EXPERT REVIEWS

Second-generation antipsychotics in the treatment of major depressive disorder: current evidence

Expert Rev. Neurother. 13(7), 851–870 (2013)

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Major depressive disorder (MDD) is a chronic and recurrent mental condition leading to huge impacts on direct and indirect personal and public medical costs. To overcome such a serious mental disorder, we currently have a number of different classes of antidepressants, such as selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, noradrenergic and specific serotonin receptor antagonists, dopamine and norepinephrine reuptake inhibitors, along with newly introduced antidepressants (e.g., vilazodone and agomelatine). However, a number of well-controlled clinical trials, meta-analyses and practical clinical studies have found that only a third of such MDD patients remit following adequate antidepressant treatment, while most MDD patients suffer from significant core depressive or residual symptoms during their clinical course. There have been some treatment approaches to overcome such a shortage of antidepressant efficacy, such as augmentation of psychotropics other than antidepressants, switching to a different antidepressant and combinations of different antidepressants. Among these different second treatment options, augmentation treatment has some favorable points compared with the combination and switching option (e.g., maintaining previous antidepressant partial response, synergistic effect between different pharmacological profile and no need to wash out previous antidepressants). Recently, second-generation antipsychotics (SGAs), olanzapine plus fluoxetine, quetiapine extended release and aripiprazole have clearly demonstrated efficacy in the treatment of MDD patients through a number of small-scale, open-label studies or randomized, placebo-controlled clinical trials. Eventually, in November 2007, aripiprazole was the first approved by the US FDA as an adjunctive treatment to antidepressants for treating MDD, followed by the approval of quetiapine and olanzapine plus fluoxetine at 2009. This comprehensive review provides an overview of the clinical trial data of SGAs for treating MDD and clinical issues raised in the use of SGA therapy in patients with MDD in clinical practice.

Keywords: antidepressant • augmentation • clinical trial • major depressive disorder • second-generation antipsychotic

Major depressive disorder (MDD) is a common, chronic, recurrent and debilitating psychiatric condition, leading to significant impairments in personal functional capacities, which also eventually impact directly and indirectly on public medical costs [1].

After the advent of the older antidepressants such as monoamine oxidase inhibitors and tricyclic antidepressants for the treatment of MDD, newer antidepressants with improved tolerability such as selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors, dopamine and norepinephrine reuptake inhibitors, noradrenergic and specific serotonergic antidepressant medications have been introduced and flourished as the first-line treatments options for patients with MDD in clinical practice. However, despite sufficient availability of different classes of antidepressants to date, most patients with MDD do not achieve an adequate response or remission with such antidepressant treatment. The lack of satisfactory clinical efficacy of first-line antidepressant treatment is clearly evidenced in a number of case studies, randomized, double-blind, placebo-controlled clinical trials (RCTs), meta-analyses

 10.1586/14737175.2013.811901 ISSN 1473-7175

and practical clinical trials. For instance, a 12-week treatment with SSRI monotherapy (citalopram) showed only a 30% remission rate in MDD patients in the STAR*D trial [2]. In addition, in a recent meta-analysis including 182 antidepressant RCTs (n = 36,385), the response and remission rates were approximately 54 and 37%, respectively [3]. Such inadequate antidepressant efficacy results in significant residual symptoms, functional incapacity, increased utilization of medical services, and frequent recurrence and relapse [4–6].

According to the cumulative evidence in the last decade, augmentation strategies including second-generation antipsychotic (SGA) augmentation, switching to different antidepressants, or a combination of different antidepressant strategies are recommended in most guidelines for partial or non responders in clinical practice [7–10]. Among such second-treatment steps, the augmentation strategy has proven its usefulness for enhancing the antidepressant effect, showing increased remission rates and early treatment effects on core depressive symptoms and comorbid symptoms without losing previous antidepressant response as well as minimizing antidepressant-mediated side effects (e.g., sexual dysfunction) [7–10]. Although classical augmentation agents including lithium and thyroid hormones have been commonly used for patients with inadequate response from antidepressant first-line therapy, they were supported by limited data and none of those augmentation agents has been officially approved by the national authority such as the US FDA.

Recently, SGAs including olanzapine, quetiapine extended release (XR) and aripiprazole have clearly demonstrated efficacy as an augmentation agent for MDD patients through a number of small-scale, open-label studies or randomized, placebo-controlled clinical trials (RPCTs). In November 2007, aripiprazole was the first approved by the US FDA as an augmentation therapy to antidepressants for treating MDD, followed by approval of quetiapine XR and olanzapine in 2009.

Overview of clinical data

Data search

The search terms used for the PubMed database included 'aripiprazole', 'olanzapine', 'quetiapine', 'risperidone', 'ziprasidone', 'amisulpride', 'paliperidone', 'iloperidone', 'asenapine' and 'lurasidone'. These terms were matched with 'depression', 'MDD', 'dysthymia', 'psychotic depression' and 'antidepressant'. The studies found were verified for publication in peer-reviewed English journals. The authors also used reference lists from identified articles and reviews to find additional studies (crossreference check). The data search and verification were handled by lead authors (C-U Pae and C Han) and independently reassessed by coauthors (S-J Lee and M Kato).

Situation of the current market

Aripiprazole, quetipaine XR and olanzapine have been sequentially approved by the US FDA. Specifically, among such SGAs, olanzapine was approved for treatment-resistant depression (TRD; defined as MDD patients who did not respond to two separate trials of two or more than two antidepressants with adequate duration and dose) as a combined agent with fluoxetine. Other SGAs may include risperidone, ziprasidone, amisulpride, paliperidone, asenapine, iloperidone and lurasidone, in which the efficacy of risperidone and amisulpride was proved in some RPCTs in patients with MDD and dysthymia. Ziprasidone and paliperidone were tested in an open-label study and case reports. However, other SGAs have not been reported tested for patients with MDD until today. The current market situation for SGAs as augmentation therapy in the treatment of MDD is summarized in Table 1.

Rationale of action mechanism of SGAs for MDD

Before the 1980s, approximately 34 studies explored the use of typical antipsychotics in MDD, and some effects on depressive symptoms were found. However, such clinical data are clearly limited particularly by the use of earlier diagnostic systems, since those clinical trials were mostly tested in patients with mixed anxiety–depressive states [11,12]. In addition, typical antipsychotics were not accepted to be truly effective in core depression symptoms such as loss of interest and motor retardation. In addition, due to their risk of tardive dyskinesia, the use of typical antipsychotics in MDD declined rapidly after the advent of SGAs having improved tolerability and safety issues [11].

Although the exact mechanism of SGAs for MDD has not yet been clearly elucidated, several plausible underlying mechanisms are listed as follows: modulation of crucial neurotransmitter receptors and transporters such as dopamine, serotonin and noreinephrine resulting in net effect of enhancement of such neurotransmitters' transmission, effects on sleep, alteration of various hormones (ACTH, sex hormones, etc.), modification of immune functions including modulation of inflammation process (cytokines, etc.), antioxidation process and modulation of neurotrophic factors (BDNF, etc) [13].

Specifically, the main pharmacological rationale of SGAs as an antidepressant augmentation would be based on their effects on monoamine transporters or receptors of crucial neurotransmitters such as serotonin, norepinephrine and dopamine, which are also the main target of contemporary antidepressants. The partial agonism at D2 and/or D3 receptors may increase dopamine neurotransmission at the prefrontal cortex. The increase in the dopamine concentration in the prefrontal cortex may be also indirectly related to the antidepressive effect of 5-HT1A receptor agonist [14,15]. The antidepressant effect may also be mediated by 5-HT1A partial agonism and/or antagonism at 5-HT2A receptors [16–18]. Although, still controversial, the antidepressant effect of 5-HT1A receptor agonists may be predominantly mediated by postsynaptic 5-HT1A receptors, while the anxiolytic effect would be mainly associated with presynptic 5-HT1A receptors [19]. The antagonism of the 5-HT2C receptors has been also found to be involved in increased dopamine and norepinephrine transmission [20]. It is also well known that high affinity at the α_2-adrenergic receptor may enhance the release of norepinephrine [21]. Unlike any other SGAs, ziprasidone was reported to block synaptic serotonin, norepinephrine and dopamine reuptake *in vitro* [22,23]. Evidence indicates that both 5-HT6 agonists and antagonists may evoke identical responses in animal models of MDD, although

Table 1. The US FDA indication approval status of atypical antipsychotic use for major depressive disorder.

Drug	Indication	Dose range	Evidence
Olanzapine	TRD in combination with fluoxetine	Olanzapine: 5–20 mg/day; mean dose: 8–14 mg/day Fluoxetine: 20–50 mg/day	Placebo-controlled studies
Risperidone	Not approved for MDD	0.5–3.0 mg/day; mean dose: 1.2–1.6 mg/day	Placebo-controlled studies
Quetiapine XR	Augmentation to antidepressants for MDD	50–300 mg/day in flexible and fixed-dose trials; mean dose: 180 mg/day	Placebo-controlled studies
Aripiprazole	Augmentation to antidepressants for MDD	5–15 mg/day; mean dose: 11–12 mg/day	Placebo-controlled studies
Paliperidone	Not approved for MDD	3 mg/day	Case report
Ziprasidone	Not approved for MDD	80–160 mg/day	Open-label study
Amisulpride	Not approved for MDD	50 mg/day in MDD and dysthymia	Open-label and randomized, (placebo)-controlled studies
Asenapine, iloperidone, setindole and lurasidone	Not approved for MDD	Not available	No clinical data with MDD

MDD: Major depressive disorder; TRD: Treatment-resistant depression; XR: Extended release.

the possible mechanisms of these effects seem to be diverse and are not clearly understood. The augmented effects were notable by combining antidepressants with a selective 5-HT6 receptor antagonist [24]. There is also a considerable amount of evidence supporting a role for the 5-HT7 receptor in MDD. The blockade of the 5-HT7 receptor led to antidepressant-like effects in animal models of MDD. It should be also worthy to mention that augmentation of 5-HT7 receptor antagonists with antidepressants was remarkable in animal models of MDD [25].

Another mechanism involving in the action of SGAs should be the alteration of the glutamate receptor activity, and thus restoring normal glutamatergic neurotransmission and reducing the chances of excitotoxicity [26]. Some SGA treatment may also cause a decrease in plasma adrenocorticotropic hormone concentration and a normalization of HPA-axis dynamics [27]. An impaired neuroprotection has also been implicated in the pathophysiology of MDD [28,29]. Interestingly, activation of the 5-HT1A receptors was shown to be neuroprotective against various brain insults such as *N*-methyl-D-aspartic acid [30]. Some SGAs have also demonstrated such neuroprotective effects indicating a potential role in the protection against excitotoxicity *in vivo* [30].

Overall 5-HT2A antagonism should be a commonly shared biological relevance for most of the SGAs as a potential mechanism of their antidepressant effect. Interactive effects with the dopaminergic system may be more distinct with the action mechanism of amisulpride and aripiprazole, while norepinephrine- and/or serotonin-reuptake inhibition should be the unique case with quetiapine or ziprasidone [31]. Each antipsychotic has a distinct profile of affinities towards different neurotransmitter receptors, which should be associated mainly with mediation of antidepressant-like effects. The potential action mechanisms of SGAs interacting with different neurotransmitter receptors that should be involved in antidepressant-like effects are presented in Table 2. Figure 1 schematically illustrates the potential net effects relating to neurotransmission and other actions.

Individual SGAs

Aripiprazole

The clinical benefit of adjunctive aripiprazole for treating patients with MDD may also stem a number of early-phase, small-scale open studies [32–41]. There have been three identically designed initial phase RPCTs [42–44] and two subsequent RPCTs [45,46] to date. Briefly, for the three RPCTs [42–44], patients with 1–3 historical failures in adequate antidepressant trials (total score ≥18 on the 17-item Hamilton Rating Scale for Depression [HAMD-17]) were screened and then entered an 8-week prospective treatment phase. Incomplete responders were then randomized for treatment with either aripiprazole or placebo for 6 weeks. The primary efficacy end point was the mean change from baseline for the Montgomery-Asberg Depression Rating Scale (MADRS) total score. Response and remission were defined as an absolute reduction of ≥50% for the MADRS total score, and at least a 50% reduction in the MADRS score plus an absolute MADRS score of ≤10, respectively. In total, 1092 prospectively identified partial responders were randomized and 940 (86.4%) patients completed the three 6-week RPCTs. In these three RPCTs, significant improvements in the mean change of the MADRS total score (range = -8.5 to -10.1) with aripiprazole augmentation over placebo (-5.8 to -6.4) were observed [42–44]. Remission rates were also significantly higher with aripiprazole augmentation (25.4–36.8%) than with placebo (15.2–18.9%) [42–44]. A pooled analysis also confirmed such superiority in efficacy of aripiprazole augmentation over placebo [47].

In one study, aripiprazole augmentation was superior to placebo in improving family and social function on the Sheehan Disability Scale [42]. However, consistent positive and favorable

Table 2. The potential action mechanisms of second-generation antipsychotics.

Drug	Potential mechanism for antidepressant-like effects
Olanzapine	5-HT2A/2C receptor antagonism, 5-HT7 receptor antagonism
Risperidone	5-HT2A receptor antagonism, α-2 receptor antagonism, 5-HT7 receptor antagonism
Quetiapine	α-2 receptor antagonism, norepinephrine transporter inhibition (metabolite), 5-HT7 receptor antagonism
Aripiprazole	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
Paliperidone	5-HT2A receptor antagonism, α-2 receptor antagonism, 5-HT7 receptor antagonism
Ziprasidone	5-HT2A/2C receptor antagonism, 5-HT1A receptor agonism, serotonin/norepinephrine/dopamine transporter inhibition
Amisulpride	5-HT7 antagonism, presynaptic D2/3 autoreceptors antagonism at low dose (50 mg)
Lurasidone	Strong 5-HT7 receptor antagonism, 5-HT1A receptor partial agonism, weak 5-HT2C receptor antagonism, weak α-2 receptor antagonism
Iloperidone	5-HT2A receptor antagonism, 5-HT6/7 receptor antagonism
Asenapine	5-HT2C/2A receptor antagonism, 5-HT6/7 receptor antagonism, 5-HT2B receptor antagonism, α-2 receptor antagonism, partial agonism at 5-HT1A receptor
Sertindole	5-HT2A receptor antagonism, 5-HT6/7 receptor antagonism

Data taken from [13,17,105,106,126,133–137].

findings were observed for such subscales of Sheehan Disability Scale in all three RPCTs. A recent pooled analysis also confirmed a superiority of aipiprazole over placebo on functioning level [48]. The patients who achieved remission showed greater functional improvements than those with response to treatment without remission. This result points out that the functioning level should be a distinctly different outcome from symptom improvement, by which treatments targeting complete remission may deliver patients more improved functioning level over and above that seen with patients who only achieve response. For all additional efficacy measures such as Clinical Global Impression-Improvement (CGI-I), aripiprazole augmentation showed significantly more improvement than placebo in these RPCTs, although some discrepancy was noted among RPCTs in secondary outcome measures.

In addition, remission was achieved in significantly more patients taking adjunctive aripiprazole versus placebo as early as week 1 [42] and week 2 [43]. A pooled analysis was conducted to assess varying levels of response (≤25% decrease for minimal, 25–50% decrease for partial, 50–75% decrease for moderate and ≥75% decrease for a robust response) to aripiprazole augmentation to placebo and the predictive value of an early response for a sustained response in such three RPCTs [48]. According to the results, aripiprazole augmentation demonstrated that a significantly greater proportion of patients achieved a partial, moderate or robust response compared with placebo. Patients who showed an early response within week 2 to aripiprazole also maintained their response through to end point, indicating that clinically meaningful decisions should be necessary when encountering partial or non responders in clinical practice. In other pooled studies, aripiprazole augmentation was found to be superior to placebo regardless of previous response level [49], current age [50], subtypes of MDD [51] and core depressive symptoms [52]. In addition, the improvement of core depressive symptoms was not significantly different in assessment between clinicians and patients themselves [53]. According to 52-week long-term trials of aripiprazole augmentation, among 323 patients who completed the trial, 221 patients (69.7%) had a CGI-S of 1 (not at all ill) or 2 (borderline ill) [54].

Although the three short-term RPCTs were not designed to identify the proper aripiprazole dose for treating patients with MDD, the mean daily dose of aripiprazole at end point across the three short-term studies was approximately 11 mg/day [42–44], while it was approximately 10 mg/day in a long-term study [54].

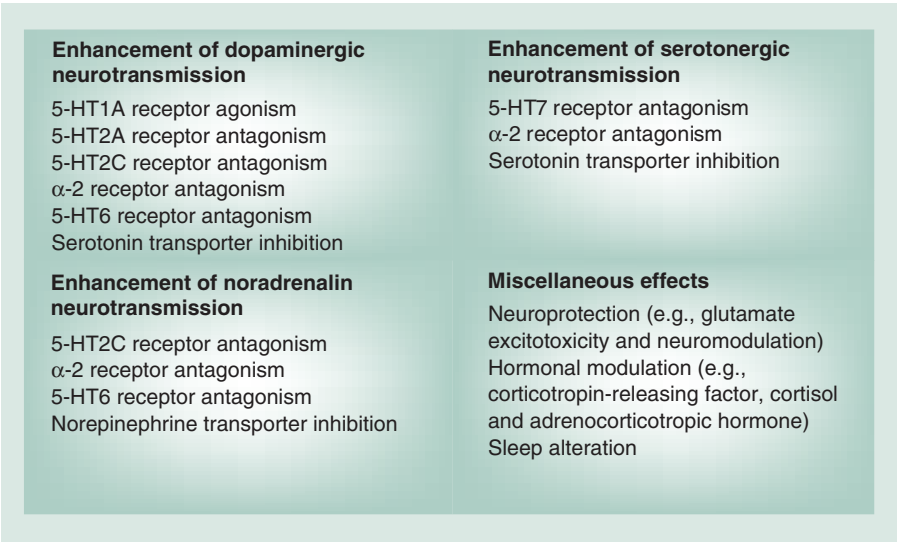

Figure 1. Potential net effects relating to neurotransmission and other actions of second-generation antipsychotics.
Data taken from [13,17,105,106,126,133–137].

After three identically designed RPCTs, the efficacy of dose increment of aripiprazole to 5 mg/day in subjects with MDD who did not respond to 4 weeks of treatment with aripiprazole 2 mg/day was investigated in a subsequent RPCT [46]. In this study, aripiprazole dose increase from 2 to 5 mg/day provided only a modest additional benefit in patients who do not benefit from lower doses. In addition, the efficacy of low-dose aripiprazole augmentation was also tested in a recent RPCT (n: 225) [45]. In this study, the weighted response difference between aripiprazole 2 mg/day and placebo in the two phases was 5.6% and the pooled difference in the MADRS score was -1.51 favoring aripiprazole augmentation over placebo, indicating a marginal efficacy of low dose of aripiprazole in such patient population.

Overall, aripiprazole augmentation was safe and well tolerated in the three RPCTs [42–44]. When the three short-term study results were pooled [42–44], the completion rates were 85.3% for aripiprazole augmentation and 87.5% for adjunctive placebo. The overall discontinuation rates owing to adverse events (AEs) in the pooled data set were low: 4.4% for aripiprazole augmentation and 1.7% for adjunctive placebo. Akathisia was the most common AE reported with aripiprazole augmentation in the three RPCTs and occurred in approximately 23% of patients with MDD; however, the vast majority of akathisia reports were considered mild-to-moderate. There were no reports of tardive dyskinesia in three RPCTs. In a pooled analysis, the mean difference in body weight was significantly different between aripiprazole augmentation (+1.73 kg) and placebo (+0.38 kg) [55]. In addition, significantly more subjects receiving aripiprazole augmentation had clinically relevant (≥7%) weight gain versus placebo. Aripiprazole augmentation showed statistically significant greater improvements versus placebo on the Sexual Functioning Inventory item 'interest in sex' in a pooled population of the three RPCTs [56]. In this pooled analysis, a significant gender difference was noted in items of interest in sex and sexual satisfaction favoring female over male. No clinically meaningful differences were observed between aripiprazole augmentation and placebo with respect to vital signs, electrocardiographic findings or laboratory abnormalities including metabolic panel in any of the three RPCTs [55,57]. Overall, the AEs' profile was reported to be consistent with those in the three short-term RPCTs in the 52-week long-term trial, where the most common AEs reported included akathisia (26%), fatigue (18%) and weight gain (17%) [54]. The summary of the controlled clinical trials of aripiprazole is presented in Table 3.

Quetiapine

There has been one open-label quetiapine study for the treatment of TRD [58], and a recent placebo-lead, open-label study investigated the effect of quetiapine in the treatment of menopause-related mood symptoms [59]. Such uncontrolled studies have suggested the clinical utility of quetiapine for treatment of MDD. To date, we have monotherapy studies monotherpay of quetiapine [60–65], where one was conducted as a maintenance study [62] and another study has been only published as an abstract [65]. Five quetiapine augmentation RPCTs were conducted for the treatment of MDD [66–70], where one was conducted as augmentation to cognitive behavioral therapy (CBT) [69]. A recent RPCT investigated the efficacy of quetiapine for the treatment of psychotic MDD [71]. Therefore, currently 12 quetipaine RPCT as monotherapy or augmentation treatment to antidepressant or CBT are available in the treatment of MDD with or without psychotic features today.

The efficacy of quetiapine augmentation was firstly tested for patients with MDD who were treated with SSRIs/venlafaxine for more than 6 weeks, in a small-scale (n: 58), 8-week RPCT [70]. The primary efficacy end point was the mean change from baseline for the HAMD-17 total score. In this RPCT, significant improvements in the mean change of the HAMD-17 total score (-11.2) with quetiapine augmentation over placebo (-5.5) were observed. The onset of quetiapine efficacy was seen by week 1 and continued until week 8. However, remission (HMAD-17 total score ≤7) rates were only numerically higher with quetiapine augmentation (31%) than with placebo (17%). The efficacy of quetiapine XR augmentation was demonstrated in the two identically designed (150, 300 mg/day and placebo) 6-week RPCTs (total n: 936) [66,67]. In both studies, the primary end point was mean changes in MADRS total score from baseline. Significantly different mean changes from baseline in MADRS score were observed (-15.3 and -15 for quetiapine XR 150 and 300 mg/day, respectively, vs -12.2 for placebo) in one study [67], while the statistically different mean change in MADRS total score was only seen in quetiapine XR 300 mg/day but not in quetiapine XR 150 mg/day, compared with that of placebo in the other study [66]. However, the efficacy of both doses of quetiapine XR was evident from week 1 onwards in both studies. In a fixed-dose augmentation study, the remission rate was significantly higher in 150 mg/day quetiapine XR (36.1%) compared with placebo (23.8%), while it was numerically higher in 300 mg/day quetiapine XR (31.1%) compared with placebo [67]. However, in another fixed-dose augmentation study, the remission rates were significantly higher with 300 mg/day quetiapine XR (46.2%) than placebo (24.5%) but not for 150 mg/day quetiapine XR (35%) [66]. A total of 114 patients with MDD who initiated on a course of fluoxetine treatment were randomized to either quetiapine augmentation or placebo for 8 weeks [68]. Quetiapine was flexibly dosed from 25 to 100 mg/day (mean dose: 47 mg/day). In this study, although quetiapine augmentation was superior to placebo on improvement in sleep over the first few weeks of treatment, it failed to separate from placebo in change of total score on MADRS score. Twenty two TRD (stage II or greater) patients who failed to show adequate response from 3 weeks of lithium augmentation were randomized to receive either CBT plus quetiapine augmentation or CBT plus placebo for 12 weeks [69]. In this study, the quetiapine plus CBT group demonstrated a significant reduction in both primary efficacy measures, compared with CBT plus placebo. Furthermore, patients with quetiapine plus CBT showed more completion rates and CBT sessions compared with those with CBT plus placebo. Finally, quetiapine was also tested in patients with psychotic MDD [71]. One hundred and twenty two patients were randomized to imipramine, venlafaxine or venlafaxine–quetiapine for 7 weeks. The primary end point was

Table 3. Randomized, double-blind, placebo-controlled clinical trials of aripiprazole in major depressive disorder.

Study (year)	Duration	Patients (n)	Primary end point	Response and remission rates	Ref.
Berman *et al.* (2007)	6 weeks	ARP: 181; PBO: 172	Change in MADRS total score PBO: -5.8; ARP: -8.8	Response: 33.7 vs 23.8%* Remission: 26 vs 15.7%*	[42]
Marcus *et al.* (2008)	6 weeks	ARP: 185; PBO: 184	Change in MADRS total score PBO: -5.7; ARP: -8.5	Response: 32.4 vs 17.4%* Remission: 25.4 vs 15.2%*	[43]
Berman *et al.* (2009)	6 weeks	ARP: 174; PBO: 169	Change in MADRS total score PBO: -6.4; ARP: -10.1	Response: 46.6 vs 26.6%* Remission: 36.8 vs 18.9%*	[44]
Fava *et al.* (2012)†	60 days, two phases	ARP: 56; PBO: 169	Difference in response rate by MADRS total score Pooled, weighted ARP–PBO difference: 5.6%	ARP: 7.4% in phase 1 and 13.1% in phase 2 PBO: 9.58% in phase 1 and 6.4% in phase 2 Pooled, weighted ARP–PBO difference: 2.3%	[45]
Mischoulon *et al.* (2012)†	60 days, two phases		Mean change in MADRS total score (mean) in ARP: -9.5	Responder rates: ARP 2 mg: 18.5%; ARP 5 mg: 12.8% PBO: 17.4% in phase 1 and 7.9% in phase 2	[46]

†Identical placebo-controlled, randomized clinical trial and analyzed differently on primary objective.
*$p < 0.05$, otherwise not significant.
ARP: Aripiprazole; MADRS: Montgomery-Asberg Depression Rating Scale; PBO: Placebo.

response on HAMD-17 at the end of treatment. According to the results, venlafaxine–quetiapine showed a significantly higher responder rate (65.9%) than venlafaxine alone (33.3%) but comparable with imipramine alone (52.4%). However, the remission rate was significantly higher in venlafaxine–quetiapine (42%) than imipramine (21%) but not venlafaxine (28%).

In six quetiapine XR monotherapy RPCTs, two studies were fixed-dose four-arm (50, 150, 300 mg/day and placebo [63]; (150, 300 mg/day, duloxetine and placebo) [64], 6-week trials, while another three were flexible-dose trials for 8 weeks [61,65] or 9 weeks [60]. The last one was a 52-week, randomized-withdrawal, RPCT following open-label stabilization phase treatment [62]. In the study by Weisler *et al.*, each dose of quetiapine XR was superior to placebo in reduction of depressive symptoms showing a magnitude of treatment difference of 2.5, 3.4 and 3.1 respectively, in the mean changes of MADRS total scores during the study [63]. In addition, all quetiapine XR-treated groups separated from placebo in the MADRS total score by day 4. The significantly greater changes in the MADRS total scores for quetiapine XR over placebo were also replicated in another fixed-dose RPCT as well [64]. In the study, quetiapine XR 150 mg/day (-49.7%) and 300 mg/day (-50.8%) and duloxetine (-48%) significantly reduced mean MADRS total score versus placebo (-37%). A significant reduction was also seen at week 1 with quetiapine XR 150 and 300 mg/day versus placebo, while it was not observed with duloxetine. In a flexible-dose, 8-week trial, quetiapine XR has also demonstrated superior efficacy over placebo [61]. At the end of treatment, quetiapine XR (-16.5) significantly reduced MADRS total scores compared with placebo (-13.1). The onset of quetiapine efficacy was evident by week 1 (the mean difference from placebo in change from randomization was -1.9) and continued until week 8. However, another flexible-dose, 8-week trial, failed to separate quetiapine XR from placebo in the mean changes of MADRS total scores from baseline to end of treatment, although quetiapine XR showed numerically greater improvements over placebo [65]. The 9-week, flexible-dose trial was investigated in elderly patients with MDD [60]. At the end of treatment, quetiapine XR (-16.3) showed significantly greater reductions in MADRS total score from baseline than placebo (-8.8). Statistically significant separation between drug and placebo was evident after 1 week of treatment. In a 52-week, longer-term RPCT, quetipiane XR was found to be significantly superior to placebo in maintaining improvement of depression symptoms during the study, evidenced by the number of subjects who relapsed (132 [34.4%] vs 55 [14.2%], hazard ratio: 0.34 [95% CI: 0.25–0.46]) [62]. The remission rates *a priori* defined were inconsistent in the short-term quetiapine monotherapy RPCTs. The two flexible-dose quetiapine monotherapy RPCTs [61,65], one fixed-dose RPCTs (all dose of 50/150/300 mg/day) [63] and one fixed-dose RPCT (150 mg/day but not with 300 mg/day) [64], all failed to demonstrate a superiority of quetiapine XR over placebo in terms of remission rates. Significant differences in both response (64 vs 30.4%) and remission (45.1 vs 17%) rates between quetiapine monotherapy and placebo were only observed in the study of elderly patients with MDD [60]. However, a recent meta-analysis (n: 1497) [72] combining three monotherapy RPCTs [61,63,64] clearly showed its efficacy in terms of primary and secondary end points. The pooled mean change in MADRS total score was significantly higher with quetiapine XR monotherapy than

that with placebo, with the weighted mean difference of -3.4. In addition, the response and remission rates were also significantly higher with quetiapine XR monotherapy with relative risks of 1.44 and 1.37, respectively.

Likewise in aripiprazole augmentation study results, a recent pooled analysis has confirmed that that quetiapine XR monotherapy improves symptoms of depression irrespective of whether patients have MDD with high or low levels of anxiety [73]. This finding was also supported by another pooled analysis, where the therapeutic effect of quetiapine XR was neither limited to nor driven by various clinical factors such as gender, age or severity of MDD [74].

The overall tolerability and safety findings for quetiapine regardless of augmentation or monotherapy in MDD trials were similar with the known profile of the medication. It has been shown in clinical trials that quetiapine as a monotherapy or augmentation therapy was found to be overall safe and tolerated for the treatment of MDD. The dosages of 50, 150 and 300 mg/day of quetiapine XR were generally tolerated, in which the overall incidence of AEs showed a trend towards higher proportions in the quetiapine XR treatment groups in a dose-dependent manner, compared with placebo treatment groups. The most common AEs were dry mouth, sedation, headache and somnolence across all the short-term RPCTs. Most AEs were mild-to-moderate in all treatment groups, and serious AEs were also infrequent in all treatment groups. The tolerability profile in elderly patients was also similar with other short-term studies, in which the most common AEs were dry mouth, somnolence and dizziness [60]. Extrapyramidal symptom (EPS) measures and AEs were generally low and equal between quetiapine and placebo groups across all the short-term studies. These favorable safety and tolerability profiles of quetiapine XR treatment for MDD were also replicated in the maintenance 52-week study, where the most common AEs (>10% any group) during the randomized period were headaches and insomnia. The mean weight increase was 2.2 kg after 52-week maintenance treatment. However, the most notable changes in clinical chemistry parameters involved glucose and triglyceride. In fact, the mean increase in glucose level was 3.4 (150 mg/day) and 4.6 mg/dl (300 mg/day), while 1.6 and 1.3 mg/dl for duloxetine and placebo, respectively, in one fixed-dose monotherapy RPCT [64]. The mean increases in triglycerides were 10 and 17.6 mg/dl for quetiapine XR 150 mg/day and quetiapine XR 300 mg/day, respectively, while 10.2 and 3.9 mg/dl for duloxetine and placebo, respectively [64]. These findings were similar across all the short-term and maintenance studies. Hence, clinicians need to be aware of metabolic concerns from the treatment of quetiapine XR for MDD patients.

The summary of controlled clinical trials of quetiapine is presented in Table 4.

Olanzapine

A combination agent of olanzapine and fluoxetine (OFC) has been the first medication approved for treatment of TRD to date. We have five RPCTs [75–78] investigating OFC in the treatment of acute TRD (at least one historical antidepressant treatment failure during the current episode and who failed a prospective antidepressant therapy during the study lead-in period). Among these studies, two were identically designed and also published together [78]. Three PRCTs [79,80] have specifically evaluated olanzapine in MDD with psychotic features (MSSPFs), of which two studies were published together [79].

In all five OFC studies for TRD, the primary end point was mean change in MADRS total score from baseline. According to the results, improvements in the mean change of the MADRS total score or remission rate were found inconsistent with OFC over various monotherapy comparators across all five studies, though numerically higher remission rates or improvement in MDD symptoms was consistently favorable to OFC over comparators. For instance, in the first small-scale RPCT of OFC for treatment of TRD, OFC (-13.6) demonstrated significantly greater improvement than either fluoxetine (-1.2) or olanzapine (-2.8) monotherapy in depressive symptoms measured by decrease in MADRS total score from baseline as well as in responder rates (60, 10 and 0%, respectively) [75]. Such differences between the three groups were evident from the first week. However, in a subsequent large RCT [76], OFC failed to separate from fluoxetine, nortriptyline and olanzapine monotherapy in the primary end point at the end of treatment, although it showed superiority over the three monotherapies at certain points in terms of various treatment end points including subgroup analysis and time of treatment onset, during the study period. Hence, the results strongly raise some methodological questions including study entry criteria and randomization among others. In a 12-week RCT, OFC (-7.2) showed significantly greater reduction in MADRS total score than olanzapine (-4.8), fluoxetine (-4.7) or venlafaxine (-3.7), sustaining such group differences until week 6. However, OFC separated from only olanzapine but not from fluoxetine and venlafaxine in reduction of MADRS total score, at the end of treatment [77]. In the last RCT that published two studies together, although Study 1 revealed failure to separate OFC (-11) from fluoxetine (-9.4) and olanzapine (-10.5) monotherapy in reduction of MADRS total score, although Study 2 clearly demonstrated the superiority of OFC (-14.5) over olanzapine (-7) and fluoxetine (-8.6) monotherapy in reduction of MADRS total score [78]. The pooled results also supported the superiority of OFC (-12.7) over fluoxetine (-9) and olanzapine (-8.8) in reduction of MADRS total score. The short-term efficacy of OFC for TRD has been supported by the results of five RPCTs and RCTs with generally similar design and duration of treatment and thus, all the five studies were pooled and reanalyzed. According to the pooled results with 1146 TRD patients [81], OFC (-13) has clearly demonstrated significantly greater improvements in MADRS total score than fluoxetine (-8.6) or olanzapine (-8.2) as well as in remission rates (25.5, 17.3 and 14%, respectively). In a another recent pooled study, OFC produced significantly more early-onset response in both scores on MADRS total and core mood items than fluoxetine (0.5 week) and olanzapine (1 week) [82]. In addition, negative predictive values for response and remission by MADRS total and core mood item ranged from 85.7 to 92.1%, indicating the utility of absence of early improvement as one of the

Table 4. Randomized, double-blind, (placebo)-controlled clinical trials of quetiapine in major depressive disorder.

Study (year)	Duration (weeks)	Patients (n)	Primary end point	Response and remission rates	Ref.
Monotherapy					
Katila *et al.* (2012)	11	QTP XR (n: 166; flexible-dosing 50–300 mg/day); PBO (n: 172)	MADRS total score change: -16 vs -9*	Response: 64.0 vs 30.4%* Remission: 45.1 vs 17%*	[60]
Bortnick *et al.* (2011)	10	QTP XR (n: 154; 50–300 mg/day); PBO (n: 156)	MADRS total score change: -16.5 vs -13.1*	Response: 61.9 vs 48%* Remission: 49.7 vs 33.6%*	[61]
Liebowitz *et al.* (2010)	52	QTP XR (n: 391; 50–300 mg/day); PBO (n: 385)	Recurrence of depressive event from randomization: risk of recurrence of depressive event was significantly reduced by 66% in QTP continuing group (HR: 0.3, 14.2% in QTP XR group vs 34.4% in PBO group)	NA	[62]
Weisler *et al.* (2009)	8	QTP XR (n: 182, 178 and 179 for 50, 150 and 300 mg/day, respectively); PBO (n: 184)	MADRS total score change: QTP XR 50 mg/day (-13.6), 150 mg/day (-14.5) and 300 mg/day (-14.2) vs -11.1*	Response: 42.7, 51.2, 44.9% in QTP XR 50, 150, 300 mg/day vs 30.3% in PBO* Remission: 25.8, 20.8, 26.1 vs 18.5%, respectively	[63]
Cutler *et al.* (2009)	8	QTP XR (n: 152; 150 mg/day) or (n: 152; 300 mg/day), duloxetine (n: 151; 60 mg/day), or PBO (n: 157)	MADRS total score change	Response: 54.4 vs 55.1 vs 49.6 vs 36.2%, for 150, 300 mg/day, duloxetine and PBO, respectively* Remission: 26.5 vs 32% vs *31.9% vs 20.4%, respectively	[64]
Earley *et al.* (2008)	8	QTP XR (n: 157, 50–300 mg/day), escitalopram (n: 157; 10–20 mg/day), PBO (n: 157)	MADRS total score change	Response: 60.4 vs 59.9 vs 51%, for QTP XR, escitalopram and PBO, respectively Remission: 35.7 vs 40.8 vs 35.3%, respectively	[65]
Augmentation therapy					
El-Khalili *et al.* (2010)	8	QTP XR (n: 148, 150 mg/day; n: 150, 300 mg/day); PBO (n: 148)	MADRS total score change	Response: 51.7, *58.9, 46.2, for QTP XR 150 mg/day, 300 mg/day and PBO, respectively Remission: 35, *42.5, 24.5, respectively	[66]
Bauer *et al.* (2009)	6	QTP XR (n: 167, 150 mg/day; n: 163, 300 mg/day); PBO (n: 163)	MADRS total score change	Response: 55.4, *57.8, 46.3%, for QTP XR 150, 300 mg/day and PBO, respectively Remission: *36.1, 31.1, 23.8%, respectively	[67]
Garakani *et al.* (2008)	8	QTP (n: 57, 25–100 mg/day); PBO (n: 57)	Responders and remitters rates at the end point	Not significantly different with PBO	[68]
Chaput *et al.* (2008)	12	QTP/CBT (n: 11); PBO plus CBT (n: 11)	*MADRS and HAMD-17 total score change: -8.5 (MADRS) and -7.5 (HAMD) vs NR (PBO)	NA	[69]
McIntyre *et al.* (2007)	8	QTP (n: 29); PBO (n: 29)	*HAMD-17 total score change: -11.2 vs -5.5	Response: 48 vs 28% Remission: 31 vs 17%	[70]
Wijkstra *et al.* (2010)	7	Venlafaxine/quetiapine (n: 41); venlafaxine (n: 39); imipramine (n: 42)	HAMD-17 total score change: -18.4 vs -13.9 vs -17.1, respectively	Response: *65.9% (vs venlafaxine) vs 33.3% vs 52.4%, respectively Remission: *41.5% (vs imipramine) vs 28.2% vs 21.4%, respectively	[71]

*$p < 0.05$, otherwise not significant.
CBT: Cognitive behavioral therapy; HAMD: Hamilton Depression Rating Scale; MADRS: Montgomery Åsberg Depression Rating Scale; MDD: Major depressive disorder; NA: Not available; NR: Not reported; PBO: Placebo; QTP: Quetiapine.

reliable predictors for overall response failure in the treatment of TRD. In a 76-week, open-label, OFC study involving 560 MDD patients with and without TRD [83], a mean decrease of MADRS total scores was 22 points at the end of treatment (-11 and -18 points at 1 and 8 weeks of treatment, respectively). The response (62%) and remission (56%) rates for the whole subjects were high and the relapse rate was low (15%). In addition, the response, remission and relapse rates for TRD patients (n: 145) were 53, 44 and 25%, respectively.

In the first two OFC studies for MDDPFs, which were published together, the primary end point was mean change in HAMD-24 total score from baseline [79]. Study 1 has demonstrated the superiority of OFC (-20.9) over placebo (-10.4) in the primary end point, and such difference was evident within week 1 and also maintained throughout the study, while olanzapine (-14.9) did not separate from placebo. The response rate was also significantly higher with OFC (63.6%) than with olanzapine (34.9%) and placebo (28%). However, in Study 2, there were no significant differences among treatments in the primary end points or response rates. In the subsequent study, the efficacy of sertraline plus olanzapine and olanzapine plus placebo was compared and the primary end point was the remission defined as a total HAMD-17 score ≤10 at the end of treatment [80]. Olanzapine plus sertraline (41.9%) showed a statistically higher remission rate than olanzapine plus placebo (23.9%). In addition, sertraline plus olanzapine consistently showed its superiority over olanzapine plus placebo in some secondary efficacy measures such as CGI-S, and the superiority was not affected by age.

The overall tolerability and safety findings for OFC trials in TRD and MDDPFs were similar with the known profile of the medication. In general, OFC was found to be safe and tolerated for the treatment of TRD and MDDPFs. According to the pooled results, the most common AEs of OFC patients (≥10%) were weight gain, followed by increased appetite, dry mouth, somnolence, fatigue, headache and peripheral edema. The mean change in weight was highest with OFC (+4.4 kg) and comparable with olanzapine (+4.6 kg), while it was the least with fluoxetine (-0.2 kg). The proportion of patients gaining weight ≥ 7% was also highest with olanzapine (42.9%) and comparable with OFC (40.4%), while it was least with fluoxetine (2.3%). The mean change in glucose (mg/dl) was +7.92 for the OFC, while it was +1.62 for fluoxetine and +9.91 for olanzapine. The mean change in cholesterol (mg/dl) was +12.4 for OFC, while it was +2.3 for fluoxetine and +3.1 for olanzapine.

The safety and tolerability profile of OFC in short-term trials was also similar in the longer-term study as well [83], in which the most frequently reported AEs were somnolence, weight gain (+5.6 kg), dry mouth, increased appetite and headache. In addition, 56% of patients had weight gain ≥7% from baseline. At end point, there were no clinically meaningful changes in vital signs, laboratory analytes or electrocardiography. There were no significant increases on any measure of EPSs as well. Likewise in quetiapine studies, clinicians need to be aware of metabolic concerns from the treatment of olanzapine for MDD patients. The summary of controlled clinical trials of olanzapine is presented in Table 5.

Risperidone

The effectiveness of risperidone were proposed in some case reports and a case-series study as augmentation therapy for the treatment of MDD [84,85]. Based on such encouraging findings for risperidone in the treatment of MDD, currently five RPCTs of risperidone have been conducted in TRD, in which three studies [86–88] investigated the clinical utility of risperidone augmentation to current antidepressant versus placebo and two studies tested the efficacy of risperidone augmentation as maintenance therapy versus placebo [89,90]. In the first 6-week trial, the primary end point was the rate of response and remission based on changes in HAM-D scores from baseline to the end of treatment [86]. According to the results, both remission and response rates were significantly higher in risperidone augmentation (24.5 and 46.2%, respectively) than in placebo treatment (10.7 and 29.5%, respectively). Such differences in both remission and response rates were evident from week 4 between the two groups. In addition, the mean change in HAMD-17 total score was also statistically greater with risperidone augmentation (-16.2) than with placebo (-13.4), with an observed difference of 2.8 points. A small-scale RPCT [87] has also supported the efficacy of risperidone augmentation for TRD versus placebo treatment, in which the primary end point was severity of suicidality, determined using the Beck Scale for Suicide Ideation (BSSI). Both groups demonstrated a 22% reduction in BSSI scores after week 1 of treatment, and an additional 20% reduction was seen in the risperidone group by the end of week 8 of treatment, although such a difference was not significant between the two groups. However, risperidone showed significantly more reduction in MDD core symptoms (separated from week 2 and throughout the study) and impulsivity than placebo treatment. In another RPCT, the primary outcome measure was remission, defined as a MADRS score ≤10 [88]. By the end of the 4-week treatment, statistically significant improvements in the rate of response (54.8 vs 33.3%) and remission (51.6 vs 24.2%) were observed in the risperidone group compared with placebo. A maintenance efficacy of risperidone augmentation (n = 241) was investigated in 241 TRD patients with one to three documented failed antidepressant trials, a failed prospective citalopram monotherapy trial, and response to risperidone augmentation of citalopram for 24 weeks [89]. The relapse rates were 53.3% for risperidone and 54.6% for placebo, respectively, although the median time to relapse was numerically longer with risperidone augmentation (102 days) than with placebo (85 days). The second maintenance study (n = 63) was also similarly designed with the study by Rapaport *et al*. In this study, the relapse rate was 56% with risperidone and 65% with placebo, without statistical difference. Although the median relapse time was numerically longer (105 days) with risperidone than with placebo (57 days), this trial was clearly underpowered to detect significant differences between groups.

Table 5. Randomized, double-blind, placebo-controlled clinical trials of olanzapine in major depressive disorder.

Study (year)	Duration (weeks)	Patients (n)	Primary end point	Response and remission rates	Ref.
TRD					
Shelton *et al.* (2001)	8	FOX/PBO (n: 10), OLZ/PBO (n: 8), OLZ/FOX (n: 10)	*MADRS total score change: -1.2 vs -2.8 vs -13.6	Response: 10 vs 0 vs *60% (vs OLZ), respectively Remission: NA	[75]
Shelton *et al.* (2005)	8	OLZ (6–12 mg/day)/FOX (25–50 mg/day; n: 146), OLZ (6–12 mg/day, n: 144), FOX (25–50 mg/day; n: 142) or NTP (25–175 mg/day; n: 68)	MADRS total score change: -8.7 vs -7 vs -8.5 vs -7.5	Response: 27.5 vs 19.3 vs 28.9 vs 30.3%, respectively Remission: 16.9 vs 12.9 vs 13.3 vs 18.2%, respectively	[76]
Corya *et al.* (2006)	12	OLZ/FOX (n: 243), OLZ (n: 62), FOX (n: 60) or VFX (n: 59)	MADRS total score change: -14.1* (vs OLZ and FOX but VFX) vs -7.7 vs -11.7 vs -13.7	Response: *43.3 (vs OLZ) vs 25.4 vs 33.9 vs 50%, respectively Remission: *29.9 (vs OLZ) vs 13.6 vs 17.9 vs 22.4%, respectively	[77]
Thase *et al.* (2007)†	8	OLZ/FOX (n: 200), OLZ (n: 199) or FOX (n: 206)	*MADRS total score change: -12.7 vs -8.8 vs -9, respectively	*Response: 40.4 vs 25.9 vs 29.6%, respectively Remission: 27.3 vs 14.7 vs 16.7%, respectively	[78]
Psychotic MDD					
Rothschild *et al.* (2004)†	8	OLZ (5–20 mg/day; n: 90), OLZ (5–20 mg/day)/FOX (20–80 mg/day; n: 45) or PBO (n: 94)	HAMD-24 total score change Trial 1: -14.9 vs -20.9* (vs PBO) vs -10.4, respectively Trial 2: -13.9 vs -15.8 vs -12.5, respectively	Response: Trial 1: 34.9 vs 63.6%* (vs PBO) vs 28%, respectively Trial 2: 36.2 vs 47.8 vs 31.8%, respectively Remission: Trial 1: 12 vs 23; vs 8%, respectively Trial 2: 15 vs 17; vs 14%, respectively	[79]
Meyer *et al.* (2009)	12	OLZ/SERT (n = 129) and OLZ/PBO (n = 130)	Remission: HAMD score of ≤10 at two consecutive assessments	*Remission: 41.9 vs 23.9%	[80]

†Two studies published together.
*$p < 0.05$, otherwise not significant.
FOX: Fluoxetine; HAMD: Hamilton Depression Rating Scale; MADRS: Montgomery Åsberg Depression Rating Scale; MDD: Major depressive disorder; NTP: Nortriptyline; OLZ: Olanzapine; PBO: Placebo; SERT: Sertraline; TRD: Treatment-resistant depression; VFX: Venlafaxine.

Risperidone was also tested in comparison with various augmentation agents in a recent RCT, 225 TRD patients were randomly assigned to receive an 8-week treatment of paroxetine 20 mg/day augmented with 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) [91]. The primary outcome was the remission rate defined as the HAMD-17 total score of ≤7. The remission rates were 26.7% for risperidone, 48.7% for valproate, 32.6% for buspirone, 42.6% for trazodone and 37.5% for thyroid hormone, without statistical significance among treatment groups, as well as in secondary outcome measures and AEs.

The overall tolerability and safety findings for risperidone augmentation short-term and long-term trials in TRD were similar with the known profile of the medication in other psychiatric disorder populations. In general, risperidone augmentation was found to be safe and tolerated for the treatment of TRD and in most trials, the mean dose of risperidone was less than 2 mg/day. The most commonly reported AEs associated with risperidone use included headache, dry mouth, increased appetite, weight gain, dizziness, fatigue and insomnia across the five trials. Extrapyramidal effects were uncommon. In fact, the development of dyskinesia, dystonia, akathisia and parkinsonism were closely monitored with diverse rating scales, and there were no significant differences between risperidone and placebo treatments in the two large scale RPCTs [86,89]. In the first maintenance trial, the only potentially clinically meaningful laboratory abnormality was the mean prolactin level at end point (35.5 ng/ml with risperidone vs 6.6 ng/ml with placebo) [89]. Galactorrhea was reported in 2.5% of risperidone-treated patients but none of the placebo-treated subjects. The mean weight change was 1.3 kg with risperidone augmentation and -0.5 kg with placebo augmentation. The summary of controlled clinical trials of risperidone is presented in Table 6.

Ziprasidone

There has been only one RPCT [92] for ziprasidoen monotherapy and two open-label studies [93,94] in the treatment of MDD. In one open-label 6-week study involving 20 MDD patients who showed an inadequate antidepressant response [93], eight (61.5%) and five (38.5%) patients were found to show response and remission based on HAMD-17 total score improvement from baseline during the study. In a subsequent randomized open-label 8-week study (n: 64), the mean change in MADRS total score in ziprasidone 80 mg/day augmentation, ziprasidone 160 mg/day augmentation and sertraline monotherapy, was -6.0, -8.3 and -4.5, respectively, without group differences. Likewise, although the response rates were also numerically higher with ziprasidone than with sertraline monotherapy, no significant differences were found for these groups: 19% versus 32% versus and 10%, respectively. Overall, these preliminary studies have suggested some potential clinical benefit of ziprasidone augmentation for MDD. In these open studies, ziprasidone augmentation was also safe and tolerable in patients with MDD.

In the recently published 12-week RPCT of ziprasidone monotherapy that was divided into two 6-week periods by the sequential parallel comparison design [92], 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 primary end point was the mean change in HAMD-17 total score from baseline. However, the study completely failed to find statistically significant difference in the reduction of depressive symptoms, response rates, or remission rates measured by various rating scales, between ziprasidone- and placebo-treated patients. The most common AEs were sedation/fatigue, followed by dry mouth, constipation and increased appetite, of which only the incidence of sedation/fatigue (16.2%) was statistically higher with ziprasidone than with placebo (2.4%). There were no statistical differences in perturbation in metabolic and cardiac parameters with the exception of prolactin between ziprasidone (mean: 2.6 ng/ml at week 12) and placebo (0.2 ng/ml). However, the difference in prolactin was not clinically relevant.

Amisulpride

Although amisulpride has not yet been approved for the treatment of MDD, its clinical effect as monotherapy or augmentation therapy for the treatment of MDD or dysthymia has been investigated in a number of small-scale, open-label studies [95,96] and RPCTs [97–104] to date. In these studies, amisulpride augmentation was compared with paroxetine monotherapy in an open-label study [95], while the other studies compared amisulpride monotherapy with placebo [100,102], various antidepressant monotherapy (paroxetine [96,98], fluoxetine [101], amineptine [100], amitriptyline [99], imipramine [102], viloxazine [103] and sertraline [104]) and other psychotropic agent (acetyl-L-carnitine [97]). Amisulpride demonstrated its comparable efficacy with various antidepressants and superiority over placebo in all studies based on various primary end points, while some AEs (e.g., female hormone disturbance) were more frequent with amisulpride than other treatment agents, although overall safety and tolerability profile was not significantly different compared with such comparators. For instance, a study investigated the effect of amisulpride monotherapy in comparison with paroxetine monotherapy for the treatment of MDD (n = 272) [98], and this study was designed as a noninferiority trial based on the proportion of responders by the primary end point of HAMD-17 total score change at the end of treatment, with a maximal allowable difference of 15%. According to the results, a high response rate was achieved in both treatments. The percentage of responders at the end of treatment was 76% with amisulpride and 84% with paroxetine, showing the group difference of 8%. However, no guidelines for defining equivalence (15% difference margin) between the two antidepressant agents are available so far. No group differences were evident in all secondary efficacy measures. In this

Table 6. Randomized, double-blind, placebo-controlled clinical trials of risperidone in major depressive disorder.

Study (year)	Duration (weeks)	Patients (n)	Primary end point	Response and remission rates	Ref.
Mahmoud *et al.* (2007)	6	RPR (1 mg/day; n: 141), PBO (n: 133)	HAMD-17 total score change: -10.8 vs -8.2, respectively*	Response: 35.6 vs 18.8%* Remission: 24.5 vs 10.7%*	[86]
Reeves *et al.* (2008)	8	RPR (0.25–2 mg/day; n: 12), PBO (n: 11)	Reduction in suicidality based on BSSI: -13.9 vs -5.7, respectively*	NA	[87]
Keitner *et al.* (2009)	4	RPR (0.25–3 mg/day; n: 64), PBO (n: 30)	Remission: MADRS score of ≤10 at two consecutive assessments	Response: 54.8 vs 33.3%* Remission: 51.6 vs 24.2%*	[88]
Rapaport *et al.* (2006)	24	RPR (0.25–2 mg/day; n: 123), PBO (n: 120)	Relapse prevention: relapse rates were 53.3 and 54.6%, respectively	Median time to relapse was 102 days with RPR and 85 days with PBO	[89]
Alexopoulos *et al.* (2008)		RPR (0.25–1 mg/day; n:32), PBO (n: 31)	Time to relapse	105 days and 57 days in the RPR and PBO groups, respectively	[90]

*$p < 0.05$, otherwise not significant.
BSSI: Beck Scale for Suicidal Ideation; HAMD: Hamilton Depression Rating Scale; MADRS: Montgomery Åsberg Depression Rating Scale; NA: Not available; PBO: Placebo; RPR: Risperidone.

trial, amisulpride was as tolerable as paroxetine, fewer patients reported at least one AE in the amisulpride group compared with the paroxetine group (26.3 versus 34.8%, respectively). Another 3-month, open-label study that included 60 patients with dysthymia and compared paroxetine monotherapy with paroxetine plus amisulpride in an outpatient setting, in which amisulpride augmentation therapy resulted in a better outcome in terms of social functioning [95]. The percentages of patients classified as responders and remitters were 54 and 32% with paroxetine monotherapy and 56 and 44% in the amisulpride augmentation therapy, without group differences. The proportion of patients experiencing at least one AE was similar and such AEs were also tolerable for both groups. As for specific AEss, no significant differences between groups were detected. However, it should be noted that galactorrhea was observed in four (18.2%) and menstrual disorder in two (9.1%) female patients with amisulpride augmentation therapy, whereas no such AEs occurred with paroxetine monotherapy. A summary of controlled clinical trials of amisulpride is presented in Table 7.

Other SGAs

Asenapine, iloperidone, setindole and lurasidone have not been tried in the treatment of MDD to date. Only one case report is available for paliperidone in the treatment of TRD [105]. In this case report of a 54-year-old female inpatient (duration of illness: 5 years), 3 mg/day of paliperidone was added to venlafaxine-XR to 37.5 mg/day (venlafaxine-XR 225 mg for 3 weeks before commencement of paliperidone). Six days after beginning the paliperidone augmentation, the patient reported improvement in her depressive symptoms, especially in mood, sleep and energy level; her HAM-D score had also decreased by 40%. During the next 2 weeks, the patient achieved full remission and also maintained it for 4 months. No serious adverse effects of paliperidone, such as EPSs or orthostatic hypotension were observed.

It may be assumed that the effect of paliperidone in the treatment of MDD should stem from potent antagonism for 5-HT2A, 5-HT7 and α2-adrenergic receptors [31,105]. In addition, although asenapine has not been approved for the treatment of MDD, it has been indicated for the treatment of manic or mixed episodes associated with bipolar I disorder with or without psychotic features as well as maintenance treatment for bipolar I disorder as adjunctive therapy with either lithium or valproate in adults [106]. Iloperidone, setindole and lurasidone may also have some potential in the treatment of MDD, since they have pharmacologically relevant potential action mechanisms like other SGAs as presented in Table 2.

Expert commentary

Evidence supporting beneficial effects and tolerability of SGAs for the treatment of MDD (TRD) as augmentation or monotherapy has been increasing, in particular, for those who respond to their current antidepressants despite of adequate dose and duration of treatment. With such mounting clinical data, aripiprazole was the first approved as an augmentation agent for the treatment of MDD followed by quetiapine XR and the combined agent of olanzapine plus fluoxetine (Symbiax) has received an indication for TRD. However, unlike aripiprazole or quetiapine XR, olanzapine itself has not yet been approved as an augmentation agents for the treatment of MDD or TRD. Other SGAs such as ziprasidone, asenapine, iloperidone, setindole and lurasidone have not received such indication, although they have potentially promising and putative action mechanisms as augmentation agent to antidepressants in their pharmacodynamic property. Some SGAs also demonstrated such potential in well-controlled clinical trials.

Despite considerable evidence that proposes SGAs may be a viable treatment option as an augmentation agent for the treatment of MDD or TRD, there are a number of issues that need to be addressed. Augmentation, combination, and switching strategies are currently available as pharmacological next treatment options for inadequate responders to current antidepressants. However, no supporting data are available regarding superiority of one strategy over other treatment options. As was seen in surveys with clinicians and treatment choice in the STAR*D trial, augmentation is potentially favoured in partial responders [2,107–111]. Indeed augmentation therapy may sustain the initial response from current antidepressant, and thereby supposed to show additional effects with such antidepressants, while switching therapy may lose such effects. Combination approaches are also common in clinical practice and broadly similar with augmentation therapy in advantage profile; however, the evidence is quite limited. Recently, it was investigated whether antidepressant combination should produce a higher remission rate in first-step acute-phase (12 weeks) and long-term (7 months) treatment compared with antidepressant monotherpay in the CO-MED trial [112], in which the remission and response rates including most secondary outcomes were not different among treatment groups at 12 weeks and 7 months, while the mean number of worsening AEs was higher with antidepressant combination than with monotherapy [113].

It is also unknown how the actual efficacy of combination therapy can be accurately evaluated, in particular, when we commence both antidepressants simultaneously, which antidepressant efficacy should come first? In addition, the beneficial effects of SGAs in comparison with other augmentation agents, including lithium, stimulants, omega-fatty acids, 5-HT1A partial agonists and thyroid hormone, which have been commonly used in clinical practice, are clear despite being insufficiently supported by well-controlled clinical trials and not being officially approved for treating MDD. Moreover, how can we differentiate the true augmentation effect from current antidepressants since SGAs are usually added after some period of current antidepressant commencement (e.g., delayed antidepressant effect). How is the comparative efficacy or other clinical usefulness among SGAs? No such direct comparison clinical trials that used different SGAs for treating MDD are available. A recent meta-analysis [11] of 16 studies including 3480 subjects and using four SGAs (olanzapine, risperidone, quetiapine and aripiprazole) showed the pooled odds ratio of SAG augmentation versus placebo remission rate was two,

Table 7. Randomized, double-blind, placebo-controlled clinical trials of amisulpride in major depressive disorder and dysthymia

Study (year)	Duration (weeks)	Patients (n)	Primary end point	Response and remission rates	Ref.
Zanardi and Smeraldi (2006)	12	AMSP (50 mg/day; n: 94), ALCAR (1000 mg/day; n: 99)	HAMD-21 total score change: -10.8 vs -10	Response based on proportion of patients showing CGI-I scores on 1 or 2: 64.4 vs 65.5% Remission: NR	[97]
Cassano and Jori. (2002)	8	AMSP (50 mg/day; n: 137), paroxetine (20 mg/day; n: 138)	Responder rate (50% decrease in HAMD-17 total score) at end point, with a maximal allowable difference of 15%	Response: 76 vs 84% Remission based on HAMD-17 (≤8): 60 vs 64%	[98]
Ravizza (1999)	24	AMSP (50 mg/day; n: 93), amitriptyline (25–75 mg/day; n: 46)	Incidence of treatment-emergent adverse events: 64 vs 73%	Response based on MADRS: 60 vs 62% Remission: NR	[99]
Boyer *et al.* (1999)	12	AMSP (50 mg/day; n: 104), amineptine (200 mg/day; n: 111), PBO (n: 108)	Response based on proportion of patients showing CGI-I scores of 1 or 2	*Response: 69 vs 74 vs 38% *Remission based on MADRS (≤10): 50.5 vs 49.5 vs 21.9%	[100]
Smeraldi (1998)	12	AMSP (50 mg/day; n: 139), fluoxetine (20 mg/day; n: 129)	Responder rate (50% decrease in MADRS total score)	Response: 74 vs 87% Remission: NR	[101]
Lecrubier *et al.* (1997)	24	AMSP (50 mg/day; n: 73), imipramine (50–100 mg/day; n: 73), PBO (n: 73)	HAMD-21 total score change and responder rate based on proportion of patients showing CGI-I scores on 1 or 2: -12.7* vs -12.2* vs -7.6	Response: 72.2* vs 68.6* vs 33.3% Remission based on MADRS (≤7): 35.6 vs 32.9 vs 21.9%	[102]
Amore and Jori (2001)	12	AMSP (50 mg/day; n: 157), sertraline (50–100 mg/day; n: 156)	Time to onset of initial improvement in baseline HAMD-21 (≥25%): *AMSP (11 days) < sertraline (15 days)	Response based on HAMD-21: 84 vs 79% Remission (≤6 in HAMD-21): 74 vs 68%	[104]

*p < 0.05, otherwise not significant.
ALCAR: Acetyl-L-carnitine; AMSP: Amisulpride; CGI-I: Clinical Global Impression-Improvement; HAMD: Hamilton Depression Rating Scale; MADRS: Montgomery Åsberg Depression Rating Scale; NR: Not reported; PBO: Placebo.

and the number needed to treat was nine without heterogeneity among studies: the pooled remission rates were 30.7% for SGAs and 17.2% for placebo. However, the mean odds ratios did not differ among the SGAs and were not affected by trial duration or method of establishing treatment resistance in each clinical trial. Hence, large, well-controlled, direct comparison studies between SGAs, SGAs and other augmentation agents, and augmentation and nonpharmacological treatment options would address the aforementioned clinical issues.

When can we consider SGA augmentation treatment for our patients? Considering currently available findings from SGA augmentation trial design, the fact that acute remission rates in MDD are greatest with the first two sequential treatments [114], and clinical consensus for antidepressant treatment failure [115,116], at least two antidepressant failures would be reasonable in such patients with MDD [42–44]. In addition, the proper timeline after commencing antidepressant should be explored more in future studies. How about prescribing SGA for first-onset or drug-naive patients? A recent study has suggested that a low-dose aripiprazole (2.5 mg/day) could augment the efficacy of regular-dose of sertraline in treatment-naive MDD patients [117], indicating augmentation of SGA may also be used in earlier treatment stages for patients with MDD. However, this strategy should wait until there is more adequate information to draw any definite conclusion on this issue.

There is no official guideline or definite study results on the adequate duration of SGA augmentation therapy, although some longer-term studies may propose that SGA augmentation therapy may be allowed until 52 weeks. However, quetiapine was tested, which showed its efficacy as a monotherapy in a placebo-controlled longer-term trial [62] but risperidone augmentation longer-term trials [89,90] have failed. A longer-term study of aripiprazole was not a placebo-controlled study [54]. Hence, drawing firm conclusions cannot be made regarding the long-term use of SGAs for MDD at this point. Prospectively designed controlled studies concerning proper time to discontinue SGA augmentation for MDD will address this issue. This inadequate evidence still warrants the discretion of clinicians as they weigh potential treatment benefits with potential risks associated with the availability of limited long-term study data.

There has been no clinical trial data of SGA augmentation for childhood and adolescent patients with MDD, and only limited data are available in older patients with MDD. In a subanalysis of aripiprazole augmentation pooled results, aripiprazole augmentation was also effective in improving depressive symptoms in older patients (50–67 years old) [50]. The results from an open trial of

aripiprazole augmentation for late-life MDD (n: 20; 50% remission rate after aripiprazole augmentation) [37] are also in line with the pooled subanalysis results [50]. Quetiapine XR monotherapy was superior to placebo in elderly patients (≥66 years of age) and risperidone augmentation was also tested but not effective in relapse prevention in an elderly population in a 6-month study. Clinicians may need to be very careful in prescription of SGAs in such populations due to a lack of clinical data, multiple treatment regimen issues in older patients, pharmacokinetic aspects, drug–drug interaction and metabolic AEs.

According to STAR*D trial, most participants (85%) had a chronic and/or recurrent course [118], although it was not intended to recruit such patients for the study. In this study, recurrent and/or chronic course was differentially associated with clinical variables, for example, chronic index episode was associated with greater sociodemographic disadvantage, while recurrent episodes were involved with an earlier age of onset and greater family histories of depression and substance abuse [118]. Remission rates were lowest and slowest for those with chronic index episodes and even in remitters, relapse was most likely for the chronic and recurrent patients [118]. With this regard, there has been no RPCT for SGA augmentation in patients with chronic and/or recurrent MDD. Only one open-label study has supported a role of aripiprazole and venlafaxine combination for such patients, demonstrating a potential role of SGA in the treatment of chronic or recurrent MDD (~70% achieved remission at some point during the trial and 66% achieved remission at study exit) [119]. This point should also be more explored in future studies.

As seen in aripiprazole and quetiapine XR pooled subanalyses, SGA augmentation or monotherpay should also be beneficial in the treatment of MDD regardless of subtypes of MDD (i.e, atypical vs non atypical, anxious vs non anxious, minimal responder vs partial responders and elderly vs non elderly populations) [51,73] and severity of core depressive symptoms [52]. In addition, risperidone augmentation was also beneficial in the reduction of suicidal ideations in MDD patients who have developed high-risk suicidal ideation during a depressive episode [87]. Therefore, the practical role of SGAs in the treatment of a specific subpopulation of MDD should be firmly evaluated in larger controlled clinical trials.

Despite SGAs having demonstrated their efficacy for the treatment of MDD in Western populations, studies with Asian populations are still very limited, and current Asian clinical data suggest some differences in various aspects of SGAs use in MDD (e.g., low dose, pharmacological pharmacokinetics) [117,120]. Further controlled clinical trials and analyses of benefit/risk ratios of currently approved SGAs with various antidepressants are greatly needed in Asian populations [121–125].

Overall the tolerability and safety findings for short-term and long-term SGAs trials in MDD were comparable with the known profile of the medication in other psychiatric disorder population. However, it appears to show more AEs than antidepressant monotherapy in patients with MDD [11]. The discontinuation rates due to any AEs were significantly higher for SGAs augmentation than for antidepressant monotherapy based on a large meta-analysis (odds ratio: 3.91) [11]. Each SGA showed a more specific AE profile in such MDD trials. In fact, the incidence of akathisia for aripiprazole augmentation was approximately four-times higher than that seen in schizophrenia trials [126]. Likewise a recent meta-analysis also suggests that patients with bipolar disorders, especially in bipolar depression, appear more vulnerable to present EPSs than those with schizophrenia [127]. It still remains whether MDD patients also have an elevated risk or susceptibility of developing EPSs. Other SGAs have also demonstrated potentially different AE profiles [128]. An elevated risk of weight gain is commonly seen in all SGAs. However, an OFC is more strongly associated with profound weight gain, whereas risperidone and quetiapine XR show more prolactin increase and sedation, respectively, compared with placebo [11]. Increasing evidence indicates that both MDD and the metabolic syndrome, albeit distinct, often co-occur and are possibly subserved by overlapping pathophysiology and causative mechanisms [129]. Contemporary antidepressants themselves may substantially impact on development of the metabolic syndrome [129]. Therefore, clinicians should routinely monitor for cardiometabolic AEs effects and EPSs during SGAs augmentation in clinical practice [130].

Currently, a number of treatment guidelines have been developed to provide clinical evidence and practical recommendations for the management of patients with MDD, incorporating integration of clinical trial data-driven evidence, clinical expertise and meta-opinion from different parts of the world. Despite some differences among such guidelines, there are broad areas of agreement in approaches for managing MDD. For instance, the Canadian Psychiatric Association and the Canadian Network for Mood and Anxiety Treatments (CANMAT) [131] guidelines consider augmentation strategy to be among the best validated pharmacological treatments for TRD: Level 1 evidence for SGA augmentation and lithium for patients who have inadequate response to the initial antidepressant, Level 2 for T3 and bupropion and Level 3 for buspirone, other antidepressants, methylphenidate, modafinil and pindolol. Unlike the American Psychiatric Association guidelines, the CANMAT guidelines differentiate evidence of each SGA augmentation. Aripiprazole (Level 1), olanzapine (Level 1) and risperidone (Level 2 evidence) are recommended as first-line agents, while quetiapine (Level 2) is recommended as second-line and ziprasidone (Level 3) is considered a third-line agent. Some guidelines are more conservative in recommending SGA augmentation for MDD. The German guidelines compiled by the German Society of Psychiatry, Psychotherapy and Neurology do not routinely recommends SGAs for such patients, although SGAs are reserved for psychotic MDD [132]. Further research data should delineate the clear position and role of SGAs in the treatment of MDD. Therefore, contemporary practice guidelines should be considered as one of the useful frameworks for the management of MDD, and its use should be prudent in conjunction with informative individual patient clinical factors, other proven clinical data sources and the application of clinical wisdom.

Five-year view

Although adjunctive SGAs treatment for the acute treatment of MDD is an advanced treatment option, there are a number of issues to be resolved: proper time to intervention, optimal patient population (presently there is no limitation in this regard), duration of treatment, treatment response and AEs predictors, use of special populations, long-term use treatment, subgroup issues, best-matched antidepressant, dosing issues (especially considering pharmacokinetic and genetic differences between Western and Asian population) and pharmacoeconomic cost/benefit assessment of adjunctive aripiprazole compared with unproven agents on an empirical trial-and-error basis.

Currently available data suggest that SGAs may be a tolerable and effective short-term treatment for patients with MDD who are inadequate responders to antidepressants regardless of the class. In addition, adjunctive quetiapine XR and aripiprazole maintained adequate effectiveness and showed tolerability for a 52-week long-term trial. Adequately powered and well-designed studies will more precisely address clinically valuable and practical information about the use of adjunctive SGAs for treating patients with MDD.

Finally, currently available findings warrant that clinicians consider the potential risk/benefit on a patient-by-patient basis when making a decision to prescribe adjunctive SGAs.

Financial & competing interests disclosure

This study was supported by a grant from the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (A120004). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Antidepressants have been the standard treatment option for major depressive disorder (MDD) based on the monoamine hypothesis.
- A number of open-label studies, well-controlled clinical trials and meta-analysis have suggested the limited efficacy of antidepressant monotherapy for the treatment of MDD.
- To treat difficult-to-treat patients with MDD, some next treatment options including augmentation, combination and switching strategies are available and such treatment strategies should be tailored and properly tried for patients with MDD, in a person-to-person basis.
- Among the different second treatment options for the treatment of MDD, augmentation treatment has some favorable points compared with the combination and switching option.
- Atypical antipsychotics showed some relevant pharmacological profiles as antidepressant effects through preclinical and pilot clinical studies.
- Olanzapine plus fluoxetine, quetiapine extended release and aripiprazole have clearly demonstrated efficacy for the treatment of MDD or treatment-resistant depression in a number of small-scale, open-label studies or randomized, placebo-controlled clinical trials and they have been recently approved by authority agencies in many countries.
- Evidence-based practice guidelines also recommend augmentation of atypical antipsychotics for treating MDD, but they are substantially different in a way of practical recommendation for clinical practice.
- Currently available findings require clinicians to consider the potential risk/benefit on a patient-by-patient basis when making a decision to prescribe adjunctive atypical antipsychotics as next treatment option for MDD, since a number of issues are involved in prescription of antipsychotics for MDD patients.

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