symptom severity (16). The clinical relevance of changes in the PANSS total score has been previously evaluated using the Clinical Global Impression (CGI) rating scale as an anchor (17, 18). It largely varies across different patient populations. Based on the CATIE study, where a very heterogeneous patient population was analyzed, a change of a 34% decrease on the PANSS total score was established as necessary to improve one category on the CGI-Severity scale (CGI-S) (18). For patients with florid positive symptoms, a 19–28% decrease in the PANSS total score was necessary to reach "minimal improvement" on the CGI-Improvement scale (CGI-I) (17). To specifically assess negative symptoms of schizophrenia, the PANSS factor score for negative symptoms (PANSS-FSNS) has been widely used in clinical trials (19). Leucht et al. found that minimal improvement corresponded to a change from baseline in PANSS-FSNS scores of −27 and −41%, as measured by the CGI-I and CGI-S (20).

Depending on the diagnostic criteria applied, negative symptoms of schizophrenia are present in 5–60% of patients with schizophrenia (21). These symptoms significantly affect a patient's quality of life as they limit functional recovery and are associated with poor functional outcomes (22). Patients with negative symptoms use more healthcare resources than patients with positive symptoms (such as: primary care, emergency care, laboratory and radiology tests, and prescription drugs), and their treatment is usually not simple, causing a clinical challenge for physicians. In contrast, positive symptoms have remarkably little association with real-life functioning and are easier to treat (23–25).

Finding the minimum clinically important change for negative symptoms may help physicians in better assessing treatment results as well as fostering the development of new instruments. In this paper, we further analyse the MCID in negative symptoms of schizophrenia, hypothesizing that as patients get better by taking their medication, more extensive changes in the PANSS-FSNS are needed to be considered clinically relevant. The previous estimation by Leucht et al. took all PANSS-FSNS changes associated with minimal improvement into account, regardless of their timepoint (20) meaning that the 27 and 41% improvement in the PANSS-FSNS associated with minimal clinical changes represent weighted averages from the first to the last instance of minimal improvement. Thus, those percentages may have overestimated the MCID in patients with predominantly negative symptoms of schizophrenia. In this work, we focus on the first instance of the MCID in patients with predominantly negative symptoms. Furthermore, to date, there is no consensus on the best method to calculate the MCID, and we apply both anchor- and distribution-based methods to get a more comprehensive picture.

## METHODS

### Study Design

Data were analyzed from a large randomized, double-blind clinical trial treating patients with schizophrenia with predominantly negative symptoms; the study's methods and results have been previously published (26). The study was

conducted at 66 study centers in 11 European countries from May 2013 to November 2014. The clinical study was approved by local independent ethics committees and was completed following clinical practice guidelines by the International Conference of Harmonization. All patients provided written informed consent. The study consisted of a 4-week lead-in period, a 26-week double-blind treatment period, and a 2-week safety follow-up with a total of 14 visits. The primary aim of the study was to assess the efficacy and safety of cariprazine treatment vs. risperidone treatment in primary, persistent, predominantly negative symptoms of schizophrenia. The primary efficacy outcome was the change from baseline in the PANSS-FSNS score at the end of the double-blind period (26 weeks). The secondary outcome parameter was change from the baseline on the Personal and Social Performance (PSP) scale. The study was well-controlled for secondary negative symptoms, assessing depression (Calgary Depression Scale for Schizophrenia), movement disorders (Simpson Angus Scale, Abnormal Involuntary Movement Scale, and Barnes Akathisia Rating Scale) and positive symptoms [PANSS factor score for positive symptoms (PANSS-FSPS)] throughout the study. Safety and tolerability were also assessed including adverse event reports, laboratory assessment, vital signs, and EEG. Patients were randomized to cariprazine 4.5 mg/d or risperidone 4 mg/d (1:1) with 2 weeks of up-titration (26).

## Patients

Male and female patients with schizophrenia and predominantly negative symptoms, between 18 and 65 years of age, who were diagnosed with schizophrenia (as defined by DSM-IV-TR) and an onset of illness ≥2 years prior, were included in the study. Patients also needed to be in stable condition for at least 6 months with no hospitalisations. For study inclusion, patients must have presented with predominantly negative symptoms for ≥6 months, a PANSS-FSNS ≥24, and a score ≥4 on at least 2 of the following 3 PANSS negative symptom items: blunted affect, passive/apathetic social withdrawal, and lack of spontaneity and flow of conversation. The presence of a current DSM-IV-TR axis I disorder other than schizophrenia, and an unstable condition (such as a hospital admission in the previous 6 months), a PANSS factor score for positive symptoms (PANSS-FSPS) >19, or a PANSS-FSPS score increase of ≥25% during study lead-in were grounds for study exclusion. Other clinical exclusion criteria included substance abuse/dependence, treatment with clozapine during the 12 months before the study, a history of non-response to an adequate trial of risperidone for a psychotic episode, or treatment with risperidone within 6 weeks of screening (26).

## MCID Analyses

The clinician-rated CGI-I scale was used to quantify minimum improvement (CGI-I = 3) and no clinical change (CGI-I = 4) on the PANSS-FSNS. To demonstrate any meaningful results by linking an objective scale measuring symptom severity to a subjective scale that estimates the clinical state correlation between the two scales must be demonstrated in the target population. This was done by Leucht et al., who performed the correlation analysis in the same population on which this work is based (20).

According to the definition of the MCID, a within-subject design was applied to estimate the difference between no clinical change and minimal improvement. Our observation was that PANSS-FSNS changes corresponding to minimal improvement get higher and higher over time, and thus, in order to capture the minimum clinically important difference, the MCID should be calculated on the basis of PANSS-FSNS changes associated with the earliest instance of minimal improvement. The MCID was estimated with the following methods.

### Anchor-Based Methods

- $MCID_1$: The mean PANSS-FSNS changes corresponding to the first instance of minimal improvement (CGI-I = 3) across all visits. In other words, $MCID_1$ is based on the original definition by Jaeschke et al. (2) for MCID, as it represents a change from baseline in the original score units of the PANSS-FSNS scale.
- $MCID_2$: The difference between the PANSS-FSNS change associated with the first instance of improvement (i.e., CGI-I = 3) and the PANSS-FSNS changes associated with the last recorded clinically unchanged status (CGI-I = 4) across all visits. Thus, $MCID_2$ represents the mean score method of Redelmeier and Lorig (27) i.e., it shows the score difference of the "slightly better" group minus that of the "about the same" group (28). Accordingly, $MCID_2$ is also expressed in the original scale units.

To test the statistical significance of the difference between unchanged and minimally improved PANSS-FSNS values, we applied a mixed model for repeated measures (MMRM) analysis with improvement and visit as fixed effects. The subject was used as random effect in the model. To avoid losing cases with minimal improvement at the first visit after baseline (Week 1), zero PANSS-FSNS change was imputed for the baseline visit (where no improvement can be present by definition).

### Distribution-Based Methods

- $MCID_3$: the effect size approach, based on the standardized response mean difference, a widely used distribution-based method to estimate the MCID, where MCID is the mean difference between the last unchanged (CGI-I = 4) and the first minimally improved (CGI-I = 3) PANSS-FSNS values divided by the pooled standard deviation (SD) of the two. It formally corresponds to the effect size calculation, making it possible to interpret the MCID in terms of the effect sizes (28).
- $MCID_4$: dichotomous variable indexing minimal improvement (not obtained = 0, obtained = 1) based on the cut-off value between no clinical change (CGI-I = 4) and minimal improvement (CGI = 3). A logistic regression model, with CGI-I as dependent and PANSS-FSNS as independent variables as well as baseline PANSS-FSNS as a covariate, was fitted to the data. To examine the accuracy of predicting improvement based on the PANSS-FSNS change, a receiver operating characteristics (ROC) curve was derived. The strategy used in the ROC analysis was to maximize both

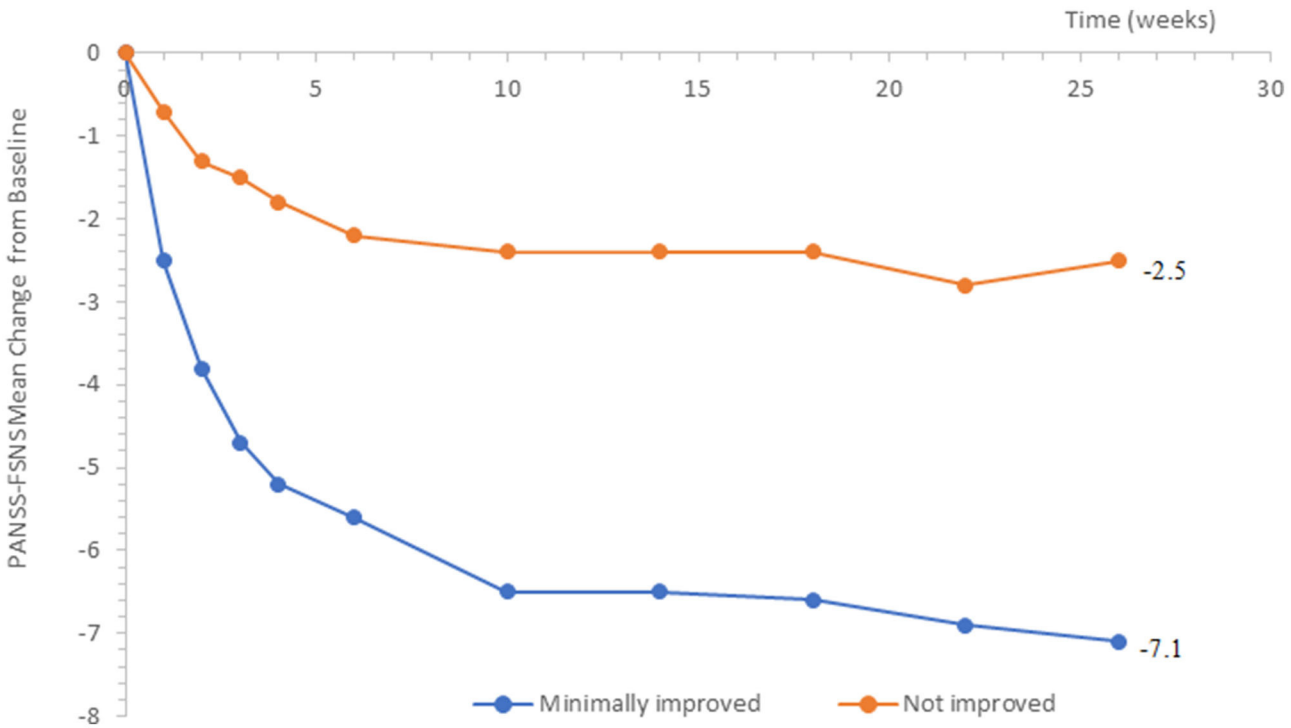


**FIGURE 1 |** Change from baseline in PANSS-FSNS (Positive- and Negative Syndrome Scale—Factor Score for Negative Symptoms) as a function of minimal change vs. no change.

sensitivity and specificity, and the MCID was estimated as a cut-off value corresponding to the maximal Youden's index (29, 30).

- $MCID_5$ as expressed in terms of ratio of odds values (p/1-p) of being in improved vs. unchanged state at a certain degree of FSNS decrease. This estimation is based on the logistic regression model as above and expresses the strength of the predictive power of unity change in FSNS for clinical improvement.

## RESULTS

The primary results of the study were previously published (26): change from baseline to week 26 in PANSS-FSNS was significantly greater with cariprazine than with risperidone [least squares mean difference (LSMD) −1.46, 95% CI −2.39 to −0.53; $p = 0.0022$; effect size = 0.31]. Also, for the secondary efficacy parameter, least squares mean change from baseline to endpoint in PSP total score, was greater for cariprazine than risperidone (LSMD 4.63, 2.71–6.56; $p < 0.0001$; statistical effect size = 0.48). In the parameters controlling for secondary negative symptoms, least squares mean changes from baseline for PANSS-FSPS, CDSS total score, and movement scales were small and similar for cariprazine and risperidone.

A total of 454 patients from the intent-to-treat population with at least one post-baseline PANSS assessment were pooled for this analysis from both the cariprazine and risperidone treatment groups; the mean factor score on the PANSS-FSNS at baseline was 27.6, with points decreasing to 19.0 points at week 26.

### By Visit Analyses

Minimal improvement on the clinical global impression scale (CGI-I = 3) was associated with PANSS-FSNS changes ranging from −2.5 points (Week 1) to −7.1 points (Week 26), consistent with our hypothesis of the MCID to be smaller at its earliest occurrence (**Figure 1**).

### Quantifying the MCID by Anchor-Based Methods

#### $MCID_{1 \text{ and } 2}$

The mean PANSS-FSNS change from baseline corresponding to the first occurrence of minimal improvement (CGI-I = 3) and the last recorded unchanged status across all visits were −3.8 and −2.3 points, respectively. The statistical analysis of the two arithmetic PANSS-FSNS means showed a significant difference (**Table 1**).

### Quantifying the MCID by Distribution-Based Methods

#### $MCID_3$

Based on the observed PANSS-FSNS changes the standardized effect size was determined according to the following formula: (PANSS-FSNS change from baseline at the first instance minimal improvement) − (Mean PANSS-FSNS Change from baseline at

**TABLE 1 |** Anchor based calculations of the MCID.

| Visit | Mean PANSS-FSNS change from baseline (*n*) at the 1st instance of minimal improvement [1] | Mean PANSS-FSNS change from baseline (*n*) at the last recorded unchanged status [2] | $MCID_1$ [1] | $MCID_2$ [1]-[2] | SD of [1] and [2] | LSMD (95% CI) | *P*-value |
|---|---|---|---|---|---|---|---|
| Overall | −3.8 (365) | −2.3 | −3.8 (18.5%) | −1.5 (7.3%) | 2.5 | 1.7 (1.1, 2.3) | <0.0001 |

*PANSS-FSNS, Positive and Negative Syndrome Scale-Factor Score for Negative Symptoms; n, number of events; CGI-I, Clinical Global Impression—Improvement; $MCID_1$ and $MCID_2$, Minimum clinically important differences according to the definitions in the text; SD, Standard deviation; LSMD, Least-square mean difference between [1] and [2], as estimated by MMRM, with corresponding 95% confidence limits. Please also note that for the computation of % changes from baseline the value of 7 was subtracted from the observed baseline severity (i.e., 27.6) since the minimum value of the PANSS-FSNS factor is 7 (i.e., the symptoms on all seven constituting items of the factor are rated as "Absent").*

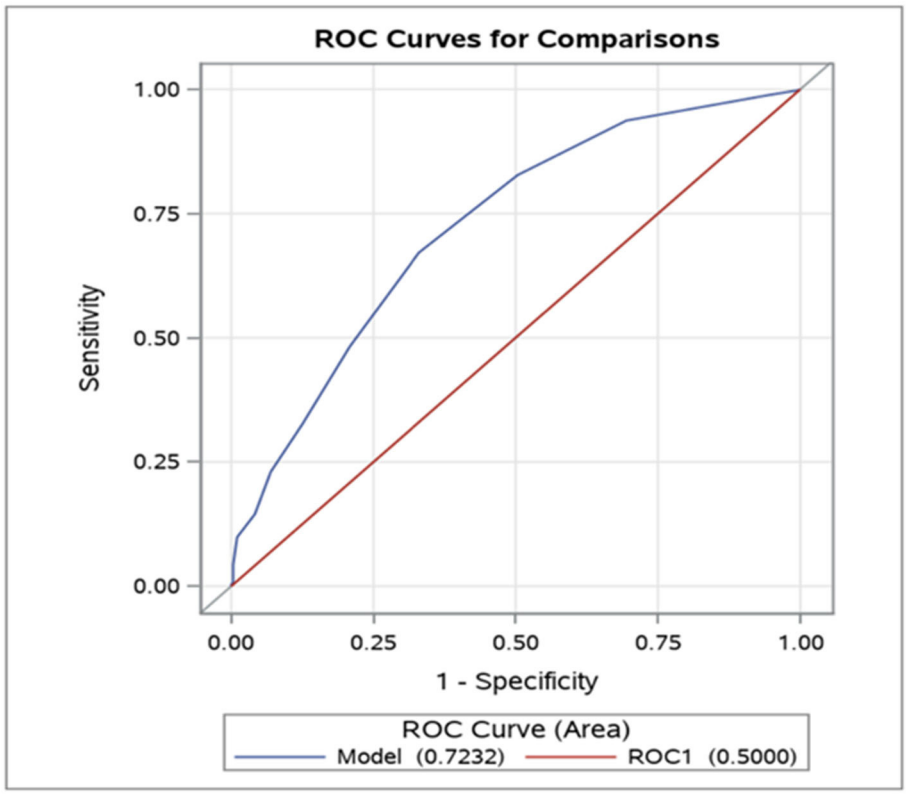


**FIGURE 2 |** Receiver Operating Characteristic (ROC) curve: predictive accuracy of the PANSS-FSNS (Positive and Negative Syndrome Scale Factor Score for Negative Symptoms) scale for differentiating minimally improved vs. clinically unchanged status. The values on the vertical and horizontal axis, respectively, depict the sensitivity ("true positive rate") and 1− specificity ("false positive rate") values for the differentiation as a function of change from baseline in the PANSS-FSNS scale. The leftmost part of the ROC curve represents the highest empirically observed improvements in the sample as compared to baseline while the rightmost part represents no improvement (or even deterioration). Please note that the ROC curve for differentiating the minimally improved from the clinically unchanged status based on the PANSS-FSNS (ROC model, depicted in blue in the figure) significantly outperforms the random classification (ROC1 model, in red), with an area under the curve (AUC, labeled as "Area") value of 0.7232 vs. 0.5000 ($p < 0.0001$).

the last recorded unchanged status)/pooled SD. Our computation resulted in a standardized effect size for the improvement with a value of 0.6 [i.e., −3.8 – (−2.3)/2.5 = −1.5/ 2.5 = −0.6].

## $MCID_4$

The ROC curve indicated statistically robust predictive values of PANSS-FSNS changes, as the model fitted to our data (Model) was highly significantly different from the reference line (ROC1) (**Figure 2**). Based on the maximal Youden's index method (29) we identified a −3 point decrease from the PANSS-FSNS at baseline as the cut-off value most effectively differentiated between true positive and false positive classifications, i.e., minimally improved and unchanged statuses (**Figure 3**).

## $MCID_5$ as Odds Ratio

The odds ratio (OR) indicates the strength of association between the decrease in FSNS and the improved state based on CGI-I. For the −1.7 shift in FSNS obtained above as estimated MCID based

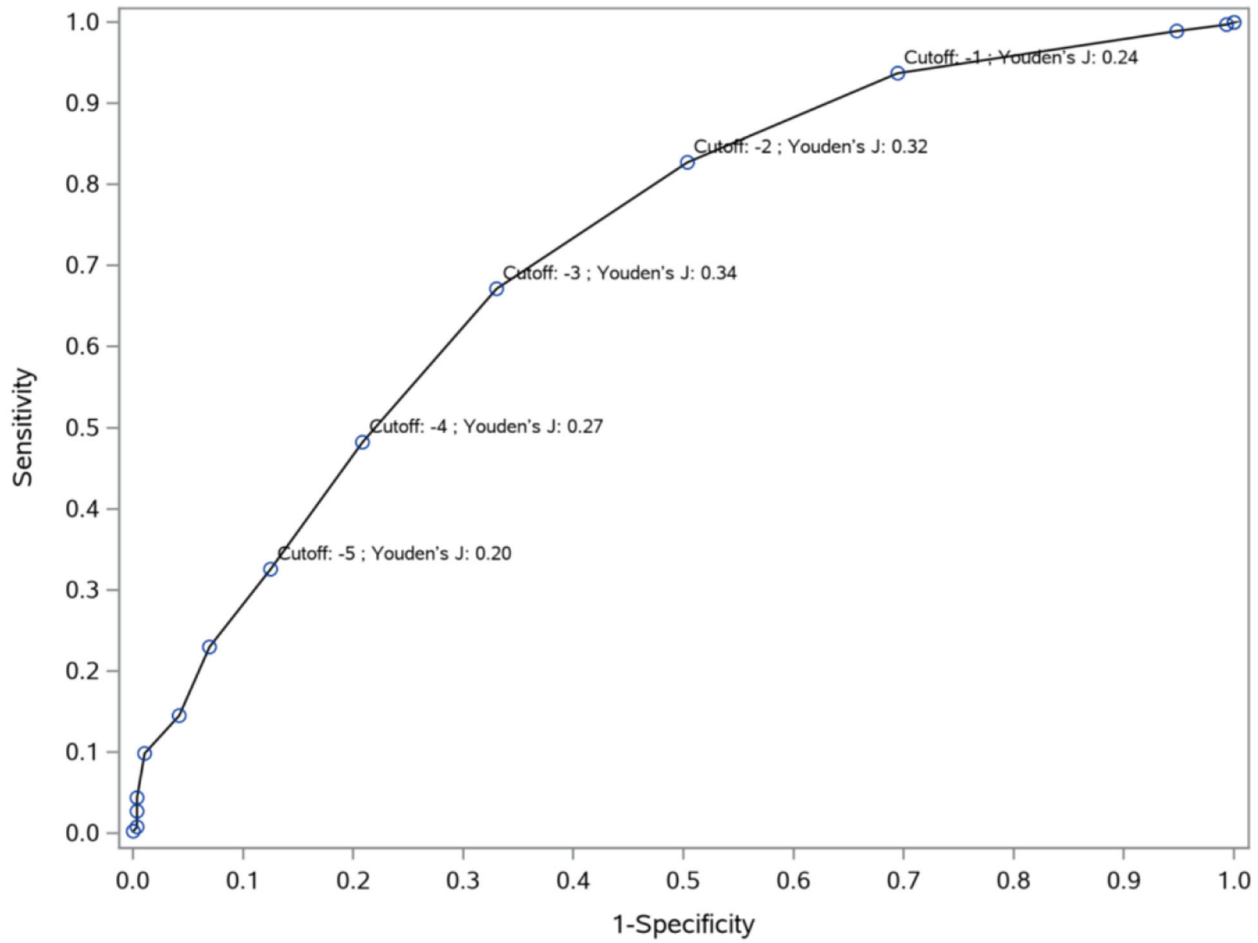


**FIGURE 3 |** Cut-off values (Youden's indices) for predicting improvement from no clinical change to minimal improvement. To differentiate minimal improvement from no clinical change, Youden's J indices were computed at different cut-off points based on the PANSS-FSNS change. The sensitivity (vertical axis) and 1- specificity (horizontal axis) values for the differentiation of minimal improvement from no clinical change are depicted in the figure for various values of change from baseline in the PANSS-FSNS (labeled as "Cutoff"). Please note that the Youden's J index, which shows the efficiency of differentiation based on the combination of sensitivity and specificity, first increases then decreases with increasingly greater improvements (i.e., with greater negative values) as compared to baseline. The highest value of the Youden's J Index is reached at the cut-off value of −3 (i.e., at a 3 point reduction of symptom severity from baseline in the PANSS-FSNS), which identifies the optimal change value that maximizes sensitivity and specificity simultaneously.

on the Least Squares Mean Difference (LSMD), the OR is 1.86 (95% CI 1.62, 2.13; $p < 0.05$) favoring CGI-I = 3 vs. 4, The logistic regression analysis described above yielded an estimated OR of 2.07 (95% CI = 1.76 – 2.44; $p < 0.05$) for a 2-point decrease in the PANSS-FSNS factor score during the study. Thus, this analysis indicates that such an improvement (i.e., 2 points) in the PANSS-FSNS factor score more than doubles the likelihood of achieving minimal clinical improvement in the study.

## DISCUSSION

Previous work has established the minimal improvement (CGI-I = 3) as being associated with a 27% decrease in the PANSS-FSNS for patients with predominantly negative symptoms of schizophrenia (20) which may still be an overestimation if the time effect of improvement is considered as well. The current analyses estimated the MCID with several methods by looking at it at its earliest occurrence.

It is important to note that the five different approaches that we adopted in the current investigation to characterize MCID complement each other and delineate the MCID from various vantage points. The distribution-free approaches characterize change over time in terms of the original units on the scale of interest (PANSS-FSNS), either as a baseline-end point difference associated with the minimal improvement on the CGI-I (score = 3) (MCID1) or the difference between unchanged and minimally improved PANSS-FSNS values (MCID2). The first one of the distribution-based methods that we adopted (MCID3) expresses the difference between unchanged and minimally improved PANSS-FSNS values (measured in the original scale units) in terms of standard deviation (statistical) units. The additional

two distribution-based approaches employ logistic regression modeling in order to predict the minimally improved status on the basis of the PANSS-FSNS change over time. They express MCID either as measures of the ROC Curve (AUC, Youden's index in case of MCID4) or an OR (MCID5).

Applying these approaches, we confirmed that over time, more and more prominent symptom changes were needed to achieve minimal clinical improvement. In view of this finding, we conclude that the absolute minimum clinically meaningful difference should be considered at the earliest instance, since this approach provides the highest assay sensitivity to detect clinically important changes of symptom severity over time (i.e., it allows to capture the lowest symptom change threshold for minimal clinical improvement). We note that the PANSS-FSNS of the patients whose clinical status remained the same slightly decreased as well, although to a much smaller extent. This slight symptom reduction of the clinically not improving patients may be attributable to unspecific changes, such as the regression to the mean effect, a phenomenon often seen when applying strict inclusion criteria for the patients regarding their symptom severity (31). The presence of such unspecific changes, which evolve gradually with time, may make it more difficult to establish a clinically important difference at later times in a trial, thereby providing additional rationale for focusing on the earlier time points. Additionally, because improvement is rated against the initial baseline, anchoring changes of symptom severity to clinical improvement can be more and more difficult and accompanied by greater variation as the patients progress over time during the study.

Overall, applying various underlying concepts to calculate the MCID, different methods led to different estimates with respect to the PANSS-FSNS change that need to be considered as minimally clinically significant. Our estimates from the anchor-based analyses, ranging from 7.3 to 18.5% for patients with predominant negative symptoms of schizophrenia, were below the estimates reported from studies that relied on more heterogeneous patient populations and did not take the time effect into consideration. However, it is important to bear in mind that the distribution-based statistical approaches showed a marked separation ($MCID_3$, i.e., statistical effect size in terms of standardized mean difference = 0.6); and highly significant predictive power for the PANSS-FSNS scale for differentiating Minimally Improved from Clinically Unchanged status in terms of ROC measures ($MCID_4$; e.g., AUC = 0.7232) and the odds ratio ($MCID_5$; OR = 2.07).

An important limitation of this investigation is that, although experienced raters met the training requirements and qualification criteria set forth before the rater training and administered the instruments, potential rating bias might have occurred. For example, the increasing PANSS-FSNS changes over time could be attributed to a possible oversight by comparing patients' clinical statuses to the previous visit instead of the baseline status (32). Furthermore, one could also argue that very early improvements might not have been real drug effects due to the two drugs' different pharmacokinetics and the onset of effect. Nevertheless, the MCID, by definition, is not about treatment-effect and could be driven by complex factors. Finally, since the CGI ratings were performed by the clinician, a further limitation of the study is that the minimally clinically important difference in the current investigation was evaluated from the clinician's perspective, not from the patient's. Patient-related outcomes were not assessed to determine the minimally clinically important change. However, we note that one study which examined patient- and clinician-rated CGI assessments simultaneously in patients with schizophrenia found only slight differences between the two approaches (18). Nonetheless, a specifically designed study is clearly needed to investigate this issue further. Further, an additional limitation derives from the use of only one particular scale. In this study we adopted one of the benchmark scales for negative symptoms of schizophrenia, the PANSS-FSNS. Assessing negative symptoms with different scales (such as the SANS, BNSS, CAINS, etc.) would yield different values as minimally important change, as scoring on these scales is different. Consequently, further research is needed to identify minimally clinically important changes on different negative symptom scales.

Negative symptoms, that are not secondary to positive ones, are known for being less responsive to antipsychotic therapy (33–35). Their presence often challenges the therapeutic strategy and makes clinicians switch the patients' medication. Our findings may help clinicians and drug developers have a more precise idea about improving predominant negative symptoms in clinical decision-making, or in terms of designing trials for patients with predominant negative symptoms.

## CONCLUSION

Applying different methods lead to different results, ranging between 7.3 and 18.5% improvement from baseline for the MCID at its earliest occurrence in patients with predominant negative symptoms of schizophrenia, suggesting even lower thresholds than previously thought.

## DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because they are part of a bigger randomized clinical study dataset, and are owned by the company Gedeon Richter. The datasets have been provided to authors to perform the presented analyses only. While the full datasets can therefore not be shared, all statistical analyses and data outputs generated for the present study/publication can be requested by the authors.

## ETHICS STATEMENT

The clinical study protocol was approved by nine central and 37 local independent Ethics Committees in relation to the 66 sites that recruited at least one patient; the study was done in accordance with good clinical practice

guidelines and the principles of the International Conference on Harmonization. All patients provided written informed consent. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

SL, PC, ÁB, IL, and GN developed the concept of the current investigation. Methodology contribution was provided by KA, PC, SL, and TAF. The statistical plan was outlined by PC and KA. KA conducted the statistical analyses under the supervision of PC. Software preparation was done by KA and PC. KA, PC, BS, and IL had a leading role in the preparation of the figures and table. Project administration was provided by ÁB, BS, IL, and GN. PC and KA interpreted the statistical outputs. Conceptual supervision for manuscript preparation and writing was provided SL, PC, and TAF. BS, IL, ÁB, and PC performed the writing. All authors contributed to the article and approved the submitted version.

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# Depressive Symptoms and PANSS Symptom Dimensions in Patients With Predominant Negative Symptom Schizophrenia: A Network Analysis

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**Introduction:** Schizophrenia is a severe psychiatric disorder with a large symptomatic heterogeneity. Moreover, many patients with schizophrenia present with comorbid psychiatric symptoms or disorders. The relation between depressive symptoms and negative symptoms, such as blunted affect, alogia, anhedonia, asociality and avolition, is particularly intriguing. The negative symptoms can be primary or secondary of depression or overlapping with depressive symptoms. The aim of the present network analysis was to better understand the interactions between depressive symptoms and the different symptoms of schizophrenia and to investigate whether negative symptoms and depressive symptoms can be better delineated.

**Methods:** A network analysis on the baseline item scores of the Positive and Negative Syndrome Scale (PANSS) and Calgary Depression Scale for Schizophrenia (CDSS) from the cariprazine-risperidone study in patients with predominant negative symptoms (PNS) was performed. The connections between all these symptoms (PANSS and CDSS) were investiged: node strength and network centrality were estimated and the Mohr 5-factor model of the PANSS was applied to test the validity of its different symptoms clusters.

**Results:** Across 460 patients with schizophrenia and PNS, the most central symptom (largest node strength) was depression (PANSS) followed by depression (CDSS), anxiety, lack of judgment and insight and tension. The PANSS negative symptom cluster together and was only poorly connected with CDSS depresson symptoms. The Mohr 5 factor model was clearly recognized in the overall clustering of symptoms.

**Conclusion:** This network analysis suggests that depression and anxiety symptoms are the most central in this PNS patient population, despite the baseline low depression scores, and that negative symptoms are a clearly independent symptom cluster that can be delineated from depressive symptoms.

**Keywords: cariprazine, risperidone, schizophrenia, negative symptoms, Positive and Negative Syndrome Scale (PANSS), Calgary Depression Scale for Schizophrenia (CDSS)**

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## INTRODUCTION

Schizophrenia is a severe mental disorder with heterogeneous symptom constellations involving cognitive, behavioral and emotional symptoms but with no single symptom being pathognomonic of the disorder (1, 2). How to best address this heterogeneity or how to best rank the importance of individual symptoms has been cause of much debate and much confusion in the literature, as well regarding the classification systems as regarding the assessment tools. Moreover, many patients with schizophrenia present with comorbid psychiatric symptoms or disorders: an increased prevalence of anxiety, depressive and substance use disorders has been documented (3) and comorbidity results in higher suicidality rates (4). Schizophrenia without psychiatric comorbidity has also been shown to be associated with better overall mental health but also with poorer illness and treatment insight compared to those patients with anxious and depressive disorder comorbidity (5). Depressive symptoms as well as full mood episodes are common in schizophrenia but should be present for only a relatively brief period (hence differentiating schizophrenia from schizoaffective disorder). Depressive symptoms show a modal prevalence of about 25% and they may occur in all phases of schizophrenia (3).

Regarding diagnostic criteria, the 5$^{th}$ edition of the Diagnostic Manual of Mental Disorders (DSM-5), in an attempt to better delineate different symptom clusters in schizophrenia, dropped the subtyping approach and chose for a dimensional approach suggesting a severity rating based on a quantitative assessment of the 5 primary symptom domains of psychosis including delusions, hallucinations, disorganized speech, abnormal psychomotor behavior, and negative symptoms while adding that the assessment of 3 other domains (cognition, depression and mania symptom domains) is also vital (2). The importance of depressive symptoms is therefore explicitly recognized. The understanding of the relation between these different domains is still suboptimal.

Regarding the assessment tools, the original Positive and Negative Syndrome Scale (PANSS) comprised a positive symptom subscore, a negative symptom subscore and a general psychopathology subscore (the latter including items such as guilt feelings, depression, poor attention and motor retardation all referring to standard depressive disorders). Later, **several other dimensional models** (based on factor analysis) of the PANSS have been suggested. The 5-factor structure, which generally includes positive, negative, cognitive/disorganization, depression/anxiety, and excitability/hostility domains, is the basis of most models, including the Lindenmayer, Marder, Mohr and the latest Wallwork models. Although several factor analyses studies have suggested that a 5-factor model captures PANSS structure better than the original PANSS subscales, no single model has achieved broad consensus, and the 3 original subscales are still widely used. In a recent paper, a network analysis illustrated the validity of the Mohr model (6).

Regarding the depressive symptoms in the PANSS, the anhedonia symptom which is a core depressive symptom is remarkably absent in the PANSS and therefore also in the more recently proposed 5-factor models like in the Mohr depression/anxiety factor of the PANSS (which has 5 items: G1 being somatic concern; G2 being anxiety, G3 being guilt feelings, G4 being tension and G6 being depression). A more recently developed depression scale for patients with schizophrenia [the Calgary Depression Rating Scale for Schizophrenia (CDSS) (3, 7, 8)] also omits anhedonia (as well as the psychomotor symptoms retardation/agitation) as depressive symptom. The reason for these omissions could well be their possible overlap with other schizophrenia symptoms: anhedonia can be a depressive symptom or a schizophrenia negative symptom, psychomotor retardation can be a depressive symptom or a schizophrenia negative symptom (withdrawal), psychomotor agitation can be a depressive symptom or a schizophrenia excitement/hostility symptom. On the other hand, suicidality as a depressive symptom is included in the CDSS but absent in the PANSS (8, 9). Again, the link between depressive symptoms and the other schizophrenia symptom domains (especially the positive symptoms, the primary negative symptoms, the cognitive symptoms and the depression/anxiety symptoms) or the differentiation between depressive symptoms and antipsychotic side effects (including dysphoria, akinesia and akathisia) are insufficiently understood (10).

The relation between depressive symptoms and negative symptoms is particularly intriguing. **Negative symptoms** (11) such as blunted affect, alogia, anhedonia, asociality and avolition can indeed be primary or secondary and it is widely believed that most of the currently available treatments are more efficacious on secondary than on primary negative symptoms (12). Secondary negative symptoms can be the consequence of positive symptoms (withdrawing because of persecutory delusions, or withdrawing as a coping strategy when feeling unable to process overwhelming external stimuli associated with psychotic experiences), or of cognitive symptoms (avolition and withdrawal because of impaired executive function or impaired retrieval of information), or of antipsychotic medication (side effects), or of environmental deprivation (social isolation and hospitalization). The negative symptoms can also be secondary of depression or overlapping with depressive symptoms (13). The relation between negative symptoms and depressive symptoms is not fully understood.

Recently, network analyses have been introduced in psychiatry research in an attempt to better understand the relations and interactions between the symptoms of a given psychiatric disorder: here symptoms are seen as a network, or as a system of entities that have connections with each other and that can influence one another (14, 15). It allows for a new conceptualization of mental disorders where symptoms can be ranked according to their centrality (number and strength of connections with the other symptoms of the disorder) and where a visualization of the relations enables to see which symptoms are more or less closely related.

The present paper reports on a centrality network analysis that was performed on the PANSS and the CDSS items in patients with "predominantly negative symptoms" (PNS) of schizophrenia that were enrolled in a double-blind trial with cariprazine or risperidone, where treatment with cariprazine resulted in a greater reduction of negative symptoms that was

statistically significant and clinically meaningful (16). The first aim of the analysis was to better understand the interactions between depressive symptoms and the different symptoms of schizophrenia and to investigate whether negative symptoms and depressive symptoms can be better delineated. The second aim was to investigate whether the validity of the Mohr 5-factor model (re-organizing the PANSS items) can be illustrated in a network analysis.

# MATERIALS AND METHODS

## Participants

The analyses were performed on patient data ($N = 460$) from the 26 week randomized, double-blind trial with long-term (>2year), stable schizophrenia and predominant negative symptoms: i.e. patients needed to be to in a stable condition (i.e., no psychiatric hospital admissions, acute exacerbations, or imprisonments) for at least 6 months before screening and they were required to suffer from predominant negative symptoms for at least 6 months with a PANSS factor score for negative symptoms of 24 or more, and a score of 4 or more on at least two of three core negative PANSS items (blunted affect, passive or apathetic social withdrawal, lack of spontaneity and flow of conversation) at screening and during a lead-in period (17). To ensure that it were not secondary negative symptoms, patients with a PANSS factor score for positive symptoms of more than 19 or with a score or 4 or more on two or more positive PANSS items (delusions, hallucinatory behavior grandiosity, suspiciousness, or unusual thought content) were ineligible as were patients with moderate or severe depressive symptoms (CDSS total score > 6) or patients with clinically relevant parkinsonism (investigator judged or score > 3 on the sum of the first eight items of the Simpson-Angus Scale) (8, 9, 17). In order to maximize the amount of information, all patients with baseline values (even those without post-baseline data) were included in the performed network analyses in both groups. Since only one patient had a CDSS suicidality item score different from 0, this one item was not integrated in the analysis.

## Statistical Analysis

The network structure was estimated for all the items (30 items of the PANSS and 9 items of the CDSS). A network is a representation of a system of nodes that are connected in one way or another (14, 15). In a network analysis edges connect the different nodes. For this study the nodes were the different items of the PANSS and the CDDS and the edges were the partial correlation coefficients between the different items. Therefore, the relationship between items is represented by an edge after controlling for all the other connections in a network. A weighed undirected network was constructed by using the R package *qgraph,* according to the guidance form Epskamp et al. (18) where the strength of the correlation between two items was represented by the thickness of a connecting line. Controlling for false positive edges was done by using the least absolute shrinkage and selection operator (lasso), which was coupled with the extended Bayesian information criterion (EBIC) for model selection,. This causes very small edges to be set to zero, therefore pushing them out of the network estimation. Every item's importance in the network was investigated using three measures, namely node strength (sum of all weighted connections), closeness (the multiplicative inverse of the sum of the length of the shortest paths between all other nodes and the node) and betweenness (number of times a node lies on the shortest path between two other nodes). The results were graphically represented with nodes that have stronger and/or more connections between each other being placed closer together.

Afterwards, node centrality was assessed based on node strength. Node centrality can be used to look at the structural importance of each node in a network (14, 15). Node strength was chosen as it stands for the direct influence of a node on the entire network.

Stability of the network was investigated by using the *bootnet* R package, by creating random subsamples with decreasing size from the whole population.

**TABLE 1 |** Baseline sociodemographic and clinical characteristics of the study population (mean ± SD).

| | |
|---|---|
| Age | 40.5 ± 10.9 |
| Duration of illness | 12.5 ± 8.7 |
| Sex, male/female (%) | 57/43 |
| PANSS-FSPS | 8.7 ± 2.7 |
| PANSS-FSNS | 27.6 ± 2.5 |
| PANSS-GPPFS | 36.2 ± 5.5 |
| CDSS | 0.8 ± 1.3 |

*PANSS-FSPS, PANSS factor score for positive symptoms; PANSS-FSNS, PANSS factor score for negative symptoms; PANSS general psychopathology factor score; CDSS, Calgary Depression Scale for Schizophrenia.*

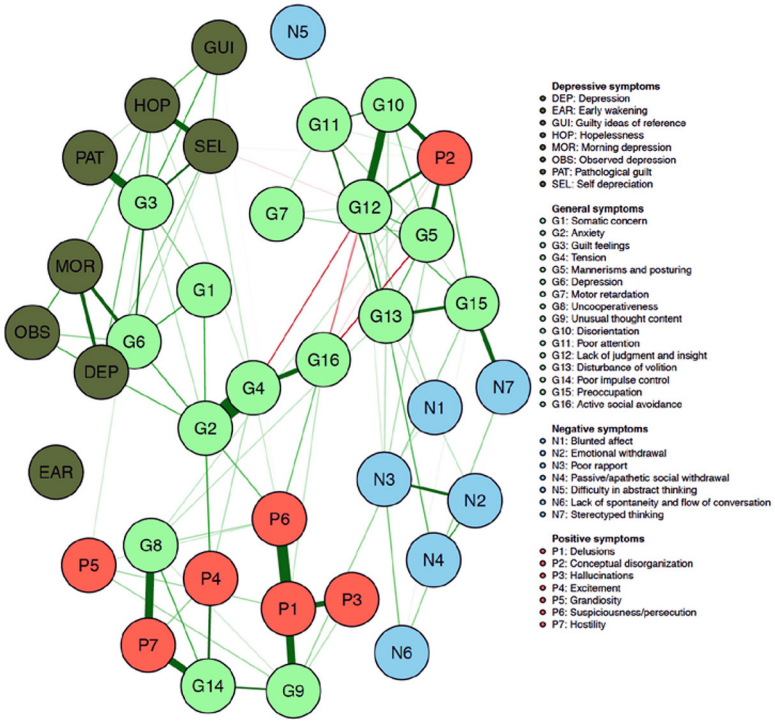
# RESULTS

The baseline clinical and sociodemographic characteristics are given in **Table 1** and describe this patient population with "persistent and predominantly negative symptoms."

**Figure 1** visualizes the results of the network analysis of the individual PANSS and CDSS symptom items, while **Figure 2** quantifies each of their ranking regarding node strength, closeness and betweenness.

The five items with the **largest node strength**, i.e., the items with the most frequent and the most intense connections with all the other CDSS and PANSS symptoms, are **depression (PANSS), depressed mood (CDSS), anxiety, lack of judgment/insight** and **tension**. The five items with the smallest node strength are lack of spontaneity and flow of conversation, motor retardation, blunted affect, difficulty abstract thinking and early wakening. The 5 negative symptoms according to the Mohr model all have a very low node strength: blunted affect (N1) comes in the 36$^{th}$ position.

The original **PANSS negative symptoms** cluster closely together (except N5 –difficulty in abstract thinking) and all are poorly connected with other items and therefore have all a small node strength (ranking: N1 in 36$^{th}$ position, N2 in 25$^{th}$ position, N3 in 23$^{rd}$ position, N4 in 32$^{nd}$ position, N5 in 37$^{th}$ position and N6 in 31$^{st}$ position.



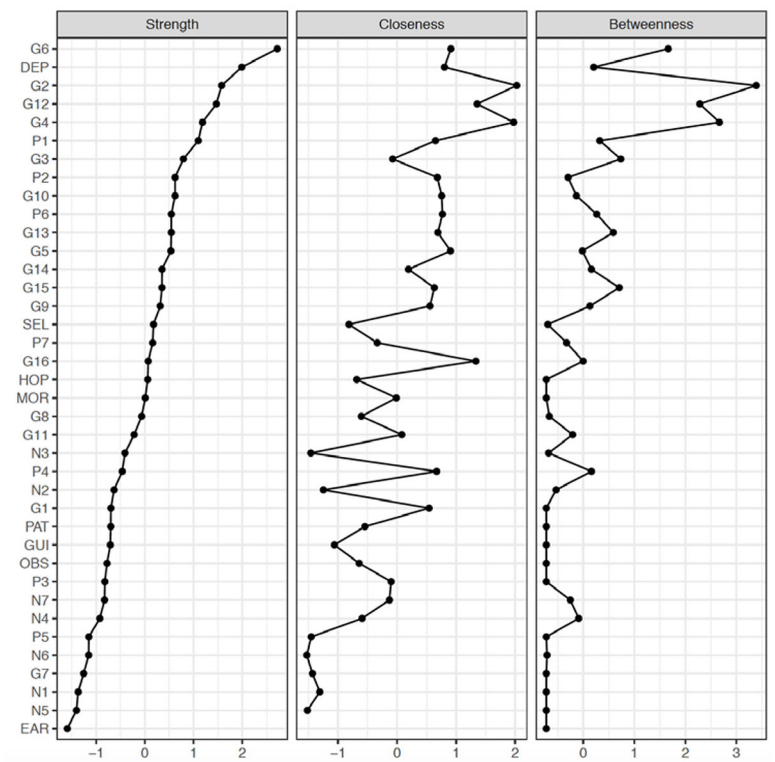




**FIGURE 1 |** Network of PANSS symptoms and CDSS symptoms in patients with persistent and predominant negative symptoms (red, positive symptoms; blue, negative symptoms; pale green, general symptoms; dark green, CDSS symptoms).

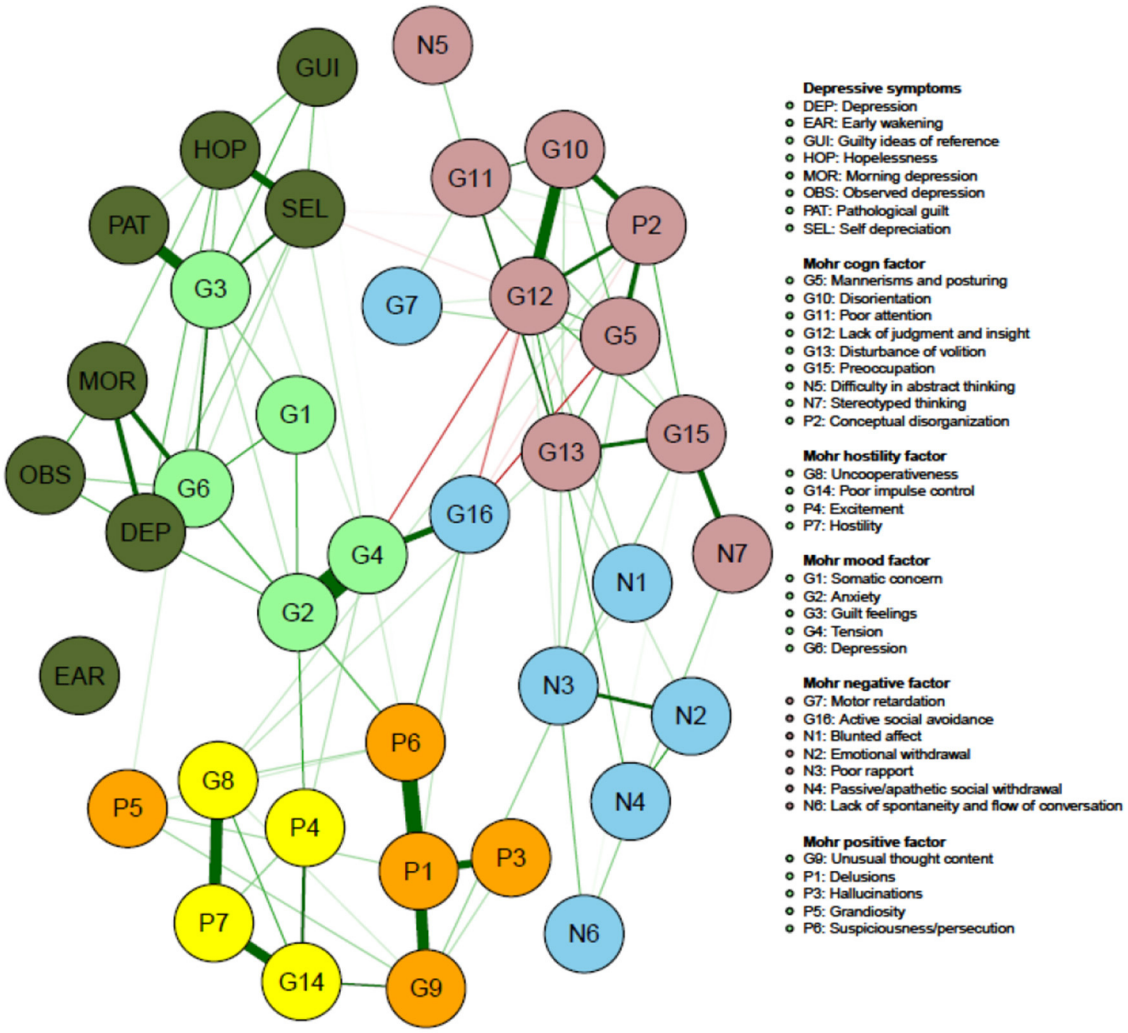



**FIGURE 2 |** Network of PANSS symptoms and CDSS symptoms in patients with persistent and predominant negative symptoms (colors illustrating the Mohr 5-factor model of the PANSS; orange, positive symptom factor; yellow, hostility factor; blue, negative symptom factor; pink, cognitive symptom factor; pale green mood factor; dark green, CDSS symptoms).

**Figure 2** illustrates that the on factor analysis based Mohr 5 factor model of the PANSS is easily recognizable which is a kind of indirect validation.

Node strength is overall low for the **Mohr negative factor** (N1 being blunted affect; N2 being emotional withdrawal; N3 being poor rapport; N4 being passive/apathetic social withdrawal; N6 being lack of spontaneity and flow of conversation; G7 being motor retardation; G16 being active social withdrawal), with G16 having the highest strength in this group (but still only in the 16$^{th}$ position on the ranking).

The **Mohr hostility/excitement symptoms** of the PANSS overall have an intermediate node strength (G8 being uncooperativeness; G14 being poor impulse control; P4 being excitement; P7 being hostility), G14 having the highest strength in this group.

Of the **Mohr positive symptoms**, P1 (delusions), P6 (suspiciousness/persecution) and G9 (unusual thought content) have a larger centrality than P3 (hallucinations) and P5 (grandiosity).

Regarding the **Mohr cognitive factor** (N5 being difficulty in abstract thinking; N7 being stereotyped thinking; G5 being mannerisms and posturing; G10 being disorientation; G11 being poor attention; G 12 being lack of judgment and insight; G 13 being disturbance of volition; G15 being preoccupation and P2 being conceptual disorganization), N5 and N7 show the lowest node strength.

Four (G2, G3, G4, G6) out of five items (G1 being somatic concern; G2 being anxiety; G3 being guilt feelings; G4 being tension; G6 being depression) of the **Mohr mood factor** show high node strength, with G6 showing the highest overall node strength.

## DISCUSSION

An important finding of this network analysis is that four of the five items with the highest node strength were anxiety and depressive symptoms, which suggests that these had the most and the strongest connection with all the other symptoms. This is remarkable since this analysis was performed in a population of patients with schizophrenia with low baseline depression scores. This finding suggests that clinicians should probably, at least in a population with predominant negative symptoms, pay more attention to these symptoms and not only focus on the more socially disturbing positive symptoms and the more functionally impairing negative symptoms. It is hence understandable that the World Federation of Societies of Biological Psychiatry considers a "regular assessment of depressive symptoms" as mandatory for Good Clinical Practice (10). Depression indeed influences overall quality of life and life satisfaction. Moreover, subjective recovery in patients with schizophrenia is to a larger extend predicted by negative (depressive and anxious) emotion, self-esteem and hopelessness than by PANSS symptoms or by functioning (19). Depression is also related to suicidality: the lifetime risk of suicide and suicide attempt is patients with schizophrenia are 5 and 25–50%, respectively. A meta-analysis showed that amongst other variables depressive symptoms are higher in patients with suicide ideation, and that history of depression and depressive symptoms are associated with suicide attempts and that hopelessness is associated with suicide (20).

When looking at the negative symptoms, all except one (N5 difficulty in abstract thinking) cluster together and are poorly connected with other symptoms (apart from N7 stereotyped thinking and G15 preoccupation, which can be all be considered as cognitive symptoms). In a population with predominantly negative symptoms, the negative symptoms appear to be well distinguishable from depressive symptoms.

This partially contradicts previously published data suggesting that depressive and negative symptoms considerably overlap and that it is hence difficult to differentiate between both (21). The association between negative symptoms and depressive symptoms has not been sufficiently investigated and results are inconsistent (22). It should be remembered that in patients with schizophrenia negative symptoms can be primary or secondary and while in our selected population the negative symptoms are primary (6). This problem of differentiation between negative symptoms and depressive symptoms was already suggested in DSM-IV where it was stated that negative symptoms are difficult to evaluate and that a more phenomenological understanding can be helpful: depressive symptoms are considered to be associated with intense painful affect while negative symptoms are associated with diminution of affect and emptiness (23). Other studies suggested that low mood, suicidal ideation and pessimism have more specificity for depression while alogia and blunted affect may have more specificity as negative symptoms and while anhedonia, anergia and avolition may be common to both (24). Along the same lines, it has also been suggested that blunted affect (in the sense of inappropriate affect is a symptom of schizophrenia while decreased sponteaneous movements are regarded as unspecific and more relevant to the assessment of depression (11). As it has been suggested that anticipatory anhedonia is present in depression while consummatory anhedonia is present as well in depression as in schizophrenia (11). Another approach to differentiate is comparing depressive symptoms in depression with depressive symptoms in schizophrenia: it has been suggested that sleep disturbances and guilty ideas of reference are more typical for depression in patients with schizophrenia (25). The presently investigated patient population (stabilized with predominant negative symptoms, and without depression) makes it probably easier to differentiate between negative symptoms and depressive symptoms: one could assume that in other populations, the differentiation between primary negative symptoms and secondary negative symptoms (e.g., secondary to depression) could be more difficult and that a network analysis could well show a different constellation in a population with acute exacerbation of schizophrenia.

Another key question is of course whether the assessment of depressive and negative symptoms with the CDSS and with the PANSS depression/anxiety subscale are satisfactory. Anhedonia/lack of positive affect is a core depressive symptom and a core negative symptom despite being completely absent in the CDSS and in the PANSS. Indeed, anhedonia is indeed probably the most specific depressive symptom, i.e., best differentiating between depression and other psychopathological states (including amongst others somatic complaints, anxiety, paranoia, schizophrenia, borderline features, etc. ….) (26). In a medically ill population, anhedonia was also shown to be the best screening symptom for depression, better than depressed mood or than fatigue (27). Anhedonia is also one of the five key constructs in negative symptoms (together with blunted affect, alogia, avolition and asociality) (13). The fact that anhedonia is absent in the CDSS and in the PANSS could well be because the authors found it difficult to disentangle the anhedonia as a depressive symptom and the anhedonia as a negative symptom. Addington indeed wrote that the "CDSS was meant to have only a single dimension with less sensitivity to overlap with other schizophrenia symptom dimensions" (8). Anhedonia indeed is a complex phenomenon including anticipatory and consummatory as well as sensory and social aspects. While in depression all aspects of the hedonic tone are impaired, the situation is more complex in schizophrenia where two anhedonia paradoxes have been described (28). The first is that schizophrenia patients seem to have a normal consummatory hedonic tone (liking, taking pleasure) while having an impaired anticipatory hedonic tone (wanting, seeking for, looking for); the second is that in contrast to patients with schizophrenia where the consummatory hedonic tone is normal, patients with prodromal phases or with schizotypy have an impaired hedonic tone (28). Since anhedonia is a core depressive symptom as well as a core negative symptom and since anhedonia seems to be intimately linked to suicidality, the complexity of the phenomenon should of course not result in deleting anhedonia from the assessment tools that are used in schizophrenia. It is therefore welcomed that newer scales like The Brief Negative Symptom Scale (BNSS) or the Clinical Assessment Interview

for Negative symptoms (CAINS) do assess anhedonia and pleasure (29, 30).

Another important finding is that the network analysis, including both the PANSS and the CDSS items, clearly confirms the Mohr 5-factor model of the PANSS: the negative symptom factor, the hostility/excitement factor, the positive symptom factor, the cognitive factor and the mood factor are visually easily recognizable (7). This confirms a recently published study where this structure was also easily recognizable in both an acute patient population and in a population with predominant negative symptoms (6).

In conclusion, the present network analysis suggests that depressive symptoms (assessed with the CDSS or with the anxiety-depression subscale of the PANSS) and anxious symptoms (assessed with the anxiety-depression subscale of the PANSS) are the most central symptoms and that they are only poorly associated with negative symptoms in this population and hence are well distinguishable. Moreover, our network analysis shows clusters of symptoms that clearly support the Mohr 5 factor model. In the investigated population of stabilized patients with predominant negative symptoms depression (both assessed with CDSS and PANSS), anxiety, lack of judgment and insight and tension are the most central symptoms, suggesting that these symptoms should clinically well be taken into account.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The clinical study protocol was approved by nine central and 37 local independent Ethics Committees in relation to the 66 sites that recruited at least one patient; the study was done in accordance with good clinical practice guidelines and the principles of the International Conference on Harmonization. All patients provided written informed consent. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

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

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.795866/full#supplementary-material

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# Cariprazine's Potential in Improving Social Dysfunction in Patients With Schizophrenia: A Perspective

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Social dysfunction is one of the most debilitating aspects of schizophrenia. Treatment of this complex phenomenon, constituted by negative, cognitive, and affective symptoms, has been difficult with the available pharmacological agents, hence it represents an unmet medical need. Cariprazine, a novel, third-generation antipsychotic with a unique mechanism of action has been proven to sufficiently alleviate negative, cognitive, and affective symptoms of schizophrenia. These characteristics make this compound a valid candidate for addressing social dysfunction too. In this perspective, we argue that cariprazine can be viewed as a "socializing drug" that has the ability to improve the patient's functionality and ultimately their quality of life. Data from animal research, clinical trials, an observational study, and patient cases are provided.

**Keywords: schizophrenia, cariprazine, antipsychotic, social dysfunction, $D_3$ receptors**

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## INTRODUCTION

Schizophrenia is a chronic mental disorder, affecting about 1% of the population worldwide (1). First described by Eugen Bleuer (2), it is characterized by three main symptom domains: positive symptoms such as hallucinations and delusions, negative symptoms including anhedonia and blunted affect (3), as well as cognitive symptoms like deficits in executive functioning and memory problems (4). In his original concept, Bleuer also included autism as one of the main symptoms of schizophrenia (2), thus emphasizing the high prevalence of social dysfunction in the disorder, as well as its importance in determining the level of disability in everyday functioning (5). Indeed, schizophrenia is one of the most debilitating disorders with high burden of disease, which translates into around 13.4 million years lived with disability (YLDs), which is equivalent to 1.7% of total YLDs (6). Even though the advent of antipsychotic medications brought improvement in the management of schizophrenia, poor social functioning still represents an unmet medical need (7). Cariprazine, a novel, third generation antipsychotic drug might be able to bring change to this notion as it has a unique mechanism of action compared to the other medications (8).

In this perspective, we argue that cariprazine can be viewed as a "socializing drug" in the treatment of schizophrenia. To prove this, first, we provide an overview of the characteristics, impact, and background of social dysfunction in schizophrenia and then highlight data from clinical trials and real-life experiences that show cariprazine's potential to improve this aspect of the disorder.

## SOCIAL DYSFUNCTION IN SCHIZOPHRENIA

Social dysfunction is a complex phenomenon that affects many different aspects of the lives of the patients including social interactions, everyday activities, and employment status (9). It has already been described as a core feature of schizophrenia in one of the earliest descriptions of the disorder, Dementia Praecox, by Kraepelin (10, 11). Social dysfunction is part of the class description of Schizophrenia Spectrum and Other Psychotic Disorders in the Diagnostic and Statistical Manual 5th Edition as well, which describes it as "For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset" (12).

Research has shown that social dysfunction is primarily, but not exclusively, related to cognitive impairments of schizophrenia (9). Indeed, among the eight separable domains of cognitive impairment identified by the NIMH-Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consensus one is deficits in social cognition, which is defined as the inability to construct representations of self, others, and interpersonal interactions (13, 14). Such disturbances in social cognition compromises everyday functioning by impairing the mental operations that underlie social behavior such as being able to understand and interpret another person's emotions and intentions (15). A meta-analysis by Fett and colleagues found social cognition to be strongly associated with community functioning e.g., independent living skills or work functioning (15).

In addition to cognitive symptoms, negative symptoms have also been reported to be involved in social dysfunction in schizophrenia (16). According to a consensus, negative symptoms are comprised of five constructs: blunted affect, alogia, anhedonia, asociality and avolition (3, 17). Asociality, defined as reduction in social initiative due to decreased interest in forming close relationships with others, contributes greatly to social dysfunction in schizophrenia (17, 18). Furthermore, avolition, the reduced initiation and persistence of goal-directed activity has also been implicated as important factor in social functioning (17, 18). To give an example, in a study involving 149 patients with schizophrenia and 143 healthy controls, the severity of avolition in patients predicted the proportion of time they spent in structured and unstructured social contexts (18).

## THE IMPACT OF SOCIAL DYSFUNCTION ON EVERYDAY FUNCTIONING

Social dysfunction is often labeled as one of the most debilitating characteristics of schizophrenia as it has a profound effect on both everyday functioning and quality of life (15, 19). It impacts education, functioning in the work environment, conduction of activities such as shopping, interpersonal relationships as well as living circumstances. For instance, findings of a study conducted in the USA reported only 18% of patients with schizophrenia to live independently (20). Similarly, another study in Singapore found 79% of patients to live with family or spouse, and reported that the percentage of patients living independently increased with age (21).

Regarding employment, about 10% of working-age patients with schizophrenia are employed in contrast to the general population, where employment rate is around 68% in the 20–29-year-old age group and 84% in the 40–49-year-old age group (22, 23). This is highly related to time of onset as well, as those who receive their diagnosis between ages 15 and 25 are more likely to be unemployed (24). Interestingly, there are indirect effects of schizophrenia on employment and education as well; children whose parents are diagnosed with schizophrenia were found we have higher odds of not graduating from primary education (25).

Another study examining the degree of dysfunction in different daily activities in people with schizophrenia found that handling medications, shopping, preparing food as well as handling finances and doing the laundry is highly difficult for patients to execute (26). In fact, only 2% of the study sample were completely independent in their daily activities (26).

Finally, in an Australian national survey involving almost two thousand patients, loneliness was reported by 80% of those affected by psychosis (27). In addition, loneliness was also identified as one of the major challenges that hinders recovery (27, 28). Importantly, loneliness is a risk factor for poorer overall cognitive performance and faster cognitive decline as well (29).

## BACKGROUND OF SOCIAL DYSFUNCTION IN SCHIZOPHRENIA

Impaired functioning of the so-called social brain i.e., brain regions that are known to be involved in social cognition, has been described in schizophrenia patients repeatedly (30). These include changed activation of the medial and inferior prefrontal cortex as well as the hypo-activation of the amygdala (30). In addition, abnormal activity in the mirror neuron system, an important neuronal function responsible for understanding the intentions of others, has also been reported in patients with schizophrenia (31).

Besides these brain regions, neurotransmitters such as dopamine and serotonin have also been investigated to understand the potential mechanisms behind social dysfunction. Regarding the dopaminergic system, the role of $D_2$ and $D_3$ receptors are of particular interest given the fact that alterations in dopamine levels are regarded as a core aspect of schizophrenia (32). Indeed, $D_3$ receptors agonism was reported to impair some aspects of cognitive function including social recognition and executive function, while antagonism is suggested to enhance cognition through inducing changes in the prefrontal cortex and hippocampus (33).

In terms of the serotonergic system, aggression and impulsive behavior (key determinants of social dysfunction) have been repeatedly associated with reduced serotonergic function (34). Evidence from Non-human primates indicate that the pharmacological reduction of serotonin promotes aggressive

behavior while the blockade of serotonin reuptake has the opposite effect (34). This has been reported in a double-blind cross-over human study as well, where the effect of a selective serotonin reuptake inhibitor was investigated in chronically violent patients with schizophrenia (35). In fact, the results showed significant reduction in the frequency of aggressive actions without deterioration of mental state (35).

## DIFFICULTIES OF IMPROVING SOCIAL DYSFUNCTION IN SCHIZOPHRENIA

Although antipsychotics, the first-line treatment for schizophrenia, are able to reduce some symptoms of the disorder, evidence regarding their effect on social dysfunction is rather limited and inconclusive (36). This also stems from the fact that there is considerable heterogeneity in how social dysfunction is defined and measured, as well as that many of the studies are neither adequately powered nor randomized (36).

### First-Generation Antipsychotics

First-generation or typical antipsychotics (FGAs) such as haloperidol are dopamine antagonists that induce considerable side effects including extrapyramidal motor symptoms (EPS) and tardive dyskinesia (TD) (37). Effects of FGAs on social dysfunction are mixed. Some studies found significant improvement in facial affect recognition in patients treated with FGAs (38, 39), while others could not report any positive change (40). Furthermore, a study conducted in 2021 reported an association between antipsychotic-induced EPS and social cognition in patients with schizophrenia, with those affected by EPS scoring worse on the different social cognition measures (37). The study also highlighted that about half of the patients treated with FGAs experienced EPS, while this number was 25% in patients treated with second-generation antipsychotics (SGAs) (37).

### Second-Generation Antipsychotics

In contrast to FGAs, SGAs or atypical antipsychotics such as risperidone are not only dopamine but serotonin antagonists as well and exhibit high affinity for $5HT_{2A}$ receptors (37). Given these properties many argued that SGAs may have a positive impact on social functioning (38, 39). In addition, such agents have lower incidents of EPS-like symptoms, however other adverse effects like weight gain is common (40, 41).

Although several studies assessed the effect of SGAs on different aspects of social dysfunction, positive outcomes were rather scarce (36). For instance, Bellack and colleagues compared risperidone and clozapine in terms of their ability to improve social skills after 16–29-week treatment and while improvement in general symptomatology was detected, no significant impact on social competence was found (42). Similarly, two randomized studies investigating risperidone, quetiapine and olanzapine draw the conclusion that SGAs are unable to significantly improve social cognition (43, 44). Importantly, the Clinical Antipsychotic Trials for Intervention Effectiveness (CATIE) trial, also failed to detect significant improvement in emotion perception after 2 months of treatment with SGAs (45).

In contrast to the previous results however, Fakra et al. found risperidone to be superior in a facial affect discrimination task in comparison with an FGA, haloperidol, after 4 weeks (46). Animal studies also reported similar results; clozapine was able to attenuate reduction of social behavior in mice whereas haloperidol failed to do so (47).

### Third-Generation Antipsychotics

Third-generation antipsychotics (TGAs), the newest additions to the antipsychotic class, are characterized by dopamine partial agonism as well as antagonism / weak partial agonism at the $5HT_{2A}$ receptors (48, 49). Currently there are three approved TGAs, namely aripiprazole, brexpiprazole and cariprazine, often named as the "ABC" drugs (49, 50). Given that these antipsychotics also act on the dopamine $D_3$ receptors, which have an important role in cognitive functioning (33), reward and motivation (51), and emotional regulation (52), they are thought to improve not only social dysfunction but negative and affective symptoms of schizophrenia too (53, 54).

Aripiprazole for instance, was found to improve social anxiety in an open-label trial, however the patient number was too small to draw conclusions regarding its efficacy in social dysfunction (55). Regarding brexpiprazole, no study on social dysfunction involving patients with schizophrenia has been conducted, only one animal research was found where dizocilpine-induced social recognition deficits in mice were improved with brexpiprazole treatment (56). As the focus of this perspective is cariprazine, the next section will focus on the available evidence on the role of cariprazine in addressing social dysfunction in schizophrenia.

## CARIPRAZINE, A "SOCIALIZING DRUG" IN THE TREATMENT OF SCHIZOPHRENIA

As mentioned before, cariprazine is a dopamine $D_3/D_2$ and serotonin $5HT_{1A}$ partial agonist and serotonin $5HT_{2A}$ antagonist (8). It has a different mechanism of action compared to the other TGAs, as it has the highest affinity for dopamine $D_3$ receptors as well as acts at the $5HT_{1A}$, $5HT_{2A}$, and $\alpha_{1B}$ receptors too (8, 54). The weakest affinity for the latter is believed to be related to why cariprazine does not induce sedation and hypotension, side effects that commonly bother patients (54). Importantly, the unique $D_3$ affinity combined with the action on the different 5HT receptors make cariprazine a potential candidate for addressing those symptoms of schizophrenia that could not be alleviated by previous antipsychotics and therefore were regarded as unmet medical needs.

Cariprazine is currently approved by the Food and Drug Administration (FDA) and European Medicine Agency (EMA) for the treatment of schizophrenia in adults (1.5–6.0 mg/day). In addition, it is approved for the treatment of depressive, acute manic, or mixed episodes associated with bipolar I disorder (3.0–6.0 mg/day) also by the FDA. Furthermore, two Phase III clinical trials found positive results for the adjunctive treatment of major depressive disorder (MDD) with cariprazine[1]. In terms of the schizophrenia indication, the efficacy of cariprazine was demonstrated in three randomized, placebo-controlled Phase

[1]https://www.gedeonrichter.com/en/news/211029

II/III clinical trials with patients who had acute exacerbation of schizophrenia (57–59).

## Evidence From Animal and Clinical Trials

In a double-blind, randomized comparative trial cariprazine was found to be superior in treating predominant negative symptoms as measured by the Positive and Negative Syndrome Scale Factor Score for Negative Symptoms (PANSS-FSNS) in patients with schizophrenia compared to an SGA, risperidone (60). Importantly, the results of this trial were repeated in a 16-week, open-label, flexible-dose observational study with 116 schizophrenia patients who also exhibited predominant negative symptoms (61). As there is a strong link between negative symptoms and social dysfunction, these results suggest that cariprazine shows some capacity to sufficiently address social symptoms too.

Indeed, when looking at the Prosocial Functioning Factor that includes the PANSS items N2, N4, N7, P3, P6 and C16 in the above-mentioned trial by Németh and colleagues, change from baseline to week 26 is significantly better with cariprazine than with risperidone (62). Furthermore, a *post-hoc* analysis of one of the Phase III, placebo-controlled studies revealed statistically significant change from baseline to week 6 in the same factor as well (63).

In addition to these results, the Németh study also measured functionality using the Personal and Social Performance (PSP) scale and found that cariprazine significantly improved this aspect from week 10 onwards, again compared to risperidone (60). Importantly, this result was driven by all three relevant subdomains of the PSP scale (60). Finally, in animal research only cariprazine was found to be effective in the social play paradigm when compared to other SGAs (64).

## Evidence From Real-World Experience

Although case reports are not regarded as the highest quality of evidence, they provide personal and specific insight to the effects of a medication (65). In terms of social dysfunction, such descriptions can shed light on the actual impact a drug can induce in real life settings (65). Despite cariprazine is a relatively new antipsychotic on the market, several cases have already been published.

For instance, in a case by Di Sciascio & Palumbo a 22-year-old woman with disorganized schizophrenia was found to improve after switching to cariprazine from olanzapine; she was able to relate to other people again and returned to work (66). Similarly, Halaris & Wuest reported that after a 37-year-old man with a history of chronic psychosis switched to cariprazine he did not only lost a lot of weight spontaneously but also regained his motivation to have a career and live independently. As a result, he started education again and passed the exams successfully (67). Such results were also found in a young female patient suffering from early-onset schizophrenia described by Molnar and colleagues (68). According to their report, the patient was initially socially active but then at the age of 15 she became irritated and physically hostile which ultimately resulted the termination of her studies (68). Soon after cariprazine treatment was initiated, significant improvement in symptoms was observed including starting to participate in the family's daily life (68).

## Safety and Tolerability of Cariprazine

Although the safety and tolerability of an antipsychotic medication is not directly related to how effective it is, they are still important aspects that have indirect impact on the overall outcome. Indeed, as mentioned before, EPS was found to negatively influence social cognition (69). Furthermore, metabolic syndrome, another common side effect of antipsychotic medications, especially SGAs, was found to influence social cognitive performance in patients with schizophrenia (70).

In terms of safety, cariprazine is a safe and generally well tolerated compound (71). The most commonly reported adverse events, according to the pooled analysis of the eight clinical trials with schizophrenia patients, were akathisia, insomnia and headache (71). Importantly, most akathisia was mild or moderate and hence the vast majority of patients remained on treatment (71). In terms of metabolic syndrome, several aspects were measured in the clinical trials including total cholesterol, high-density lipoprotein cholesterol, fasting triglycerides, fasting glucose, weight and body mass index (BMI) (71). Overall, the mean increase from baseline was 1 kg and in general cariprazine was found to be metabolically neutral (71).

# CONCLUSIONS

The present perspective aimed at providing an overview of social dysfunction in schizophrenia, its treatment via different generation of antipsychotics and the role of cariprazine in improving such symptoms of the disorder. We argue that based on the reviewed evidence, cariprazine, a potent $D_3$ partial agonist can be regarded as a "socializing drug" given its efficacy in treating negative, cognitive, and affective symptoms that has been proven in animal research, clinical trials, an observational study, as well as in individual cases. We understand that the reviewed evidence is limited in a sense that no study has been conducted to specifically measure the efficacy of cariprazine in improving social dysfunction and hence encourage further research to investigate this aspect in a meaningful design.

# DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

# AUTHOR CONTRIBUTIONS

PM, RB, and YB conceptualized the perspective. PM prepared the first draft which was reviewed by RB and YB. All authors contributed to the article and approved the submitted version.

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# Cariprazine Use in Combination With a Mood Stabilizer in First Episode Mania

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**Background:** Cariprazine's efficacy and safety have been previously tested in adult patients with acute mania associated with bipolar I disorder, but there is no available data in FEM. The objective of this study is to assess the efficacy and safety of cariprazine in combination with a mood stabilizer in treating FEM as well as to evaluate patients' adherence to the treatment.

**Methods:** FEM patients were recruited from the acute inpatient unit at Lleida University Hospital Santa Maria, between January and June 2021. Their symptoms were evaluated using the Young Mania Rating Scale (YMRS) and the Clinical Global Impressions–Severity (CGI-S) scale at admission and at discharge. Akathisia was assessed using the Barnes Akathisia Rating Scale. Patient adherence to medication treatment was assessed 30 days after discharge using the Morisky, Green and Levine Medication Adherence Scale. Socio-demographic and clinical information were further collected.

**Results:** Eleven patients with FEM were involved, seven women and four men. Their mean age was 26.00+/-6.37 years. Mean hospitalization was 17.36+/−4.7 days. Cariprazine was combined with a mood stabilizer: lithium in seven patients and divalproex in four. Mean YMRS change from baseline was −24.55+/−7.5 and the mean CGI-S change from baseline was −2.55+/−0.82. Regarding adverse events, two (18.2%) patients presented with akathisia. At the 30-day treatment-adherence assessment, six (54.5%) patients were adherent and four (36.4%) had moderate adherence.

**Conclusion:** In this sample, cariprazine in combination with mood stabilizers proved to be safe and effective in the treatment of FEM with more than half the patients being adherent to treatment. Therefore, cariprazine add-on is a good choice for promoting the long-term adherence of patients, thus minimizing the risk of relapse and improving prognosis.

**Keywords: first episode mania, cariprazine, bipolar disoder, acute mania, presicion medicine, treatment adherence**

## INTRODUCTION

Bipolar disorder (BD) is a chronic and disabling mental disorder, characterized by recurrent mood episodes of depression, mania, hypomania and mixed affective states with periods of full or partial remission (1). It is associated with high burden of disease and psychosocial dysfunction, affecting more than 1% of the general population (2). Mania is the most recognizable phase of the disorder, and its presence is key for diagnosis (2). Its characteristic symptoms include, among others, grandiosity, reduced need for sleep, distractibility, increased flight of ideas, impulsivity, and occasionally, it is further accompanied by psychotic symptoms (3). Mania has been associated with impaired psychosocial functioning and cognition (4), and patients sometimes require hospitalization in order to stabilize their psychopathological condition (5).

Given the recurring nature of the disorder, the emphasis of treatment is not only on the resolution of acute symptoms, but also on the assurance of long-term prophylaxis of mood episodes (6). Therefore, treatment by a multidisciplinary team is recommended, combining psychological and pharmacological treatment options (7). Regarding the treatment of manic episodes, the main objectives are the resolution of acute manic symptoms, behavioural and cognitive symptoms as well as psychotic symptoms, if present (6). Clinical guidelines for the pharmacological treatment of acute mania offer recommendations based on evidence, safety, and tolerability (8). One of the most recently published ones is *The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders* (6) which recommends oral monotherapy, if possible, with aripiprazole, asenapine, risperidone, quetiapine or cariprazine. If monotherapy is insufficient, second-generation antipsychotics can be combined with a mood-stabilizing agent: lithium or valproate (6). Lithium is considered to be the gold standard for the maintenance treatment of BD; however, its onset of action is slower than that of antipsychotics in the treatment of acute mania (9). Therefore, many clinicians combine lithium or other mood stabilizers with an atypical antipsychotic in order to treat the manic phase of BD. In fact, a combination therapy is recommended as first-line treatment option with greater efficacy than monotherapy with lithium or divalproex alone [Ogawa et al. (10); Pacchiarotti et al. (8)]. This latter treatment approach was applied for the purposes of the present study in first-episode mania (FEM) patients.

For FEM patients, medication adherence is an important aspect to consider, as it impacts on the efficacy of pharmacotherapy and therefore later disease-outcome (11). Thus, treatment should be initiated with cautious use of medications and slow titration, as early experiences of tolerability and side-effects prime later expectations and subsequent adherence, especially in FEM (12).

Cariprazine is a dopamine D2–D3 partial agonist with high affinity to D3 receptors. It is approved for the treatment of schizophrenia and the depressive and manic/mixed episodes associated with bipolar I disorder by the Food and Drug Administration, and it has shown efficacy as adjunctive treatment for major depressive disorder (13). It binds with high affinity to dopamine D2 and D3 receptors and to serotonin 5HT1A and 5HT2B receptors and with moderate affinity to serotonin 5HT2A receptors (14). A distinctive characteristic of cariprazine is that it has the highest affinity for D3 receptors among other antipsychotics; in fact, it is greater than that of dopamine itself (14). This makes cariprazine the only antipsychotic that can occupy the D3 receptors in the presence of dopamine in the living brain (15). Three short-term clinical trials have confirmed the efficacy of cariprazine over placebo (16–18), and a long-term (19) clinical trial confirmed the safety and tolerability of cariprazine in patients with bipolar I mania. The dose range in mania is 3–6 mg/day (20) with treatment-emergent affective switches reported with very low doses (21). Based on cariprazine's good tolerability and safety profile, it could not only treat mania effectively, but also improve treatment-adherence, therefore improving long-term outcomes of patients with FEM (22).

Although clinical trials are the gold standard of clinical research, they have some disadvantages, including that the data is not generalisable, as there are marked differences between patients involved in clinical trials and those seen in real-world settings (23). For instance, patients enrolled in trials are carefully screened using rigorous criteria, and comorbidities and adjunctive medications are highly controlled – all these aspects do not seem feasible in clinical practice (24). Therefore, it is important to supplement the knowledge gained from clinical trials with data gained from real-world evidence, such as electronic health and medical records, electronic devices and applications, case series or observational and naturalistic studies (25).

The objective of this study is to assess cariprazine's efficacy and safety in combination with mood stabilizers in treating FEM as well as patients' adherence to the treatment.

## METHODS

This study is an observational study including patients over the age of 18 with a diagnosis of FEM where the medical decision was taken to initiate cariprazine treatment before the start of the study. Patients were recruited from the acute inpatient unit at Santa Maria University Hospital (Lleida, Spain) between January and June 2021. Diagnosis was based on the clinical assessment of the presentation at first inpatient hospitalization, following the DSM-5 A-D criteria for a manic episode (3).

Patients with a Young Mania Rating Scale (YMRS) (26) [Spanish version (27)] total score $\geq$ 18 at admission were included. Exclusion criteria included the presence of mixed symptoms, previous manic or psychotic episodes; mental intellectual disability; previous antipsychotic-use; and manic episode attributable to the physiological effects of substances or other medical conditions.

All patients were treated with cariprazine flexible doses (3–6 mg/day) in combination with a mood stabilizer: lithium (800–1,200 mg/day) or divalproex (1,000–1500 mg/day). Following the local recommendations for inpatients with severe mania (8), in addition to the antipsychotic treatment, a mood stabilizer

was introduced in all cases. No specific timing of the start of the mood stabilizer is provided by the guidelines, but authors chose to start it on day 2 of cariprazine treatment, as it is the usual practice in their hospital. Treatment with both medications were maintained.

Socio-demographic and clinical information were collected. Patients were evaluated using YMRS and Clinical Global Impressions-Severity of Illness (CGI-S) scales at admission and discharge. Response (≥50% reduction in YMRS score at discharge) and remission (YMRS score ≤12 at discharge) were further assessed, using conventional cut-off criteria (28).

Based on previous safety studies of cariprazine (19, 29), the development of akathisia was measured using the Barnes Akathisia Rating Scale (BARS) (30). Further safety assessment included the evaluation of insomnia, headache and suicidality using a clinical interview conducted by the treating psychiatrist. Clinical laboratory tests conducted at baseline and discharge evaluated prolactin and metabolic (total cholesterol, LDL, HDL, triglycerides, and fasting glucose) changes, in line with common clinical practice for therapeutic monitoring (31).

Patient adherence to medication treatment was assessed 30 days after discharge using the Morisky Green Levine Medication Adherence Scale (MGLS) (32). Patients were categorized as: MGL = 0–1 representing low adherence, MGL = 2–3 representing moderate adherence, and MGL = 4 representing high adherence.

Descriptive statistics were calculated for the demographic and safety data. For evaluating the change on the YMRS and CGI-S measures, the related-samples Wilcoxon Signed Rank Test was conducted.

The study was carried out following the latest version of the Declaration of Helsinki, and the local ethics committee approved the study (CEIC-2341).

**TABLE 1 |** Summary of patient characteristics.

| | |
|---|---|
| **Total patients**, *N* | 11 |
| **Male**, *n* (%) | 4 (36.4) |
| **Female**, *n* (%) | 7 (63.6) |
| **Age, *n* (%)** | |
| 0–19 years | 1 (9.1) |
| 20–25 years | 5 (45.5) |
| 26–30 years | 2 (18.2) |
| 31–36 years | 3 (27.3) |
| **Duration of hospitalization, *n* (%)** | |
| 0–9 days | 0 (0) |
| 10–15 days | 4 (36.4) |
| 16–20 days | 3 (27.3) |
| 21–25 days | 4 (36.4) |
| **Cariprazine dose***, *n* (%) | |
| 3.0 mg/day | 3 (27.3) |
| 4.5 mg/day | 4 (36.4) |
| 6.0 mg/day | 4 (36.4) |
| **Concomitant mood stabilizers and their dose, *n* (%)** | |
| *Lithium* | *7 (63.6)* |
| - 800 mg/day | 1 (9.1) |
| - 1,000 mg/day | 2 (18.2) |
| - 1,200 mg/day | 4 (36.4) |
| *Divalproex* | *4 (36.4)* |
| - 1,000 mg/day | 3 (27.3) |
| - 1,500 mg/day | 1 (9.1) |
| **Psychiatric comorbid conditions, *n* (%)** | |
| PTSD | 1 (9.1) |
| ADHD | 1 (9.1) |
| SUD | 4 (36.4) |
| **DSM-5 criteria, *n* (%)** | |
| Bipolar I disorder, current or most recent episode manic with psychotic features | 8 (72.7) |
| Bipolar I disorder, current or most recent episode manic without psychotic features | 3 (27.3) |

*PTSD, post-traumatic stress disorder; ADHD, attention-deficit/hyperactivity disorder; SUD, substance use disorder.*
**Dose at discharge.*

## RESULTS

For a summary of patient characteristics, refer to **Table 1**. Seven women and four males with FEM were included in the study ($N = 11$) with a mean age of 26 +/−6.37 years. Mean hospitalization for the observed episode was 17.36 +/−4.7 days. Mean cariprazine dose was 4.64 mg +/−1.25 mg/day, administered once daily in the morning. Lithium carbonate was given to seven patients with a mean dose of 1085.71 +/−157.36, and divalproex sodium to four patients with a mean dose of 1,125 +/−250 mg/day. Regarding psychiatric comorbid conditions, one patient had attention-deficit hyperactivity disorder, one had post-traumatic stress disorder and four had substance use disorder.

The mean YMRS score was 35.55 +/−7.79 at admission and 11 +/−2.19 at discharge, $p = 0.003$, change from baseline was −24.55 +/−7.5 (**Figure 1**). All patients achieved a clinically significant response (≥50% reduction in YMRS score at discharge). Eight (72.7%) patients achieved clinically significant remission (YMRS ≤12) and three (27.3%) patients showed minimal symptoms at the end of the hospitalization (YMRS = 13–19). Those with minimal symptoms at discharge showed psychotic symptoms at admission; had larger duration of untreated mania; and received the highest dose of cariprazine (6 mg/day) during the hospitalization. Mean CGI-S decreased from 4.82 +/−0.87 at admission to 2.27 +/−0.65 at discharge, $p = 0.003$, change from baseline is therefore −2.55 +/−0.82 (**Figure 2**).

For a summary of the safety outcomes, refer to **Table 2**. Regarding adverse events, two (18.2%) patients developed akathisia (one moderate and one marked), one (9.1%) experienced insomnia and two (18.2%) reported headache. No suicidal behaviour was noted in any of the patients. Mean change in prolactin level from baseline to discharge was −4.97 +/−5.05 ng/mL for females and −3.28 +/−2.7 ng/mL for males. Mean change of metabolic parameters was: 1.90 +/- 8.87 mg/dL for total cholesterol; 1.84 +/−13.49 mg/dL for LDL cholesterol; −2.97 +/−6.06 mg/dL for HDL cholesterol; 16.71 +/−21.09 mg/dL for Triglycerides; and 7.85 +/−13.78 for fasting glucose.

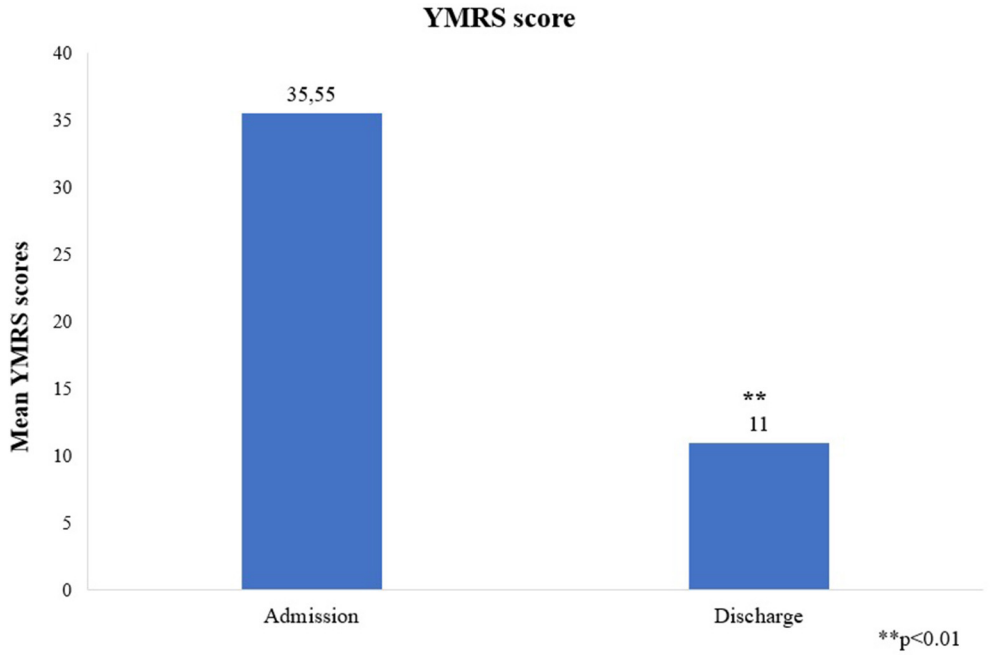


**FIGURE 1 |** Mean YMRS scores at admission and discharge. YMRS, Young Mania Rating Scale. $^{**}p < 0.01$.

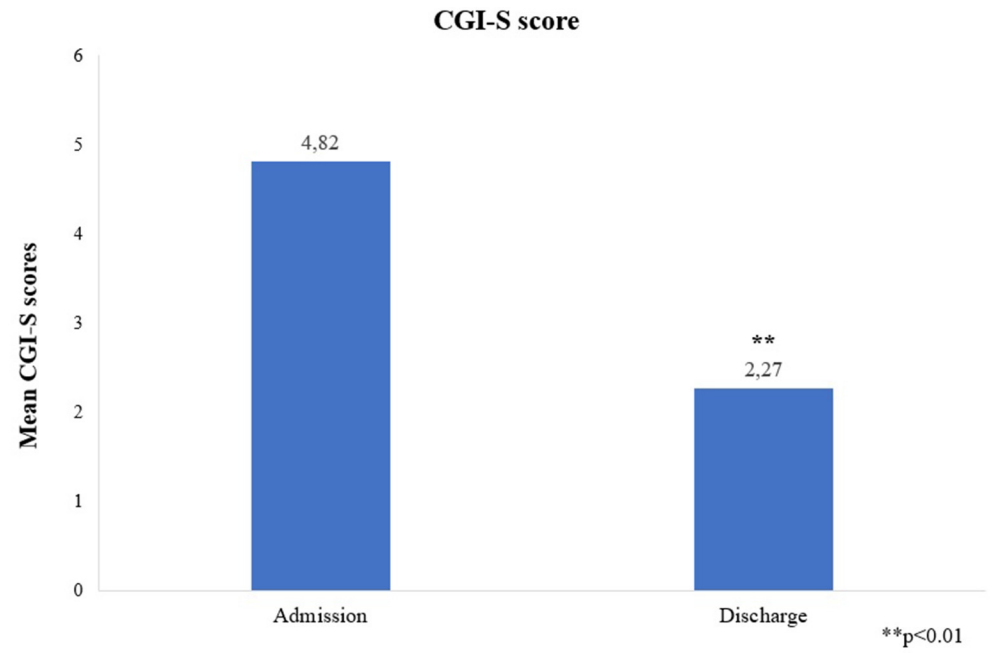


**FIGURE 2 |** Mean CGI-S scores at admission and discharge. CGI-S, Clinical Global Impression – Severity Scale. **p < 0.01.

Regarding treatment-adherence, six (54.5%) patients displayed high adherence, four (36.4%) moderate adherence and one (9.1%) patient had low adherence to the medication, as shown by the MGLS score at day 30 after discharge.

## DISCUSSION

This was the first study to specifically investigate cariprazine's efficacy in combination with a mood stabilizer in FEM. In this sample, mean YMRS scores and CGI-S scores showed a

**TABLE 2 |** Summary of the safety outcome measures.

| | |
|---|---|
| **TE adverse events, *n* (%)** | |
| Akathisia | 2 (18.2) |
| Headache | 2 (18.2) |
| Insomnia | 1 (9.1) |
| Suicidality | 0 (0) |
| **TE laboratory changes, mean (SD)** | |
| Prolactin – males (ng/mL) | −3.28 (2.7) |
| Prolactin – females (ng/mL) | −4.97 (5.05) |
| Total cholesterol (mg/dL) | 1.9 (8.87) |
| LDL cholesterol (mg/dL) | 1.84 (13.49) |
| HDL cholesterol (mg/dL) | −2.97 (6.06) |
| Triglycerides (mg/dL) | 16.71 (21.09) |
| Fasting glucose (mg/dL) | 7.85 (13.78) |
| **Adherence*, *n* (%)** | |
| Low | 1 (9.1) |
| Moderate | 4 (36.4) |
| High | 6 (54.5) |

*TE, treatment-emergent.*
**Based on the Morisky Green Levine Medication Adherence Scale.*

great reduction from admission to discharge with all patients achieving clinically significant response. Furthermore, 72% patients achieved clinically significant remission.

These findings are in line with those of clinical trials. The short-term efficacy and safety/tolerability of cariprazine was confirmed in three 3-week placebo-controlled studies (16–18) in adult patients with acute manic or mixed episodes associated with bipolar I disorder. Flexible-dose cariprazine 3–12 mg/day was used in two studies (16, 17) and a fixed/flexible dose scheme (3–6 mg/day or 6–12 mg/day) was used in the third (18). In each trial, improvement from baseline to week 3 in YMRS score, CGI-S scores as well as rates of response were significantly greater for cariprazine- than for placebo-treated patients. Remission rates also showed statistical significance in favour of cariprazine over placebo (33). This aspect is of high significance, as the persistence of symptoms after the acute treatment of mania was shown to be associated with worse illness-outcome and an increased risk of relapse (33). Therefore, the fact that cariprazine patients achieved response and remission has clinical significance in the improvement of prognosis (33).

In general, the first stages of most diseases require a simpler approach and treatment response is usually more favourable, obtaining a greater benefit with less risk (34). After the first episode, multiple relapses and a progressive worsening of psychosocial functioning and cognition often occur. However, it is thought that first episodes represent a window of intervention to improve clinical results and patient's quality of life (5). Despite that, guidelines focusing on the treatment of FEM are scarce (35). Treatment in FEM yields complete remission of the manic syndrome in most cases, but it may take longer for males, younger patients, or those with psychotic features or a longer duration of untreated mania (11).

Furthermore, BD is associated with more frequent relapses than other psychiatric diseases (36) with non-adherence to pharmacological treatment (37) and residual symptoms after an acute manic episode being the best predictors of relapse (33). There are several factors influencing adherence: individual-specific sociodemographic factors, insight, cognition as well as illness-specific factors, like illness-severity or comorbidities (38). Of note, there are medication-specific factors as well, like the complexity of the medication regimen and side-effects (39). Regarding cariprazine, it is given orally once daily; can be taken with or without food; can be taken at any time of the day; and neither age, gender nor smoking influence dose administration (40), making the medication regimen easy to comply with.

Regarding side-effects, akathisia incidence in our sample (18.2%) was similar to those reported in acute double-blind studies (pooled data of the three short-term studies: 19.8% for the 3–6 mg/day dose-range) (29). Prevalence of insomnia and headache, (9.1 and 18.2%, respectively) were also similar to the outcomes of the pooled analysis (8.7, 13.7% in the same dose-range) (29).

Regarding the metabolic parameters, there was a slight increase observed in triglycerides, fasting glucose and cholesterol levels (except for HDL cholesterol) in our sample. These findings are generally similar to those observed in clinical trials (29). In addition, mean metabolic variations were inferior to 5% for total cholesterol and LDL cholesterol but not for HDL cholesterol; mean triglyceride variations were inferior to 20–30% and mean fasting glucose increase was inferior to 10 mg/dL, which are within normal ranges (31, 41).

Mean change in prolactin level from baseline to discharge in this sample was similar to those reported in *post-hoc* analyses conducted on pooled data of the three short-term studies Patel et al. (42). Decrease in prolactin level was seen as a consequence of the D2 partial agonism, especially in females.

Psychotic features are common in bipolar mania, some studies estimating it to be around 68% (43) which is similar to our sample, where 72.7% of the patients experienced psychotic symptoms. The presence of psychotic symptoms leads to an earlier age of onset and more severe mood episodes, requiring more frequent hospitalizations – making it crucial to find an effective treatment for this patient population (44). A study explored the pharmacological treatments and found that having bipolar mania with psychotic features is associated with receiving a combination therapy of an antipsychotic and an anticonvulsant agent (44). However, there is no evidence of superiority of any first-line antipsychotic (8). In our study, cariprazine in combination with lithium or divalproex sufficiently addressed psychotic symptoms in FEM.

Overall, cariprazine has an easy medication regimen and a favourable safety profile. Cariprazine's long-term tolerability was demonstrated by Ketter and colleagues (19) in a 16-week open-label cariprazine 3–12 mg/day study, with akathisia being a common adverse event. They showed low rates of sedation or weight gain and although akathisia occurred in one-third of the patients, it yielded low rates of discontinuation as it was managed effectively. Therefore, cariprazine could be a good choice of pharmacotherapy to ensure adherence from the first stages of the disease. In terms of 30-day adherence, in our study, six (54.5%) patients displayed high adherence, four (36.4%) moderate adherence and one (9.1%) patient had low adherence to the medication. This is an encouraging data for adherence, but studies are needed to examine this further.

One of the limitations of the data presented here is the small sample size. In addition, conclusions regarding the efficacy and risk/benefit profile of cariprazine are difficult to be drawn on due to the lack of an active comparator; multiple doses; and the concomitant medication. Also, many of the patients in this sample had a psychiatric comorbid condition which is known to negatively influence many aspects of the disorder – including less favourable treatment response, especially to lithium – making it complicated to draw accurate conclusions from these findings. Furthermore, patients were followed up for a short period only, warranting the need for longer observations to conclude long-term effects.

## CONCLUSIONS

In this sample, cariprazine in combination with a mood stabilizer (lithium or divalproex) was effective in resolving the acute manic episode of FEM patients and it proved to be safe and well-tolerated with a low rate of adverse effects. Since the BD internationals guidelines recommend choosing treatment based on not only efficacy, but also short-term and long-term safety and tolerability, cariprazine is a good choice of pharmacotherapy. Given cariprazine's gentle safety profile and ease of administration, it likely improves patient's adherence to treatment and therefore helps minimizing the risk of relapse and improves prognosis.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitè d'Ètica d'Investigació amb medicaments de Lleida (CEIC-2341). The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

RP-G and VL-B were responsible for conception and design as well as initial drafting of the manuscript. GA-H and EA were responsible for revising the manuscript critically for important intellectual content of the version of the manuscript to be published. All authors read and approved the final manuscript.

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# Remission of Persistent Negative Symptoms and Psychosocial Consequences by Combined Clozapine and Cariprazine Treatment in a Patient With Long-Standing Treatment-Resistant Schizoaffective Disorder

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This patient case report describes a 45-year old white unmarried man with disability pension due to schizoaffective disorder, diagnosed at the age of 24. He lives in an apartment and has housing support. Retrospectively, the patient displayed prodromal markers of a disorder within the schizophrenia spectrum many years before the onset of frank psychosis, indeed since childhood. Over the years several symptoms and signs across schizophrenia domains have been manifest: positive, negative, cognitive, and affective, among which the negative and affective symptoms and signs were the earliest to appear. While the positive, disorganized, and catatonic symptoms responded to treatment – when duly tested and complied with – the negative and affective symptoms have been notoriously difficult to handle. We now report on the successful introduction of cariprazine (CAR) to his ongoing clozapine (CLZ) medication, the result of which has been a near-complete remission of his persistent negative and psychosocial issues. We interpret this remarkable alleviation of the patient's disease – and concomitant improvement of his quality of life – in terms of neuroreceptor target complementarity between CLZ and CAR, with particular emphasis on the contributions from the D3 and D2 receptor partial agonist components of the latter agent.

**Keywords: Antipsychotic polypharmacy, negative symptoms (schizophrenia), cognitive symptoms of schizophrenia, psychosocial symptoms, quality-of-life, reward system, DA D2/D3 partial agonism**

## INTRODUCTION

Schizophrenia is a devastating disorder with significant suffering and socioeconomic impact on life quality of the individuals afflicted, as well as on their families and caregivers. The lifetime prevalence is close to ∼1% and therefore also linked to substantial associated health costs and significant burden to society (1). While antipsychotic medication is often helpful towards much of the positive symptom expressions of the disease, it has been estimated that about every third or

fourth patient may suffer persistent residual symptoms despite adequate antipsychotic treatment (2). Among antipsychotic drug-refractory issues the negative and cognitive symptom domains appear to be particularly difficult to manage, are associated with prominent morbidity and poor functional outcome, and therefore represent major unmet medical needs in schizophrenia (3).

The Second Generation Antipsychotic (SGA) clozapine (CLZ) has become a frequently tried treatment option in treatment-refractory patients where other monotherapies have failed, triggered by the seminal paper by Kane (4) and the subsequent market reintroduction of the compound. CLZ is also endorsed as a third-line option in many schizophrenia Treatment Guidelines (5). While often efficacious, CLZ (monotherapy) treatment may nonetheless leave some patients with only partial resolution, hence left in a state with residual symptom issues – particularly regarding negative and cognitive traits. Indeed, a meta-analysis suggests but a ∼40% response rate to CLZ in treatment-resistant patients (6). Moreover, CLZ carries many side effect liability risks, e.g., metabolic effects, hypersalivation, constipation and enuresis. The recently launched Third Generation Antipsychotic (TGA) partial dopamine agonist agent cariprazine (CAR) has been shown to be an effective 'broad-spectrum' option in the treatment of schizophrenia (3, 7, 8). Of particular note, this agent has proven effective not only to manage positive symptoms, but also to bring about clearcut improvement (superior to risperidone) in patients with long-standing predominant primary negative symptoms in a carefully controlled randomized double-blind study (9). This action of CAR has been attributed to its very high affinity and partial DA receptor agonism at the D2 and, in particular, D3, receptors, hence distinguishing CAR from older agents from the First and Second Generation Antipsychotic drug classes (FGA and SGA, respectively), including CLZ.

## CASE PRESENTATION

Below we detail the disease-relevant background history of our patient (overview in **Table 1**), followed by a section describing the clinical changes upon the recent introduction of CAR to his antipsychotic treatment regime (CLZ and valproate).

### Background History

Varying expressions of mental health issues were identified in the family history of our patient. Thus, the maternal grandfather and a maternal aunt suffered from compulsive controlling behaviour. The grandfather, who was an introvert person, committed suicide. The father of the patient was described as aloof, and a paternal aunt suffered from depressions.

The early years of the patient were characterized by introversion, anxiety proneness and orderliness. During adolescence he had few friends, but did well in school, being meticulous about his studies. Premorbidly, the patient was disposed to social anxiety, fear of change, with hypochondriacal sensations and thoughts; according to his mother, from 14 years of age he rarely if ever showed any signs of joy. Nevertheless, it was some time after the patient started university studies that his mental health started to seriously deteriorate. He lost drive, and found it harder and harder to focus on and remember things. Moreover, his habitual orderliness and health worries grew into obsessiveness and compulsiveness, and intense hypochondriacal fears. He became nonreactive to his environment. By the time the patient was 21 his mother was seriously concerned and arranged for him to see a psychotherapist. However, the therapy did not work – he continued to deteriorate and was transferred to psychiatry. For the subsequent 2 years the patient entered into fruitless treatment trials with citalopram, nefazodone, venlafaxine and psychiatric day care. Another round of psychotherapy was also undertaken. A detailed overview of the pharmacological treatment history is found in **Table 2**.

Following the introduction of nefazodone and venlafaxine, respectively, the patient attempted to commit suicide twice, which prompted periods of psychiatric inpatient care. During the second round of psychotherapy the lowered mood intensified, which however – which was new – was briefly interrupted by hour-long hypomania-like episodes. The patient was diagnosed with bipolar depression. However, it was at this point also speculated that his clinical presentation (with prominent affective blunting, alogia, apathy and anhedonia), despite the hypomania-like episodes and absence of psychosis, could actually be signs of schizophrenia. However, the patient did not accept treatment with an antipsychotic, which was suggested. He did accept a treatment trial with lithium though, which, unfortunately, had no positive effect (**Table 2**). About a year later, at age 24, the patient – during a period of work as a cleaner – decompensated severely and displayed overt psychosis. At this time, a diagnosis within the schizophrenia spectrum was rather obvious, as was the need for antipsychotic treatment. However, the patient was not cooperating adequately and was committed to psychiatric inpatient care at three separate occasions after having stopped his medication (risperidone plus lithium, ziprasidone plus lithium and valproate, and risperidone plus lithium, respectively; **Table 2**) during the following 3 years. During these admission episodes the patient was intensely psychotic and disorganized, and his response to antipsychotic treatment weakened more and more with each new episode. In the end, after also having tried perphenazine plus lithium, combined treatment with CLZ and valproate reduced the positive psychotic symptoms to a minimum, but notably negative symptoms persisted and dominated the picture (**Table 2**). The patient attained retrospective insight, and has since been very careful not to change his medication out of fear of becoming psychotic again. While the aforementioned antipsychotic regimen thus worked to prevent more psychotic relapses, it came at a price. The treatment is accompanied by side effects (i.e., hypersalivation and nocturnal enuresis) and has not accomplished alleviation of the negative symptoms: hedonic deficiency, weak social-, self care- and volitional drive, marked taciturnity and hyporeactive affectivity.

Rehabilitation efforts between age 27 and 37 failed, probably partly because of the patient's evasive and introverted attitude, and partly because of a general sense of social defeat, social stigma, and fear of failure. At 37 the patient accepted disability pension.

**TABLE 1 |** Timeline of patient biographic and medical events until 37 years of age.

| Age | Events | Comments |
|---|---|---|
| *0-2 y* | Birth and early development | 48 hour long delivery. Strongly icteric at birth. Late in reaching developmental milestones: walking, potty training. |
| *3–5 y* | Preschool years | Quiet, shy, afraid of knives, spiders and new things. Orderly. |
| *6–18 y* | School years | When starting school the patient complained about one foot being malformed (upon examination the foot was normal). Socially uncomfortable, few friends, conscientious. Lack of joy. At 11 the patient unexpectedly and suddenly became agitated with pressured speech and throwing things around. Graduated from high school with good grades. |
| *19–21 y* | University studies | Dropped out after 2 years. Described feelings of indifference, lack of motivation, and difficulties in concentrating and remembering. |
| *21 y* | Started psychotherapy | The psychotherapy was initiated by the patient's mother motivated by her observation that the patient had become "like a zombie": increasingly withdrawn and passive, while at the same time obsessively controlling things and ruminating over being physically ill. However, the psychotherapy was terminated as the patient's condition worsened during the treatment and the patient was referred to the psychiatric services. |
| *21–22 y* | Initiated contact at the open psychiatric care clinic | The patient received 3 months of citalopram- and open day care treatment, subsequently followed by a new trial of psychotherapy focusing on low self-esteem. The treatment had no positive effect. Once again, the psychotherapy had to be terminated due to worsening of the patient during treatment, including aggravation of depressive mood, obsessivity and hypochondriacal concerns about cancer, now alternating with 6–12 h long hyperactive and elated episodes. |
| *23 y* | Started work as a cleaner | Quit the job due to lack of energy. |
| | Started treatment with nefazodone | |
| | Suicide attempt | One week after nefazodone initiation the patient intoxicated himself with zolpidem (was found by the mother). |
| | First period of psychiatric inpatient care | Following the suicide attempt the patient was admitted for 12 days of psychiatric inpatient care. During the stay the patient – who was reported to be passive and showing no spontaneous speech – was diagnosed with bipolar depression. A psychometric evaluation demonstrated evenly distributed cognitive functions within the normal range (IQ: 108).<br>The patient was prescribed to continue the nefazodone treatment and was discharged with a plan of continued open psychiatric care and treatment. |
| | Started treatment with venlafaxine at the open care clinic | Due to absence of effect after about 2 months of treatment nefazodone was switched to venlafaxine. |
| | Another suicide attempt | About 2 weeks after the initiation of venlafaxine treatment the patient intoxicated himself with caffeine tablets. |
| | Second period of psychiatric inpatient care | After the second suicide attempt the patient was admitted for renewed psychiatric evaluation and treatment for 4 months. No signs of positive psychotic symptoms were observed, but as the patient – apart from the brief episodes of hyperactivity and elation that continued to appear – was fundamentally withdrawn, apathetic and showed signs of affective blunting and anhedonia schizophrenia was suggested. Treatment with risperidone was initiated but had to be discontinued because the patient did not accept it. The patient was discharged. |
| *24 y* | Continued contact at the open psychiatric care clinic | After discharge the patient had contact with the day care unit and for 5 months he accepted treatment with lithium. The status of the patient did not change during the lithium treatment: he continued to appear depressive and apathetic with blunted affect, occasionally interrupted by brief hypomania-like episodes.<br>Subsequently, the patient stopped attending the open psychiatric clinic and withdrew the lithium treatment with the motivation that he did not want to be dependent on pills. He denied side effects. |
| | Started another job as a cleaner | After about 8 months the patient was fired because of "inadequate behaviour". |
| | Resumed contact with the open psychiatric clinic, including the day care unit | When the patient came back to the day care unit he appeared unconcentrated, absent minded, sometimes inappropriately laughing and expressing vague ideas of reference and feelings of being influenced – perhaps by God – via the radio and television. The patient had lost about 10 kg of weight. His apartment was found to be completely disorganized. |
| | Third period of psychiatric inpatient care | The patient was hospitalized by force for about 6 months. During the hospitalization the patient made stereotyped movements with his hands and arms, and reported on experiencing chaotically changing feelings – in stark contrast to earlier emotional numbness – which made thinking unnecessary, depersonalization, derealization as well as telepathic and other nonverbal messages from people, including celebrities. He also described having auditory hallucinations with commenting, imperative and discussing voices. Schizoaffective disorder was diagnosed |
| *25 y* | Treatment with risperidone, lithium and valproate was started during the forced hospitalisation | Under treatment with risperidone, lithium and valproate productive psychotic symptoms become reduced, but the patient was indifferent, anhedonic and apathetic.<br>When venlafaxine and reboxetine, respectively, was added, and when risperidone was switched to ziprasidone, positive psychotic symptoms reemerged. With continued risperidone-, lithium- and valproate treatment psychosis attenuated slowly.<br>The patient was discharged from forced inpatient care to the open psychiatric clinic. Indifference and emotional numbness remained. |

*(Continued)*

**TABLE 1** | Continued

| Age | Events | Comments |
|---|---|---|
| *26 y* | The patient stopped taking the prescribed medication | Within weeks after discontinuing the medication the patient suffered a psychotic relapse with similar symptoms as previously. |
| | Fourth period of psychiatric inpatient care | The patient was hospitalized by force for a second time and during a 1 month stay the treatment was reinstated, after which the patient was discharged for continued open care.<br>Shortly after discharge the patient caused a fire and indoor flooding in his apartment (when he noticed the fire he opened all the water taps) and was brought by the police to the psychiatric emergency unit. |
| | Fifth period of psychiatric inpatient care | Another period of forced psychiatric care ensued for 7 months. The psychotic symptoms were now even more difficult to treat than before; risperidone and perphenazine yielded unsatisfactory results. Finally positive psychotic symptoms responded to treatment with clozapine and valproate, although negative symptoms remained prominent and unchanged (PANSS positive symptom score was reduced from 24 to 5, while PANSS negative symptom score only dropped from 26 to 21). The patient was discharged to live in an apartment with housing support. |
| *27–37 y* | For about 10 years the patient took part in several rehabilitation trials, which all failed. At age 37 the patient received disability pension | The patient lives more or less isolated in his apartment, reluctant to accept housing support. He dreads becoming psychotic again and does not want to change his medication. He suffers no relapse of psychosis, but negative symptoms and side effects from the treatment are prominent. |

## Clinical Course Since the Initiation of Cariprazine Treatment

For many years following his disability pension, the patient lived more or less in isolation. Apart from his mother and housing supporters – whom he was not keen on seeing – he met very few people. His life was dominated by negative symptoms, anxiety, compulsive checks, and side effects from the drug treatment. He suffered from a reduced ability to translate will and wishes into action. He often stayed in bed, but h were also spent checking the stove and water taps, triggered by a fear of fire and indoor flooding. Because of such obsessive thoughts the patient seldom left his apartment. The personal hygiene was neglected, he seldom shaved, and the apartment was filled with unwashed dishes and unread mail. The housing supporters offered help but were often rejected. The patient often missed appointments – e.g., at the psychiatric open clinic - despite reminder calls, and he did not accept home visits. He occasionally heard voices, which made him scared of becoming uncontrollably psychotic again. Because of this he did not for a long time want to lower the dose of CLZ in spite of the difficult-to-tolerate cholinergic system side effects (hypersalivation, constipation and nocturnal enuresis). Treatment with SSRI:s (citalopram, sertraline) only minimally affected anhedonia, obsessive-compulsive symptoms and phobias. He refused treatment with aripiprazole, which was suggested. Eventually, after repeated motivation, the patient agreed on lowering the dose of CLZ by small steps from 600 mg daily (age 29) to 450 mg daily (age 34). Side effects decreased somewhat, but did not cease, and the patient's condition remained virtually unchanged.

At age 44 (year 2019) – after recurrent persuasion – the patient accepted a treatment trial with CAR. CAR treatment was started with 1.5 mg per day for 4 days, followed by 3 mg per day for 12 days, after which the dose was raised to 4.5 mg per day [slow titration strategy (10)]. The patient reported no side effects and no adverse reactions were observed. 2 months after the initiation of CAR the patient – whom had now shaved off his long beard – was talkative and described that he had "*a warm feeling in the body*". He also said that he wanted to fix certain things: mend the bicycle and buy a new mobile phone (the old one had been broken for 3 years). Another 2 months on, the patient – on his own initiative – suggested that the dose of CLZ should be lowered more to reduce side effects: the dose was lowered to 425 mg per day. Another 5 months later the patient reported that he was feeling happy and alert, and that he had started to get up at seven o'clock in the morning (for many years he had used to sleep or stay in bed until the afternoon). He also described that he had started to go out. The patient reported this with a normal speech flow and reactivity under the conversation. The dose of CLZ was lowered to 400 mg per day. Subsequently the patient made some friends and continued to see them; the bike was fixed and a new phone was purchased. About 11 months after the initiation of CAR treatment the dose was increased from 4.5 mg to 6 mg per day. Some 4 months thereafter the patient reports that he has stopped obsessively controlling the lock of his door and that other controls are less time consuming: they have been reduced from about 2 hours to about 30 mins per day. For the next 8 months the dose of CLZ is further reduced to 275 mg per day. Following the CLZ reduction constipation disappeared, and hypersalivation and nocturnal enuresis were significantly, although not completely, reduced. (While the plasma level of CLZ at this dose is regrettably not available, 300 mg/d resulted in 1470 nmol/L; see, **Table 2**). The patient had never had any metabolic complications from CLZ. No signs of psychotic relapse or exacerbation of other symptoms have been noticed or reported. Since the initiation of CAR (and CLZ dose reduction) the patient has started to accept the housing supporters, despite not really needing them as much as before as he has often made the dishes and cleaned the apartment by himself. Likewise, the need to be reminded of things had disappeared. The patient's mother has reported that the patient has become more open and active in their contact. Another striking observation is that the patient has become increasingly

**TABLE 2 |** Overview of pharmacological treatment history*.

| Date (age) | Treatment | Comment | CGI-S |
|---|---|---|---|
| 1997 (21y) | Citalopram, dose unknown. | No effect. Terminated after 3 months treatment. Passive, indifferent, depressive, obsessive, hypochondriacal. | 4 |
| Jan 1998 (22y) | Nefazodone 100 mg. Zolpidem 7.5 mg. | One week after introduction of Nefazodone, suicide attempt through overdose of Zolpidem. No information about adherence, or if the patient withdrew Nefazodone prior to the suicide attempt. 12 days of psychiatric inpatient care followed. | |
| Jan 1998 (22y) | Nefazodone raised to 200 mg. | During inpatient period the patient was withdrawn without spontaneous speech. No effect from Nefazodone treatment. | 5 |
| Feb 1998 (22y) | Nefazodone raised to 400 mg. | No effect. Nefazodone was terminated after 2 months in conjunction with switch to Venlafaxine. | |
| Mar 1998 (22y) | Venlafaxine up to 150 mg. | Two weeks after introducing Venlafaxine, suicide attempt through overdose of caffeine tablets. Adherence unknown, or whether the patient withdrew Venlafaxine prior to the suicide attempt. The patient was hospitalized 4 months. Venlafaxine terminated. | |
| Apr 1998 (22y) | Risperidone 3 mg. | During the inpatient period the patient was withdrawn, apathetic, blunted and anhedonic, which evoked suspicion of schizophrenia despite lack of signs of psychosis. After 4 months the patient refused to continue the Risperidone treatment and was discharged to day care without medication. No significant treatment effect was observed. | 5 |
| Nov 1998 (23y) | Lithium up to 6 x 42 mg. | Accepted Lithium monotherapy for 5 months, but then refused. No significant treatment effect was observed. | 5 |
| Apr 1999 (23y) | No pharmacological treatment. | No psychiatric contact | |
| Nov 1999 (24y) | No pharmacological treatment. | Resumed contact with day care. Was absent-minded, disorganized, occasionally giggling and expressing ideas of reference/influence. The condition worsened. Eventually hospitalized 5 months. | 6 |
| Feb 2000 (24y) | Risperidone 4 mg. Lithium, 6 x 42 mg. | Psychosis considerably reduced after reintroduction of Risperidone combined with Lithium, but feelings of emptiness/numbness remained along with apathy and blunting. Erratic adherence to Risperidone/Lithium treatment after discharge. | 5 |
| Nov 2000 (25y) | Venlafaxine up to 150 mg added to Risperidone/Lithium. | Psychotic symptoms reappeared. Hospitalized for a month. | 6 |
| Dec 2000 (25y) | | Venlafaxine terminated. Continued Risperidone/Lithium. | 5 |
| Feb 2001 (25y) | | Plasma-Lithium 0.82 mmol/L | |
| Mar 2001 (25y) | Reboxetine up to 6 mg added to Risperidone/Lithium. | Continued Reboxetine for 2 months. No effect on depressive or negative symptoms. Was briefly hospitalized. After discharge psychotic symptoms reappeared and Reboxetine was terminated. | 5 |
| May 2001 (25y) | Risperidone tapered and switched to Ziprasidone up to 80 mg. Continued Lithium. | After introduction of Ziprasidone hypomania developed and psychosis intensified. Hospitalized 6 weeks. | 6 |
| | Valproate up to 600 mg added to Ziprasidone/Lithium. | Improved, but withdrew the treatment upon discharge. About a month later overt psychosis developed. Forcibly admitted. | 6 |
| Sep 2001 (26y) | Risperidone up to 6 mg and Lithium 6 x 42 mg was reinstated. | Psychosis started to slowly attenuate but did not go into remission. Emptiness, numbness, apathy, and blunting remained. After discharge the patient withdrew treatment and did not attend day care as recommended. Decompensated quickly, caused fire in his apartment, and was forcibly admitted again. Was admitted nearly 2 years, though with extended permission periods from the ward towards the end. | 6 |
| Oct 2001 (26y) | Lithium 6 x 42 mg reinstated. Lithium combined with Risperidone 6 mg for 2 months, followed by tapering Risperidone and switch to Perphenazine (up to 24 mg) for 1 month, after which also Perphenazine was tapered. | PANSS Oct 2001: Total 91, positive 24, negative 26.<br>Effect of Lithium/Risperidone and Lithium/Perphenazine, respectively, was unsatisfactory.<br>While tapering Perphenazine, Clozapine was introduced. | 5 |

*(Continued)*

**TABLE 2 |** Continued

| Date (age) | Treatment | Comment | CGI-S |
|---|---|---|---|
| Dec 2001 (26y) | Clozapine successively raised to 500 mg during 2 months. Lithium was terminated and Clozapine continued as monotherapy. | PANSS Feb 2002: Total 94, positive 19, negative 34. | 5 |
| May 2002 (26y) | | Positive psychotic symptoms attenuated slowly, but negative symptoms remained.<br>PANSS: Total 48, positive 5, negative 21.<br>Moved to open ward. | 4 |
| July 2002 (26y) | Clozapine raised to 600 mg. | | |
| Sep 2002 (27y) | Valproate up to 1200 mg added. | Valproate introduced to reduce risk of relapse into mania. | |
| Sep 2003 (28y) | | After managing gradually more extended periods of permission from the hospital the patient was discharged. P-Clozapine: 1765 nmol/L. P-Valproate: 488 micromol/L. | 4 |
| Apr 2004 (28y) | Clozapine raised to 650 mg. | | |
| Feb 2005 (29y) | Clozapine decreased to 600 mg. | | |
| Mar 2005 (29y) | | P-Clozapine: 404 nmol/L. Reason for low level unknown. Non-adherence?<br>P-Valproate: 379 micromol/L. | |
| Apr 2005 (29y) | Citalopram up to 90 mg added. | Marginal effect of Citalopram on anhedonia, obsessions-compulsions or phobias. P-Clozapine: 1,000 nmol/L. | 4 |
| Feb 2006 (30y) | | P-Clozapine: 1,880 nmol/L.<br>P-Citalopram 741 nmol/L.<br>P-Valproate: 391 micromol/L. | |
| Mar 2006 (30y) | Desmopressin 0,2 mg. Oxybutynin up to 5 mg + 2.5 mg + 15 mg. | Nocturnal enuresis issues. Desmopressin tried, but withdrawn after 2 weeks due to lack of effect. Switched to Oxybutynin. Oxybutynin yielded some, but insufficient, effect on cholinergic complications. After a year the patient withdrew it. | |
| May 2007 (31y) | Clozapine decreased to 500 mg. | P-Clozapine: >4,000 nmol/L. Reason for high level unknown. No trough concentration? Increased caffeine consumption? The patient had not changed his smoking habits. | |
| Apr 2008 (32y) | Clozapine decreased to 450 mg. | | |
| Dec 2010 (35y) | | P-Valproate: 651 micromol/L. | |
| Feb 2013 (37y) | Citalopram tapered and switched to Sertraline up to 200 mg. | No further effect on anhedonia, obsessions-compulsions or phobias was observed. | 4 |
| Jul 2014 (38y) | | Quit smoking. | |
| Sep 2014 (39y) | | P-Clozapine: 2,850 nmol/L. Remained non-smoking. | |
| Jun 2015 (39y) | | P-Clozapine: 3,410 nmol/L. Remained non-smoking. | |
| Jun 2019 (43y) | Cariprazine up to 4.5 mg added to Clozapine 450 mg/Valproate 1,200 mg/Sertraline 200 mg | About 2 months after introduction of Cariprazine the patient describes “a warm feeling in the body” and wants to plan and fix things. He is well groomed and chatty. Another month later the patient gets up at 7 am and frequently leaves his apartment. Upon contact he shows normal reactivity. | 3 |
| Oct 2019 (44y) | Clozapine decreased to 425 mg. | | |
| Mar 2020 (44y) | Clozapine decreased to 400 mg. | | |
| May 2020 (44y) | Clozapine decreased to 375 mg. Cariprazine raised to 6 mg. | | |
| Sep 2020 (45y) | Clozapine decreased to 350 mg. | Time required for compulsive checks has decreased from 2 h to 30 mins per day. | 2 |
| Dec 2020 (45y) | Clozapine decreased to 325 mg. | | |

*(Continued)*

**TABLE 2** | Continued

| Date (age) | Treatment | Comment | CGI-S |
|---|---|---|---|
| Mar 2021 (45y) | Clozapine decreased to 300 mg. | P-Clozapine: 1,470 nmol/L. | |
| May 2021 (45y) | Clozapine decreased to 275 mg. | May 2021 medication Cariprazine 6 mg/Clozapine 275 mg/Valproate 1,200 mg/Sertraline 200 mg. | |

**Periodically the patient has also used alimemazine, propiomazine and levomepromazine, occasionally benzodiazepines in small doses. Due to his fear of becoming addicted, none of these treatments have been used since 2014. In periods he has also received physiotherapeutic treatment.*
*CGI-S, Clinical Global Impression Severity score.*

social: he regularly sees his friends and has resumed contact with his father, whom he hadn't seen for many years. In conclusion, the life quality of the patient has improved notably. Moreover, as seen in **Table 2**, his CGI-S scores (11, 12) that had recurrently ranged between moderately and severely ill (scores 4–6) across the years ever since 1997, following the introduction of CAR in 2019 dropped to mildly to minimally ill (scores 2–3).

## DISCUSSION

This case report describes a 45-year old male with an extensive history of psychiatric disease afflictions (social anxiety, phobias, obsessive-compulsiveness, hypochondriacal fears, attentional deficits, affective blunting, hypohedonia, abulia, suicidal attempts, bipolar depression, hypomania etc.) before finally presenting with overt psychosis at the age of 24 (including ideas of reference and influence, auditory hallucinations, emotional turmoil, stereotyped psychomotor signs and disorganisation). Following several years of at best partially successful antipsychotic treatments and prominent sustained negative and cognitive symptoms, the introduction 2 years ago of CAR alongside his ongoing CLZ treatment has turned his clinical picture into near-complete remission.

The treatment record of our patient up to the psychosis debut had included fruitless trial attempts with lithium, citalopram, nefazodone, venlafaxine, as well as unsuccessful psychiatric day care and psychotherapeutic approaches. Following the schizoaffective disorder diagnosis, several efforts to find an efficacious antipsychotic treatment regimen were also instituted: risperidone, ziprasidone and perphenazine in combination with lithium (**Table 2**), but with inadequate clinical efficacy which may have been due to a lack of compliance from the patient. The patient did not accept the use of long-acting injection antipsychotics. Although eventually a schedule based on CLZ and valproate was found to successfully alleviate his positive symptoms, the prominent affective blunting, negative and cognitive symptomatology (presenting already prior to his *bona fide* diagnosis of schizophrenia) continued to constitute a dominating part of his issues, along with anankastic behaviours. Retrospectively, the disease history of our patient (extending into childhood/adolescence; see, **Table 1**) may also be seen to be consistent with the neuro/sociodevelopmental theories of schizophrenia (13, 14).

We decided to introduce CAR in the treatment of our patient based on the consideration that it would furnish a complementary neuroreceptor profile to that of CLZ, with net potential benefits both regarding efficacy and adverse event readouts (15–17). Thus, CAR (monotherapy) has been shown to greatly improve predominant primary negative symptoms in patients with schizophrenia (9, 18), including marked enhancements also in the "Personal & Social Performance" domain (9), as well as in the recovery of attentional cognitive processes (19). Further, CAR also appears beneficial from a relapse prevention point-of-view (20, 21), which may be viewed as advantageous in the present context as the patient was afraid of relapsing into psychosis upon lowering the dose of CLZ. We also hoped that the addition of CAR would enable a further dose reduction of CLZ to reduce CLZ-induced side effects. Interestingly, a case series published during the review process of the current manuscript describes the successful treatment of negative symptoms by addition of CAR to CLZ in five treatment-resistant schizophrenic patients, adding further support for the potential clinical usefulness of this combination (22).

As seen in **Figure 1**, CLZ and CAR display entirely different target profile "fingerprints". Thus, CLZ is an antagonist with quite poor affinity for the DA D2 (and D3) receptor but carries high affinities for H1, 5-HT2A, 5-HT2C, alpha1, and muscarinic sites. For comparison, CAR is a high-affinity D2/D3/5-HT1A partial agonist with preference for the D3 receptors, but lacking appreciable affinity for the set of sites for which CLZ displays high potency. There is complementarity between the two antipsychotics also from a pharmacokinetic perspective; at steady-state CLZ has a half-life of ∼12–14 h while CAR [together with its active metabolite di-desmethyl-CAR (23)] has an effective half-life of ∼7 days (20) and may thus be viewed as a "long-acting oral" medication.

Upon reflection, the history of our patient may install some hope regarding the possibility to treat stationary cases with refractory schizophrenia. In particular, one may speculate that the primary or enduring negative and cognitive deficit states often seen in schizophrenia are not necessarily the result of irreversible neurodegeneration, but may rather represent dynamic brain states that are still amenable to intervention and change. In part the negative syndrome might be driven by a motivational-volitional disorder that hinges back to a disturbance of the reward system of the brain (24). The potential of CAR to improve predominant primary negative symptoms (9), along with its pharmacological ability to modulate the transmission of dopamine via D3/D2 receptor partial agonism within the mesolimbic and mesocortical systems, is congruent with such a hypothesis.

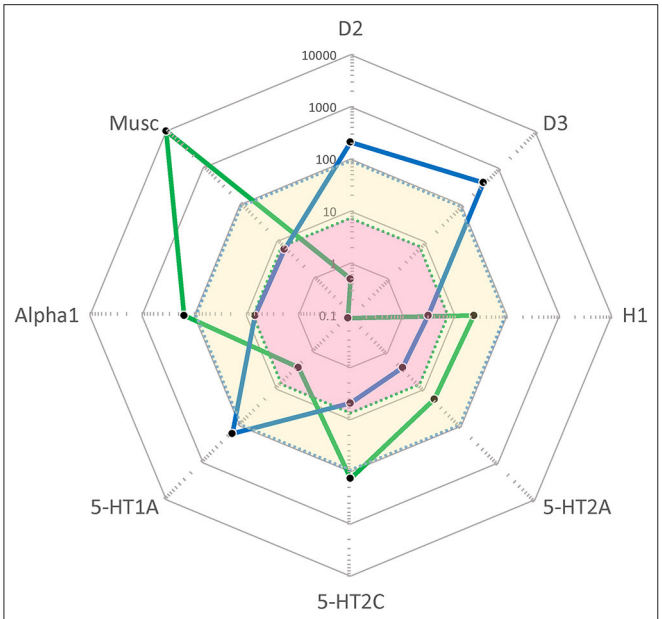


**FIGURE 1 |** "Cobweb" depiction of Clozapine (CLZ; blue) and Cariprazine (CAR; green) target profiles overlaid on the *free* (unbound) steady-state plasma concentrations (nmol/L) of these antipsychotics at average clinical dosage (CLZ: yellow area; CAR: pink area). Black dots correspond to drug affinities reported in the literature (in nM) for the targets labeled on the edges of the cobweb; the closer to the center, the higher affinity for the target in question. (For further detail, see Hjorth [16]). D2, dopamine D2 receptor; D3, dopamine D3 receptor; H1, histamine H1 receptor; 5-HT2A, serotonin 2A receptor; 5-HT2C, serotonin 2C receptor; 5-HT1A, serotonin 1A receptor; Alpha1, α1-adrenoceptor; Musc, ACh muscarinic receptors.

## STRENGTHS AND LIMITATIONS

Obviously, the main limitation of the work is that it concerns the description of a single patient case, and therefore cannot be immediately generalized to a wider patient population. Apart from the use of PANSS when CLZ was introduced, the symptomatic presentation (its positive, negative and cognitive, as well as social and quality-of-life dimensions) were not consistently assessed with validated scales during the course of the illness, e.g., with formal assessments of negative symptoms using the SANS scale (25). This of course limits a stricter objective quantification of the treatment response. This said, the global illness severity has been regularly assessed with the CGI-S instrument (11, 12) already from the outset of the patient's contact with psychiatry, and confirms the striking improvement experienced after the addition of CAR to his ongoing antipsychotic treatment with CLZ (**Table 2**). In addition, the extended and detailed account of the patient's disease journey, encompassing diagnosis and close management follow-up from clinical as well as pharmacological viewpoints is a clearcut strength, particularly as two of the authors (MB & MS) have been able to regularly monitor the clinical course of this patient across several years.

## CONCLUSION

CAR is a promising new agent in the treatment of schizophrenia spectrum conditions. Besides having antipsychotic properties, CAR can potentially alleviate predominant primary negative symptoms, as well as social and cognitive deficits, all of which represent still unmet treatment needs in schizophrenia. Due to its unique target profile fingerprint–including dopamine partial agonism and D3 over D2 receptor preference–CAR may complement the pharmacological and clinical profile of CLZ and modulate dopamine transmission within brain systems that are important for reward and cognition. We report on a case with a long-standing treatment resistant schizoaffective disorder in which treatment with CLZ and valproate had reduced the positive but not the negative and psychosocial symptoms, but where following addition of CAR a remarkable improvement took place. Severe, functionally debilitating, negative and psychosocial symptoms, including anhedonia, abulia, affective blunting, alogia and social amotivation and withdrawal, almost disappeared, and obsessive symptoms concomitantly decreased, overall resulting in an amazing quality-of-life enhancement. Moreover, after the introduction of CAR to the ongoing CLZ treatment, the dose of the latter could be reduced which considerably reduced side effects. We hypothesise that the pharmacological complementarity between CAR and CLZ underlies this action, where CAR's high affinity partial agonism at D2/D3/5-HT1A receptors and preference for the D3 receptor, supplements the target impact of CLZ, thereby resulting in an efficacious and clinically beneficial neuroreceptor/circuit interaction outcome. Needless to say, controlled studies of adequate size and duration are warranted to further substantiate the findings in this case report.

## DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the data are extracted from a patient medical journal and is thus personally confidential within the framework of the medical professionals involved in his treatment. Requests to access the datasets should be directed to mats.m.bogren@skane.se

## ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## AUTHOR CONTRIBUTIONS

MB and MS oversaw the patient's clinical management and MB wrote the original draft. MB, MS, and SH conceptualized and

researched the subject, conceptualized, reviewed, and edited the manuscript. All authors contributed to the article and approved the submitted version.

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SYSTEMATIC REVIEW
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# Brain Derived Neurotrophic Factor and Cognitive Dysfunction in the Schizophrenia-Bipolar Spectrum: A Systematic Review and Meta-Analysis

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**Background:** Cognitive impairment is a core feature of disorders on the schizophrenia-bipolar spectrum, i.e., schizophrenia, bipolar disorder, and schizoaffective disorder. Brain-derived neurotrophic factor (BDNF) has been proposed to be a biomarker of cognitive impairment in these disorders as it plays a critical role in neuroplasticity and proposed to mediate some of the psychotropic effects of medication. However, despite numerous studies investigating the association between circulating BDNF and these disorders, no solid conclusions have been drawn regarding its involvement in cognitive impairment.

**Objectives:** The current systematic review and meta-analysis aims to examine blood BDNF levels and cognitive dysfunction in patients on the schizophrenia-bipolar spectrum as well as to evaluate whether circulating BDNF measurements can act as a biomarker for cognitive dysfunction.

**Methods:** Studies were identified by searching Embase and Medline databases for English language articles published in peer-reviewed journals between 2000 January and 2021 June according to the PRISMA guidelines. A total of 815 articles were identified of which 32 met the inclusion criteria for the systematic review – reporting on comparisons between blood BDNF levels and cognitive functions of schizophrenia or bipolar disorder patients versus healthy controls (no studies involving schizoaffective patients were specifically obtained for the time being). Twenty-four of these studies (19 with schizophrenia and 5 with bipolar disorder patients) were eligible to be included in the meta-analysis.

**Results:** Our findings indicated that circulating BDNF levels were significantly reduced in patients experiencing an acute episode of schizophrenia or bipolar disorder compared to healthy controls. Cognitive function was also found to be significantly worse in patients, however, correlations between BDNF levels and cognitive impairment were not always detected. Interventions, especially pharmacotherapy seemed to improve certain aspects of cognition and increase circulating BDNF levels.

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**Conclusion:** Circulating BDNF alone does not seem to be a valid biomarker of cognitive dysfunction in patients with disorders on the schizophrenia-bipolar spectrum, owing to several confounding factors. Changes of the circulating levels of BDNF should be evaluated in a wider context of other stress-, immune-, and inflammatory-related factors.

**Keywords: schizophrenia, schizoaffective disorder, bipolar disorder, BDNF, cognition, biomarker**

## INTRODUCTION

Schizophrenia is a serious psychiatric disorder characterized by considerable distortions of thinking and perception driven by three core symptom domains; positive symptoms, negative symptoms, and cognitive dysfunction (1). Bipolar disorder is also a major psychiatric condition, but it is recognized by the alternation of mood episodes and behavioral activation (1). The prevalence of both disorders is around 1% of the general population (2, 3). An intermediate phenotype between schizophrenia and bipolar disorder is schizoaffective disorder, which is characterized by the concurrent occurrence of an equal admixture of both schizophrenic and major affective disorder symptoms cross-sectionally and/or longitudinally (1). Together, the three disorders can be referred to as schizophrenia-bipolar spectrum disorders.

Cognitive dysfunction, defined broadly as the inability to properly process information, has been well established to be a core feature of these disorders (4, 5). In bipolar disorder, cognitive impairment usually manifests in specific cognitive domains such as attention, verbal memory, or executive functioning with greater severity throughout the acute manic-depressive episodes compared to the euthymic states (6–8). In contrast, the same cognitive deficits in schizophrenia tend to be stable across time without considerable improvements between psychotic episodes (9, 10). Deficits in cognition have also been described in schizoaffective disorder and at a greater extent than in patients with bipolar disorder (11). Importantly, cognitive impairment has been proposed to be a crucial factor in achieving improved functioning and quality of life in these patient groups (12–14). However, since currently there are no effective treatments for cognitive impairment in the schizophrenia-bipolar spectrum, it remains a major unmet clinical need (15). Thus, investigating potential biomarkers of cognitive dysfunction is not only crucial for understanding the pathophysiology of disorders on the schizophrenia-bipolar spectrum, but also for the development of potential treatments and interventions (16, 17). One of the candidates for such biomarker is brain-derived neurotrophic factor (BDNF).

Brain-derived neurotrophic factor is a member of the nerve growth factor family, which functions include enhancing the growth and maintenance of various neuronal systems, ensuring neuronal plasticity, modulating neurotransmitter activity, and contributing to learning and memory throughout life (18–21). It facilitates neuronal plasticity *via* the stimulation of dendritic growth, the formation of synapses as well as neurogenesis in brain areas related to memory such as the hippocampus (21, 22). Activation of BDNF release from axons is influenced negatively by several factors including inflammation, stress as well as age (21). Since BDNF can be readily measured in blood, several studies have associated its peripheral concentrations with central functions and neuropathology. For instance, circulating BDNF levels have been associated with hippocampal volume and spatial memory in older adults, with lower levels of BDNF correlating with smaller volume of the hippocampus and worse performance on neurocognitive tests (23). Furthermore, in terms of stress, animal studies found that social isolation in mice resulted in decreased BDNF levels in several brain areas including the prefrontal cortex, hippocampus, and hypothalamus (24). In view of these results and that it can cross the blood–brain barrier, BDNF has gained considerable attention as a possible biomarker for neurocognitive processes in several psychiatric and neuropsychiatric disorders (25) such as Alzheimer's disease (26), autism spectrum disorder (27), or disorders on the schizophrenia-bipolar spectrum (28).

Several studies measured the concentrations of BDNF in the blood and examined its relationship with cognitive symptoms in patients on the schizophrenia-bipolar spectrum compared to healthy controls in order to better understand the role of BDNF. The findings of such studies however were quite mixed; a meta-analysis by Ahmed et al. did not observe significant connection between cognitive impairment and BDNF levels in the blood based on five schizophrenia studies (29). Another systematic review and meta-analysis involving 21 studies with schizophrenia patients reported a positive correlation between cognitive impairment and reduced blood BDNF levels, especially in chronic samples (30). In the case of bipolar disorder, meta-analyses have consistently reported reduced BDNF levels in manic and depressive episodes compared to healthy controls (31, 32), but the connection between BDNF levels and cognition in these reviews were not examined.

The present systematic review and meta-analysis aims to update the existing literature regarding circulating BDNF levels and cognitive functioning in the schizophrenia-bipolar spectrum in comparison to healthy controls, in order to conclusively demonstrate whether blood BDNF can act as a biomarker of cognitive dysfunction.

## METHODS

### Search Strategy

Studies for the systematic review were identified by searching Embase and Medline databases for English language articles published in peer-reviewed journals between 1 January 2000 and 1 June 2021 according to the PRISMA guidelines (33)

with search terms "(schizo* OR bipolar) AND (BDNF* OR 'Brain Derived Neurotrophic Factor') AND ('Neurocognit*' OR Cognit*)." Searches by hand and *via* the reference section of published reports and previous review papers were also conducted in order to identify additional relevant studies.

## Inclusion and Exclusion Criteria

The inclusion criteria for studies were the following: (1) original research conducted with human subjects; (2) involved patients with diagnosis on the schizophrenia-bipolar spectrum; (3) included at least one cognitive assessment; (4) reported enzyme-linked immunosorbent assay (ELISA) measurement of BDNF levels in blood serum or plasma; (5) included healthy controls. Papers were excluded if they examined only genetic BDNF data or baseline blood BDNF levels were not adequately reported. Studies that did not report BDNF levels or cognitive scores for the total patient sample were excluded from the meta-analyses.

## Statistical Analyses

Means, standard deviations (SDs), and effect sizes were calculated in Microsoft Excel. The effect size was calculated for differences between baseline BDNF levels of schizophrenia patients and healthy controls or bipolar patients and healthy controls in ng/ml using mean, SD, and sample sizes. In case of cognitive scores, the effect size was based on the differences between baseline Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) scores of schizophrenia patients and healthy controls using mean, SD, and sample sizes. As effect size measure, Hedge's g was computed since the studies included in the meta-analyses had relatively small sample sizes and Hedge's g is less biased in case when variance equality assumptions are not met.

The meta-analyses were performed using the "meta" package in R studio, with standardized mean difference used as effect size measurement. While $Z$ statistic was calculated to determine the significance of the effect size, $Q$ statistic was computed to provide an estimation of the degree of homogeneity of the effect sizes of the different studies. The degree of inconsistency was signalized with the $I^2$ metric ($I^2 > 75\%$ indicating large heterogeneity, >50% moderate heterogeneity, and <50% low heterogeneity). To present the effect sizes of individual studies, a forest plot was created.

Due to the heterogeneity of studies, separate analyses for schizophrenia and bipolar disorder patients were performed with three random-effects meta-analyses. The first analysis examined the difference in circulating BDNF levels between schizophrenia patients and healthy controls, the second examined the difference in circulating BDNF levels between bipolar disorder patients and healthy controls, and the third looked at the difference in cognitive functions measured by RBANS between schizophrenia patients and healthy controls. Data was scarce to conduct an analysis for the difference between bipolar disorder patients and healthy controls in terms of cognitive functions. Similarly, conducting a meta-analysis of correlation coefficients was impossible due to the scarcity and heterogeneity of data. In these cases, qualitative analyses were performed.

# RESULTS

## Search Results

A summary of article selection for the systematic review is presented in the PRISMA chart (**Figure 1**). A total of 815 articles were identified and 69 were determined as potentially eligible to be included in the review based on the titles and abstracts. After evaluating the articles fully, only 32 met the inclusion criteria as in several articles there were no control group present (21 studies) or the reporting on BDNF levels (6 studies) or cognitive functions (9 studies) was inadequate. The majority of studies (26 studies) were conducted with schizophrenia patients; 16 of them were with either first-episode patients (FEP) (34–41) or patients with chronic schizophrenia (CH) (42–48). In the bipolar studies there were patients in euthymic state (49–52) and in depressive (53) and manic (50) episodes involved. No studies involving schizoaffective patients were obtained which is a relevant shortcoming. Altogether, 4,754 schizophrenia and 476 bipolar disorder patients were compared to 3,526 healthy controls in the systematic review. In terms of level of evidence, most of the studies were level B according to the rating system by Siwek et al., meaning that the design of the studies were of lower quality, mostly case-control studies, and there were only a few randomized controlled trials (level A) (54).

Studies where BDNF levels or RBANS scores were not reported for the total patient population were excluded from the meta-analyses. The first analysis that compared baseline BDNF levels between schizophrenia patients and healthy controls included 19 studies. The second analysis that looked at baseline BDNF levels of bipolar disorder patients versus healthy controls included five studies (49, 51–53, 55). The third and final analysis examined the differences of baseline RBANS scores between schizophrenia patients and healthy controls also included 5 studies (34, 48, 56–58).

## Blood Brain-Derived Neurotrophic Factor Levels

Circulating BDNF concentrations were measured either in the plasma (9 studies) or in the serum (23 studies). Statistically significant difference between patients and healthy controls was detected in 25 studies (21 with schizophrenia and 4 with bipolar disorder patients) as summarized in **Table 1**. Importantly, 24 of these studies reported decreased blood BDNF levels in patients compared to controls; only one study by Asevedo et al. found higher BDNF levels in schizophrenia patients than in controls (59). Out of the seven studies where no significant difference was reported, two were conducted with euthymic bipolar disorder patients (49, 52), while the rest was with schizophrenia patients (37, 46, 60–62). The other two studies examining euthymic bipolar patients found reduced BDNF levels compared to healthy controls, nonetheless, it was highlighted that the levels were still higher than what was found in manic bipolar patients (50, 51).

When analyzing the effect sizes, large effect size (Hedges' $g$ of 0.8 or larger) was detected in 15 studies (1 study with bipolar and 14 with schizophrenia patients), medium (Hedges' $g$ of 0.5

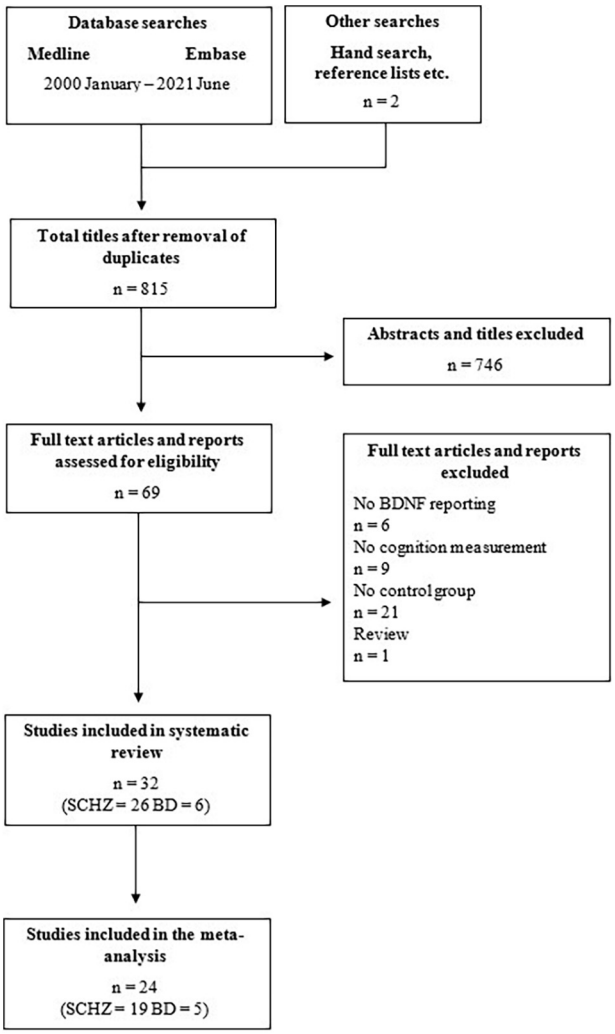


**FIGURE 1 |** PRISMA flowchart demonstrating the search strategy that was utilized for the systematic review and meta-analysis.

to 0.8) in 5 studies, and small (Hedges' $g$ under 0.5) in 11 studies (**Table 1**). Large effect sizes were predominantly acquired in studies with first episode schizophrenia (34, 35, 38, 41, 63). In contrast, small effect sizes were more likely to be seen in studies involving bipolar patients (4 out of 6 studies) (49, 51, 52, 55). The smallest effect sizes were associated with patients with CH and/or patients receiving antipsychotic medication monotherapy (40, 46, 58, 60, 61). Importantly, female patients also seemed to have BDNF levels closer to normal compared to males (52, 64).

The meta-analysis of 19 schizophrenia studies was conducted with a total of 2,970 patients versus 1,920 healthy controls (**Figure 2**). The random effects estimate showed a moderate reduction of BDNF levels in schizophrenia patients compared to healthy controls ($g = -0.65$, 95% CI: −0.90 to −0.40). The level of heterogeneity was high ($I^2 = 93\%$, $p < 0.01$). The meta-analysis of the 5 bipolar disorder studies involved a total of 392 patients and 293 controls (**Figure 3**). In case of bipolar disorder patients, the random effects model reported a small reduction of BDNF levels in bipolar disorder patients in contrast to health controls ($g = -0.32$, 95% CI: −0.71 to 0.06) with slightly lower heterogeneity ($I^2 = 79\%$, $p < 0.01$).

## Cognitive Dysfunction

The assessment of cognitive functions varied within the reviewed literature. Most commonly (12 studies) the RBANS (65) was applied, whereas 7 studies used other validated scales such as the MATRICS$^{TM}$ Consensus Cognitive Battery (MCCB) (40, 43, 66), the Cambridge Neuropsychological Test Automated Battery (CANTAB) (51, 67) or the Brief Assessment of Cognition in Schizophrenia (BACS) (60, 68). The RBANS is a brief test that evaluates five indexes: immediate memory, visuospatial/constructional, language, attention, and delayed memory (65). In contrast, the BACS measures cognition functions *via* verbal memory, verbal fluency, working memory, motor speed, attention, and executive functioning (68), while the MCCB evaluates peed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition (66). The rest of the studies chose a combination of individual assessments that measured specific cognitive domains such as executive functioning, inhibition, or different aspects of memory (e.g., verbal or visual memory) *via* tests such as the Wisconsin Card Sorting Test (WCST) or specific parts of the Wechsler Adult Intelligence Scale (WAIS) (44, 50, 59).

Importantly, almost all studies (29 out of 32) reported significant difference between patients and controls, with patients exhibiting deficits in several cognitive domains. Concerning schizophrenia studies, differences between first episode and chronic patients were detected; higher scores were found in the chronic population compared to the first-episode population on the RBANS, with mean scores of 70.3 and 66.0, respectively (**Table 2**). Differences between males and females were also prevalent; female patients, especially in chronic populations, had lower cognitive impairment than male patients (35, 47, 64).

The meta-analysis of 5 schizophrenia studies was conducted with a total of 871 patients versus 610 healthy controls (**Figure 4**). The random effects estimate showed a large reduction of RBANS scores in schizophrenia patients compared to healthy controls ($g = -2.26$, 95% CI: −3.43 to −1.09). The level of heterogeneity was high ($I^2 = 99\%$, $p < 0.01$).

In case of bipolar disorder, patients in all states (manic, depressive or euthymic) were found to perform worse than controls on the different cognitive tests (49–52). Interestingly, significant difference between manic compared to euthymic patients was found in only one domain (verbal memory) in a study by Mora et al. (50). Nonetheless, the scores of euthymic patients were still lower than that of healthy controls (50). Similar results were acquired in patients treated with lithium, where poorer results on all cognitive domains compared to controls were reported (51). Importantly, the study also highlighted that excellent lithium responders had numerically better results than non-excellent responders (51). Due to heterogeneity of cognition

**TABLE 1 |** Summary of studies.

| Study | Diagnosis | Patient N | Control N | BDNF type | BDNF in patients versus controls | BDNF ES (95% CI) | Cognition measures | Cognition in patients versus controls | BDNF-cognition relationship | Level of evidence (54) |
|---|---|---|---|---|---|---|---|---|---|---|
| Asevedo et al. (59) | SZ | 30 | 27 | Plasma | ↑ | 1.04 (0.52; 1.57) | Verbal learning, verbal fluency, working memory, set shifting, inhibition, executive function tests | Deficits in verbal learning | BDNF levels positively correlated with semantic generation tasks | B |
| Carlino et al. (42) | CH-SZ | 40 | 40 | Serum | ↓ | – | Processing speed, attention, executive function, working memory tests | Significantly poorer neurocognitive performance | Serum truncated-BDNF abundance predicted for high cognitive deficits | B |
| Chang et al. (55) | BD-II | 228 | 135 | Plasma | ↓ | −0.23 (−0.44; −0.01) | WMS | Significantly lower scores on 5 subtests of WMS | BDNF more likely to be associated with clinical characteristics than with memory | B |
| Chou et al. (49) | EU-BD-I | 23 | 33 | Plasma | NS | −0.02 (−0.55; 0.51) | Attention, memory, executive function tests | Cognitive deficits present | Deficits in cognition not significantly correlated with BDNF except two items from tests | B |
| Dell'Osso et al. (53) | D-BD-I | 16 | 15 | Plasma | ↓ | −1.71 (−2.55; −0.87) | Cognitive disturbances factor score form HRSD | NA | BDNF levels may be related to severity of depression and retardation symptoms | B |
| Dias et al. (52) | EU-BD-I | 65 | 50 | Serum | NS | 0.19 (−0.18; 0.56) | Attention and mental control, perceptual-motor skills, executive functions, verbal fluency and abstraction, visuospatial attention, memory tests | Significantly worse results on 11 out of the 16 neurocognitive tests | Significant positive association between serum BDNF levels and a test of verbal fluency in both BD patients and controls | B |
| Dong et al. (64) | SZ | 818 | 467 | Serum | ↓ | CLZ, MA: −0.85 (−1.02; −0.67)<br>CLZ, FE: −0.13 (−0.40; 0.15)<br>RISP, MA: −0.86 (−1.08; −0.64)<br>RISP, FE: −0.55 (−0.86; −0.24)<br>TYP, MA: −0.99 (−1.19; −0.78)<br>TYP, FE: −0.09 (−0.47; 0−29) | RBANS | Significantly lower scores | Association between BDNF and cognitive performance in only male patients and female patients taking typical antipsychotics | B |
| Hori et al. (46) | CH-SZ | 86 | 51 | Serum | NS | −0.32 (−0.67; 0.03) | IGT | Significantly lower scores in IGT | Negative correlation between BDNF levels and mean net scores on the trials in the final two blocks | B |
| Hori et al. (60) | SZ | 146 | 51 | Serum | NS | −0.24 (−0.56; 0.08) | BACS | NA | Negative correlations between serum BDNF levels and scores for verbal memory, attention and processing speed | B |
| Li et al. (70) | SZ | 472 | 225 | Serum | ↓ | −1.56 (−1,72; −1.40) | RBANS | Significantly lower RBANS total score | Serum BDNF independently positively correlated with attention and immediate memory | B |
| Man et al. (34) | FEP-SZ | 80 | 80 | Serum | ↓ | −1.22 (−1.56; −0.88) | RBANS | Significantly lower cognitive performance on the RBANS total and four of its five subscale scores | No significant correlation between BDNF and any index or total scores of RBANS | B |

*(Continued)*

**TABLE 1 |** (Continued)

| Study | Diagnosis | Patient N | Control N | BDNF type | BDNF in patients versus controls | BDNF ES (95% CI) | Cognition measures | Cognition in patients versus controls | BDNF-cognition relationship | Level of evidence (54) |
|---|---|---|---|---|---|---|---|---|---|---|
| Mora et al. (50) | EU-BD and MA-BD | 84 (52 EU; 32 MA) | 49 | Serum | ↓ | EU: −0.50 (−0.89; −0.10)<br>MA: −0.89 (−1.35; −0.44) | Executive function, selective attention, inhibition, processing speed, cognitive flexibility, sustained attention, perseverative behavior, verbal learning, recall, recognition, visual memory tests | Worse performance in executive functioning, inhibition, processing speed, verbal and visual memory | BDNF levels associated with executive functioning and verbal memory, together with other demographic variables | B |
| Niitsu et al. (61) | SZ | 63 | 52 | Serum | NS | 0.17<br>(0,20; 0.54) | WAIS-R, VFT, WCST, TMT, Stroop test, DSDT | Significantly worse performance on all tests | Serum BDNF levels related to the impairment of verbal working memory in patients | B |
| Penadés et al. (62) | SZ | 70 | 15 | Serum | NS | 0.25 (−0.31; 0.81) | Global cognition, working memory, processing speed, verbal memory, non-verbal memory, executive function tests | Significantly worse performance on most tests | No significant correlation between serum BDNF level and cognition | A |
| Qu et al. (35) | DN-FEP-SZ | 256 | 177 | Serum | ↓ | M: −1.07 (−1.28; −0.86)<br>F: −0.85 (−1.09; −0.62) | RBANS | Cognitive function decreased | No association between BDNF and cognitive function | B |
| de Azua et al. (36) | FEP-SZ | 45 | 45 | Plasma | ↓ | −0.78 (−1.20; −0.35) | Learning ability, immediate and delayed memory, abstract thinking, and processing speed tests | Cognitive performance of patients significantly worse | Plasma BDNF levels at 6 months after first hospitalization positively associated with several cognitive domains | B |
| Rybakowski et al. (51) | EU-BD-I | 60 | 60 | Plasma | ↓ | −0.43 (−0.80; −0.07) | CANTAB | Lithium-treated patients had poorer results on all domains of neuropsychological tests | Performance on neuropsychological tests and plasma BDNF levels in excellent lithium responders is different compared to patients lacking the optimal effect of lithium but not different compared to matched healthy controls | B |
| Tang et al. (82) | SZ | 109 | 40 | Serum | ↓ | DS: −2.44 (−2.86; −2.02)<br>NDS: −2.25 (−2.66; −1.84) | Processing speed, attention, executive function, working memory tests | Significantly worse performance | No correlations between BDNF levels and the cognitive tests in SZ and HC groups | B |
| Theleritis et al. (37) | FEP-SZ | 87 | 152 | Plasma | NS | 0.26 (−0.01; 0−52) | IQ, verbal memory and learning, visual memory, executive function, working memory, attention, concentration, processing speed, verbal fluency tests | NA | No association between BDNF plasma levels and cognitive functions | B |
| Vinogradov et al. (43) | CH-SZ | 56 | 15 | Serum | ↓ | −0.59 (−1.16; −0.03) | MCCB | Decrement in cognitive functioning (∼ 1 SD below the normal mean) | No significant association between change in BDNF and change in global cognition | A |
| Wei et al. (44) | CH-SZ | 189 | 60 | Serum | ↓ | −1.00 (−1.30; −0.70) | Executive function test | Executive function impaired | BDNF may be a useful biomarker for executive dysfunction | B |
| Wu et al. (45) | CH-SZ | 83 | 52 | Serum | ↓ | TD: −1.00 (−1.43; −0.57)<br>WTD: −0.65 (−1.05; −0.25) | RBANS | Significantly lower scores in almost all subscales | No significant associations between BDNF and RBANS total score or any cognitive index | B |

*(Continued)*

**TABLE 1 |** (Continued)

| Study | Diagnosis | Patient N | Control N | BDNF type | BDNF in patients versus controls | BDNF ES (95% CI) | Cognition measures | Cognition in patients versus controls | BDNF-cognition relationship | Level of evidence (54) |
|---|---|---|---|---|---|---|---|---|---|---|
| Wu et al. (38) | DN-FEP-SZ | 354 | 152 | Serum | ↓ | −1.08 (−1.27; −0.89) | RBANS | Extensive cognitive impairment | No significant association between BDNF levels and RBANS total score or its index scores | B |
| Xiao et al. (63) | DN-FEP-SZ | 58 | 55 | Serum | ↓ | −0.99 (−1.39; −0.65) | Verbal fluency, attention and processing speed, attention distribution, working memory, motor speed, and executive function tests | Significantly worse on nearly all neurocognitive tests | BDNF levels positively correlated with the animal subscale of the VFT and negatively correlated with TMT-part B scores | B |
| Xiu et al. (39) | SZ | 232 | 60 | Serum | ↓ | −0.81 (−1.10; −0.53) | Executive function tests | Significantly lower scores | Lower BDNF levels were correlated with executive dysfunction | B |
| Xiu et al. (56) | DN-FEP-SZ | 327 | 391 | Serum | ↓ | −0.88 (−1.04; −0.73) | RBANS | Significantly lower scores | No relationship between BDNF and cognitive impairments | B |
| Yang et al. (40) | FEP-SZ, CH-SZ | 65<br>34 FEP,<br>31 CH | 35 | Plasma | ↓ | FEP: −0.44 (−0.91; 0.04)<br>CH: −0.62 (−1.11; −0.13) | MCCB | Index scores remarkably lower | Low BDNF levels were associated with cognitive impairments | B |
| Zhang et al. (69) | SZ | 575 | 405 | Serum | ↓ | Val/Val: −0.77 (−1.02; −0.52)<br>Val/Met: −0.82 (−1.00; −0.65)<br>Met/Met: −0.88 (−1.15; −0.60) | RBANS | Significantly lower in cognitive scores in nearly all subscales | Higher serum BDNF levels were associated with better cognitive function | B |
| Zhang et al. (48) | CH-SZ | 251 | 206 | Serum | ↓ | −0.93 (−1.13; −0.74) | RBANS | Significantly lower scores | BDNF positively associated with immediate memory | B |
| Zhang et al. (47) | CH-SZ | 248 | 188 | Serum | ↓ | −0.91 (−1.10; −0.72) | RBANS | Worse performance on most of the cognitive tasks | BDNF positively associated with immediate memory in female patients | B |
| Zhang et al. (57) | SZ | 108 | 47 | Serum | ↓ | −1.70 (−2,05; −1.36) | RBANS | Significantly lower scores | Metabolic adverse effects of olanzapine may aggravate cognitive dysfunction in patients with schizophrenia through an interaction between BDNF | B |
| Zhang et al. (58) | AC-SZ | 68 | 47 | Plasma | ↓ | −0.52 (−0.89; −0.14) | RBANS | Decreased compared to controls | Increase in plasma levels of BDNF significantly correlated with the change in the RBANS total scores | B |

*AC, acute; BACS, Brief Assessment of Cognition in Schizophrenia; BD, bipolar disorder; BDNF, brain-derived neurotrophic factor; CANTAB, Cambridge Neuropsychological Test Automated Battery; CH, chronic; CLZ, clozapine; D, depressed; DN, drug-naïve; DS, deficit schizophrenia; DSDT, Digit Span Distraction Test; ES, effect size; EU, euthymic; F, female; FEP, first episode; HRSD, Hamilton Rating Scale for Depression; IGT, Iowa Gambling Task; MA, manic; M, male; MCCB, MATRICS Consensus Cognitive Battery; NDS, non-deficit schizophrenia; NA, not available, NS, not significant; RBANS, Repeatable Battery for the Assessment of Neuropsychological; RISP, risperidone; SZ, schizophrenia; TD, tardive dyskinesia; TMT, Trail Making Test; TYP, typical; VFT, Verbal Fluency Test; WAIS-R, Wechsler Adult Intelligence Scale Revised; WCST, Wisconsin Card Sorting Test; WMS, Wechsler Memory Scale; WTD, without tardive dyskinesia.*

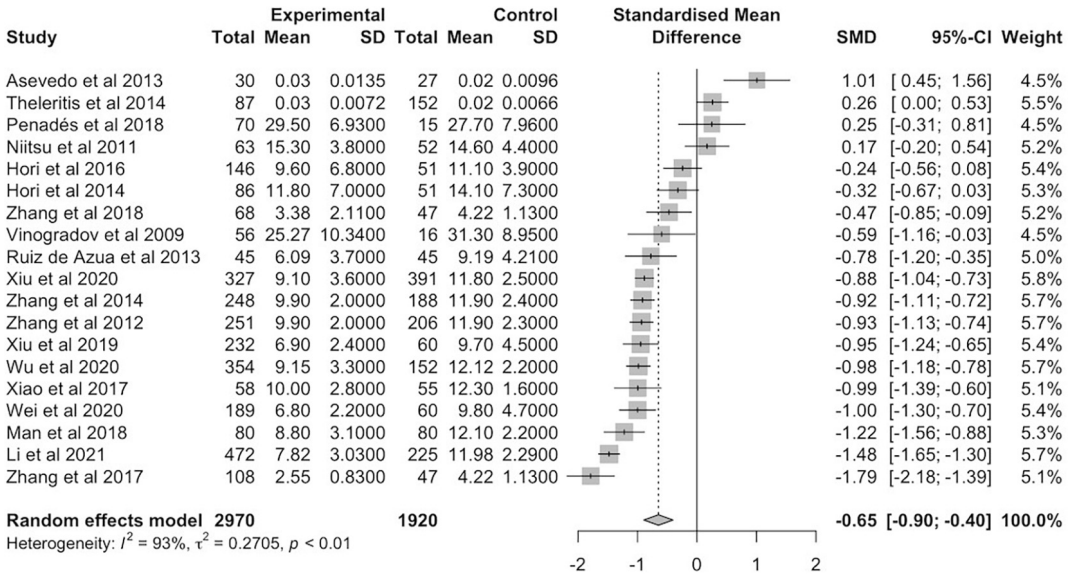


**FIGURE 2 |** Forest plot of standardized mean difference (SMD) in BDNF levels found in blood of patients with schizophrenia and healthy controls.

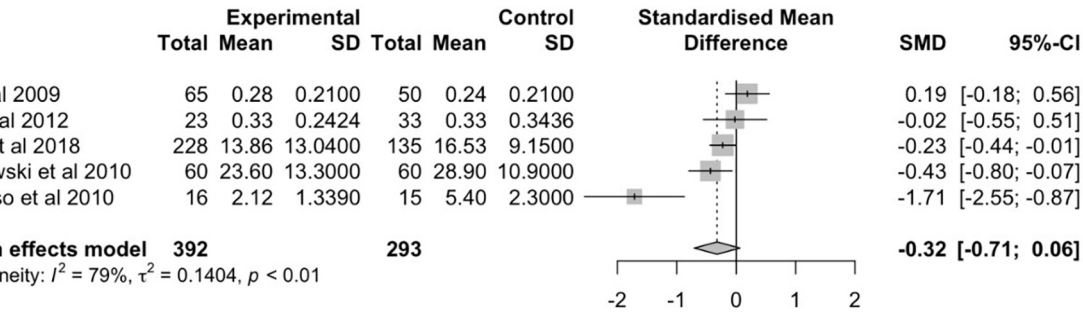


**FIGURE 3 |** Forest plot of standardized mean difference (SMD) in BDNF levels found in blood of patients with bipolar disorder and healthy controls.

measurements no meta-analysis could be conducted in patients with bipolar disorder.

## Correlation Between Blood Brain-Derived Neurotrophic Factor Levels and Cognitive Dysfunction

Correlations between circulating BDNF levels and cognitive functions in patients were calculated in 26 studies, out of which 16 studies reported Pearson's correlation coefficients, 5 Spearman's correlation coefficients and 5 partial correlation coefficients. Again, most of the studies correlated cognitive functions to BDNF serum levels, and only a few to plasma levels. In terms of cognitive functions, total scores, index scores, or individual test scores were included in the correlation analyses. All in all, 19 studies found significant correlations between circulating BDNF levels; correlation coefficients and $p$-values are shown in **Table 3**.

Most studies reported negligible ($r < 0.3$) (38–40, 46, 48, 52, 58, 60, 61, 63, 64, 69) or low ($0.3 < r < 0.49$) (39–42, 44, 45, 59, 64, 70) positive correlations between circulating BDNF levels and cognitive functions and only three studies found moderate ($0.5 < r < 0.7$) correlations (42, 47, 64). For instance, Dong et al. reported moderate positive correlation between baseline serum BDNF level and RBANS total score but only in female patients taking typical antipsychotic medications ($r = 0.55$, $p < 0.05$) (64). In contrast, correlations between BDNF serum levels and RBANS total scores were low in male patients taking typical antipsychotic medications ($r = 0.30$; $p < 0.01$) or risperidone ($r = 0.39$; $p < 0.01$) (64). Similarly, Zhang et al. found moderate positive correlation between BDNF serum levels and immediate memory index score from RBANS but only in chronic female schizophrenia patients (47). Finally, Carlino et al. found moderate positive correlation between low truncated-BDNF expression and performance on Trail Making Test Part B ($r = 0.55$; $p < 0.001$) in CH patients (42).

In general, significant correlations between circulating BDNF levels and cognitive assessments were more prevalent in the CH population, with 6 out of 7 studies reporting statistically significant correlation coefficients (42, 44–48). The specific

**TABLE 2 |** Baseline RBANS scores in first episode and chronic schizophrenia patients.

| Study | Schizophrenia patients | | Healthy controls | | Effect size | 95% confidence interval |
|---|---|---|---|---|---|---|
| | Subject (sex) | Mean RBANS score (SD) | Subject (sex) | Mean RBANS score (SD) | | |
| **First-episode schizophrenia** | | | | | | |
| Man et al. (34) | 80 | 64.0 (12.9) | 80 | 79.0 (12.3) | −1.19 | −1.50, −0.88 |
| Qu et al. (35) | 160 (M) | 66.4 (14.5) | 208 | 82.6 (13.1) | −1.16 | −1.39, −0.94 |
| | 118 (F) | 67.0 (17.6) | 181 | 80.5 (15.3) | −0.82 | −1.06, −0.58 |
| Xiu et al. (56) | 256 | 66.6 (15.9) | 180 | 80.2 (15.0) | −0.88 | −1.07, −0.69 |
| Summary, means | 685 | 66.0 (15.2) | 860 | 81.6 (14.5) | −1.01 | −1.25, −1.77 |
| **Chronic schizophrenia** | | | | | | |
| Dong et al. (64) (CLZ) | 357 (M) | 64.9 (14.7) | 193 (M) | 80.2 (15.0) | −1.02 | −1.20, −0.83 |
| | 63 (F) | 72.6 (17.4) | 274 (F) | 80.0 (15.3) | −0.46 | −0.74, −0.19 |
| Dong et al. (64) (RIS) | 135 (M) | 64.2 (16.0) | 193 (M) | 80.2 (15.0) | −1.02 | −1−26, −0.79 |
| | 48 (F) | 73.2 (14.3) | 274 (F) | 80.0 (15.3) | −0.44 | −0.75, −0.13 |
| Dong et al. (64) (TYP) | 184 (M) | 64.6 (13.9) | 193 (M) | 80.2 (15.0) | −1.06 | −1.28, −0.85 |
| | 31 (F) | 78.1 (18.4) | 467 (F) | 80.0 (15.3) | −0.12 | −0.48, 0.24 |
| Wu et al. (45) (WTD) | 35 | 63.9 (9.1) | 52 | 82.4 (12.5) | −0.74 | −1.14, −0.33 |
| | 48 | 73.4 (11.6) | 52 | 82.4 (12.5) | −1.62 | −2.11, −1.13 |
| Zhang et al. (48) | 251 | 71.7 (16.4) | 206 | 76.9 (16.0) | −0.33 | −0.51, −0.14 |
| Zhang et al. (47) | 216 (M) | 71.1 (15.2) | 72 (M) | 79.6 (13.1) | −0.57 | −0.84, −0.30 |
| | 63 (F) | 75.1 (17.1) | 90 (F) | 76.9 (14.8) | −0.11 | −0.43, 0.21 |
| Summary, means | 1,431 | 78.1 (14.9) | 2,066 | 79.9 (13.9) | −0.68 | −1.25, −0.77 |

*CLZ, clozapine; F, female; M, male; RISP, risperidone; SD, standard deviation; TYP, typical; WTD, without tardive dyskinesia.*

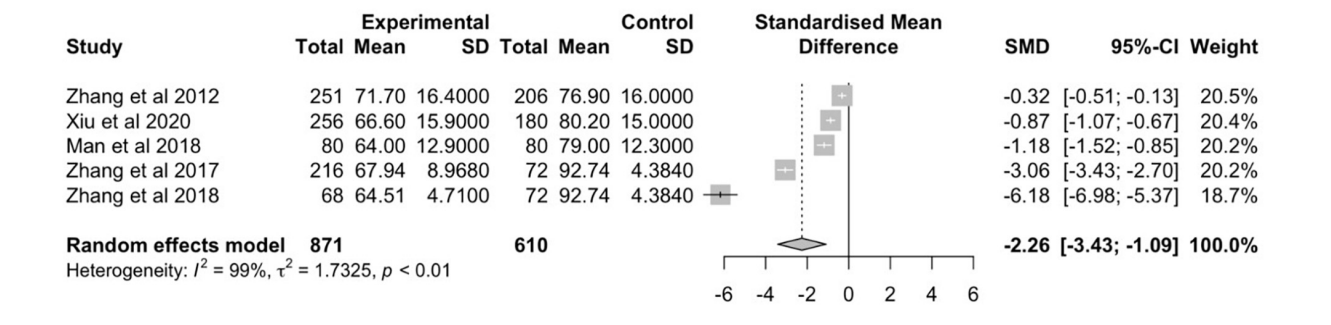


**FIGURE 4 |** Forest plot of standardized mean difference (SMD) in total mean RBANS scores measured in patients with schizophrenia and healthy controls.

domains associated with circulating BDNF levels were immediate (45, 47, 69), delayed (45) and working memory (42), decision making (46), speed of processing (42), executive (42), and verbal functioning (44). Interestingly, Wu et al. found different correlation directions depending on whether patients had tardive dyskinesia or not; serum BDNF levels of patients with TD correlated negatively with RBANS total score, and immediate and delayed memory indexes (45).

In case of (drug naïve) first episode patients, non-significant correlations between circulating BDNF levels and cognitive functioning were detected in the majority of studies (34, 35, 56). Only two studies by Wu et al. and Xiao et al. found significant correlations; Wu et al. reported negative correlation between delayed memory index from RBANs and serum BDNF levels ($r = -0.26$; $p < 0.05$), however only in patients with high baseline BDNF levels (38), Xiao et al. found negative correlation between serum BDNF levels and executive functioning ($r = -0.40$; $p < 0.01$) and positive correlation with verbal function ($r = 0.27$; $p < 0.05$) (41).

The rest of the studies examining schizophrenia detected significant correlations between circulating BDNF levels and semantic generation task (59), and verbal memory, attention and processing speed (60), verbal and executive functioning (39), and RBANS total score (58, 69, 70). Interestingly, correlations were different for schizophrenia patients with and without type 2 diabetes mellitus in a study by Li et al.; serum BDNF levels correlated with total RBANS score in non-diabetic schizophrenia patients only ($r = 0.33$; $p < 0.001$) (70).

Finally, in bipolar patients, circulating BDNF levels were reported to significantly correlate with specific domains of cognition in 2 out of the 3 studies that calculated coefficients, namely divided attention ($p < 0.05$) (49), faces memory ($p < 0.01$) (49), and verbal fluency ($r = 0.26$; $p < 0.05$) (52).

**TABLE 3 |** Correlations between BDNF levels and cognition.

| Study | Diagnosis | BDNF type | Cognition measurement | Correlation measure | Correlation coefficient |
|---|---|---|---|---|---|
| Asevedo et al. (59) | SZ | Serum | Semantic generation task<br>Letter memory task | Spearman's correlation | 0.38*<br>−0.45* |
| Carlino et al. (42) | CH-SZ | Serum | TMT Part B<br>Digit symbol coding<br>Digit span forward | Partial correlation | 0.55*** (low truncated BDNF)<br>0.36* (low truncated BDNF)<br>0.36* (low truncated BDNF) |
| Chou et al. (49) | EU-BD | Plasma | Sounds RT (divided attention)<br>Faces 2 true positive (faces memory) | Partial correlation | Data missing*<br>Data missing** |
| Dias et al. (52) | EU-BD | Serum | Test of verbal fluency (COWAT) | Pearson's correlation | 0.26* |
| Dong et al. (64) | SZ | Serum | RBANS total score | Pearson's correlation | 0.18** (CLZ, M)<br>0.39** (RISP, M)<br>0.30** (TYP, M)<br>0.55* (TYP, F) |
| Hori et al. (46) | CH-SZ | Serum | Card block 61–80 (IGT)<br>Card block 81–100 (IGT) | Pearson's correlation | 0.23*<br>0.27* |
| Hori et al. (60) | SZ | Serum | Verbal memory (BACS)<br>Attention and processing speed (BACS) | Pearson's and Spearman's correlation | 0.19*<br>0.16* |
| Li et al. (70) | SZ | Serum | RBANS total score | Pearson's correlation | 0.33*** (without T2DM) |
| Niitsu et al. (61) | SZ | Serum | Information subscale (WAIS-R) | Spearman's correlation | 0.29* |
| Wei et al. (44) | CH-SZ | Serum | VFT total score | Partial correlation | 0.33* |
| Wu et al. (45) | CH-SZ | Serum | RBANS total score<br>Immediate memory index (RBANS)<br>Delayed memory index (RBANS) | Pearson's correlation | −0.38* (TD)<br>0.32* (WTD)−0.36* (TD)<br>−0.38* (TD) |
| Wu et al. (38) | DN-FEP-SZ | Serum | Delayed memory index (RBANS) | Pearson's correlation | −0.26* (high−BDNF) |
| Xiao et al. (41) | DN-FEP-SZ | Serum | TMT Part B<br>VFT-animals | Spearman's correlation | −0.40**<br>0.27* |
| Xiu et al. (39) | SZ | Serum | VFT total score<br>WCST sub-score | Partial correlation | 0.30*<br>−0.27* |
| Yang et al. (40) | SZ | Plasma | Learning and memory (MCCB) | Pearson's correlation | 0.28* |
| Zhang et al. (69) | SZ | Serum | RBANS total score | Pearson's correlation | 0.21* |
| Zhang et al. (48) | CH-SZ | Serum | Immediate memory index (RBANS) | Pearson's correlation | 0.23*** |
| Zhang et al. (47) | CH-SZ | Serum | RBANS total score<br>Immediate memory index (RBANS) | Pearson's correlation | 0.34** (F)<br>0.51*** (F) |
| Zhang et al. (58) | AC-SZ | Plasma | RBANS total score<br>Attention index (RBANS) | Spearman's correlation | 0.28*<br>0.27* |

*p-Value: *<0.05, **<0.01, ***<0.001.*

*AC, acute; BACS, Brief Assessment of Cognition in Schizophrenia; BD, bipolar disorder; BDNF, brain-derived neurotrophic factor; CH, chronic; CLZ, clozapine; COWAT, Controlled Oral Word Association Test; DN, drug naïve; F, female; FEP, first episode; EU, euthymic; IGT, Iowa Gambling Task; M, male; MCCB, MATRICS Consensus Cognitive Battery; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; RISP, risperidone; SZ, schizophrenia; TD, tardive dyskinesia; TMT, Trail Making Test; TYP, typical; VFT, Verbal Fluency Test; WAIS-R, Wechsler Adult Intelligence Scale Revised; WCST, Wisconsin Card Sorting Test; WTD, without tardive dyskinesia.*

## Changes in Brain-Derived Neurotrophic Factor Levels and Cognitive Dysfunction After Treatment

Altogether, 4 of the 32 reviewed studies examined the changes in BDNF levels and cognitive functions before and after treatment, all with schizophrenia patients. Two studies focused on the effects of pharmacotherapy (38, 58) and two studies on the impact of non-pharmacological interventions such as cognitive remediation (62) and computerized auditory training (43) as summarized in **Table 4**. In case of the latter, 56 schizophrenia outpatients were randomized to 10 weeks of computerized

**TABLE 4 |** Brain-derived neurotrophic factor levels and cognition scores at baseline and after treatment.

| Study | Patient (*N*) | Treatment | BDNF, mean (SD) | | Cognition measure | Cognition, mean (SD) | |
|---|---|---|---|---|---|---|---|
| | | | Before | After | | Before | After |
| Penadés et al. (62) | 35 | 4-month cognitive remediation | 26.1 (7.4) | 27.9 (9.1) | Global cognition | 43.26 (4.62) | 48.48 (4.32) |
| | | | | | Working memory | 47.95 (9.91) | 50.35 (8.84) |
| | | | | | Processing speed | 43.15 (7.21) | 48.82 (6.28) |
| | | | | | Verbal memory | 37.99 (7.86) | 44.75 (7.71) |
| | | | | | Non-verbal memory | 44.24 (8.35) | 47.90 (6.12) |
| | | | | | Executive function | 40.88 (7.94) | 49.11 (6.55) |
| | | | | | Quality of life EQ-5D | 4.79 (1.12) | 6.74 (1.12) |
| Vinogradov et al. (43) | 29 | 50-h computerized auditory training | 25.3 (10.3) | 32.2 (15.1) | Global cognition | – | – |
| | | | | | Speed of processing | | |
| | | | | | Verbal working memory | | |
| | | | | | Verbal learning | | |
| | | | | | Verbal memory | | |
| | | | | | Problem solving | | |
| | | | | | Non-verbal working memory | | |
| | | | | | Visual learning | | |
| | | | | | Visual memory | | |
| | | | | | Social cognition | | |
| Wu et al. (38) | 190 | 12-week risperidone monotherapy | 9.1 (3.3) | 10.8 (6.3) | RBANS | – | – |
| Zhang et al. (58) | 68 | 12-week olanzapine monotherapy | 3.4 (2.1) | 4.7 (1.7) | RBANS | 322.57 (23.55) | 339.34 (43.51) |

*N, number; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SD, standard deviation.*

auditory training or control condition (computer game) and were compared to 16 matched healthy controls. According to the results, statistically significant change was detected in global cognition as well as BDNF levels in response to the training (43). By week 10, the BDNF levels in patients were comparable to that of healthy controls; at baseline these were significantly lower than of the healthy controls (43). Nonetheless, no significant association was found between the changes in BDNF levels and the cognitive measurements (43). The other study that examined the effects of non-pharmacological treatment on BDNF levels and cognitive impairment randomized 70 patients to either cognitive remediation therapy (CRT) or social skills training (control group) for 4 weeks (62). Although some improvements in cognition were detected, the authors could not report any significant changes in serum BDNF levels in response to the CRT (62). Moreover, the association between cognitive improvements and BDNF levels were also non-significant (62). Both RCTs evaluated cognition *via* the MCCB (43, 62).

In terms of pharmacological therapies, Zhang et al. designed a 12-week open-label, prospective observational trial to examine the effects of olanzapine on BDNF and cognitive functioning and thus to evaluate if BDNF can act as a biomarker for cognition (58). At baseline, the 95 patients exhibited significantly worse cognitive performance as measured by RBANS and lower plasma BDNF levels than the 72 controls (58). In response to olanzapine treatment, significant improvements in immediate memory, attention, and total RBANS score as well as increased plasma BDNF levels compared to baseline were detected (58). Importantly, the increase in BDNF plasma levels showed correlation with the change in the RBANS scores (58). Based on the results, the authors concluded that plasma BDNF levels might be a potential biomarker for cognitive functioning in patients with acute schizophrenia (58).

Similarly, Wu et al. conducted a 12-week, flexible-dose, prospective, observational trial in 354 drug-naïve FEP with schizophrenia (38). The aim was to evaluate the impact of risperidone treatment on serum BDNF levels and cognitive functioning measured by RBANS (38). According to the results, poorer cognitive functioning and lower serum BDNF levels were detected at baseline in patients compared to 152 controls (38). In response to treatment, significant improvement in memory, delayed memory and RBANS total score as well as slight increase in BDNF levels was found (38). Interestingly, when separating patients to low-BDNF and high-BDNF baseline groups, different responses to antipsychotic medication were acquired (38). Those in the low-BDNF group had increased, while those in the high-BDNF group had decreased plasma levels after risperidone treatment (38). In addition, correlations between lower BDNF levels and delayed memory were also detected, but only in patients who had higher baseline BDNF levels (38).

## DISCUSSION

To our knowledge this is the first systematic review and meta-analysis that examined circulating BDNF levels and cognitive dysfunction in patients on the schizophrenia-bipolar spectrum. The aim of the paper was threefold: to update the existing literature regarding the differences between patients and healthy controls in blood BDNF levels and

cognitive functioning, to compare patients with schizophrenia, bipolar disorder, and schizoaffective disorder in terms of circulating BDNF levels and cognitive dysfunction, and to understand the relationship between BDNF and cognition in these patient populations. The relevance of the results is discussed below.

The results confirmed that there is a moderate reduction in patients with schizophrenia and small reduction in patients with bipolar disorder in serum or plasma BDNF levels compared to healthy controls. The results are in line with previous meta-analyses that also found moderate quality evidence of reduced blood BDNF levels in these patient groups (16, 71–73). Similarly to the results of a comparative meta-analysis by Fernandes et al., the present study also agrees that the decrease in circulating BDNF levels compared to healthy controls is greater in acute patients than in those in chronic or euthymic states (73). Differences in blood BDNF levels also seem to depend on several other factors including sex, age, or medication, which was again shown by previous research as well (74, 75).

In contrast to circulating BDNF levels, cognitive impairment was found to be pronounced in all states and stages of the disorders, confirming that indeed cognitive deficits are a core feature of the schizophrenia-bipolar spectrum. Interestingly however, better scores on different cognition assessments were reported in patients with CH compared to patients in first episode. In terms of the relationship between circulating BDNF levels and cognitive functioning, significant but negligible correlations were found in more than one third of the reviewed studies. Differences between patient groups were also prevalent in this aspect of the analysis as well; significant correlations were more likely to be found in chronic patients compared to first episode patients, and in female patients compared to males.

All in all, circulating BDNF levels alone do not seem to be a valid biomarker of cognitive dysfunction in patients on the schizophrenia-bipolar spectrum. Although BDNF has been repeatedly found to be reduced in patients compared to healthy controls, the correlations between BDNF and cognition are weak. This is especially true for drug naïve first episode patients who have high levels of cognitive dysfunction and low levels of blood BDNF, yet the two are not correlated. Indeed, the relationship between cognition and BDNF is more pronounced in patients with CH, suggesting that factors such as age or state of disorder might be mediating this relationship. This has been proposed by previous reviews as well; although the meta-analysis by Bora et al. found correlation between cognitive symptoms and BDNF levels, they also concluded that the relationship between the two might be rather indirect (30). In addition, Fernandes et al. came to similar conclusions too, suggesting that reduced BDNF levels might be connected to the suppressive effects of stress (73).

If putting these results into context, it is likely that the reason why most reduction in BDNF levels was detected in first-episode, drug naïve patients is due to that fact that these patients experience the highest levels of stress. As the stress levels are lower in chronic, medicated, and euthymic patients, the BDNF levels are less influenced by it and hence correlations between cognitive symptoms are more prevalent. The fact that most correlations in this patient population were found in executive functioning, immediate memory, and processing speed – neurocognitive functions all mediated by the hippocampus and prefrontal cortex – further supports this notion.

Finally, it deserves attention from clinical point of view that blood BDNF levels and cognitive symptoms were found to improve after certain therapies and antipsychotic medications. In case of pharmacotherapy, the improvement in cognitive functioning and circulating BDNF levels were even correlated. Some experimental results suggest that $D_3$ receptors may also play a role in influencing BDNF levels and cognitive improvement (76–79). Thus, further research needs to investigate whether novel medications targeting $D_3$ receptors have different effects on BDNF levels in patients on the schizophrenia-bipolar spectrum and how these potential changes in BDNF levels would relate to cognitive impairment.

## Limitations

The main limitation of this systematic review is the heterogeneity of the studies; large differences in sample sizes, patient populations, BDNF measurements (plasma or serum) and cognitive scales were prevalent. Due to this heterogeneity the relationship between BDNF levels and cognitive dysfunction could not be quantified, as neither the Hedges–Olkin nor the Schmidt–Hunter method is suitable for a small number of heterogeneous studies (80). In addition, according to Rosenfeld et al., there is significant difference between BDNF serum and plasma levels, nonetheless as previous reviews, this review also analyzed serum and plasma BDNF levels together (81). Furthermore, in some articles, potential overlap in samples were detected, hence, introducing bias to the analysis. The systematic review also did not account for neither the maturity of BDNF nor BDNF polymorphism, which could play an important role in determining BDNF levels in the periphery. Finally, no studies with exclusively schizoaffective patients were obtained, hence, this patient group is missing from the schizophrenia-bipolar spectrum.

# CONCLUSION

While it has been confirmed that blood BDNF levels, especially during the acute phases are decreased, there are several factors that influence circulating BDNF levels making it unreliable as a biomarker of cognitive dysfunction alone. In contrast, circulating BDNF might be considered as a psychiatric state marker and thus, changes in BDNF levels in the plasma/serum should be evaluated in the context of a wider pattern of risk and protective factors such as inflammatory, immune, and metabolic parameters. Nonetheless, this does not necessarily mean that targeting BDNF would not influence cognition positively. Future research should

investigate how different treatments influence circulating BDNF levels and cognitive symptoms, especially executive functioning, and memory, and whether there is a correlation between the changes detected.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## AUTHOR CONTRIBUTIONS

ZD, IS, and PB contributed to conception of the manuscript. ZD wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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CASE REPORT
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# Case Report: Functional and Symptomatic Improvement With Cariprazine in Various Psychiatric Patients: A Case Series

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Cariprazine is a third-generation antipsychotic medication approved for the treatment of schizophrenia and bipolar disorder, with unique pharmacodynamic and pharmacokinetic properties. In this case series, the functional and symptomatic improvement of three patients who had been diagnosed with different psychiatric disorders and who exhibited various symptoms from psychotic to mood symptoms is described. The first case is about a young male patient with bipolar disorder and cocaine abuse who managed to become abstinent from cariprazine. The second and third cases describe patients with psychosis suffering from positive, cognitive and mood symptoms who were non-adherent to previous medication. In both cases, cariprazine was well-tolerated and effective in alleviating symptoms, thus improving their everyday functioning as well. In the discussion, the associations between symptom domains and the receptor profile of cariprazine are also highlighted, providing an explanation of the observed effects. It is concluded that cariprazine is a good treatment option for patients with symptoms of psychosis and addiction; is well-tolerated without the induction of side effects such as weight gain or sedation; and is appropriate for patients who have problems with adherence.

**Keywords: partial agonist, cariprazine, schizophrenia, drug abuse, bipolar disorder, cocaine-seeking relapse, antipsychotic**

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## INTRODUCTION

Cariprazine is a third-generation antipsychotic medication with a unique mechanism of action; it is a dopamine $D_3/D_2$ and serotonin $5HT_{1A}$ partial agonist and serotonin $5HT_{2A}$ antagonist with preferential binding to the $D_3$ receptors (1). Research showed that cariprazine has almost 10-fold greater *in vitro* affinity for the $D_3$ receptor than for the $D_2$, while *in vivo*, the occupancy of the $D_3$ and $D_2$ receptors are balanced (2, 3). Cariprazine also has a high affinity for the $5HT_{1A}$ and $5HT_{2B}$ receptors and a low affinity for $5HT_{2A}$, $5HT_{2C}$, histaminergic, adrenergic, and cholinergic receptors – as seen in **Table 1** (4). It is metabolized by the CYP3A4 enzyme into two major active metabolites: desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR), both pharmacologically equipotent to cariprazine and known to be jointly responsible for the overall therapeutic effect (5). According to the product label (6), the mean concentrations of DDCAR and DCAR relative to cariprazine by the end of a 12-week treatment are 400 and 30%, respectively

**TABLE 1 |** Receptor profile and binding affinities of cariprazine.

| Receptor | Binding profile | Affinity category | Ki (nM) |
|---|---|---|---|
| Dopamine type 3 | Partial agonist | High | 0.085 |
| Dopamine type 2L | Partial agonist | High | 0.49 |
| Dopamine type 2S | Partial agonist | High | 0.69 |
| Serotonin type 2B | Antagonist | High | 0.58 |
| Serotonin type 1A | Partial agonist | High | 3.0 |
| Serotonin type 2A | Antagonist | Moderate | 19.0 |
| Histamine type 1 | Antagonist | Moderate | 23.0 |
| Serotonin type 7 | Antagonist | Low | 111.0 |
| Serotonin type 2C | Antagonist | Low | 134.0 |
| Alpha type 1A | Antagonist | Low | 155 |
| Muscarinic | Antagonist | No appreciable affinity | $IC_{50}$ > 1,000 |

*Ki, Inhibition Constant; PDSP, Psychoactive Drug Screening Program. All Ki values have been taken from the PDSD Ki database except for alpha type 1A and muscarinic Ki values that are from Citrome 2015 (4).*

**TABLE 2 |** Pharmacokinetic proprieties of cariprazine.

| Pharmacokinetic | Drug information |
|---|---|
| Absorption | Following multiple-dose administration, peak plasma concentrations for cariprazine and the major active metabolites occur at approximately 3–8 h post dose |
| Distribution | Based on a population pharmacokinetic analysis, the apparent volume of distribution (V/F) was 916 L for cariprazine, 475 L for DCAR, and 1,568 L for DDCAR, indicating an extensive distribution of cariprazine and its major active metabolites. Cariprazine and its major active metabolites are highly bound (96–97% for CAR, 94–97% for DCAR, and 92–97% for DDCAR) to plasma proteins. |
| Metabolism | Cariprazine is metabolized by CYP3A4 and, to a lesser extent, by CYP2D6, to DCAR and HCAR. DCAR is further metabolized by CYP3A4 and to a lesser extent by CYP2D6 to DDCAR and HDCAR. DDCAR is further metabolized to HDDCAR by CYP3A4. |
| Elimination | Mainly through hepatic metabolism. Following administration of 12.5 mg/day cariprazine to patients with schizophrenia, 20.8% of the dose was excreted in urine as cariprazine and its metabolites. Unchanged cariprazine is excreted by 1.2% of the dose in urine and 3.7% of the dose in feces. |

*HCAR, hydroxy cariprazine; HDDCAR, hydroxy didesmethyl cariprazine.*

(**Table 2**). This unique pharmacokinetic profile and mechanism of action, i.e., the $D_3$ affinity combined with the actions of the different 5HT receptors, makes cariprazine capable of alleviating the symptoms of different psychiatric disorders, such as schizophrenia or bipolar I disorder.

Indeed, cariprazine is currently approved for the treatment of schizophrenia in adults (1.5–6.0 mg/day), as well as for the treatment of depressive, acute manic, or mixed episodes associated with bipolar I disorder (3.0–6.0 mg/day) by the Food and Drug Administration (FDA). In Europe, the European Medicines Agency (EMA) also approved cariprazine for the treatment of schizophrenia in adults. Moreover, recent results of Phase II clinical trials found support for the notion that cariprazine is also effective for the adjunctive treatment of the major depressive disorder (MDD) (7).

The aim of the current paper was to present three patient cases who have been successfully treated with cariprazine and achieved improvements in both their symptoms and functionality. A short summary of the cases is presented in **Table 3**. The present report was written following the CARE guidelines (8).

## CASE 1: IMPROVEMENT OF DYSTHYMIC DISORDER AND SUBSTANCE ABUSE IN A BIPOLAR PATIENT

The first case describes a 35-year-old male patient with bipolar disorder who had been followed by the Adult Mental Health Service (AMHS) for about 10 years.

The family history of the patient revealed psychiatric disorders on the paternal side; the patient's father suffers from bipolar disorder and was hospitalized for anticonservative gestures, while his uncle was diagnosed with schizophrenia. In terms of birth and childhood, the patient was born at full term with vaginal delivery, and during his early school years, he showed sufficient performance with the help of a support teacher. Nonetheless, from the ages of 7–9, he had several serious nightmares from which he could not be awakened. He then began to use drugs such as cannabis, Lysergic acid diethylamide (LSD), and Methylenedioxymethamphetamine (MDMA) at the age of 13. About 4 years later, he switched to heroin and cocaine and was therefore referred to the Addiction Treatment Service. He received treatment with buprenorphine for about 3 years, which allowed him to become drug-free. Due to this episode of substance abuse and difficulties in interpersonal relationships, the patient obtained a high school qualification later than his peers.

In 2012, the patient was presented at the AMHS for the first time due to repeated suicide attempts, for example, *via* ingesting dangerous doses of drugs. He exhibited a dysphoric mood with high levels of anxiety. Nonetheless, he had no serious alterations in thoughts or sensory disturbances, and his drug test was also negative. A treatment with valproic acid (1,000 mg/day), quetiapine prolonged release (250 mg/day), and paroxetine (30 mg/day) was started. Some improvement in affective symptoms was achieved, allowing the patient to work at a mechanical company.

Due to a later relapse of dysthymic disorder, he sought urgent help from the AMHS. His medication regimen was changed (valproic acid 1,000 mg/day, paroxetine 30 mg/day, bupropion 300 mg/day, and quetiapine prolonged release 600 mg/day), but it did not yield sufficient improvements. As self-medication, the patient started to use cocaine again on a weekly basis, hoping that this will allow him to improve his dysthymic symptoms and return to work.

In 2020, cariprazine was offered as an add-on therapy to his existing medication regimen (valproic acid, selective serotonin reuptake Inhibitors, and bupropion), which the patient accepted. Cariprazine was started at 1.5 mg/day for 7 days with a subsequent increase to 3 mg/day. By the third week of cariprazine

**TABLE 3 |** Summary and comparison of the clinical cases.

| | Case 1 | Case 2 | Case 3 |
|---|---|---|---|
| Sex | M | M | F |
| Family history | Psychological disorders | Negative | Depressive disorder |
| Illness duration | 10 years | 3 years | 3 years |
| Age at first psychiatric evaluation at AMHS | 25 years | 35 years | 29 years |
| Diagnosis | Bipolar disorder | Schizophrenia | Schizophrenia |
| Suicide attempts | Yes | No | No |
| Drug abuse | Cannabis, LSD, MDMA, heroin, cocaine | No | No |
| Previous treatments | Valproic acid 1,000 mg/day, quetiapine prolonged release 250 mg/day, and paroxetine 30 mg/day<br>Valproic acid 1,000 mg/day, paroxetine 30 mg/day, bupropion 300 mg/day, and quetiapine prolonged release 600 mg/day | Amitriptyline 10 mg/day and perphenazine 4 mg/day | Olanzapine 5 mg/day up titrated to 10 mg/day<br>Olanzapine 10 mg/day and venlafaxine up to 150 mg<br>Lurasidone up to 148 mg<br>Aripiprazole up to 30 mg<br>Paliperidone up to 9 mg |
| Dosages of cariprazine | 1.5 mg/day increased to 3 mg/day after 7 days | 1.5 mg/day increased to 3 mg/day after 7 days | 1.5 mg/day increased to 3 mg/day after 6 days and further increased to 4.5 mg/daily after 7 days |

treatment, the use of cocaine progressively decreased, and then, it was completely terminated. In addition, feelings of anguish and other affective symptoms were also reduced. After 2 months of cariprazine treatment, a state of euthymia was observed with good tolerability and no cocaine consumption.

## CASE 2: ALLEVIATING COGNITIVE SYMPTOMS OF PSYCHOSIS

The second case is about a 38-year-old male patient with psychosis, keratoconus, and obesity. The patient was born vaginally, but during early childhood, he showed a delay in psychomotor development, for which he was referred to a child neuropsychiatry clinic and was assigned a speech therapist and a support teacher. He had no family history of psychiatric disorders, although his parents might have mild intellectual disability. Until his first visit to the AMHS, he was functioning well with a fair level of autonomy; he had temporary jobs such as gardening, obtained a driving license, and had a group of peers linked to the parish. He never took psychotropic drugs and lived with his elderly parents.

In 2021, the patient presented at the AMHS with various neuropsychiatric symptoms: he had two episodes of short-lived prosopagnosia, initial insomnia, and stopped driving his car due to fear of not being able to find the road. In addition, he also developed difficulties in writing and choosing the right words, stuttering as well as mental confusion. During his hospitalization in the intensive care unit, various examinations, such as magnetic resonance imaging (MRI), electroencephalogram (EEG), and brain computed tomography (CT), were carried out to understand the nature of his symptoms. As all the tests were negative, he was discharged and referred to the outpatient psychiatric clinic.

During his first visit, he appeared to be perplexed, confused, depressed, and anxious. Furthermore, he presented with obsessive ideation with doubts of harm, ideas of reference and influence such as "it seems to me that the television talks about me," and repetition of fixed phrases and automatisms. Although he had social and cognitive (attention, concentration) difficulties, no alterations in sensation and perception were reported. Due to his symptoms, he was unable to continue working.

The patient received a combination treatment (amitriptyline 10 mg/day and perphenazine 4 mg/day), which was ineffective due to non-adherence. Then, treatment with cariprazine was initiated with 1.5 mg/day and increased to 3.0 mg/day due to good tolerability and a partial response after a week. At the same time, amitriptyline 10 mg/day and perphenazine 4 mg/day was still prescribed. In response to treatment with cariprazine, the patient was more relaxed and less confused with a more fluid and organized speech at the control visit. Further improvements were seen after 1 month; delusional thoughts and concentration difficulties disappeared, sleep became regular, and social skills returned almost to the level of premorbid functioning.

Three months after the initiation of cariprazine treatment, the patient returned to work and remained adherent to the medication, which did not induce any side effects. Importantly, no weight gain occurred with cariprazine, which, given his obesity, would have influenced adherence negatively and would have been harmful to the physical health of the patient.

## CASE 3: ACHIEVING EUTHYMIA AFTER FREQUENT SWITCHING

The third case report describes a 32-years old Albanian female patient who moved to Italy at the age of 18 after finishing high school and getting married, leaving her parents and siblings behind. Although at first, she worked in a manufactory, later she decided to stay at home and focus on the upbringing of her two children. Her family history was positive for depressive disorder, but her personal history was negative.

Before seeking help at the psychiatric unit, she had been maintaining an extramarital relationship for several months and developed delusional beliefs such as that her phone was under the control of her lover and his friends. In addition, she also developed ideas of reference, interpreting promotional messages as personal messages with which her lover tried to communicate.

When she first sought help at the psychiatric unit, she seemed cooperative, attentive, and oriented to time, person, place, and circumstances. She had normal personal hygiene and clothing and could maintain attention and concentration. Her speech was rapid, but appropriate in volume, quantity, and quality. The content of her thoughts was characterized by the abovedescribed delusional beliefs, causing growing feelings of anguish and anxiety. No hallucinations were reported. Her mood was dysphoric, and she reported sleep disturbances. Although her level of awareness and insight was poor, she acknowledged impairments in social and personal functioning.

In 2019, pharmacological treatment with olanzapine 5 mg/day was initiated. After an up-titration to 10 mg/day, a rapid decrease in dysphoria, anxiety, and hyperarousal was detected along with restoration of sleep patterns. Nonetheless, after a few months of treatment, the patient developed a depressed mood which was then addressed with the antidepressant therapy (venlafaxine 150 mg/day). In 4–6 weeks, full remission was achieved.

Six months later, the patient showed up again at the clinic; she stopped taking olanzapine due to side effects (excessive sedation and weight gain), which resulted in the reoccurrence of psychotic symptoms. First, lurasidone (148 mg/day) was prescribed without any success, then aripiprazole (30 mg/day), which was stopped because of the development of akathisia, and finally paliperidone (9 mg/day), which was also terminated due to amenorrhea.

Pharmacological treatment with cariprazine (1.5 mg/day) was initiated in 2021. After 6 days of treatment, the dose was increased to 3.0 mg/day, and after another week, it was further increased to 4.5 mg/day due to good response and no adverse effects. Within a few weeks, the patient achieved remission of psychosis and eventually euthymia, so she started looking for a new job.

## DISCUSSION

The above-described clinical cases provide a detailed insight into the characteristics of cariprazine in terms of both effectiveness and tolerability. They show how cariprazine has the ability to address a range of symptoms from delusions to cognitive disturbances regardless of disorder type and without the induction of metabolic, endocrine, or cardiovascular side effects that are common with other antipsychotic medications.

For instance, the first case of the series describes the effectiveness of cariprazine in a bipolar disorder patient with symptoms of mood and addiction. The efficacy of cariprazine in bipolar depression was established in three short-term, double-blind, placebo-controlled, randomized Phase II/III clinical trials where the change from baseline to week 6 on the Montgomery Asberg Depression Rating Scale (MADRS) was significantly greater in patients treated with cariprazine (1.5–3.0 mg/day) compared with patients on placebo (9–11). The effectiveness of cariprazine in mood is attributed to the fact that it acts as a partial agonist at the presynaptic $D_3$ receptors in the ventral tegmental area (12) as well as it has a relatively high affinity for the $5HT_{1A}$ receptors that are related to the antidepressant effect (13). Importantly, $D_3$ receptors might also be involved in substance abuse as they are highly expressed in the reward circuitry of the limbic system, which is responsible for motivation and emotions (14, 15). Indeed, results from preclinical studies indicate that $D_3/D_2$ partial agonists might be effective in preventing relapse of cocaine abuse (16) and that $5HT_{2B}$ antagonists may contribute to the prevention of MDMA relapse (17). In line with these preclinical studies, other cases have also shown the benefits of cariprazine in the treatment of bipolar disorder with substance abuse (18, 19). Similar to the present case, Sanders and Miller described a 51-year-old male bipolar disorder patient with alcohol use and cocaine craving, who became abstinent with cariprazine monotherapy (18). In addition, there are two running clinical trials that aim to examine the efficacy of cariprazine in substance abuse disorder, indicating that there is a definite potential for using cariprazine in the field of addiction (20, 21).

The other cases describe patients with different psychotic symptoms; while in the case of the second patient, cognitive disturbances and mood symptoms were prevalent, the third patient was suffering more from positive symptoms, mainly delusional thoughts. Regarding the latter, the efficacy of cariprazine in acute schizophrenia was studied in three short-term, double-blind, placebo-controlled, Phase II/III clinical trials where the primary outcome measure was mean change from baseline to week 6 on the Positive and Negative Syndrome Scale (PANSS) (22–24). Importantly, pooled results of these trials indicated statistically significant differences versus placebo on all 5 PANSS factors: positive, negative, cognitive, anxiety/depression, and hostility/excitement (25). These results can be explained again by the unique receptor profile of cariprazine. The high affinity for the $D_3$ receptor seems to be responsible for the effect on the negative, cognitive, and anxiety/depression symptoms, while the $D_2$ for the positive and hostility/excitement symptoms (4). The other receptor affinities such as serotonergic, histaminergic, adrenergic, and cholinergic receptor affinities also account for the effectiveness on negative and cognitive symptoms as well as for the favorable safety profile (4). Indeed, the incidence of sedation, hyperprolactinemia, and metabolic side effects are low with cariprazine (26) which has been also highlighted in the second patient as a definite advantage, given that he had already been suffering from obesity and further weight gain would have worsened his physical health. The absence of weight gain was important for the third patient as well, as previously this was one of the reasons why she stopped her treatment with olanzapine. Although the most common side effect of cariprazine is akathisia (26), it has not been reported by any of the patients. In fact, in the third patient case, aripiprazole, another partial agonist, was terminated due to akathisia, whereas no such incidence happened when the patient switched to cariprazine. Finally, choosing cariprazine as a treatment for the second patient was also supported not only by the fact that cariprazine is a well-tolerated medication but also because it has a long half-life (27). This was important given the fact that this patient showed poor adherence previously.

It is also important to note that the described patients also experienced functional improvement. Being able to return to work is often less emphasized than symptomatic improvements even though it is a clear indication of the patient's level of functioning. *Post hoc* analyses of clinical trials and other reviews also suggest that cariprazine has the ability to improve everyday functioning in patients with schizophrenia (28, 29) and bipolar disorder (30).

To conclude, the pharmacokinetic and pharmacodynamic characteristics of cariprazine make this third-generation antipsychotic medication a first-line treatment option in patients with symptoms of psychosis, addiction, and mood, who also displayed poor adherence to treatment as well as high metabolic and cardiovascular risks. Cariprazine provides a solution to all these aspects, allowing the patients to achieve full remission and functional improvement.

## DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## 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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