Psychiatr. Pol. ONLINE FIRST Nr 83: 1–11
Published ahead of print 27 November 2017
www.psychiatriapolska.pl
ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
DOI: https://doi.org/10.12740/PP/OnlineFirst/80710

Cariprazine – a novel antipsychotic drug and its place in the treatment of schizophrenia

Błażej Misiak[1], Przemysław Bieńkowski[2], Jerzy Samochowiec[3]

[1] Department of Genetics, Wroclaw Medical University
[2] Department of Psychiatry, Medical University of Warsaw
[3] Department of Psychiatry, Pomeranian Medical University in Szczecin

Summary

Although the development of second-generation antipsychotics was a cornerstone in the treatment of schizophrenia, several unmet treatment needs in the field still exist. It is particularly important to note that available antipsychotics have limited efficacy in the treatment of negative symptoms and cognitive impairment. At this point, it should be noted that primary negative symptoms, i.e., those that are not due to depression, extrapyramidal symptoms or psychotic withdrawal, might affect even one-fourth of patients with schizophrenia and are associated with poor clinical and functional outcomes. Cariprazine, is an emerging antipsychotic drug, D3/D2 receptor partial agonist, with affinity to several serotonin receptors. In this article, we provide an overview of pharmacokinetic and pharmacodynamic properties of cariprazine, showing its unique receptor profile. Next, we discuss results of double-blind, placebo-controlled, randomized clinical trials and post hoc analyses of cariprazine that have been published to date. These studies have provided evidence for efficacy of cariprazine in the treatment of schizophrenia exacerbations compared to placebo, with safety and good tolerability. In addition, one clinical trial published to date revealed superior efficacy of cariprazine compared to risperidone in the treatment of predominant negative symptoms that had been also associated with concomitant improvement of functional performance. Overall, current evidence in the field supports the use of cariprazine in exacerbation of schizophrenia and suggests promising efficacy in the treatment of predominant negative symptoms.

Key words: cariprazine, negative symptoms, psychosis

Introduction

Schizophrenia is a severe mental illness with multiple psychopathological symptoms, including positive, negative and affective symptoms as well as cognitive impairment. Although the development of antipsychotics as a mainstay treatment of schizophrenia was a cornerstone in psychiatry, their efficacy and tolerability still

leave much to be desired. Both first – and second-generation antipsychotics (FGAs and SGAs) are efficacious in the treatment of positive symptoms. While the treatment with SGAs is associated with lower risk of extrapyramidal symptoms compared to FGAs, both groups of antipsychotics have limited efficacy in terms of improving negative symptoms and cognitive impairment. In addition, the treatment with some SGAs is associated with serious metabolic side effects that might be also associated with a severity of negative symptoms and cognitive deficits.

Negative symptoms of schizophrenia are a heterogeneous dimension that, according to recently reached consensus, represents five constructs: blunted affect, alogia, anhedonia, asociality and avolition [1]. They might appear already in the premorbid phase of psychosis and are present in about 60% of schizophrenia outpatients [2]. Patients who develop primary negative symptoms, i.e., those that are not secondary to depression, drug-induced extrapyramidal symptoms or psychotic withdrawal, represent a relatively homogeneous group in terms of clinical characteristics and outcomes. This subgroup of patients comprises approximately 15–25% of all schizophrenia patients [3]. In some patients, negative symptoms are not only primary but also persistent. These patients were the basis of differentiating the so-called deficit schizophrenia (DS) by Carpenter et al. [4]. A diagnosis of DS is based on the following four criteria: 1) at least 2 out of 6 negative symptoms (restricted affect, diminished emotional range, poverty of speech, curbing of interests, diminished sense of purpose and diminished social drive); 2) negative symptoms (2 or more) are stable and present for the preceding 12 months and always after clinical stabilization; 3) negative symptoms are primary, and 4) the patient meets the DSM criteria of schizophrenia.

According to various studies, the prevalence of DS has been estimated at 15% in first-episode psychosis, 25%–30% in clinical samples and 14–17% in population cohorts [5–7]. In general, patients with primary negative symptoms, especially those with deficit schizophrenia subtype, present several unfavorable clinical characteristics, including poorer premorbid adjustment with insidious onset of psychosis, higher levels of neurological soft signs, more robust cognitive impairments, a number of electrophysiological disturbances, more pronounced structural brain abnormalities, worse psychosocial functioning and poorer long-term outcomes (for review see [7]).

Effective treatment of negative symptoms is increasingly being recognized as one of major challenges of current psychopharmacology. Although several neurostructural and neurofunctional abnormalities have been found to serve as neural substrates of negative schizophrenia symptoms, aberrant dopaminergic neurotransmission still serves as one key pathophysiological mechanisms. Indeed, it has been widely reported that lower mesocortical dopaminergic activity gives rise to negative symptoms [8]. Recently a renewing interest in down-regulation of dopaminergic neurotransmission as an underlying mechanism of negative symptoms has spurred a growing body of studies on the pivotal role of dopamine D3 receptors. Indeed, D3 receptors located within the ventral striatum, the bed nucleus of stria termonalis, the hippocampus and the hypothalamus act in a number of processes that condition attention, memory and

language skills [9]. Studies in this field have led to the development of cariprazine, a novel dopamine D3 and D2 receptors partial agonist, that has been approved in Europe for the treatment of schizophrenia in adults. In this article, we provide an overview of cariprazine as an emerging antipsychotic drug with particular attention on its promising role in the treatment of negative symptoms.

Mechanisms of action

An overview of cariprazine's receptor profile that underlies its efficacy was provided in Table 1.

Table 1. **An overview of cariprazine's receptor profile underlying its efficacy**

Receptor	Activity	Clinical effects
D3	Partial agonist	Improvement of positive, negative and depressive symptoms, pro-cognitive effects
D2	Partial agonist	Improvement of positive symptoms
5-HT_{1A}	Partial agonist	Improvement of negative and depressive symptoms
5-HT_{2A}	Antagonist	Lower risk of extrapyramidal symptoms
5-HT_{2B}	Antagonist	Improvement of depressive symptoms, pro-cognitive effects
5-HT_{2C}	Antagonist	Improvement of depressive symptoms
5-HT_{7}	Antagonist	Improvement of depressive symptoms, pro-cognitive effects

Cariprazine is a partial agonist of D2 and D3 receptors with almost 10-fold higher affinity to D3 than D2 receptors [10]. A unique feature of partial agonists is that they elicit differential activities depending on the environment: they block receptors in the presence of agonists with higher intrinsic activity but itself they act as agonists [11]. This property of the D3/D2 partial agonists accounts for improvement of psychotic symptomatology with little or no adverse effects, such as extrapyramidal symptoms or hyperprolactinemia. It is also important to note that the D3 receptors are mainly located within the ventral striatum, while extrapyramidal side effects are mainly related to the dorsal striatum [12].

In animal models, interactions of cariprazine with D3 receptors have been shown to exert pro-cognitive properties in terms of improving working memory impairments, attention set-shifting, recognition memory, and learning abilities [13, 14]. In addition, the D3 partial agonism mediated by cariprazine might lead to improvement of depressive symptomatology by attenuating chronic stress – and anxiety-induced anhedonic-like behaviors [15]. Finally, it has been reported that the D3/D2 partial agonism might account for cariprazine's anti-abuse activities by reducing the rewarding effects in rats [16].

Cariprazine also exerts its biological activity via interactions with serotonin receptors, including 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, 5-$HT_{2C,}$ and 5-HT_{7} (for review see [17, 18]).

Partial agonism of 5-HT_{1A} receptors might enhance dopaminergic neurotransmission in mesocortical pathways leading to improvement of negative and depressive symptomatology. The 5-HT_{2A} antagonism may promote dopaminergic neurotransmission in the nigrostriatal circuitry, providing further explanation of lower risk of motor side effects in the course of treatment with cariprazine. In turn, antagonism of 5-HT_{2C} and 5-HT_7 receptors is believed to play a role in antidepressant activity. Interestingly, the 5-HT_7 antagonism might be related to pro-cognitive properties of cariprazine since this mechanism has been found in the action of vortioxetine [19].

Finally, cariprazine exerts some antagonism of histamine H1 receptors, muscarine M1 receptors and α_1 receptors. However, due to a relatively low affinity for these receptors, it is expected that the treatment with cariprazine will be associated with low risk of sedation, metabolic side effects and hypotension.

Pharmacokinetics

Cariprazine is an orally-administered antipsychotic drug that reaches peak concentrations in 3–4 hours [17, 20, 21]. The recommended dosage in schizophrenia is between 1.5 to 6 mg/day. It has two major metabolites: desmethyl cariprazine and didesmethyl cariprazine that have similar pharmacological and dose-dependent pharmacokinetic activities. Cariprazine and its metabolites are mainly eliminated by the CYP3A4 enzymes and to a lesser extent by the CYP2D6 enzymes. It is also a weak competitive inhibitor of CYP2D6 and CYP3A4 isozymes. Therefore, it is contraindicated to use cariprazine with potent or moderate CYP3A4 inhibitors, including boceprevir, diltiazem, erythromycin, fluconazole, indinavir, itraconazole, ketoconazole, clarithromycin, cobicistat, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil or voriconazole. The use of grapefruit juice should be also avoided during the treatment with cariprazine. Additionally, cariprazine should not be used together with potent or moderate CYP3A4 inducers, including bosentan, efavirenz, etravirine, phenobarbital, phenytoin, carbamazepine, modafinil, nafcillin, rifampicin or St John's wort. CYP2D6 inhibitors should not affect the metabolism of cariprazine because of negligible share of this metabolic pathway. Cariprazine strongly binds to proteins and its half-life is between 2 and 4 days. However, didesmethyl cariprazine has even longer half-life, which is 1–3 weeks.

Randomized clinical trials

To date, results of four randomized, double-blind, placebo-controlled trials of cariprazine in exacerbation of schizophrenia were published [21–24]. All studies lasted 6 weeks and shared similar methodology in terms or primary and secondary endpoints. In three studies [21, 23, 24], recruited patients had similar mean illness duration that varied between 9.9 and 12.5 years for various treatment arms, while in one study [22], mean illness duration was relatively longer (17.2–18.0 years in various treatment arms).

In the first study (phase II) addressing the efficacy of cariprazine in exacerbation of schizophrenia [21], 732 patients were randomized to receive placebo, different doses of cariprazine (1.5 mg/d, 3.0 mg/d and 4.5 mg/d) and risperidone (4.0 mg/d). Authors found significant improvements of the PANSS total score and the CGI score in patients receiving all selected doses of cariprazine and risperidone. Although the authors stated that the study was not designed to detect differences between cariprazine and risperidone, mean changes in symptoms severity were greater in patients receiving risperidone. Most frequent adverse effects of cariprazine (≥5% and at least twice the rate observed in the placebo group) were insomnia, extrapyramidal symptoms, akathisia, sedation, nausea, dizziness and constipation. Interestingly, there were small changes in metabolic parameters that were similar in all subgroups of patients.

Another clinical trial (phase III) performed in acutely relapsed patients compared cariprazine (3 mg/d and 6 mg/d) and aripiprazole (10 mg/d) with placebo [24] in 617 randomized patients. All doses of cariprazine and aripiprazole proved to be effective in terms of improving the PANSS total score and the CGI score. The largest least square mean difference in changes of the PANSS total score and the CGI score was observed in patients receiving cariprazine 6 mg/d (-8.8 and – 0.5, respectively). Common adverse effects (≥10%) included insomnia (in all groups), akathisia (6 mg/d) and headache (placebo, cariprazine 6 mg/d). However, it should be noted that differences between cariprazine and aripiprazole were assessed using the PANSS total score and thus comparisons of scores in distinct PANSS subscales have not been made. Therefore, this clinical trial did not allow to compare differences between cariprazine and aripiprazole in terms of improving specific symptom domains (positive and negative symptoms).

In another study of schizophrenia exacerbation, various doses of cariprazine have been tested in 446 randomized patients [23]. Patients were randomized to placebo, cariprazine 3–6 mg/d and cariprazine 6–9 mg/d. Importantly, there were no significant differences in the rate of completers between distinct treatment arms. Withdrawal of consent as a reason of premature discontinuation was significantly more common in patients receiving cariprazine 6–9 mg/d and insufficient therapeutic response appeared to be most common in the placebo group. However, there were no significant differences in the rates of premature discontinuation due to adverse effects between distinct treatment arms. At week 6, significant differences favoring cariprazine over placebo were found for the PANSS total score (least squares mean; cariprazine 3–6 mg/d: – 6.8 and cariprazine 6–9 mg/d: – 9.9) and the CGI score (cariprazine 3–6 mg/d: – 0.3 and cariprazine 6–9 mg/d: – 0.5). Common treatment adverse effects (≥5%) included akathisia, extrapyramidal disorder and tremor with mild to moderate severity. This clinical trial confirmed the presence of small and similar changes in metabolic parameters across all studied groups.

An independent clinical trial by Durgam et al. [22] also tested the effects of various cariprazine doses on symptomatic outcomes in acute schizophrenia. In this study, 392 patients were randomized to cariprazine 1.5–4.5 mg/d, cariprazine 6–12 mg/d

and placebo. Rates of completers were similar in all subgroups of patients. Patients receiving cariprazine 1.5–4.5 mg/d had significantly higher reductions in the PANSS total score and the PANSS negative symptoms scores in the unadjusted data analysis using the method of multiple testing. Akathisia, restlessness, tremor, back pain and extrapyramidal disorder were common treatment adversities (incidence ≥5% and twice the rate observed in the placebo group). No significant between-group differences in metabolic changes were found.

It is also of great importance that one 26-week, double-blind, placebo-controlled, randomized trial tested the efficacy of cariprazine vs. risperidone monotherapy in schizophrenia patients with persistent and predominant negative symptoms [25]. In this study authors enrolled 461 stable patients with schizophrenia (aged 18–65 years, duration of illness >2 years) at 66 study centers. The inclusion criterion was a stable course of the illness within 6 months before the study with persistent and predominant negative symptoms. The PANSS negative factor score (representing a total score of the following PANSS items: N1 – blunted affect, N2 – emotional withdrawal, N3 – poor rapport, N4 – passive/apathetic social withdrawal, N6 – lack of spontaneity and flow of conversation, G7 – motor retardation, and G16 – active social avoidance) was at least 24 (with 3 or more negative symptoms scored at least 4). They were randomly assigned to the treatment with fixed dose of cariprazine (3 mg/d, 4.5 mg/d or 6 mg/d) or risperidone (3 mg/d, 4 mg/d or 6 mg/d). Target dosage of cariprazine and risperidone was 4.5 mg/d and 4 mg/d, respectively. These antipsychotics were administered in monotherapy; previous treatment was discontinued over 2 weeks before the study.

The primary outcome was a change in the PANSS negative factor score at week 26. There were greater least squares mean changes of the PANSS negative factor score in the cariprazine group compared to the risperidone group (-8.90 vs. – 7.44, effect size estimated at 0.31). Improvement of negative symptoms in the cariprazine group appeared to be independent of changes in other psychopathological symptoms. The effect size estimate of this difference is considered significant in placebo-controlled trials. In this study, a comparison to the group treated with antipsychotic drug with proven efficacy (risperidone) has been designed and thus this observation seems to have even greater clinical relevance. Interestingly, statistical significance between cariprazine and risperidone groups appeared already at week 14. Additionally, improvement of predominant and persistent negative symptomatology was accompanied by improvement of functional performance as assessed by means of the Personal and Social Performance Scale (PSP). The PSP captures the following areas of functioning: self-care, socially useful activities, personal and social relationships as well as aggressive behaviors. This clinical trial revealed significant differences in favor of cariprazine (estimated by means of least squares mean) in the following areas: self-care (-0.20), socially useful activities (-0.35) as well as personal and social relationships (-0.25).

These results suggest that improvement of predominant and persistent negative symptoms in the course of treatment with cariprazine is associated with significant

improvement of functioning in various areas of daily life activities. Adverse effects of treatment included insomnia, akathisia, headache and anxiety. Extrapyramidal symptoms occurred at similar rates in both treatment groups. However, discontinuation and the use of rescue medications were rare.

Post hoc analyses

One post hoc analysis addressed the effects of cariprazine on hostility compared to placebo in exacerbation of schizophrenia [26]. Authors included data from three placebo-controlled, double-blind, randomized clinical trials described above [21, 23, 24]. They analyzed change of the PANSS hostility item (P7) score from baseline to week 6, controlling for changes of the PANSS positive symptoms score and sedation level. The mean difference of results in the PANSS P7 item score was significant for both adjusted and unadjusted data.

Two recent post hoc analyses suggest safety and tolerability of cariprazine [27, 28]. A post hoc analysis by Nasrallah et al. [27] included data from two 48-week, flexible-dose extension studies (RGH-MD-11 and RGH-MD-17). The only adverse effects associated with discontinuation of at least 2% of patients were akathisia, worsening of schizophrenia and psychotic disorder. Treatment-emergent adversities (≥10% of patients) included akathisia, insomnia, weight gain and headache. Mean levels of prolactin, total cholesterol, low – and high-density lipoproteins decreased with no dose-response relationship. Mean changes of cardiovascular parameters, aminotransferase and alkaline phosphatase levels were insignificant.

Another post hoc analysis [28] included above-mentioned double-blind, placebo-controlled, randomized trials performed in patients with exacerbation of schizophrenia [21–24]. The incidence of treatment-emergent adverse effects versus placebo was similar for cariprazine 1.5–3 mg/d and higher for doses 4.5–6 mg/d or 9–12 mg/d. A dose-response relationship was found for akathisia, extrapyramidal symptoms and diastolic blood pressure. Mean changes in metabolic parameters were similar in the cariprazine groups and the placebo group. Importantly, there were no increases of prolactin levels and the QTc interval prolongation. Small increases in body weight (1–2 kg) compared to placebo were observed.

One meta-analysis addressed tolerability and safety profile of cariprazine in patients with psychotic disorders, bipolar disorder and major depression episode [29]. Authors found that the risk of discontinuation due to adverse effects was similar to that observed in the placebo group. Cariprazine was associated with higher risk of extrapyramidal symptoms, including akathisia, tremor and anxiety. The cariprazine group had higher risk of clinically significant weight gain but no significant differences were found for other metabolic parameters and cardiovascular adversities when compared to the placebo group.

To date, one meta-analysis of double-blind, placebo-controlled randomized clinical trials performed in patients with exacerbation of schizophrenia (representing 2,144

patients) tested the effects of various cariprazine doses (low doses <6 mg/d and high doses ≥6 mg/d) on symptomatic outcomes [30]. Both high and low doses were effective in improving all symptom domains of schizophrenia. Effect size estimates of symptomatic improvement vs. placebo were compared to those observed in meta-analyses of other antipsychotics. Authors found that effect size estimates of overall symptomatic improvement were similar to lurasidone, asenapine, ziprasidone, and aripiprazole but lower than risperidone, quetiapine and olanzapine. However, the effect size estimates for negative symptoms were superior to many antipsychotics including aripiprazole with a slightly more favorable effect of cariprazine low doses.

Summary of evidence and future directions

Convincing evidence from clinical trials supports the efficacy of cariprazine in the treatment of schizophrenia exacerbations. These trials have also found that cariprazine treatment is safe and well tolerated. As similar to the majority of antipsychotics, the development of extrapyramidal symptoms and disturbances that are captured in frame of the so-called metabolic syndrome should be monitored during the treatment with cariprazine. The efficacy of cariprazine seems to be particularly high in terms of improving negative symptomatology. At this point, it is important to note that one clinical trial provided reliable evidence for high efficacy of cariprazine monotherapy in the treatment of persistent and predominant negative schizophrenia symptoms as compared to risperidone that was also associated with improvement of functional outcomes [25]. This point is particularly convincing in light of current evidence in the field. On the basis of meta-analysis, it has been shown that only some second-generation antipsychotics, including amisulpride, clozapine, olanzapine, and risperidone, might be more effective in the treatment of negative symptoms compared to first-generation of antipsychotics [31].

It is also important to note that the majority of clinical trials addressing the effects of second-generation antipsychotics on negative symptoms did not analyze the efficacy in terms of improving persistent and predominant negative symptomatology and included placebo comparisons. Only amisulpride has been investigated for efficacy towards predominant negative symptoms; however, a placebo-controlled study design has been also implemented [32]. A 12-week trial comparing amisulpride and ziprasidone revealed similar improvements of negative symptoms, overall psychopathology and global illness severity [33].

In summary, cariprazine is an emerging antipsychotic drug that can change clinical decisions, especially in schizophrenia patients with predominant negative symptoms. There is also some evidence from preclinical studies that suggests potential pro-cognitive and antidepressant properties of cariprazine that need to be addressed in future clinical trials.

Conflict of interest
This article was funded by Gedeon Richter Marketing Polska Sp. z o.o.

References

1. Marder SR, Galderisi S. *The current conceptualization of negative symptoms in schizophrenia*. World Psychiatry. 2017; 16(1): 14–24.
2. Bobes J, Arango C, Garcia-Garcia M, Rejas J. *Prevalence of negative symptoms in outpatients with schizophrenia spectrum disorders treated with antipsychotics in routine clinical practice: Findings from the CLAMORS study*. J. Clin. Psychiatry. 2010; 71(3): 280–286.
3. Kirkpatrick B, Fenton WS, Carpenter WT Jr., Marder SR. *The NIMH-MATRICS consensus statement on negative symptoms*. Schizophr. Bull. 2006; 32(2): 214–219.
4. Carpenter WT Jr., Heinrichs DW, Wagman AM. *Deficit and nondeficit forms of schizophrenia: The concept*. Am. J. Psychiatry. 1988; 145(5): 578–583.
5. Kirkpatrick B, Castle D, Murray RM, Carpenter WT Jr. *Risk factors for the deficit syndrome of schizophrenia*. Schizophr. Bull. 2000; 26(1): 233–242.
6. Kirkpatrick B, Buchanan RW, Ross DE, Carpenter WT Jr. *A separate disease within the syndrome of schizophrenia*. Arch. Gen. Psychiatry. 2001; 58(2): 165–171.
7. Mucci A, Merlotti E, Ucok A, Aleman A, Galderisi S. *Primary and persistent negative symptoms: Concepts, assessments and neurobiological bases*. Schizophr. Res. 2017; 186: 19–28.
8. Mitra S, Mahintamani T, Kavoor AR, Nizamie SH. *Negative symptoms in schizophrenia*. Industr. Psychiatry J. 2016; 25(2): 135–144.
9. Tóth M, Varrone A, Steiger C, Laszlovszky I, Horváth A, Kiss B et al. *Brain uptake and distribution of the dopamine D3/D2 receptor partial agonist [11 C] cariprazine: An in vivo positron emission tomography study in nonhuman primates*. Synapse. 2013; 67(5): 258–264.
10. Kiss B, Horváth A, Némethy Z, Schmidt E, Laszlovszky I, Bugovics G et al. *Cariprazine (RGH-188), a dopamine D(3) receptor-preferring, D(3)/D(2) dopamine receptor antagonist-partial agonist antipsychotic candidate: In vitro and neurochemical profile*. J. Pharmacol. Exp. Ther. 2010; 333(1): 328–340.
11. Bolonna AA, Kerwin RW. *Partial agonism and schizophrenia*. Br. J. Psychiatry. 2005; 186: 7–10.
12. Schwartz JC, Diaz J, Pilon C, Sokoloff P. *Possible implications of the dopamine D(3) receptor in schizophrenia and in antipsychotic drug actions*. Brain Res. Brain Res. Rev. 2000; 31(2–3): 277–287.
13. Zimnisky R, Chang G, Gyertyan I, Kiss B, Adham N, Schmauss C. *Cariprazine, a dopamine D(3)-receptor-preferring partial agonist, blocks phencyclidine-induced impairments of working memory, attention set-shifting, and recognition memory in the mouse*. Psychopharmacol. 2013; 226(1): 91–100.
14. Laszy J, Laszlovszky I, Gyertyan I. *Dopamine D3 receptor antagonists improve the learning performance in memory-impaired rats*. Psychopharmacol. 2005; 179(3): 567–575.
15. Duric V, Banasr M, Franklin T, Lepack A, Adham N, Kiss B et al. *Cariprazine exhibits anxiolytic and dopamine D3 receptor-dependent antidepressant effects in the chronic stress model*. Int. J. Neuropsychopharmacol. 2017; 20(10): 788–796.
16. Roman V, Gyertyan I, Saghy K, Kiss B, Szombathelyi Z. *Cariprazine (RGH-188), a D(3)-preferring dopamine D(3)/D(2) receptor partial agonist antipsychotic candidate demonstrates anti-abuse potential in rats*. Psychopharmacol. 2013; 226(2): 285–293.

17. Frankel JS, Schwartz TL. *Brexpiprazole and cariprazine: Distinguishing two new atypical antipsychotics from the original dopamine stabilizer aripiprazole*. Ther. Adv. Psychopharmacol. 2017; 7(1): 29–41.

18. Stahl SM. *Mechanism of action of cariprazine*. CNS Spectr. 2016; 21(2): 123–127.

19. Stahl SM. *Modes and nodes explain the mechanism of action of vortioxetine, a multimodal agent (MMA): Enhancing serotonin release by combining serotonin (5HT) transporter inhibition with actions at 5HT receptors (5HT1A, 5HT1B, 5HT1D, 5HT7 receptors)*. CNS Spectr. 2015; 20(2): 93–97.

20. Citrome L. *Cariprazine: Chemistry, pharmacodynamics, pharmacokinetics, and metabolism, clinical efficacy, safety, and tolerability*. Expert Opin. Drug Metab. Toxicol. 2013; 9(2): 193–206.

21. Durgam S, Starace A, Li D, Migliore R, Ruth A, Németh G et al. *An evaluation of the safety and efficacy of cariprazine in patients with acute exacerbation of schizophrenia: A phase II, randomized clinical trial*. Schizophr. Res. 2014; 152(2–3): 450–457.

22. Durgam S, Litman RE, Papadakis K, Li D, Németh G, Laszlovszky I. *Cariprazine in the treatment of schizophrenia: A proof-of-concept trial*. Int. Clin. Psychopharmacol. 2016; 31(2): 61–68.

23. Kane JM, Zukin S, Wang Y, Lu K, Ruth A, Nagy K et al. *Efficacy and safety of cariprazine in acute exacerbation of schizophrenia: Results from an international, phase III clinical trial*. J. Clin. Psychopharmacol. 2015; 35(4): 367–373.

24. Durgam S, Cutler AJ, Lu K, Migliore R, Ruth A, Laszlovszky I et al. *Cariprazine in acute exacerbation of schizophrenia: A fixed-dose, phase 3, randomized, double-blind, placebo – and active-controlled trial*. J. Clin. Psychiatry. 2015; 76(12): e1574–1582.

25. Németh G, Laszlovszky I, Czobor P, Szalai E, Szatmári B, Harsányi J et al. *Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: A randomised, double-blind, controlled trial*. Lancet. 2017; 389(10074): 1103–1113.

26. Citrome L, Durgam S, Lu K, Ferguson P, Laszlovszky I. *The effect of cariprazine on hostility associated with schizophrenia: Post hoc analyses from 3 randomized controlled trials*. J. Clin. Psychiatry. 2016; 77(1): 109–115.

27. Nasrallah HA, Earley W, Cutler AJ, Wang Y, Lu K, Laszlovszky I et al. *The safety and tolerability of cariprazine in long-term treatment of schizophrenia: A post hoc pooled analysis*. BMC Psychiatry. 2017; 17(1): 305.

28. Earley W, Durgam S, Lu K, Laszlovszky I, Debelle M, Kane JM. *Safety and tolerability of cariprazine in patients with acute exacerbation of schizophrenia: A pooled analysis of four phase II/III randomized, double-blind, placebo-controlled studies*. Int. Clin. Psychopharmacol. 2017; 32(6): 319–328.

29. Lao KS, He Y, Wong IC, Besag FM, Chan EW. *Tolerability and safety profile of cariprazine in treating psychotic disorders, bipolar disorder and major depressive disorder: A systematic review with meta-analysis of randomized controlled trials*. CNS Drugs. 2016; 30(11): 1043–1054.

30. Corponi F, Serretti A, Montgomery S, Fabbri C. *Cariprazine specificity profile in the treatment of acute schizophrenia: A meta-analysis and meta-regression of randomized-controlled trials*. Int. Clin. Psychopharmacol. 2017; 32(6): 309–318.

31. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. *Second-generation versus first-generation antipsychotic drugs for schizophrenia: A meta-analysis*. Lancet. 2009; 373(9657): 31–41.

32. Danion JM, Rein W, Fleurot O. *Improvement of schizophrenic patients with primary negative symptoms treated with amisulpride. Amisulpride Study Group*. Am. J. Psychiatry. 1999; 156(4): 610–616.

33. Olie JP, Spina E, Murray S, Yang R. *Ziprasidone and amisulpride effectively treat negative symptoms of schizophrenia: Results of a 12-week, double-blind study*. Int. Clin. Psychopharmacol. 2006; 21(3): 143–151.

Address: Błażej Misiak
Department of Genetics
Wroclaw Medical University
50-368 Wrocław, Marcinkowskiego Street 1
e-mail: blazej_misiak@interia.pl.