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RESEARCH TOPIC
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Content

Novel Antipsychotics Within and Beyond Clinical Trials: The Treatment of Overlapping Psychiatric Disorders with D3-D2 Partial Agonists

Novel, third-generation antipsychotic medications, such as cariprazine, have a unique mechanism of action characterized by D3-D2 partial agonism. Over the past few years, several papers have been published detailing the efficacy and safety of such antipsychotics in schizophrenia, mania, and bipolar depression based on the results of several phase II and III clinical trials. While such data is vital, it is high time to explore the characteristics of novel antipsychotics further - not just within, but beyond the scope of clinical trials, as well as to increase the understanding of the role of D3-D2 partial agonism both theoretically and from experience in overlapping psychiatric disorders such as schizophrenia, schizoaffective disorder, bipolar disorder, mania or even major depression.

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. Moving from previous treatment aims such as response and remission to recovery, the ultimate goal of modern psychiatry is to provide the right treatment to the patient at the right time. Given the fact that many of the major psychiatric disorders have shared genetic, neural as well as symptomatic elements, there is a high probability that there are common medical solutions too. Based on the results of several phase II and III clinical trials that have shown efficacy in schizophrenia, mania, and bipolar depression, there is a high possibility that dopamine partial agonists, such as cariprazine can be safe and efficacious in other psychiatric disorders as well.

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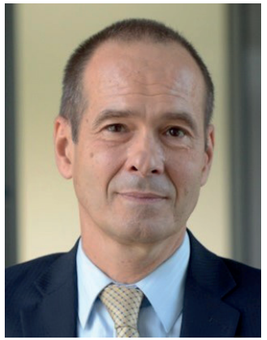

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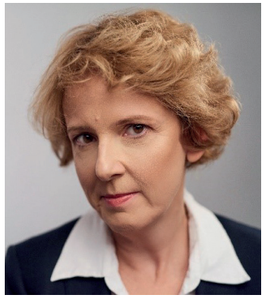

SYMPTOMS OF SCHIZOPHRENIA

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.

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 (MCID1); 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 (MCID2); with the effect size approach (MCID3); as the Youden Index based cut-off value between no clinical change and minimal improvement (MCID4); as the relative likelihood of minimal improvement (MCID5).

Results: The MCID1 and MCID2 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.

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.

ANTIPSYCHOTIC PHARMACOLOGY

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.

Potential Mechanisms for Why Not All Antipsychotics Are Able to Occupy Dopamine D3 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 D2 receptors (D2Rs) and D3 receptors (D3Rs). In terms of mode of action, these antipsychotics are either antagonist or partial agonist at the above-mentioned receptors. Although D2Rs and D3Rs 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 D3Rs and D2Rs, only very few can significantly occupy D3Rs in vivo. The relative importance of the level of endogenous extracellular dopamine in the brain and the degree of in vitro D3Rs receptor affinity and selectivity as determinant factors for in vivo D3Rs occupancy by antipsychotics, are also discussed.

Preferential Effects of Cariprazine on Counteracting the Disruption of Social Interaction and Decrease in Extracellular Dopamine Levels Induced by the Dopamine D3 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) D3 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 D3-preferring D3/D2 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 D2 receptor preference), and ABT-925 (a selective DA D3 antagonist) to counteract the social deficit and neurochemical alterations induced by the D3 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 D3 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.

SCHIZOPHRENIA TREATMENT

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.

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.

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 ≥ 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.

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.

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.

SCHIZOPHRENIA CASES

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.

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.

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.

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.

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.

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