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Atypical Antipsychotic Augmentation for Treatment-Resistant Depression: A Systematic Review and Network Meta-Analysis

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Abstract

Background: Previous meta-analyses of atypical antipsychotics for depression were limited by few trials with direct
comparisons between two treatments. We performed a network meta-analysis, which integrates direct and indirect evidence
from randomized controlled trials (RCTs), to investigate the comparative efficacy and tolerability of adjunctive atypical
antipsychotics for treatment-resistant depression (TRD).
Methods: Systematic searches resulted in 18 RCTs (total n = 4422) of seven different types and different dosages of atypical
antipsychotics and a placebo that were included in the review.
Results: All standard-dose atypical antipsychotics were significantly more efficacious than placebo in the efficacy (standardized
mean differences [SMDs] ranged from -0.27 to -0.43). There were no significant differences between these drugs. Low-dose
atypical antipsychotics were not significantly more efficacious than the placebo. In terms of tolerability, all standard-dose
atypical antipsychotics, apart from risperidone, had significantly more side-effect discontinuations than placebo (odds ratios
[ORs] ranged from 2.72 to 6.40). In terms of acceptability, only quetiapine (mean 250–350 mg daily) had significantly more
all-cause discontinuation than placebo (OR = 1.89). In terms of quality of life/functioning, standard-dose risperidone and

standard-dose aripiprazole were more beneficial than placebo (SMD = -0.38; SMD = -0.26, respectively), and standard-dose risperidone was superior to quetiapine (mean 250–350 mg daily).

Conclusions: All standard-dose atypical antipsychotics for the adjunctive treatment of TRD are efficacious in reducing depressive symptoms. Risperidone and aripiprazole also showed benefits in improving the quality of life of patients. Atypical antipsychotics should be prescribed with caution due to abundant evidence of side effects.

Keywords: Atypical antipsychotics, network meta-analysis, systematic review, treatment-resistant depression

Introduction

Major depression is among the most impairing, common, and costly mental disorders. Approximately 5–12% of males and 9–26% of females will suffer from at least one episode of depression over their lifetime, and about 50% of patients will experience a second depressive episode (Crown et al., 2002; Kessler et al., 2003; Finley, 2009). Although there were several available treatments for depression over the past two decades, a substantial number of patients either did not respond adequately to these drugs or were unable to tolerate their adverse effects (Berlim and Turecki, 2007; Shelton et al., 2010). These patients are broadly defined as having treatment-resistant depression (TRD). Recent clinical trials indicated that only approximately half of depressed patients with initial antidepressant monotherapy showed a favorable treatment response, and only about one-third achieved remission of symptoms (Trivedi et al., 2006); thus, there is need for additional treatment strategies for those patients with TRD. One common alternative approach to the treatment of patients with TRD is augmentation strategies for those who failed to respond to the initial antidepressant (Vieta and Colom, 2011).

The use of atypical antipsychotics has rapidly increased worldwide in the last decade. In 2007 and 2008, there were an estimated 3.7 million patients in per year in the US who were prescribed an atypical antipsychotic medication for depression (Alexander et al., 2011). Currently, three atypical antipsychotic drugs—aripiprazole, quetiapine, and olanzapine—have received approval from the US Food and Drug Administration (FDA) as adjunctive therapies for adult TRD (Hicks et al., 2010). However, clinicians remain unclear as to how to select the optimal atypical antipsychotic for TRD. The mechanisms of atypical antipsychotics differ in their selectivity for 5-HT$_2$ receptors and/or dopamine D$_2$ receptors and in their effects on different brain regions (Blier and Szabo, 2005; Guo et al., 2012a, 2012b), and prominent pharmacologic effects may differ between dosage levels.

The evidence for the efficacy of adjunctive atypical antipsychotic therapy for TRD has been investigated in several previous traditional meta-analyses (Papakostas et al., 2007; Nelson and Papakostas, 2009; Komossa et al., 2010; Spielmans et al., 2013). However, these findings of previous meta-analyses were derived from the combined data of different atypical antipsychotics, and cannot provide hierarchical evidence on the efficacy and tolerability of atypical antipsychotics for depression due to a very limited number of trials with direct comparisons between two active agents. More importantly, the question of the superiority of a given dosage in efficacy and tolerability of atypical antipsychotics has not previously been assessed in the comprehensive setting of a systematic review and meta-analysis.

To address the above concerns, we employed a network meta-analysis, which is a new methodological approach that allows the integration of direct evidence (from studies directly comparing interventions) with indirect evidence (information about two treatments derived via a common comparator, e.g. placebo) from multiple treatment comparisons to estimate the interrelations across all treatments (Salanti et al., 2008). Previously, we conducted a network meta-analysis of comparative efficacy, acceptability, and tolerability of all augmentation agents in treatment-resistant depression in this way (Zhou et al., 2014), but did not investigate the issue of different doses of atypical antipsychotics in the previous study. Further, this methodological approach has previously been used to assess the efficacy of several mental disorders, such as major depression (Cipriani et al., 2009), bipolar disorder (Cipriani et al., 2011), and schizophrenia (Leucht et al., 2013). The aim of this network meta-analysis of randomized controlled trials (RCTs) is to provide comprehensive evidence on the efficacy, tolerability, acceptability, and quality of life of all atypical antipsychotic in the augmentation treatment of patients with TRD.

Methods

This study was conducted according to the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Moher et al., 2009). The protocol has been registered on PROSPERO (CRD42014009666) and published in Systematic Reviews (Liu et al., 2014).

Data Sources and Searches

Seven electronic databases (PubMed, Embase, the Cochrane Library, Web of Science, CINAHL, LiLACS, and PsycINFO) were searched for publications from 1970 up to November 2013 (updated to January 31, 2014) with targeted Medical Subject Headings and text words. Several clinical trial registry agencies, pharmaceutical company websites, and FDA reports were also reviewed. Supplementary Table 1 details the systematic search terms and strategy. There were no search restrictions placed based on language, publication year, or publication type. Additional studies were searched in the reference lists of all identified publications, including relevant meta-analyses and systematic reviews. All relevant authors and principal manufacturers were contacted to supplement incomplete reports of the original papers or to provide new data from unpublished studies.

Study Selection

Two independent reviewers (Drs Qin and Liu) selected studies for inclusion, with divergences in judgment resolved by consensus. They scanned citations at the title/abstract level and then retrieved short-listed studies in full text. Potentially relevant articles were reviewed in full to ensure that they satisfied all the following criteria: (1) RCTs, including cross-over trials and cluster-randomized trials; (2) adult patients (aged more than

18 years) diagnosed with a current episode of major depressive disorder according to standard diagnostic interviews; (3) patients who had an inadequate response to at least one course of conventional antidepressant treatment prior to enrollment in the study; (4) usage of an adjunctive atypical antipsychotic medication; (5) comparator against a different type or different dosage of the adjunctive atypical antipsychotic or against an adjunctive placebo; and (6) one or more outcome(s) of depressive symptoms in acute treatment. Standard dose was defined as equal to or more than the defined daily dose by the FDA-approved indications, and low dose was defined as less than half the defined dose by the FDA-approved indications (Psychopharmacology Institute, 2013)

To reduce inconsistency among trials in this review, RCTs were excluded if trials: (i) included patients with bipolar depression; (ii) co-administered a psychotherapeutic intervention; or (iii) were for relapse prevention or maintenance treatment.

Outcome Measures

We assessed efficacy with continuous measures and categorical measures, respectively. Because previous studies reported that categorical measures may inflate treatment differences relative to the mean change in the continuous scale (Kirsch and Moncrieff, 2007), we chose continuous measures of depressive symptom severity as the primary outcome for efficacy. The primary outcome for efficacy was mean change scores in depressive symptoms, as measured by the mean change score of depression rating scales from baseline to endpoint. The secondary outcome for efficacy was response and remission in depressive symptoms, as estimated by the proportion of patients who achieved a decrease of a certain percentage or moved below the threshold in depression rating scores (Frank et al., 1991).

When a study reported multiple depression rating scales, the Montgomery and Asberg Depression Rating Scale (Montgomery and Asberg, 1979) was used as the primary measure, as it is the more commonly-used measure of depressive symptoms, followed by the Hamilton Depression Rating Scale (Hamilton, 1960) or other rating scales. Acute phase was defined as 4 to 12 weeks. For trials with multiple durations of acute treatment, the eight-week outcomes were used. Results from intention-to-treat analyses were preferred over results from completer analyses.

Tolerability (side-effect discontinuation) was defined as the proportion of patients who dropped treatment during the study due to side effects. The acceptability (all-cause discontinuation) was defined as the proportion of patients who dropped treatment during the study for any reason, which was previously reported to encompass efficacy and tolerability (Cipriani et al., 2009, 2011).

We also examined continuous measures of quality of life and functional improvement (QoL/functioning; Healy, 2000; Bech, 2005), including the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott et al., 1993), the Short Form 36 Health Survey (SF-36; Ware and Sherbourne, 1992), and the Sheehan Disability Scale (SDS; Sheehan et al., 1996). When data were reported on more than one measure, we first chose data from the Q-LES-Q, then the SDS, and finally the SF-36.

Data Extraction and Quality Assessment

Two independent reviewers (Drs Liu and Zhou) abstracted the data and assessed study quality with good inter-rater agreement (κ statistic = 0.87, 0.88, respectively). The reviewers independently extracted the key study parameters using a standardized data abstraction form and assessed the risk of bias according to the Cochrane Handbook (Higgins and Green, 2011). Disagreements between reviewers were resolved by consensus.

Data Synthesis and Analysis

Bayesian network meta-analyses were performed to compare the relative outcomes of different types and dosages of atypical antipsychotic agents. The pooled estimates of standardized mean differences (SMD) with 95% credible intervals (CrIs) were calculated for continuous outcomes, and odds ratios (OR) with 95% CrIs were calculated for categorical outcomes. The SMD is the difference of means between the two groups divided by the pooled standard deviation (SDs) of the measurements; a negative SMD value indicates greater symptomatic relief (Attari et al., 2006). In the presence of minimally informative priors, CrIs can be interpreted similarly to confidence intervals, and conventional levels of statistical significance at a two-sided $p < 0.05$ can be assumed if 95% CrIs do not include 0 (Salanti et al., 2008). If means and SDs were not provided, we calculated them from p values or other statistical indices as described elsewhere (Berard et al., 2006).

The pooled estimates were obtained using the Markov Chains Monte Carlo method. Two Markov chains were run simultaneously with different arbitrarily-chosen initial values. To ensure convergence, trace plots and the Brooks-Gelman-Rubin statistics were assessed (Brooks and Gelman, 1998). Convergence was found to be adequate after running 50 000 samples for both chains. These samples were then discarded as "burn-in" and posterior summaries were based on 100 000 subsequent simulations. The node splitting method was used to calculate the inconsistency of the model, which separated evidence on a particular comparison into direct and indirect evidence (Lu and Ades, 2006). Probability values were summarized and reported as the surface under the cumulative ranking curve (SUCRA), a simple transformation of the mean rank used to provide a hierarchy of the treatments and accounts for both the location and the variance of all relative treatment effects (Lu and Ades, 2004; salanti et al., 2011). Network meta-analyses were performed using the WinBUGS software package (version 1.4.3, MRC Biostatistics Unit) with random effects models for multi-arm trials. The other analyses were performed and presented by the Stata 11.0 and R 2.11.1 software packages.

The first sensitivity analysis was performed on a network excluding trials with low-dose drugs, and the second sensitivity analysis was performed by omitting trials with small sample sizes (each arm of less than ten patients). Moreover, network meta-regression analyses were used to investigate whether potential heterogeneity could be explained by differences in publication year and the placebo response rate. Publication bias was examined using the funnel plot method.

Results

Study Characteristics

After screening 5 259 citations (Figure 1), 17 articles were included in this review (Shelton et al., 2001, 2005; Corya et al., 2006; Khullar et al., 2006; Mattingly et al., 2006; Berman et al., 2007, 2009; Mahmoud et al., 2007; McIntyre et al., 2007; Thase et al., 2007; Marcus et al., 2008; Reeves et al., 2008; Bauer et al., 2009; Keitner et al., 2009; El-Khalili et al., 2010; Fava et al., 2012; Kamijima et al., 2013) comprised of 18 RCTs with a total of 4 422 patients treated with seven different types (and dosages)
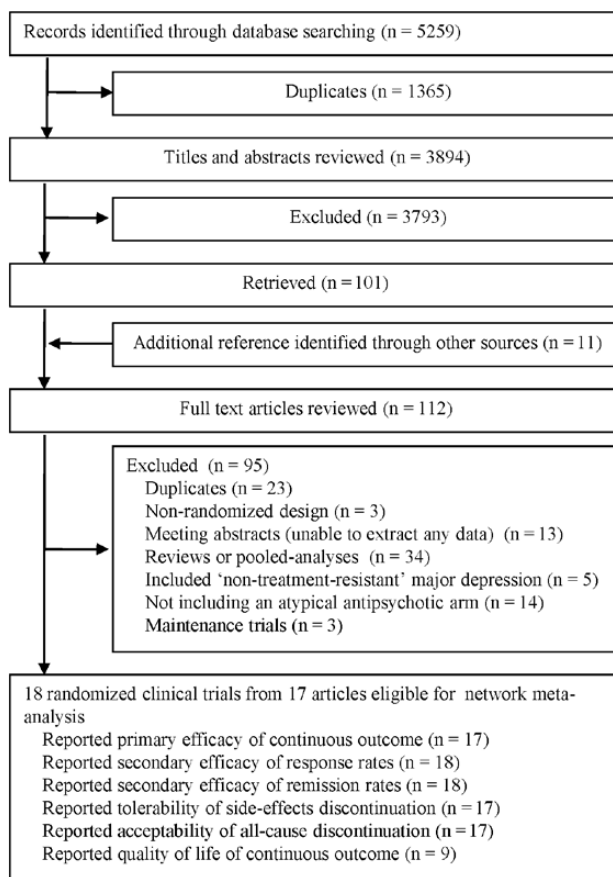
Figure 1. Flowchart of study selection.

of atypical antipsychotic agents: standard-dose aripiprazole (n = 746 patients), low-dose aripiprazole (n = 253 patients), standard-dose olanzapine/fluoxetine (OFC, n = 599 patients), low-dose OFC (n = 59 patients), quetiapine (mean 250–350 mg daily, n = 345 patients), quetiapine (mean 150–250 mg daily, n = 344 patients), and standard-dose risperidone (n = 217 patients).

Table 1 summarizes the characteristics and outcome measures of all included trials. The studies were published between 2001 and 2013. Sample sizes ranged from 15 to 586 patients, with a median sample size of 240.9 per trial. The mean age of participants was 44.1 years (range: 18–65 years). All studies involved both female and male patients, and the overall female-to-male ratio was approximate 1.8:1. The mean duration of acute treatment was 7.0 weeks (range: 4–12 weeks). Three RCTs had a low-dose treatment arm for comparison with a standard-dose treatment arm or placebo. Most trials (15/18) were augmentation treatment with selective serotonin reuptake inhibitors or selective noradrenalin reuptake inhibitors, and most (11/18) recruited patients that previously failed at least two conventional antidepressant treatment trials.

The risk of bias of included RCTs was assessed according to Cochrane metrics (Supplementary Figure 1). The overall quality of studies was rated as good, even though many reports did not provide details about randomization and allocation concealment, while none of the RCTs met the criteria for high risk of bias on the basis of question-based entries. Funnel plot asymmetry was seen, showing a potential publication bias (Supplementary Figure 2).

Results of Network Meta-Analysis

There were eight nodes and ten comparisons of primary outcomes in the network plot of different types (and dosages) of atypical antipsychotic agents (Figure 2). The pooled effect estimates for primary efficacy and tolerability outcomes from the network meta-analysis were provided (Figure 3). Compared with placebo, all standard-dose agents were significantly more effective (SMD ranged from -0.27 to -0.43), while low-dose OFC and low-dose aripiprazole were not. No significant differences in efficacy outcomes were found between these atypical antipsychotics. In terms of tolerability, all standard-dose agents, except for risperidone, had significantly more side-effect discontinuations than placebo (OR ranged from 2.72 to 6.40). Quetiapine (mean dose 250–350 mg daily) and standard-dose OFC had significantly more side-effect discontinuations than low-dose OFC (OR = 5.68, 95% credible interval [CrI] 1.38 to 90.42; OR = 8.53, 95% CrI 1.08 to 36.67, respectively).

The pooled effect estimates for QoL/functioning and acceptability outcomes from the network meta-analysis were provided (Figure 4). In terms of the QoL/functioning outcome, only standard-dose risperidone and standard-dose aripiprazole were significantly more beneficial than placebo (SMD = -0.38, 95% CrI -0.65 to -0.12, and SMD = -0.26, 95% CrI -0.40 to -0.11, respectively). Moreover, standard-dose risperidone was significantly more beneficial than quetiapine (mean dosage: 250–350 mg daily; SMD = 0.35, 95% CrI 0.02 to 0.70). In terms of acceptability outcome, only quetiapine (mean dose 250–350 mg daily) had a significantly higher rate of all-cause discontinuation than placebo (OR = 1.89, 95% CrI 1.19 to 3.10).

In regard to the secondary efficacy outcomes for response rates and remission rates (Supplementary Figure 3), the results were consistent with those of the primary outcome for efficacy, except that low-dose aripiprazole was somewhat more effective than placebo.

All loops (i.e. networks of three comparisons that arise when collating studies involving different selections of competing treatments) were consistent, since all their 95% CIs included 0 (i.e. the direct estimate of the summary effect was not significantly differentiated from the indirect estimate; Supplementary Figure 4). Supplementary Table 2 presents the results of the overall SUCRA-based probabilities for all atypical antipsychotic drugs in terms of efficacy, tolerability, acceptability, and QoL/functioning; however, the few significant findings in the network meta-analysis restrict the interpretation of hierarchical evidence based on SUCRA.

Sensitivity Analysis and Meta-Regression

The first sensitivity analysis of the network meta-analysis model was conducted by refitting the model by omitting studies with low-dose atypical antipsychotic agents. No material change in either the groups of pooled estimated effects or rank ordering was found (Supplementary Figure 5). The second sensitivity analysis, performed by omitting studies with small sample sizes, showed that the model was robust, as the statistical significances and rank ordering of efficacy and tolerability outcomes showed little change (Supplementary Figure 6). In the meta-regression analysis to assess potential biases in publication year, there was no statistical significance for this variable (Supplementary Figure 7).

Discussion

This network meta-analysis provides useful and comprehensive evidence regarding the efficacy, acceptability, tolerability, and quality of life of various atypical antipsychotics used for

Table 1. Baseline Characteristics of Included Studies

Trial	Treatment comparators	Antide-pressants	Patients	Mean Age (years)	Female (%)	Duration (weeks)	Prior Failed Trials	Rating Scale	Primary efficacy (mean)	Side-effects dis-continuation	All-cause discon-tinuation	Quality of Life (mean)
Bauer et al., 2009	Quetiapine (mean 250–400mg daily) vs Quetiapine (mean 150–250mg daily) vs Placebo	SSRI/SNRI	487	45.4	67.6	6	1 historical	MADRS	-14.94;-15.26;-12.21	19/163;11/167;6/161	30/163;21/167;16/161	12.81;14.7;12.58
Berman et al., 2007	Standard dose Aripiprazole vs Placebo	SSRI/SNRI	353	45.4	62.8	6	1–3 historical, 1 prospective	MADRS	-8.8;-5.8	6/182;4/176	22/182;16/176	-1.09;-0.63
Berman et al., 2009	Standard dose Aripiprazole vs Placebo	SSRI/SNRI	343	45.3	73.1	6	1–3 historical, 1 prospective	MADRS	-10.1;-6.4	11/177;3/172	30/177;23/172	9.8;5.2
Corya et al., 2006	Standard dose OFC vs Low dose OFC vs placebo	Fluoxetine	341	45.7	72.5	12	1 or more historical, 1 prospective	MADRS	-14.06;-11.97;-11.7	29/243;2/59; 3/60	60/243;13/59; 12/60	-
El-Khalili et al., 2010	Quetiapine (mean 250–400mg daily) vs Quetiapine (mean 150–250mg daily) vs Placebo	SSRI/SNRI	432	45.5	72.5	6	1 historical	MADRS	-14.7;-13.6;-11.7	27/149;16/148;1/148	45/149;34/148; 23/148	11.82; 10.37; 11.32
Fava et al., 2012	Low dose aripiprazole vs Placebo	SSRI/SNRI	221	45.1	64.4	4	1–3 historical, 1 prospective	MADRS	-8.54;-8.1	0/56;0/169	2/56;2/169	-
Kamjijima et al., 2013	Standard dose Aripiprazole vs Low dose aripiprazole vs Placebo	SSRI/SNRI	586	38.7	42.0	6	1–3 historical, 1 prospective	MADRS	-9.6;-10.5; -7.4	7/194;8/197; 2/195	17/194;17/197; 12/195	-1.03; -0.96;-0.46
Keitner et al., 2009	Standard dose Risperidone vs Placebo	Various	95	45.2	56.7	4	1 prospective	MARDS	-	6/62;1/33	8/62;7/33	1.2;0.5
Khullar et al., 2006	Quetiapine (mean 250–400mg daily) vs Placebo	SSRI/SNRI	15	-	-	8	At least 1 historical	MADRS	-14.88;-5.29	0/8;0/7	1/8;1/7	-
Mahmoud et al., 2007	Standard dose Risperidone vs Placebo	Various	268	46.1	73.5	6	1 prospective	HAMD-17	-10.9;-8.7	8/141;3/133	26/141;16/133	15.2;11
Marcus et al., 2008	Standard dose Aripiprazole vs Placebo	SSRI/SNRI	369	44.5	66.7	6	1–3 historical, 1 prospective	MADRS	-8.5;-5.7	7/191;2/190	29/191;28/190	-1.3;-0.7
Mattingly et al., 2006	Quetiapine (mean 250–400mg daily) vs Placebo	SSRI/SNRI	37	-	-	8	1 historical, 1 prospective	MADRS	-17;-8.7	0/24;0/13	3/24;2/13	-
McIntyre et al., 2007	Quetiapine (mean 150–250mg daily) vs Placebo	SSRI/SNRI	58	44.5	62.1	8	1 or more trials	HAMD-17	-11.37;-5.61	8/29;2/29	11/29;13/29	-
Reeves et al., 2008	Standard dose Risperidone vs Placebo	Various	23	43.5	69.6	8	1 prospective	MADRS	-22.09;-14.44	0/12;0/11	1/12;4/11	-
Shelton et al., 2001	Standard dose OFC vs placebo	Fluoxetine	20	42.0	-	8	2 historical, 1 prospective	MARDS	-13.6;-1.2	0/10;0/10	1/10;3/10	-
Shelton et al., 2005	Standard dose OFC vs placebo	Fluoxetine	288	42.1	69.8	8	1 or more historical, 1 prospective	MARDS	-8.71;-8.51	10/146;4/142	30/146;28/142	-
Thase 2007	Standard dose OFC vs placebo	Fluoxetine	203	44.1	61.2	8	1 or more historical, 1 prospective	MADRS	-10.8;-9.4	27/200;5/206*	52/200;40/206*	-1.6;-1.1*
Thase 2007	Standard dose OFC vs placebo	Fluoxetine	198	44.9	68.0	8	1 or more historical, 1 prospective	MADRS	-14.6;-9	27/200;5/206*	52/200;40/206*	-1.6;-1.1*

*A pooled result of Thase 2007

HAM-D, Hamilton Depression Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; OFC, olanzapine/fluoxetine; SNRI, selective noradrenalin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitors
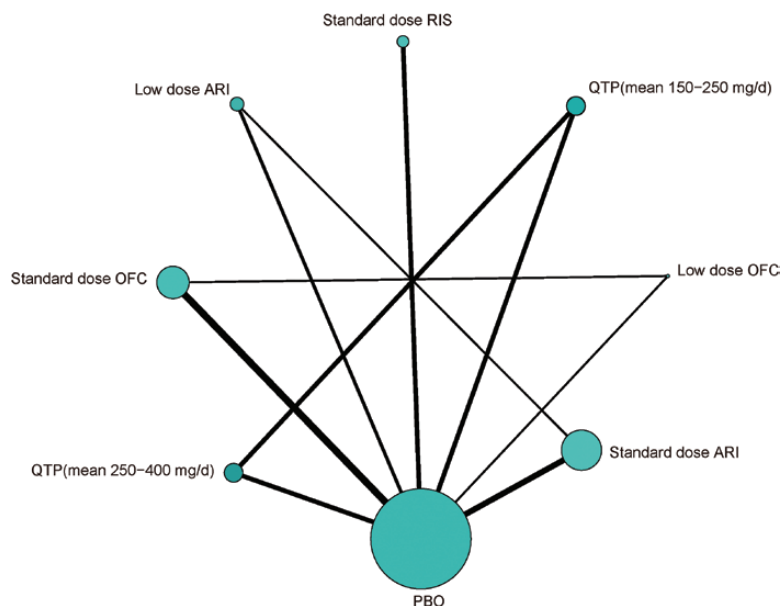
Figure 2. Network plot of eligible comparisons for primary outcome. The width of the lines is proportional to the number of trials comparing every pair of treatments, and the size of every node is proportional to the number of randomized participants (sample size). ARI, aripiprazole; OFC, olanzapine/fluoxetine; PBO, placebo; QTP, quetiapine; RIS, risperidone.

S1-QTP	1.85 (0.19 to 7.14)	1.85 (0.79 to 3.57)	0.99 (0.36 to 4.00)	1.45 (0.42 to 9.09)	1.54 (0.57 to 6.25)	**5.68 (1.38 to 90.42)**	**6.40 (2.94 to 17.83)**
-0.03 (-0.49 to 0.38)	s-RIS	0.57 (0.18 to 3.62)	0.30 (0.09 to 2.05)	0.73 (0.22 to 4.78)	0.52 (0.16 to 3.47)	2.10 (0.47 to 43.16)	2.37 (0.87 to 11.14)
-0.06 (-0.34 to 0.19)	-0.04 (-0.45 to 0.41)	S2-QTP	1.09 (0.41 to 3.85)	0.85 (0.25 to 5.26)	0.90 (0.34 to 3.57)	3.32 (0.81 to 52.63)	**3.73 (1.77 to 10.13)**
-0.12 (-0.48 to 0.16)	-0.10 (-0.51 to 0.29)	-0.06 (-0.40 to 0.22)	s-ARI	0.51 (0.12 to 1.42)	0.87 (0.22 to 2.36)	7.59 (0.60 to 37.02)	**2.72 (1.34 to 6.82)**
-0.16 (-0.59 to 0.17)	-0.14 (-0.60 to 0.29)	-0.10 (-0.51 to 0.24)	-0.04 (-0.34 to 0.24)	L-ARI	1.25 (0.21 to 4.26)	10.26 (0.58 to 53.19)	2.88 (1.00 to 12.96)
-0.16 (-0.51 to 0.13)	-0.14 (-0.54 to 0.27)	-0.10 (-0.43 to 0.20)	-0.04 (-0.30 to 0.25)	0.00 (-0.32 to 0.36)	s-OFC	**8.53 (1.08 to 36.67)**	**3.52 (1.74 to 8.48)**
-0.40 (-0.91 to 0.06)	-0.38 (-0.92 to 0.17)	-0.34 (-0.83 to 0.13)	-0.28 (-0.72 to 0.18)	-0.24 (-0.72 to 0.27)	-0.24 (-0.64 to 0.16)	L-OFC	0.43 (0.09 to 4.05)
-0.43 (-0.72 to -0.21)	**-0.41 (-0.77 to -0.06)**	**-0.37 (-0.64 to -0.14)**	**-0.31 (-0.49 to -0.12)**	-0.27 (-0.53 to 0.01)	**-0.27 (-0.48 to -0.08)**	-0.03 (-0.45 to 0.38)	PBO

Treatment   Depression symptom scores (SMD with 95% CrI)   Side-effects discontinuation (OR with 95% CrI)

Figure 3. Network meta-analysis of primary efficacy and tolerability outcomes. Drugs are reported in order of efficacy ranking. Comparisons between treatments should be read from left-to-right, and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. To obtain standardized mean differences (SMDs) for comparisons in the opposite direction, negative values should be converted into positive values, and vice versa. For the primary efficacy, SMDs less than 0 favor the column-defining treatment. For the tolerability, odds ratios (ORs) higher than 1 favor the column-defining treatment. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold and underlined. CrI, credible intervals; L-ARI, low dose aripiprazole; L-OFC, low dose olanzapine/fluoxetine; PBO, placebo; S1-QTP, quetiapine (mean 250–400 mg daily); S2-QTP, quetiapine (mean 150–250 mg daily); S-ARI, standard dose aripiprazole; S-OFC, standard dose olanzapine/ fluoxetine; S-RIS, standard dose risperidone.

the adjunctive treatment of treatment-resistant depression. All included standard-dose atypical antipsychotic agents were found to be significantly more efficacious than adjunctive placebo. Low-dose atypical antipsychotics were not found to be efficacious. Two standard-dose medications—risperidone and aripiprazole—showed statistically significant benefits in functioning and quality of life. In terms of tolerability, all standard-dose atypical antipsychotics, with the exception of risperidone, had significantly more side-effect discontinuations than placebo. Only quetiapine (mean dosage: 250–350 mg daily) had significantly more all-cause discontinuations than placebo. In summary, the reviewed atypical antipsychotic agents demonstrated efficacy in reducing depressive symptoms, but were accompanied by substantial risks of adverse events, including akathisia (aripiprazole), sedation (quetiapine, OFC, aripiprazole), and weight gain (all drugs, especially OFC; Ucok and Gaebel, 2008).

s-RIS	0.74 (0.37 to 1.64)	0.62 (0.26 to 1.79)	0.77 (0.39 to 1.72)	0.74 (0.37 to 1.74)	0.49 (0.24 to 1.14)	0.83 (0.34 to 2.64)	0.97 (0.53 to 1.92)
-0.13 (-0.43 to 0.17)	**S-ARI**	0.94 (0.43 to 1.79)	1.08 (0.61 to 1.81)	1.05 (0.56 to 1.89)	0.69 (0.36 to 1.23)	1.34 (0.50 to 3.01)	1.26 (0.88 to 1.87)
-0.15 (-0.52 to 0.21)	-0.03 (-0.28 to 0.23)	**L-ARI**	1.29 (0.53 to 2.69)	1.27 (0.49 to 2.70)	0.82 (0.32 to 1.79)	1.59 (0.48 to 4.11)	1.36 (0.72 to 2.96)
-0.20 (-0.59 to 0.18)	-0.07 (-0.39 to 0.25)	-0.05 (-0.43 to 0.34)	**s-OFC**	1.02 (0.53 to 1.82)	0.66 (0.34 to 1.18)	1.25 (0.55 to 2.51)	1.21 (0.83 to 1.82)
-0.29 (-0.64 to 0.05)	-0.16 (-0.42 to 0.11)	-0.14 (-0.47 to 0.20)	-0.09 (-0.45 to 0.27)	**S2-QTP**	0.63 (0.41 to 1.04)	1.06 (0.47 to 3.06)	1.23 (0.78 to 2.01)
-0.35 (-0.70 to -0.02)	-0.23 (-0.49 to 0.04)	-0.20 (-0.54 to 0.14)	-0.16 (-0.51 to 0.20)	-0.07 (-0.28 to 0.15)	**S1-QTP**	1.63 (0.72 to 4.70)	**1.89 (1.19 to 3.10)**
..	..	..	..	..	..	**L-OFC**	0.97 (0.46 to 2.34)
-0.38 (-0.65 to -0.12)	**-0.26 (-0.40 to -0.11)**	-0.23 (-0.49 to 0.03)	-0.18 (-0.47 to 0.10)	-0.09 (-0.31 to 0.13)	-0.03 (-0.24 to 0.18)	..	**PBO**

■ Treatment ■ QoL/functioning (SMD with 95% CrI) ▢ All-cause discontinuation (OR with 95% CrI)

Figure 4. Network meta-analysis of quality of life (QoL/functioning) and acceptability outcomes. Drugs are reported in order of efficacy ranking. Comparisons between treatments should be read from left-to-right, and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For the QoL/functioning, standardized mean differences (SMDs) lower than 0 favor the column-defining treatment. To obtain SMDs for comparisons in the opposite direction, negative values should be converted into positive values, and vice versa. For the acceptability, odds ratios (ORs) higher than 1 favor the column-defining treatment. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold and underlined. CrI, credible interval; L-ARI, low dose aripiprazole; L-OFC, low dose olanzapine/fluoxetine; PBO, placebo; S1-QTP, quetiapine (mean 250–400 mg daily); S2-QTP, quetiapine (mean 150–250 mg daily); S-ARI, standard dose aripiprazole; S-OFC, standard dose olanzapine/ fluoxetine; S-RIS, standard dose risperidone.

These findings have clinically-relevant implications for comprehensively balancing the risk-benefit profiles of these adjunctive atypical antipsychotics for TRD (Kennedy, et al., 2009). In our network analysis, among these atypical antipsychotics, standard-dose risperidone appeared to be the most beneficial in balancing efficacy, tolerability, and quality of life. However, these findings were restricted to a relatively limited number of trials in which risperidone was compared with other atypical antipsychotics. Moreover, patients in the adjunctive risperidone trials had mild to moderate refractory depression, failing to respond to only one course of conventional antidepressant therapy, while patients in trials with adjunctive other atypical antipsychotics had depressions with inadequate response to at least two courses of antidepressant treatments. Thus, the significant benefits for risperidone require further validation with patients experiencing more refractory depression. Nonetheless, risperidone did show antidepressant efficacy in patients with adult TRD, and should be considered as a recommendation in clinical guidelines although it has not yet received approval for that indication from the FDA.

Low-dose antipsychotic agents, including aripiprazole and OFC, appeared not to be effective in reducing depressive symptoms. There are two possible limitations in the interpretation of these results. First, there were only three trials reported using low-dose atypical antipsychotics, so a significant treatment effect may be obscured by the limited data (Barnes et al., 2006). Second, low-dose aripiprazole did show significant efficacy in comparison to placebo in both response and remission outcomes. Thus, the low-dose atypical antipsychotics may still be promising augmentation agents for TRD and deserve further study. Lower doses of atypical antipsychotic medication show a lower incidence of severe side-effects, thus an increase in tolerability and compliance (Taylor, 2000; Hicks et al., 2010; Bauer et al., 2013).

As outlined in previous studies, acceptability may encompass efficacy and tolerability outcomes (Cipriani et al., 2009, 2011). In our analysis, under the reviewed atypical antipsychotics only quetiapine (mean dosage: 250–350 mg daily) had significantly more all-cause discontinuations than placebo. Thus, high doses of atypical antipsychotics may worsen the risk-benefit balance for refractory patients.

This study has several limitations. The first major limitation is that the number of included trials is relatively small, especially with low-dose drugs, which restricts the interpretation of the findings. Second, there are different definitions of treatment resistance, which may have resulted in comparisons of different patient populations. However, the methods used to define treatment resistance in studies reviewed here were similar to those of previous meta-analyses. Third, changes in QoL measures may lag behind reported or observed changes in depressive symptom measures; thus, the interpretation of QoL/functioning is limited by the absence of longer-term data (Bech, 2005). Finally, although there were no significant differences in efficacy among these atypical antipsychotics as a group, individual patients may respond preferentially to one agent or another.

There are additional issues that need to be discussed. First, we do not address the clinically important issue of adjunctive atypical antipsychotic therapy for preventing relapse in the medium and long term (i.e. ≥6 months). One systematic review of long-term, two-armed, parallel randomized controlled antidepressant trials initially identified 2 693 abstracts, but ultimately included only six trials (Deshauer et al., 2008). Even if continuing adjunctive treatment is shown to reduce relapse rates, the increased side-effect burden and cost of continuing two agents raises additional and clinically-important considerations (Papakostas et al., 2004), so that it is not at all clear how long patients should continue to take atypical antipsychotic agents, even if they help in

the short term. Second, in this network meta-analysis, placebo responses in these included studies ranged from about 10% to about 40%, which may cause significant problems in interpreting the data, particularly the comparative SMDs. However, a previous meta-analysis reported that the superiority of the drug versus placebo would be a worse performance when examining studies with placebo response rates ≥40% in adjunctive trials (Iovieno and Papakostas, 2012). And the magnitude of the placebo response seems to be related to the study population (e.g. biological validity of illness, baseline severity of illness, chronicity of the index episode of depression, age of participants, medical and psychiatric comorbidity) and study design (probability of receiving placebo, trials durations, study outcome measures) rather than the intervention itself (Brunoni et al., 2009; Papakostas et al., 2015). Third, we found no usable data for analyses of other currently-prescribed atypical antipsychotics, such as ziprasidone, that met our inclusion criteria.

In conclusion, this meta-analysis found evidence that all the reviewed standard-dose atypical antipsychotics were significantly effective in reducing depressive symptoms in patients with treatment-resistant depression. Although no significant differences were found in efficacy between any two atypical antipsychotics, standard-dose risperidone and standard-dose aripiprazole showed more benefits in improving quality of life of patients than a placebo. Clinicians prescribing atypical antipsychotics should be cautious, given the evidence of potential treatment-related side effects.

Supplementary Material

For supplementary material accompanying this paper, visit http://www.ijnp.oxfordjournals.org/

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Statement of Interest

The authors have declared that no competing interests exist.

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