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Review

REVIEW

Major Depressive Disorder (MDD) and Schizophrenia– Addressing Unmet Needs With Partial Agonists at the D2 Receptor: A Review

Jasmina Mallet, Philip Gorwood, Yann Le Strat, Caroline Dubertret

INSERM U1266, Institute of Psychiatry and Neurosciences of Paris (IPNP), France (Drs Mallet, Gorwood, Le Strat, and Dubertret); AP-HP; Psychiatry Department, University Hospital Louis Mourier; Paris Diderot University, France (Drs Mallet, Le Strat, and Dubertret); GHU Paris, CMME, Sainte-Anne hospital; University of Paris, France (Dr Gorwood).

Correspondence: Professor Philip Gorwood, MD, PhD, CMME, GHU Paris Psychiatrie, 100 rue de la Sante, 75014 Paris, France (p.gorwood@ghu-paris.fr).

Abstract

Second-generation antipsychotics are common candidates for the adjunctive treatment of major depressive disorder and for the treatment of schizophrenia. However, unmet needs remain in the treatment of both disorders. Considering schizophrenia, antipsychotics are the most common treatment and have demonstrated good efficacy. Still, side effects of these treatments are commonly reported and may impact adherence to the medication and functioning in patients with schizophrenia. Regarding major depressive disorder, despite the availability of several classes of antidepressants, many patients do not achieve remission. Adjunctive treatment with antipsychotics may improve clinical and functional outcomes. Compared with dopamine D2 receptor antagonism that is exhibited by most antipsychotics, partial agonism may result in improved outcomes in major depressive disorder and in schizophrenia. Aripiprazole, cariprazine, and brexpiprazole have partial agonism at the dopamine D2 receptor and could potentially overcome limitations associated with D2 antagonism. The objectives of this review were (1) to discuss the goal of treatment with second-generation antipsychotics in major depressive disorder and schizophrenia, and the clinical factors that should be considered, and (2) to examine the short- and long-term existing data on the efficacy and safety of D2 receptor partial agonists (aripiprazole, cariprazine, and brexpiprazole) in the adjunctive treatment of major depressive disorder and in the treatment of schizophrenia.

Keywords: schizophrenia, major depressive disorder, antipsychotics, treatment, side effect

Introduction

An Unmet Need in the Pharmacological Treatment of Major Depressive Disorder (MDD)

Inadequate Response to Antidepressant Monotherapy

Despite the availability of effective antidepressants, many patients with MDD do not achieve clinical response or remission (Rush et al., 2006). Surprisingly, when comparing response rate in large samples in 182 drug-placebo comparisons (clinical trials), response rates to antidepressant treatment have not improved over the past 3 decades (Papakostas and Fava, 2009). Many patients with MDD do not achieve adequate response or remission even though different classes of antidepressants are available (Han et al., 2013).

Regarding antidepressant treatment, about 1 patient out of 3 reported feeling "frustrated," the majority of which (59.3% of patients) because of the lack of response (Mago et al., 2018). These feelings can contribute to medication nonadherence and

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therefore worsen clinical outcomes (Mago et al., 2018). Moreover, patients with inadequate response to antidepressants often fail to regain a normal quality of life (IsHak et al., 2015). Anxiety might be involved in such poor response as often associated with MDD (about 1 of 2 patients) and with greater morbidity such as increased suicidality, functional impairment, longer duration of episodes, worse response to treatment, and worse health-related quality of life (Trivedi et al., 2006; Fava et al., 2008; Zimmerman et al., 2014).

Efficacy of Adjunctive Antipsychotics on Clinical Symptoms in MDD

For patients with an inadequate response to antidepressant, a second-generation antipsychotic (SGA) is a recommended treatment option (Gelenberg et al., 2010; Bauer et al., 2015). In a large meta-analysis of 10 randomized controlled trials (RCTs) assessing adjunctive treatment with a SGA together with standard antidepressants, in patients with MDD and inadequate initial response (n = 1500), response and remission rates were significantly higher for patients who received adjunctive treatment with an SGA than for those who received adjunctive placebo (57.2% vs 35.4%, and 47.4% vs 22.3%, respectively) (Papakostas et al., 2007). In another systematic review of the efficacy and safety profiles of SGA used for adjunctive treatment, the pooled response and remission rates were positive for all SGA except the combination of olanzapine and fluoxetine (Spielmans et al., 2013). Noticeably, even in patients showing minimal response after 8 weeks of treatment with antidepressant, 6 weeks of adjunctive aripiprazole treatment significantly reduced time to response and remission compared with patients who received adjunctive placebo (Nelson et al., 2012). However, in a meta-analysis examining adverse events (AEs) with an incidence greater than placebo ($P \leq .10$, based on odds ratio), aripirazole was associated with more akathisia and quetiapine with more sedation (Spielmans et al., 2013). This work will thus review studies examining the efficacy and tolerability of existing partial D2 receptors agonists.

An Unmet Need in the Pharmacological Treatment of Schizophrenia

The Impact of Treatment Side Effects on Adherence and Functioning

Side effects of antipsychotic medications are significantly associated with lower adherence in patients with schizophrenia and consequently with increased healthcare resource use. A study reported the impact of each side effect on complete adherence in a sample of 876 schizophrenia patients, of whom 86.2% reported a side effect (Dibonaventura et al., 2012). In another sample of 1825 patients diagnosed with a psychotic disorder, 77% reported medication side effects, 61% reported impairment in their daily life as a result of medication side effects, and 30% reported moderate or severe impairment in their daily life as a result of medication side effects (Morgan et al., 2012). Side effects markedly affect quality of life through small shifts in functional status and, if not addressed early, can cause long-term distress and contribute to chronic health complications (Awad and Hogan, 1994; Barnes and Schizophrenia Consensus Group of British Association for Psychopharmacology, 2011).

When considering international guidelines, APA guidelines recommend choosing a medication that offers good clinical response without intolerable side effects, while NICE guidelines recommend regular monitoring of side effects based on the side-effect profile of the prescribed antipsychotic (Kuipers, et al., 2014; Lehman et al., 2010). Patients who experience serious side effects may decide that the adverse effects outweigh the benefits of medication.

Addressing Unmet Needs in MDD and Schizophrenia With Antipsychotic Pharmacology

Association Between Receptor Blockade and Clinical Efficacy

The best-known mechanism for antipsychotics is the D2 receptor blockade. Howes and colleagues reviewed the evidence for the major implication of dopamine in the emergence of schizophrenia (Howes and Kapur, 2009; Howes et al., 2012). They proposed a new dopamine hypothesis with a framework that links risk factors, including pregnancy and obstetric complications, stress and trauma, drug use, and genetic vulnerability, to increased presynaptic striatal dopaminergic function. It explains how a complex array of pathological conditions may converge neurochemically to cause psychosis through aberrant salience and lead to the occurence of schizophrenia. However, it is important to remember that second-generation antipsychotics and particularly partial agonists also bind to a range of other receptors, contributing to their efficacy (Table 1). Conversely, the blockade of such receptors can also lead to specific side effects. Determining the optimal level of intrinsic activity at the receptor is crucial to avoid an activity close to agonism (potential lack of efficacy, side effects such as nausea, vomiting, insomnia, and motor effects) or on the contrary, closer to antagonism (and potential increased risk of extrapyramidal symptoms and raised prolactin levels) (Citrome et al., 2015).

There are several mechanisms that might, at least in part, explain antidepressive efficacy of antipsychotics: blockade of neurotransmitter receptors other than dopamine, blockade of monoamine transporters, effects on sleep, decrease in cortisol levels, and increase in neurotrophic growth factors (Sagud et al., 2011). However, many side effects reported with SGAs could lead to diminished treatment adhesion and also inhibit the clinician from prescribing such adjunct treatment (Thase, 2016). D2 partial agonism became a new approach, stabilizing dopamine function while mitigating side effects. Aripiprazole was the first D2 partial agonist to be approved for the treatment of schizophrenia and as an augmenting agent in major depression. However, some side effects (such as activation, agitation, and akathisia) have been ascribed to its high level of intrinsic activity at the D2 receptor (Parikh et al., 2017). This led to the development of other molecules.

Distinct Receptor Profiles: Aripiprazole, Brexpiprazole, Cariprazine

Concerning pharmacologic properties, aripirazole, brexpiprazole, and cariprazine all exhibit D2 receptor partial agonism, but each displays a distinct receptor profile. Aripiprazole preferentially binds to D2 receptors over D3 receptors (Shapiro et al., 2003). Cariprazine has an approximately 10-fold higher affinity for human D3 compared with human D2 (S or L) receptors (Kiss et al., 2010). Brexpiprazole, a serotonin-dopamine activity modulator, is a partial agonist at 5-HT1A and dopamine D2 receptors and antagonist at 5-HT2A and noradrenaline α1B and α2C receptors, all at similar potency. Brexpiprazole shows a lower intrinsic activity at the D2 receptor compared with aripiprazole, and a greater affinity at the 5-HT2A receptor compared with aripiprazole (Maeda et al., 2014). These properties would result in less akathisia and extrapyramidal symptoms. Finally, brexpiprazole and cariprazine bind less strongly to H_1 receptors than aripiprazole (Table 1), suggesting a lower

Table 1. In Vitro Receptor Binding Affinities of D_2 Partial Agonists

Receptors	D2 partial agonists (affinities)		
	Aripiprazole	Brexpiprazole	Cariprazine
5-HT1A	1.70*a*	0.12	2.60*d*
5-HT2A	3.40[a]	0.47	18.80[d]
5-HT2B	0.36[b]	1.90	0.58[d]
5-HT7	39.00[a]	3.70	112.20[e]
D2	0.34*a*	0.30	0.49(D2L)*d*,0.69 (D2S)*d*
D3	0.80*a*	1.10	0.08*d*
α1A	25.70[b]	3.80	155.00[d]
α1B	34.80[b]	0.17	NR
α1D	NR	2.60	208.90[e]
α2C	37.90[b]	0.59	NR
H1	61.00[a]	19.00	23.20[d]
M1	6780[b]	67% inhibition at 10 μM	>1000 (IC50)[d]

Abbreviations: IC_{50}, half-maximal inhibitory concentration; NR, not reported.
Binding affinity (Ki, nM), indicating partial agonism (bold characters) or antagonism (italics). Data are from different experiments and are not intended for direct comparison; alternate sources may report different values, and there may be discrepancies due to species differences; partial agonist/antagonist activity from Stahl 2013, Maeda et al., 2014, and Kiss et al., 2010; brexpiprazole data are mean values calculated by nonlinear regression analysis using data from 3 assays performed in duplicate or triplicate. Prescribing information (PI) data used where available, otherwise published data: *a*Abilify PI February 2018 (human); *b*Shapiro et al. Neuropsychopharmacology 2003;28(8):1400–1411 (human); *c*Rexulti PI February 2018 (human); *d*Vraylar PI November 2017 (human); *e*Kiss et al. J Pharmacol Exp Ther 2010;333(1):328–340 (human).

antihistaminic activity resulting in less sedation, somnolence, and weight gain.

Finally, several properties of aripiprazole are probably not yet known for brexpiprazole and cariprazine: possible absence of long-term dopamine-related neurochemical adaptations (involving a lack of dopamine supersensitivity and treatment resistance) and specific changes of the neuronal transcriptome in relevant biological functions (for review, see de Bartolomeis et al., 2015).

Methods

Several Medline searches were performed to review the literature from January 2000 to January 2019, and the following keywords were used: (schizophrenia OR psychotic disorder) OR (depressive disorder OR treatment-resistant depression)) AND (brexpiprazole OR cariprazine OR aripiprazole). We selected studies published in English that included only human participants with an abstract available, which restricted the results to 1368 papers. After exclusion of reviews and expert opinions, 336 papers were examined. Then we excluded doublons or nonrelated topics and meta-analyses of RCT were preferred over unique RCT (when both information were available in the retrieved literature), themselves preferred over open-label studies. Additional unpublished clinical trials were identified through the ClinicalTrials.gov electronic database. Concerning efficacy, 12 studies were finally judged suitable for the assessment of schizophrenia disorder and major depressive disorder. The evaluation of safety for SCZ and MDD included 10 and 11 studies, respectively.

The Role of Partial Agonists in the Treatment of Schizophrenia

Efficacy of D2 Partial Agonists in the Short-Term Treatment of Schizophrenia Symptoms

Aripiprazole

In a pooled analysis of 5 RCTs (see Table 2), aripiprazole treatment resulted in a significantly greater decrease in PANSS total score from baseline to week 4/6 than placebo (–14.4 vs –2.4) with an effect size of 0.57 (Kane et al., 2008).

Cariprazine

Data from 4 short-term studies of cariprazine 1.5–12 mg (n = 1275) vs placebo (n = 568) were pooled in a meta-analysis (Zhao et al., 2018). There was a significant benefit of cariprazine vs placebo on the PANSS total score (standardized mean difference [SMD]: –0.37 [95% confidence interval (CI) = –0.47 to –0.27], $P < .001$).

Brexpiprazole

Efficacy of brexpiprazole was evaluated in patients with acutely exacerbated schizophrenia in 3 short-term, randomized, double-blind, placebo-controlled studies. The pooled data for 2 studies showed that combined brexpiprazole 2 mg (n = 359) and 4 mg (n = 359) was superior to placebo (n = 358) in change of PANSS total score (least square mean difference [LSMD] from placebo: –5.46, $P = .0004$, and –6.69, $P < .0001$, respectively) and CGI-S (LSMD: –0.25, $P = .0035$, and –0.38, $P < .0001$, respectively) (Correll et al., 2016).

Long-Term Efficacy on Relapse Prevention in Schizophrenia

Aripiprazole

In a 26-week, randomized, double-blind, placebo-controlled, parallel-group, multi-center study, 310 patients with DSM-IV schizophrenia were randomly assigned to receive a once-daily fixed dose of aripiprazole, 15 mg, or placebo (Pigott et al., 2003). The time to relapse following randomization was significantly longer for aripiprazole compared with placebo, with estimated Kaplan-Meier survival rate at week 26 of 62.6% for aripiprazole vs 39.4% for placebo ($P < .001$).

Cariprazine

The efficacy on relapse of cariprazine (3–9 mg/d) was evaluated in a multinational randomized, double-blind, placebo-controlled, parallel-group study of 97 weeks (Durgam et al.,

2016b). Relapse occured in 24.8% of cariprazine-treated patients vs 47.5% of placebo-treated patients (hazard ratio = 0.45 [95% CI = 0.28 to 0.73], P = .001 for time to relapse). Long-term cariprazine treatment was thus significantly more effective than placebo for relapse prevention in patients with schizophrenia. The long-term safety profile in this study was consistent with the safety profile observed in previous cariprazine clinical trials.

Brexpiprazole

In a recent study in 524 patients (Fleischhacker et al., 2017), patients already stabilized with brexpiprazole (1–4 mg/d, n = 202) were randomized to double-blind maintenance treatment with either brexpiprazole (at their stabilization dose, n = 97) or placebo (n = 105) for up to 52 weeks. The risk of impending relapse was significantly reduced in 13.5% of brexpiprazole patients compared with 38.5% of placebo patients (P < .0001). During the maintenance phase, the incidence of AEs was comparable with placebo. The long-term efficacy on symptoms was also evaluated with improvement with brexpiprazole, whereas patients switched to placebo showed worsening.

Efficacy of D2 Partial Agonists on Functional Outcomes in Schizophrenia

Assessing Functional Outcomes in Clinical Studies Is an Important Challenge for New Antipsychotic Agents

Patients who achieve symptomatic remission have significantly better social functioning, better self-reported quality of life, and better insight into their illness than those who do not achieve symptomatic remission (Brissos et al., 2011). A variety of factors may contribute to impairment in everyday functioning in patients with schizophrenia, including functional incapacity, cognitive performance and social cognition, clinical symptoms (including depression), environmental factors, and poor health status (Harvey and Strassnig, 2012). Overall, 63% of patients with psychosis have obvious or severe dysfunction in socializing (Morgan et al., 2012). Finally, 32% of patients with psychosis have obvious or severe dysfunction in quality of self-care (Morgan et al., 2012), functional remission being an important outcome in schizophrenia (Mallet et al., 2018). Several functioning scales exist, the Personal and Social Performance scale (PSP) or the Global Assessment Functioning (GAF) being the most frequently used.

Efficacy of Aripiprazole

The PSP mean score increased over 12 weeks of treatment with oral aripiprazole, and this effect was maintained over an additional 38 weeks with the same oral antipsychotic (Fleischhacker et al., 2014).

Efficacy of Cariprazine

A 26-week, double-blind study compared the PSP mean score with cariprazine (n = 227) vs risperidone (n = 227) and found better improvement with cariprazine (P < .001 at week 26) (Németh et al., 2017). Another long-term study (20 weeks open-label, 26–72 weeks double-blind) compared cariprazine with placebo (Durgam et al., 2016b). PSP total score improved during open-label cariprazine treatment. Subsequent double-blind cariprazine treatment exhibited no PSP score change (mean change: 0.0), whereas patients switched to placebo showed worsening (mean change: –7.2).

Efficacy of Brexpiprazole

The pooled results of 2 short-term studies showed better improvement at week 6 in PSP total score with brexpiprazole 2 mg (n = 343) and 4 mg (n = 342) vs placebo (n = 333) (P < .01 and P < .001, respectively) (Correll et al., 2016).

The long-term efficacy has been tested in 2 recent studies. The first evaluated mean change from baseline in GAF score with brexpiprazole 1–4 mg (n = 95) vs placebo (n = 102) (Fleischhacker et al., 2017). In this double-blind maintenance phase, patients with brexpipazole showed an increasing functioning score, whereas patients with placebo showed worsening from week 12 to week 52 (P < .001). The other study was an open-label design in 1015 patients with PSP score as a secondary outcome. Patients with brexpiprazole (n = 410) at week 52 showed a mean improvement in PSP score of 7.7 points over the course of treatment to a total of 68.3 points. This is above the threshold for potentially clinically meaningful response in stabilized patients with schizophrenia (an increase of 4–7 points) and close to functional remission (a total score of >70 points) (Forbes et al., 2018).

Safety and Tolerability of D2 Partial Agonists in the Treatment of Schizophrenia

Activating and Sedating Side Effects Are Common Causes of Concern

There is heterogeneity among different SGAs with regard to AEs considered as activating (akathisia, restlessness, agitation, anxiety, insomnia) and sedating (somnolence, fatigue, sedation) (Németh et al., 2017). A recent analysis of absolute risk increase with SGAs in schizophrenia found that only brexpiprazole (1–4 mg) and paliperidone (3–12 mg) (D2 antagonist) were neither activating nor sedating. Cariprazine (1.5–6 mg) was predominantly activating, while aripiprazole (2–30 mg/d) was similarly activating and sedating (Citrome, 2017).

Short-Term Safety and Tolerability

Aripiprazole

In a pooled analysis of 5 placebo-controlled trials (4–6 weeks duration), aripiprazole showed a favorable safety and tolerability profile with low potential for extra-pyramidal symptoms (EPS), weight gain, prolactin elevation, QT(c) prolongation, and sedation (aripiprazole, n = 926 patients; placebo, n = 413 patients; haloperidol, n = 200 patients) (Marder et al., 2003).

Brexpiprazole

A recent pooled analysis of 2 studies comparing placebo with brexpiprazole (2 or 4 mg) showed that no treatment-emergent AEs appeared with an incidence ≥5% and twice that of placebo in patients treated with brexpiprazole 2–4 mg (Kane et al., 2016). More specifically, akathisia rates were low (5.8%, pooled brexpiprazole group), sedation rates were low (2.3%, pooled brexpiprazole group), and mean body weight increase was 1.1 kg.

Cariprazine

A pooled analysis of 4 studies using 3 daily dose subgroups (n = 539, 1.5–3 mg; n = 575, 4.5–6 mg; n = 203, 9–12 mg) showed a general good tolerability (Earley et al., 2017). The incidence of treatment-emergent AEs vs placebo was similar for cariprazine 1.5–3 mg/d and higher for cariprazine 4.5–6 and 9–12 mg/d; a dose-response relationship was observed for akathisia, extrapyramidal symptoms, and diastolic blood pressure. The mean changes in metabolic parameters were generally similar in cariprazine-treated and placebo-treated patients. There was no significant prolactin level increase or heart rate-corrected QT interval value >500 ms; small increases in mean body weight (~1 to 2 kg) vs placebo were observed.

Table 2. Review of Efficacy and Safety of Partial Agonists in Schizophrenia and Major Depressive Disorder

Schizophrenia: Clinical efficacy						
Authors	Design	Duration	Drug	Titration	Main outcome	Results and comments
	Short-term					
Kane, 2018	Pooled analysis of 5RCT	4 weeks	Aripiprazole vs Placebo	5–30 mg	PANSS total score	Improvement in the aripiprazole group vs placebo group (-14.4 vs -2.4) $P<.001$, ES = 0.57
Zhao, 2018	Meta-analysis, 4 RCT	6 weeks	Cariprazine vs Placebo	3–9 mg	PANSS total score	Improvement in the cariprazine group vs placebo group SMD -0.37 $P<.00001$
Correll, 2016	Pooled analysis of 2RCT	6 weeks	Brexpiprazole vs Placebo	1) 2 mg 2) 4 mg	(a) PANSS total score (b) CGI-s	Improvement in the brexpiprazole group vs placebo group (a) SMD = (1)– 5.46, $P=.0004$, and (2)– 6.69, $P<.0001$ (b) SMD = (1)– 0.25, $P=.0035$, and (2)– 0.38, $P<.0001$
	Long term					
Pigott, 2003	RCT	26 weeks	Aripiprazole vs Placebo	15 mg	Relapse	- Improvement in the aripiprazole group vs placebo group -Estimated Kaplan-Meier survival rate at week 26 was 62.6% for aripiprazole vs 39.4%, for placebo, $P<.001$ - $P<.001$ (log-rank test) for time to relapse with aripiprazole vs placebo; RR of relapse = 0.50 (95% CI: 0.35, 0.71)
Durgam, 2016b	RCT after open-label stabilization	Up to 97 weeks	Cariprazine vs placebo	3–9 mg	Relapse	Improvement in the cariprazine group vs placebo group- Relapse in 24.8% of cariprazine-treated patients vs 47.5% of placebo-treated patients; HR = 0.45 (95% CI: 0.28–0.73); $P=.001$ for time to relapse with cariprazine vs placebo
Fleischhacker, 2017	Double-blind (RCT) maintenance after stabilization	52 weeks	Brexpiprazole vs Placebo	1–4 mg	(1) Relapse (2) PANSS total score	(1) Risk of impending relapse reduced by 71% vs placebo; 13.5% of brexpiprazole patients vs 38.5% of placebo patients experienced an impending relapse ($P<.0001$) (2) Improvements sustained during the double-blind phase, worsening in placebo group ($P<.001$)
Schizophrenia: functional outcomes						

Table 2. *Continued*

Schizophrenia: Clinical efficacy						
Authors	Design	Duration	Drug	Titration	Main outcome	Results and comments
Fleischhacker, 2014	Pooled analysis of 2 RCT	1)12 weeks 2) 38 weeks 3)52 weeks	Aripiprazole vs Placebo	- Oral 10–30 mg until 38 weeks -Monthly 50 mg -Monthly 400 mg	PSP total score	(1) Improvement in the aripiprazole group vs placebo group ($P < .001$) (2) During the double-blind maintenance phase, PSP total score stable in the aripiprazole once-monthly 400 mg and oral aripiprazole groups but decreased in the aripiprazole once-monthly 50 mg group ($P < .05$); no difference between aripiprazole once-monthly 400 mg and oral aripiprazole (3) During the double-blind, placebo-controlled phase, greater functional deterioration with placebo ($P < .001$)
Németh, 2017	RCT	26 weeks	Cariprazine vs Risperidone (3–6 mg)	3–6 mg	PSP total score	Improvement in the cariprazine group vs placebo group ($P < .001$)
Durgam, 2016b	(1) Open label then (2) Double-blind study (RCT)	1)20 weeks 2) 26/72 weeks	Cariprazine vs Placebo	3–9 mg	PSP total score	(1) PSP increase during open label in the cariprazine group (mean change = 11.1 [14.6]) (2) No effect during double-blind under cariprazine, decreasing under placebo (mean change = –7.2 [16.2])
Correll, 2016	Pooled analysis of 2 short-term studies (RCT)	6 weeks	Brexpiprazole vs Placebo	-2 mg -4 mg	PSP total score	(1) 2 mg: mean change (increasing) $P < .01$ (2) 4 mg: mean change (increasing) $P < .001$
Fleischhacker, 2017	Single-blind than double-blind maintenance phase (RCT)	Up to 52 weeks	Brexpiprazole vs Placebo	1–4 mg	GAF score	GAF increase at week 24, 36, and 52 (mean change from baseline 0.9; 1; 06 in brexpiprazole groups vs -4.5; -5.8; -6 in placebo group) $P < .001$ vs placebo at week 36, 52, $P < .01$ at week 24
Forbes, 2018	Open label study from 3RCT+de novo patients	Up to 52 weeks	Brexpiprazole	1–4 mg	PSP total score (secondary outcome)	Improvement (mean change in score of 7.7), irrespective of prior treatment
MDD: Clinical efficacy						
Authors	Design	Duration	Drug	Titration	Main outcome	Results
	Short-term					
Thase, 2008	Pooled analysis of 2 RCT	6 weeks (after 8-week prospective antidepressant therapy treatment phase)	Aripiprazole vs placebo	2–20 mg	MADRS	Improvement in the aripiprazole group vs placebo group (mean change -8.7 vs -5.7; $P < .001$)

Table 2. *Continued*

Schizophrenia: Clinical efficacy						
Authors	Design	Duration	Drug	Titration	Main outcome	Results and comments
Dunner, 2012	Pooled analysis of 3 RCT	6 weeks (after8-week prospective antidepressant therapy treatment phase with a switch to another ADT medication, either of the same class or of a different class from what they had been treated)	Aripiprazole vs Placebo	2–15 mg	MADRS	Improvement in the aripiprazole group vs placebo group (in between-class (-9.2 vs -6.2 $P<.001$) & within-class (-9.8 vs -6.6, $P<.001$)groups)
Thase, 2019	Pooled analysis of 3 RCT	6 weeks	Brexpiprazole vs Placebo	2–3 mg	MADRS in patients with (1) anxious distress (2) no anxious distress	Improvement in the brexpiprazole groups vs placebo groups (1) SMD = –3.00 (CI95% = –4.29, –1.71; $P<.0001$) (2) SMD = -1.38 (CI 95% = –2.71,–0.05; $P=.043$)
Durgam, 2016a	RCT	8 weeks (after 1-2 weeks screening)	Cariprazine vs placebo	1) 1–2 mg/d 2) 2–4.5 mg/d	MADRS	Improvement in the cariprazine group under 2–4.5 mg vs placebo (not in the 1–2 mg/d group) 1) LSMD = -0.9; $P=.2404$ 2) LSMD = -2.2; $P=.0114$)
Earley, 2018	RCT	8 weeks (after 8 week prospective treatment)	Cariprazine vs placebo	1.5–4.5 mg	(1) MADRS (2) CGI-I	No difference in MADRS scores, improvement in CGI-I scores in cariprazine groups vs placebo (1) LSMD = -0.2, $P=.795$ (2) LSMD: -0.2; $P=.041$
Fava, 2018	RCT	8 weeks (after 8 weeks prospective treatment)	Cariprazine vs placebo	1) 0.1–0.3 mg 2) 1.0–2.0 mg	MADRS	No statistical difference (1) ns (nonspecified) (2) LSMD = –1.8; $P=.227$
	Long-term					
Berman, 2011	Open label after short term RCT+ de novo patients	52 weeks	aripiprazole	Mean dose 10.1 mg	CGI-S = 1 or 2: remission percentage	69.7% remission
Bauer, 2019	RCT after 8 weeks prospective treatment	24 weeks	Brexpiprazole vs placebo	1–3 mg	Full remission: MADRS ≤10, or ≥50% decrease	NS (OR: 0.83; $P=.2641$)
Hobart, 2019	Open label from 3RCT	1)26 weeks 2)52 weeks	brexpiprazole	0.5–3 mg	CGI-S and CGI-I	CGI-S: improvement at weeks 26 and 52 CGI-I:improvement at weeks 26 and 52
MDD: functional outcomes						
Fabian, 2012	Pooled analysis of 3 RCT	6 weeks (after 8 weeks prospective treatment)	Aripiprazole vs placebo	2–20 mg	SDS total score	Improvement in the aripiprazole group vs placebo group: -1.2 vs -0.7, $P \leq .001$
Hobart, 2018	Pooled analysis of 6 RCT	6 weeks	brexpiprazole	1–3 mg	SDS total score	Improvement (LSMD = -0.40 (95% CI: -0.56, -0.23; $P<.0001$)

Table 2. *Continued*

Schizophrenia: Clinical efficacy						
Authors	Design	Duration	Drug	Titration	Main outcome	Results and comments
Durgam, 2016a	RCT	1) 4 weeks 2) 8 weeks	Cariprazine vs Placebo	a)1–2 mg b) 2–4.5 mg	SDS total score	1) improvement ($P<.01$) in LSMD with a) and b) (not placebo) 2) no difference in total sore at week 8
Earley, 2018	RCT	8 weeks	Cariprazine vs Placebo	1.5–4.5 mg	SDS total score	LSMD: -0.7, $P=.278$
Hobart, 2019	Open label from 3RCT	(1) 26 weeks (2) 52 weeks	Brexpiprazole	0.5–3 mg	SDS	Improvement in the brexpiprazole groups; mean (SD) change from baseline (1) –0.7 (2.1) (2) –1.2 (2.3)

Abbreviations: CGI-I, Clinical Global Impression Scale- Improvement, CGI-S, Clinical Global Impressions Scale-Severity; ES, effect size; GAF, Global Assessment Functionning; LSMD, Least Standardized Mean Difference; MADRS, Montgomery-Asberg Depression Rating Scale; NS, nonsignificant; PANSS, Positive and Negative Syndrom Scale; PSP, Personal and Social Performance Scale; RCT, randomized control trial; SDS, Shehaan Disability Scale; SMD, Standardized Mean Difference.

Long-Term Safety and Tolerability

Aripiprazole

In a 26-week double-blind study of stabilized patients randomly assigned to receive placebo (n = 153) or aripiprazole (n = 153; 15 mg/d), aripiprazole was well tolerated, with no evidence of marked sedation and no evidence of hyperprolactinemia or prolonged heart rate-corrected QT interval. Extrapyramidal symptoms were comparable in the aripiprazole and placebo groups. Modest mean weight loss at endpoint was evident in both groups (Pigott et al., 2003).

Brexpiprazole

In Fleischhacker et al. (2017), a total 524 patients were enrolled, 202 of whom were stabilized on brexpiprazole and randomized to brexpiprazole (n = 97) or placebo (n = 105). During the maintenance phase (weeks 12–52), the incidence of AEs was comparable with placebo.

Cariprazine

In a randomized, double-blind, placebo-controlled trial by, stable patients who completed open-label treatment (first step) could be randomized to continued cariprazine (n = 99; 3, 6, or 9 mg/d) or placebo (n = 101) for double-blind treatment (up to 72 weeks) (Durgam et al., 2016b). Akathisia (19.2%), insomnia (14.4%), and headache (12.0%) were reported in ≥10% of patients during open-label treatment; there were no cariprazine AEs ≥10% during double-blind treatment.

A recent study by the same group (Durgam et al., 2017) showed that open-label treatment with cariprazine at flexible doses ranging from 1.5 to 4.5 mg/d was generally safe and well tolerated for up to 1 year without any apparent loss of efficacy. The results of this long-term extension study are similar to those observed in the short-term double-blind lead-in study (Durgam et al., 2014). Approximately 50% (46/93) of patients completed the 48 weeks of open-label treatment. The most common AEs were akathisia (14 %), insomnia (14 %), and weight increase (12 %). Serious AEs occurred in 13% of patients; 11% discontinued due to AEs. Mean changes in metabolic parameters were generally small and not clinically relevant.

Effect of Partial Agonists on Body Weight in Schizophrenia

Short-Term Effect on Body Weight

A recent study explored the effects of brexpiprazole and aripiprazole on body weight when used as monotherapy to treat schizophrenia in short-term (4/6 weeks) and long-term (≤52 weeks) studies (Weiss et al., 2018). In short-term ones, the mean weight increase was 1.2 kg for brexpiprazole and 0.6 kg for aripiprazole.

A pooled analysis of 4 studies including a 6-week double-blind treatment period (comparing placebo [n = 300], risperidone 4 mg/d [n = 140], cariprazine [doses ranging from 1.5 mg to 12 mg/d, n = 1317], and aripiprazole 10 mg/d [n = 152]) showed similar results. The mean body weight increase was greater in all active treatment groups than in the placebo group. Regarding cariprazine, the mean increase in body weight was lower in the lower dose groups than in the 9- to 12-mg group. In the approved dose range, weight gain of 7% or more occurred in approximately 8% of cariprazine patients, which was less than that in the cariprazine 9- to 12-mg (17.2%) and risperidone (16.7%) groups and was similar to the aripiprazole (6.0%) group. Taken together, these results suggest that cariprazine, aripiprazole, and brexpiprazole in the approved dose range are on the lower end of the atypical antipsychotic weight gain hierarchy.

Long-Term Effect on Body Weight

In the pooled results of different studies by Weiss et al (2018), in the long term (week 52) the mean weight increase was 2.1 kg for brexpiprazole (n = 724, 2–4 mg/d) and 3.0 kg for aripiprazole (n = 674, 10–30 mg/d). The authors concluded that brexpiprazole and aripiprazole had a similar effect on body weight over the course of 1 year. However, in the RCT by Pigott et al. (2003), with different methods, aripiprazole (n = 151, 15 mg) and placebo (n = 151) were responsible for a modest and comparable weight loss in the 2 groups at the end point (26 weeks).

In the RCT by Fleischhacker et al. (2017), in the final phase patients were assigned with brexpiprazole (n = 97) or placebo (n = 105). During the maintenance phase, patients had a mean weight decrease from baseline to their last visit (week 52) in the brexpiprazole (–0.3 kg) and placebo (–2.2 kg) groups, and the

incidence of potentially clinically relevant weight gain was 5.2% in the brexpiprazole group compared with 1.0% in the placebo group. In the long-term 72-week RCT comparing placebo (n = 99) with cariprazine (n = 101; daily dose 3, 6, or 9 mg) (Durgam et al., 2016b), weight gain ≥7% (which is clinically relevant) was reported in 10.6% of open-label patients, 32.3% of placebo-treated patients, and 27.0% of cariprazine-treated patients during double-blind treatment, showing a good tolerability.

Short- and Long-Term Effect on Laboratory Parameters in Schizophrenia

Short-term aripiprazole treatment is associated with a decrease in prolactin, and minimal effects on glucose and lipid parameters (Marder et al., 2003). Regarding RCTs, for brexpiprazole as well as for cariprazine, mean changes from baseline in lipid parameters in the short- and long-term of the double-blind treatment were generally not clinically relevant (Correll et al., 2016; Earley et al., 2017).

Finally, long-term treatment with D2 partial agonist was generally well tolerated (Pigott et al., 2003; Durgam et al., 2016b; Fleischhacker et al., 2017), with no new or unexpected AEs compared with the short-term studies and only small mean changes in metabolic parameters.

Conclusion

The Role of Partial Agonists in the Treatment of Schizophrenia

Goals in the treatment of schizophrenia include symptom resolution, maintenance of symptomatic efficacy, and improvement in functioning. To achieve these goals with a low incidence of adverse effects, D2 receptor partial agonists are valuable choices. Aripiprazole, brexpiprazole, and cariprazine are both efficacious in the treatment of schizophrenia (on clinical symptoms but also on patient functioning) in the short and the long term. On the whole, the majority of the data available are positive for each molecule use when compared with placebo or first-generation antipsychotics. Few studies include other atypical antipsychotics, making a direct comparison difficult. Future RCT are needed with a head-to-head comparison between each partial agonist.

In clinical practice, partial agonists may be considered in those patients who may be especially sensitive to EPS-related side effects or have experienced problems with somnolence or prolactinemia with other antipsychotic treatments. However, the clinician must keep in mind that partial agonist may also provide side effects such as akathisia or weight increase in the short term and possibly cardiovascular side effects in the long term (for review, refer to Citrome, 2015). The aripiprazole starting and recommended dose is 10–15 mg/d (maximum 30 mg/d), the brexpiprazole starting dose is 1 mg/d with a recommended dose range 2–4 mg/d (maximum 4 mg/d), and the cariprazine starting dose is 1.5 mg/d (recommended dose range 1–6 mg/d) (Citrome, 2015).

MDD and Partial Agonists

Several long-term studies have demonstrated high rates of inadequate response with antidepressant therapy in MDD, even after several switches with other agents or after combinations (Rush et al., 2006; Papakostas and Fava, 2009). One option is to address this inadequate antidepressant response with an adjunctive SGA. According to international guidelines, only 1 D2 receptor antagonist is indicated for the adjunctive therapy to any antidepressants for the treatment of MDD: quetiapine (in the European Union and United States) (Bauer et al., 2015). In the United States, olanzapine is also available in combination with fluoxetine for the treatment of treatment-resistant depression (named Symbiax, www.fda.gov). Aripiprazole and brexpiprazole are indicated as an adjunctive therapy to antidepressants for the treatment of MDD in adults in the United States, and cariprazine is in development for the same indication (Durgam et al., 2016a).

Efficacy of D2 Partial Agonist Antipsychotics in the Short- and Long-Term Treatment of MDD

Short-Term Efficacy on Symptoms

Adjunctive Aripiprazole

The efficacy of adjunctive aripiprazole in MDD has been investigated in a pooled analysis of 2 short-term studies (Thase et al., 2008): greater improvement in Montgomery-Asberg Depression Rating Scale (MADRS) total score was observed compared with adjunctive placebo (week 6, $P < .001$). Similar improvements vs adjunctive placebo were also observed in a later pooled analysis of 3 studies (Dunner et al., 2012).

Adjunctive Brexpiprazole—The efficacy of adjunctive brexpiprazole (2–3 mg; n = 770) has been investigated in a pooled analysis of 4 short-term studies (Thase et al., 2019). Greater improvement from baseline in MADRS total score (week 6, $P < .001$) compared with adjunctive placebo (n = 788).

Adjunctive Cariprazine

Cariprazine is in development as an adjunctive therapy to antidepressant. One phase II RCT (Durgam et al., 2016a) evaluated the efficacy and safety of cariprazine as adjunctive therapy in patients with MDD who have inadequate response to standard antidepressant therapy alone. Compared with placebo (n = 264), reduction in MADRS total score at week 8 was significantly greater with adjunctive cariprazine 2–4.5 mg/d (n = 271) but not with 1–2 mg/d (n = 273). Among 2 phase-III RCTs, 1 study failed to meet the primary endpoint (Earley et al., 2018), and the outcome of the other study is not publicly available.

Short-Term Efficacy on Functioning in MDD

In a comprehensive review of depression research (not focused on individual treatments), symptomatic improvement was not necessarily accompanied by improvement in functioning or quality of life (McKnight and Kashdan, 2009; Saltiel and Silvershein, 2015). Improving functioning is still an unmet need in the treatment of MDD.

Adjunctive Aripiprazole

In a study pooling three 6-week trials (Fabian et al., 2012), adjunctive aripiprazole (vs placebo) has shown efficiency (mean change from baseline) in the total score and in social and family life domains of the Sheehan Disability Scale (SDS), which is a patient-rated measure of functional disability (Sheehan and Sheehan, 2008).

Adjunctive Brexpiprazole

A recent pooled analysis of data from six 6-week RCT studies (n = 2066 randomized) of adjunctive brexpiprazole (2 and 3 mg/d in fixed-dose studies; 1–3 mg/d in flexible-dose studies) vs placebo in patients with MDD and inadequate response to antidepressant showed improved functioning with adjunctive brexpiprazole (mean change from baseline to week 6; total score and work and family life domains, $P < .001$) (Hobart et al., 2018).

Adjunctive Cariprazine

In the phase II study of adjunctive cariprazine (Durgam et al., 2016a), significantly greater improvements in SDS total score were found in both cariprazine groups (2–4.5 mg/d and 1–2 mg/d) during double-blind treatment (week 4), but no significant differences were detected at week 8. Mean change in SDS family/home was significantly greater with cariprazine 2–4.5 mg/d vs placebo at all study visits, including week 8 ($P = .01$). No significant improvements in SDS work/school and social life were found in either cariprazine group at week 8. The phase III study failed to show an improvement in SDS scores at week 8 with adjunctive cariprazine (1.5–4.5 mg/d) (Earley et al., 2018).

Long-Term Efficacy on Symptoms of MDD

Adjunctive Aripiprazole

In an open label study following a short-term RCT (Berman et al., 2011), endpoint CGI-S scores suggest that adjunctive aripiprazole provides clinically meaningful, persistent efficacy with long-term treatment (up to 52 weeks). Nearly 70% of participants who continued long-term treatment had a stable CGI-S score of 1 (normal) or 2 (borderline ill), indicating that scores are consistent with remission from symptoms. On average, most improvement in CGI-S scores occurred in the first month of treatment and was sustained over a year of treatment. To our knowledge, there is no double-blind long-term study using a placebo-controlled discontinuation design.

Adjunctive Brexpiprazole

In a recent study (Bauer et al., 2019), patients with inadequate response to antidepressant were randomized to antidepressant with brexpiprazole 1–3 mg/d or antidepressant and placebo (24 weeks). The primary endpoint was full clinical remission (MADRS total score ≤10 and ≥50% decrease from randomization, i.e., baseline, in MADRS total score for at least 8 consecutive weeks). Adjunctive brexpiprazole did not differentiate from antidepressant with placebo on the primary endpoint of full remission. In a 52-week open-label study (from 3RCT), adjunctive treatment with open-label brexpiprazole 0.5 to 3 mg/d was associated with continued improvement in efficacy measures and functional outcomes (Clinical Global Impressions-Severity and Improvement Scales; SDS scale) (Hobart et al., 2019a).

Safety and Tolerability of D2 Partial Agonist Antipsychotics in the Short- and Long-Term Treatment of MDD

Despite demonstrated efficacy in MDD, the side-effect profile of SGA may limit their use in clinical practice. A meta-analysis of 3549 patients from 14 clinical studies demonstrated that SGAs are associated with tolerability concerns (Spielmans et al., 2013). In a real-world study, clinicians' concerns over side effects prevented or delayed prescription of an adjunctive antipsychotic in 13% of patients (McIntyre and Weiller, 2015).

Short-Term Safety and Tolerability in the Treatment of MDD

Aripiprazole

In a review and pooled analysis of 3 RCTs (Pae et al., 2011), adjunctive aripiprazole was safe and well-tolerated. The overall discontinuation rates due to AE were low (4.4% vs 1.7% with placebo). Akathisia was the most common adverse events (AE) (in 22.7% of patients in the pooled analysis [antidepressant+aripiprazole 2–20 mg (n = 543) vs 4.1%, antidepressant+placebo (n = 538)]). Restlessness was also common (12.2% vs 2.4%) as well as fatigue and insomnia (around 8%).

Brexpiprazole

In a review and pooled analysis of 4 studies (Thase et al., 2019), adjunctive brexpiprazole was safe and well-tolerated, with discontinuation rates around 2%. Akathisia was found in 8% of patients with adjunctive brexpiprazole (1–3 mg, n = 1032) and in 2.6% with placebo (n = 819). Weight increase was also more frequent (5.8% vs 1.6%).

Cariprazine

In phase II study comparing adjunctive cariprazine (1–2 mg, n = 273, or 2–4.5 mg, n = 273) vs placebo (n = 266) (Durgam et al., 2016a), treatment emergent adverse events (TEAE) were reported in ≥10% of patients in either cariprazine dosage group. In the 2-to 4.5-mg group, the most common AEs were akathisia (22.3%), insomnia (13.6%), and nausea (12.8%) (6.6%, 9.9%, and 7.0%, respectively, in the 1- to 2-mg group).

Short-Term Effect on Body Weight in the Treatment of MDD

Several clinical trials evaluated mean change from baseline to last visit in body weight, as it can be a frequent side effect with antipsychotics (clinicalTrials.gov).

Aripiprazole and Brexpiprazole

In a pooled analysis (Weiss et al., 2018), the overall weight profiles for brexpiprazole and aripiprazole (adjunctive to antidepressant) were similar. The mean weight increase was 1.5 kg for brexpiprazole and 1.6 kg for aripiprazole.

Cariprazine

In one RCT comparing antidepressant with adjunctive brexpiprazole (1–2 mg, n = 273 or 2–4.5 mg, n = 271) with placebo (n = 264) (Durgam et al., 2016a), the percentage of patients with ≥7% body weight increase at week 8 from baseline was low in all groups (placebo, 1.9%; 1–2 mg/d, 1.5%; 2–4.5 mg/d, 3.3%).

Long-Term Safety and Tolerability in the Treatment of MDD

Long-term safety and tolerability of classical parameters

Aripiprazole

In a 52-week open-label study (n = 994) (Berman et al., 2011), long-term adjunctive aripiprazole therapy was well tolerated, with an acceptable long-term safety and tolerability profile in patients who had not responded to treatment with 1 or more antidepressant. However, the discontinuation rate due to AE was high in the total group (22.7%). Common (>15% of patients) spontaneously reported AEs were akathisia (26.2%), fatigue (18.0%), and weight gain (17.1%). The incidence of serious AEs was 4.0% (e.g. suicidal ideations, depression, pneumonia, cholecystitis). No clinically relevant changes in other metabolic parameters were seen.

Brexpiprazole

In a 24-week randomized study comparing brexpiprazole 1–3 mg to placebo in adjunction to antidepressant (Bauer et al., 2019), the most frequent TEAE in patients receiving antidepressant with brexpiprazole was weight increase (9.5% vs 5.0% in

antidepressant with placebo, which was lower than the incidence reported in a 52-week open label study [25.5%] (Nelson et al., 2016). The incidence of TEAEs leading to withdrawal was 6.3% in the antidepressant + brexpiprazole group and 3.4% in the antidepressant + placebo group. Activating side effects were infrequently reported (akathisia, 4.7% vs 0.9%; restlessness, 4.1% vs 0.5%; insomnia, 1.8% vs 0.9%; anxiety, 1.6% vs 0.9%, and agitation 0.7% vs 0% for antidepressant + brexpiprazole and antidepressant + placebo, respectively). Sedating side effects were also relatively uncommon (fatigue, 3.8% vs 1.4%; somnolence, 2.9% vs 1.4%, and sedation, 0% vs 0%). The proportion of patients with EPS-related TEAEs was 9.2% in the antidepressant + brexpiprazole group and 3.6% in the antidepressant + placebo group. The EPS-related TEAEs with an incidence ≥2% in either treatment group were (brexpiprazole vs placebo): akathisia (4.7% vs 0.9%) and tremor (2.9% vs 2.0%). Overall, brexpiprazole was well tolerated, wih no unexpected side effects.

Long-Term Effect on Body Weight—In a review and pooled analysis (Weiss et al., 2018), at week 52, the mean weight increase was 3.2 kg for brexpiprazole (n = 1015, 0.25–3 mg/d) and 4.0 kg for aripiprazole (n = 303, 2–30 mg/d). Overall, in adjunctive treatment of MDD, brexpiprazole and aripiprazole had a similar effect on relevant body weight changes (7%) over the course of 1 year.

Long-Term Effect on Sexual Functioning in the Treatment of MDD

Aripiprazole

In a 52-week, open-label safety study of adjunctive aripiprazole (antidepressant SSRI/SNRI [n = 245] or bupropion [n = 47]), sexual functioning in patients with MDD on antidepressants was modestly improved after adding aripiprazole, in both men and women, with a similar pattern/level of change across all antidepressant medications (Clayton et al., 2014).

Brexpiprazole

In a 52-week open label study of adjunctive brexpiprazole as an adjunctive treatment to antidepressant, brexpiprazole was associated at week 26 and week 52 with an improvement in sexual functioning (mean change from baseline in MSFQ scores) (Hobart et al., 2019b).

Effect on Biological Parameters in the Treatment of MDD

Aripiprazole

In short-term studies, the incidence of potentially clinically relevant laboratory abnormalities was similar to placebo, and prolactin levels decreased with aripiprazole treatment (Nelson et al., 2009). During >46 weeks' aripiprazole exposure, median changes in fasting parameters were small (<10 mg/dL) (Berman et al., 2011).

Brexpiprazole

In short-term studies, mean changes in fasting metabolic parameters were small (all less than 2 mg/dL), whereas in long-term treatment, triglycerides increased by 14.2 mg/dL at week 58. Other parameters showed only small changes from baseline to week 58 (<10 mg/dL) (Newcomer et al., 2018).

Cariprazine

In a short-term study, mean changes in fasting metabolic parameters were small (all <5 mg/dL) (Durgam et al., 2016a).

New Adjunctive Treatment Opportunities for Patients With MDD

Inadequate response to antidepressant treatment remains a substantial burden in clinical
practice. The efficacy, safety, and tolerability of the D2 receptor partial agonists aripiprazole and brexpiprazole as adjunctive treatment to antidepressants have been demonstrated in both short- and long-term studies. Cariprazine is in development as an adjunctive treatment for MDD. They represent a valuable treatment option for patients with MDD and an inadequate response to antidepressant. However, no study comparing each partial agonist exists to date, making a head-to-head comparison difficult. Besides, further research is needed to appreciate the superiority of partial agonists over other augmenting agents in depressive disorder (lithium, quetiapine, lamotrigine, thyroid hormons…). Data are scarce but more information about the pros and cons of different strategies with augmenting agents in MDD are exposed in other reviews (Edwards et al., 2013; Tundo et al., 2015).

In clinical practice, augmentation with partial agonists should be considered after failed trials antidepressant agents across at least 2 classes of antidepressants, particularly when symptoms severity or the urgency for rapid benefit is sufficient to justify the potential risks (Thase, 2016). Clinicians must consider the main side-effects reported in RCT, explaining relevant dropout rate (weight gain, akathisia, metabolic parameters) (for review, see Citrome, 2015). Besides, few data are available on late-onset side-effects (tardive dyskinesia, insulin-resistance/diabetes mellitus), and further studies are needed to determine the side-effect profiles over years. The aripiprazole starting dose is 2–5 mg/d and the recommended dose is 5–10 mg/d (maximum 15 mg/d), the brexpiprazole starting dose is 0.5 or 1 mg/d and recommended dose is 2 mg/d (maximum dose 3 mg/d) (Citrome, 2015).

Conclusion and Future Perspectives

MDD and schizophrenia both represent therapeutic challenges for clinicians, functional burden for patients, and a major public health concern. The efficacy, safety, and tolerability of the D2 receptor partial agonists aripiprazole and brexpiprazole as adjunctive treatment to antidepressants or as monotherapy in schizophrenia has been demonstrated in both short- and long-term studies. Cariprazine is in development as an adjunctive treatment for MDD and has demonstrated efficacy, safety, and tolerability in the treatment of schizophrenia. D2 receptor partial agonists represent a valuable option for many patients. Further studies should compare efficacy and safety profiles between partial agonists, both in MDD and in schizophrenia and over years. Further research is needed to appreciate the superiority of partial agonists over other augmenting agents in depressive disorder. While the efficacy and side effects of SGA may differ in schizophrenia and MDD, no study has yet examined this hypothesis.

Statement of Interest

J.M. and C.D. declare that they have no conflict of interest. Y.L.S. has received speaker honoraria from Janssen-Cilag, Lundbeck, Otsuka, and Takeda. P.G. received during the last 5 years research grants from Ethypharm and Servier and fees for presentations at congresses or participation in scientific boards from Alcediag-Alcen, Biocodex, Bristol-Myers-Squibb, Ethypharm, Janssen, Lilly, Lundbeck, Otsuka, Sanofi Pasteur MSD, and Servier.

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