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REVIEW

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Physical illness in schizophrenia and the role of tolerability in antipsychotic selection: an expert consensus with a focus on cariprazine

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Abstract

Background Schizophrenia is a highly heterogeneous disease, and a high percentage of patients are at high risk of developing somatic comorbidities, which must be taken into account in disease management and treatment selection.

Main body Antipsychotics are often associated with side effects that worsen the somatic comorbidities. Among the different options, cariprazine is generally safe and usually well tolerated in both acute and long-term treatment and is often a good choice when balancing clinical benefits and side effects. Given the lack of consensus on the priority of symptoms to treat and the reasons for switching therapy based on the balance between side effects and symptom resolution, twelve psychiatrists met for an expert meeting to discuss the most common and worrisome antipsychotic side effects leading to switching, the most important somatic comorbidities, and the best way to address specific symptoms in both the acute and maintenance phases of treatment in schizophrenia. Special attention was given to metabolic comorbidities, sexual dysfunction, and cardiovascular disease. This paper aims to examine the relationship between schizophrenia and specific somatic comorbidities, to discuss how the balance between efficacy and tolerability influences treatment choice in the acute and maintenance treatment of schizophrenia, and how these two variables may have different priorities at different stages of treatment.

Conclusion The choice of treatment is based primarily on efficacy and tolerability. Cariprazine is beneficial in patients with positive and negative symptoms, and it has a side-effect profile with low rates of metabolic side effects, sedation, and sexual dysfunction.

Keywords Schizophrenia, Cariprazine, Metabolic comorbidities, Sexual dysfunctions, Cardiovascular diseases, Somatic comorbidities, Switch therapy, Antipsychotics

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Introduction

Schizophrenia is a highly heterogeneous disease in terms of genetic factors, clinical manifestations, and treatment response. It is typically characterized by a chronic course and the need for acute and maintenance treatment [1–5]. According to the World Health Organization (WHO), schizophrenia affects approximately 24 million people (0.32%) worldwide [6], and patients have an average life expectancy 14.5 years shorter than the general population [7]. More specifically, in economically developed countries, people with schizophrenia die 20–25 years prematurely [8] for the same causes of death in the general population, e.g., cancer or heart disease [9]. Premature mortality in schizophrenia may be related to several causes, including long-term antipsychotic use and a higher risk of developing cardiovascular, neoplastic, and respiratory diseases compared with the general population, a risk not exclusively related to drug treatment [10–12]. Importantly, it is under debate the association between mortality and the use of antipsychotics. Indeed, mortality rates varied in different studies. For example, a meta-analysis showed a consistent trend of an increased long-term mortality risk in schizophrenia patients who did not use antipsychotic medication during follow-up [13]. It has also been reported that high exposure to benzodiazepine is associated with a 70% higher risk of death compared with no use of it [14]. Nevertheless, other studies reported that the mortality rate of antipsychotic users is lower than that of non-users [15].

Core symptoms of schizophrenia are categorized as positive, negative, and cognitive [5, 16–19], and patients show significant interindividual differences in both clinical features and neurobiological abnormalities [20]. In addition to these symptoms, many patients also reported affective symptoms, e.g., depression and anxiety symptoms (Emsley et al., 1999). The prevalence of depressive symptoms or episodes is of 7 to 75% depending on the phases of schizophrenia itself [Subodh B. N., Sandeep Grover, Depression in schizophrenia: Prevalence and its impact on quality of life, disability, and functioning, Asian Journal of Psychiatry, Volume 54, 2020, 102425, https://doi.org/10.1016/j.ajp.2020.102425]. In addition, dramatic changes in symptoms can occur over time within the same individual, with significant interplay between different symptom clusters [21]. This heterogeneity makes treatment decisions particularly challenging [1].

A high percentage of patients with schizophrenia have or are at high risk of developing somatic comorbidities [22], which must be taken into account in disease management and treatment selection. Moreover, antipsychotics are often associated with adverse events, and only 20% of patients report favorable treatment outcomes, with the remainder experiencing numerous psychotic episodes, persistent symptoms and side effects [23]. For example, antipsychotic treatment has been associated with side effects such as weight gain, dyslipidemia, dysregulation of glucose metabolism, QTc prolongation, and sudden cardiac death. However, some studies suggest that certain antipsychotics may have an overall beneficial effect on mortality despite the side effects [12, 14, 24, 25]. For instance, clozapine, the only drug approved for the treatment of resistant schizophrenia, is associated with many tolerability problems, including sedation, hypersalivation, postural hypotension, dysphagia, gastrointestinal hypomotility, weight gain, diabetes mellitus, dyslipidemia, and even rare but very serious adverse reactions such as agranulocytosis, cardiomyopathy, myocarditis, pneumonia, paralytic ileus, and seizures [26]. Nonetheless, clozapine is also associated with the most beneficial outcomes in terms of reduced mortality [12].

Accordingly, the choice of antipsychotic treatment for patients with schizophrenia should consider several factors, such as (1) history of response to antipsychotics–efficacy; (2) side effects of each antipsychotic and history of tolerability; (3) symptoms to be improved; and (4) obstacles to treatment.

Given the large number of antipsychotics approved for the treatment of schizophrenia [27, 28], the need for specific treatment algorithms based on patient characteristics has been discussed to determine medication choice, dosing, switching strategies, duration of treatment, concomitant medications, and strategies to promote or improve tolerability [29].

Among the different options, cariprazine showed broad efficacy and benefit for patients with schizophrenia, with relatively strong efficacy against negative and cognitive symptoms, resulting in good functional improvements [30, 31]. Cariprazine is generally safe and usually well tolerated in both acute and long-term treatment [30, 32] and is often a good choice when balancing clinical benefits and side effects [28, 33–35].

Currently, there is no consensus on the priority of symptoms to treat and the reasons for switching therapy based on the balance between side effects and symptom resolution. To address this gap, 12 psychiatrists experienced in the treatment of schizophrenia met for an expert meeting to discuss the most common and worrisome antipsychotic side effects leading to switching, the most important somatic comorbidities, and the best way to address specific symptoms in both the acute and maintenance phases of treatment in schizophrenia. Special attention was given to metabolic comorbidities, sexual dysfunction, and cardiovascular disease.

The aims of this paper are 1) to examine the relationship between schizophrenia and specific somatic comorbidities, such as (a) metabolic syndrome, (b) sexual dysfunction, and (c) cardiovascular disease, through a narrative review of the existing evidence; 2) to discuss

how the balance between efficacy and tolerability influences treatment choice in the acute and maintenance treatment of schizophrenia, and how these two variables may have different priorities at different stages of treatment; 3) to discuss the role of cariprazine in the treatment of schizophrenia in the presence of specific somatic comorbidities; and 4) to present the consensus reached on points 2 and 3 above.

Methods

A bibliographic search of PubMed was conducted by two of the authors (AF and AC) from February to March 2024, including all types of papers written in English without restrictions on the year of publication. Different combinations of relevant keywords were used, e.g., schizophrenia; schizophrenia AND cariprazine; schizophrenia AND therapy; schizophrenia AND metabolic comorbidities; schizophrenia AND sexual dysfunction; schizophrenia AND cardiovascular diseases; cariprazine AND schizophrenia AND metabolic comorbidities; cariprazine AND schizophrenia AND sexual dysfunction; cariprazine AND schizophrenia AND cardiovascular diseases. Article references were screened for relevant information on these topics using titles and abstracts. Further full-text screening of previously published review articles was performed to identify gaps in the selected literature and to comprehensively address the importance of this topic.

The results of the literature search were then discussed and integrated with the existing knowledge and opinions of the participants of an expert meeting held in Milan on March 18, 2024. During the meeting, the following topics were discussed for consensus.

1. Which of the following treatment-related issues is most important to address in the acute and maintenance phases for patients with schizophrenia?

i. Efficacy on positive symptoms.
ii. Efficacy on negative symptoms.
iii. Efficacy on cognitive symptoms.
iv. Tolerability.
v. Functioning and Quality of Life.
vi. Efficacy on Psychiatric Comorbidity.

How likely are the treatment regimens to be switched due to tolerability issues in the acute and maintenance phases?

2. What are the most common or troublesome side effects (a) during the acute phase of treatment and (b) during the maintenance phase of treatment for women and men?

What are the most troublesome side effects for women and men during acute and maintenance treatment?

3. What percentage of patients with mild/moderate side effects in acute and maintenance therapy do not switch therapy, and why?
4. What are the clinical characteristics of patients who may benefit most from cariprazine in terms of efficacy and tolerability in the acute and maintenance phases?
5. What is the main reason why you do not immediately switch stable patients with side effects during the acute and maintenance phase?
6. What are the most common or important somatic comorbidities to consider in patients with schizophrenia?
7. What is the best way to address somatic comorbidity in patients with schizophrenia?

All participants were asked to discuss the above topics based on both the available literature and their clinical experience.

Results

Relationship between schizophrenia and specific somatic comorbidities

Approximately half of the patients with schizophrenia have at least one comorbidity, worsening prognosis and contributing to the high rate of morbidity and mortality [36]. Some of the extrinsic causes are unhealthy lifestyles, smoking, drug use disorders, consumption of fast food, lack of exercise and the side effects of pharmacotherapy [37, 38].

Craney and colleagues [39] used a modified version of the Elixhauser Comorbidity Index in a population-based study to assess comorbidities in schizophrenic patients (both men and women). They found that 33% of patients had at least three comorbidities, compared to 12% of healthy controls. Additionally, only 29% of individuals with schizophrenia had no claims for comorbidities, as opposed to 54% of the control group. The identified somatic comorbidities included cardiovascular diseases (e.g., heart failure and hypertension), neurological disorders (e.g., paralysis and headache), pulmonary conditions (e.g., chronic obstructive pulmonary disease), metabolic diseases, renal, gastrointestinal, oncological, sexual disorders, and dependencies on tobacco and drugs [39].

Among them, the most commonly reported are somatic comorbidities, sexual dysfunctions, metabolic syndromes, and cardiovascular conditions [40].

In the next sections, we will focus on the discussion of the impact of these comorbidities on schizophrenic patients.

Table 1 Receptor profiles and effects on cardiovascular, sexual and metabolic comorbidities

Comorbidity	Receptor profiles	Effects
Sexual desire	Agonists D2 receptor	Increased
	Antagonists D2 receptor	Decreased
Orgasm	5-HT1a agonists	Facilitation
	5-HT2 agonists	Delay
Sexual behaviour	antagonists of 5-HT2a and 5-HT2c	Stimulation
Erection, lubrication, and ejaculation	alfa1 antagonists	Decreased
Peripheral effect		Stimulating effects
Erection	alfa2 antagonists	Stimulation
Sedation	H1 antagonists	Increased
Erection and the lubrication	M1 antagonists	Decreased
Cardiovascular comorbidities	Agonists D2 receptor	Increased
	Antagonists D2 receptor	Increased
	Serotonin receptor agonist	Increased
Metabolic dysfunction	Agonists D2 receptor	Increased
	Antagonists D2 receptor	Increased
	Serotonin receptor agonist	Increased

Schizophrenia and metabolic comorbidities

Patients with schizophrenia may develop metabolic disorders or abnormalities, such as insulin resistance and impaired glucose tolerance, during pharmacological therapy (Table 1). It is important to consider that these disorders may already be present before antipsychotic drugs are prescribed [41, 42], and it seems that schizophrenia itself is a risk factor for metabolic disorders [43–47].

Moreover, patients have a high chance of developing metabolic syndrome, even without antipsychotic medication [48]. Nevertheless, there is an additional increased risk of 53.8% for metabolic syndrome among users of clozapine versus 20.7% in the control [49].

According to a large-scale clinical study, up to 60% of patients with first-episode drug-naïve schizophrenia have at least one of the five components of metabolic syndrome (body weight, BMI, total cholesterol, high low-density lipoprotein [LDL], and decreases in high-density lipoprotein [HDL]) compared with only 36% in the general population [50].

There is an additional increased risk of 53.8% for metabolic syndrome among users of clozapine versus 20.7% in the control [49].

A meta-analysis found that improvements in overall symptom severity were associated with increases in body weight, body mass index, total cholesterol, and LDL, and decreases in HDL levels in 18 commonly used antipsychotics [27].

Schizophrenia and sexual dysfunctions

Sexual dysfunctions are associated with schizophrenia [51, 52], with a prevalence of 16–96% [53]. This condition may be related to the disease itself (e.g., negative symptoms, decreased initiative, and motivation), biological vulnerability [54], psychosocial factors, somatic health, and the use of psychotropic medications [55]. The association between schizophrenia and sexual dysfunctions is present in both sexes [56], with various impacting factors, such as age [57], smoking status [58], age of onset, duration of illness [56], psychopathology, and prolactin levels [59] being related to sexual dysfunctions in patients with schizophrenia. Additionally, antipsychotic medication is a significant risk factor for sexual dysfunction. Long-term use of hyperprolactinaemic antipsychotics, such as haloperidol, risperidone, paliperidone, amisulpride and others, has been linked to drug-induced sexual dysfunctions [51, 60–63].

Sexual dysfunctions caused by antipsychotics can be divided based on the mechanisms of action of the drugs (Table 1).

Liu and colleagues reported that 29.6% male male-medicated chronic inpatients with schizophrenia experience global sexual dysfunction, with negative symptoms being a risk factor [64].

Different types of dysfunctions affect male and female patients differently. For example, low desire affects more females than males (10% vs. 5%, respectively).

Interestingly, neither economic conditions nor the type of treatment (i.e., classical or atypical antipsychotics) are determinant factors for differences in types of sexual dysfunctions [52].

Among adolescents with psychosis, sexual risk behavior is prevalent, and 95% of pregnancies are unplanned [65]. Importantly, the management of sexual dysfunctions is also related to patients' acceptance of the problem. Montejo and colleagues reported that while 46% of patients exhibited sexual dysfunction (50% of males and 37% of females), only 37% spontaneously reported it, and 32% reported poor tolerance, with severity and tolerance of sexual dysfunction being worse in males [63].

Furthermore, therapy interruptions due to sexual side effects have been noted. For example, Rosenberg and colleagues reported that 41.7% of men and 15.4% of women stopped their medications because of sexual side effects [66].

Schizophrenia and cardiovascular disease

Cardiovascular complications are associated with schizophrenia, with sudden cardiac arrest being a cause of death in patients with schizophrenia, having a standardized mortality rate of 4.5 compared to the general population [67]. This association appears to be due to risk factors such as obesity or smoking [68], as well as the use of some typical and atypical antipsychotics correlated with a high rate of sudden cardiac death [69], raised cholesterol/HDL ratio and nicotine addiction. Importantly, some risk factors are already present at the onset of the psychotic disorder. For example, patients with a first episode of psychosis were more likely to be cigarette smokers and eat fast food, although these risk factors may be explained by unemployment [70, 71].

Antipsychotic agents (Table 1) may be correlated with repolarization abnormalities, such as iatrogenic prolongation of the QT interval on the ECG [72]. A high percentage of patients treated with antipsychotics present QTc prolongation [73], which can lead to polymorphic ventricular tachycardia, ventricular fibrillation, and even heart arrest [74].

Due to the QT prolongation side effect of some antipsychotics, the US FDA has increased concerns about this serious issue, leading to the withdrawal of five medications from the market and product warnings for several others, including haloperidol [75]. On the other hand, Olsen and colleagues [76] investigated a group of second-generation antipsychotics (SGAs), such as risperidone, olanzapine (high doses are associated with QTc prolongation), quetiapine and ziprasidone, finding that none led to QTc prolongation [77].

Fanoe and colleagues [78] classified different antipsychotics into classes A, B, and B* according to their reported effects at therapeutic levels on QT interval induction, arrhythmia, and cardiac conduction disturbances. Clinical monitoring of cardiotoxicity, such as creatine kinase, cardiac troponins, and B-type natriuretic peptide detection, as well as ECG monitoring, can be proposed as important pathological biomarkers [72].

Management of comorbidities in schizophrenic patients

Many of the schizophrenic patients contact the practitioner rather frequently. Patients often experience difficulties in recognizing and coping with their physical problems. Therefore, they often face delays in the diagnosis and treatment of such somatic co-morbidities [79, 80]. The critical point is that general practices have neither specific management policies nor guidelines for the diagnosis and treatment of somatic co-morbidity in schizophrenia patients, and the development and implementation of a set of guidelines would improve the quality of care for schizophrenia patients [48]. Beecroft and colleagues suggested that the health needs of patients might be better met if the GP adopted a more proactive follow-up policy, which encouraged the patient to see their GP who was responsible for physical health service provision [81]. Nevertheless, this statement is not always true since patients could trust only their psychiatrists in some case.

Interestingly, Leijala and colleagues [82] investigated the associations between somatic comorbidity and antipsychotic treatment adherence among patients with schizophrenia but, contrary to the reported link between somatic comorbidity and poor adherence from Sprah and colleagues [83], they did not find evidence to support the association. The authors suggested that the factors related to somatic comorbidity and psychiatric readmissions among patients with schizophrenia are probably quite complex. One explanation could be that patients are accustomed to seeking help for medical problems by using psychiatric services or may have difficulties using other healthcare services [82].

There are interesting data are from Osborn and colleagues concerning cardiovascular risk assessment in general practice. Indeed, while the interest in risk assessment among the psychotic patients was higher than the researchers expected, it was lower than the control group and the schizophrenic patients [84].

Even if these patients are less inclined to request medical assistance [85], when they seek it, the care provided is highly valued [86]. It has been reported that patients who visit the general practices regularly are often satisfied with the care provided. Moreover, their health needs may be better met if the general practices applied a more proactive follow-up policy which encouraged the patients to see their general practices [81].

Importantly, general practices know from experience that coming too close to a psychotic or paranoid patient can result in his withdrawal from medical care. Therefore, they need to strongly balance the necessary care without losing alliance with the patient [48].

The role of cariprazine in the management of schizophrenia

Cariprazine is a new-generation antipsychotic, a dopamine D3/D2 receptor partial agonist, approved by the US FDA for the treatment of schizophrenia, manic or mixed episodes in adults with bipolar depression, adjunctive therapy in major depressive disorders (MDD), and by the EMA for the management of schizophrenia [87, 88]. Cariprazine shows certain pharmacokinetic (e.g., long

half-life) and pharmacodynamic advantages (e.g., partial agonism at D3 and D2 receptors and low affinity to histaminergic, alpha-adrenergic, and cholinergic receptors), leading to relatively good efficacy and tolerability, making it one of the drugs of choice in the long-term management of schizophrenia [29]. Cariprazine also acts as an agonist of serotonin 5-HT1A receptors and as an antagonist of the 5-HT2B receptors [89, 90]. Cariprazine monotherapy is indicated for patients with schizophrenia spectrum disorders, but for partial responses and patients with comorbidities, combinations may be necessary [29].

In clinical trials, cariprazine has demonstrated effectiveness across different symptom domains, particularly negative symptoms of schizophrenia [16]. Clinical evidence has shown that cariprazine could be especially effective on negative symptoms [91], both in patients with chronic schizophrenia [92] and in the early stages [93]. Studies in patients with schizophrenia demonstrated significant differences versus placebo on negative symptoms at doses as low as 1.5 mg/d [94]. In phase II [94] and phase III [95] randomized placebo-controlled clinical studies in patients with acute exacerbation of schizophrenia, cariprazine was effective and generally well tolerated at all doses tested [96]. A recent clinical review highlighted that common side effects of cariprazine treatment include akathisia, extrapyramidal symptoms, insomnia, headache, dizziness, tremor, and gastrointestinal disturbances [97, 98]. Despite these side effects being well managed, most patients remained on treatment [96]. Importantly, Cariprazine having effect on negative symptoms, improve the motivation of schizophrenic patients [Correll, C. U., Demyttenaere, K., Fagiolini, A., Hajak, G., Pallanti, S., Racagni, G., & Singh, S. (2020). Cariprazine in the Management of Negative Symptoms of Schizophrenia: State of the art and Future Perspectives. *Future Neurology*, *15*(4). https://doi.org/10.2217/fnl-2020-0012] and this could in turn be of benefit to improve the lifestyle of patients, increment the physical activity. Physical activity is indeed a critical factor for a successful management of the disease since helps patients to control physical comorbidities [Arnautovska U, Kesby JP, Korman N, Rebar AL, Chapman J, Warren N, Rossell SL, Dark FL, Siskind D. Biopsychology of Physical Activity in People with Schizophrenia: An Integrative Perspective on Barriers and Intervention Strategies. Neuropsychiatr Dis Treat. 2022 Dec 15;18:2917–2926. doi: https://doi.org/10.2147/NDT.S393775. PMID: 36544549; PMCID: PMC9763049].

Cariprazine and metabolic comorbidities

Pilinger and colleagues [27] found that among 18 antipsychotics tested, cariprazine, lurasidone, and ziprasidone had the most favorable profiles concerning metabolic side effects. Cariprazine was identified as the optimal choice for minimizing total cholesterol alterations and showed the best overall metabolic outcomes, making it one of the safest options for patients at risk of developing metabolic complications. The authors highlighted that selecting treatments with fewer metabolic side effects is crucial for achieving clinical improvement. Therefore, they recommended updating guidelines to account for variations in metabolic risk, considering individual patient factors, clinical circumstances, and the preferences of patients, caregivers, and clinicians [27].

More recently, a real-world retrospective observational study evaluated cariprazine's effects on weight and metabolic parameters, reporting that it had a neutral impact on both. The study found minimal average weight change during cariprazine treatment, with most patients experiencing neither significant weight gain nor loss. Other metabolic markers, such as HbA1c, triglyceride levels, LDL, and HDL, remained stable throughout treatment [99].

Cariprazine and sexual dysfunctions

Antipsychotic-induced prolactin elevation may lead to distressing side effects such as menstrual disturbances, changes in libido, and erectile dysfunction [100]. Despite an association between schizophrenia and breast cancer related to long-term use of prolactin-increasing antipsychotics, this correlation does not exist with prolactin-sparing drugs like cariprazine [12]. Cariprazine does not produce hyperprolactinemia [101] and has been observed to have low rates of sexual dysfunction and a decrease in prolactin levels during treatment [96]. However, a case report indicated that cariprazine might be associated with hypersexuality behavior [102]. More studies are needed to further investigate cariprazine's effects on sexual functions.

Cariprazine and cardiovascular disease

Cariprazine is effective and well-tolerated in patients with a high cardiovascular risk profile [103]. It has a low incidence of cardiovascular side effects [104], and treatment with cariprazine did not have significant effects on QTc interval or cause arrhythmias in both experimental animals and humans [104]. Cariprazine inhibits hERG 1 A and hERG 1 A/3.1 currents in a concentration-dependent manner without affecting the membrane trafficking of these channels [105]. This suggests a lower cardiotoxicity risk compared to other antipsychotics.

Consensus results

Based on the results of the discussion on the above topics, 100% agreement was achieved on the following issues:

1. Efficacy on positive symptoms is usually considered by practicing clinicians to be the most important issue during the acute treatment phase. Tolerability is, instead, particularly important in the long-term maintenance phase.
2. The most common or bothersome side effects during the acute phase are sedation and extrapyramidal symptoms. The most common adverse events during the maintenance phase are metabolic effects, especially in women, while prolactin-related effects and sexual dysfunction are usually more concerning in men.
3. A large number of patients experience mild, moderate or severe side effects in both the acute and maintenance phases.
4. In the acute phase, patients who may benefit most from cariprazine include those with predominant negative or cognitive symptoms and those with any other symptom of schizophrenia (including positive symptoms) who do not have severe agitation. Patients with significant agitation may be treated with cariprazine only if it is combined with a sedative such as a benzodiazepine or a second antipsychotic. In the maintenance phase, the main advantages of cariprazine are its relatively favorable side-effect profile in terms of low rates of tolerability issues, such as metabolic side effects, sedation and sexual dysfunction, coupled with a continued good ability to treat residual and prevent new negative and cognitive symptoms, and an acceptable ability to treat residual and prevent new positive symptoms.
5. The majority of patients with mild or moderate side effects are usually not immediately switched to another antipsychotic during the acute phase, as concerns about efficacy usually outweigh concerns about tolerability. However, during the maintenance phase, when control of acute symptoms is no longer a problem, even mild or moderate side effects may warrant consideration of a change in medication.
6. The most common or important somatic comorbidities to consider in patients with schizophrenia are obesity, dyslipidemia, hypertension, hyperglycemia and other risks for cardiovascular disease.
7. Increased clinician and patient awareness of the long-term implications of side effects, such as metabolic problems, is associated with a growing tendency to consider switching antipsychotics during the maintenance phase because of these concerns.

Concluding remarks

The choice of treatment and the decision to change an ongoing treatment is based primarily on efficacy and tolerability, but the relative weight of efficacy and tolerability differs in the acute and maintenance phases. Most patients develop and continue to experience side effects. In the acute phase, the treatment of symptoms is often the main priority, with particular attention to positive symptoms, while tolerability issues and side effects, unless severe, are of lower priority. In the maintenance phase, even side effects, such as metabolic problems, are of greater concern because of their high long-term risk. Cariprazine, with its relatively favorable tolerability profile compared to a number of other antipsychotics, is usually considered a favorable choice. In the acute phase, cariprazine is particularly beneficial in patients with predominantly negative or cognitive symptoms and for dual disorder patients. This drug is usually effective for positive symptoms as well, but in patients with significant agitation, it should usually be combined with a medication such as a benzodiazepine or a second antipsychotic. In the maintenance phase, the advantages of cariprazine include a favorable side-effect profile with low rates of metabolic side effects, sedation, and sexual dysfunction and continued efficacy in the treatment and prevention of negative and cognitive symptoms as well as positive symptoms.

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