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REVIEW ARTICLE

Augmentation Treatments with Second-generation Antipsychotics to Antidepressants in Treatment-resistant Depression

Masaki Kato · Chia-Ming Chang

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Abstract Various classes of antidepressants have been used in the treatment of major depressive disorder (MDD); however, the efficacy of these treatments remains uncertain. A number of well-controlled clinical trials, meta-analyses and practical clinical studies have found that approximately 30 % of MDD patients remit following antidepressant treatment, leaving approximately 70 % of patients with significant residual symptoms. In these latter patients with what is considered treatment-resistant MDD, typical antipsychotics have sometimes been administered in order to augment the antidepressant effects but safety and tolerability concerns significantly reduce their usage in MDD patients. The advent of second-generation antipsychotics (SGAs), which have diverse pharmacodynamic profiles relative to antidepressants, has dramatically increased the usage of such drugs for patients with MDD. Recently, SGAs such as aripiprazole, quetiapine and olanzapine in combination with fluoxetine have been approved for the treatment of MDD, especially in the case of treatment resistance. This article reviews the efficacy and tolerability of SGA augmentation when added to antidepressant therapy for treatment-resistant MDD patients in acute phase studies published to date.

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M. Kato (✉)
Department of Neuropsychiatry, Kansai Medical University, 10-15 Fumizono-cho, Moriguchi, Osaka 570-8506, Japan
e-mail: masaki.kato@unibo.it

C.-M. Chang
Department of Psychiatry, Chang Gung Memorial Hospital at Linko and College of Medicine, Chang Gung University, Taiwan, Republic of China

1 Introduction

Major depressive disorder (MDD) is a debilitating disease with a lifetime prevalence of 16 % [1] that imposes significant burdens not only on the patients themselves but also on those around them and general social health. MDD is associated with serious consequences, including suicide, which have a substantial negative impact with both direct and indirect costs worldwide. A lower prevalence of MDD (1–7 %) has been reported in Asian countries such as Japan, Korea, Taiwan and Hong Kong relative to western countries [2, 3], but the suicide rates in Japan and Korea are among the highest in the world. The treatment-resistant state of depression could relate to this high suicide rate, which is obviously an issue of concern. Even though the ever-expanding options for antidepressants have revolutionized the treatment of mood disorders, treatment efficacy is inadequate, as 60–70 % of patients do not experience remission. The efficacy of antipsychotics in treating depressive symptoms has previously been confirmed [4] but tolerability issues such as extrapyramidal side effects and over-sedation have limited the use of such drugs when treating MDD. Recently, however, the introduction of second-generation antipsychotics (SGAs), with varied neuropharmacological profiles with improved efficacy and fewer side effects relative to conventional antipsychotics, has rekindled interest in the use of this class of drugs to treat mood and anxiety disorders, including as an adjunctive therapy [5, 6]. Therefore, this study reviews the efficacy and tolerability of SGA augmentation in conjunction with

antidepressant therapy for treatment-resistant depression (TRD) in acute-phase studies published to date.

2 Second-generation Antipsychotic Indications in Major Depressive Disorder (USA, Asia)

Several SGAs are available in the USA (Table 1), including three that are approved for indications related to MDD. In 2007, aripiprazole (Abilify) was the first drug to obtain US Food and Drug Administration regulatory approval for the adjunctive treatment of MDD in conjunction with antidepressants. This was soon followed by the quetiapine-XR formulation (Seroquel) and olanzapine in combination with fluoxetine (OFC; Symbyax) in 2009, when these drugs received approval from the US Food and Drug Administration for the acute treatment of MDD. Other antipsychotics including asenapine, clozapine, lurasidone, iloperidone, pariperidone, risperidone and ziparsidone are not approved for the treatment of MDD.

Although SGAs are not presently available for the treatment of MDD in Japan, aripiprazole is under application, and quetiapine-XR is undergoing clinical trials for TRD. In Korea and Taiwan, aripiprazole and quetiapine are indicated as adjunctive medication for MDD.

3 Meta-analysis of Second-generation Antipsychotic Augmentation in Treatment-resistant Depression

3.1 Summary of Protocol for Meta-analysis

Two meta-analyses have reviewed SGA efficacy as an augmentation therapy with antidepressant medications in TRD patients [5, 6]. In 2009, Nelson and Papakostas [5] performed a meta-analysis of four of 10 SGAs used in 16 acute-phase (up to 12 weeks), parallel-group, double-blind, placebo controlled trials involving the random assignment of a total of 3,480 patients to adjunctive treatment with an SGA ($n = 2{,}014$) or a placebo ($n = 1{,}466$). Here, patients had to have nonpsychotic MDD that was considered treatment resistant either by history or as determined by a prospective trial. The subjects who showed: (1) response to therapy, defined as an improvement of 50 % or greater from baseline to endpoint on the Hamilton Depression Rating Scale (HAM-D) or the Montgomery Åsberg Depression Rating Scale (MADRS); (2) remission, defined according to each individual trial; and (3) discontinuation were extracted from included trials and entered into the meta-analysis using a fixed-effects model. In a 2010 Cochrane Reviews report, Komossa et al. [6] evaluated meta-analysis results for five SGAs used in 28 parallel-group, double-blind trials that had no limits in terms of

Table 1 Second-generation antipsychotics: indications in major depressive disorders

Drug	Indication for MDD	USA	Korea	Taiwan	Japan
Aripiprazole	Adjunctive treatment of MDD (efficacy established in adult patients with MDD who had an inadequate response to antidepressant therapy during the current episode)	○	○	○	□
Asenapine	None	×	×	×	×
Clozapine	None	×	×	×	×
Iloperidone	None	×	×	×	×
Lurasidone	None	×	×	×	×
Olanzapine	As OFC, acute treatment of TRD (MDD in adults who do not respond to two separate trials of different antidepressants of adequate dose and duration in the current episode)	○	×	×	×
Paliperidone	None	×	×	×	×
Quetiapine	As quetiapine XR, adjunctive therapy to antidepressants for the treatment of MDD (efficacy established in adults with MDD who had an inadequate response to antidepressant treatment)	○	○	○	×
Risperidone	None	×	×	×	×
Ziprasidone	None	×	×	×	×

○ approved, □ under application, × not currently approved

MDD major depressive disorder, *OFC* olanzapine–fluoxetine combination, *TRD* treatment-resistant depression, *XR* extended release

study duration and comparator used (placebo, benzodiazepine, or an antidepressant). In that study, trials were included in the meta-analysis regardless of whether psychotic features or treatment-resistant symptoms were present. Responses on the HAM-D or MADRS or a 'much improved' score of 1 or 2 on the Clinical Global Impressions Scale was used as the primary outcome in the meta-analysis. MADRS and HAM-D scores at the end of the studies, remissions, relapse (as defined by the authors), anxiety symptoms as assessed by the Hamilton Anxiety Scale at the end of the study, the number of patients who dropped out for any reason including inefficacy of treatment or adverse events, and the number of participants re-hospitalized were used as secondary outcomes in random-effect models. In the analysis by Komossa et al. [6], some studies combined several interventions within one comparison group (e.g. a three-arm study comparing olanzapine, fluoxetine and OFC); thus the total number of participants in the control (placebo) group were divided up among the number of interventions. In the current review, the focus is on the results of the meta-analyses that included only TRD for treatment efficacy and results regardless of treatment resistance for adverse effects. The number needed to treat (NNT) and number needed to harm (NNH) were taken from the risk difference.

3.2 Results for Effectiveness

The meta-analysis by Nelson and Papakostas [5] examined the pooled odds ratios (ORs) of 16 studies including 3,480 subjects and using four SGAs (olanzapine, risperidone, quetiapine and aripiprazole). Among the studies, the pooled OR of augmentation versus placebo response rate was 1.69 [95 % confidence interval (CI) 1.46 to 1.95, $p < 0.00001$], the NNT was nine, and there was no heterogeneity among studies. The overall pooled response rate for treatment with SGAs was 44.2 % compared with 29.9 % for placebo. The remission rate pooled OR was 2.00 (95 % CI 1.69 to 2.37, $p < 0.00001$), and the NNT was nine without heterogeneity among studies. The pooled remission rates were 30.7 % for SGAs and 17.2 % for placebo.

3.2.1 *Aripiprazole*

The pooled OR for three studies ($n = 1{,}065$) in which subjects taking aripiprazole were compared with subjects taking a placebo in conjunction with antidepressants showed a significant benefit for the aripiprazole group in response rate (OR = 2.07, 95 % CI 1.58 to 2.72, NNT = 7, $p < 0.00001$) and remission rate (OR = 2.09, 95 % CI 1.55 to 2.81, NNT = 8, $p < 0.00001$) [5]. The mean difference in the MADRS score at endpoint was −3.04 (95 % CI −4.09 to −2.00, $p < 0.00001$), showing a significant benefit for the aripiprazole group [6].

3.2.2 *Olanzapine*

Analysis of five studies ($n = 1{,}000$) found a statistically significant benefit of olanzapine augmentation treatment in response rate (OR = 1.39, 95 % CI 1.05 to 1.84, NNT = 11, $p = 0.02$) and remission rate (OR = 1.83, 95 %CI 1.30 to 2.56, NNT = 10, $p = 0.0005$) compared with an adjunctive placebo treatment [5]. When the number of control groups was corrected according to the number of interventions, no significant benefit was found in response rate ($n = 808$, OR = 1.43, 95 % CI 0.98 to 2.08), but a benefit was observed in the remission rate ($n = 793$, OR = 1.67, 95 % CI 1.09 to 2.56). The mean difference in MADRS score at endpoint was −2.84 ($n = 808$, 95 % CI −5.48 to −0.20, $p = 0.035$), with a significant difference in favour of olanzapine [6].

3.2.3 *Quetiapine*

The analysis of five studies ($n = 1{,}029$) that used quetiapine augmentation in conjunction with antidepressants showed a statistically significant improvement in response rate (OR = 1.60, 95 % CI 1.24 to 2.08, NNT = 9, $p = 0.0004$) and remission rate compared with adjunctive placebo treatment (OR = 1.89, 95 % CI 1.41 to 2.54, NNT = 8, $p < 0.0001$) [5]. The mean difference in the MADRS score at endpoint was −2.67 ($n = 919$, 95 % CI −4.00 to −1.43, $p = 0.00009$), demonstrating a significant difference in favour of the quetiapine group [6].

3.2.4 *Risperidone*

An analysis of three studies ($n = 336$) revealed a statistically significant benefit of risperidone augmentation over placebo in response rate (OR = 1.83, 95 % CI 1.18 to 2.82, NNT = 7, $p = 0.007$) and remission rate (OR = 2.63, 95 % CI 1.51 to 4.57, NNT = 6, $p = 0.0006$) [5]. The relatively small sample size, approximately 35 % of that in other SGA analyses, along with a broad confidence interval suggests a need for further studies. In fact, the mean difference in HAM-D score at endpoint between risperidone and placebo was not statistically significant ($n = 509$, mean difference −1.69, 95 % CI −4.13 to 0.74) [6].

3.3 Adverse Events and Discontinuation

Nelson and Papakostas [5] reported that the pooled OR for 15 studies ($n = 3{,}508$) comparing SGAs and placebo for the rate of discontinuation due to adverse events was 3.91 (95 % CI 2.68 to 5.72, $n = 15$, $p < 0.00001$) with a higher risk for the SGA group and a NNH of 17 without

heterogeneity among studies. The pooled discontinuation rate due to adverse events was 9.1 % in the SGA group against 2.3 % in the placebo group.

3.3.1 Aripiprazole

An analysis of three studies ($n = 1{,}088$) investigating discontinuation due to adverse effects showed a significantly higher pooled discontinuation rate for the aripiprazole augmentation group compared with the placebo group (OR = 2.68, 95 % CI 1.23 to 5.81, $p = 0.01$, NNH = 38) [5]. The adverse consequences of aripiprazole use manifested as an increased incidence of akathisia (OR = 6.77, 95 % CI 4.22 to 10.84, $p < 0.00001$, NNH = 6) and weight gain (OR = 5.93, 95 % CI 2.15 to 16.36, $p = 0.00058$, NNH = 24), with a mean difference in change from baseline weight of 1.07 kg (95 % CI 0.30 to 1.84, $p = 0.0063$) [6]. No significant difference in the risk of sedation was observed between aripiprazole and placebo.

3.3.2 Olanzapine

An analysis of four studies ($n = 1{,}017$) found a significantly higher pooled risk of discontinuation (OR = 3.85, 95 % CI 2.03 to 7.29, $p < 0.0001$, NNH = 13) with the use of olanzapine compared with placebo [5]. A higher risk of weight gain was also observed in the olanzapine compared with the placebo group (OR = 4.77, 95 % CI 1.82 to 12.50, $p = 0.0015$, NNH = 6); the pooled mean difference in weight change from baseline relative to placebo was 4.58 kg (95 % CI 4.06 to 5.09, $p < 0.00001$) [6]. A significantly higher rate of sedation was also found in the olanzapine group (OR = 3.53, 95 % CI 1.64 to 7.60, $p = 0.0013$, NNH = 8).

3.3.3 Quetiapine

An analysis of five studies ($n = 1{,}011$) found a significantly higher risk of discontinuation due to adverse effects (OR = 5.52, 95 % CI 2.71 to 11.24, $p < 0.00001$, NNH = 11) with the use of quetiapine compared with placebo. Three studies ($n = 995$) found a significantly higher risk of weight gain (OR = 3.06, 95 % CI 1.22 to 7.68, $p = 0.017$, NNH = 31) associated with the use of quetiapine, with a pooled mean difference in weight change from baseline of 1.11 kg (95 % CI 0.56 to 1.66, $p = 0.000078$) relative to placebo. A significantly higher rate of sedation was also observed for the quetiapine group (OR = 8.79, 95 % CI 4.90 to 15.77, $p < 0.00001$, NNH = 6).

3.3.4 Risperidone

An analysis of three studies ($n = 392$) found a trend towards increased withdrawal due to adverse events with the use of risperidone, but the pooled OR reached significance (OR = 2.84, 95 % CI 0.91 to 8.91, $p = 0.07$, NNH = 24), possibly due to the small sample size. No significant differences in weight gain and sedation were observed compared with the placebo group. However, a significant increase in prolactin levels, 29.42 ng/ml, was found when the pooled mean difference from baseline was compared between the risperidone and placebo groups (95 % CI 19.49 to 39.34, $p < 0.00001$).

4 Randomized Controlled Trials of Second-generation Antipsychotic Augmentation in Treatment-resistant Depression

In this section, previous randomized controlled trials (RCTs) for each SGA are reviewed in more detail.

4.1 Aripiprazole

Three 6-week, double-blind RCTs by Berman and colleagues [7, 8] and Marcus et al. [9] presented data on aripiprazole augmentation in conjunction with selective serotonin reuptake inhibitors (SSRIs) and selective serotonin/norepinephrine reuptake inhibitors (SNRIs) compared with adjunctive placebos for TRD (Table 2). In those trials, aripiprazole therapy was initiated at 5 mg/day, with the possibility of decreasing to 2 mg/day if not tolerated, and the dose was titrated up to a maximum of 20 mg/day, with a mean dose of approximately 11 mg/kg at the end of the studies. In all three trials, a benefit of aripiprazole augmentation in terms of treatment efficacy was observed in response rate, remission rate and mean change in the MADRS total score (aripiprazole −8.8, −8.5, −10.1 and placebo −5.8, −5.7, −6.4, respectively) at week 6. When the three trials were pooled, a subpopulation analysis in older patients (50–67 years of age) also showed a greater benefit of aripiprazole augmentation [10]. An open-label nonrandomized trial in a Taiwanese population also reported a benefit in efficacy with aripiprazole [11].

Aripiprazole augmentation in conjunction with antidepressants was generally well tolerated in TRD patients in short-term trials [7–9]. An analysis of tolerability in pooled data from two controlled studies ($n = 737$) found the most common adverse events that occurred in more than 10 % of patients were akathisia (24.8 %) and restlessness (12.1 %) [12]. With aripiprazole, akathisia generally occurred in the first 3 weeks of treatment (76 %) and was of mild to moderate severity; only three (0.8 %) aripiprazole-treated patients discontinued treatment due to akathisia [12]. The mean weight change was significantly greater with adjunctive aripiprazole compared with placebo (1.73 kg versus 0.38 kg), and more patients (5.2 %) receiving

Table 2 Placebo-controlled trials for augmentation therapy with second generation antipsychotics in treatment-resistant depression

	SGA (mean dose, *mean modal dose)	Antidepressant	N (M/F) (mean age)	N Efficacy*/ safety	Duration (weeks)	Primary endpoint	Response rate (%) SGA/placebo	Remission rate (%) SGA/placebo
Berman et al. [7]	Aripiprazole (11.8 mg)	SSRI/SNRI	358 (133/235) (45.4 years)	353/358	6	Mean change in MADRS PLB < APZ	33.7/23.8 $p < 0.05$	26.0/15.7 $p < 0.05$
Marcus et al. [9]	Aripiprazole (11.0 mg)	SSRI/SNRI	381 (127/254) (44.5 years)	369/381	6	Mean change in MADRS PLB < APZ	32.4/17.4 $p < 0.001$	25.4/15.2 $p < 0.05$
Berman et al. [8]	Aripiprazole (10.7 mg)	SSRI/SNRI	349 (94/255) (45.3 years)	343/348	6	Mean change in MADRS PLB < APZ	46.6/26.6 $p < 0.001$	36.8/18.9 $p < 0.001$
Shelton et al. [16]	Olanzapine (*13.5 mg)	Fluoxetine	20 (5/15) (42.0)	20/20	8	Mean change in MADRS PLB < OLZ	60.0/10.0 NS	–
Shelton et al. [15]	Olanzapine (*8.5 mg)	Fluoxetine	288 (87/201) (42.1)	288/288	8	Mean change in MADRS PLB = OLZ	27.5/28.9 NS	#16.9/13.3 NS
Corya et al. [17]	Olanzapine (6 or 12 mg)	Fluoxetine	303 (45.7 years)	286/303	12	Mean change in MADRS PLB = OLZ	43.3/33.9 NS †OC (n = 100, 19)	#29.9/17.9 NS †OC (n = 69, 10)
Thase et al. [18]	Olanzapine (*8.6 mg)	Fluoxetine	406 (44.5 years)	401/406	8	Mean change in MADRS total scores PLB < OLZ	40.4/29.6 $p < 0.05$	27.3/16.7 $p < 0.05$
Thase study 1	Olanzapine	Fluoxetine	206	203/206	8	Mean change in MADRS PLB = OLZ	36.6/29.4 NS	23.8/17.6 NS
Thase study 2	Olanzapine	Fluoxetine	200	198/200	8	Mean change in MADRS PLB < OLZ	44.3/29.7 $p < 0.001$	30.9/15.8 $p < 0.05$
McIntyre and Gendron [22]	Quetiapine (182 mg)	Various antidepressants	58 (44.5 years)	58/58	8	Mean change in HAM-D PLB < QTP	HAM-D 48.0/28.0 NS	HAM-D ##31/17 NS
Bauer et al. [20]	Quetiapine (150, 300 mg)	Various antidepressants	493 (158/329) (45.4 years)	487/491	6	Mean change in MADRS PLB < QTP	150/300/PLB 55.4/57.8/ 46.3 150 mg NS 300 mg $p < 0.05$	150/300/PLB ### 36.1/ 31.1/23.8 150 mg $p < 0.05$ 300 mg NS
El-Khalili et al. [21]	Quetiapine (150, 300 mg)	Various antidepressants	446 (119/313) (45.5 years)	432/445	6	Mean change in MADRS 150 mg NS 300 mg PLB < QTP	150/300/PLB 51.7/ 58.9/46.2 150 mg NS 300 mg $p < 0.05$	150/300/PLB ###35.0/42.5/ 24.5 150 mg NS 300 mg $p < 0.001$
Mahmoud et al. [24]	Risperidone (1 or 2)	Various antidepressants	268 (71/197) (46.1 years)	218/268	6	Mean change in HAM-D-17 PLB < RIS	HAM-D-17 46.2/29.5 $p < 0.01$	HAM-D-17 24.5/10.7 $p < 0.01$
Keitner et al. [26]	Risperidone (1.6 mg)	Various antidepressants	97 (42/55) (45.2 years)	95/95	4	MADRS remission PLB < RIS	54.8/33.3 $p < 0.05$	51.6/24.2 $p < 0.05$
Reeves et al. [25]	Risperidone (1.17 mg)	Various antidepressants	23 (7/16) (44.5 years)	23/23	8	Severity of suicidality (Beck Scale for Suicide Ideation) PLB = RIS	50.0/36.4 NA	33.3/18.2 NA

The data in a meta-analysis by Nelson et al. [5] and the Cochran data [6] were referred. Thase et al. [18] includes two trials (study 1 and study 2). Response was defined as an improvement of ≥50% from baseline to endpoint on the HAM-D or the MADRS, and remission was defined as a MADRS total score of ≤10 and ≥50% reduction in MADRS total score in the trials except trials by Shelton et al. [15] and Corya et al. [17] (two subsequent MADRS total score ≤8), McIntyre and Gendron [22] and Mahmoud et al. [24] (HAM-D-17 score ≤7), Bauer et al. [20], El-Khalili et al. [21] and Keitner et al. [26] (MADRS total score ≤8), trial by Reeves et al. [25] did not predefine response/remission criteria

APZ aripiprazole, *HAM-D* Hamilton Depression Rating Scale, *MADRS* Montgomery Åsberg Depression Rating Scale, *NA* not assessed, *NS* not significant ($p > 0.05$), *OC* observed cases, *OLZ* olanzapine, *PLB* placebo, *QTP* quetiapine, *RIS* risperidone, *SGA* second-generation antipsychotic

*Modal dose, #remission was defined as two subsequent MADRS total scores ≤8, ## remission was defined as HAM-D total score ≤7, ### remission was defined as MADRS total score ≤8, †OC method

aripiprazole than receiving placebo (0.6 %) had a weight gain of 7 % or more [13]. The difference in weight gain with SGA adjunctive therapy was small, and no other adverse event related to metabolic function, such as changes in mean waist circumference, total cholesterol, high or low-density lipoprotein cholesterol, triglycerides, fasting plasma glucose, or haemoglobin A1C, was associated with aripiprazole augmentation in short-term trials. Common adverse events and the severity of these effects were similar in older patients to those in younger aged patients [10]. One study reported the longer-term tolerability of adjunctive aripiprazole treatment in an open-label 52-week trial with 994 patients [14]. Common spontaneously reported adverse events were akathisia (26.2 %), fatigue (18.0 %) and weight gain (17.1 %). The majority (75.2 %) of treatment-emergent adverse events were mild or moderate in nature. No clinically relevant changes in other metabolic parameters were seen.

4.2 Olanzapine

Five trials were performed to evaluate the efficacy of OFC compared with fluoxetine monotherapy in patients with TRD by Shelton and colleagues [15, 16], Corya et al. [17] and Thase et al. [18] (Table 2). Olanzapine was initiated at either 5 or 6 mg/day, and doses were titrated up to a maximum of 12, 18, or 20 mg/day, with a modal dose of 8–13 mg/day at the end of those studies. Of those trials, two found a significant benefit of OFC compared with fluoxetine only for the primary outcome of a mean MADRS score change at endpoint (olanzapine: −13.6, $n = 10$; −14.5, $n = 97$; placebo: −1.2, $n = 10$, −8.6; $n = 101$) [16, 18]. However, three trials found no significant difference (olanzapine: −11.0, $n = 101$, −8.7; $n = 146$; −14.1, $n = 230$: placebo: −9.4, $n = 102$; −8.5, $n = 142$; −11.7, $n = 56$) [15, 17, 18]. Only one trial [18] observed significantly better remission and response rates for OFC therapy. Regarding tolerability, the most common adverse events were metabolic abnormalities including weight gain, altered glucose levels, altered cholesterol levels and increased appetite. When the data were pooled, a clinically significant weight gain of more than 7 % was observed in 40 % of the OFC group, with a mean weight change from baseline of 4.42 kg, which was significantly different from fluoxetine monotherapy [19]. The mean change in glucose level at endpoint for the OFC group (+7.92 mg/dl) was significantly higher than that in the fluoxetine-alone group (+1.62 mg/dl). Similarly, the mean cholesterol level at endpoint was significantly higher for the OFC group (+12.4 mg/dl) relative to the fluoxetine group (+2.3 mg/dl). The rate of appetite increase was also significantly higher in OFC (24 %) than in fluoxetine. The pooled incidences of other adverse events occurring in more than 10 % of cases were dry mouth (18.6 %), somnolence (15.6 %), fatigue (14.0 %) and peripheral oedema (11.2 %).

4.3 Quetiapine

Two 6-week large, double-blind RCTs by Bauer et al. [20] and El-Khalili et al. [21] as well as an 8-week small RCT by McIntyre and Gendron [22] investigated quetiapine augmentation in conjunction with SSRIs/SNRIs compared with adjunctive placebo for TRD (Table 2). In those trials, quetiapine was initiated at 5 mg/day, and the dose was titrated up to a maximum of 150, 300, or 600 mg/day, with a mean dose of 182 mg/day (small 8-week study) and 150 or 300 mg/day (two large 6-week studies) at the end of the trials. The benefit of quetiapine augmentation as assessed by the MADRS total score at endpoint was observed in all studies except the study by El-Khalili et al. [21], which found no significant difference between quetiapine augmentation (150 mg/day) and placebo augmentation in response rate or remission rate at the study endpoint. Furthermore, McIntyre and Gendron [22] found no significant difference in the rates of response or remission between quetiapine and placebo. However, the pooled analysis of the two largest studies ($n = 936$) found a significant benefit of quetiapine augmentation in MADRS total score, response rate and remission rate at week 6 and at the study endpoint compared with placebo augmentation [23]. As for adverse events in this pooled analysis, the most common and clinically significant side effects were somnolence (quetiapine: 300 mg; 26.0 %, 150 mg; 22.5 %; placebo: 3.6 %) and sedation (quetiapine: 300 mg, 17.0 %; quetiapine: 150 mg, 13.0 %; placebo: 4.2 %) [23]. These adverse effects were also the most common reason for withdrawal from the study. Mean weight gains were +1.3 kg, +0.9 kg and + 0.2 kg in the quetiapine-XR 300 mg/day, 150 mg/day and placebo groups, respectively. Moreover, the proportions of patients in each group showing weight gains of 7 % or more were 7.2 %, 3.2 % and 1.7 %, respectively, revealing a dose-dependent increase [23]. Extrapyramidal symptom measures and adverse events were generally low and equal between the quetiapine and placebo groups.

4.4 Risperidone

Three double-blind RCTs [24–26] investigated the effects of risperidone augmentation in conjunction with various antidepressant therapies in patients with TRD (Table 2). In those trials, risperidone was initiated at 0.25–1 mg/day, and the dose was titrated to a maximum of either 2 or 3 mg/day, with a mean dose of 1–2 mg/day at the end of the studies. The primary endpoints and durations varied among the three studies. Mahmoud et al. [24] found that

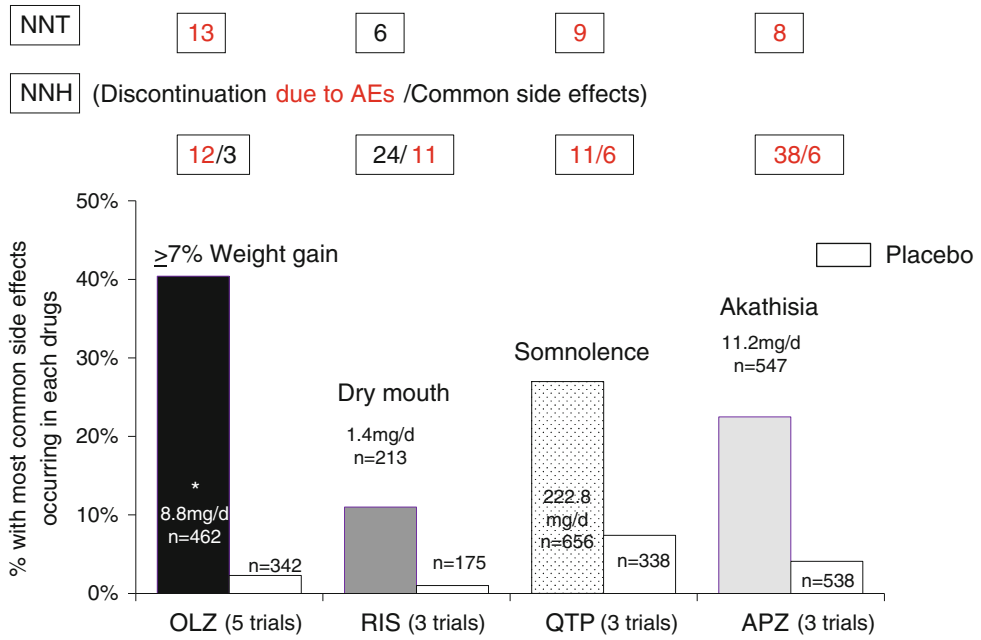

Fig. 1 The number needed to treat (remission rate) and number needed to harm (rates of discontinuation due to adverse events and most common side effects) of each drug (%). Pooled data from controlled trials of olanzapine [19], risperidone [24–26], quetiapine [20, 22], aripiprazole [7–9]. The Cochran data [6] and data in a meta-analysis [5] were referred. Mean doses of risperidone, quetiapine and aripiprazole were shown (*mean modal dose in the olanzapine group). *AE* adverse event, *APZ* aripiprazole, *NNH* number needed to harm, *NNT* number needed to treat, *OLZ* olanzapine, *QTP* quetiapine, *RIS* risperidone

total endpoint scores on the 17-item HAM-D were significantly lower for the risperidone augmentation group (13.4) compared with the placebo group (16.2) in a 6-week study ($n = 274$). Reeves et al. [25] observed no significant difference between risperidone and placebo augmentation in the severity of suicidality as assessed by the Beck Scale for Suicide Ideation, which was the primary endpoint of this 8-week, small-sample ($n = 23$) study. Furthermore, the mean MADRS score change at study endpoint was not statistically significant between the risperidone (−22.1) and placebo group (−14.4). Keitner et al. [26] investigated the remission rate, assessed by MADRS, and found a significantly higher rate for the risperidone group (51.6 %) compared with the placebo group (24.2 %) after 4 weeks in subjects with TRD ($n = 95$). Two studies ($n = 241$ and $n = 63$) evaluated the sustained effect of risperidone over a 6-month period [27, 28]. In both studies, no significant benefit of risperidone was found, and relapse rates were similar in the two studies. In terms of adverse effects, the most common symptoms were somnolence, dry mouth, fatigue, weight gain and insomnia. In the larger study, the rate of extrapyramidal symptoms was not significantly different in risperidone augmentation (akathisia 0.7 %, dystonia 0 %, tremor 0.7 %) compared with placebo augmentation (akathisia 0 %, dystonia 0.8 %, tremor 0.8 %) [24]. In that study, however, subjects treated with risperidone gained significantly more weight (1.3 kg) compared to placebo-treated patients (0.1 kg, $p < 0.001$) [24]. Likewise, clinically significant weight gain was more common with risperidone (8.3 %) in maintenance studies compared with placebo treatment (2.6 %) [29].

5 Risk Benefit Analysis

To bring out the characteristic of each SGA in the clinical site, the NNT for remission rate and the NNH for the rate of discontinuation due to adverse events and the most common adverse events (aripiprazole; akathisia, olanzapine; weight gain, risperidone; dry mouth and quetiapine; somnolence) were calculated (Fig. 1). The data were extracted from nine studies that had all data for the rate of remission, discontinuation due to adverse events and most common adverse effects in each SGA [7, 9, 19, 22–26]. As for treatment efficacy, the NNT was six for risperidone, eight for aripiprazole, nine for quetiapine and 13 for olanzapine. All SGAs have good efficacy with NNT less than 10 except olanzapine, while for discontinuation due to adverse events, the NNH was 11 for quetiapine, 12 for olanzapine, 24 for risperidone and 38 for aripiprazole. A relatively higher risk of adverse event-related discontinuation was observed with quetiapine and olanzapine compared with risperidone and aripiprazole. Weight gain more than 7 % frequently occurred in 40 % of patients treated by

olanzapine with NNH of three. This side effect could be one considerable reason for the higher discontinuation rate. The rate of somnolence induced by quetiapine was approximately 30 % with NNH of six. This common side effects were also associated with a higher risk of discontinuation. The rate (20 %) and NNH (six) of akathisia, which is a common side effects of aripiprazole, were similar to the common side effects of quetiapine; however, there was a relatively lower risk of discontinuation induced by aripiprazole with NNH of 38, indicating that akathisia seems not to be the critical reason for discontinuation. The rate of dry mouth induced by risperidone was approximately 10% with NNH of 24. The results of risperidone should be cautiously interpreted due to a much smaller sample size compared with studies of the other drugs; moreover, this agent is not approved for use in patients with TRD.

6 Conclusions

Based on clinically evaluated evidence, SGAs may act as a successful adjunctive medical agent for patients who fail to respond to pharmacological monotherapy with antidepressants. The SGAs evaluated in this review, including aripiprazole, olanzapine, quetiapine and risperidone, have varying degrees of efficacy in TRD patients and account for approximately a −3-point difference on rating scales for depression and approximately a 10 % improvement in remission rate compared with placebo augmentation, although there is no clear evidence to recommend one over the others. Conversely, each SGA has particular adverse properties that could be severe, leading patients to discontinuation from the treatment or could be mild with fewer risks of discontinuation. Risks and benefits should be recognized when clinicians are considering subsequent pharmacotherapy following failed treatment with antidepressants.

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