WILANOWSKA, Wiktoria, GREGUŁA, Anna, STACHYRAK, Karol, MIKA, Dawid, MATUSZEWSKA, Justyna, MAZUR, Bartosz, BABKIEWICZ-JAHN, Kamila, OLEKSAK, Izabela, WELIAN-POLUS, Iwona and TUREK, Kamila. Cariprazine: An Antipsychotic Medication with High Therapeutic Potential. Journal of Education, Health and Sport. 2024;67:49405. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.67.49405
https://apcz.umk.pl/JEHS/article/view/494015

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).© The Authors 2024;
This article is published with open access at Licensee Open Journal Systems of Nicolaus Copernicus University in Torun, Poland

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 03.03.2024. Revised: 05.05.2024. Accepted: 08.05.2024. Published: 13.05.2024.

Cariprazine: An Antipsychotic Medication with High Therapeutic Potential

1. Wiktoria Wilanowska [WW]

Stefan Kardynał Wyszyński Province Specialist Hospital in Lublin, Kraśnicka 100 avenue, 20-718 Lublin, Poland

https://orcid.org/0009-0000-8388-8479

wiktoria.wilanowska@gmail.com

2. Anna Greguła [AG]

Independent Public Health Care Center in Łęczna, Krasnystawska 52 street, 21-010 Łęczna, Poland

https://orcid.org/0009-0007-3712-7960

aniagregula19@gmail.com

3. Karol Stachyrak [KS]

Independent Public Health Care Center in Łęczna Krasnystawska 52 street, 21-010 Łęczna, Poland

https://orcid.org/0009-0008-3175-1866

karol.stachyrak@gmail.com

4. Dawid Mika [DM]

1st Military Clinical Hospital with SPZOZ Polyclinic in Lublin, Raclawickie 23 avenue, 20-049 Lublin, Poland

https://orcid.org/0009-0003-5254-5344

mikadawid@gmail.com

5. Justyna Matuszewska [JM]
1st Military Clinical Hospital with SPZOZ Polyclinic in Lublin, Raclawickie 23 avenue, 20-049 Lublin, Poland
https://orcid.org/0009-0005-6038-037X
matuszewskajustyna97@gmail.com
6. Bartosz Mazur [BM]
Stefan Kardynał Wyszyński Province Specialist Hospital in Lublin, Kraśnicka 100 avenue, 20-718 Lublin, Poland
https://orcid.org/0000-0003-0601-4350
bartoszmazur27@gmail.com
7. Kamila Babkiewicz-Jahn [KBJ]
1st Military Clinical Hospital with SPZOZ Polyclinic in Lublin, Raclawickie 23 avenue, 20-049 Lublin, Poland
https://orcid.org/0009-0001-1597-273X
kamila.babkiewicz@gmail.com
8. Izabela Oleksak [IO]
1st Military Clinical Hospital with SPZOZ Polyclinic in Lublin, Raclawickie 23 avenue, 20-049 Lublin, Poland
https://orcid.org/0000-0001-7155-9010
i.oleksak203@gmail.com
9. Iwona Welian-Polus [IWP]
Ludwik Rydygier Specialist Hospital in Cracow, 1 Złota Jesień Street, 31-826 Cracow, Poland
https://orcid.org/0000-0001-7193-9734
iwelian@wp.pl
10. Kamila Turek [KT]
Medical University of Lublin, Racławickie 1 avenue, 20-059 Lublin, Poland
https://orcid.org/0009-0000-6888-8913
kamila.turek26@gmail.com

ABSTRACT

Introduction and purpose

Cariprazine is an atypical antipsychotic drug approved for the treatment of schizophrenia, as well as manic and mixed episodes associated with bipolar disorder. It functions as a dopamine multifunctional agent, a partial agonist at dopamine and serotonin receptors. Unlike the majority of antipsychotics, which primarily target positive symptoms through dopaminergic antagonism, often neglecting negative, cognitive, and affective symptoms, the unique cariprazine's pharmacological profile, particularly potent blockade of D3 dopamine receptors, suggests the potential for numerous clinical applications. The aim of this study is to present current knowledge of cariprazine, focusing particularly on its mechanism of action, potential applications, adverse effects, and pharmacokinetic properties that could impact its clinical use.

Methods and materials

A review of the literature available in the PubMed database was performed using the key words: cariprazine; atypical antipsychotic drug; antipsychotic medication; schizophrenia treatment; bipolar disorder treatment; mania treatment; depression treatment, dopamine agonist.

Conclusions

Cariprazine demonstrates a unique pharmacological profile, offering potential benefits in managing a wide range of psychiatric disorders, including schizophrenia, bipolar disorder (mania, depression, mixed episodes), unipolar depression, and co-occurring substance use disorders. Clinical studies have shown efficacy in reducing symptoms and improving negative and cognitive function, with a favorable metabolic profile, minimal impact on cardiovascular system, and generally mild adverse effect profile. However, further research is necessary to explore its full therapeutic potential and optimize its clinical use in diverse patient populations.

Key words: cariprazine; atypical antipsychotic drug; antipsychotic medication; schizophrenia treatment; bipolar disorder treatment; mania treatment; depression treatment, dopamine agonist

Cariprazine: Antipsychotic Medication with High Therapeutic Potential – literature review

1. Introduction

Schizophrenia is a severe central nervous system disorder affecting approximately 1% of the global population. It is characterized by a range of symptom domains including positive (e.g. delusions, hallucinations), negative (e.g. social and emotional withdrawal, alogia, ambivalence, anhedonia), cognitive (e.g. executive dysfunction, attention deficit) and affective symptoms (e.g. depression, anxiety) [1]. Antipsychotic medications represent the standard treatment approach for schizophrenia. They are frequently utilized in the management of bipolar disorder, due to the shared dysregulation of dopamine, which precipitates psychotic symptoms in both conditions [2]. However, given most of registered drugs act as full dopamine antagonists, they are predominantly effective in alleviating positive symptoms, which are linked to excessive dopamine secretion in the mesolimbic system, leaving negative, cognitive, and affective symptoms remain as unmet treatment needs. Cariprazine, a new, antipsychotic medication, acting as a partial agonist at dopamine and serotonin receptors, represents a promising form of schizophrenia and bipolar disorder treatment, potentially targeting those remaining domains.

2. Methodology

A review of the literature available in the PubMed database was performed using the keywords: cariprazine; atypical antipsychotic drug; antipsychotic medication; schizophrenia treatment; bipolar disorder treatment; mania treatment, dopamine agonist.

3. State of knowledge

Cariprazine, an atypical antipsychotic drug, was approved by the European Commission on July 19, 2017, for the treatment of schizophrenia in adults in European Union countries under

the brand name Reagila. Prior, in September 2015, the FDA approved its use under the name Vraylar for the treatment of schizophrenia and manic or mixed episodes associated with bipolar disorder (BD) [3]. Cariprazine is a a partial agonist at D2/D3 receptors, with preferential binding to the D3 receptor [4]. Unlike first generation antipsychotic drugs - classical dopamine antagonists, the medication doesn't completely inhibit dopaminergic transmission. The signal transmitted by dopamine cells in the limbic system is attenuated, but not completely blocked, which is sufficient enough to achieve antipsychotic action. The absence of a distinct antagonistic impact on D2 and D3 receptors may alleviate negative subjective reactions to the antipsychotic, including depressive symptoms. According to theories linking deficits in dopamine transmission in the prefrontal cortex with the predominant presence of chronic negative symptoms in schizophrenia, cariprazine may significantly attenuate these symptoms, thereby exhibiting an advantage over a complete dopamine receptor antagonists [5].

4. Receptor profile

Cariprazine differs pharmacologically from other antipsychotic drugs, both typical and atypical. It preferentially acts on dopamine D3 receptors functionally linked in the limbic system and cerebral cortex associated with emotional and motivational spheres. It demonstrates higher potency for the D3 receptor than dopamine itself. Partial agonism towards D3 receptors located in the limbic system and frontal cortex may, according to many authors, translate into additional antidepressant effects and limitation of deficit ("negative") symptoms of schizophrenia. This expectation is justified by the fact that cariprazine is also a partial agonist of serotonin 5-HT1A receptors, the stimulation of which is associated with the antidepressant action of for example selective serotonin reuptake inhibitors (SSRI) [3, 6, 7]. In addition to its antidepressant effects, preclinical studies suggest that cariprazine may have the potential to enhance cognition and could even be beneficial in managing stimulant abuse [3]. Apart from regulation of dopamine transmission in the mesolimbic pathway and prefrontal cortex, it's also crucial to consider its impact on the nigrostriatal system and the tubuloinfundibular pathway. Cariprazine's partial agonism towards D2/D3 receptors in the nigrostriatal system aids in alleviating Parkinsonian symptoms, which are common side effects of antipsychotic treatment. On the other hand, cariprazine may induce psychomotor

agitation more frequently than other antipsychotics, spanning from mild to clinically significant akathisia. Partial stimulation of dopamine receptors in the tubuloinfundibular pathways results in minimal impact on prolactin levels, unlike other atypical antipsychotic drugs such as risperidone [5, 8]. Cariprazine displays antagonist effects on 5-HT2A, 5-HT2B, and H1 receptors, with no anticholinergic activity [2,9].

5. Pharmacological profile

Cariprazine should be administered orally, once daily, at doses ranging from 1.5 mg/day to 6.0 mg/day. Starting dose of 1,5mg/day is potentially therapeutic [4]. It is rapidly absorbed, is unaffected by food, achieves a peak plasma level in 4-8 hours and has high bioavailability. The drug, similar to other second-generation antipsychotic drugs, undergoes hepatic metabolism. The half-life of cariprazine and its metabolites - desmethyl-cariprazine (DCAR) and desmethyl-cariprazine (DDCAR) is long (7-8 days); steady state is achieved within 4 to 8 weeks. They are eliminated by CYP3A4 and also, to a lesser extent, by CYP2D6 [9,10]. Cariprazine interacts with inhibitors, including antibiotics (e.g. erythromycin, clarithromycin), antifungal medications (e.g. ketoconazole, itraconazole), antiviral drugs, or diltiazem, as well as with inducers of the 3A4 isoenzyme, such as phenytoin or carbamazepine [3]. It can be assumed that the use of cariprazine will reduce fluctuations in the concentration of antipsychotic medication in patients prone to discontinuing treatment on their own.

6. Indications for use

Besides the general indication registered in Europe for treating schizophrenia, cariprazine may also be used for managing patients exhibiting persistent negative and depressive symptoms in the context of schizophrenia-related psychosis, and for the treatment of depression, whether unipolar or bipolar [11,12]. Its registration in the USA extends to the treatment of manic and mixed episodes in bipolar I disorder [4,11]. It can be anticipated that cariprazine could also be used to improve the efficacy of antidepressant medications and in combination therapy for schizophrenia. [13]. Other potential indications may include: substance use (dual diagnosis), major depressive disorder including treatment-resistant cases and drug-resistant schizophrenia.

6.1. Substance use

Comorbidity of schizophrenia and substance use disorder (SUD), referred to as dual disorder (DD) increases morbidity and mortality compared to schizophrenia alone. Dysregulation of dopaminergic pathways appears to be a shared pathophysiological foundation of this comorbidity. Among substance users, a noteworthy observation involves the upregulation of D3 receptors, which are also found to be dysregulated in several mental disorders, including schizophrenia [7]. Initial clinical observations indicate that cariprazine, owing to its receptor profile, exhibits both antipsychotic and anti-craving properties, suggesting its potential early consideration in patients with dual diagnosis [7, 14]. Strong binding affinity to the D3 receptor could potentially attenuate the impact of elevated dopamine levels induced by stimulants in the mesolimbic system. Among stimulant users exhibiting low D2 receptor activity, cariprazine may function as partial agonist and stabilize dopamine levels, which are frequently disrupted by substance use. There are multiple cases of patients with dual diagnosis (DD), who have not shown improvement with other extensively researched medications like bupropion, naltrexone, and methylphenidate, nevertheless responded positively after incorporating cariprazine. Psychotic symptoms in these patients were effectively treated by other antipsychotics; however, only cariprazine demonstrated a reduction in methamphetamine craving. and functional improvement [15]. Other research suggests that cariprazine may be also beneficial in drug-induced psychosis, accompanied by negative symptoms [16]. In addition, the use of cariprazine resulted in a decrease in cocaine self-administration in rats, indicating that partial agonists/antagonists with modest D3R/D2R selectivity might effectively treat psychostimulant-use disorders and potentially comorbidities with other affective disorders [17]. There are cases, which involved comorbidity of schizophrenia with substance use disorder (cocaine and cannabis), where the results indicated a reduction in the frequency, quantity, and craving for cocaine and cannabis, ultimately resulting in the patient ceasing its use. However, no definitive conclusions can be drawn for clinical practice, thus it would be advisable to conduct randomized controlled studies to evaluate the efficacy of cariprazine in this population [18].

6.2. Bipolar and unipolar depression

The initial model suggests, that serotonin reuptake inhibition does not seem to have a significant impact in bipolar depression, while norepinephrine activity appears to be crucial. It is likely that the early antidepressant effect could be attained through agonistic activity at 5HT-1A receptors, antagonism at alpha1 noradrenergic and 5-HT2A receptors, the presence of a norepinephrine reuptake inhibition appears essential to sustain it. Cariprazine aligns with these criteria [19]. The efficacy of pharmacological interventions in adults with acute bipolar depression (type I, II, or not otherwise specified) was conducted. Cariprazine was found to be more efficacious than placebo in adults with acute bipolar depression as well as in treatment-resistant bipolar depression [20, 21]. In randomized, double-blind, placebo-controlled trial, adults diagnosed with major depressive disorder who had an insufficient response to antidepressant monotherapy were allocated in a 1:1:1 ratio to receive either placebo, cariprazine at a dosage of 1.5 mg/day, or at a dosage of 3.0 mg/day. The adjunctive use of cariprazine at 1.5 mg/day exhibited effectiveness in reducing depressive symptoms among adults with major depressive disorder and insufficient response to antidepressants alone [22]. In addition, cariprazine displayed antidepressant efficacy when used as augmentation therapy for the treatment of major depressive disorder [23, 24] and drug-resistant unipolar depression. [25, 26]

6.3. Drug-resistant schizophrenia

Despite many schizophrenia medication options, approximately 30%–50% of patients continue to experience treatment resistance, defined as the persistence of psychotic symptoms following at least two successive trials of antipsychotic monotherapy at adequate doses, duration, and with patient compliance. The only medication recommended by FDA for this indication is clozapine, which has demonstrated superior efficacy in reducing positive symptoms, suicidal risk, and hospitalization frequency. However, despite its superiority over other antipsychotics, up to 40%–70% of patients fail to achieve a full satisfactory response or discontinue the treatment due to adverse effects. Recent meta-analysis of randomized controlled trials assessing treatment approaches for clozapine-resistant schizophrenia revealed that aripiprazole, risperidone, pimozide, amisulpride, sulpiride, sertindole and quetiapine exhibited no difference in efficacy compared to placebo [27]. In patients who have undergone ineffective antipsychotic treatment trials, the addition of cariprazine to clozapine resulted in observable improvements in patient functioning, reductions in the severity of positive,

negative, depressive, and anxiety symptoms [28, 29, 30]. There are cases of patients with clozapine-resistant schizophrenia, who show improvement after the use of cariprazine alone with significantly fewer side effects [14,31,32]. Cariprazine may be useful, when aiming to ameliorate the metabolic burden associated with clozapine or other antipsychotic treatment, as it is noted for low potential for weight gain and metabolic side effects [18, 33, 34].

7. Pro-cognitive effect

Cariprazine exhibited superiority over other antipsychotics in enhancing cognitive functions in human and animal studies [35]. Greater improvements in this domain were observed compared to placebo in patients with bipolar I depression, mania, schizophrenia [36]. In rodents, cariprazine enhances recognition, learning, and spatial memory with scopolamine-induced memory impairment. This beneficial effect on cognition is likely attributed to cariprazine's interaction with D3 receptors and agonism at 5-HT1A receptors. The cognitive-enhancing properties of cariprazine are probably the result of integrated modulation in the hippocampus, amygdala and prefrontal cortex [37].

8. Adverse effects

Cariprazine was shown to be generally well-tolerated in adults and children aged 5-17 years. Safety observations in pediatric subjects were in line with the established safety profile in adults [38, 39]. Most common side effects compared to placebo include akathisia, extrapyramidal symptoms, restlessness, dyspepsia and nausea [2, 4]. Akathisia was the main adverse event leading to discontinuation in cariprazine treatment. However, it can be effectively managed by using a beta-blocker, such as propranolol [26]. Cariprazine was not associated with clinically meaningful changes in body weight, glycemic or prolactin levels [4,33]. There are no metabolic concerns reported with its use [40,41]. Furthermore, clinical studies have reported a decrease in total cholesterol and low-density lipoprotein (LDL) in treated individuals. There were no significant changes in aminotransferase levels or alkaline phosphatase, and no correlation with dosage [33]. Regarding cardiovascular concerns, cariprazine did not lead to any clinically significant alterations in electrocardiogram parameters, including QT interval [4,33]. Additionally, parameters such as blood pressure and pulse did not exhibit clinically significant changes [3]. The occurrence of orthostatic

hypotension is comparable between the cariprazine and placebo groups [33]. Individuals with hypersensitivity to cariprazine may manifest dermatological complications such as rash, urticaria, angioedema of the face, tongue or pharynx [2]. It is crucial to consider breastfeeding women, who should be informed about the potential impact on milk supply when prescribed dopamine receptor agonists such as cariprazine [42]. Furthermore, newborns born to pregnant patients receiving cariprazine in the third trimester may experience extrapyramidal symptoms or withdrawal symptoms [4].

9. Conclusions

Cariprazine is safe and well-tolerated drug in both pediatric and adult group. It demonstrates comparable efficacy to existing medications, with superiority in alleviating negative, cognitive, and affective symptoms associated with schizophrenia, bipolar disorder, depression. In numerous cases of comorbidity with substance use, cariprazine demonstrated anticraving properties. This suggests its potential in attenuating drug cravings and reducing the likelihood of relapse in individuals with concurrent psychiatric and substance-related conditions. Adding cariprazine in cases of treatment-resistant schizophrenia may help to diminish the adverse effects associated with last-resort medications such as clozapine, and in some instances, it may even serve as a substitute for it. Cariprazine's favorable cardiac and metabolic profile, along with manageable extrapyramidal symptoms (e.g. akathisia), adds to its appeal in psychiatric treatment. It seems particularly important to develop more strategies for identifying and treating patients who would benefit from therapy with partial agonists of dopamine receptors, such as cariprazine.

Author’s contribution

Conceptualization Wiktoria Wilanowska, Bartosz Mazur; methodology Justyna Matuszewska; software, Dawid Mika; check, Dawid Mika and Kamila Turek; formal analysis, Anna Greguła and Iwona Welian-Polus; investigation, Karol Stachyrak and Wiktoria Wilanowska; resources, Izabela Oleksak; data curation, Kamila Babkiewicz-Jahn; writing - rough preparation, Wiktoria Wilanowska; writing - review and editing, Justyna Matuszewska, Kamila

Babkiewicz-Jahn; visualization, Izabela Oleksak; supervision, Bartosz Mazur and Dawid Mika; project administration, Karol Stachyrak; receiving funding, Iwona Welian-Polus.

All authors have read and agreed with the published version of the manuscript.

Funding statement

The study did not receive special funding

Institutional Review Board Statement

Not applicable

Informed Consent Statement

Not applicable

Data availability statement

Not applicable

Acknowledgments

Not applicable

Conflict of Interest Statement

The authors report no conflict of interest.

References

1. Laszlovszky I, Barabássy Á, Németh G. Cariprazine, A Broad-Spectrum Antipsychotic for the Treatment of Schizophrenia: Pharmacology, Efficacy, and Safety. Adv Ther [Internet]. June 6, 2021 [cited March 1, 2024];38(7):3652-73. Available from: https://doi.org/10.1007/s12325-021-01797-5

2. Edinoff A, Ruoff MT, Ghaffar YT, Rezayev A, Jani D, Kaye AM, Cornett EM, Kaye AD, Viswanath O, Urits I. Cariprazine to Treat Schizophrenia and Bipolar Disorder in Adults. Psychopharmacol Bull. 2020 Sep 14;50(4):83-117. PMID: 33012874; PMCID: PMC7511151.

3. Stahl SM. Mechanism of action of cariprazine. CNS Spectr [Internet]. March 9, 2016 [cited March 1, 2024];21(2):123-7. Available from: https://doi.org/10.1017/s1092852916000043

4. Citrome L. Cariprazine for the Treatment of Schizophrenia: A Review of this Dopamine D3-Preferring D3/D2 Receptor Partial Agonist. Clin Schizophr Relat Psychoses [Internet]. June 2016 [cited March 2, 2024];10(2):109-19. Available from: https://doi.org/10.3371/1935-1232-10.2.109

5. Corponi F, Serretti A, Montgomery S, Fabbri C. Cariprazine specificity profile in the treatment of acute schizophrenia. Int Clin Psychopharmacol [Internet]. November 2017 [cited March 2, 2024];32(6):309-18. Available from: https://doi.org/10.1097/yic.0000000000000189

6. Leggio GM, Bucolo C, Platania CB, Salomone S, Drago F. Current drug treatments targeting dopamine D3 receptor. Pharmacol Ther [Internet]. September 2016 [cited March 2, 2024];165:164-77. Available from: https://doi.org/10.1016/j.pharmthera.2016.06.007

7. Grunze H. The role of the D3 dopamine receptor and its partial agonist cariprazine in patients with schizophrenia and substance use disorder. Expert Opin Pharmacother [Internet]. October 10, 2023 [cited March 2, 2024]:1-8. Available from: https://doi.org/10.1080/14656566.2023.2266359

8. Culpepper L, Vieta E, Kelly DL, Patel MD, Szatmári B, Hankinson A, Earley WR. Minimal Effects of Cariprazine on Prolactin Levels in Bipolar Disorder and Schizophrenia. Neuropsychiatr Dis Treat [Internet]. May 2022 [cited March 2, 2024];Volume 18:995-1011. Available from: https://doi.org/10.2147/ndt.s348143

9. Mazza M, Marano G, Traversi G, Carocci V, Romano B, Janiri L. Cariprazine in Bipolar Depression and Mania: State of the Art. CNS & Neurological Disorders Drug Targets [Internet]. November 23, 2018 [cited March 2, 2024];17(10):723-7. Available from:

https://doi.org/10.2174/1871527317666180828120256

10. Patel A, Patel A, Patel D, Patel K, Bambharoliya T. Mini Review on Cariprazine: A Promising Antipsychotic Agent. CNS & Neurological Disorders Drug Targets [Internet]. March 24, 2022 [cited March 2, 2024];21. Available from: https://doi.org/10.2174/1871527321666220324121935

11. Pinto JV, Saraf G, Vigo D, Keramatian K, Chakrabarty T, Yatham LN. Cariprazine in the treatment of Bipolar Disorder: A systematic review and meta-analysis. Bipolar Disord [Internet]. November 19, 2019 [cited March 2, 2024];22(4):360-71. Available from: https://doi.org/10.1111/bdi.12850

12. Generoso MB, Taiar I, Cordeiro Q, Shiozawa P, Kasper S. Cariprazine for treating psychosis: an updated meta-analysis. Int J Psychiatry Clin Pract [Internet]. May 11, 2022 [cited March 2, 2024]:1-3. Available from: https://doi.org/10.1080/13651501.2022.2071740

13. Muneer A. Pharmacotherapy of Acute Bipolar Depression in Adults: An Evidence Based Approach. Korean J Fam Med [Internet]. 2016 [cited March 2, 2024];37(3):137. Available from: https://doi.org/10.4082/kjfm.2016.37.3.137

14. Montgomery A, Rogowska M, Dratcu L. Cariprazine — an Alternative Treatment for Clozapine-resistant Schizophrenia? Clin Psychopharmacol Neurosci [Internet]. February 28, 2023 [cited March 2, 2024];21(1):202-6. Available from: https://doi.org/10.9758/cpn.2023.21.1.202

15. Truong TT, Li B. Case Series: Cariprazine for treatment of methamphetamine use disorder. Am J Addict [Internet]. October 29, 2021 [cited March 2, 2024];31(1):85-8. Available from: https://doi.org/10.1111/ajad.13241

16. Ricci V, Di Salvo G, Maina G. Remission of persistent methamphetamine-induced psychosis after cariprazine therapy: presentation of a case report. J Addict Dis [Internet]. June 26, 2021 [cited March 2, 2024]:1-4. Available from: https://doi.org/10.1080/10550887.2021.1945398

17. Gogarnoiu ES, Vogt CD, Sanchez J, Bonifazi A, Saab E, Shaik AB, Soler-Cedeño O, Bi GH, Klein B, Xi ZX, Lane JR, Newman AH. Dopamine D3/D2 Receptor Ligands Based on Cariprazine for the Treatment of Psychostimulant Use Disorders That May Be Dual Diagnosed with Affective Disorders. J Med Chem [Internet]. January 20, 2023 [cited March 2, 2024]. Available from: https://doi.org/10.1021/acs.jmedchem.2c01624

18. Duque-Yemail JD, Avila JC. Switching Clozapine to Cariprazine in Three Patients with Persistent Symptoms of Schizophrenia: A Case Series. Neuropsychiatr Dis Treat [Internet]. July 2022 [cited March 2, 2024];Volume 18:1433-40. Available from: https://doi.org/10.2147/ndt.s367922

19. Fountoulakis KN, Ioannou M, Tohen M, Haarman BC, Zarate CA. Antidepressant efficacy of cariprazine in bipolar disorder and the role of its pharmacodynamic properties: A hypothesis based on data. Eur Neuropsychopharmacol [Internet]. July 2023 [cited March 2, 2024];72:30-9. Available from: https://doi.org/10.1016/j.euroneuro.2023.03.009

20. Yildiz A, Siafis S, Mavridis D, Vieta E, Leucht S. Comparative efficacy and tolerability of pharmacological interventions for acute bipolar depression in adults: a systematic review and network meta-analysis. Lancet Psychiatry [Internet]. September 2023 [cited March 2, 2024];10(9):693-705. Available from: https://doi.org/10.1016/s2215-0366(23)00199-2

21. Teobaldi E, Pessina E, Martini A, Cattaneo CI, De Berardis D, Martiadis V, Maina G, Rosso G. Cariprazine Augmentation in Treatment-Resistant Bipolar Depression: Data from a Retrospective Observational Study. Curr Neuropharmacol [Internet]. January 29, 2024 [cited March 2, 2024];22. Available from: https://doi.org/10.2174/1570159x22666240129095852

22. Sachs GS, Yeung PP, Rekeda L, Khan A, Adams JL, Fava M. Adjunctive Cariprazine for the Treatment of Patients With Major Depressive Disorder: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study. Am J Psychiatry [Internet]. February 15, 2023 [cited March 2, 2024]. Available from: https://doi.org/10.1176/appi.ajp.20220504

23. Xie M, Qiu Y, Wang M, Wei X, Tao Y, Duan A, Shang J, Gao W, Wang Z. Adjunctive cariprazine as a novel effective strategy for treating major depressive disorder: A systematic review and meta-analysis. J Psychiatr Res [Internet]. February 2024 [cited March 2, 2024]. Available from: https://doi.org/10.1016/j.jpsychires.2024.02.018

24. Nuñez NA, Joseph B, Pahwa M, Kumar R, Resendez MG, Prokop LJ, Veldic M, Seshadri A, Biernacka JM, Frye MA, Wang Z, Singh B. Augmentation strategies for treatment resistant major depression: A systematic review and network meta-analysis. J Affect Disord [Internet]. April 2022 [cited March 2, 2024];302:385-400. Available from: https://doi.org/10.1016/j.jad.2021.12.134

25. Pessina E, Martini A, Raffone F, Martiadis V. Cariprazine augmentation in patients with treatment resistant unipolar depression who failed to respond to previous atypical antipsychotic add-on. A case-series. Front Psychiatry [Internet]. November 27, 2023 [cited March 2, 2024];14. Available from: https://doi.org/10.3389/fpsyt.2023.1299368

26. Do A, Keramatian K, Schaffer A, Yatham L. Cariprazine in the Treatment of Bipolar Disorder: Within and Beyond Clinical Trials. Front Psychiatry [Internet]. December 14, 2021 [cited March 2, 2024];12. Available from: https://doi.org/10.3389/fpsyt.2021.769897

27. YYeh TC, Correll CU, Yang FC, Chen MH, Tseng PT, Hsu CW, Carvalho AF, Stubbs B, Thompson T, Chu CS, Yu CL, Il Shin J, Yang SN, Tu YK, Liang CS. Pharmacological and nonpharmacological augmentation treatments for clozapine-resistant schizophrenia: a systematic review and network meta-analysis with normalized entropy assessment. Asian J Psychiatry [Internet]. November 2022 [cited March 2, 2024]:103375. Available from: https://doi.org/10.1016/j.ajp.2022.103375

28. Siwek M, Chrobak AA, Gorostowicz A, Król P, Dudek D. Cariprazine augmentation of clozapine in schizophrenia—a retrospective chart review. Front Pharmacol [Internet]. January 4, 2024 [cited March 2, 2024];14. Available from: https://doi.org/10.3389/fphar.2023.1321112

29. Pappa S, Kalniunas A, Sharma H, Raza-Syed A, Kamal M, Larkin F. Efficacy and safety of cariprazine augmentation in patients treated with clozapine: a pilot study. Ther Adv Psychopharmacol [Internet]. January 2022 [cited March 2, 2024];12:204512532211320. Available from: https://doi.org/10.1177/20451253221132087

30. Oloyede E, Clark I, Mace S, Whiskey E, Taylor D. Clozapine augmentation with cariprazine for negative symptoms: a case series and literature review. Ther Adv Psychopharmacol [Internet]. January 2022 [cited March 2, 2024];12:204512532110666. Available from: https://doi.org/10.1177/20451253211066642

31. Collison-Ani E, Faher A, Au M, Burrah G. Cariprazine for treating coprophagia and organic psychosis in a young woman with acquired brain injury. BMJ Case Rep [Internet]. January 2023 [cited March 2, 2024];16(1):e248855. Available from: https://doi.org/10.1136/bcr-2022-248855

32. Viegas F, Ferreira T, Campos C. Using Cariprazine to Ameliorate Negative Symptoms and Metabolic Side Effects of Clozapine and Paliperidone – Clinical Cases. Neuropsychiatr Dis Treat [Internet]. June 2022 [cited March 2, 2024];Volume 18:1145-9. Available from: https://doi.org/10.2147/ndt.s343747

33. Tarzian M, Ndrio M, Kaja S, Beason E, Fakoya AO. Cariprazine for Treating Schizophrenia, Mania, Bipolar Depression, and Unipolar Depression: A Review of Its Efficacy. Cureus [Internet]. May 21, 2023 [cited March 2, 2024]. Available from: https://doi.org/10.7759/cureus.39309

34. Wu H, Siafis S, Hamza T, Schneider-Thoma J, Davis JM, Salanti G, Leucht S. Antipsychotic-Induced Weight Gain: Dose-Response Meta-Analysis of Randomized Controlled Trials. Schizophr Bull [Internet]. February 8, 2022 [cited March 2, 2024]. Available from: https://doi.org/10.1093/schbul/sbac001

35. Brondino N, Olivola M, Bassetti N, Parente S, Arienti V, Civardi SC, Topa PA. Cognitive Effects of Lurasidone and Cariprazine: A Mini Systematic Review. Curr Neuropharmacol [Internet]. July 27, 2023 [cited March 2, 2024];21. Available from:

https://doi.org/10.2174/1570159x21666230727140843

36. McIntyre RS, Daniel DG, Vieta E, Laszlovszky I, Goetghebeur PJ, Earley WR, Patel MD. The Efficacy of Cariprazine on Cognition: A Post Hoc Analysis From Phase II/III Clinical Trials in Bipolar Mania, Bipolar Depression, and Schizophrenia. CNS Spectr [Internet]. February 23, 2022 [cited March 2, 2024]:1-30. Available from: https://doi.org/10.1017/s109285292200013x

37. Zlatanova HI, Georgieva-Kotetarova MT, Vilmosh NB, Kandilarov IK. Evaluation of the Effect of Cariprazine on Memory and Cognition in Experimental Rodent Models. Int J Environ Res Public Health [Internet]. November 9, 2022 [cited March 2, 2024];19(22):14748. Available from: https://doi.org/10.3390/ijerph192214748

38. Yeung PP, Johnson KA, Riesenberg R, Orejudos A, Riccobene T, Kalluri HV, Malik PR, Varughese S, Findling RL. Cariprazine in Pediatric Patients with Autism Spectrum Disorder: Results of a Pharmacokinetic, Safety and Tolerability Study. J Child Adolesc Psychopharmacol [Internet]. July 12, 2023 [cited March 2, 2024]. Available from: https://doi.org/10.1089/cap.2022.0097

39. Riccobene T, Riesenberg R, Yeung PP, Earley WR, Hankinson AL. Pharmacokinetics, Safety, and Tolerability of Cariprazine in Pediatric Patients with Bipolar I Disorder or Schizophrenia. J Child Adolesc Psychopharmacol [Internet]. October 1, 2022 [cited March 2, 2024];32(8):434-43. Available from: https://doi.org/10.1089/cap.2021.0139

40. Mucci F, Della Vecchia A, Baroni S, Marazziti D. Cariprazine as a therapeutic option for schizophrenia: a drug evaluation. Expert Opin Pharmacother [Internet]. January 6, 2021 [cited March 2, 2024]:1-12. Available from: https://doi.org/10.1080/14656566.2020.1845315

41. Hope J, Keks NA. Cariprazine: A new partial dopamine agonist with a familiar profile. Australas Psychiatry [Internet]. February 13, 2022 [cited March 2, 2024]:103985622110642. Available from: https://doi.org/10.1177/10398562211064254

42. Naughton S, O'Hara K, Nelson J, Keightley P. Aripiprazole, brexpiprazole, and cariprazine can affect milk supply: Advice to breastfeeding mothers. Australas Psychiatry [Internet]. February 24, 2023 [cited March 2, 2024]:103985622311595. Available from: https://doi.org/10.1177/10398562231159510