Future NEUROLOGY

Cariprazine in the management of negative symptoms of schizophrenia: state of the art and future perspectives

Christoph U Correll*[,1,2,3] [iD], Koen Demyttenaere[4] [iD], Andrea Fagiolini[5] [iD], Göran Hajak[6] [iD], Stefano Pallanti[7] [iD], Giorgio Racagni[8] [iD] & Swaran Singh[9] [iD]

[1]Department of Psychiatry Research, The Zucker Hillside Hospital, 75–59 263rd Street Glen Oaks, NY 11004, USA
[2]Department of Psychiatry & Molecular Medicine, Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY 11549, USA
[3]Department of Child & Adolescent Psychiatry, Charité Universitätsmedizin Berlin, Berlin, Germany
[4]University Psychiatric Center KU Leuven, Campus Gasthuisberg & University of Leuven, Psychiatry Research Group, Department of Neurosciences, Faculty of Medicine, Herestraat 49, Leuven 3000, Belgium
[5]Department of Molecular Medicine, University of Siena School of Medicine, Siena 53100, Italy
[6]Department of Psychiatry, Psychosomatic Medicine & Psychotherapy, Sozialstiftung Bamberg, St.-Getreustrasse 18, Bamberg 96049, Germany
[7]Istituto di Neuroscienze via Lamarmora 24, Firenze, Italy
[8]Dipartimento di Scienze Farmacologiche e Biomolecolari, Università degli Studi di Milano, Via G. Balzaretti 9, Milano 20123, Italy
[9]Mental Health & Wellbeing, Warwick Medical School, University of Warwick, Coventry, CV4 7AL, UK
*Author for correspondence: CCorrell@northwell.edu

In schizophrenia, dopaminergic hyperactivity in the mesolimbic regions, or possibly even selectively so in the dorsal striatum, seems to cause the emergence of psychotic symptoms, whereas dopaminergic hypoactivity in cortical regions underlies the negative symptoms and cognitive deficits. Managing the negative symptoms is a major current challenge in the treatment of schizophrenia with a dearth of novel modalities to address this clinical issue. Cariprazine is a novel second-generation antipsychotic that specifically targets the D3 receptor mainly associated to negative symptoms. The review summarizes the main issues regarding negative symptom management and the role of cariprazine treatment.

Dopamine (DA) is a key brain neurotransmitter that contributes to control of different functions, such as cognition, motivation and rewards, as well as locomotion [1–3]. Alterations in dopaminergic function represent a hallmark in numerous mental diseases, including schizophrenia. The role of DA in schizophrenia is dual: on the one side, dopaminergic hyperactivity, traditionally located in the mesolimbic regions, seems to cause emergence of psychotic symptoms, although more recent data implicate hyperdopaminergia in the dorsal striatum [3]; on the other side, dopaminergic hypoactivity in cortical regions underlies the negative symptoms and cognitive deficits. Primary and enduring negative symptoms are a core feature of schizophrenia, and patients presenting with negative symptoms account for a distinct clinical subpopulation [4]. Both the diagnosis and management of negative symptoms are still challenging [5]. Cariprazine is a novel second-generation antipsychotic that specifically targets the D3 receptor that is involved in the pathophysiology of negative symptoms of schizophrenia and represents a novel therapeutic opportunity to treat this subpopulation of patients [6]. Cariprazine was approved in 2015 by US FDA for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar I disorder, and in 2017 by EMA for the same indications.

The review summarizes the main issues regarding negative symptom management and the role of cariprazine treatment.

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Table 1. Main 'A's that define negative symptoms.	
Anhedonia	Inability to experience pleasure
Avolition	Lack of energy and a seeming absence of interest in routine activities
Asociality	Severe impairments in social relationships
Alogia	A negative thought disorder occurring with poverty of speech and content
Affective flattening	Markedly decreased emotional response to a stimulus

Patient functioning & social recovery in early psychosis

In a modern community-orientated mental health service, between 30 and 60% of all patients with first-episode psychosis experience a good outcome – namely, full interepisodic remissions, good symptomatic and social outcome, good occupational outcome, and good global functioning – at 3 years, as reported in the Costed study [7]. This analysis, which compared the determinants of outcome of severe mental disorders in the Nottingham cohort (1980–1982) and the cohort treated in 1995–1997, was aimed to assess the 3-year outcome of an inception cohort of first-episode psychoses treated in a modern, community-oriented service and to compare outcomes with an earlier cohort treated in hospital-based care [7]. Similar proportions of two cohorts were in remission at the time of follow-up but a higher proportion of the determinants of outcome of severe mental disorders cohort was in hospital; patients in the cohort treated in 1995–1997 had higher rates in the three component of disability (average disability, role handicap and social disability), indicating serious dysfunction in the majority of cases [7]. The move from institutional to community care that occurred between the two studies had, therefore, unfortunately neither improved clinical outcomes nor diminished the level of disability. These data are consistent with a meta-analysis of 50 years of research indicating that recovery rates in schizophrenia, that were at a median of 13.5% had not improved during this observation period [8]. Although the reasons for this apparent worsening of disability were not clear, several social changes that occurred in the intervening period, such as fragmentation of social networks, greater demands on people seeking work, easier availability of illicit drugs and failure to provide adequate recovery-based care in the community, might all have contributed to this [7].

Early intervention is crucial to improving outcomes, with early intervention in psychosis (EIP) services now being well-established in England and many other parts of the world. The UK's Schizophrenia Commission report concluded that the development of EIP was the most positive development in mental health services since the beginning of community care [9]. One example of such an EIP is the National Institute of Mental Health-funded Recovery After an Initial Schizophrenia Episode – Early Treatment Program (RAISE-ETP) study that compared the 2-year outcomes of a comprehensive program – emphasizing continued antipsychotic medications, resiliency-focused training, family education/support and vocational/educational recovery – versus usual community care, for the first episode of psychosis [10]. Results of this study indicated that there was an improvement in both QoL and the Positive and Negative Syndrome Scale (PANSS) total score as well as treatment engagement, depressive symptoms and percent of time being at work or in education with comprehensive care. The effect on QoL and PANSS total score was significantly more evident when the duration of untreated psychosis was <74 weeks, thus supporting the importance to get disease control as soon as possible [10]. Furthermore, early intervention reduces the long-term suicide rate [11] and long-term full functional recovery is predicted by functional and vocational recovery at 12 months [12]. EIP were found to be significantly superior in a meta-analysis of ten studies (n = 2076) over usual care on all meta-analyzable outcomes [13]. Main predictors of functional recovery in first-episode psychosis appear to be shorter duration of untreated psychosis, lower scores on most cognitive variables and concurrent remission of positive and negative symptoms [14]. Negative symptoms are common and associated with adverse clinical outcomes [15], and they account for much of the social, occupational and interpersonal handicaps related to schizophrenia [16,17]. Even in youth with early onset psychosis, the presence of negative symptoms at first episode was significantly associated with multiple treatment failures [18].

Negative symptoms in schizophrenia: how to recognize & manage them

Negative symptoms are related to all three domains of schizophrenia – emotions, cognition and behavior – and include avolition, alogia, anhedonia, affective flattering as well as asociality (Table 1) [19]. Negative symptoms appear early during the course of illness, especially during prodromal phases, and related deficiencies persist when schizophrenia progresses, and positive symptoms occur [5]. Negative symptoms may be measured, for example, by PANSS or the Negative Symptom Assessment-4 that focuses on the measurement of restricted speech quality, low

emotional expression, reduced social drive and reduced interests [20]. Additional rating scales developed to capture more of the social aspects pertaining to negative symptoms, include the Brief Negative Symptom Scale and Clinical Assessment Interview for Negative Symptoms [21]. However, there is currently no consensus in the filed as to which rating scale captures negative symptoms the best and is most sensitive to change.

To correctly diagnose primary negative symptoms, it is essential to rule out the presence of other mental conditions including mental retardation, dementia, depression, anxiety, substance misuse, paranoia, pharmacological side effects such as extrapyramidal symptoms and sedation, physical conditions like sleep apnea, chronic pain, and environmental factors such as hospitalization and social deprivation, that each can mimic secondary negative symptoms [5]. In the CATIE study, almost 40% of the entire population had clinically relevant negative symptoms, considering that 18.9% of patients had prominent negative symptoms and 20.9% had prominent positive and negative symptoms; among remnant patients, 20.4% had prominent positive symptoms, and 28.7% had neither prominent positive nor prominent negative symptoms [4]. Negative symptoms mainly affect the functional performance and the patient's likelihood to perform everyday skills, particularly social interaction, but they do not modify as much the functional capacity that is mainly driven by cognitive performance [22–24].

Current options to treat schizophrenia are first- and second-generation antipsychotics that mostly improve positive symptoms, but generally do not significantly ameliorate cognitive functioning and negative symptoms, except for those secondary to relevant/untreated positive symptoms [25]. Even after psychotic symptoms are very well controlled and general functioning is restored, neurocognition and negative symptoms must be managed as effectively as possible in order to achieve full outcomes desired [26]. However, despite the availability of treatments having statistically significant effects on negative symptoms in meta-analysis (second-generation antipsychotics, antidepressants, glutamatergic medications and combinations of pharmacological with psychological interventions), the average improvements are probably too small to be clinically meaningful [27].

The recent approval of additional partial DA agonist second-generation antipsychotics including cariprazine, may offer both a novel therapeutic opportunity to manage negative symptoms and a pharmacological tool to investigate further the pathophysiology of dopaminergic transmission involved in negative and cognitive symptomatology associated with schizophrenia.

Alterations of D3 receptor-mediated transmission in schizophrenia

Cloned for the first time in 1990, the D3 receptor, a membrane receptor coupled with inhibitory protein G, shows a localized distribution in the brain, in other words, higher in the ventral part of the caudate putamen and the frontal cortex, which potentially reflects its role in limbic brain functions and its involvement in several psychiatric disorders including schizophrenia [28]. The affinity of DA for this receptor is higher than for D2 receptor. Asymmetric synapses at the head of dendritic spines in medium-sized spiny neurons of the striatum and nucleo accubens surprisingly showed D3 receptor immunoreactivity [28]. These synapses are constituted with edges of glutamatergic terminals distantly located from DA terminals; therefore, D3 receptors is involved in a particular mechanism of transmission, in which DA is released in the interstitial space where it is diluted, to activate postsynaptic receptors of distal nondopaminergic synapses. This modality of activation is possible thanking to the higher affinity of DA to the D3 receptors than to other DA receptor subtypes [29]. Furthermore, the D3 receptor seems to be less sensitive to rapid (i.e., phasic changes on a second time scale) than to slower (i.e., tonic changes on a minute to hour range) changes in synaptic DA concentrations [30]. Phasic DA release from mesolimbic DA neurons determines behaviorally salient responses, whereas tonic release affects the amplitude of these responses [30], therefore an amplified D3 receptor sensitivity would lead to aberrant salience, which is supposed to be present in schizophrenia [28]. In mouse models mimicking both positive and negative symptoms treated with D3 receptor antagonists, it seems that blocking the D3 receptor generates antipsychotic-like effects. Based on these evidence, a hypothetical role of D3 receptor antagonists in contributing to restoring the glutamate/GABA homeostasis in the prefrontal cortex, and a normal glutamate signal in projecting subcortical areas such as the striatum and nucleus accumbens has been proposed (Figure 1) [28].

Most theories about clinical manifestations of schizophrenia and their treatment postulate an imbalance of DA and glutamate/GABA neurotransmissions, leading to uncontrolled excitatory activity in the prefrontal cortex. Presynaptic dopaminergic function is increased in the striatum of schizophrenic patients. This issue has led to the theory of the 'sensitized state' in schizophrenia. Nevertheless, lack of DA in the prefrontal cortex is an important feature of the disease, as shown in a MRI study demonstrating that functional connectivity of ventral tegmental
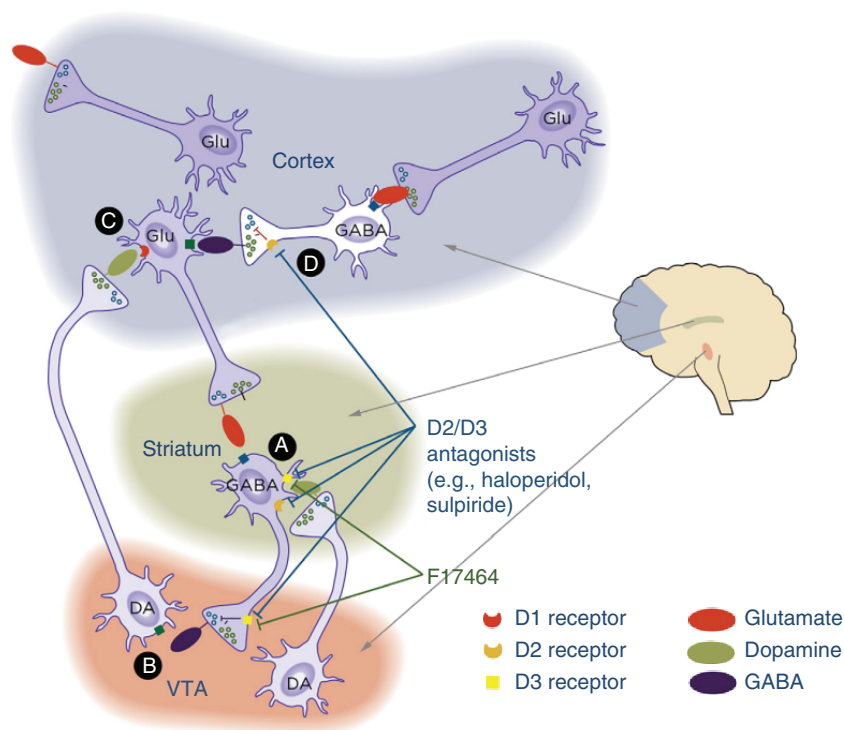
Figure 1.   Schematic representation of potential mechanism of action of D3 receptor-selective antagonists. Based on antipsychotic-like effects observed in mouse models mimicking both positive and negative symptoms, this hypothetical model postulated that a D3 receptor antagonist may interfere with glutamate at the level of asymmetrical synapses in the nucleus accumbens **(A)**, or regulate dopamine neuron activity in the VTA, through regulation of GABA release by striato-nigral GABA terminals which express D3 receptors **(B)**, thus normalizing dopamine release in the prefrontal cortex (cortex) **(C)**.
DA: Dopamine; Glu: Glutamate; VTA: Ventral tegmental area.
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Table 2. Inhibition constant of partial agonists and olanzapine versus D2 and D3 receptors.		
	D2 (k_i nM)	**D3 (k_i nM)**
Cariprazine	0.5	0.1
Aripiprazole	0.9	1.6
Brexpiprazole	0.3	1.1
Olanzapine	147	10–100
k_i (nM): Inhibition constant.		

area neurons, the main source of meso-cortico-limbic DA, is damaged in schizophrenia and replaced by antipsychotic medication [31].

Pharmacological profile of partial agonists & unique features of cariprazine

Cariprazine is a piperazine derivative, belonging with aripiprazole and brexpiprazole to the family of partial DA agonist second-generation antipsychotics [1]. These partial DA agonists have high affinity for D2 and D3 receptors and 5-HT$_{1A}$ receptors, as well as show antagonistic activity on 5-HT$_{2A}$ receptors. Low or null affinity has been detected for histaminergic H1 receptors and α-adrenergic receptors [32].

The binding affinity of cariprazine for the D2 receptor is 1000-fold higher than DA (K_i cariprazine 0.49 nM, K_i DA 540 nM), similar to brexpiprazole and tenfold higher than aripiprazole (Table 2) [24,33,34].

The affinity of cariprazine to D3 is higher than that of DA itself, which is not true for any available drug so far. Moreover, in the living brain where DA is present, only cariprazine has the capacity to replace DA at the D3 receptors [32].
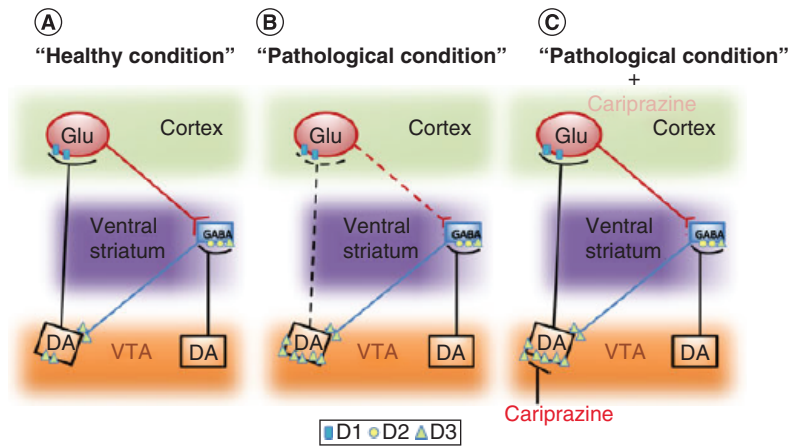
Figure 2.   Schematic representation of dopaminergic signal in healthy and pathologic condition, in which the hypothetical role of cariprazine is highlighted.
DA: Dopamine; Glu: Glutamate; VTA: Ventral tegmental area.
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The specificity for D2 and D3 receptors and the lack of binding affinity for D1 and D4 receptors well differentiates cariprazine from haloperidol that has similar binding activity on D2 receptors, but tenfold lower affinity for D3 receptor [32].

The high affinity for D3 receptor represents the main pharmacological feature of cariprazine that distinguishes it from other available antipsychotics, which was demonstrated *in vitro* with purified proteins and in animal models, having been confirmed in human imaging studies [35]. A positron emission tomography imaging study performed in patients with schizophrenia demonstrated that after 2 weeks of treatment with 1 mg/day of cariprazine, the occupancies were 76% for D3 and 45% for D2, suggesting selectivity for D3 over D2 receptors even at lower doses than that recommended in clinical practice (1.5–6 mg/day) [35].

Compared with healthy controls, and in schizophrenia, D3 receptors are overexpressed in the dopaminergic neurons projecting from the ventral tegmental area to the cortex and inhibit DA release in the prefrontal cortex, thus eventually reducing glutamatergic signaling; by acting as partial agonist at the dopaminergic D3 receptors of the mesocortical pathways, cariprazine may reduce the 'pathologic' inhibition and may contribute to normalize DA release within the prefrontal cortex. This hypothetical mechanism of action of cariprazine is depicted on Figure 2 [1].

Long-term treatment with cariprazine induces an increased expression of D3 receptor in the forebrain, and this effect seems to be unique, since other antipsychotic agents such as haloperidol, fluphenazine, clozapine, olanzapine, risperidone and asenapine, do not alter D3 receptor levels [1]. Upregulation of dopaminergic receptors is usually observed with antagonist agents; despite its activity as partial agonist, cariprazine increased D3 receptors, thus suggesting that it can act as an antagonist *in vivo* [1].

In addition to its effect on dopaminergic signaling, cariprazine increases $5HT_{1a}$ receptor levels in the cerebral cortex, but does not alter $5HT_{2a}$ levels, differently from other antipsychotic drugs that generally modify the expression of both receptors [1].

Cariprazine is safe and effective at the dose range of 1.5–6 mg daily. It is mainly metabolized by CYP3A4 (and, to a lesser extent, CYP2D6), generating two active metabolites: desmethyl cariprazine and di-desmethyl cariprazine. The steady state is reached around weeks 1–2 for cariprazine and desmethyl cariprazine and around weeks 4–8 for di-desmethyl cariprazine [36]. By comparison, aripiprazole and brexpiprazole also have long half-lives, but they and their active metabolites have half-lives of 3–4 days, not weeks [32].

The very long half-life for cariprazine has two important clinical consequences: since cariprazine takes about five half-lives to get to steady state, it means that the total cariprazine (especially of di-desmethyl cariprazine) exposure is rising for many weeks after initiating a dose, even if the daily dose stays the same. Second, after discontinuing, it will take many weeks before the active drug is washed out – a potential advantage for schizophrenia patients who frequently show poor compliance [32].

Cariprazine activity from clinical trials to practice

Nemeth and colleagues conducted the hallmark study on the role of cariprazine in improving negative symptoms in patients with schizophrenia [37]. In this study, cariprazine was compared with risperidone in patients with persistent predominant negative symptoms. The study population consisted of patients with stable illness for at least 6 months – without any hospitalization or acute exacerbation – and a high PANSS-Factor Score for Negative Symptoms (FSNS), consisting of a total score of 24 or more score and a rating of at least moderate on at least two of three core negative symptoms. Altogether, 461 patients were randomized to receive double-blind cariprazine 4.5 mg/day (range = 3–6 mg) or risperidone 4 mg/day (range = 3–6 mg) for 26 weeks. Both agents significantly improved the PANSS-FSNS after 26 weeks of treatment, but from week 14 onwards and at all other time points afterward, cariprazine was statistically superior to risperidone in ameliorating negative symptoms. The reduction of negative symptoms was not due to greater improvement with cariprazine versus risperidone in positive symptoms, depression or differences in extrapyramidal side effect ratings, ruling out pseudospecificity of the superiority of cariprazine over risperidone for negative symptoms. Additionally, cariprazine improved personal and social functioning more than risperidone, already starting from the week 9 of treatment, which preceded the significant difference from risperidone observed for negative symptoms [37].

The clinical relevance of the superiority of cariprazine versus risperidone was not only indicated by the improvement of functioning, but also a greater proportion of patients who responded to treatment, defined as a ≥20% decrease in PANSS-FSNS (69 vs 58%) [37]. The corresponding number to treat (NNT) for cariprazine was nine (meaning that after each nine patients treated with cariprazine, one patient more than with risperidone would be a treatment responder), whereby an NNT ≤10 is considered clinically relevant as per NICE guidelines [38]. Similarly, defining treatment response by a CGI improvement score of much or very improved, cariprazine achieved treatment response in 48 versus 34% of patients with risperidone, translating into an NNT of seven. On the Personal and Social Performance Scale, cariprazine showed superiority in the self-care score, socially useful activities score and personal/social relationship score [37]. In summary, in patients with persistent prominent negative symptoms and stabilized for at least 6 months, cariprazine was beneficial in improving personal and social functioning, starting from the 9th week and the treatment was clinically relevant in improving persistent negative symptoms and functioning (Figure 3).

The overall efficacy of cariprazine in the acute phase of schizophrenia has been demonstrated in pivotal trials and in the subsequent meta-analysis [39–42]. Using PANSS individual items and PANSS derived factors from pivotal studies results, a *post hoc* analysis examined the effect of cariprazine in negative symptoms and confirmed the results reported by Nemeth *et al.* [37]. The negative symptom improvements were statistically significant in favor of cariprazine versus risperidone on items N2 (emotional withdrawal) and N4 (passive/apathetic social withdrawal) and in avolition/social amotivation and expressive deficit factors. The mean changes in positive symptoms were observed at week 26, thus indicating the specificity of the negative symptom changes. Indeed, changes in negative symptoms were not secondary to other domains such as depression/anxiety, uncontrolled excitement/hostility and positive symptoms [43]. Furthermore, a *post hoc* analysis from short-term pivotal studies described also the effects of cariprazine on hostility associated with schizophrenia and indicated that cariprazine significantly improved the hostility item versus placebo, and this effect increased with greater levels of baseline hostility [44].

Cariprazine (1.5–3.0 and 4.5–6.0 mg/day) was statistically superior versus placebo, but not versus aripiprazole and risperidone (in this case after adjusting for positive symptoms, correction for pseudospecificity), in a subset of patients with relevant negative symptoms, in other words, PANSS-FSNS ≥24, PANSS-Factor Score for Positive Symptoms ≤19 and scores of ≥4 on ≥2 of three PANSS items (blunted affect [N1], passive/apathetic social withdrawal [N4] and lack of spontaneity/flow of conversation [N6]) in the acute phase of two randomized clinical trials [45].

Long-term treatment with cariprazine can prevent relapse in schizophrenic patients (Figure 4) [46–48]. Based on data from randomized clinical trials, stopping cariprazine may delay the incidence of schizophrenia relapse and the drug could be considered as a long acting oral medication.

Concerning safety, cariprazine within the FDA-recommended dose range of 1.5–6 mg/day for schizophrenia has shown to be safe and well tolerated in a pooled analysis of long-term, open-label, flexible-dose studies (RGH-MD-11 and RGH-MD-17) in patients who received at least one dose of cariprazine (safety population) during the open-label extension period. In this study, treatment-emergent adverse events of akathisia, insomnia, weight increased and headache were reported in more than 10% of patients. Changes in serum chemistry and hematology
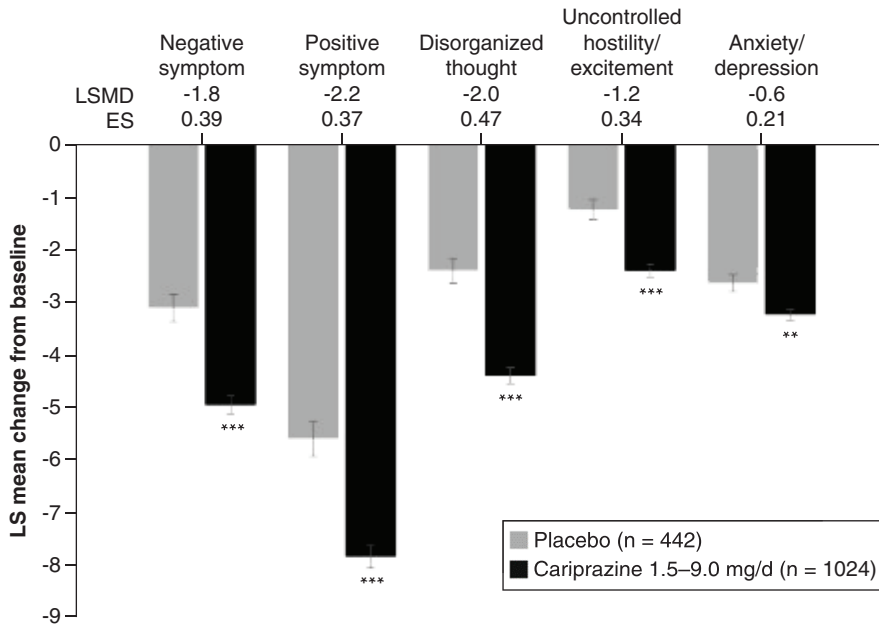
Figure 3.   Mean change from baseline to week 6 in the Positive and Negative Syndrome Scale factors (pooled intent-to-treat population).
Error bars display the standard error of the LS mean.
**p < 0.01; ***p < 0.001.
ES: Effect size; LS: Least squares; LSMD: LS mean difference.
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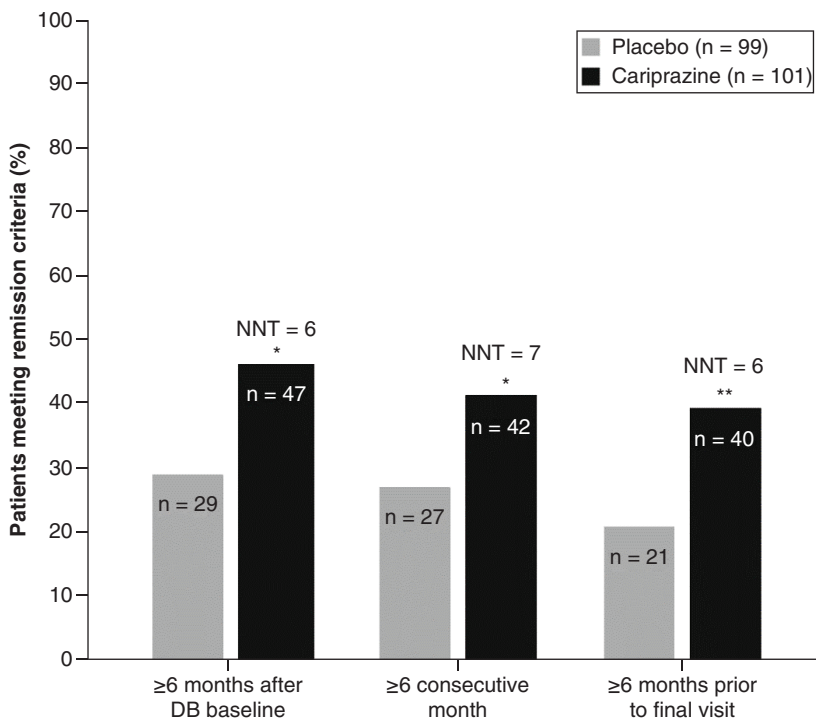

Figure 4.   6-month sustained remission rates during the double-blind phase, considering patients who met symptomatic remission criteria and various time component criteria with cariprazine and placebo.
NNT: Number to treat.
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parameters were not clinically meaningful; mean prolactin levels decreased in all dose groups [49]. Furthermore, in a 1-year, open-label study, cariprazine used even at higher doses than that recommended (3–9 mg/day) ameliorated overall symptomatology, without reporting unexpected safety issues or deaths. Triglycerides and cholesterol, as well as QTc decreased, and indicating that cariprazine was safe, including in the important areas of cardiometabolic and cardiac health [50].

In a large network meta-analysis of 402 randomized controlled trials combining direct and indirect comparisons in a Bayesian hierarchical model, 132 studies (33%) with 32,015 (60%) participants reported usable results for negative symptoms (21 antipsychotics). The effect size of cariprazine was -0.32 (95% CI: -0.44 to -0.20), while other drugs such as clozapine, amisulpride and olanzapine showed the highest effects in reducing these symptoms [51]. However, since all of the trials in this network meta-analysis were short-term studies in acutely exacerbated patients with schizophrenia, much of the reduction of the negative symptoms is likely to have been secondary to positive symptom reduction, raising the issue of pseudospecificity and requiring dedicated negative symptoms studies with adequate design features.

Therapeutic goal of the long-term treatment of schizophrenia

Recently, schizophrenia care has become influenced by the term P4 medicine, which stands for predictive, preventive, personalized and participatory. All treatments and other services should be optimized for each individual in order to improve the recovery, intended as vocational and/or educational functioning, independent living, better physical health, instrumental competence, social integration and improved QoL [52]. However, in clinical practice, only a small portion of patients with schizophrenia achieves recovery [53]. One way to try overcome such overall poor outcomes is to match different pharmacological properties to individual patient needs, and to select antipsychotic therapy based on different efficacy and tolerability profiles, individual patient characteristics and preference that may influence the choice of pharmacological action of the treatment. Multiple meta-analyses have indicated that the efficacy differences between antipsychotics (excluding clozapine) are relatively small [54,55], while tolerability profiles in terms of weight changes, sedation, QTc prolongation, prolactin increase and need for antiparkinsonian
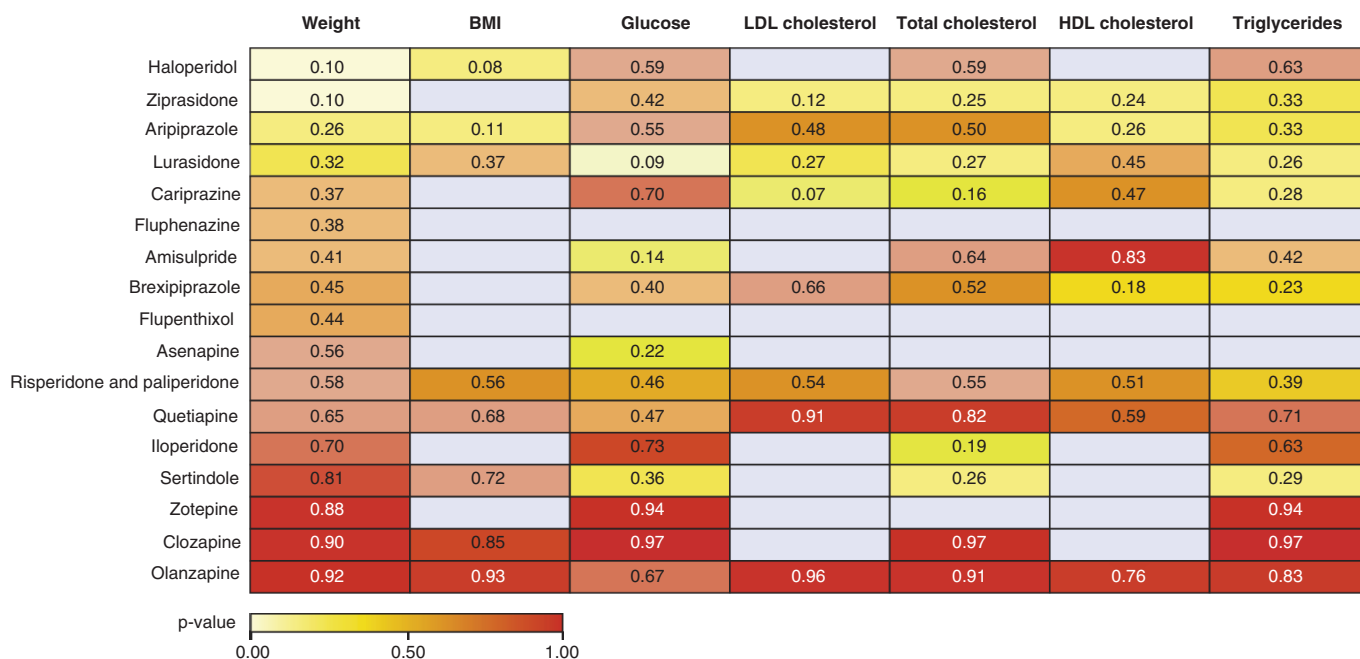
	Weight	BMI	Glucose	LDL cholesterol	Total cholesterol	HDL cholesterol	Triglycerides
Haloperidol	0.10	0.08	0.59		0.59		0.63
Ziprasidone	0.10		0.42	0.12	0.25	0.24	0.33
Aripiprazole	0.26	0.11	0.55	0.48	0.50	0.26	0.33
Lurasidone	0.32	0.37	0.09	0.27	0.27	0.45	0.26
Cariprazine	0.37		0.70	0.07	0.16	0.47	0.28
Fluphenazine	0.38						
Amisulpride	0.41		0.14		0.64	0.83	0.42
Brexipiprazole	0.45		0.40	0.66	0.52	0.18	0.23
Flupenthixol	0.44						
Asenapine	0.56		0.22				
Risperidone and paliperidone	0.58	0.56	0.46	0.54	0.55	0.51	0.39
Quetiapine	0.65	0.68	0.47	0.91	0.82	0.59	0.71
Iloperidone	0.70		0.73		0.19		0.63
Sertindole	0.81	0.72	0.36		0.26		0.29
Zotepine	0.88		0.94				0.94
Clozapine	0.90	0.85	0.97		0.97		0.97
Olanzapine	0.92	0.93	0.67	0.96	0.91	0.76	0.83

p-value
0.00   0.50   1.00

Figure 5.   Heat map of antipsychotic drugs ranked according to associated degree of alteration in body weight, BMI and metabolic parameters. Numbers reflect p-value, which rank antipsychotics on a continuous scale from 0 to 1. A higher p-value indicates a greater increase in the metabolic parameter, with the exception of HDL cholesterol, for which a higher p-value indicates a smaller increase. Grey squares indicate that data were not available. Cariprazine showed low risk in increasing cholesterol and triglycerides and greater risk in increasing weight.
HDL: High-density lipoprotein; LDL: Low-density lipoprotein.
This image has been reproduced from a paper previously published under the CC-BY license [58].

medications are quite different. In this context, it is important to consider that the estimated prevalence and relative risk of modifiable cardiovascular disease risk factors is one- to five-times greater in patients with schizophrenia compared with the general population [56] and that some antipsychotics differentially increase the risk for insulin resistance and obesity [57]. As other partial DA agonist second-generation antipsychotics, cariprazine shows neutral or low effects on weight gain and lipid and/or glucose abnormalities (Figure 5) [57,58].

Conclusion & future perspective

Cariprazine represents a good therapeutic option since it is beneficial in improving negative symptoms in both the acute and long-term setting. In addition, cariprazine can effectively control positive symptoms and reduce the frequency of relapse, thus suggesting that it can be used as first-line therapy. Its unique pharmacological profile based on high affinity on D2 and, especially, D3 receptor, partial DA agonist activity, and low/absent affinity for histaminergic and cholinergic receptors may contribute to the observed efficacy for negative symptoms and low rates of adverse events, including the important metabolic and cardiac side effects. The long, combined half-life of cariprazine and its active metabolites may further allow for a longer maintenance of therapeutic blood levels during intermittent, partial or even full nonadherence. Additional comparative data would be helpful to characterize efficacy, effectiveness and safety of cariprazine more fully versus other available antipsychotics.

Executive summary

Patient functioning & social recovery in early psychosis
- Early intervention is crucial to improving outcomes.
- Negative symptoms are common and associated with adverse clinical outcomes.
- Negative symptoms account for much of the social, occupational and interpersonal dysfunction related to schizophrenia.

Negative symptoms in schizophrenia: how to recognize & manage them
- Negative symptoms are related to all three domains of schizophrenia – emotions, cognition and behavior.
- To correctly diagnose primary negative symptoms, it is essential to rule out the presence of other mental conditions and adverse medication effects that can mimic negative symptoms.
- Neurocognition and negative symptoms must be managed as effectively as possible to maximize the achievement of the desired outcomes.

The role of the D3 receptor in schizophrenia
- Among the D1–D5 dopaminergic receptors, the D3 receptor has been specifically associated with negative symptoms of schizophrenia.

Pharmacological profile of partial dopamine agonists & unique features of cariprazine
- Cariprazine is a piperazine derivative, belonging with aripiprazole and brexipiprazole to the family of partial dopamine agonist second-generation antipsychotics.
- Cariprazine may help normalize dopamine release within the prefrontal cortex.
- Cariprazine is safe and effective at the dose range of 1.5–6 mg daily.

Cariprazine activity from clinical trials to practice
- In patients with persistent predominant negative symptoms and stabilized for at least 6 months, cariprazine was beneficial in improving negative symptoms, global clinical illness severity as well as personal and social functioning.
- Long-term treatment with cariprazine can prevent relapse in schizophrenic patients.

Therapeutic goals of the long-term treatment of people with schizophrenia
- Schizophrenia care has become influenced by the term P4 medicine.
- Cariprazine shows neutral or low effects on weight gain and lipid and/or glucose abnormalities, which are relevant outcomes both medically and regarding QoL and well-being.

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