Dopamine D_3 Receptors: From Bench to Bedside

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Dopamine D_3 receptors belong to the dopamine D_2-like receptor family, which also includes D_2 and D_4 receptors. These receptors have limited anatomical distribution and are mainly expressed in brain regions and pathways that typically mediate the actions of antipsychotic drugs and medication used against Parkinson's disease (PD). The development of cariprazine, the first D_2/D_3 partial agonist with prominent affinity and preferential activity at D_3 receptors over other dopamine receptor subtypes was a landmark that provided new insights into the neurochemical and physiological functions of D_3 receptors. Preclinical studies and clinical trials provided evidence for the clinical advantages of cariprazine in the treatment of schizophrenia and bipolar disorder. Cariprazine became the first antipsychotic drug approved for the treatment of manic, mixed and depressive episodes in bipolar I disorder. Antagonism of D_3 receptors may play a role in ameliorating symptoms of levodopa-induced dyskinesia and psychosis in PD patients treated with levodopa/carbidopa. Accordingly, D_3 receptors constitute attractive targets for developing novel drugs for the improved treatment of different psychiatric and neurological disorders.
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INTRODUCTION

Dopamine (DA) is a major brain neurotransmitter that controls locomotor, cognition and reward behaviors (Baldessarini & Tarazi 1996). Its activity is mediated by two receptor families: the 'D_1-like' family includes D_1 and D_5 receptors that stimulate adenylyl cyclase activity, while the 'D_2-like' receptors (D_2, D_3, and D_4) inhibit the production of cAMP, and also regulate other systems, including potassium channels, AKT (AKT serine/threonine kinase), β-arrestin and intracellular calcium levels (Sibley & Monsma 1992; Gingrich & Caron 1993; Beaulieu et al. 2007). Alterations in dopaminergic neurotransmission have been associated with the pathophysiology of different neurological and psychiatric brain disorders, including Parkinson's disease (PD), Huntington's disease, attention-deficit hyperactivity disorder (ADHD), bipolar and mood disorders, schizophrenia, and drug addiction (Klein et al. 2019).

DOPAMINE D_3 RECEPTOR

Cloning of DA D_3 receptors (D_3R) revealed that they belong to the G-protein coupled receptor (GPCR) family, and are involved in mediating the actions of antipsychotic drugs (APDs) and medications used against PD (Sokoloff et al. 1990). The anatomical distribution of these receptors is restricted to limbic regions, including the islands of Calleja, the shell of nucleus accumbens (NAc) and the olfactory tubercles, substantia nigra, internal segment of the globus pallidus, anteroventral nucleus of the thalamus, and rostral pars reticulata of the substantia nigra. In addition, D_3Rs and D_3 mRNA positive neurons were observed in the nucleus basalis, anteroventral, mediodorsal, and geniculate nuclei of the thalamus, mammillary nuclei, the basolateral, basomedial, and cortical nuclei of the amygdala with much lower levels of expression in basal ganglia or other brain structures. The distribution of D_3Rs appears to be critically

involved in the regulation of important functions, such as motivation, emotion, and reward as well as cognition (Gurevich & Joyce 1999; Sokoloff & Le Foll 2017), which represent key pathologic domains for several neurological and psychiatric disorders, including PD and schizophrenia and PD (Sokoloff et al. 2006).

DA D_3Rs are detected at the levels of asymmetric synapses at the head of dendritic spines. In contrast, DA D_1Rs and DA D_2Rs are localized either pre-synaptic or spread all over dendrites and dendritic spines in neurons of the caudate putamen and NAc (Gurevich & Joyce 1999). Evidence suggests that D_3Rs may exert a tonic inhibition of DA neurons in the ventral tegmental area (VTA) projecting to the NAc by stimulating GABA release, whereas D_3Rs expressed on dopaminergic neurons of the VTA inhibits DA synthesis and release. Accordingly, D_3Rs exert a negative feedback loop on DA signaling mechanisms either by acting directly on its auto-receptors or by modulating GABA release, which eventually leads to a downregulation of DA release in prefrontal cortex (Sokoloff et al. 2006; Stahl 2017).

Similar to the majority of GPCR, D_3Rs may form homo- and heterodimers (Maggio et al. 2015) with D_2Rs (Scarselli et al. 2001) and D_1Rs (Marcellino et al. 2008), as well as with the adenosine A2 receptors (Torvinen et al. 2005) and they may also interact with nicotinic acetylcholine receptors (nAChRs) (Collo et al. 2013), a property that could increase their functional heterogeneity. In addition, D_3Rs may positively regulate several intracellular pathways such as ERK1/2 (Extracellular Signal-Regulated Protein Kinase) and AKT through G-protein-dependent or independent mechanisms (Cussac et al. 1999; Collo et al. 2008), suggesting that their functional activity may be different depending on the interactions with other membrane receptors or transduction proteins.

The high expression of the D_3Rs in the ventral striatum suggested that selective D_3R antagonists would exert antipsychotic activity with minimal or no side effects including extrapyramidal side effects (EPS) (Schwartz et al. 2000). Other studies also suggested that D_3R antagonists can improve the learning performance in memory-impaired rats and may reverse cognitive deficits in rodents and monkeys. Additionally, D_3Rs are implicated in executive functions and motivational behaviors that are often disrupted in schizophrenia (Lumme et al. 2007; Simpson et al. 2014), suggesting that D_3Rs may represent attractive targets to ameliorate the negative symptoms and cognitive deficits in schizophrenia patients (Joyce & Millan 2005). Interestingly, D_3R stimulation may display neurotrophic and neuro-protective effects on DA neurons during development (Van Kampen et al. 2006).

A new pharmacological concept emerged as a viable and effective intervention for developing novel and improved drugs for schizophrenia. Partial agonism at D_2Rs and D_3Rs may result in the stabilization of DA neurotransmission across different brain regions and pathways (Mailman & Murphy 2010; Pich & Collo 2015). In schizophrenia patients, partial agonism at D_2Rs and D_3Rs appears to reduce the DA hyperactivity postulated to occur in the mesolimbic pathway, and stimulate the DA hypoactivity hypothesized to occur in the mesocortical pathway. The development of the first partial D_2/D_3 agonist, aripiprazole, for the treatment of schizophrenia is considered as landmark in the treatment of this debilitating disease, and was hailed as the first "Third Generation" antipsychotic drug (Mailman & Murphy 2010). This led to the introduction of two other partial D_2/D_3 agonists that share a similar mechanism of action: brexpiprazole and cariprazine (Frankel & Schwartz 2017). In contrast to aripiprazole and brexpiprazole, cariprazine has a prominent affinity for DA D_3Rs over other DA receptor subtypes.

CARIPRAZINE: NOVEL ANTIPSYCHOTIC DRUG FOR SCHIZOPHRENIA AND BIPOLAR DISORDER

Cariprazine is a piperazine derivative first approved in the USA in 2015 for the treatment of schizophrenia and for treatment of acute manic or mixed episodes associated with bipolar I disorder. In 2019, the Food and Drug Administration (FDA) expanded cariprazine label and approved it for the treatment of depressive episodes associated with bipolar I disorder (bipolar depression) in adults (FDA Label, 2019). Cariprazine has been approved in other countres as well.

CARIPRAZINE: PHARMACOLOGICAL PROFILE

Cariprazine has a unique pharmacodynamic profile that distinguishes it rendering from other typical and atypical APDs (Miyamoto et al. 2005). It is a partial agonist at DA D_2Rs and D_3Rs as well as 5-HT_{1A} receptors, while acting as antagonist at 5-HT_{2A} and 5-HT_{2B} receptors. It shows low to moderate affinity for several other neurotransmitter receptors

that may be responsible for the occurrence of undesirable adverse events (Kiss et al. 2010). Cariprazine displayed potent affinity and occupancy at D_3Rs. In fact, cariprazine's affinity for D_3Rs is higher than DA's affinity for the same receptors, which suggests that cariprazine's blockade of D_3Rs is not displaced by DA, unlike most other DA agonists/antagonists whose D_3 binding is reversible by DA. Cariprazine's selective actions as a potent DA D_3R partial agonist may stabilize abnormalities in DA neurotransmission in different brain regions including the cerebral cortex, and therefore may improve negative symptoms and cognitive deficits in schizophrenia patients (Kiss et al. 2010). The activity of cariprazine on 5-HT_{1A}Rs and 5-HT_{2A}Rs may further improve psychotic or manic symptoms while maintaining a benign EPS profile (Veselinovic et al. 2013).

CARIPRAZINE: MOLECULAR EFFECTS

A series of studies examined and compared the long-term effects of cariprazine vs. other dissimilar APDs on regulation of different DA (D_1, D_2, and D_3), 5-HT (5-HT_{1A} and 5-HT_{2A}) and glutamate (NMDA and AMPA) receptor subtypes in rat forebrain regions to better characterize the receptor signature profile of cariprazine vs other APDs.

DOPAMINE RECEPTORS

Long-term administration of cariprazine resulted in significant increases in DA D_3R levels in olfactory tubercle, Islands of Calleja and shell of nucleus accumbens (Choi et al. 2014). Such increases appear to be specific for cariprazine since long-term administration of other typical and atypical antipsychotic agents failed to alter levels of forebrain D_3Rs (Tarazi et al. 1997a, 1997b, 2001, 2008). Cariprazine-induced increases in D_3Rs suggest that this drug acts an antagonist in vivo to normalize disturbances in DA D_3R-mediated neurotransmission in patients with schizophrenia and bipolar mania, and consequently may improve their mood, cognitive, and executive functions (Baldessarini & Tarazi 2005; Harvey et al. 2010). Repeated administration of cariprazine also increased DA D_2Rs in frontal cortex and hippocampus; an effect shared by other atypical APDs (Tarazi et al. 2001, 2008). Such changes may contribute to the beneficial therapeutic effects of cariprazine in schizophrenia and bipolar mania.

SEROTONIN AND GLUTAMATE RECEPTORS

Long-term administration of cariprazine increased serotonin 5-HT_{1A}Rs in the cerebral cortex. This finding is in agreement with the long-term term effects of other APDs including olanzapine, risperidone, quetiapine, and asenapine, which also triggered an increase in cortical 5-HT_{1A}Rs (Tarazi et al. 2002; 2008; Choi et al. 2017). The effects of cariprazine and other dissimilar APDs validate cortical 5-HT_{1A}R as common targets that mediate the beneficial actions of cariprazine and other atypical APDs. In contrast, long-term administration of cariprazine did not alter 5-HT_{2A}R levels in the cerebral cortex, whereas several other atypical APDs significantly decreased these receptors in the same the brain region, suggesting that 5-HT_{2A}Rs are less likely to contribute to the mechanism of action of cariprazine in vivo (Tarazi et al. 2002; 2008; Choi et al. 2017). These discrepancies may result from differences in 5-HT_{2A} receptor occupancy or from differences in the treatment regimens and selected doses for different APDs.

Long-term administration of cariprazine and other atypical APDs decreased NMDA receptors in caudate putamen and NAc (Choi et al. 2017; Tarazi et al. 2002, 2003, 2009). Downregulation of striatal NMDA receptors by cariprazine and several atypical APDs may contribute, at least in part, to the benign EPS profile of atypical antipsychotic agents (Tarsy et al. 2002). Cariprazine also decreased NMDA and increased AMPA receptors in the hippocampus, which may improve psychotic symptoms by reducing hyperglutamatergic activity postulated to occur in the hippocampus of schizophrenia patients (Tsai & Coyle 2002).

CARIPRAZINE: BEHAVIORAL EFFECTS

Acute administration of cariprazine blocked amphetamine-induced hyperactivity, inhibited apomorphine-induced climbing and attenuated the locomotor stimulating effect of non-competitive NMDA antagonists such as phencyclidine (PCP) (Gyertyan et al. 2011). In animal models of cognition, acute injection of cariprazine was able to normalize scopolamine-induced deficits in a water labyrinth task, and more effectively than risperidone, olanzapine, and aripiprazole (Gyertyan et al. 2011). Moreover, acute cariprazine pretreatment (0.08-0.15 mg/kg) significantly attenuated deficits on social recognition memory, spatial working memory and extradimensional attention set-shifting, disrupted

by acute PCP treatment (Zimnisky et al. 2013). Administration of cariprazine to PCP-treated DA D_3R knock-out mice did not result in any attenuation of PCP-induced behavioral effects. These findings further support the critical role D_3Rs play in mediating the effects of cariprazine (Zimnisky et al. 2013).

Neill and colleagues provided additional evidence on the ability of cariprazine to normalize the behavioral abnormalities observed after a sub-chronic treatment with PCP in female rats. PCP-induced alterations in cognition and social behavior, which were still present one week at the end of PCP administration, were normalized by a single dose of cariprazine (0.05 mg/kg) administered 1 hour before the behavioral tests (Neill et al. 2016). The efficacy of cariprazine was also investigated in an experimental model that combines PCP treatment and social isolation. This model triggered long-term neurodevelopmental, behavioral, structural and neurochemical alterations with a translational relevance for the symptoms seen in schizophrenia patients (Reinwald et al. 2018). A single dose of cariprazine (0.1-0.3 mg/kg) reduced the hyperactivity, reversed the cognitive deficits in the novel object recognition test, and corrected the pro-social behavioral and body-sniffing in rats exposed to a combination of PCP and social isolation (Watson et al. 2016). These findings suggest that cariprazine may be effective in improving negative symptoms and cognitive deficits observed in schizophrenia patients.

Recent studies have also shown that cariprazine is able to exert antidepressant- and anxiolytic-like behaviors in animal models of depression and anxiety (Papp et al. 2014; Duric et al. 2017). Long-term administration of cariprazine normalized the reduction of sucrose intake, an index for anhedonic-like behavior, that was induced chronic stress exposure in a D_3R-dependent mechanism (Papp et al. 2014; Duric et al. 2017). In contrast, cariprazine treatment failed to reverse anhedonic-like behavior in transgenic mice lacking the expression of D_3Rs and exposed to chronic stress (Duric et al. 2017). Additional behavioral experiments found that cariprazine was able to reduce drinking latency in the novelty-induced hypophagia test, an index for anxiolytic-like behaviors, in chronically stressed rats (Duric et al. 2017). Neurochemical study demonstrated that cariprazine increased DA, serotonin, and norepinephrine efflux in rat NAc and hippocampus in a D_3R-dependent mechanism. Increases in concentrations of different neurotransmitters in different forebrain regions may also contribute to the procognitive, prosocial, and antipsychotic-like actions of cariprazine in different animal models (Meltzer et al. 2018).

CARIPRAZINE: METABOLISM

Cariprazine is safe and effective at the dose range of 1.5-6 mg daily. It is mainly metabolized by by the cytochrome P450 3A4 enzyme (CYP3A4), and to a lesser extent CYP2 D_6, generating two active metabolites (desmethyl-cariprazine and didesmethyl-cariprazine [DDCAR]). The steady state is reached around week 1-2 for cariprazine and desmethyl-cariprazine and around week 4-8 for DDCAR (Nakamura et al. 2016). Cariprazine has a half-life of only 2-4 days, but DDCAR has a half-life of 1-3 weeks, the longest of any atypical antipsychotic (Citrome 2013). DDCAR has the same potent actions on neurotransmitter receptor binding and contributes to the clinical actions of the parent drug. The long half-life of DDCAR suggests that missing a daily dose of cariprazine may not have detrimental effects.

The pharmacokinetic of cariprazine and its metabolites are not affected by CYP2D6 poor metabolizer status, age, weight, sex or race (Nakamura et al. 2016). Cariprazine and its metabolites are weak inhibitors of cytochrome P450 enzymes including CYP1A2, CYP2C9, CYP2D6, CYP3A4, CYP2C19, and CYP2E1 (Periclou et al. 2021). The dose of cariprazine has to be reduced or it can be given every-other-day if co-administered with a strong CYP3A4 inhibitor such as ketoconazole. The association with CYP3A4 inducers, such as carbamazepine, is not recommended.

CARIPRAZINE: CLINICAL TRIALS

Schizophrenia

Several clinical trials have extensively evaluated the efficacy, safety, and tolerability of cariprazine in humans (Garnock-Jones 2017; De Berardis 2016). Cariprazine was effective in adult patients diagnosed with schizophrenia and generally well tolerated in three 6-week randomized double-blind, placebo- and/or active-controlled phase II and phase III studies. The safety and tolerability profiles of cariprazine in these trials were relatively benign since treatment with this drug was not associated with alterations in metabolic parameters, excessive sedation, prolactin production, prolongation of QT interval, or substantial increases in body weight (Calabrese et

al. 2015). Nevertheless, akathisia stands out as main adverse event since the incidence of akathisia and EPS was higher with cariprazine than with placebo. Accordingly, Open-label extension studies reported that both low and high doses of cariprazine were generally well tolerated and did not result in any new safety concerns (Durgam et al. 2014, 2015, 2017; Kane et al. 2015; Cutler et al. 2018).

A recent randomized, placebo-controlled clinical trial that compared the effects of cariprazine versus risperidone on negative symptoms in schizophrenia patients reported that cariprazine was significantly superior to risperidone in improving the persistent negative symptoms of schizophrenia after 14 weeks of treatment and continued to improve until the endpoint, at week 26 (Nemeth et al. 2017a). The reduction of the Positive and Negative Syndrome Scale factor scores for negative symptoms (PANSS-FSNS) was paralleled by a greater improvement in functioning (self-care, interpersonal relationship, and social activities), with a consequent increase in the quality of life (Nemeth et al. 2017b). This is the first study that was powered to compare the effects of two different antipsychotic agents on negative symptoms of schizophrenia, and showed clinical superiority of cariprazine over risperidone in improving a subset of schizophrenia symptoms that are more resistant to treatment by current pharmacotherapies. It also highlights the advantages of the partial agonist activity of cariprazine as a novel mechanism of action with improved efficacy, safety and tolerability.

Acute mania and mixed episodes

Several double-blind, placebo-controlled, randomized phase II/III clinical trials have examined the short-term effects (3-week treatment) of multiple doses of cariprazine (3-12 mg/day) for the treatment of acute mania or mixed episodes in patients diagnosed with bipolar I disorder (Calabrese et al. 2015; Durgam et al. 2015; Sachs et al. 2015). Cariprazine-treated patients experienced significant improvement in their symptoms compared with placebo-treated patients as assessed on the Young Mania Rating Scale (YMRS). A higher number of cariprazine-treated patients met criteria for optimal response ($\geqslant$50% improvement on YMRS score from baseline) and remission (YMRS score $\leqslant$12) at the end of 3 weeks compared with placebo-treated individuals. A longer 16-week open label trial showed that cariprazine exhibits sustained benefits in improving the symptoms of mania or mixed episodes in bipolar I disorder (Ketter et al. 2018). Cariprazine was approved for the treatment of bipolar mania at doses from 3 to 6 mg/day.

Bipolar depression

Several double-blind, placebo-controlled, randomized phase II/III clinical trials have investigated cariprazine at doses of 1.5-3.0 mg/day for the treatment of depressive episodes in bipolar I disorder (Durgam et al. 2016; Earley et al. 2019). These trials showed that 6-week treatment with cariprazine (1.5 and 3.0 mg/day) significantly improved the scores on Montgomery-Asberg Depression Rating Scale (MADRS) compared with placebo. Both patients with and without manic symptoms showed significant improvement in MADRS score from baseline compared with placebo, but for patients with manic symptoms, both 1.5 mg/day and 3.0 mg/day were significant but only 1.5 mg/day was significant for patients without manic symptoms (McIntyre et al. 2020). Both 1.5 mg/day and 3.0 mg/day are approved doses for bipolar depression.

Major depressive disorder

Cariprazine is under investigation as an augmenting agent to standard antidepressants in unipolar major depressive disorder (MDD). An earlier trial that examined the effects of very low dose (0.1-0.3 mg/day or 1-2 mg/day) cariprazine failed to achieve statistical significance between drug- and placebo-treated patients (Fava et al. 2018). Another study using higher doses of cariprazine (1-2 mg/day and 2-4.5 mg/day) demonstrated statistically significant reductions from baseline to week 8 for the higher dose (2-4.5 mg/day) group compared with placebo (Durgam et al. 2016). Additional clinical trials are currently in progress to determine the efficacy, safety and tolerability of cariprazine as adjunctive treatment in MDD patients.

SUMMARY AND CONCLUSIONS

D_3Rs belong to the DA D_2-like' receptor family, which also include D_2 and D_4 receptors. It is linked to several signal transduction cascades including inhibition of cAMP production and regulation of potassium channels, AKT (AKT serine/threonine kinase), β-arrestin and intracellular calcium levels. These receptors have limited anatomical distribution and mostly restricted to limbic regions that are critically

involved in the regulation of important functions, such as cognition, motivation, emotion, and reward. Lower levels of D_3R expression in extrapyramidal brain regions implies that blockade of these receptors is less likely to trigger undesirable EPS of both acute (akathisia, dystonia, Parkinsonism) and delayed (tardive dyskinesia) nature.

D_3Rs constitute attractive targets for the development of novel drugs for improved treatment of different psychiatric diseases including schizophrenia, bipolar disorder and depression. Several antipsychotic drugs, such as aripiprazole and brexpiprazole, have been postulated to exhibit dual actions at both D_2Rs and D_3Rs. However, these drugs tend to target D_2Rs more preferentially in vivo at therapeutic doses, and therefore minimizing the contribution of D_3Rs to the beneficial therapeutic actions of APDs.

The development of cariprazine was a major step forward in designing a novel APD with higher affinity and preferential activity at D_3Rs vs. D_2Rs and other DA receptor subtypes in vivo. Cariprazine acts a partial agonist at DA D_3Rs and D_2Rs as well as at serotonin 5-HT_{1A} receptors, while acting as antagonist at serotonin 5-HT_{2A} and 5-HT_{2B} receptors. Preclinical studies demonstrated that cariprazine is active in several animal models predictive of antipsychotic activity, negative symptoms, cognitive functions and EPS. Behavioral studies using genetically altered mice that selectively lack the expression of D_3Rs provided additional support for the unique ability of these receptors to mediate the behavioral actions of cariprazine. The ability of long-term administration of cariprazine to induce changes in different neurotransmitter receptors including DA, 5-HT and glutamate receptor subtypes that closely resemble the receptor signatures of other atypical APDs further validate cariprazine as a novel atypical APD but with distinct mechanism of action that primarily targets D_3Rs.

Clinical trials indicated that cariprazine is superior to placebo in improving symptoms of different psychiatric diseases. Cariprazine is now FDA-approved for (1) treatment of schizophrenia in adults; (2) acute treatment of manic or mixed episodes associated with bipolar I disorder in adults; and (3) treatment of depressive episodes associated with bipolar I disorder (bipolar depression) in adults (Cariprazine FDA Label, 2019). Cariprazine became the first APD to be approved for both episodes (manic and depressive) of bipolar disorder. Additional trials are in progress to evaluate the therapeutic benefits of cariprazine as adjunctive treatment in MDD patients.

D_3Rs do not only mediate the therapeutic benefits of drugs for the improved treatment of schizophrenia, bipolar disorder and MDD. Recent studies suggest that D_3Rs can be targeted to improve levodopa-induced dyskinesia and psychosis in patients diagnosed with PD. These are typical complications that results from years of treatment with levodopa/carbidopa, the standard treatment for PD. A new D_3R antagonist, mesdopetam, was evaluated in healthy volunteers and was found to be safe and well-tolerated (Sjöberg et al. 2021). Ongoing trials are evaluating the efficacy, safety and tolerability of this novel D_3R antagonist in PD patients suffering from levodopa-induced dyskinesia and psychosis. The findings should further highlight the importance of D_3Rs as pivotal targets that mediate the actions of dissimilar drugs, and should encourage the development of novel D_3R agonists/partial agonists/antagonists for the improved treatment of different neurological and psychiatric disorders.

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Dopamin D_3 receptor: az alapoktól a klinikumig

A D_3 receptor a dopamin D_2-szerű receptorai közé tartozik a D_2 és D_4 receptorokkal együtt. E receptorok előfordulása az agyban anatómilailag korlátozott, és elsősorban azokban az agyi régiókban és pályában expresszálódnak, melyek az antipszichotikumok és a Parkinson-kór kezelésében alkalmazott gyógyszerek hatásait közvetítik. A cariprazin, az első prominens D_3 affinitással és aktivitással rendelkező D_2/D_3 parciális agonista kifejlesztése mérföldkő volt, mely egyben jelentős új ismereteket is nyújtott a D_3 receptorok neurokémiai és fiziológiai funkcióját illetően. A preklinikai és klinikai vizsgálatok alátámasztották a cariprazin hatékonyságát a szkizofrénia és a bipoláris zavar kezelésében. A cariprazin lett az első olyan antipszichotikum, melyet a bipoláris I zavar mániás, kevert és depressziós epizódjainak kezelésére egyaránt jóváhagytak. A D_3 receptorokon kifejtett antagonista hatás szerepet játszhat a levodopa-indukálta diszkinézia és pszichózis enyhítésében levodopa/karbidopa kezelésben részesülő Parkinson-kóros páciensek esetében. Így a D_3 receptorok vonzó célpontot jelentenek számos különböző pszichiátriai és neurológiai betegség jövőbeni kezelésében.

Kulcsszavak: antioszichotikum, bipoláris zavar, cariprazin, dopamine D_3 receptor, Parkinson-kór, szkizofrénia