# Pharmacotherapies for Treatment-Resistant Depression: How Antipsychotics Fit in the Rapidly Evolving Therapeutic Landscape

Manish K. Jha, M.B.B.S., Sanjay J. Mathew, M.D.

One in three adults with major depressive disorder (MDD) do not experience clinically significant improvement after multiple sequential courses of antidepressants and have treatment-resistant depression (TRD). The presence of TRD contributes to the morbidity and excess mortality associated with MDD and has been linked to significantly increased health care expenses. In the absence of a consensus definition of TRD, this report takes a broad approach by considering inadequate response to one or more courses of antidepressants and focuses on atypical antipsychotics that are approved by the U.S. Food and Drug Administration for treatment of depression (aripiprazole, brexpiprazole, cariprazine, extended-release quetiapine, and olanzapine-fluoxetine combination). While multiple acute-phase studies have demonstrated the efficacy of these medications in improving depressive symptoms, clinically meaningful improvement (i.e., remission) remains limited, with significant concerns about side effects (including weight gain, metabolic dysfunction, extrapyramidal symptoms, and tardive dyskinesia), especially with long-term use. With the rapidly evolving landscape of antidepressant treatments over the past few years, which has witnessed approval of rapid-acting antidepressants (e.g., esketamine nasal spray and dextromethorphan-bupropion combination) and several more in the late-stage pipeline (e.g., zuranolone and psilocybin), it remains to be seen whether the use of atypical antipsychotics will go the way of the older and rarely prescribed antidepressants (such as tricyclics and monoamine oxidase inhibitors). Pragmatic clinical trials are needed to compare the effectiveness of atypical antipsychotics with TRD-specific pharmacotherapies and neuromodulation treatments and to identify the optimal sequencing of these varied approaches for patients with MDD. When using atypical antipsychotics, clinicians and patients are encouraged to use a shared decision-making approach by personalizing treatment selection based on anticipated side effects, tolerability, cost, and feasibility.

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Major depressive disorder (MDD), an often chronic and/or recurrent condition, affects one in five adults and is the second leading cause of disability in the United States (1, 2). Even with multiple sequential courses of antidepressants, over one-third of patients with MDD do not experience clinically significant improvement and may have treatment-resistant depression (TRD) (3). The presence of TRD exacerbates the burden associated with MDD and contributes substantially to health-care-related expenses (4, 5). Furthermore, the presence of TRD is associated with higher rates of intentional self-harm and all-cause mortality (6). The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial showed that only one-third of individuals with MDD attained remission (i.e., no depression symptoms or symptoms of minimal severity) with an initial antidepressant (7), and remission rates declined markedly with subsequent treatment steps (3). Given the limited efficacy of conventional antidepressants (3), there is an urgent need to develop novel approaches to managing TRD. In this report, we provide a brief overview of TRD and potential treatment options for it, including atypical antipsychotics that modulate dopamine and serotonin neurotransmission. Atypical antipsychotics were initially developed for the treatment of schizophrenia, but these medications are now used more broadly, for multiple indications, including manic and depressive episodes of bipolar disorder, irritability associated with autism spectrum disorders, and Tourette's syndrome. Several medications of this class have received U.S. Food and Drug Administration (FDA) approval for treatment of MDD: aripiprazole, brexpiprazole, cariprazine, extended-release quetiapine, and olanzapine-fluoxetine combination. Atypical antipsychotics are the most extensively studied class of medications for antidepressant augmentation (8), and they are routinely prescribed in clinical practice for patients with TRD (9–11). Therefore, we restrict our focus here to atypical antipsychotics, with a brief discussion of

ketamine/esketamine and other novel pharmacotherapies to provide the context for how atypical antipsychotics fit into the rapidly evolving therapeutic landscape. Several psychological treatments (e.g., cognitive-behavioral therapy [CBT] and the cognitive-behavioral analysis system of psychotherapy) and pharmacological treatments (e.g., lithium, liothyronine, buspirone, and *S*-adenosyl-L-methionine) have been studied in patients with TRD and were reviewed in a recent meta-analysis and will not be discussed here (8). While neuromodulation strategies (such as ECT and transcranial magnetic stimulation [TMS]) are essential tools for the management of TRD, they were reviewed in a recent report (12) and will not be reviewed here.

## WHAT IS TREATMENT-RESISTANT DEPRESSION?

A recent systematic review found that no consensus definition for TRD exists (13). In the context of MDD, most studies define the presence of TRD as nonresponse to either one or two antidepressant medication treatments, delivered at an adequate dosage and duration. However, these studies vary in the definition of nonresponse, adequate dosage and duration of prior treatment, and whether these treatments were in the current depressive episode (13). Even when similar criteria are used for dosage and duration of antidepressant treatment in the current depressive episode, studies have differed in the definition of nonresponse (≤25% improvement for phase 3 esketamine studies [14, 15] vs. <50% improvement for an NIMH-funded study of ketamine for TRD [16]). Additionally, definitions for nonresponse to treatment do not incorporate the substantial burden of commonly co-occurring symptoms, such as anxiety (17), irritability (18), and impairments in day-to-day functioning (19) that patients with MDD often experience. The focus on acute-phase treatment outcomes to define TRD has overlooked the chronic and recurrent nature of MDD and has led to calls for shifting the terminology toward "difficult-to-treat" depression (20), which may help incorporate response persistence, burden of side effects, and impact of therapies on daily functioning and quality of life (21). In the absence of a consensus definition for TRD (13), we have taken the broader approach of considering inadequate response to one course of antidepressant medication as meeting an operationalization definition of TRD. This more liberal definition is relevant to evaluating the evidence for atypical antipsychotics, given that studies of aripiprazole and brexpiprazole have included among inclusion criteria a history of nonresponse to at least one antidepressant and inadequate response to a prospective trial with another antidepressant during the current depressive episode, whereas studies of extended-release quetiapine and cariprazine required a history of inadequate response to a minimum of one antidepressant in the current episode.

Confirming the presence of TRD can be facilitated by systematic assessments of symptom severity (such as the 9-item Patient Health Questionnaire [22]), side effects, and adherence using a measurement-based care approach (23). This approach allows for prospective assessments of treatment response that incorporate changes in antidepressant medication dosages as well as duration of treatment. In the absence of structured symptom assessments, tools such as the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire can be used to establish the presence of TRD (24). Because unrecognized bipolar depression or presence of subthreshold symptoms may account for reduced likelihood of response to commonly used antidepressants (25, 26), a careful diagnostic assessment is needed to establish the presence of MDD and potential comorbid conditions. Additionally, medical conditions such as obstructive sleep apnea that are frequently comorbid in individuals with TRD and can exacerbate symptoms should be systematically assessed (11, 27). Similarly, systematic assessment of pain in individuals with MDD (28) may be warranted given the comorbidity of chronic pain conditions with MDD and their association with treatment nonresponse (29, 30).

## ATYPICAL ANTIPSYCHOTICS IN THE MANAGEMENT OF TRD

Aripiprazole (31), brexpiprazole (32), extended-release quetiapine (33), and most recently cariprazine (34) have received approval from the FDA as augmentation agents after inadequate response to an antidepressant, and olanzapine is approved in combination with fluoxetine (35) for the TRD indication specifically per the prescribing label (i.e., patients who did not respond to two different antidepressants after at least 6 weeks at or above the minimally effective labeled dosage in their current episode) (35).

### Aripiprazole

Aripiprazole, a partial agonist of dopamine $D_2$ receptors and serotonin 1A receptors (5-$HT_{1A}$) and an antagonist of 5-$HT_{2A}$ receptors, was the first antipsychotic medication to receive FDA approval for adjunctive treatment of MDD, in 2007 (31). In initial randomized controlled trials (RCTs), 6-week augmentation with aripiprazole (2–20 mg/day) (36–38) after inadequate response to an 8-week course of antidepressant treatment was associated with higher remission rates than placebo (25.4% compared with 15.2% [38] and 26.0% compared with 15.7% [37]), with a number needed to treat (NNT) of 10. Subsequent similarly designed RCTs had similar results, with NNTs of 9 to 11 for aripiprazole (at dosages of 3 mg/day, 3–15 mg/day, or 3–12 mg/day) compared with placebo (39, 40). Augmentation with aripiprazole (at 2–15 mg/day) was also associated with higher rates of remission (44%) compared with placebo (29%) (NNT=7) in a study of elderly patients who did not attain remission with 12 weeks of treatment with extended-release venlafaxine (41). In a large multicenter Veterans Health Administration (VHA) trial of 1,522 patients with nonpsychotic MDD (42), remission rates with 12-week augmentation with aripiprazole (2–15 mg/day; remission rate, 28.9%) were higher than when switching to sustained-release bupropion (300–400 mg/day; remission

rate, 22.3%) but did not differ significantly from augmentation with sustained-release bupropion (300–400 mg/day; remission rate, 26.9%).

### Brexpiprazole

Brexpiprazole is pharmacologically similar to aripiprazole and was approved by the FDA as adjunctive treatment for MDD in 2015 (32, 43). Initial RCTs found significantly greater reductions in depressive symptoms with adjunctive brexpiprazole at 2 mg/day (44) and 3 mg/day (45) but not at 1 mg/day (45) after inadequate response to 8 weeks of antidepressant treatment. However, remission rates with adjunctive brexpiprazole (14.7%, 14.9%, and 14.1% with 1, 2, and 3 mg/day, respectively) did not differ from placebo (9.0% and 10.8%) (44, 45), with NNTs ranging from 17 to 31. Subsequent acute-phase RCTs had similar reductions in depressive symptoms but no differences in rates of remission (NNTs of 28 and 42) (46, 47). A longer-term (24-week) study found that adjunctive brexpiprazole had similar rates of improvement but higher rates of adverse event–related withdrawal (6.3%) compared with placebo (3.4%) (48). Similar to aripiprazole studies, a significant majority (>80%) of individuals had a nonresponse to just one antidepressant prior to their enrollment in the trials (44–48).

### Extended-Release Quetiapine

Quetiapine targets multiple neurotransmitter systems, with high affinity for histamine $H_1$, alpha-1 adrenergic, and 5-$HT_{2A}$ receptors and low affinity for dopamine $D_2$ receptors (49, 50), and was approved by the FDA as adjunctive treatment for MDD in 2009 (33). Its metabolite *N*-desalkylquetiapine is a potent inhibitor of norepinephrine reuptake and a partial agonist of 5-$HT_{1A}$ receptors (51). In two phase 3 trials of individuals with MDD who had continuing depressive symptoms after ≥6 weeks of treatment with an adequate dosage of an antidepressant (amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline, or venlafaxine), extended-release quetiapine at 300 mg/day was more effective than placebo in reducing depression severity in both studies (52), and the 150 mg/day dosage was more effective in one study (52) but not the other (53). In a pooled analysis, rates of remission were 41.8% (NNT=11) with 150 mg/day and 46.3% (NNT=7) with 300 mg/day of extended-release quetiapine, compared with 32.0% for placebo (54). In these studies, rates of withdrawal due to adverse effects were higher with extended-release quetiapine (8.9% at 150 mg/day and 15.4% at 300 mg/day) compared with placebo (1.9%) (54).

### Olanzapine-Fluoxetine Combination

While approved by the FDA for TRD in 2009 (35), the use of olanzapine-fluoxetine combination (OFC) has been limited by its potential for weight gain and metabolic dysfunction. In terms of efficacy, in two similarly designed studies of patients with TRD, one study found significantly greater improvement in depressive symptoms with OFC compared with both olanzapine monotherapy and fluoxetine monotherapy, whereas the other study did not find a significant difference (55). In a subsequent study with venlafaxine monotherapy as a fourth arm, OFC was superior only to olanzapine monotherapy (56).

All three antipsychotic medications and OFC are associated with weight gain, although quetiapine and OFC have a higher weight gain liability than aripiprazole and brexpiprazole (33, 35). In acute-phase studies, mean weight gain with OFC was 4.0 kg, compared with a mean decrease of 0.3 kg with placebo (35). With OFC, ≥7% weight gain was observed in 22% and 66% of patients in acute- and maintenance-phase studies, respectively (35). In acute-phase studies of MDD, ≥7% weight gain occurred in 3%, 7%, and 2%, respectively, of those treated with extended-release quetiapine at 150 mg/day and 300 mg/day and with placebo (33). Longer-term treatment with extended-release quetiapine in patients with MDD resulted in continued weight gain (57). In acute-phase trials of MDD, significantly greater weight gain occurred with aripiprazole (mean=1.7 kg) and brexpiprazole (mean=1.3–1.6 kg) compared with placebo (mean=0.3–0.4 kg) (31, 32). In a long-term study, 30% of those treated with brexpiprazole had ≥7% weight gain (32). Similar patterns of metabolic dysfunction, including hyperglycemia and hyperlipidemia, are noted with these medications, warranting periodic monitoring with physical examination and blood tests to detect these changes promptly.

Additionally, in the clinical development program (31), akathisia was reported in 25% of patients with MDD who were treated with aripiprazole augmentation, compared with 4% with placebo, and in the multicenter VHA trial of patients with nonpsychotic MDD (42), it was reported in 14.9% of those treated with aripiprazole augmentation, compared with 5.3% of those who received augmentation with sustained-release bupropion and 4.3% of those who were switched to sustained-release bupropion. Higher dosages of brexpiprazole were associated with higher rates of akathisia (2% with placebo and 4%, 7%, and 14% with 1, 2, and 3 mg/day of brexpiprazole, respectively) (32). Finally, while rates of tardive dyskinesia are lower with atypical antipsychotics than with the first-generation antipsychotics (e.g., haloperidol and chlorpromazine), the annualized incidence of tardive dyskinesia with these medications ranges from 1.7% to 2.9% (58), which warrants continued monitoring if they are used in the long term. A recent analysis of an insurance claims database found that 1 in 2 patients with new-onset tardive dyskinesia were diagnosed with a mood disorder, and most had prescriptions for atypical antipsychotics (59). Research is needed to specifically estimate the incidence of tardive dyskinesia associated with use of atypical antipsychotics for treatment of MDD.

## CARIPRAZINE FOR ADJUNCTIVE THERAPY IN MDD

Cariprazine is a partial agonist of both dopamine $D_2$ and $D_3$ receptors, with preferential binding to $D_3$ over $D_2$, especially

at lower dosages (60). An initial phase 2 study demonstrated no significant difference from placebo for cariprazine augmentation at low dosages (0.1–0.3 mg or 1–2 mg) (61). A subsequent RCT enrolled patients with MDD who had not responded to one or two antidepressant treatments and randomized them to double-blind augmentation with placebo, cariprazine at 1–2 mg/day, or cariprazine at 2–4.5 mg/day (62). The titration protocols differed between the two cariprazine dosages, with the target dosage of 1 mg/day achieved by week 1 in the 1–2 mg/day group and the target of 2 mg/day achieved by week 1 in the 2–4.5 mg/day group (62). Compared with placebo, there was significantly greater reduction in depression severity with both cariprazine dosages by week 2, but it was maintained until week 8 only in the 2–4.5 mg/day arm (62). Rates of remission were similar in the three arms: 29.9% with placebo, 31.9% with cariprazine at 1–2 mg/day, and 32.1% with cariprazine at 2–4.5 mg/day (62). A subsequent phase 3 study that enrolled patients with MDD in an 8-week prospective treatment with open-label antidepressant treatment and then randomized those with inadequate response to 8 weeks of augmentation with cariprazine (1.5–4.5 mg/day) or placebo did not find any significant improvement in depressive symptoms with cariprazine (63).

This issue of the *Journal* includes a report on a phase 3 trial of cariprazine augmentation in MDD (64). The trial enrolled 757 patients with MDD with inadequate response (<50% improvement in depressive symptoms) to one to three antidepressants in the current episode (of adequate dosage per prescribing label and of at least 6 weeks' duration) and randomized them in a 1:1:1 ratio to 6 weeks of augmentation with placebo, cariprazine at 1.5 mg/day, or cariprazine at 3 mg/day. This study used fixed-dose arms, whereas previous studies had allowed for flexible dosing within specified dosage ranges. The study found significantly greater improvement in depressive symptoms with cariprazine at 1.5 mg/day (−14.1 points in Montgomery-Åsberg Depression Rating Scale [MADRS] score) compared with placebo (−11.5 points in MADRS score) but not with 3 mg/day (−13.1 points in MADRS score). Remission rates at week 6 did not differ significantly among the treatment arms (placebo, 23.3%; cariprazine 1.5 mg/day, 25.2%; cariprazine 3 mg/day, 16.7%). Over 85% of patients enrolled in the study had only one prior antidepressant failure, which is a limitation for the generalizability of these findings to the broader group of patients with TRD.

The average weight gain associated with cariprazine in the study was 0.68 kg (SD=2.4) with the 1.5 mg/day dosage and 0.78 kg (SD=2.8) with the 3 mg/day dosage, compared with 0.11 kg (SD=2.8) with placebo. The proportion of those with ≥7% weight gain was 0.8% in the placebo group and 4.0% and 1.2%, respectively, in the groups receiving 1.5 mg/day and 3 mg/day cariprazine. The two cariprazine dosages were similar to placebo in rates of clinically significant treatment-emergent changes in cholesterol, glucose, and triglyceride levels (64). Akathisia was the most common extrapyramidal symptom among treatment-emergent adverse effects, with rates of 0.8%, 5.2%, and 7.9%, respectively, in the placebo, cariprazine 1.5 mg/day, and cariprazine 3 mg/day groups. Notably, discontinuation due to an adverse effect was more common with cariprazine at 3 mg/day (7.1%) than with placebo (2.4%) and cariprazine at 1.5 mg/day (1.2%).

Cariprazine is similar to aripiprazole and brexpiprazole in its partial agonist effect on the dopamine $D_2$ receptor, signifying that in the absence of full agonist effects, it has functional agonist activity (albeit at lower levels), while in the presence of a full agonist, it serves as an antagonist (65). Cariprazine has a 10-fold greater affinity for $D_3$ than $D_2$ receptors in in vitro studies (66). Greater selectivity of cariprazine for $D_3$ than $D_2$ receptors has also been demonstrated in a human positron emission tomography study; the mean $D_3$ and $D_2$ receptor occupancies with a low dosage of cariprazine (1 mg/day) were 76% and 45%, respectively (60). With higher dosages of cariprazine (12 mg/day), near 100% occupancies of both receptors were observed (60). Cariprazine and its two major active metabolites, desmethyl cariprazine and didesmethyl cariprazine, have long half-lives, and the steady state of these metabolites is attained in 2–4 weeks (67, 68).

With the recent (December 2022) approval of cariprazine as adjunctive treatment for MDD (34), head-to-head trials are needed to understand the effectiveness and tolerability of other antipsychotics with a similar indication (aripiprazole, brexpiprazole, extended-release quetiapine, and OFC). The acute-phase studies suggest lower weight gain potential with cariprazine compared with extended-release quetiapine and OFC, and similar to or lower than with aripiprazole and brexpiprazole. Rates of akathisia with cariprazine are also similar to or lower than those with aripiprazole and brexpiprazole.

## KETAMINE AND ESKETAMINE

Unlike atypical antipsychotics, which were developed initially for other indications, clinical trials of the repurposed anesthetic agent ketamine and its *S*-enantiomer esketamine started with a focus on their rapid antidepressant effects. In fact, TRD specifically was the first indication pursued for the esketamine nasal spray. A panel of international experts synthesized the available evidence for ketamine and esketamine in a recent report in the *Journal* (69), and we refer readers additionally to recent meta-analyses of ketamine and esketamine effects (70–73). These medications represent a paradigm shift in the management of TRD. Esketamine nasal spray is the first non-monoaminergic antidepressant that has been approved by the FDA, and it has rapid antidepressant effects (69). In parallel with the FDA approval of esketamine nasal spray in 2019, there has been a rapid increase in clinics offering ketamine (primarily intravenously) in an off-label fashion (74).

Several key issues related to use of ketamine and esketamine remain unanswered. One issue is the optimal duration of acute-phase treatment. Early studies of intravenous

ketamine deemed individuals who did not respond to the first infusion as nonresponders (75, 76). However, subsequent studies have shown that intermittent, repeated doses increase response rates (77, 78). In the phase 3 esketamine program, clinical benefit continued to accrue beyond the first 4 weeks of treatment (when administered twice weekly), and a recent report of ketamine in community practices found increasing rates of response and remission with continued infusions over a 6-week period (79, 80). Longer-term treatment options after initial improvement with ketamine or esketamine remain a challenge. While continuation-phase administration of esketamine reduces the likelihood of relapse (14), other pharmacological treatments have proven to be of little utility in prolonging the transient improvement with ketamine or esketamine.

A study of individuals who had at least a partial response to a single infusion of ketamine and received three additional ketamine infusions along with 4 weeks of double-blind treatment with either lithium or placebo did not find a significant difference between the two treatment arms in maintenance of initial response (81). Studies of drugs targeting glutamate neurotransmission have proven to be of limited benefit in prolonging the antidepressant effect of ketamine. A study of individuals with TRD who responded to ketamine and were randomized to 6 weeks of double-blind treatment with either D-cycloserine, a partial agonist of the glycine co-agonist of the *N*-methyl-D-aspartate (NMDA) glutamate receptor and NMDA receptor antagonist (at higher dosages), or placebo did not find any significant difference between the two groups in overall depression severity (82). Two placebo-controlled studies of riluzole, a glutamate-modulating agent with neuroprotective and synaptic-plasticity-enhancing effects, for relapse prevention after improvement with ketamine were negative (83, 84). Based on preclinical studies that suggested a key role of mechanistic target of rapamycin complex 1 (mTORC1) in the antidepressant-like effects of ketamine, a recent study used a single-dose pretreatment with rapamycin, an inhibitor of mTORC1, to block the antidepressant effect of ketamine infusion. However, contrary to their hypotheses, the authors found that rapamycin unexpectedly prolonged the antidepressant effect of ketamine (85).

Apart from pharmacological approaches, various therapeutic interventions have been investigated with regard to their potential for preventing early relapse following treatment with ketamine. In an initial open-label study, Wilkinson et al. (86) demonstrated the feasibility of adding a 10-week course of CBT to prolong the antidepressant effect of ketamine (four infusions over 2 weeks). A subsequent RCT of acute-phase responders to ketamine (six infusions over 3 weeks) demonstrated greater sustained improvement with 14 additional weeks of CBT compared with treatment as usual (87). In a recent study, a type of self-training paradigm that promotes positive self-associations, "automated self-association training" (ASAT), was paired with either a single ketamine infusion or a placebo infusion (normal saline) (88). The study found that ketamine in conjunction with ASAT kept depression measures significantly and stably low 30 days after a single infusion, while ketamine paired with sham treatment culminated in depression scores increasing linearly to approach those of the placebo plus ASAT group. Further longer-term and multicenter studies are needed to investigate the potential role of digital therapeutics and psychotherapies in enhancing or maintaining response to ketamine and esketamine.

## OTHER NOVEL ANTIDEPRESSANT PHARMACOTHERAPIES

Recent approvals by the FDA of dextromethorphan-bupropion combination (where inhibition of CYP2D6 by bupropion increases the bioavailability of dextromethorphan) for treatment of MDD (89) and brexanolone for postpartum depression (90) represent examples of drugs with non-monoaminergic mechanisms that possess antidepressant properties. Phase 2 clinical trials suggest efficacy of inhaled nitrous oxide (91) and MIJ821, a novel NMDA receptor subtype antagonist (92), for TRD. Esmethadone (an NMDA receptor antagonist) and seltorexant (an orexin-2 receptor antagonist) are two examples of novel-mechanism compounds that demonstrated superiority over placebo in phase 2 studies as augmentation agents in individuals with MDD who experienced inadequate response to one to three antidepressants of adequate dosage and duration in their current episode (93, 94). Drugs targeting kappa opioid receptors represent another potential novel mechanism as adjunctive treatment after inadequate response to antidepressant medications (95, 96). Pimavanserin, an antipsychotic medication that is approved by the FDA for Parkinson's disease psychosis, demonstrated initial efficacy compared with placebo as an augmentation agent in patients with MDD who had inadequate response to one or two antidepressants of adequate dosage and duration in the current episode (97). However, two subsequent phase 3 trials did not find any significant difference between augmentation with pimavanserin and placebo (98). While an initial study suggested targeting inflammation as a novel treatment for patients with TRD (99), subsequent trials of drugs targeting inflammation, including minocycline (100) and sirukumab (NCT02473289), did not demonstrate any significant difference compared with placebo. Despite antidepressant effects of ketamine, esketamine, and dextromethorphan-bupropion combination, there is more limited evidence for antidepressant effects of other modulators for glutamate receptors (70). According to sponsor reports, two phase 3 trials of esmethadone (as monotherapy and as an augmentation agent) did not attain their primary outcome of significant reduction in depression symptoms compared with placebo (101, 102). Lanicemine, a parenterally administered low-trapping NMDA channel blocker, did not significantly improve depression compared with placebo in a large study (N=302) of individuals with MDD with a history of

inadequate response to three or more antidepressants (including one antidepressant in the current depressive episode) (103). Rapastinel, another parenterally administered NMDA receptor modulator with glycine-site partial agonist properties (104), was evaluated in a large phase 3 program as adjunctive treatment and did not differ significantly from placebo (acute-phase studies: NCT02932943, N=457; NCT02943564, N=658; and NCT02943577, N=429; relapse prevention study: NCT02951988, N=604).

Psychedelic drugs that act as agonists of 5-$HT_{2A}$ receptors have emerged as novel treatment options for patients with TRD. In an initial open-label study of patients with TRD (N=20) who received two sessions of psilocybin (10 mg and 25 mg, 7 days apart, plus psychological support), there was significant improvement in depressive symptoms that persisted for 6 months (105). A randomized waiting-list-controlled trial of two sessions of psilocybin (20 mg/70 kg and 30 mg/70 kg, 7 days apart, plus supportive psychotherapy) also found significant improvement in individuals with MDD (106). A subsequent double-blind RCT (N=59) compared psilocybin at 25 mg (two sessions administered 3 weeks apart) plus daily placebo pills for 6 weeks versus psilocybin at 1 mg (two sessions administered 3 weeks apart) plus escitalopram (10 mg/day for 3 weeks followed by 20 mg/day for the next 3 weeks) in patients with TRD. The two treatment arms did not differ significantly in the primary outcome of reduction in self-reported depressive symptoms (107). However, rates of remission were higher with psilocybin at 25 mg (57%) than with psilocybin at 1 mg plus escitalopram (28%), with an NNT of 4 (107). A recent phase 2 double-blind RCT compared a single administration of psilocybin at a dose of 25 mg, 10 mg, or 1 mg (control), along with psychological support in patients with TRD (N=233). Three weeks after the treatment, there was significantly greater improvement in depressive symptoms and higher rates of remission with 25 mg (29%), but not with 10 mg (9%), compared with 1 mg (8%), with an NNT of 5 for psilocybin 25 mg compared with 1 mg (108). Finally, a small RCT of ayahuasca (N=29), a psychedelic mixture that contains *N,N*-dimethyltryptamine and the monoamine oxidase inhibitors harmine and harmaline, in patients with TRD found significantly greater improvement in depressive symptoms compared with placebo, with an NNT of 4 for remission (36% vs. 7%) (109).

## WHAT IS THE FUTURE OF ATYPICAL ANTIPSYCHOTICS IN THE MODERN ERA OF TRD?

Current practice guidelines recommend the use of atypical antipsychotics after inadequate response to initial pharmacotherapy with a first-line antidepressant treatment (110, 111). Besides the FDA-approved atypical antipsychotics discussed above, lumateperone is currently in phase 3 trials for MDD (NCT05061706 and NCT04985942), lurasidone has been shown to be efficacious in MDD with mixed features (112), and there are positive RCTs for ziprasidone and risperidone as adjunctive treatment after inadequate response to antidepressant treatment in patients with MDD (8, 113). As there is no clear evidence for superior efficacy of one atypical antipsychotic over another for treatment of MDD, shared decision-making approaches that incorporate information regarding tolerability, anticipated side effects, and costs may be helpful in selecting the specific atypical antipsychotic to use as an augmentation agent. Because of concerns about weight gain and metabolic dysfunction, use of extended-release quetiapine and OFC should generally be avoided. Aripiprazole appears to have rates of weight gain and metabolic dysfunction similar to those of cariprazine but has higher rates of akathisia, which may often be a dose-limiting side effect. Finding the optimal dosage of these medications can be a challenge. While rates of side effects increase with higher dosages of atypical antipsychotics, there is no clear evidence for improved efficacy in symptom reduction with higher dosages. When atypical antipsychotics are effective, patients and clinicians face substantial uncertainty regarding the advisability of both the long-term use of these medications in the absence of continuation-phase data (while incurring the risk of weight gain and tardive dyskinesia) and of discontinuing the medication, with the potential risk of relapse or recurrence. Additional practical challenges with atypical antipsychotics include monitoring of metabolic dysfunction and extrapyramidal symptoms while managing patients with virtual visits (telehealth).

Potential alternatives to atypical antipsychotics in clinical practice, where their use is often preceded by at least two prior trials of first-line antidepressants (9), include TRD-specific treatments such as intranasal esketamine (NCT05554627, a Veterans Affairs study comparing esketamine and aripiprazole) and TMS (NCT02977299, a study comparing switch to another antidepressant and augmentation with aripiprazole or TMS). Minimal or no separation from placebo in attainment of remission with the FDA-approved atypical antipsychotics raises the question of whether these statistically significant findings in large phase 3 trials are clinically robust and meaningful and whether the incremental improvements with the medications are worth the risks. Furthermore, the strength of evidence is limited in individuals who have not sufficiently improved with two or more adequate trials of antidepressants, given that a substantial majority of patients in phase 3 adjunctive trials of atypical antipsychotics had experienced only one prior failed trial. Therefore, large-scale multistage pragmatic clinical trials are needed to understand the real-world comparative effectiveness of medications for TRD and how to sequence them to optimize the care of individual patients (114).

In this era of newly FDA-approved antidepressant medications (e.g., esketamine nasal spray and dextromethorphan-bupropion combination) that are in widespread clinical use (off-label ketamine) or are currently in late-stage clinical development (e.g., zuranolone and psilocybin) and have rapid onset (days to weeks) of antidepressant effects, it remains to be seen whether patient and clinician expectations have fundamentally transformed, such that the use of drugs with

traditionally slower onset of action (weeks to months) will decrease. In this regard, the prescribing patterns for atypical antipsychotics may go the way of older classes of antidepressants (e.g., tricyclics and monoamine oxidase inhibitors), where therapies with fewer long-term side effects and more rapid onset of effect may be preferred. Alternatively, precision medicine approaches that allow for the rational selection of an atypical antipsychotic for TRD, based on biological markers and/or clinical features, may help identify the subgroup of patients for whom atypical antipsychotics would be a preferred option. Ongoing development of novel non-dopamine $D_2$ receptor antipsychotics and promising early-phase trials for drugs targeting trace amine-associated receptor 1 (115) and muscarinic cholinergic receptors (116, 117) may herald a new era for the drug treatment of schizophrenia. However, studies will be needed to evaluate how these safe and generally well-tolerated antipsychotic medications may be effectively repurposed for individuals with TRD.

In summary, four atypical antipsychotics (aripiprazole, brexpiprazole, extended-release quetiapine, and most recently cariprazine) are approved by the FDA as acute-phase augmentation agents after inadequate response to an initial antidepressant. However, their long-term safety in patients with MDD is not well established, and they are potentially concerning regarding weight gain, metabolic dysfunction, extrapyramidal symptoms, and tardive dyskinesia. With the rapidly evolving landscape of therapies for TRD, studies are needed to compare the efficacy and safety of atypical antipsychotic augmentation strategies with other evidence-based and emerging treatments and to determine how to sequence these approaches for the optimal treatment of patients with MDD.

## AUTHOR AND ARTICLE INFORMATION

Center for Depression Research and Clinical Care, Department of Psychiatry, UT Southwestern Medical Center, and O'Donnell Brain Institute, UT Southwestern Medical Center, Dallas (Jha); Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston (Mathew); Michael E. DeBakey VA Medical Center, Houston (Mathew); Menninger Clinic, Houston (Mathew).

Send correspondence to Dr. Mathew (sjmathew@bcm.edu).

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