

Second Generation Antipsychotics in the Treatment of Major Depressive Disorder: An Update

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Less than one third of patients who suffer from major depressive disorder (MDD) report remission following antidepressant treatments requiring more diverse treatment approaches. Augmentation of second generation antipsychotics (SGAs) has been increasingly recognized as an important treatment option. The authors have previously provided a comprehensive review of SGAs for the treatment of MDD in 2013. Since then, numerous additional clinical trials have been conducted to investigate diverse issues regarding the utility of SGAs in MDD. Moreover, a new SGA, brexpiprazole, was recently approved by the Food and Drug Administration in July 2015 for the treatment of MDD as an augmentation agent to antidepressants. Thus, the aim of this study was to provide a concise update of all the available SGAs for the treatment of MDD, in particular on the additional clinical trials which have been published since 2013.

Key Words: Antidepressive Agents; Depressive Disorder; Clinical Trial; Antipsychotic Agents; Depressive Disorder, Treatment-Resistant

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INTRODUCTION

With the evolution of antidepressants development from monoamine oxidase inhibitors (MAOI) and tricyclic antidepressants (TCA) to selective serotonin reuptake inhibitors (SSRIs), the safety and tolerability of antidepressants have improved greatly.¹ Although diverse antidepressants are increasingly available in the market, more than 30% of patients with depression still do not receive a satisfactory response.² Therapeutic lag, about 2-4 weeks, often observed between antidepressant administration and the onset of clinical improvement is another problem with conventional antidepressants.³ Diverse antidepressants selectively targeting multiple receptors/transporters such as serotonin norepinephrine reuptake inhibitors (SNRI), norepinephrine-dopamine reuptake inhibitor (NDRI), serotonin partial agonist-reuptake inhibitors (SPARI), and others were developed but failed to solve the above important obstacles caused by multifactorial etiologies of major depressive disorder (MDD).⁴⁻¹² See Fig. 1 for evolution

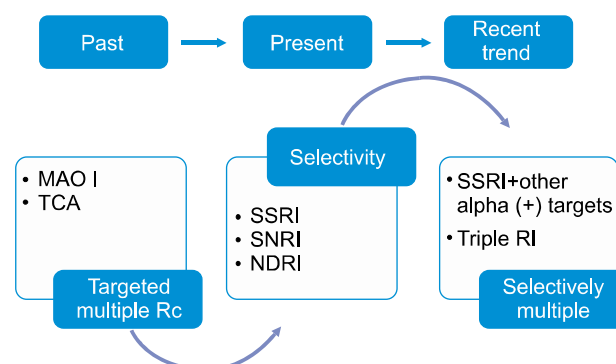


FIG. 1. Evolution of antidepressant. MAOI: monoamine oxidase inhibitors, NDRI: norepinephrine-dopamine reuptake inhibitor (NDRI), Rc: receptors, RI: reuptake inhibitor, SNRI: norepinephrine reuptake inhibitor, SSRI: selective serotonin reuptake inhibitors, TCA: tricyclic antidepressants.

of antidepressants.

There has been substantial progress in the search for further treatment strategies for treatment-resistant MDD (TRD); psychotropics augmentation other than antidepressants, and antidepressant switches and combinations regardless of antidepressant classes. Among them, augmentation treatment with atypical antipsychotic agents has been recognized as an important option. Moreover, second generation anti-psychotics (SGAs) have been an area of focus after successful augmentation using risperidone to SSRIs was found in 1991.¹³ Thereafter, three SGAs including olanzapine (2007), quetiapine extended release extended release (2007) and aripiprazole (2009) were approved by the US FDA as an augmentation therapy to antidepressants for treating MDD. In this respect, we have previously provided a comprehensive review of second-generation antipsychotics in the treatment of MDD, which was published in 2013.¹⁴

Our previous review included the state of the current market, rationales for the action mechanisms of SGAs for MDD, an overview of the clinical trial data of SGAs for treating MDD, and clinical issues rose in the use of SGA therapy in patients with MDD in clinical practice. Thereafter, brexpiprazole, a dopamine D₂ receptor partial agonist, was recently approved by the US Food and Drug Administration (FDA) on the 10th of July 2015 for the treatment of schizophrenia and for an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD).¹⁵ Thus, we aimed to provide a concise update of SGAs in the treatment of MDD by focusing mainly on the additional clinical trials which have been published since our last review.

DATA SEARCH

The search terms used for the PubMed database included 'aripiprazole', 'olanzapine', 'quetiapine', 'amisulpride', 'asenapine', 'iloperidone', 'lurasidone', 'paliperidone', 'risperidone', 'sertindole', and 'ziprasidone'. In addition, we added 'brexpiprazole', and 'cariprazine', which were not included in our previous review. These terms were matched with 'depression', 'MDD', 'dysthymia', 'psychotic depression' and 'antidepressant'.

Although our previous studies were published in January 2014, the paper was written in 2013. Thus, we tried to focus this update on studies published since January 2013. In order to do so, randomized, placebo and/or comparator controlled clinical trials were principally considered for our review, so open-label studies, case reports, studies less than 20 participants, studies not including MDD, and post-hoc analyses were not included unless they were concluded by the authors to be relevant to the discussion in this review. Studies conducted in patients having schizoaffective disorders, schizophrenia, and bipolar disorders were also excluded.

The studies searched for and reviewed were all published in peer-reviewed journals in English. The reference

lists from searched for and identified articles were also cross checked to find further studies. The data search and verification was handled by senior authors (CU Pae and C Han) and independently reassessed by coauthors (SJ Lee and TY Jun).

THE CURRENT MARKET STATUS

Until recently, only 3 SGAs aripiprazole, quetiapine XR and olanzapine had a formal US FDA approval in the treatment of MDD. Among them, olanzapine was approved for the treatment of TRD, which is defined as MDD patients who did not respond to two separate trials of two or more than two antidepressants after an appropriate duration and dose, as a combined agent with fluoxetine. As stated earlier, brexpiprazole just recently received FDA approval not only for schizophrenia, but also for the treatment of MDD as an adjunctive therapy to antidepressants in July 2015, which is the biggest change since 2013.¹⁵ In addition, a RPCT was recently published for ziprasidone and lurasidone. A RPCT regarding asenapine, cariprazine, iloperidone, and sertindole have still not been published.

The General information on SGA, including the current market situation for MDD is summarized in Table 1.

1. Individual SGAs

1) SGAs having US FDA approval in the treatment of MDD

(1) Brexpiprazole: Brexpiprazole is a dopamine D₂ receptor partial agonist. It was recently approved by the US Food and Drug Administration (FDA) on the 10th of July, 2015 for the treatment of schizophrenia and as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD).¹⁵ Studies have shown that brexpiprazole has lower intrinsic activity at the dopamine D₂ receptor and has an approximately 10-fold higher affinity for serotonin 5-HT_{1A} and 5-HT_{2A} receptors than aripiprazole.¹⁶

Numerous clinical trials investigating brexpiprazole in the treatment of depression have been completed and are still on going. Among them, two phase III clinical trials have been recently published (Table 1). The two studies were identical in design and were conducted by the same research group.^{17,18} In both studies, subjects included had a history of inadequate response to 1-3 treatment trials of standard antidepressant medications for their current depressive episode. Moreover, all patients entered a prospective 8-week phase on physician-determined, open-label antidepressant therapy (ADT). Those with inadequate response were randomized to receive antidepressants with brexpiprazole or with a placebo for 6 weeks. The primary outcome measure was changed from the baseline to week 6 according to the Montgomery-Asberg Depression Rating Scale (MADRS) total score. The first study showed that brexpiprazole 3 mg/day led to a greater improvement in the MADRS total score than the placebo (-8.29 vs. -6.33 ; $p=.0079$). However, brexpiprazole 1 mg/day did not show

TABLE 1. General information of second generation antipsychotic in the treatment of major depressive disorder^a

Drug	FDA Indication	Possible action mechanism	Dose range	Level of evidence ^b
Aripiprazole	Augmentation to antidepressants	5-HT1A/2C receptor partial agonism, 5-HT2A/2B receptor antagonism, 5-HT6 receptor antagonism, weak 5-HT7 receptor antagonism, D2/3 receptor partial agonism, neuroprotective effects	5-15 mg/day	1
Brexiprazole	Augmentation to antidepressants	Partial agonist activity at serotonin 5-HT1A and dopamine D2 receptors, and antagonist activity at serotonin 5-HT2A receptors	1-3 mg/day	1
Olanzapine	Combination with fluoxetine for TRD	5-HT2A/2C receptor antagonism, 5-HT7 receptor antagonism	5-20 mg/day	1
Quetiapine XR	Augmentation to antidepressants	α -2 receptor antagonism, norepinephrine transporter inhibition (metabolite), 5-HT7 receptor antagonism	50-300 mg/day	1
Amisulpride	None for MDD	5-HT7 antagonism, presynaptic D2/3 autoreceptors antagonism	50 mg/day	1
Asenapine	None for MDD	5-HT2C/2A receptor antagonism, 5-HT6/7 receptor antagonism, 5-HT2B receptor antagonism, α -2 receptor antagonism, partial agonism at 5-HT1A receptor	Not available	4
Cariprazine	None for MDD	D2/3 receptor partial agonism, 5-HT1A receptor partial agonism, 5-HT2A /5-HT7 receptor antagonism	0.1-4.5mg/day	4
Iloperidone	None for MDD	5-HT2A receptor antagonism, 5-HT6/7 receptor antagonism	Not available	4
Lurasidone	None for MDD	5-HT7 receptor antagonism, 5-HT1A receptor partial agonism, weak 5-HT2C receptor antagonism, weak α -2 receptor antagonism	Not available	1
Paliperidone	None for MDD	5-HT2A receptor antagonism, α -2 receptor antagonism, 5-HT7 receptor antagonism	3 mg/day	4
Risperidone	None for MDD	5-HT2A receptor antagonism, α -2 receptor antagonism, 5-HT7 receptor antagonism	0.5-3.0 mg/day	1
Sertindole	None for MDD	5-HT2A receptor antagonism, 5-HT6/7 receptor antagonism	Not available	4
Ziprasidone	None for MDD	5-HT2A/2C receptor antagonism, 5-HT1A receptor agonism, serotonin/norepinephrine/dopamine transporter inhibition	80-160 mg/day	1

^aTable adapted from article by Han et al.¹⁴ ^bLevel of evidence defined based on the CANMAT guideline, Level 1: Meta-analysis or replicated double-blind (DB), randomized controlled trial (RCT) that includes a placebo condition, Level 2: At least one DB-randomized controlled trial (RCT) with placebo or active comparison condition, Level 3: Prospective uncontrolled trial with at least ten or more subjects; Level 4: Anecdotal reports or expert opinion.

TABLE 2. Published Phase III randomized controlled double-blind studies of brexpiprazole in treatment of major depressive disorder

Author (year)	Design	Duration	Dosage	N	Primary outcome	Results
Thase (2015) ¹⁷	Aug in TRD	6 weeks (+8 wk OL)	BPX 1 mg/d BPX 3 mg/d PBO	213 211 203	MADRS	BPX 3 mg > PBO in MADRS improvement (p=.0079) BPX 1 mg = PBO in MADRS improvement
Thase (2015) ¹⁸	Aug in TRD	6 weeks (+8 wk OL)	BPX 2 mg/d PBO	175 178	MADRS	BPX 2 mg > PBO in MADRS improvement (p=.0002)

Aug: augmentation, BPX: brexpiprazole, MADRS: montgomery-åberg depression rating scale, OL: open label, PBO: placebo, TRD: treatment resistant depression.

superior results compared to the placebo (−7.64 vs. −6.33; p=.0737). In terms of adverse reactions, mean changes from the baseline on the Abnormal Involuntary Movement Scale (LS mean difference=0.08; p=.0141) and the Barnes Akathisia Rating Scale (LS mean difference=0.17; p=.0001) total scores were significantly greater in the brexpiprazole 3 mg/day group than in the placebo group. In the second study, brexpiprazole 2 mg/day showed superior efficacy over the placebo in changes from the baseline to week 6 in

the MADRS total score (−8.36 vs. −5.15; p=.0002). Brexpiprazole improved according to the Sheehan Disability Scale (SDS) mean score versus the placebo as well (−1.35 vs. −0.89; p=.0349). The most common treatment-related adverse events (TAEs) were weight gain (brexpiprazole, 8.0%; placebo, 3.1%) and akathisia (7.4% vs. 1.0%). Overall, brexpiprazole augmentation was safe and well tolerated in two phase III RCTs (Table 2).

(2) Aripiprazole: Aripiprazole was the first SGA to receive

US FDA approval as an augmentation therapy to antidepressants for the treatment of MDD in November 2007. Consequently, the clinical benefits of adjunctive aripiprazole for treating patients with MDD has been shown in the numerous open label and RPCTs.¹⁹ Three identically designed initial phase RPCTs showed that aripiprazole augmentation was superior over placebo augmentation in the treatment of MDD patients with 1-3 historical failures in adequate antidepressant trials.²⁰⁻²²

A post hoc analysis of these 3 RPCTs, which was recently published in 2014, investigated the efficacy and safety of aripiprazole augmentation for standard antidepressant treatment (ADT) in MDD patients with a prior, inadequate response to one to three ADTs.²³ Patients received the prospective ADT for 8 weeks. Thereafter, patients were classified as 'ADT minimal improvers' defined as patients who maintained a CGI-I score of 3 at weeks 6 and 8 of phase B, and 'ADT non-improvers' defined as patients with a CGI-I score of 4 at weeks 6 and 8. These patients received either a placebo or aripiprazole augmentation for 6 weeks. The results showed that response rate for ADT minimal improvers receiving adjunctive aripiprazole was higher than in the placebo group (38.8% vs. 26.6% $p < 0.05$). The remission rate was also higher for aripiprazole than for the placebo adjunctive in ADT non-improvers (24.0% vs. 10.3%, $p < 0.05$). The most common adverse events for ADT minimal improvers and non-improvers receiving adjunctive aripiprazole were akathisia, restlessness and insomnia. In another study, which pooled same 3 RPCTs, stratified patients based MADRS total score (mild, ≤ 24 ; moderate, 25-30; severe, ≥ 31).²⁴ The study showed that aripiprazole produced greater improvement than the placebo in the MADRS total score regardless of MDD severity at the baseline. Moreover, adjunctive aripiprazole increased the likelihood of response in all subgroups. Another pooled study investigated the efficacy of adjunctive aripiprazole in patients with MDD whose symptoms worsened with antidepressant monotherapy.²⁵ The study included 1065 patients who did not show a positive response with ADT monotherapy (N=160 for whose symptoms worsened and N=905 whose depressive symptoms showed no change). Adjunctive aripiprazole showed greater efficacy over the placebo in response rate (36.6% vs. 22.5%) and remission rate (25.4% vs. 12.4%) for ADT-Worseners. Similarly superior efficacy of aripiprazole in response rate (37.5% vs. 22.5%) and remission rate (29.9% vs. 17.4%) were noted for ADT-Non-Worseners.

Since January 2013, two more RPCTs studying the efficacy of aripiprazole adjunctive use in the treatment of MDD were published.²⁶ The first study, The Aripiprazole Depression Multicenter Efficacy (ADMIRE) study, was designed to evaluate the efficacy and safety of aripiprazole augmentation in Japanese patients with MDD.²⁷ Subjects with an inadequate response to 8 weeks of ADT were randomized to receive placebo augmentation, fixed dose aripiprazole, or flexible dose aripiprazole for 6 weeks. The primary efficacy endpoint was mean change in the MADRS total score from the end of prospective treatment (baseline)

to the end of randomized treatment. The result showed the mean MADRS total scores improved more significantly in the aripiprazole fixed and flexible groups than in the placebo group. Aripiprazole was well tolerated, and the majority of AEs were mild (aripiprazole flexible dose 59.3%, fixed dose 54.8%, placebo 48.7%) or moderate (17.0%, 15.7%, 10.8%) in severity. However, higher rate of akathisia was a concern (aripiprazole flexible dose 36.6%, fixed dose 14.2%, and placebo 4.1%). A subgroup post-hoc analysis further showed that the efficacy was consistently greater with aripiprazole than placebo and was not related to any clinical factors such as gender, age, number of adequate ADT uses for the current episode, diagnosis of MDD, number of depressive episodes, current episode duration, onset age of MDD, elapsed time after the first episode of MDD, type of SSRI/SNRI, or severity at the end of SSRI/SNRI treatment phase.²⁸ The second study, a 12 week RPCT, further showed positive effects of aripiprazole for elderly with TRD. TRD patients older than 60 years old were randomized into two groups: venlafaxine extended-release (ER) with aripiprazole or venlafaxine ER with a placebo.²⁹ The results showed a greater proportion of the participants in the aripiprazole group achieved remission than did those in the placebo group (44% vs. 29%, $p < 0.05$). However, aripiprazole augmentation was associated with more akathisia (24% vs. 1%) and Parkinsonism (17% vs. 2%) than placebo augmentation. However, aripiprazole was not associated with an increase in cardio-metabolic risk as measured by changes in whole body adiposity, plasma lipids, glucose, or insulin.

A 6-week, randomized, rater-blinded, direct comparison study compared aripiprazole augmentation (n=52) and antidepressant switching (n=49) in patients with MDD.³⁰ The mean change in the MADRS score from the baseline was significantly higher in the aripiprazole augmentation group, with a difference in magnitude of -8.7 ($p < 0.0001$), with the intergroup difference first observed in week 2. The numbers of responders (60% vs. 32.6%, $p < 0.01$) and remitters (54% vs. 19.6%, $p < 0.0001$) were also significantly higher in the aripiprazole augmentation group compared with the switching group. The tolerability profiles were comparable between the two groups. The same research group also compared aripiprazole augmentation, antidepressant combination, and switching therapy in patients with MDD who are partial- or non-responsive to current antidepressants.³¹ The primary efficacy measure was the proportion of patients showing an improvement in the Clinical Global Impression-Clinical Benefit (CGI-CB) score at week 8. Among 295 patients (aripiprazole augmentation N=156, antidepressant combination N=93, and antidepressant switching N=46), improvement was significantly greater with aripiprazole augmentation (74.1%) than with antidepressant combinations (48.1%; $p < 0.001$) and similar to with antidepressant switching (73.5%, $p=0.948$). Tolerability profiles were similar across the three groups, but mean weight gain for the antidepressant switching group (0.1 kg) was significantly less than that for

the aripiprazole augmentation group (1.3 kg, $p < 0.05$).

(3) Quetiapine: Quetiapine received US FDA approval as an augmentation therapy to antidepressants for treating MDD in 2009. Unlike aripiprazole, however, its clinical efficacy in MDD has been shown in numerous clinical trials involving it both as an augmentation and monotherapy.¹⁹ Until 2012, ten RPCTs (N=4 for monotherapy and N=6 for augmentation therapy) investigating efficacy of quetiapine in MDD were published.³²⁻⁴¹ In terms of monotherapy, two studies used fixed-doses and showed that quetiapine XR was more effective than a placebo in reducing depressive symptoms starting at week 1.^{35,42} Among them, one study further showed that significant reduction was seen at week 1 with quetiapine XR 150 mg/day and 300 mg/day versus placebo ($p < .01$), but not with duloxetine.³⁵ One study used flexible-dose and demonstrated superior efficacy over a placebo,³² while another study was a 52-week, randomized-withdrawal, RPCT following a open-label stabilization phase treatment showing that the risk of depression recurrence was significantly ($p < .001$) reduced by 66% in patients randomized to continue with quetiapine XR versus patients randomized to switch to placebo.³³ In terms of augmentation therapy, 6 quetiapine augmentation RPCTs were conducted for the treatment of MDD.³⁶⁻⁴¹ Among them, one failed to show superior efficacy over placebo, but the quetiapine dosages used in study were lower than the others (flexible dose from 25-100 mg/day, mean dose: 47 mg/day). Interestingly, one study showed that the quetiapine plus CBT group demonstrated a significant reduction in both primary efficacy measures, compared with CBT plus placebo.³⁹

Thereafter, 3 more RPCTs demonstrating the efficacy of quetiapine as a monotherapy in the treatment of MDD were published. Locklear et al investigated the efficacy of quetiapine XR monotherapy on the quality of life and sleep in elderly patients with MDD.⁴³ In this 11-week study (9-week randomized; 2-week post-treatment), MDD patients older than 66 were randomized to quetiapine XR (flexible dosing 50-300 mg/day) or placebo. The primary efficacy measures included the MADRS total score change from randomization at Week 9, the Quality of Life, Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF), and the Pittsburgh Sleep Quality Index (PSQI) global score to assess the quality of life and quality of sleep respectively. At Week 9, the reduction of the MADRS totals were significantly greater in quetiapine XR (N=166) than in placebo. In addition, quetiapine XR significantly improved the Q-LES-Q-SF percentage of the total score (16.86; difference: 7.69; 95% CI: 4.99, 10.39; $p < 0.001$) versus placebo (9.17). Improvement in the PSQI global score was also greater for quetiapine XR (-6.42 ; difference: 3.52; 95% CI: 4.26, 2.79; $p < 0.001$) than for the placebo (2.89). McIntyre has recently published a RPCT which extended quetiapine's possible efficacy in patients having MDD with comorbid fibromyalgia syndrome.⁴⁴ In this 8 week study, the mean change in the HAM-D score (primary efficacy measure) from the baseline to week 8 was significantly

greater in the quetiapine XR (mean dosage=224mg/day) group than in the placebo group (10.0 versus 5.8; $p = 0.001$). Except for on the Sheehan Disability Scale (SDS), improvements in all secondary outcome scores including BPI, HAM-A, CGI, FIQ, and Q-LES-Q-SF were also greater for quetiapine than for the placebo. Overall, quetiapine XR was well tolerated in patients with a dual diagnosis of MDD and fibromyalgia. However, quetiapine was related to worsening of Triglycerides (elevation), high-density lipoprotein cholesterol levels (reduction), and weight gain than placebo, which all are consistent with the known metabolic profile for quetiapine. Among the three, only the one study by Wang failed to show superior efficacy of quetiapine XR over the placebo in the treatment of MDD.⁴⁵ The study was a 10-week (8-week active treatment/2-week post-treatment) study which included 471 patients randomized to receive quetiapine XR (N=157), escitalopram (N=157), or a placebo (N=157). The results showed that neither quetiapine XR (150/300 mg/day) nor escitalopram (10/20 mg/day) showed significant separation from the placebo, indicating that it was a failed study rather than negative study.

An interesting study which pooled data from the two 6-week RPCTs^{36,37} as an augmentation therapy in the treatment of MDD was published recently.⁴⁶ The study investigated the effects of psychiatric history and baseline demographics and disease characteristics on efficacy outcomes by evaluating population subgroups. The study did not find major differences between responders and non-responders with regard to psychiatric history, baseline demographics or disease characteristics. In addition, a predictive association between the number of depressive episodes, disease severity at the baseline, or baseline MADRS item scores and efficacy outcomes were not observed. The study might indicate that quetiapine XR monotherapy is effective for the treatment of MDD across a broad range of disease severities.

(4) Olanzapine: A olanzapine and fluoxetine combination agent (OFC) has only recently been approved for treating TRD. Five RPCTs (two identically designed studies were published together in one article) investigating OFC in the treatment of acute TRD have been available since 2012.^{5,47-49} The primary efficacy measure was the mean change in the MADRS total score from the baseline in all five OFC trials. Among them, study 1 by Thase showed no statistically significant difference in the MADRS mean change (olanzapine/fluoxetine combination: -11.0 , fluoxetine: -9.4 , olanzapine: -10.5).⁴⁹ The remaining four studies, including study 2 by Thase, showed that an olanzapine/fluoxetine combination produced significantly greater improvement than its comparator including olanzapine and fluoxetine monotherapy,^{5,47-49} nortriptyline,⁴⁷ or venlafaxine.⁴⁸ In addition, three RPCTs (two identically designed studies were published together in one article) investigated the efficacy of OFC in treatment of MDD with psychotic features. Study 1 by Rothschild demonstrated the superiority of OFC (-20.9) over placebos (-10.4) in the mean change of the HAMD-24 total score from the baseline

to the endpoint while olanzapine (-14.9) did not separate from the placebo.⁵⁰ However, study 2 by Rothschild did not show a significant difference among the treatment groups.⁵⁰ The third study demonstrated a statistically higher remission rate for olanzapine plus sertraline (41.9%) than for olanzapine plus placebo (23.9%), indicating that olanzapine could be effective not only as an augmentation with fluoxetine but also with other SSRIs.⁵¹

Only one RPCT was published since January 2013. Brunner and colleagues evaluated the relapse prevention in TRD patients on OFC.⁵² The study included 4 phases. TRD was defined as patients who failed to show a satisfactory response to >2 different antidepressants for >6 weeks within the current MDD episode. Patients first underwent a 3-4 days screening period (Phase I) followed by a 6-8 weeks open-Label acute treatment period (Phase II) using OF. Thereafter, patients who showed response ($>50\%$ improvement in MADRS and <3 in CGI-S) received stabilization treatments for 12 weeks (Phase III). Finally, patients who were still stabilized were randomized to either an OFC or fluoxetine alone group for up to 27 weeks (Phase IV). The primary efficacy measure (relapse time) was significantly longer in OFC group than in fluoxetine alone group ($p < 0.001$). Relapse rates were also lower for OFC vs. fluoxetine (15.8% vs. 31.8%, $p < 0.001$). In addition, the mean total MADRS score increased from 5.36 at the baseline to 8.07 at the endpoint for OFC where as it increased from 5.40 at the baseline to 11.82 at the endpoint for fluoxetine treated patients ($p < 0.001$). In terms of safety, no significant differences between treatment groups were observed in the occurrence of SAEs ($p = 0.621$). However, the rate of patients who experienced clinically significant ($>7\%$) weight gain was greater for OFC than fluoxetine (OFC: 11.8%, fluoxetine: 2.3%; $p < 0.001$). At the endpoint, the mean differences were significant for weight gain (OFC: +1.14 kg, fluoxetine: -2.78 kg; $p < 0.001$). In addition, the OFC group (14.9%) had higher prolactin values than the fluoxetine alone group (6.3%) ($p < 0.009$).

2) SGAs which have not received US FDA approval in the treatment of MDD

(1) Amisulpride: Despite amisulpride not being approved for the treatment of MDD, its clinical usefulness for MDD or dysthymia patients as a monotherapy or augmentation therapy has been actively tested in open-label^{53,54} RCT studies and RPCTs.⁵⁵⁻⁶² In terms of RCTs, 7 studies were conducted in the treatment of MDD or dysthymia as a monotherapy. 2 RCTs showed its superior efficacy over placebo,^{58,60} while all studies showed its comparable efficacy with various antidepressants including amitriptyline, amineptine, imipramine, fluoxetine, sertraline, and paroxetine.⁵⁵⁻⁶² Among them, one study was designed to compare the incidences of treatment emergent adverse events between amisulpride and amitriptyline,⁵⁷ which showed comparable rates of TEA (AMI vs. AMSP: 73% vs. 64%). However, all the above studies were published before 2006 rendering a need for updated studies. In addition, all

RCTs investigated its effects as a monotherapy.

(2) Risperidone: Similar to amisulpride, risperidone's clinical effects in the treatment of MDD has been actively investigated up until 2009. In terms of RCTs, 5 were conducted and showed its clinical effects as an augmentation therapy for the treatment of TRD. Two studies showed superior efficacy of risperidone augmentation to current antidepressants compared to placebo in response and remission among treatment resistant depression or difficult to treat depression.^{63,64} One study showed the efficacy of risperidone augmentation for TRD versus a placebo treatment in decrease suicidality.⁶⁵ Two studies tested the efficacy of risperidone augmentation as maintenance therapy versus placebo.^{66,67} Both studies showed that while the relapse rates of risperidone (53.3%-56%) and placebo (54.6%-65%) were similar, the median time to relapse was numerically longer with risperidone augmentation (102-105 days) than with the placebo (57-85 days). The latest RCT, which was published in 2011, compared the efficacy of augmentation of risperidone 2 mg/day (N=45), sodium valproate 600 mg/day (N=39), buspirone 30 mg/day (N=46), trazodone 100 mg/day (N=47) or thyroid hormone 80 mg/day (N=48) in TRD patients taking paroxetine 20 mg/day. The results showed no statistical significance among treatment groups in remission rates and AEs. However, there has only one study published since 2010 and all of the RCTs only investigated its effect as an augmentation therapy as opposed to a monotherapy.

(3) Ziprasidone: Unlike for amisulpride and risperidone, studies investigating the clinical effects in the treatment of MDD using ziprasidone have not been conducted until very recently. There was only one published RPCT for ziprasidone in the treatment of MDD as of 2012.⁶⁸ One hundred and twenty (120) patients were randomized to ziprasidone monotherapy (drug-drug) for 12 weeks, placebo for 6 weeks followed by ziprasidone (placebo-drug) for 6 weeks, or placebo (placebo-placebo) for 12 weeks. The results did not show a statistically significant difference in response or remission rates among the three groups. However, the dosage of ziprasidone used might not have been sufficient to produce an antidepressant response (a daily dose of ziprasidone; phase I=81.4 mg, Phase II=113.8 mg). Relatively high pooled placebo responses and remission rates in phase II (29.9% and 32.7%) are another possible factor preventing the detection of the statistical significance of ziprasidone over placebo.

Thereafter, 2 post-hoc analyses were recently published. Jeon et al conducted a post-hoc analysis to investigate effects of ziprasidone monotherapy in treatment of psychomotor symptoms of MDD.⁶⁹ The study involved drug-drug for 12 weeks, placebo-drug for 6 weeks respectively, and placebo-placebo for 12 weeks. In phase I, more significant improvement in HDRS-17 ($F=5.95$, $p=0.017$) and Quick Inventory of Depressive Symptomatology Scale, Self-Rated (QIDS-SR) ($F=5.26$, $p=0.025$) scores were found in the ziprasidone monotherapy group than in the placebo treatment among patients presenting psychomotor symptoms,

although there was no significant differences in the HDRS-17 ($F=2.32$, $p=0.15$) and QIDS-SR ($F=3.70$, $p=0.074$) scores between the two treatment groups among those without psychomotor symptoms. In phase II, the ziprasidone monotherapy showed no superior efficacy over placebo in HDRS-17 and QIDS-SR scores in patients with or without psychomotor symptoms. Heo et al.⁷⁰ conducted another post-hoc analysis utilizing data from the study by Papakostas to investigate the effects of ziprasidone monotherapy in anxious depression. The results failed to show superior efficacy of ziprasidone over placebo in anxious depression. The second RPCT investigating augmentation of ziprasidone to antidepressants in the treatment of MDD was very recently published.⁷¹ During an open label trial (phase I), patients with MDD were prescribed escitalopram for 8 weeks. The starting dosage of escitalopram was 10 mg/day, which could be escalated to 30 mg/day. After remaining on a stable escitalopram dosage for 4 weeks, patients were randomly assigned to a placebo group ($N=68$) or a ziprasidone augmentation group ($N=71$). Rates of clinical response were significantly higher for the adjunctive ziprasidone group ($N=25$ [35.2%]) than for the adjunctive placebo group according to the mixed-effects model with repeated-measures analyses ($N=14$ [20.5%], $p=0.04$). In addition, mean improvement in HAM-D total scores were significantly greater for ziprasidone (-6.4) than for placebo (-3.3) augmentation.

(4) Other SGAs: Although asenapine, iloperidone, and sertindole were not investigated for the treatment of MDD, such SGAs have been also found to exert proper and relevant pharmacodynamics including interaction with multiple neurotransmitters receptors associated with putative action mechanisms as antidepressants as presented in Table 1.

Cariprazine is a new SGA which received US FDA approval for the treatment of schizophrenia and bipolar I disorder on September 15th, 2015.⁷² An unpublished phase II study was conducted to investigate cariprazine's efficacy in MDD patients who have failed to respond to at least 2 antidepressant therapies.⁷³ Two hundred thirty-two (232) patients were randomized to receive adjunctive cariprazine 0.1-0.3 mg/d, adjunctive cariprazine 1.0-2.0 mg/d, or adjunctive placebo, for 8 weeks. No significant differences among three treatment groups was found in the mean change of the MADRS from the baseline to week 8. Another 8-week RPCT (NCT01469377) was completed, but the results are still not available. In addition, two more RPCTS (NCT01838876 and NCT01715805) investigating its efficacy in treating MDD as an augmentation agent to ADT are still ongoing.

Regarding paliperidone, only one case is still available in the treatment of TRD.⁷⁴ In the case report, a 54-year-old female inpatient with depression showed symptom remission 2 weeks after 3 mg/day of paliperidone was added to venlafaxine-XR. Full remission was maintained for 4 months with no serious adverse effects.

A recent randomized, double-blind, placebo-controlled

study evaluated the efficacy and safety of lurasidone in major depressive disorders having mixed features.⁷⁵ The study enrolled patients, aged 18-75, meeting DSM-IV-TR criteria for major depressive disorders who presented with two or three protocol-defined manic symptoms on most days for at least 2 weeks prior to the screening. They were randomly assigned to 6 weeks of a double-blind treatment with either lurasidone at 20-60 mg/day ($N=109$) or placebo ($N=100$). The primary efficacy endpoint was mean change from baseline to week 6 of the MADRS total score. Lurasidone showed superior efficacy over placebo in mean change from baseline to week 6 in MADRS total score (-20.5 vs. -13.0 ; $p < 0.001$; effect size of 0.80). In terms of safety, nausea, somnolence, dizziness, akathisia, abdominal discomfort, dry mouth, and Parkinsonism were observed more frequently with lurasidone than with the placebo. The rate of discontinuation due to adverse events was 2.8% in the lurasidone group and 5.0% in the placebo group. It was the first placebo-controlled clinical trial that included patients with major depressive disorders associated with subthreshold hypomanic symptoms (mixed features). Depressive disorders presenting with mixed features are known to have complex courses and be associated with significant morbidity, so the study has both clinical and research significance.

A summary of RPCTs of SGAs published after our previous review article other than Brexipradoxole is presented in Table 3.

DISCUSSION

Increasing evidence has shown that SGAs may provide some benefits for the treatment of MDD (TRD) as either an augmentation or monotherapy. Accordingly, aripiprazole was the first SGA to receive FDA approval as an augmentation agent for the treatment of MDD followed by quetiapine XR and the combined agent of olanzapine plus fluoxetine (Symbiax). Recently, brexipradoxole, a newly developed SGA, was added to the above list by receiving FDA approval in July 2015 for the treatment of MDD as an augmentation to ADT. Besides of numerous post-hoc and open label studies, 8 RPCTs (aripiprazole=2, quetiapine=3, olanzapine=1, ziprasidone=1, and lurasidone=1) have been published since January 2013 illustrating that mounting evidence in utility of diverse SGAs in treating MDD.

In our previous review, we commented that there are a number of issues that need to be addressed despite considerable evidence supporting SGAs' viable role as augmentation agents for the treatment of MDD or TRD.¹⁴ On the other hand, many issues have already been addressed in the past decade, which are illustrated in the 8 meta-analyses of SGA in the treatment of MDD published so far (Table 4).

Even before aripiprazole was approved for MDD, off-label use of SGAs for MDD were not uncommon, especially in TRD.⁷⁶ In light of the increasing off-label use of diverse SGAs for the treatment of TRD, the initial concern in mid-2000s was whether SGAs were truly safe and effective

TABLE 3. Randomized, double-blind, placebo-controlled trials of SGAs in major depressive disorder since 2013

Study (year)	Duration	Design	Patients (n)	Primary end point	Other results
Aripiprazole					
Lenze et al (2015) ²⁹	12 weeks	Aug, age > 60 year	VFX+ARP (91)	Remission by MADRS	Secondary measure: NNT=6.6
Kamijima (2013) ²⁷	14 weeks	Aug	VFX+PBO (90) ADT+PBO (195) ADT+ARP Fix (194) ADT+ARP Flex (197)	PBO: 29% ; ARP: 44% ^a Changes in MADRS PBO: -7.4; ARP Fix: -10.5 ^a ARP Flex: -9.6 ^a	Response: Flex (39.2%) ^a , Fix (42.1%) ^a , PBO (28.2%) / Remission: Flex (30.4%) ^a , Fix (32.5%) ^a , PBO (20.5%)
Quetiapine					
Locklear et al (2013) ⁴³	11 weeks	Mono, age > 66	QTP XR flex (166) PBO (172)	Changes in MADRS PBO: -8.79; QTP: -16.33 ^a	Q-LES-Q-SF % improvement PBO: 9.17; QTP: 16.86 ^a
McIntyre et al (2014) ⁴⁴	8 weeks	Mono, FM with MDD	QTP XR flex (61) PBO (59)	Change in HAM-D PBO: -5.8; QTP: -10.0 ^a	BPI, HAM-A, CGI, FIQ, Q-LES-Q-SF improved greater in QTP than in PBO
Wang et al (2014) ⁴⁵	10 weeks	Mono	QTP XR (157) EPAM (157) PBO (157)	Changes in MADRS (QTP: -19.5; EPAM: -19.8; EPAM: -18.3)	Response and remission: no significant difference among groups
Olanzapine					
Brunner et al (2014) ⁵²	27 weeks	With FOX in TRD	OF (221) FOX (223)	Time-to-relapse OZA/FOX ^a longer than FOX	MADRS increase from baseline to endpoint OF: 5.36 to 8.07 ^a FOX: 5.40 to 11.82;
Ziprasidone					
Papakostas et al (2015) ⁶⁸	8 weeks	Aug	EPAM+ZIP: 71 EPAM+PBO: 68	Response by HAMD-D EPAM+ZIP: 35.2% ^a , EPAM+PBO: 20.5%	HAM-D total scores improvement EPAM+ZIP: -6.4 ^a , EPAM+PBO: -3.2
Lurasidone					
Suppes et al (2015) ⁷⁵	6 weeks	Mono, MDD with mixed features	LSD (109) PBO (100)	Changes in MADRS LSD: -20.5 ^a PBO: -13.0	Response: LSD (64%), PBO (30.0%) ^a Remission: LSD (49.1%), PBO (23.0%) ^a

^ap < 0.05 vs placebo, otherwise not significant.

ARP: aripiprazole, Aug: augmentation, BPI: brief pain inventory short form, EPAM: escitalopram, FIQ: fibromyalgia impact questionnaire, Fix: fixed dosing, Flex: flexible dosing, FM: fibromyalgia, FOX: fluoxetine, GAS: global assessment scale, HAMD-D: 17-item hamilton depression rating scale, LSD: lurasidone, MADRS: montgomery-asberg depression rating scale, Mono: monotherapy, NNT: number needed to treat, OF: olanzapine and fluoxetine combination, PBO: placebo, PHQ: patient health questionnaire, Q-LES-Q-SF: quality of life enjoyment and satisfaction questionnaire short form, QTP: quetiapine, XR: extended release, ZIP: ziprasidone.

for TRD. Thus, the first meta-analysis was conducted by Papakostas to address these two important concerns.⁷⁷ The study included 10 RPCTs involving more than 1500 outpatients with TRD, which showed that SGA augmentation (olanzapine, risperidone, and quetiapine) yielded greater clinical remission/response than placebo augmentation. However, the rate of discontinuation due to adverse events was lower for placebo than for SGA augmentation treated patients (RR=3.38, CI-1.98to5.76, p < 0.0001), so the safety issue surrounding SGA augmentation became the concern since the first meta-analysis. In the second meta-analysis, which was published in 2009, 6 more RPCTs were added and the SGAs included were broadened to include aripiprazole.⁷⁸ In line with the first meta-analysis, the results showed that SGAs were effective as augmentation agents for MDD but are associated with an increased risk of discontinuation due to adverse events.⁷⁹

With an increasing number of RPCTs being published, subsequent meta-analysis investigated the efficacy of specific SGAs (aripiprazole or quetiapine) rather than diverse SGAs as a whole.^{80,81} The study by Arbaizar contained 4 RPCTs (2 RPCTs for TRD and 2 RPCTs for bipolar depression), and it showed that aripiprazole is effective for increasing response rates in depressive patients. In terms of safety, akathisia was more frequently reported in patients taking aripiprazole than in patients taking the placebo. Similarly, a meta-analysis containing 3 RPCTs showed that the response rate of the quetiapine XR-treated group was significantly greater than that of the placebo-treated group.⁸¹ Although the overall discontinuation rate of quetiapine XR was not significantly higher than that of the placebo's, the discontinuation rate due to adverse events was higher in the quetiapine XR group than in the placebo group.

TABLE 4. Meta-analysis investigating second generation antipsychotics in the treatment of MDD

Study	RCTs	Patients	SGAs included	Design	Results
Papakostas (2007) ⁷⁷	10	1,500 with TRD	OZP:5 / RIP: 2 QTP:3	Aug	SGA > PBO in remission ([RR]=1.75, p < .0001) or clinical response (RR=1.35, p=.001)
Nelson (2009) ⁷⁸	16	3,480	OZP:5 / RIP: 3 QTP:5 / ARP:3	Aug	SGA > PBO in response ([OR]=1.69, p < .00001) or remission (OR=2.00, p < .00001). Discontinuation due to adverse events SGA > PBO ([OR]=3.91, p < 0.00001)
Arbaizar (2009) ⁸⁰	4	1,488	ARP only	Mono	ARP > PBO in response (ARP-PBO=7.7%, 95% CI: 1.5-14.2) ARP > POB in akathisia (ARP-PBO=20.3%, 95% CI: 16.9-23.7)
Maneeton (2012) ⁸¹	3	1,497	QTP	Mono	QTP > PBO in response ([RR]=1.44, 95% CI: 1.26-1.64) or in remission response ([RR]=1.37, 95% CI: 1.12-1.68). Discontinuation due to adverse events QTP > PBO ([RR]=2.90, 95% CI: 1.87-4.48)
Spielmanns (2013) ⁸²	14	3,549	OZP:5 / RIP: 3 QTP:3 / ARP:3	Aug	All four drugs had statistically significant effects on remission. The number needed to treat (NNT) was 19 for OFC and nine for other 3
Wen (2014) ⁸³	17	3,807	OZP:5 / RIP: 3 QTP:5 / ARP:5	Aug	SGA > PBO in response ([RR]=1.68, p < .00001) or remission ([RR]= 1.90, p < .00001). Discontinuation due to adverse events SGA > PBO ([RR]=3.32, p < .00001)
Zhou (2015) ⁸⁵	48	6,654	OZP:4 / RIP: 3 QTP:6 / ARP:4	Aug	QTP, ARP, thyroid hormone, and lithium > PBO in response QTP, ARP > thyroid hormone and lithium in response
Zhou (2015) ⁸⁶	18	4,422 with TRD	OZP:5 / RIP: 3 QTP:5 / ARP:5	Aug	All standard dose SGA > PBO in efficacy (the mean change score of depression rating scales from baseline to endpoint), but low dose SGA=PBO in efficacy Discontinuation due to adverse events standard dose SGA (except for RIP) > PBO ([OR]=2.72-6.40)
Wang (2015) ⁸⁷	11	3,341 with TRD	OZP:2 / RIP: 1 QTP:3 / ARP:5	Aug	SGA > AD monotherapy in response ([RR]=1.38, 95% CI: 1.25-1.53) or remission ([RR]=1.62, 95% CI: 1.42-1.85) Response rate of SGA differed according to the degree of TRD (TRD 1: RR=1.24; TRD 2: RR=1.37; TRD 2-4: RR=1.58). SGA=AD monotherapy in remission for non-TRD trials

AD: antidepressant, ARP: aripiprazole, Aug: augmentation trial, Mono: monotherapy trial, OR: odds ratio, OZP: olanzapine, PBO: placebo, Pfs-MDD: MDD with psychotic features, RIP: risperidone, RR: relative ratio, QTP: quetiapine, SGA: second generation antipsychotics, TRD: treatment resistant depression.

The meta-analyses by Papakostas et al.⁷⁷ and Nelson Papakostas⁷⁸ analyzed efficacy only in terms of dichotomous response and remission outcomes using clinician-rated depression measures, and safety was only assessed using the discontinuation due to adverse events. Spielmanns et al.⁸² tried to fulfill this gap by conducting a meta-analysis to provide a comprehensive estimate of the efficacy and safety profiles including functional status, quality of life, and drug-related side effects. The study included 14 RCTs containing four SGAs (aripiprazole, olanzapine, quetiapine, and risperidone). With regard to efficacy, all four drugs had statistically significant effects on remission with a NNT of 19 for olanzapine and a NNT of 9 for other SGAs. In terms of response, aripiprazole (NNT=7), quetiapine (NNT=10) and risperidone (NNT=8) showed higher remission rates than of the placebo, but OF combinations did not (NNT=19). In terms of quality of life and functioning, only risperidone was more efficacious than adjunctive placebo with a small-to-moderate effect size, but its effect should be interpreted cautiously because it is largely driven by post hoc analyses. The

study also investigated SGAs' safety in detail. With the exception of adjunctive risperidone, which was not associated with an increased rate of any spontaneously reported adverse events, the other 3 showed associations with various safety profile concerns. Adjunctive aripiprazole had a very high rate of akathisia (NNH=4) and was also linked to sedation (NNH=14), whereas OF combination led to a higher risk of weight gain of $\geq 10\%$ (NNH= 9), sedation (NNH=5), abnormal metabolic laboratory results (NNH=10), and elevated prolactin (NNH=6). Adjunctive quetiapine was highly associated with sedation (NNH=3) and metabolic laboratory results (NNH=6) and was associated with significant weight gain of $\geq 7\%$ (NNH=37). Wen et al repeated and extended the above 3 studies by comparing long-term and short-term outcomes among patients treated with SGAs and also examined whether the response rates to SGAs would be affected by sedative drugs (lorazepam, benzodiazepine and hypnotics).⁸³ In line with the previous research, the study showed that SGA augmentation yielded higher response and remission, but had a higher discontinuation rate due to adverse effects than the placebo.

In addition, the study showed that short-term (4-week duration) treatment subgroup did not have a statistically greater effect than the placebo (OR=1.70 [95%CI=0.98-2.95]), whereas the long-term (6-, 8-, 12-week duration) treatment subgroups did (OR=1.68 [95%CI=1.45-1.94], $p < .00001$).

Traditional meta-analysis usually cannot answer a comparative effectiveness question across multiple treatments, especially when there are limited head-to-head trials.⁸⁴ Zhou et al.⁸⁵ sought to investigate this important issue using network meta-analysis. The study compared 11 augmentation therapies with each other and with a placebo in TRD. The 11 augmentation therapies included buspirone, lithium, methylphenidate, bupropion, thyroid hormone, lamotrigine, pindolol, and 4 SGAs (risperidone, aripiprazole, quetiapine, and olanzapine). The results showed that quetiapine (OR=1.92; 95% CI, 1.39-3.13), aripiprazole (OR=1.85; 95% CI, 1.27-2.27), thyroid hormone (OR=1.84; 95% CI, 1.06-3.56), and lithium (OR=1.56; 95% CI, 1.05-2.55) were significantly more effective than the placebo in terms of response rate, and this efficacy was more robust for quetiapine and aripiprazole than for thyroid hormone or lithium. In terms of tolerability, quetiapine, olanzapine, aripiprazole, and lithium were significantly less well tolerated than the placebo. Zhou et al conducted another network meta-analysis to compare efficacy and tolerability of adjunctive SGAs for TRD.⁸⁶ The primary outcome measure was the mean change of scores of depression rating scales from the baseline to the endpoint (depression severity). The results showed that all 4 standard-dose-SGAs were significantly more efficacious than the placebo in decreasing depression severity, and no significant difference existed among 4 SGAs. In addition, all SGAs except for risperidone showed a higher discontinuation rate due to adverse effects than the placebo.

The latest meta-analysis sought to investigate which depression subgroups would be good candidates for SGA augmentation.⁸⁷ The study suggested that the effect size of SGA augmentation needs to become larger as the degree of treatment resistance to ADT became higher. In contrast, SGAs failed to show superior efficacy over antidepressant monotherapies in terms of remission rates for non-TRD trials.

In addition, while SGAs may have some potential benefits in the treatment of MDD with comorbid conditions, there have only been a handful of trials. For instance, the effects of quetiapine XR was recently shown in an 8-week RPCT in patients with MDD comorbid with fibromyalgia.⁴⁴ All measures of depressive symptoms, pain, and quality of life were more significantly improved in the quetiapine XR group than in the placebo group. In particular, the improvement of depressive symptoms was almost double in the quetiapine XR group compared to the placebo group. The promising effects of quetiapine for treating comorbid somatic symptoms in MDD patients were also demonstrated in a previous 6-week small scale RPCT.⁸⁸ In the study, patients were assigned to either citalopram 40 mg/d plus placebo

(N=20) or citalopram 40 mg/d plus quetiapine (300-600 mg/d, N=21). The mean change of the HAMD total score was the primary efficacy measure. The mean changes in the HAMD scores from the baseline to the endpoint were numerically higher in the citalopram plus quetiapine group (-12.3) than in the citalopram plus placebo group (-10.7). However, remission rates were significantly higher in the citalopram plus quetiapine group (41.1%) than in the citalopram plus placebo group (26.3%). As stated above, SGAs may have some potential benefits in the treatment of MDD with comorbid medical conditions; however, large-scale RPCTs with existing various SGAs as an augmentation therapy for MDD with physical disorders or somatic symptoms are necessary to confirm their role in this aspect.

Diverse issues regarding the use of SGAs in the treatment of MDD have been addressed within past 2 decades. However, issues surrounding the optimal intervention time, specific patient population for SGA augmentation therapy, treatment duration, clinical predictors to treatment response and AEs, usefulness on special populations of interest, long-term treatment issues, best-matched antidepressants, dosing guides, and pharmacoeconomics are yet to be resolved. Above all, the currently available evidence only indicates that clinicians have to carefully pay attention to evaluation of practical and individual risks and benefits at the time of the decision to prescribe an SGA augmentation therapy.

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CONFLICT OF INTEREST STATEMENT

None declared.

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