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Comparative Efficacy, Acceptability, and Tolerability of Augmentation Agents in Treatment-Resistant Depression: Systematic Review and Network Meta-Analysis

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ABSTRACT

Objective: To comparatively analyze the efficacy, acceptability, and tolerability of various augmentation agents in adult patients with treatment-resistant depression.

Data Sources: An electronic literature search of PubMed, EMBASE, the Cochrane Library, Web of Science, EBSCO, PsycINFO, EAGLE, and NTIS for trials published up to December 2013 was conducted. Several clinical trial registry agencies and US Food and Drug Administration reports were also reviewed. No language, publication date, or publication status restrictions were imposed.

Study Selection: Randomized controlled trials comparing 11 augmentation agents (aripiprazole, bupropion, buspirone, lamotrigine, lithium, methylphenidate, olanzapine, pindolol, quetiapine, risperidone, and thyroid hormone) with each other and with placebo for adult treatment-resistant depression were included.

Data Extraction: The proportion of patients who responded to treatment was defined as primary efficacy, and the proportion of all-cause discontinuation and side-effects discontinuation were respectively defined as acceptability and tolerability, which were assessed with odds ratios (ORs) and a Bayesian random-effects model with 95% credible intervals (CrIs).

Results: A total of 48 trials consisting of 6,654 participants were eligible. In terms of the primary efficacy, quetiapine (OR = 1.92; 95% CrI, 1.39–3.13), aripiprazole (OR = 1.85; 95% CrI, 1.27–2.27), thyroid hormone (OR = 1.84; 95% CrI, 1.06–3.56), and lithium (OR = 1.56; 95% CrI, 1.05–2.55) were significantly more effective than placebo. Sensitivity analyses indicated that efficacy estimates for aripiprazole and quetiapine were more robust than those for thyroid hormone and lithium. In terms of acceptability, no significant difference was found between active agents and placebo. In terms of tolerability, compared to placebo, quetiapine (OR = 3.85; 95% CrI, 1.92–8.33), olanzapine (OR = 3.36; 95% CrI, 1.60–8.61), aripiprazole (OR = 2.51; 95% CrI, 1.11–7.69), and lithium (OR = 2.30; 95% CrI, 1.04–6.03) were significantly less well tolerated.

Conclusions: Quetiapine and aripiprazole appear to be the most robust evidence-based options for augmentation therapy in patients with treatment-resistant depression, but clinicians should interpret these findings cautiously in light of the evidence of potential treatment-related side effects.

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Major depressive disorder (MDD) is a common mood disorder that is predicted to be the second-leading cause of disability worldwide by 2020.[1] Achieving symptomatic remission from MDD is an essential intermediate step in the recovery process; despite the availability of novel and effective treatments for MDD over the past 2 decades, a substantial number of patients either do not respond adequately to these drugs or are unable to tolerate their adverse effects.[2,3] Furthermore, failure to achieve remission from MDD has been shown to increase vulnerability to functional impairment and suicide.[4] This inadequate response to conventional antidepressant therapy has been termed *treatment-resistant depression* (TRD), but there remains no universally accepted definition of TRD at the present time.[5] The prevalence of TRD is difficult to estimate, but TRD has been associated with poorer long-term outcomes and a higher risk of recurrence.[6]

Several secondary strategies have been proposed for patients with TRD, including dose optimization, switching to another therapeutic class, or combination/augmentation strategies.[7] Augmentation strategies involve the addition of a nonstandard agent to the treatment regimen.[8] One advantage to augmentation is that it eliminates the transition period between one antidepressant to another, thereby building on any partial response (20%–50% improvement).[9] The application of lithium and thyroid hormones (triiodothyronine [T_3] and thyroxine [T_4]) as augmentation agents began in the 1980s, and until recently, lithium was still deemed a good option for bipolar depression.[9,10] Additionally, a recent systematic review showed only equivocal support for T3 augmentation of selective serotonin reuptake inhibitors (SSRIs).[11] The past decade has seen significant advances in evidence-based guidelines on the efficacy of atypical antipsychotics as augmentation agents for TRD[12,13]; however, the choice of first-line augmentation agents for TRD patients continues to be debated.[8] Previous conventional pairwise meta-analyses have not generated clear conclusions regarding the efficacy and acceptability of available treatments[8,9] because they have been limited by small sample sizes and a paucity of direct comparisons among agents.

Clinicians would benefit from solid evidence-based recommendations regarding TRD management, since the choice of an augmentation agent is often a difficult clinical decision and frequently involves a lengthy trial-and-error process.[14] Evidence-based guidance is required

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Clinical Points

- This systematic review and network meta-analysis compared the efficacy, acceptability, and tolerability of 11 augmentation agents in patients with treatment-resistant depression.
- Quetiapine and aripiprazole appear to be the most robust evidence-based options for augmentation therapy in patients with treatment-resistant depression.
- Clinicians should interpret these findings cautiously in light of the evidence of potential treatment-related harm.

to make informed treatment decisions, but comparative trials of augmentation agents for TRD are scarce. This approach enables a coherent analysis of random trials data for comparisons of multiple treatments without adversely affecting randomization of treatments within each trial, and its usefulness has been previously demonstrated in several studies on various medical conditions and interventions.[15–18] Therefore, the present systematic review and network meta-analysis aimed to integrate the available data from existing direct and indirect comparisons to assess the relative efficacy, acceptability, and tolerability of augmentation agents in TRD patients using a previously validated network meta-analysis strategy applied to multiple sclerosis patients.

METHOD

The study protocol has been made freely available to the public on our institutional Web site (www.pengxielab.com/research/evidence-based-medicine/).

Data Sources and Searches

We conducted a systematic literature search (from 1970 to December 2013) of MEDLINE/PubMed, EMBASE, the Cochrane Library, Web of Science, PsycINFO, and EBSCO, the European Association for Gray Literature Exploitation (EAGLE), the National Technical Information Service (NTIS), and ProQuest for randomized controlled trials (RCTs) concerning augmentation therapy for TRD patients with medical subject headings (MeSH) and text words. Supplementary eTable 1 (available at PSYCHIATRIST.COM) shows the full details of the search strategy and search results. Several clinical trial registries, pharmaceutical company Web sites, and relevant reports from the US Food and Drug Administration (FDA) Web site were also reviewed. Additional RCTs were obtained by scanning the reference lists of identified publications. No language, publication date, or publication status restrictions were applied. Relevant principal manufacturers and study authors were contacted to supplement incomplete original reports or to provide new data from unpublished studies.

Selection Criteria

Two investigators (Y.L. and B.Q.) independently assessed literature eligibility and updated searching; disputes were resolved by a third reviewer (X.Z.). Our meta-analysis focused on RCTs of adult patients with a primary diagnosis of MDD (treatment-refractory type) according to standardized diagnostic criteria. We used broad TRD criteria for study inclusion, which were identified as studies including MDD patients who had 1 historical treatment failure and failed to respond to at least 1 first-line antidepressant during the current MDD episode.[5,19] Treatment-resistant depression levels were staged per criteria developed by Thase and Rush.[20] Both published and unpublished RCTs comparing one active drug with another active drug or placebo at an orally administered therapeutic dose, regardless of fixed dose and flexible dose, were included. In addition, because of the likely overlap in physiological effects, data on T3 and T4 were combined a priori as thyroid hormone augmentation.

Because a network meta-analysis requires a reasonably homogeneous sample,[21] we excluded RCTs conducted with bipolar disorder patients (accounting for more than 20% of bipolar depression patients), patients with psychotic features, and patients with serious concomitant medical illness. We also excluded relapse-prevention studies and trials involving males only or females only (eg, sex-hormone treatment studies). We excluded trials that compared the continuation of an original drug with an augmentation agent that lacked a placebo augmentation, since a significant placebo effect has been previously reported.[22]

Comparability of Duration and Dosages

As there is no precise definition for the acute phase of TRD, we defined the *acute phase* as 6 weeks of acute augmentation therapy for conventional treatment-resistant MDD. If 6-week data were not available, we used data from 2 to 14 weeks, aiming for the data point closest to the 6-week mark. As clear definitions of dosage equivalence among different augmentation drugs could not be found in the published literature, a working definition was established for the purpose of the present analysis according to previously published classifications (Supplementary eTable 2).[12,23] This standard was employed to detect inequalities in dosing that could affect comparative efficacy.

Outcome Measures

The primary efficacy outcome (response) was defined as a reduction of 50% or more in scores from baseline to posttreatment on the depression scale used in the respective studies,[24] eg, the Hamilton Depression Rating Scale (HDRS),[25] the Montgomery-Asberg Depression Rating Scale (MADRS),[26] and others. The secondary efficacy outcome (remission) was achievement of remission of depressive symptoms posttreatment, defined as an HDRS score of ≤ 7, a MADRS score of ≤ 10, or other comparable criteria for the various scales used.[24] If a study employed more than 1 depression scale, precedence was given to the HDRS, as it is the more commonly used measure of depressive symptoms in this study.

The acceptability outcome was *all-cause discontinuation*, defined as the percentage of patients who terminated the study for any reason. The tolerability outcome was *side-effects*

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discontinuation, which was defined as the percentage of medicated patients who terminated the study due to adverse effects.

Data Extraction and Quality Assessment

We extracted the following information from the studies: study characteristics (eg, first author, corresponding author, study title, publication year, journal, study period, study center[s], and sponsorship), participant characteristics (eg, number of patients, diagnostic criteria, definition and stage of TRD, mean baseline score, age, and gender), intervention details (eg, mean doses and ranges, concomitant medications), and main outcome measures. Study quality was independently assessed by 2 reviewers (Y.L. and B.Q.) using the Cochrane Collaboration's risk-of-bias method.[27]

Data Synthesis and Analysis

We chose a dichotomous efficacy outcome (responses and remission) to facilitate clinician comprehension.[28] When dichotomous efficacy outcomes were not available and baseline scores, end point means, and standard deviations of the depression rating scales were reported, the number of treatment responders was estimated using a validated imputation method.[29] Intention-to-treat datasets were used whenever available.

First, pairwise meta-analyses were performed by synthesizing studies that compared the same interventions with a random-effects model when significant heterogeneity existed or a fixed-effects model when no significant heterogeneity existed. The effect sizes were expressed as odds ratios (ORs) and their 95% confidence intervals (CIs). The presence of statistical heterogeneity was assessed by the χ^2 test and I^2 statistic.[30]

Next, a random-effects model network meta-analysis within a Bayesian framework was performed in WinBUGS. Network meta-analysis combines direct and indirect evidence for all relative treatment effects and provides estimates with maximum power if the assumptions behind the methodology are satisfied.[31] The relative effect sizes were calculated as ORs and their 95% credible intervals (CrIs). The dichotomous outcomes were modeled in every treatment group of every study, and the relations among the ORs across studies were specified through various comparisons.[31] To assess significance, 95% CrI (according to whether the CrI included the null value) was used. The rankogram was used to show the absolute probabilities to be the first-best regimen, the second-best, and so on. For each intervention, cumulative probabilities were calculated as the surface under the cumulative ranking curve, which expresses the probability of the drug being the superior intervention among all competitive options. To estimate inconsistency for each comparison included in the network, the difference between direct and indirect estimates was calculated whenever indirect estimates could be constructed with a single common comparator.[32] We calculated the differences between direct and indirect evidence in all closed loops in the network; inconsistent loops were identified by a significant disagreement (95% CI that excludes 0) between direct and indirect evidence.[33]

Finally, we performed some sensitivity analyses within the network meta-analysis according to the following variables: therapeutic dose (including only studies within the therapeutic dose range), acute treatment duration (including only studies of 4- to 12-week duration), imputation method (excluding studies with imputation), bipolar patients (excluding studies with less than 20% bipolar depression patients), blinded design (including only studies with blinding), refractory duration (including only studies using greater than or equal to 4 weeks as a criterion), study time (excluding studies published before 2004), sponsorship (excluding studies without sponsorship statements), placebo response (excluding studies with placebo response of more than 40%), intervention type (excluding only studies augmented with tricyclic antidepressants), and thyroid hormone augmentation splitting (splitting of thyroid hormone augmentation therapy into T3 and thyroid hormone). In addition, a subgroup analysis was conducted within a pairwise meta-analysis of studies of lithium augmented with tricyclic and nontricyclic antidepressants.

To investigate the effect of sponsorship (ie, whether the sponsor was the manufacturer of the test or comparator drug) on the outcome estimate, we also carried out a meta-regression analysis. Analyses were done in Review Manager 5.0 (pairwise meta-analysis and I^2 calculations), in R 2.15.3 (estimation of consistency, rankogram, and surface under the cumulative ranking curve graphs), and WinBUGS 1.4.3 (network meta-analysis models).

RESULTS

Study Characteristics

In total, 48 trials reported between 1978 and 2012 and consisting of a total of 6,654 participants were included in our analyses (PRISMA[34] flowcharts are shown in Figure 1).[35–82] Results with 11 augmentation agents fulfilled all criteria for inclusion: aripiprazole, bupropion, buspirone, lamotrigine, lithium, methylphenidate, olanzapine, pindolol, quetiapine, risperidone, and thyroid hormone.

Table 1 shows the clinical and methodological characteristics as well as the main outcomes of each trial. The mean duration of the studies was 6.2 weeks, and the mean sample size was 67.8 participants per group (range, 4–286). In terms of demographic characteristics, about two-thirds of total participants (64.9%) were women. Twenty-three studies (4,368 participants) included individuals aged 65 years or younger, and the overall mean age of participants was 43.81 years (SD = 11.39). In terms of clinical characteristics, there were 35 trials with TRD patients of stage I or greater, 12 trials of stage II or greater, and only 1 trial of stage III or greater. The overall mean baseline score at study entry was 21.16 (5.50) for HDRS-17, 20.30 (2.62) for HDRS-21, 28.21 (7.24) for HDRS-25, and 27.97 (6.33) for MADRS. From the total patient pool, 6,534 patients were included in the primary efficacy analysis (45 studies), 6,425 in the acceptability analysis (44 studies), 5,851 in the secondary

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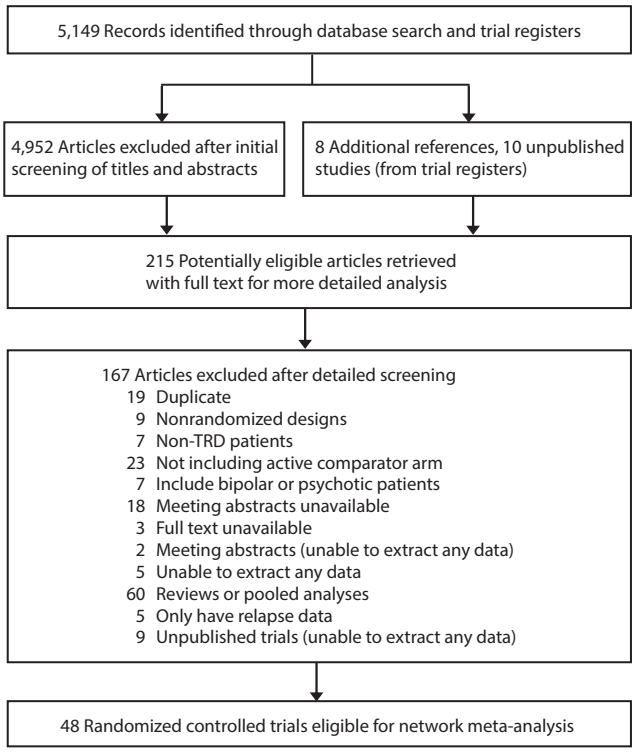
Figure 1. Study Selection Process



efficacy analysis (31 studies), and 5,540 in the tolerability analysis (39 studies).

The overall quality of studies was rated as good, even though many reports did not provide details about randomization and allocation concealment, and only a few RCTs in every question-based entry met criteria for low risk of bias (Supplementary eFigure 1).

Pairwise Meta-Analyses

From the pairwise meta-analysis, all augmentation agents had at least 1 placebo-controlled RCT. Supplementary eTable 3 summarizes the results for efficacy and acceptability from the traditional pairwise meta-analysis. A subgroup analysis showed that there was no significant difference in efficacy between augmentation of lithium with tricyclic antidepressants (TCAs) and placebo augmentation, while the augmentation of lithium with non-TCAs was more beneficial than placebo augmentation; however, these findings were limited by small samples (Supplementary eFigure 2). Overall, statistical heterogeneity in all direct comparisons was moderate (Supplementary eTable 4), although for most comparisons, the 95% CIs were wide (range, 0%–85%) and included values showing no heterogeneity or very high heterogeneity, which reflected the small number of included studies for each pairwise comparison.

Network Meta-Analyses

Figure 2 shows the network of eligible comparisons for the primary efficacy outcome. The results of primary efficacy (response rates) from the network meta-analysis are displayed in Figure 3. In terms of response rates, quetiapine (OR = 1.92; 95% CrI, 1.39–3.13), aripiprazole (OR = 1.85; 95% CrI, 1.27–2.72), thyroid hormone (OR = 1.84; 95% CrI, 1.06–3.56), and lithium (OR = 1.56; 95% CrI, 1.05–2.55) were significantly more effective than placebo. In regard to the secondary efficacy outcomes for remission rates (Figure 4), thyroid hormone (OR = 2.94; 95% CrI, 1.56–6.67), risperidone (OR = 2.17; 95% CrI, 1.30–4.00), quetiapine (OR = 2.08; 95% CrI, 1.45–3.45), buspirone (OR = 1.86; 95% CrI, 1.03–4.41), aripiprazole (OR = 1.83; 95% CrI, 1.22–2.75), and olanzapine (OR = 1.79; 95% CrI, 1.18–2.97) were significantly more effective than placebo.

In terms of the acceptability outcome (all-cause discontinuation) (Figure 3), there were no significant differences between any active agents, either with each other or with placebo. In terms of the tolerability outcome (side-effects discontinuation) (Figure 4), compared to placebo, quetiapine (OR = 3.85; 95% CrI, 1.92–8.33), olanzapine (OR = 3.36; 95% CrI, 1.60–8.61), aripiprazole (OR = 2.51; 95% CrI, 1.11–7.69), and lithium (OR = 2.30; 95% CrI, 1.04–6.03) were significantly less well tolerated. Moreover, quetiapine was significantly less well tolerated than thyroid hormone.

All loops (networks of 3 or 4 comparisons that arose when collating studies involving different selections of competing treatments) were consistent, since their 95% CIs included 0 (ie, the direct estimate of the summary effect did not differentiate from the indirect estimate) (Supplementary eFigure 3). Inconsistency analysis revealed no statistical inconsistencies in primary efficacy (9 loops) or primary acceptability (5 loops). However, the limited number of included studies hampers definitive conclusions regarding consistency.

All antidepressants were ranked according to their overall probability to be the superior treatment (surface under the cumulative ranking curve estimates) in terms of the primary outcomes for efficacy and acceptability (Supplementary eFigure 4). However, we could not draw a conclusion regarding superiority, as there were few significant differences among these treatments. The common heterogeneity SD was 0.23 (95% CrI, 0.01–0.57) for primary efficacy, 0.41 (95% CrI, 0.08–0.78) for acceptability, 0.22 (95% CrI, 0.01–0.59) for secondary efficacy, and 0.38 (95% CrI, 0.02–0.88) for tolerability.

Sensitivity Analyses and Meta-Regression

The sensitivity analyses results for primary efficacy and acceptability outcomes were showed in Supplementary eTables 5 and 6. Overall, most sensitivity analyses found stronger primary efficacy estimates for aripiprazole and quetiapine than for thyroid hormone and lithium. In the meta-regression analysis used to adjust the data for potential sponsorship bias (Supplementary eTable 7), the effect sizes and surface under the cumulative ranking curve did not substantially change, indicating that the effect of sponsorship on the outcome estimate was negligible.

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Table 1. Characteristics and Outcome Measures of Included Studies

Study	Main Inclusion Criteria[a]	Treatment Groups	Duration	Rating Scale	Primary Efficacy (response rate)	Acceptability (all-cause discontinuation)	Tolerability (side-effects discontinuation)
Appelberg et al, 2001[35]	Age, 18–74 y; *DSM-IV* criteria for unipolar, nonpsychotic MDD; stage I	Buspirone vs placebo	6 wk	CGI-S	17/51:16/51	6/51:10/51	NA
Barbee et al, 2011[36]	Age, 18–65 y; *DSM-IV*/*ICD-10* criteria for unipolar, nonpsychotic MDD; 17-HDRS ≥ 15; ≥ stage II	Lamotrigine vs placebo	10 wk	MADRS	16/48:16/48	14/48:17/48	7/48:10/48
Bauer et al, 2010[37]	*DSM-IV* criteria; MADRS ≥ 25; stage I–II	Lithium vs quetiapine	6 wk	MADRS	102/229:120/231	47/229:35/231	18/229:23/231
Bauer et al, 2009[38]	Age, 18–65 y; *DSM-IV* criteria for MDD; 17-HDRS ≥ 20; stage I	Quetiapine vs placebo	6 wk	MADRS	185/330:74/163	51/330:18/163	30/330:5/163
Baumann et al, 1996[39]	Age, 18–65 y; *DSM-III* criteria for unipolar, nonpsychotic MDD; 21-HDRS ≥ 18; stage I	Lithium vs placebo	1 wk	21-HDRS	6/10:2/14	0/10:0/14	0/10:0/14
Berman et al, 2009[40]	Age, 18–65 y; *DSM-IV* criteria for unipolar, nonpsychotic MDD; 17-HDRS ≥ 14; stage I–III	Aripiprazole vs placebo	6 wk	MADRS	81/177:45/172	30/177:23/172	11/177:3/172
Berman et al, 2007[41]	Age, 18–65 y; *DSM-IV* criteria for unipolar, nonpsychotic MDD; 17-HDRS ≥ 14; stage I–III	Aripiprazole vs placebo	6 wk	MADRS	61/184:41/178	24/184:18/178	6/184:4/178
Browne et al, 1990[42]	Age, 22–66 y; *DSM-III* criteria for MDD; 21-HDRS ≥ 18; stage I	Lithium vs placebo	7–9 d	21-HDRS	3/7:2/10	0/7:0/10	0/7:0/10
Chaput et al, 2008[43]	Age, 23–66 y; *DSM-IV* criteria for unipolar MDD; 21-HDRS ≥ 20; ≥ stage II	Quetiapine vs placebo	12 wk	21-HDRS	3/11:1/11	1/11:6/11	NA
Corya et al, 2006[44]	Age, ≥ 18 y; *DSM-IV* criteria for unipolar, nonpsychotic MDD; CGI-S ≥ 4; stage II	Olanzapine vs placebo	12 wk	MADRS	120/302:19/60	73/302:12/60	31/302:3/60
Dorée et al, 2007[45]	Age, 18–65 y; *DSM-IV* criteria for unipolar, nonpsychotic MDD; 17-HDRS ≥ 20; stage I–II	Lithium vs quetiapine	8 wk	17-HDRS	5/10:8/10	3/10:0/10	2/10:0/10
El-Khalili et al, 2010[46]	Age, 18–65 y; *DSM-IV* criteria for unipolar, nonpsychotic MDD; HDRS ≥ 20; stage I	Quetiapine vs placebo	6 wk	MADRS	160/298:66/148	79/298:23/148	43/289:1/148
Fang et al, 2011[47]	Age, 18–65 y; *DSM-IV* criteria for unipolar, nonpsychotic MDD; 17-HDRS ≥ 17; ≥ stage II	Buspirone vs risperidone vs thyroid hormone	8 wk	17-HDRS	26/46:21/45:28/48	7/46:10/45:3/48	0/46:2/45:0/48
Fava et al, 2012[48]	Age, 18–65 y; *DSM-IV* criteria for unipolar, nonpsychotic MDD; 17-HDRS ≥ 18; stage I–III	Aripiprazole vs placebo	30 d	MADRS	10/56:29/169	2/56:2/169	NA
Gitlin et al, 1987[49]	Age, 18–65 y; RDC criteria for unipolar MDD; 17-HDRS ≥ 16; stage I	Thyroid hormone vs placebo	2 wk	17-HDRS	0/7:4/9	0/7:0/9	0/7:0/9
GlaxoSmithKline 2009[50]	Age, 18–65 y; *DSM-IV* criteria for unipolar, nonpsychotic MDD; 17-HDRS ≥ 16; stage I	Bupropion vs placebo	12 wk	17-HDRS	63/166:58/159	67/166:47/159	39/166:31/159
Gonul et al, 1999[51]	*DSM-IV* criteria for MDD; ≥ stage I	Buspirone vs pindolol	3 wk	HDRS	4/7:2/7	NA	NA
Gulrez et al, 2012[52]	Age, 18–75 y; *DSM-IV* criteria for unipolar MDD; 17-HDRS ≥ 16; ≥ stage I	Bupropion vs placebo	4 wk	17-HDRS	NA	NA	NA
Heninger et al, 1983[53]	Age, 18–70 y; *DSM-III* criteria for nonpsychotic MDD; 17-HDRS ≥ 17; stage I	Lithium vs placebo	12 d	17-HDRS	5/8:0/7	0/8:0/7	0/8:0/7
Joffe et al, 1993[54]	RDC criteria for unipolar, nonpsychotic MDD; 17-HDRS ≥ 16; stage I	Lithium vs placebo vs thyroid hormone	2 wk	17-HDRS	9/18:3/16:10/17	1/18:0/16:0/17	1/18:0/16:0/17
Joffe et al, 2006[55]	Age, 23–52 y; *DSM-IV* criteria for unipolar, nonpsychotic MDD; stage I	Lithium vs placebo vs thyroid hormone	2 wk	17-HDRS	NA	0/9:0/8:0/10	0/9:0/8:0/10

(continued)

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Table 1 (continued). Characteristics and Outcome Measures of Included Studies

Study	Main Inclusion Criteria[a]	Treatment Groups	Duration	Rating Scale	Primary Efficacy (response rate)	Acceptability (all-cause discontinuation)	Tolerability (side-effects discontinuation)
Katona et al, 1995[56]	*DSM-III* criteria for nonpsychotic MDD; stage I	Lithium vs placebo	6 wk	17-HDRS	15/29:8/33	6/29:9/33	2/29:2/33
Keitner et al, 2009[57]	Age, 18–65 y; *DSM-IV* criteria for unipolar, nonpsychotic MDD; MADRS ≥ 25; stage I	Risperidone vs placebo	4 wk	MADRS	34/64:11/33	10/64:7/33	6/64:1/33
Khullar et al, 2006[58]	*DSM-IV* criteria for unipolar, nonpsychotic MDD; stage I	Quetiapine vs placebo	8 wk	MADRS	4/8:1/7	1/8:1/7	0/8:0/7
Landén et al, 1998[59]	Age, 21–82 y; *DSM-IV* criteria for MDD; stage I	Buspirone vs placebo	4 wk	CGI	29/58:28/61	3/58:4/61	1/58:2/61
Mahmoud et al, 2007[60]	Age, 18–65 y; *DSM-IV* criteria for unipolar, nonpsychotic MDD; CGI-S ≥ 4; stage I	Risperidone vs placebo	6 wk	17-HDRS	49/141:33/133	30/141:18/133	8/141:3/133
Marcus et al, 2008[61]	Age, 16–65 y; *DSM-IV* criteria for unipolar, nonpsychotic MDD; 17-HDRS ≥ 14; stage I–III	Aripiprazole vs placebo	6 wk	MADRS	60/191:32/190	29/191:28/190	7/191:2/190
Mattingly et al, 2006[62]	*DSM-IV* criteria for unipolar, nonpsychotic MDD; 17-HDRS ≥ 20; stage I	Quetiapine vs placebo	8 wk	MADRS	12/24:2/13	3/24:2/13	0/24:0/13
McIntyre et al, 2007[63]	Age, 18–65 y; *DSM-IV* criteria for unipolar, nonpsychotic MDD; 17-HDRS ≥ 18; stage I	Quetiapine vs placebo	8 wk	17-HDRS	14/29:8/29	11/29:13/29	8/29:2/29
Moreno et al, 1997[64]	Age, 18–70 y; *DSM-III* criteria for unipolar MDD; 25-HDRS ≥ 18; stage I	Pindolol vs placebo	2 wk	25-HDRS	0/5:2/5	0/5:0/5	0/5:0/5
Nierenberg et al, 2003[65]	Age, 18–70 y; *DSM-III* criteria for unipolar, nonpsychotic MDD; 17-HDRS ≥ 18; ≥ stage I	Lithium vs placebo	6 wk	17-HDRS	2/18:3/17	2/18:2/17	NA
Nierenberg et al, 2006[66]	Age, 18–75 y; *DSM-IV* criteria for unipolar, nonpsychotic MDD; stage II	Lithium vs thyroid hormone	12 wk	QIDS-C/ HDRS	11/69:17/73	NA	16/69:7/73
Patkar et al, 2006[67]	Age, 18–65 y; *DSM-IV* criteria for nonpsychotic MDD; 21-HDRS ≥ 15; ≥ stage I	Methylphenidate vs placebo	4 wk	21-HDRS	12/30:7/30	3/30:7/30	2/30:2/30
Pérez et al, 1999[68]	Age, 18–65 y; *DSM-IV* criteria for unipolar MDD; 17-HDRS > 16; ≥ stage I	Pindolol vs placebo	10 d	17-HDRS	10/40:10/40	1/40:1/40	0/40:0/40
Perry et al, 2004[69]	Age, 18–75 y; *DSM-IV* criteria for unipolar, nonpsychotic MDD; 25-HDRS ≥ 25; stage I	Pindolol vs placebo	3 wk	25-HDRS	4/22:4/20	1/22:3/20	1/22:1/20
Ravindran et al, 2008[70]	Age, 18–65 y; *DSM-IV* criteria for nonpsychotic MDD; MADRS ≥ 20; stage I–III	Methylphenidate vs placebo	5 wk	MADRS	34/73:30/72	11/73:4/72	6/73:0/72
Reeves et al, 2008[71]	Age, 19–60 y; *DSM-IV* criteria for unipolar, nonpsychotic MDD; MADRS ≥ 25; stage II	Risperidone vs placebo	8 wk	MADRS	6/12:4/11	1/12:4/11	0/12:0/11
Santos et al, 2008[72]	Age, 18–64 y; *DSM-IV* criteria for unipolar, nonpsychotic MDD; ≥ stage II	Lamotrigine vs placebo	8 wk	MADRS	4/17: 5/17	3/17:4/17	2/17:0/17
Schindler and Anghelescu, 2007[73]	*DSM-IV* criteria for unipolar, nonpsychotic MDD; 17-HDRS ≥ 17; ≥ stage II	Lamotrigine vs lithium	8 wk	17-HDRS	9/17:7/17	2/17:2/17	0/17:0/17
Shelton et al, 2006[74]	*DSM-IV* criteria for unipolar MDD; stage II	Bupropion vs risperidone	6 wk	NA	NA	0/10:1/10	NA
Shelton et al, 2005[75]	Age, 18–65 y; *DSM-IV* criteria for unipolar, nonpsychotic MDD; MADRS ≥ 20; stage II	Olanzapine vs placebo	8 wk	MADRS	40/146:41/142	30/146:28/142	10/146:4/142
Shelton et al, 2001[76]	*DSM-IV* criteria for unipolar, nonpsychotic MDD; 21-HDRS ≥ 20; stage II	Olanzapine vs placebo	8 wk	MADRS	6/10:1/10	1/10:3/10	0/10:0/10
Sokolski et al, 2004[77]	*DSM-IV* criteria for nonpsychotic MDD; 17-HDRS > 21; ≥ stage III	Pindolol vs placebo	4 wk	17-HDRS	4/4:0/5	0/4:0/5	0/4:0/5

(continued)

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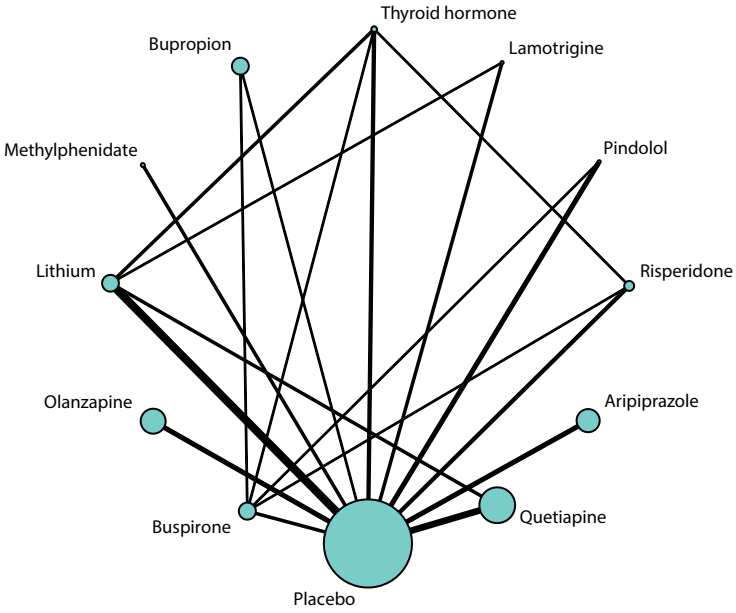
Table 1 (continued). Characteristics and Outcome Measures of Included Studies

Study	Main Inclusion Criteria[a]	Treatment Groups	Duration	Rating Scale	Primary Efficacy (response rate)	Acceptability (all-cause discontinuation)	Tolerability (side-effects discontinuation)
Stein and Bernadt, 1993[78]	RDC criteria for MDD; 17-HDRS ≥ 18; stage I	Lithium vs placebo	3 wk	17-HDRS	2/16:4/18	NA	NA
Steiner et al, 1978[79]	MDD; stage I	Thyroid hormone vs placebo	5 wk	NA	3/4:3/4	0/4:0/4	0/4:0/4
Thase et al, 2007[80]	Age, 18–65 y; *DSM-IV* criteria for unipolar, nonpsychotic MDD; 17-HDRS ≥ 22; stage II	Olanzapine vs placebo	8 wk	MADRS	80/200:60/206	52/200:40/206	27/200:5/206
Trivedi et al, 2006[81]	Age, 18–75 y; *DSM-IV* criteria for nonpsychotic MDD; 17-HDRS ≥ 14; stage I	Bupropion vs buspirone	12 wk	QIDS-SR-16/ 17-HDRS	88/279:77/286	35/279:59/286	NA
Zusky et al, 1988[82]	Age, 18–80 y; *DSM-III* criteria for unipolar, nonpsychotic MDD; 17-HDRS ≥ 12; ≥ stage I	Lithium vs placebo	3 wk	17-HDRS	3/9:2/9	1/9:1/9	1/9:1/9

[a]Thase and Rush treatment-resistant depression staging was used to classify resistance levels.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale; *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; *DSM-III* = *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition; HDRS = Hamilton Depression Rating Scale; *ICD-10* = *International Statistical Classification of Diseases and Related Health Problems, 10th revision*; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = major depressive disorder; NA = not available; QIDS-C=Quick Inventory of Depressive Symptomatology–Clinician Rating; QIDS-SR-16=16-item Quick Inventory of Depressive Symptomatology–Self-Report; RDC = Research Diagnostic Criteria.

Figure 2. Network Plot of Eligible Comparisons for Primary Efficacy[a]



[a]Line width is proportional to the number of trials comparing each treatment pair. Nodal size is proportional to the number of randomized participants (sample size).

DISCUSSION

This systematic review and network meta-analysis provide a useful and complete picture of the efficacy, acceptability, and tolerability of 11 augmentation therapies for adults with unipolar TRD. We found that quetiapine, aripiprazole, thyroid hormone, and lithium were significantly more effective than placebo in primary efficacy. In terms of acceptability outcome, no significant differences were detected, either between agents or between agents and placebo. In regard to tolerability outcome, quetiapine, olanzapine, aripiprazole, and lithium were significantly less well tolerated. Nonetheless, considering the primary efficacy values for thyroid hormone and lithium were less robust than those of quetiapine and aripiprazole in most sensitivity analyses, our findings support the use of quetiapine and aripiprazole as the best-evidence choices for augmentation therapy in adult TRD patients.

Implications

As the first augmentation agent to be introduced, lithium has been the longest-studied augmentation therapy for TRD patients.[83] However, lithium is not widely utilized in clinical

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Figure 3. Network Meta-Analysis of Primary Efficacy and Acceptability[a]

ARI	1.61 (0.54–4.18)	1.39 (0.48–3.54)	1.93 (0.53–5.17)	1.16 (0.42–2.72)	1.29 (0.31–3.72)	1.23 (0.49–2.74)	3.79 (0.43–15.28)	1.46 (0.62–3.33)	1.18 (0.43–2.82)	3.84 (0.75–12.82)	1.24 (0.72–2.41)
1.49 (0.70–2.66)	BUP	0.94 (0.39–1.98)	1.42 (0.32–3.92)	0.84 (0.25–2.07)	0.95 (0.19–2.81)	0.90 (0.28–2.10)	2.79 (0.27–11.56)	1.07 (0.37–2.51)	0.85 (0.27–1.99)	2.72 (0.51–8.92)	0.85 (0.39–1.97)
1.53 (0.76–2.59)	1.08 (0.60–1.73)	BUS	1.64 (0.38–4.43)	0.97 (0.30–2.28)	1.09 (0.22–3.15)	1.04 (0.33–2.32)	3.21 (0.32–13.28)	1.22 (0.43–2.74)	0.96 (0.34–2.09)	3.04 (0.65–9.27)	0.99 (0.46–2.22)
1.71 (0.66–3.59)	1.24 (0.44–2.80)	1.19 (0.44–2.61)	LAM	0.74 (0.21–1.97)	0.85 (0.15–2.76)	0.81 (0.22–2.15)	2.49 (0.23–10.76)	0.95 (0.28–2.55)	0.78 (0.20–2.18)	2.51 (0.37–9.24)	0.70 (0.30–2.06)
1.23 (0.62–2.04)	0.89 (0.41–1.61)	0.84 (0.44–1.47)	0.82 (0.33–1.70)	LIT	1.26 (0.28–3.61)	1.21 (0.43–2.66)	3.73 (0.40–15.28)	1.37 (0.65–2.70)	1.15 (0.38–2.71)	3.70 (0.71–12.10)	1.18 (0.61–2.46)
1.39 (0.56–2.78)	1.01 (0.38–2.19)	0.96 (0.38–2.04)	0.95 (0.29–2.30)	1.19 (0.49–2.51)	MPD	1.29 (0.31–3.64)	3.98 (0.32–17.58)	1.53 (0.39–4.39)	1.24 (0.28–3.69)	4.03 (0.54–15.31)	1.06 (0.42–3.60)
1.37 (0.71–2.25)	0.99 (0.46–1.84)	0.95 (0.48–1.70)	0.93 (0.36–2.03)	1.17 (0.62–2.07)	1.11 (0.45–2.30)	OLZ	3.37 (0.38–13.60)	1.29 (0.55–2.80)	1.05 (0.38–2.41)	3.41 (0.66–11.20)	1.11 (0.62–2.07)
2.00 (0.73–4.35)	1.45 (0.49–3.33)	1.38 (0.51–3.04)	1.35 (0.39–3.44)	1.71 (0.63–3.89)	1.63 (0.49–4.06)	1.53 (0.56–3.41)	PDL	0.81 (0.09–3.16)	0.66 (0.07–2.61)	2.14 (0.14–9.92)	0.36 (0.09–2.71)
1.00 (0.50–1.58)	0.72 (0.33–1.26)	0.68 (0.35–1.15)	0.67 (0.26–1.41)	0.83 (0.51–1.26)	0.81 (0.33–1.61)	0.76 (0.40–1.24)	0.59 (0.21–1.26)	QTP	0.87 (0.32–1.88)	2.83 (0.56–9.06)	0.94 (0.52–1.63)
1.29 (0.65–2.24)	0.93 (0.44–1.77)	0.88 (0.46–1.58)	0.87 (0.32–1.94)	1.10 (0.56–2.02)	1.05 (0.41–2.27)	0.99 (0.50–1.81)	0.76 (0.27–1.72)	1.35 (0.72–2.51)	RIS	3.48 (0.78–10.58)	1.15 (0.59–2.46)
1.04 (0.47–1.97)	0.75 (0.32–1.50)	0.71 (0.34–1.34)	0.70 (0.24–1.63)	0.87 (0.45–1.59)	0.85 (0.30–1.92)	0.80 (0.36–1.57)	0.61 (0.20–1.47)	1.09 (0.53–2.08)	0.85 (0.40–1.59)	THY	0.36 (0.12–1.51)
1.85 (1.27–2.72)	1.29 (0.78–2.34)	1.25 (0.82–2.12)	1.12 (0.57–2.59)	**1.56 (1.05–2.55)**	1.37 (0.74–2.99)	1.40 (0.96–2.24)	0.96 (0.47–2.33)	**1.92 (1.39–3.13)**	1.49 (0.94–2.51)	**1.84 (1.06–3.56)**	PBO

Treatment | Response rate, OR (95% CrI) | All-cause discontinuation, OR (95% CrI)

[a]Drugs are reported in alphabetical order. Comparisons between treatments should be read from left to right. The estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For the response rate and all-cause discontinuation, ORs greater than unity favor the column-defining treatment. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold.

Abbreviations: ARI = aripiprazole, BUP = bupropion, BUS = buspirone, CrI = credible interval, LAM = lamotrigine, LIT = lithium, MPD = methylphenidate, OLZ = olanzapine, OR = odds ratio, PBO = placebo, PDL = pindolol, QTP = quetiapine, RIS = risperidone, THY = thyroid hormone.

Figure 4. Network Meta-Analysis of Secondary Efficacy and Tolerability[a]

ARI	2.90 (0.54–9.48)	20.60 (0.60–114.10)	3.65 (0.54–12.53)	1.39 (0.31–4.26)	0.97 (0.06–4.28)	0.95 (0.22–2.80)	5.75 (0.30–28.64)	0.84 (0.21–2.44)	1.28 (0.20–4.29)	4.34 (0.68–15.42)	**2.51 (1.11–7.69)**
1.17 (0.49–2.10)	BUP	9.56 (0.26–53.44)	1.68 (0.22–5.92)	0.65 (0.13–2.10)	0.44 (0.03–1.94)	0.44 (0.09–1.38)	2.67 (0.13–13.66)	0.39 (0.09–1.21)	0.59 (0.08–2.03)	2.03 (0.29–7.52)	1.10 (0.43–3.77)
1.03 (0.37–2.00)	0.90 (0.47–1.51)	BUS	0.98 (0.02–5.07)	0.37 (0.01–1.74)	0.26 (0.00–1.45)	0.26 (0.01–1.24)	1.66 (0.02–9.85)	0.23 (0.01–1.06)	0.31 (0.01–1.47)	1.11 (0.03–5.36)	0.16 (0.03–3.83)
1.40 (0.10–6.24)	1.30 (0.09–5.84)	1.54 (0.10–7.01)	LAM	0.57 (0.10–2.04)	0.40 (0.02–1.90)	0.39 (0.07–1.40)	2.39 (0.10–12.64)	0.35 (0.06–1.20)	0.53 (0.06–2.06)	1.81 (0.23–7.43)	0.87 (0.32–3.87)
1.31 (0.55–2.46)	1.21 (0.52–2.56)	1.43 (0.57–3.20)	2.47 (0.23–10.59)	LIT	0.83 (0.05–3.40)	0.83 (0.20–2.22)	5.07 (0.27–24.29)	0.68 (0.27–1.43)	1.10 (0.20–3.34)	3.29 (0.98–8.48)	**2.30 (1.04–6.03)**
0.61 (0.01–3.05)	0.58 (0.01–2.96)	0.69 (0.01–3.63)	1.32 (0.01–8.89)	0.52 (0.01–2.65)	MPD	2.60 (0.20–12.16)	15.07 (0.34–91.05)	2.28 (0.19–10.83)	3.42 (0.20–16.56)	11.70 (0.70–59.13)	3.34 (0.90-37. 6)
1.07 (0.53–1.83)	1.00 (0.46–2.03)	1.19 (0.49–2.66)	2.22 (0.16–10.32)	0.90 (0.39–1.81)	54.17 (0.32–114.40)	OLZ	7.33 (0.40–35.90)	1.06 (0.30–2.81)	1.61 (0.28–5.08)	5.47 (0.95–18.50)	**3.36 (1.60–8.61)**
1.52 (0.44–3.71)	1.43 (0.39–3.87)	1.70 (0.42–4.93)	3.15 (0.17–15.47)	1.28 (0.33–3.42)	96.43 (0.36–170.10)	1.50 (0.43–3.79)	PDL	0.45 (0.03–2.19)	0.69 (0.03–3.52)	2.38 (0.10–12.61)	0.55 (0.12–7.78)
0.92 (0.44–1.51)	0.85 (0.41–1.61)	1.01 (0.44–2.09)	1.84 (0.15–8.17)	0.75 (0.40–1.22)	49.56 (0.28–97.23)	0.91 (0.44–1.56)	0.78 (0.22–1.96)	QTP	1.75 (0.33–5.19)	**5.64 (1.28–16.72)**	**3.85 (1.92–8.33)**
0.88 (0.40–1.62)	0.81 (0.37–1.65)	0.95 (0.42–2.01)	1.80 (0.13–8.36)	0.73 (0.31–1.48)	51.34 (0.26–93.88)	0.87 (0.39–1.68)	0.75 (0.20–1.97)	1.00 (0.49–1.93)	RIS	4.69 (0.73–17.09)	2.50 (0.95–10.0)
0.65 (0.25–1.33)	0.59 (0.24–1.26)	0.69 (0.29–1.47)	1.28 (0.09–5.88)	0.52 (0.24–0.97)	40.79 (0.18–69.97)	0.64 (0.25–1.36)	0.55 (0.13–1.51)	0.73 (0.33–1.46)	0.77 (0.33–1.54)	THY	0.74 (0.25–2.94)
1.83 (1.22–2.75)	1.64 (1.00–3.27)	**1.86 (1.03–4.41)**	1.37 (0.31–17.97)	1.46 (0.85–2.91)	3.13 (0.63–205.97)	**1.79 (1.18–2.97)**	1.26 (0.54–3.87)	**2.08 (1.45–3.45)**	**2.17 (1.30–4.00)**	**2.94 (1.56–6.67)**	PBO

Treatment | Response rate, OR (95% CrI) | All-cause discontinuation, OR (95% CrI)

[a]Drugs are reported in alphabetical order. Comparisons between treatments should be read from left to right. The estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For the remission rate and side-effects discontinuation, ORs greater than unity favor the column-defining treatment. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold.

Abbreviations: ARI = aripiprazole, BUP = bupropion, BUS = buspirone, CrI = credible interval, LAM = lamotrigine, LIT = lithium, MPD = methylphenidate, OLZ = olanzapine, OR = odds ratio, PBO = placebo, PDL = pindolol, QTP = quetiapine, RIS = risperidone, THY = thyroid hormone.

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practice, possibly because of a perceived narrow range of application and the need to monitor lithium serum levels on a regular basis. Lithium augmentation has generally been well tolerated with all antidepressant classes, and the combination of lithium with antidepressants has not been associated with serious side effects, but a significant proportion of these data derives from lithium augmentation of TCAs.[84]

Thyroid hormone augmentation strategies have also been extensively evaluated[85,86] but are rarely applied in clinical practice because of screening requirements for thyroid dysfunction prior to treatment initiation and regular monitoring of thyroid hormone levels during treatment.[87,88] Although previous augmentation studies with thyroid hormone have reported few side effects, many clinicians are hesitant to interfere with thyroid function in euthyroid individuals and often have concerns about potential adverse effects such as tachycardia, nervousness, and insomnia.[88,89] Therefore, thyroid hormone is also not a favorable augmentation choice for acute TRD.

Mounting evidence supports the efficacy of atypical antipsychotics as augmentation agents for TRD.[12,13,90] Currently, 3 atypical antipsychotic drugs (aripiprazole, quetiapine, and olanzapine) have received approval from the FDA as adjunctive therapies for adult TRD, but none have been approved for use as conventional monotherapy.[91] In this network meta-analysis, 2 atypical antipsychotics—quetiapine and aripiprazole—were found to be superior options compared to the other augmentation agents; however, further confirmation of these findings is required from head-to-head RCTs.

Study Limitations

Our study has several limitations. First, almost all trials involved relatively homogeneous samples of patients resistant to SSRI therapy, and after excluding trials with TCA augmentation, efficacy estimates had no substantive changes, with the exception of lithium. Second, TRD stage was determined by the number of failed medication trials and duration of refractory illness. And, in most trials, they included heterogeneous refractory patients, such as stage I–III TRD. Despite the sensitivity analysis of refractory duration revealing no substantive changes, further research is needed on homogeneous samples of patients within the same TRD stage.

Third, all results must be tempered by potential biases that result from the choice of therapy dosage and duration.[92] In this study, acute-phase treatment was defined as a treatment duration of 6 weeks, while the duration of all trials ranged from 1 to 14 weeks. Some agents—such as lithium, thyroid hormone, and pindolol—were associated with relatively short treatment durations of 2 to 3 weeks. Thus, the possible effect of treatment duration on treatment impact must be considered. As for biases pertaining to dose, the narrow dosage ranges for lithium and thyroid hormone mean that the appropriate dose was a critical issue for tolerability.[93] In addition, lowering the starting dose of aripiprazole to 2.5 mg would obviously decrease the risk of its major side effect of akathisia, thus introducing potential dose-related bias.[94] Therefore, the potential impact of variability in dosing must also be taken into account, although, according to the sensitivity analysis, the estimated effect would likely not change substantially.

Fifth, although the quality assessments of the included trials were moderate, most did not report adequate information about randomization, allocation concealment, and blinding, perhaps undermining the validity of the conclusions. Nonetheless, all studies were similar in terms of design and conduct, and, as has been commonly found in other systematic reviews, the scant information in terms of quality assessment could be more an issue of reporting than any real defects in study design.[95]

There are several other limitations to take into account when considering the present findings. Since the population of TRD patients is already relatively small and patient recruitment faces several challenges (such as poor compliance and suicide-related behavior), small sample sizes in RCTs impede the development of clear conclusions. Moreover, we found no available data for ziprasidone; however, in a recent preliminary open trial,[96] adjunctive ziprasidone showed superiority and was generally well tolerated compared to sertraline monotherapy in TRD patients. Thus, further studies on the use of other atypical antipsychotics in TRD patients are urgently needed. Furthermore, widespread concern exists about the potential bias of financial sponsorship, especially surrounding the commercial interests of drug manufacturers. Although sensitivity analyses and meta-regression analysis indicated no significant bias of sponsorship on outcome, the possibility of bias in the original publications themselves cannot be ruled out.

Clinical trial design influences participant expectations of improvement. Rutherford et al[97] reported that a significantly higher expected likelihood and magnitude of improvement in a comparator trial compared to a placebo-controlled trial. Trials that include both comparator and placebo groups may be useful in delineating meaningful improvement from expectancy effects. In addition, from a practical clinical standpoint, there are probably important moderators of response that have not been studied in these trials but are anecdotally often employed in clinical practice. These include bipolar spectrum disorder, family history of bipolar disorder, rejection sensitivity, nonpsychotic paranoia, and thyroid hormone level in the low-normal range. Although lack of original data about individual patients limited analyses of these potential moderators in the current study, their investigation in future trials would be of significant clinical relevance.

Future Research

Our results apply to 11 adjunctive medications in acute treatment (2–14 weeks) of adult TRD but do not cover another clinically important issue of adjunctive therapy for preventing relapse in the medium and long term (ie,

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≥6 months). In clinical practice, pharmacotherapy of a major depressive episode goes beyond acute treatment, to continuation treatment or even maintenance treatment, and many patients may be on medication for up to 2 years after recovery. However, clinical trials are generally of far shorter duration, and it is of note that the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study[98] showed high relapse rates for responders and remitters after a standard 12 weeks of treatment and also higher risk of tardive dyskinesia with long-term antipsychotic use in this population. However, 1 systematic review[99] of long-term, 2-arm, parallel randomized controlled antidepressant trials initially identified 2,693 abstracts, only to ultimately include 6 trials. Even if continuing adjunctive treatment is shown to reduce relapse rates, because of the increased side effect burden and cost of continuing 2 agents, there will be additional questions. Thus, it is difficult to assess the risk-benefit profile of these medications prescribed over the long term.

CONCLUSIONS

Quetiapine and aripiprazole appear to be the best evidence-based options for augmentation therapy in adult TRD patients, but clinicians should interpret these findings cautiously in light of the evidence of potential treatment-related adverse effects. More head-to-head and longer-term RCTs are required to strengthen the evidence regarding augmentation therapy for TRD (including potential moderators of response), and further development and validation of new augmentation agents with greater efficacy, acceptability, and tolerability are still needed.

Drug names: aripiprazole (Abilify), bupropion (Wellbutrin, Aplenzin, and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), methylphenidate (Metadate, Ritalin, and others), olanzapine (Zyprexa and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), sertraline (Zoloft and others), ziprasidone (Geodon and others).

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Comparative Efficacy, Acceptability, and Tolerability of Augmentation Agents in Treatment-Resistant Depression: Systematic Review and Network Meta-Analysis

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SUPPLEMENTARY TABLES

Supplementary eTable 1. Results from the Systematic Search Strategy*

Database	Citations
Pubmed	805
Cochrane	1663
Web of Science	418
Embase	291
Ebsco host	257
PsycInfo	364
Database Total	***3798***
Grey Databases	85
Trial registers: Australian Clinical Trials Registry, USA (clinicaltrials.gov), UN (ISRCTN), Netherlands (Trial Register), Japan (UMIN-CTR), Chinese (ChiCTR), and World Health Organization (WHO)	1266
Total	***5822***

Explicit search strategy: title/abstract = (depressi OR antidepressant*) AND (Augmentation augment* OR potentiat* OR adjunct* OR co-administration OR combin*) AND (*refractory* OR *resistan* OR *recurren* OR chronic* OR persist* OR non-respon*: non-response non-responsive non-respond OR nonrespon* OR not respon* OR no respon* OR inadequate respon* OR partial respon* OR insufficient respon* OR unrespon* OR difficult-to-treat OR incomplete respon* OR failed to respon* OR failure to respon* OR severe)
Other sources: Relevant principal manufacturers (e.g., GlaxoSmithKline, Lilly, AstraZeneca, Pfizer, Janssen, Bristol-Myers Squibb) were contacted. Additional relevant studies were obtained by scanning relevant systematic reviews, meta-analyses, and reviews as well as reference lists of eligible trial.

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Supplementary eTable 2. Dosing Classification Based on Dosage Range Quartiles

Drug	Dosage Range	Low	Medium	High
Aripiprazole	10-30 mg/day	＜10	10-15	＞15
Bupropion	50-450 mg/day	＜150	150-300	＞300
Buspirone	30-50 mg/day	＜30	30-50	＞50
Lamotrigine	50-200 mg/day	＜100	100-200	＞200
Lithium	500-1200 mg/day,	＜600	600-900	＞900
	0.5-1.2 mmol/l	＜0.5	0.5–1.2	＞1.2
Methylphenidate	18-54 mg/day	＜30	30-40	＞40
Olanzapine	5-20 mg/day	＜6	6-18	＞18
Pindolol	7.5-10 mg/day	＜7.5	7.5	＞7.5
Quetiapine	50-400 mg/day	＜300	300-400	＞400
Risperidone	0.5-2.0 mg/day	＜1	1-2	＞2
Thyroid hormone	40-120 mg/day	＜40	40-120	＞120
Triiodothyronine	25-50 μg/day	＜25	25-50	＞50

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Supplementary eTable 3. Summary Estimates for Efficacy and Acceptability from Traditional Pairwise Meta-Analysis

Comparison	Number of studies	Number of patients	Primary Efficacy OR (95% CI)	Secondary Efficacy OR (95% CI)	Acceptability OR (95% CI)	Tolerability OR (95% CI)
Aripiprazole vs						
Placebo	4	1317	1.93 (1.50 to 2.49)	1.95 (1.47 to 2.59)	1.24 (0.88 to 1.74)	2.68 (1.23 to 5.81)
Bupropion vs						
Buspirone	1	565	1.25 (0.87 to 1.80)	0.98 (0.69 to 1.41)	0.55 (0.35 to 0.87)	..
Placebo	2	385	1.07 (0.68 to 1.67)	2.03 (0.42 to 9.83)	1.61 (1.02 to 2.56)	1.27 (0.75 to 2.16)
Risperidone	1	20	..	..	0.30 (0.01 to 8.33)	..
Buspirone vs						
Bupropion	1	565	0.80 (0.56 to 1.15)	1.02 (0.71 to 1.46)	1.81 (1.15 to 2.86)	..
Pindolol	1	14	3.33 (0.36 to 30.70)	..	..	..
Placebo	2	221	1.14 (0.66 to 1.97)	..	0.61 (0.25 to 1.50)	0.52 (0.05 to 5.87)
Risperidone	1	91	1.49 (0.65 to 3.39)	1.33 (0.54 to 3.28)	0.63 (0.22 to 1.83)	0.19 (0.01 to 4.01)
Thyroid hormone	1	94	0.93 (0.41 to 2.10)	0.81 (0.34 to 1.89)	2.69 (0.65 to 11.13)	Not estimable
Lamotrigine vs						
Lithium	1	34	1.61 (0.41 to 6.24)	1.44 (0.27 to 7.68)	1.00 (0.12 to 8.06)	Not estimable
Placebo	2	130	0.93 (0.44 to 1.95)	..	0.74 (0.34 to 1.59)	0.89 (0.34 to 2.30)
Lithium vs						
Lamotrigine	1	34	0.62 (0.16 to 2.42)	0.70 (0.13 to 3.72)	1.00 (0.12 to 8.06)	Not estimable
Placebo	9	254	2.66 (1.50 to 4.72)	2.65 (0.69 to 10.12)	0.87 (0.35 to 2.17)	1.37 (0.32 to 5.87)
Quetiapine	2	480	0.71 (0.50 to 1.02)	0.50 (0.13 to 1.92)	1.99 (0.49 to 8.10)	0.87 (0.47 to 1.61)
Thyroid hormone	3	196	0.65 (0.32 to 1.32)	0.52 (0.25 to 1.09)	0.85 (0.45 to 1.61)	2.86 (1.14 to 7.18)
Methylphenidate vs						
Placebo	2	205	1.42 (0.81 to 2.50)	4.46 (0.47 to 42.51)	1.10 (0.14 to 8.67)	3.09 (0.21 to 45.37)
Olanzapine vs						
placebo	4	1076	1.41 (0.89 to 2.23)	1.79 (1.28 to 2.51)	1.24 (0.90 to 1.70)	3.68 (1.94 to 6.97)
Pindolol vs						
Buspirone	1	14	0.30 (0.03 to 2.76)	..	..	..
Placebo	4	141	1.15 (0.26 to 5.04)	1.35 (0.58 to 3.11)	0.45 (0.08 to 2.55)	0.90 (0.05 to 15.49)
Placebo vs						
Aripiprazole	4	1317	0.52 (0.40 to 0.67)	0.51 (0.39 to 0.68)	0.81 (0.57 to 1.13)	0.37 (0.17 to 0.81)
Bupropion	2	385	0.94 (0.60 to 1.47)	0.49 (0.10 to 2.39)	0.62 (0.39 to 0.98)	0.79 (0.46 to 1.34)
Buspirone	2	221	0.88 (0.51 to 1.51)	..	1.63 (0.67 to 3.97)	1.93 (0.17 to 21.90)
Lamotrigine	2	130	1.07 (0.51 to 2.25)	..	1.35 (0.63 to 2.90)	1.13 (0.43 to 2.92)
Lithium	9	254	0.38 (0.21 to 0.67)	0.38 (0.10 to 1.44)	1.15 (0.46 to 2.85)	0.73 (0.17 to 3.14)
Methylphenidate	2	205	0.70 (0.40 to 1.24)	0.22 (0.02 to 2.14)	0.91 (0.12 to 7.21)	0.32 (0.02 to 4.76)
Olanzapine	4	1076	0.71 (0.45 to 1.12)	0.56 (0.40 to 0.78)	0.81 (0.59 to 1.11)	0.27 (0.14 to 0.52)
Pindolol	4	141	0.87 (0.20 to 3.81)	0.74 (0.32 to 1.72)	2.23 (0.39 to 12.65)	1.11 (0.06 to 18.93)
Quetiapine	6	1071	0.61 (0.47 to 0.79)	0.53 (0.39 to 0.71)	0.72 (0.51 to 1.00)	0.16 (0.07 to 0.33)
Risperidone	3	394	0.57 (0.37 to 0.87)	0.39 (0.23 to 0.68)	1.16 (0.40 to 3.38)	0.36 (0.11 to 1.12)
Thyroid hormone	4	75	0.98 (0.07 to 14.33)	0.20 (0.03 to 1.20)	Not estimable	Not estimable
Quetiapine vs						
Lithium	2	480	1.40 (0.98 to 2.00)	2.02 (0.52 to 7.81)	0.50 (0.12 to 2.04)	1.15 (0.62 to 2.14)
placebo	6	1071	1.63 (1.26 to 2.11)	1.90 (1.42 to 2.54)	1.40 (1.00 to 1.96)	6.34 (2.99 to 13.45)
Risperidone vs						

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Bupropion	1	20	..	..	3.32 (0.12 to 91.60)	..
Buspirone	1	91	0.67 (0.29 to 1.54)	0.75 (0.30 to 1.86)	1.59 (0.55 to 4.63)	5.34 (0.25 to 114.49)
Placebo	3	394	1.77 (1.14 to 2.72)	2.54 (1.47 to 4.41)	0.86 (0.30 to 2.51)	2.81 (0.90 to 8.82)
Thyroid hormone	1	93	0.63 (0.28 to 1.42)	0.61 (0.25 to 1.46)	4.29 (1.10 to 16.76)	5.57 (0.26 to 119.35)
Thyroid hormone vs						
Buspirone	1	94	1.08 (0.48 to 2.44)	1.24 (0.53 to 2.90)	0.37 (0.09 to 1.53)	Not estimable
Lithium	3	196	1.55 (0.76 to 3.16)	1.92 (0.92 to 4.02)	1.18 (0.62 to 2.23)	0.35 (0.14 to 0.88)
Placebo	4	75	1.55 (0.55 to 4.36)	4.90 (0.84 to 28.73)	Not estimable	Not estimable
Risperidone	1	93	1.60 (0.70 to 3.63)	1.65 (0.68 to 3.99)	0.23 (0.06 to 0.91)	0.18 (0.01 to 3.84)

Summary estimates for primary efficacy (response rates) and secondary efficacy (remission rates), acceptability (all-cause discontinuation) and tolerability (side-effects discontinuation) from meta-analyses of direct comparisons between pairs of active drugs or active drug versus placebo. OR=odds ratio. CI=confidence interval. For efficacy outcomes, ORs greater than unity favor the first treatment. For acceptability and tolerability outcomes, ORs less than unity favor the first treatment.

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Supplementary eTable 4. Statistical Heterogeneity and Publication Bias from Traditional Pairwise Meta-Analysis

Comparison	Heterogeneity		Publication bias	
	I^2	Chi^2	Begg's Test (*P*)	Egger's test (*P*)
Aripiprazole vs Placebo	0.00%	1.96	0.734	0.232
Buspirone vs Placebo	0.00%	0.00	1.000	NA
Lamotrigine vs Placebo	0.00%	0.18	1.000	NA
Lithium vs Placebo	0.00%	5.17	0.711	0.958
Lithium vs Quetiapine	0.00%	0.18	1.000	NA
Lithium vs Thyroid hormone	0.00%	0.09	1.000	NA
Methylphenidate vs Placebo	0.00%	0.48	1.000	NA
Olanzapine vs placeb	0.00%	3.39	0.806	0.394
Pindolol vs Placebo	27.60%	4.14	0.734	0.998
Quetiapine vs Placeb	0.00%	3.24	0.035	0.001
Risperidone vs Placebo	0.00%	0.08	1.000	0.846

Abbreviations: NA, not available

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Supplementary eTable 5A. Sensitivity Analysis of Effect Sizes for Primary Efficacy and Acceptability Outcomes in the Network Meta-Analysis Model

	Therapy dose		Therapy duration		Exclusion of imputation		Exclusion of bipolar patients	
	Efficacy	Acceptability	Efficacy	Acceptability	Efficacy	Acceptability	Efficacy	Acceptability
Comparison	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)
Aripiprazole versus:								
Bupropion	1.65 (0.76 to 3.07)	1.53 (0.50 to 3.98)	1.54 (0.80 to 2.63)	1.74 (0.54 to 4.81)	1.48 (0.71 to 2.65)	1.50 (0.58 to 3.59)	1.47 (0.66 to 2.70)	1.59 (0.52 to 4.26)
Buspirone	1.69 (0.82 to 2.95)	1.31 (0.44 to 3.33)	1.65 (0.87 to 2.73)	1.53 (0.49 to 4.12)	1.53 (0.76 to 2.59)	1.28 (0.49 to 3.09)	1.51 (0.67 to 2.70)	1.34 (0.43 to 3.67)
Lamotrigine	1.63 (0.39 to 4.45)	2.18 (0.29 to 8.22)	1.83 (0.74 to 3.71)	1.97 (0.51 to 5.47)	1.74 (0.66 to 3.63)	1.86 (0.57 to 4.70)	1.78 (0.68 to 3.73)	1.91 (0.52 to 5.12)
Lithium	1.29 (0.63 to 2.20)	1.22 (0.43 to 2.97)	1.53 (0.78 to 2.64)	1.17 (0.37 to 3.07)	1.24 (0.63 to 2.04)	1.02 (0.41 to 2.29)	1.40 (0.68 to 2.38)	1.01 (0.34 to 2.56)
Methylphenidate	1.54 (0.60 to 3.18)	1.21 (0.28 to 3.52)	1.38 (0.60 to 2.67)	1.33 (0.30 to 4.03)	1.39 (0.57 to 2.77)	1.22 (0.32 to 3.33)	1.39 (0.55 to 2.82)	1.29 (0.31 to 3.74)
Olanzapine	1.49 (0.76 to 2.55)	1.15 (0.44 to 2.57)	1.38 (0.78 to 2.17)	1.26 (0.47 to 2.95)	1.37 (0.72 to 2.24)	1.18 (0.52 to 2.45)	1.36 (0.70 to 2.24)	1.23 (0.49 to 2.77)
Pindolol	2.22 (0.79 to 4.97)	3.60 (0.40 to 14.81)	0.01 (0.00 to 0.05)	3.09E+05 (0.00 to 639.40)	2.01 (0.74 to 4.40)	3.87 (0.46 to 15.24)	2.00 (0.72 to 4.40)	3.87 (0.44 to 15.84)
Quetiapine	1.12 (0.57 to 1.81)	1.31 (0.54 to 2.93)	1.09 (0.60 to 1.67)	1.52 (0.60 to 3.64)	1.01 (0.52 to 1.59)	1.19 (0.54 to 2.49)	1.03 (0.51 to 1.64)	1.41 (0.59 to 3.30)
Risperidone	1.43 (0.71 to 2.59)	1.12 (0.39 to 2.68)	1.33 (0.71 to 2.27)	1.28 (0.43 to 3.23)	1.29 (0.65 to 2.24)	1.11 (0.44 to 2.50)	1.30 (0.64 to 2.28)	1.18 (0.42 to 2.87)
Thyroid hormone	1.13 (0.49 to 2.20)	3.65 (0.69 to 12.29)	1.24 (0.44 to 2.78)	6.29 (0.79 to 25.87)	1.05 (0.47 to 1.98)	3.64 (0.77 to 11.80)	1.08 (0.47 to 2.08)	4.05 (0.72 to 14.32)
Bupropion versus:								
Buspirone	1.07 (0.59 to 1.74)	0.94 (0.39 to 1.99)	1.11 (0.66 to 1.70)	0.97 (0.38 to 2.16)	1.08 (0.60 to 1.71)	0.91 (0.43 to 1.81)	1.07 (0.56 to 1.75)	0.92 (0.37 to 2.00)
Lamotrigine	1.07 (0.25 to 3.02)	1.69 (0.19 to 6.51)	1.26 (0.47 to 2.72)	1.38 (0.28 to 4.01)	1.26 (0.45 to 2.80)	1.42 (0.36 to 3.70)	1.32 (0.46 to 3.00)	1.45 (0.31 to 4.06)
Lithium	0.84 (0.38 to 1.54)	0.94 (0.28 to 2.37)	1.06 (0.49 to 1.98)	0.82 (0.20 to 2.21)	0.90 (0.42 to 1.61)	0.78 (0.26 to 1.80)	1.03 (0.46 to 1.95)	0.76 (0.20 to 1.99)
Methylphenidate	1.01 (0.37 to 2.22)	0.94 (0.19 to 2.81)	0.95 (0.38 to 1.96)	0.93 (0.17 to 2.88)	1.01 (0.38 to 2.17)	0.93 (0.21 to 2.58)	1.03 (0.37 to 2.31)	0.98 (0.19 to 2.95)
Olanzapine	0.98 (0.45 to 1.83)	0.89 (0.28 to 2.09)	0.95 (0.49 to 1.67)	0.88 (0.25 to 2.16)	0.99 (0.47 to 1.82)	0.90 (0.32 to 1.93)	1.01 (0.45 to 1.91)	0.93 (0.28 to 2.19)
Pindolol	1.45 (0.49 to 3.42)	2.80 (0.27 to 11.84)	0.01 (0.00 to 0.03)	1.29E+05 (0.00 to 450.40)	1.45 (0.50 to 3.36)	2.96 (0.31 to 11.77)	1.48 (0.49 to 3.46)	2.95 (0.28 to 12.35)
Quetiapine	0.73 (0.34 to 1.29)	1.01 (0.34 to 2.36)	0.75 (0.38 to 1.27)	1.05 (0.33 to 2.62)	0.73 (0.34 to 1.28)	0.90 (0.34 to 1.95)	0.76 (0.34 to 1.36)	1.05 (0.35 to 2.56)
Risperidone	0.93 (0.43 to 1.79)	0.85 (0.27 to 1.99)	0.91 (0.46 to 1.64)	0.87 (0.26 to 2.13)	0.93 (0.44 to 1.75)	0.83 (0.30 to 1.84)	0.95 (0.44 to 1.84)	0.87 (0.27 to 2.05)
Thyroid hormone	0.74 (0.31 to 1.49)	2.74 (0.51 to 8.95)	0.84 (0.30 to 1.88)	4.16 (0.52 to 16.38)	0.75 (0.32 to 1.50)	2.70 (0.56 to 8.48)	0.79 (0.33 to 1.62)	2.92 (0.51 to 9.95)
Buspirone versus:								
Lamotrigine	1.02 (0.25 to 2.86)	1.94 (0.23 to 7.35)	1.16 (0.45 to 2.49)	1.55 (0.32 to 4.36)	1.20 (0.45 to 2.60)	1.68 (0.42 to 4.34)	1.27 (0.46 to 2.89)	1.74 (0.36 to 4.95)
Lithium	0.80 (0.41 to 1.40)	1.08 (0.33 to 2.59)	0.98 (0.47 to 1.81)	0.91 (0.24 to 2.37)	0.85 (0.44 to 1.47)	0.91 (0.31 to 2.04)	1.00 (0.48 to 1.87)	0.91 (0.24 to 2.35)
Methylphenidate	0.96 (0.37 to 2.08)	1.08 (0.22 to 3.14)	0.88 (0.36 to 1.80)	1.04 (0.19 to 3.15)	0.96 (0.38 to 2.03)	1.09 (0.24 to 3.01)	1.00 (0.37 to 2.24)	1.17 (0.22 to 3.51)
Olanzapine	0.94 (0.48 to 1.68)	1.03 (0.33 to 2.32)	0.88 (0.47 to 1.52)	0.99 (0.29 to 2.32)	0.94 (0.49 to 1.68)	1.06 (0.37 to 2.22)	0.98 (0.46 to 1.86)	1.11 (0.32 to 2.62)
Pindolol	1.38 (0.50 to 3.16)	3.26 (0.32 to 13.87)	0.01 (0.00 to 0.03)	1.71E+05 (0.00 to 501.30)	1.37 (0.52 to 3.10)	3.51 (0.36 to 14.28)	1.43 (0.50 to 3.31)	3.54 (0.32 to 14.92)
Quetiapine	0.70 (0.36 to 1.19)	1.16 (0.41 to 2.57)	0.69 (0.37 to 1.15)	1.17 (0.39 to 2.77)	0.70 (0.36 to 1.17)	1.06 (0.40 to 2.22)	0.74 (0.36 to 1.32)	1.26 (0.41 to 3.00)

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Risperidone	0.89 (0.46 to 1.60)	0.96 (0.34 to 2.10)	0.84 (0.46 to 1.44)	0.95 (0.32 to 2.14)	0.88 (0.47 to 1.58)	0.97 (0.37 to 1.99)	0.92 (0.46 to 1.73)	1.02 (0.34 to 2.29)
Thyroid hormone	0.70 (0.33 to 1.32)	3.06 (0.66 to 9.36)	0.77 (0.31 to 1.62)	4.43 (0.67 to 16.24)	0.71 (0.34 to 1.35)	3.10 (0.71 to 9.28)	0.76 (0.35 to 1.51)	3.37 (0.66 to 10.79)
Lamotrigine versus:								
Lithium	1.07 (0.29 to 2.85)	1.00 (0.15 to 3.50)	0.95 (0.39 to 1.94)	0.74 (0.19 to 2.10)	0.82 (0.33 to 1.68)	0.67 (0.20 to 1.72)	0.90 (0.36 to 1.83)	0.66 (0.17 to 1.84)
Methylphenidate	1.31 (0.27 to 3.95)	1.05 (0.10 to 4.38)	0.87 (0.29 to 2.04)	0.87 (0.15 to 2.95)	0.93 (0.29 to 2.27)	0.81 (0.16 to 2.51)	0.90 (0.28 to 2.20)	0.87 (0.15 to 2.86)
Olanzapine	1.28 (0.31 to 3.56)	1.00 (0.13 to 3.66)	0.87 (0.35 to 1.81)	0.83 (0.21 to 2.32)	0.92 (0.35 to 1.95)	0.78 (0.24 to 1.98)	0.89 (0.34 to 1.88)	0.82 (0.22 to 2.22)
Pindolol	1.90 (0.36 to 6.00)	3.13 (0.16 to 15.65)	0.01 (0.00 to 0.03)	1.68E+05 (0.00 to 403.70)	1.34 (0.38 to 3.49)	2.58 (0.24 to 10.84)	1.31 (0.37 to 3.37)	2.58 (0.23 to 11.37)
Quetiapine	0.95 (0.24 to 2.59)	1.12 (0.16 to 4.01)	0.68 (0.28 to 1.36)	0.99 (0.28 to 2.73)	0.67 (0.27 to 1.37)	0.78 (0.25 to 1.98)	0.67 (0.26 to 1.35)	0.93 (0.27 to 2.55)
Risperidone	1.22 (0.30 to 3.49)	0.97 (0.12 to 3.63)	0.84 (0.32 to 1.82)	0.84 (0.20 to 2.48)	0.86 (0.32 to 1.92)	0.74 (0.21 to 2.00)	0.85 (0.31 to 1.87)	0.79 (0.20 to 2.24)
Thyroid hormone	0.96 (0.22 to 2.79)	3.16 (0.25 to 14.12)	0.78 (0.22 to 2.07)	4.13 (0.40 to 18.14)	0.70 (0.24 to 1.60)	2.43 (0.39 to 8.71)	0.70 (0.24 to 1.62)	2.71 (0.36 to 10.41)
Lithium versus:								
Methylphenidate	1.26 (0.50 to 2.72)	1.13 (0.24 to 3.24)	0.96 (0.39 to 2.03)	1.35 (0.25 to 4.22)	1.18 (0.49 to 2.47)	1.33 (0.32 to 3.63)	1.05 (0.42 to 2.28)	1.50 (0.30 to 4.53)
Olanzapine	1.22 (0.64 to 2.21)	1.08 (0.37 to 2.40)	0.96 (0.49 to 1.72)	1.29 (0.39 to 3.13)	1.16 (0.62 to 2.03)	1.29 (0.50 to 2.68)	1.03 (0.53 to 1.86)	1.43 (0.46 to 3.33)
Pindolol	1.82 (0.65 to 4.23)	3.40 (0.35 to 14.15)	0.01 (0.00 to 0.04)	4.24E+05 (0.00 to 648.20)	1.69 (0.63 to 3.85)	4.24 (0.47 to 16.78)	1.51 (0.53 to 3.50)	4.51 (0.45 to 19.00)
Quetiapine	0.90 (0.55 to 1.41)	1.18 (0.53 to 2.30)	0.74 (0.44 to 1.12)	1.46 (0.62 to 3.12)	0.84 (0.52 to 1.27)	1.25 (0.62 to 2.27)	0.76 (0.45 to 1.17)	1.55 (0.69 to 3.22)
Risperidone	1.17 (0.59 to 2.18)	1.04 (0.34 to 2.45)	0.93 (0.44 to 1.75)	1.30 (0.36 to 3.37)	1.09 (0.56 to 1.99)	1.21 (0.44 to 2.72)	0.98 (0.49 to 1.83)	1.36 (0.41 to 3.38)
Thyroid hormone	0.91 (0.45 to 1.66)	3.37 (0.63 to 11.00)	0.87 (0.28 to 2.05)	6.37 (0.71 to 26.47)	0.87 (0.45 to 1.57)	3.92 (0.81 to 12.48)	0.80 (0.40 to 1.47)	4.59 (0.78 to 15.80)
Methylphenidate versus:								
Olanzapine	1.11 (0.44 to 2.31)	1.29 (0.31 to 3.69)	1.12 (0.49 to 2.23)	1.33 (0.29 to 3.92)	1.11 (0.46 to 2.28)	1.27 (0.34 to 3.44)	1.12 (0.44 to 2.32)	1.30 (0.31 to 3.71)
Pindolol	1.64 (0.48 to 4.21)	4.06 (0.33 to 18.41)	0.01 (0.00 to 0.04)	2.85E+05 (0.00 to 644.50)	1.63 (0.50 to 4.14)	4.17 (0.36 to 18.02)	1.65 (0.48 to 4.22)	4.10 (0.33 to 18.47)
Quetiapine	0.83 (0.33 to 1.68)	1.47 (0.37 to 4.16)	0.88 (0.37 to 1.69)	1.59 (0.37 to 4.78)	0.82 (0.34 to 1.61)	1.28 (0.35 to 3.47)	0.85 (0.33 to 1.69)	1.48 (0.37 to 4.34)
Risperidone	1.06 (0.41 to 2.32)	1.25 (0.28 to 3.75)	1.08 (0.44 to 2.25)	1.34 (0.27 to 4.16)	1.05 (0.42 to 2.25)	1.20 (0.30 to 3.43)	1.07 (0.40 to 2.32)	1.24 (0.27 to 3.73)
Thyroid hormone	0.84 (0.29 to 1.91)	4.11 (0.53 to 15.69)	1.00 (0.30 to 2.54)	6.55 (0.57 to 29.41)	0.85 (0.30 to 1.93)	3.91 (0.58 to 14.44)	0.89 (0.31 to 2.04)	4.29 (0.52 to 17.00)
Olanzapine versus:								
Pindolol	1.56 (0.55 to 3.54)	3.43 (0.39 to 13.99)	0.01 (0.00 to 0.04)	2.99E+05 (0.00 to 559.00)	1.53 (0.56 to 3.45)	3.53 (0.41 to 13.65)	1.54 (0.55 to 3.45)	3.46 (0.39 to 14.09)
Quetiapine	0.78 (0.41 to 1.30)	1.24 (0.52 to 2.66)	0.81 (0.46 to 1.29)	1.32 (0.53 to 3.01)	0.77 (0.41 to 1.25)	1.08 (0.49 to 2.17)	0.79 (0.41 to 1.30)	1.25 (0.53 to 2.76)
Risperidone	1.00 (0.50 to 1.85)	1.06 (0.38 to 2.46)	1.00 (0.52 to 1.76)	1.12 (0.38 to 2.71)	0.99 (0.50 to 1.80)	1.02 (0.40 to 2.20)	1.00 (0.50 to 1.85)	1.05 (0.37 to 2.43)
Thyroid hormone	0.79 (0.35 to 1.56)	3.47 (0.67 to 11.47)	0.93 (0.33 to 2.13)	5.49 (0.68 to 22.13)	0.80 (0.36 to 1.57)	3.32 (0.70 to 10.62)	0.83 (0.37 to 1.67)	3.60 (0.64 to 12.45)
Pindolol versus:								
Quetiapine	0.49 (0.31 to 0.73)	0.77 (0.08 to 2.97)	7.50E+30 (20.19 to 8.62E+26)	1.84E+06 (0.00 to 1.16E+03)	0.59 (0.22 to 1.26)	0.64 (0.07 to 2.42)	0.61 (0.22 to 1.34)	0.77 (0.08 to 3.03)
Risperidone	0.77 (0.42 to 1.28)	0.65 (0.06 to 2.61)	8.99E+30 (24.11 to 1.07E+27)	1.45E+06 (0.00 to 9.83E+02)	0.76 (0.27 to 1.73)	0.60 (0.06 to 2.34)	0.77 (0.27 to 1.78)	0.65 (0.06 to 2.57)

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Thyroid hormone	0.79 (0.47 to 1.21)	2.15 (0.14 to 10.03)	8.77E+30 (21.23 to 9.43E+26)	6.05E+06 (0.01 to 4.19E+03)	0.62 (0.20 to 1.46)	1.98 (0.14 to 9.07)	0.64 (0.20 to 1.54)	2.24 (0.14 to 10.53)
Quetiapine versus:								
Risperidone	0.77 (0.21 to 2.01)	0.92 (0.34 to 2.00)	1.27 (0.69 to 2.27)	0.92 (0.31 to 2.07)	1.33 (0.71 to 2.44)	1.00 (0.40 to 2.08)	1.31 (0.69 to 2.46)	0.91 (0.32 to 1.97)
Thyroid hormone	0.60 (0.36 to 0.90)	3.00 (0.60 to 9.55)	1.18 (0.43 to 2.73)	4.51 (0.57 to 17.74)	1.07 (0.52 to 2.05)	3.26 (0.71 to 10.16)	1.08 (0.53 to 2.14)	3.11 (0.56 to 10.27)
Risperidone versus:								
Thyroid hormone	0.72 (0.33 to 1.36)	3.52 (0.78 to 10.88)	0.96 (0.38 to 2.02)	5.18 (0.81 to 19.11)	0.85 (0.40 to 1.58)	3.47 (0.83 to 10.45)	0.87 (0.41 to 1.65)	3.66 (0.78 to 11.63)
Placebo versus:								
Aripiprazole	0.49 (0.31 to 0.73)	0.86 (0.43 to 1.54)	0.54 (0.38 to 0.75)	0.81 (0.39 to 1.44)	0.54 (0.37 to 0.79)	0.81 (0.44 to 1.32)	0.54 (0.37 to 0.80)	0.81 (0.41 to 1.40)
Bupropion	0.77 (0.42 to 1.28)	1.19 (0.51 to 2.63)	0.80 (0.47 to 1.26)	1.26 (0.50 to 2.91)	0.77 (0.43 to 1.26)	1.12 (0.53 to 2.29)	0.77 (0.40 to 1.29)	1.16 (0.49 to 2.63)
Buspirone	0.79 (0.47 to 1.21)	1.02 (0.45 to 2.18)	0.86 (0.52 to 1.30)	1.10 (0.46 to 2.46)	0.80 (0.47 to 1.21)	0.95 (0.45 to 1.96)	0.79 (0.42 to 1.29)	0.98 (0.39 to 2.27)
Lamotrigine	0.77 (0.21 to 2.01)	1.70 (0.26 to 5.96)	0.95 (0.42 to 1.82)	1.43 (0.46 to 3.44)	0.90 (0.39 to 1.77)	1.39 (0.50 to 3.12)	0.93 (0.41 to 1.82)	1.40 (0.47 to 3.28)
Lithium	0.60 (0.36 to 0.90)	0.95 (0.44 to 1.89)	0.80 (0.46 to 1.26)	0.85 (0.35 to 1.84)	0.65 (0.40 to 0.95)	0.76 (0.38 to 1.43)	0.73 (0.43 to 1.11)	0.74 (0.32 to 1.57)
Methylphenidate	0.72 (0.33 to 1.36)	0.94 (0.27 to 2.42)	0.72 (0.35 to 1.31)	0.96 (0.27 to 2.55)	0.73 (0.34 to 1.35)	0.91 (0.28 to 2.24)	0.73 (0.33 to 1.37)	0.95 (0.27 to 2.44)
Olanzapine	0.70 (0.43 to 1.03)	0.90 (0.48 to 1.61)	0.72 (0.48 to 1.01)	0.92 (0.47 to 1.70)	0.71 (0.45 to 1.04)	0.88 (0.50 to 1.49)	0.71 (0.44 to 1.04)	0.90 (0.48 to 1.63)
Pindolol	1.04 (0.42 to 2.16)	2.81 (0.37 to 10.97)	0.01 (0.00 to 0.03)	2.10E+05 (0.00 to 474.90)	1.05 (0.43 to 2.18)	2.90 (0.39 to 10.87)	1.05 (0.42 to 2.17)	2.84 (0.38 to 11.08)
Quetiapine	0.53 (0.33 to 0.73)	1.02 (0.58 to 1.79)	0.57 (0.37 to 0.77)	1.10 (0.60 to 2.04)	0.53 (0.33 to 0.73)	0.88 (0.53 to 1.50)	0.54 (0.33 to 0.75)	1.03 (0.57 to 1.90)
Risperidone	0.67 (0.40 to 1.06)	0.87 (0.41 to 1.72)	0.69 (0.42 to 1.08)	0.92 (0.41 to 1.90)	0.67 (0.40 to 1.06)	0.83 (0.41 to 1.57)	0.68 (0.40 to 1.07)	0.86 (0.40 to 1.72)
Thyroid hormone	0.53 (0.27 to 0.92)	2.84 (0.65 to 8.78)	0.65 (0.25 to 1.38)	4.53 (0.68 to 17.38)	0.55 (0.28 to 0.94)	2.72 (0.67 to 8.21)	0.56 (0.28 to 0.99)	2.96 (0.64 to 9.67)

Abbreviations: SMD= standardized mean difference, OR=odds ratio, CrI= credibility interval.

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Supplementary Table e5B. Sensitivity Analysis of Effect Sizes for Primary Efficacy and Acceptability Outcomes in the Network Meta-Analysis Model

	Blinding		Refractory duration		Thyroid hormone		Exclusion of triiodothyronine	
	Efficacy	Acceptability	Efficacy	Acceptability	Efficacy	Acceptability	Efficacy	Acceptability
Comparison	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)
Aripiprazole versus:								
Bupropion	1.92 (0.75 to 3.97)	0.96 (0.35 to 2.34)	1.50 (0.73 to 2.63)	1.52 (0.54 to 3.79)	1.63 (0.76 to 2.94)	1.63 (0.52 to 4.43)	1.49 (0.70 to 2.70)	1.72 (0.55 to 4.62)
Buspirone	1.30 (0.61 to 2.35)	2.06 (0.71 to 4.89)	1.56 (0.79 to 2.61)	1.27 (0.46 to 3.15)	1.82 (0.86 to 3.20)	1.38 (0.42 to 3.87)	1.54 (0.75 to 2.64)	1.52 (0.50 to 4.04)
Lamotrigine	2.30 (0.79 to 5.27)	2.02 (0.62 to 5.08)	1.77 (0.70 to 3.62)	1.92 (0.55 to 4.99)	1.74 (0.67 to 3.57)	1.95 (0.52 to 5.24)	1.71 (0.66 to 3.60)	1.95 (0.51 to 5.31)
Lithium	1.09 (0.52 to 1.85)	1.10 (0.47 to 2.51)	1.35 (0.71 to 2.20)	1.12 (0.42 to 2.59)	1.22 (0.61 to 2.03)	1.13 (0.41 to 2.70)	1.21 (0.58 to 2.05)	1.16 (0.41 to 2.81)
Methylphenidate	1.39 (0.55 to 2.81)	1.18 (0.33 to 3.06)	1.39 (0.58 to 2.72)	1.26 (0.32 to 3.56)	1.38 (0.56 to 2.74)	1.30 (0.31 to 3.84)	1.38 (0.56 to 2.78)	1.31 (0.30 to 3.87)
Olanzapine	1.36 (0.70 to 2.27)	1.14 (0.55 to 2.26)	1.37 (0.74 to 2.22)	1.21 (0.50 to 2.63)	1.37 (0.71 to 2.25)	1.24 (0.49 to 2.83)	1.37 (0.70 to 2.24)	1.25 (0.48 to 2.84)
Pindolol	1.97 (0.70 to 4.33)	3.69 (0.47 to 14.83)	2.01 (0.75 to 4.30)	3.94 (0.43 to 16.63)	2.04 (0.75 to 4.50)	3.88 (0.42 to 15.90)	1.99 (0.73 to 4.39)	4.07 (0.43 to 17.16)
Quetiapine	0.99 (0.50 to 1.58)	1.22 (0.60 to 2.49)	1.04 (0.55 to 1.60)	1.41 (0.62 to 3.15)	0.99 (0.51 to 1.57)	1.48 (0.61 to 3.42)	0.99 (0.49 to 1.57)	1.49 (0.61 to 3.44)
Risperidone	1.24 (0.61 to 2.21)	1.17 (0.49 to 2.52)	1.33 (0.67 to 2.30)	0.95 (0.34 to 2.21)	1.10 (0.51 to 2.01)	1.43 (0.46 to 3.71)	1.31 (0.64 to 2.30)	1.29 (0.44 to 3.21)
Thyroid hormone	0.95 (0.42 to 1.81)	4.33 (0.96 to 13.42)	1.09 (0.51 to 2.02)	3.46 (0.71 to 11.39)	1.03 (0.39 to 2.24)	3.10 (0.18 to 15.81)	1.17 (0.36 to 2.81)	7.76 (0.85 to 33.76)
Bupropion versus:								
Buspirone	0.78 (0.28 to 1.72)	2.52 (0.67 to 6.49)	1.08 (0.62 to 1.70)	0.90 (0.40 to 1.86)	1.16 (0.64 to 1.88)	0.92 (0.36 to 2.03)	1.08 (0.59 to 1.75)	0.98 (0.40 to 2.11)
Lamotrigine	1.38 (0.38 to 3.62)	2.48 (0.59 to 6.86)	1.27 (0.46 to 2.80)	1.47 (0.35 to 3.98)	1.16 (0.40 to 2.58)	1.46 (0.30 to 4.08)	1.24 (0.43 to 2.80)	1.37 (0.29 to 3.87)
Lithium	0.65 (0.23 to 1.33)	1.34 (0.44 to 3.37)	0.97 (0.46 to 1.74)	0.85 (0.27 to 2.05)	0.81 (0.36 to 1.51)	0.84 (0.23 to 2.11)	0.87 (0.38 to 1.65)	0.81 (0.22 to 2.06)
Methylphenidate	0.83 (0.26 to 1.99)	1.44 (0.33 to 4.02)	0.99 (0.38 to 2.12)	0.96 (0.21 to 2.78)	0.92 (0.34 to 2.00)	0.97 (0.18 to 2.92)	1.00 (0.37 to 2.21)	0.92 (0.17 to 2.78)
Olanzapine	0.81 (0.31 to 1.70)	1.39 (0.48 to 3.12)	0.98 (0.48 to 1.78)	0.93 (0.31 to 2.10)	0.91 (0.42 to 1.69)	0.93 (0.27 to 2.22)	0.99 (0.46 to 1.85)	0.87 (0.26 to 2.09)
Pindolol	1.17 (0.33 to 2.98)	4.51 (0.47 to 18.67)	1.44 (0.51 to 3.23)	3.04 (0.30 to 13.04)	1.35 (0.46 to 3.08)	2.90 (0.26 to 12.13)	1.44 (0.49 to 3.37)	2.90 (0.26 to 12.48)
Quetiapine	0.59 (0.22 to 1.17)	1.48 (0.55 to 3.44)	0.74 (0.36 to 1.27)	1.08 (0.39 to 2.49)	0.66 (0.30 to 1.17)	1.09 (0.35 to 2.64)	0.71 (0.32 to 1.26)	1.04 (0.34 to 2.51)
Risperidone	0.74 (0.27 to 1.62)	1.42 (0.47 to 3.38)	0.94 (0.45 to 1.77)	0.71 (0.23 to 1.63)	0.73 (0.30 to 1.49)	1.05 (0.28 to 2.76)	0.94 (0.43 to 1.80)	0.88 (0.27 to 2.12)
Thyroid hormone	0.57 (0.19 to 1.31)	5.31 (0.95 to 17.76)	0.77 (0.34 to 1.52)	2.59 (0.50 to 8.38)	0.69 (0.23 to 1.63)	2.30 (0.12 to 11.87)	0.83 (0.26 to 1.99)	5.13 (0.59 to 21.67)
Buspirone versus:								
Lamotrigine	1.92 (0.60 to 4.75)	1.17 (0.28 to 3.26)	1.20 (0.46 to 2.57)	1.75 (0.42 to 4.67)	1.03 (0.37 to 2.29)	1.77 (0.35 to 5.07)	1.18 (0.44 to 2.63)	1.53 (0.33 to 4.22)
Lithium	0.90 (0.41 to 1.65)	0.63 (0.20 to 1.62)	0.91 (0.48 to 1.58)	1.01 (0.32 to 2.36)	0.72 (0.34 to 1.34)	1.02 (0.27 to 2.56)	0.83 (0.39 to 1.53)	0.90 (0.26 to 2.20)
Methylphenidate	1.16 (0.42 to 2.60)	0.68 (0.15 to 2.05)	0.94 (0.38 to 1.99)	1.14 (0.25 to 3.25)	0.82 (0.31 to 1.78)	1.17 (0.21 to 3.56)	0.95 (0.37 to 2.07)	1.02 (0.20 to 3.04)
Olanzapine	1.13 (0.53 to 2.12)	0.66 (0.23 to 1.53)	0.93 (0.49 to 1.64)	1.10 (0.37 to 2.41)	0.81 (0.39 to 1.50)	1.12 (0.31 to 2.71)	0.94 (0.48 to 1.71)	0.97 (0.29 to 2.26)
Pindolol	1.62 (0.56 to 3.72)	2.15 (0.22 to 9.21)	1.35 (0.51 to 2.98)	3.62 (0.36 to 15.56)	1.19 (0.43 to 2.70)	3.53 (0.30 to 15.07)	1.36 (0.49 to 3.12)	3.26 (0.29 to 13.90)
Quetiapine	0.82 (0.38 to 1.46)	0.70 (0.25 to 1.66)	0.70 (0.37 to 1.16)	1.28 (0.47 to 2.81)	0.59 (0.28 to 1.03)	1.32 (0.40 to 3.18)	0.68 (0.34 to 1.17)	1.15 (0.39 to 2.64)

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Risperidone	1.02 (0.50 to 1.87)	0.65 (0.24 to 1.45)	0.89 (0.47 to 1.58)	0.84 (0.29 to 1.79)	0.65 (0.28 to 1.33)	1.27 (0.31 to 3.38)	0.89 (0.47 to 1.60)	0.96 (0.33 to 2.11)
Thyroid hormone	0.78 (0.35 to 1.49)	2.33 (0.55 to 6.99)	0.73 (0.36 to 1.36)	3.00 (0.65 to 9.18)	0.61 (0.21 to 1.45)	2.79 (0.14 to 14.39)	0.78 (0.28 to 1.76)	5.44 (0.75 to 21.42)
Lamotrigine versus:								
Lithium	0.57 (0.18 to 1.34)	0.68 (0.19 to 1.88)	0.87 (0.36 to 1.74)	0.72 (0.21 to 1.87)	0.80 (0.33 to 1.64)	0.73 (0.20 to 1.93)	0.81 (0.32 to 1.66)	0.75 (0.20 to 2.01)
Methylphenidate	0.73 (0.20 to 1.89)	0.74 (0.14 to 2.27)	0.90 (0.29 to 2.18)	0.82 (0.16 to 2.63)	0.91 (0.29 to 2.22)	0.86 (0.15 to 2.85)	0.94 (0.29 to 2.29)	0.86 (0.15 to 2.87)
Olanzapine	0.72 (0.24 to 1.65)	0.71 (0.22 to 1.77)	0.89 (0.35 to 1.87)	0.79 (0.23 to 2.06)	0.91 (0.36 to 1.95)	0.82 (0.22 to 2.22)	0.93 (0.35 to 1.99)	0.82 (0.22 to 2.24)
Pindolol	1.04 (0.26 to 2.81)	2.28 (0.22 to 9.81)	1.30 (0.39 to 3.26)	2.58 (0.23 to 11.48)	1.35 (0.39 to 3.49)	2.55 (0.22 to 11.14)	1.35 (0.38 to 3.53)	2.67 (0.23 to 12.01)
Quetiapine	0.52 (0.17 to 1.17)	0.75 (0.24 to 1.94)	0.67 (0.27 to 1.34)	0.92 (0.28 to 2.41)	0.66 (0.26 to 1.34)	0.96 (0.28 to 2.59)	0.66 (0.26 to 1.37)	0.98 (0.28 to 2.64)
Risperidone	0.66 (0.21 to 1.56)	0.73 (0.20 to 1.94)	0.86 (0.33 to 1.90)	0.62 (0.16 to 1.69)	0.73 (0.26 to 1.67)	0.94 (0.22 to 2.79)	0.89 (0.32 to 1.98)	0.85 (0.21 to 2.46)
Thyroid hormone	0.50 (0.15 to 1.26)	2.70 (0.42 to 9.90)	0.70 (0.25 to 1.59)	2.27 (0.36 to 8.21)	0.68 (0.21 to 1.72)	2.02 (0.10 to 10.52)	0.79 (0.20 to 2.24)	5.13 (0.45 to 23.47)
Lithium versus:								
Methylphenidate	1.36 (0.54 to 2.99)	1.20 (0.30 to 3.15)	1.08 (0.44 to 2.24)	1.27 (0.29 to 3.57)	1.19 (0.48 to 2.50)	1.31 (0.28 to 3.80)	1.22 (0.48 to 2.65)	1.30 (0.27 to 3.82)
Olanzapine	1.33 (0.69 to 2.46)	1.16 (0.45 to 2.30)	1.06 (0.58 to 1.84)	1.22 (0.45 to 2.64)	1.18 (0.62 to 2.09)	1.25 (0.44 to 2.80)	1.20 (0.62 to 2.21)	1.23 (0.42 to 2.82)
Pindolol	1.92 (0.67 to 4.45)	3.77 (0.42 to 15.09)	1.56 (0.58 to 3.45)	4.00 (0.41 to 17.00)	1.75 (0.63 to 3.99)	3.91 (0.39 to 16.19)	1.76 (0.62 to 4.11)	4.10 (0.39 to 17.41)
Quetiapine	0.94 (0.57 to 1.50)	1.19 (0.60 to 2.10)	0.79 (0.48 to 1.18)	1.37 (0.66 to 2.64)	0.84 (0.51 to 1.28)	1.42 (0.66 to 2.84)	0.85 (0.51 to 1.32)	1.41 (0.65 to 2.85)
Risperidone	1.21 (0.60 to 2.32)	1.18 (0.43 to 2.52)	1.03 (0.53 to 1.86)	0.96 (0.31 to 2.21)	0.94 (0.44 to 1.86)	1.42 (0.43 to 3.62)	1.15 (0.55 to 2.26)	1.27 (0.40 to 3.14)
Thyroid hormone	0.91 (0.46 to 1.70)	4.38 (0.89 to 13.53)	0.83 (0.44 to 1.47)	3.46 (0.68 to 11.24)	0.86 (0.38 to 1.74)	3.00 (0.19 to 14.91)	1.03 (0.31 to 2.61)	7.63 (0.79 to 33.26)
Methylphenidate versus:								
Olanzapine	1.12 (0.44 to 2.34)	1.25 (0.36 to 3.22)	1.12 (0.46 to 2.26)	1.29 (0.32 to 3.56)	1.12 (0.46 to 2.33)	1.30 (0.30 to 3.75)	1.12 (0.45 to 2.31)	1.31 (0.30 to 3.81)
Pindolol	1.62 (0.47 to 4.14)	4.07 (0.38 to 18.17)	1.64 (0.50 to 4.09)	4.20 (0.34 to 19.09)	1.68 (0.50 to 4.24)	4.05 (0.32 to 18.02)	1.64 (0.49 to 4.18)	4.26 (0.32 to 19.63)
Quetiapine	0.81 (0.32 to 1.62)	1.33 (0.39 to 3.50)	0.84 (0.35 to 1.65)	1.50 (0.40 to 4.20)	0.82 (0.33 to 1.62)	1.54 (0.38 to 4.48)	0.81 (0.32 to 1.61)	1.56 (0.38 to 4.57)
Risperidone	1.02 (0.38 to 2.24)	1.28 (0.33 to 3.52)	1.08 (0.42 to 2.30)	1.01 (0.23 to 2.97)	0.90 (0.33 to 2.01)	1.49 (0.31 to 4.67)	1.08 (0.41 to 2.34)	1.35 (0.29 to 4.16)
Thyroid hormone	0.78 (0.27 to 1.80)	4.77 (0.69 to 16.97)	0.89 (0.33 to 2.01)	3.69 (0.51 to 13.78)	0.85 (0.26 to 2.15)	3.30 (0.15 to 17.09)	0.96 (0.25 to 2.57)	8.20 (0.63 to 38.95)
Olanzapine versus:								
Pindolol	1.51 (0.54 to 3.43)	3.44 (0.43 to 13.71)	1.53 (0.57 to 3.35)	3.55 (0.39 to 14.77)	1.56 (0.56 to 3.51)	3.44 (0.37 to 13.89)	1.53 (0.55 to 3.46)	3.62 (0.38 to 15.07)
Quetiapine	0.76 (0.39 to 1.25)	1.13 (0.56 to 2.19)	0.78 (0.43 to 1.25)	1.27 (0.56 to 2.67)	0.76 (0.40 to 1.23)	1.30 (0.54 to 2.85)	0.75 (0.39 to 1.23)	1.31 (0.54 to 2.88)
Risperidone	0.96 (0.47 to 1.78)	1.09 (0.46 to 2.25)	1.01 (0.51 to 1.82)	0.85 (0.30 to 1.93)	0.84 (0.39 to 1.60)	1.26 (0.41 to 3.12)	1.00 (0.50 to 1.85)	1.14 (0.39 to 2.71)
Thyroid hormone	0.73 (0.32 to 1.45)	4.05 (0.90 to 12.68)	0.83 (0.38 to 1.60)	3.12 (0.63 to 10.12)	0.79 (0.29 to 1.79)	2.76 (0.16 to 13.90)	0.90 (0.28 to 2.21)	6.85 (0.75 to 29.36)
Pindolol versus:								
Quetiapine	0.60 (0.21 to 1.31)	0.68 (0.08 to 2.53)	0.60 (0.23 to 1.29)	0.78 (0.08 to 3.00)	0.58 (0.21 to 1.25)	0.82 (0.09 to 3.21)	0.59 (0.21 to 1.27)	0.81 (0.08 to 3.19)
Risperidone	0.75 (0.26 to 1.74)	0.65 (0.07 to 2.47)	0.78 (0.28 to 1.77)	0.52 (0.05 to 2.08)	0.64 (0.21 to 1.48)	0.79 (0.07 to 3.26)	0.78 (0.27 to 1.80)	0.70 (0.06 to 2.83)
Thyroid hormone	0.58 (0.18 to 1.38)	2.47 (0.18 to 11.38)	0.63 (0.21 to 1.51)	1.92 (0.12 to 9.09)	0.60 (0.16 to 1.58)	1.70 (0.04 to 9.81)	0.70 (0.16 to 1.95)	4.20 (0.16 to 22.44)

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Quetiapine versus:								
Risperidone	1.31 (0.68 to 2.46)	1.02 (0.43 to 2.00)	1.33 (0.71 to 2.43)	0.73 (0.25 to 1.54)	1.15 (0.56 to 2.22)	1.05 (0.34 to 2.41)	1.39 (0.71 to 2.63)	0.94 (0.33 to 2.08)
Thyroid hormone	1.00 (0.48 to 1.94)	3.78 (0.84 to 11.60)	1.08 (0.55 to 2.06)	2.64 (0.54 to 8.28)	1.08 (0.43 to 2.35)	2.28 (0.14 to 11.35)	1.24 (0.40 to 3.08)	5.62 (0.64 to 23.39)
Risperidone versus:								
Thyroid hormone	0.80 (0.37 to 1.51)	3.90 (0.99 to 11.75)	0.86 (0.41 to 1.59)	3.93 (0.91 to 12.00)	1.03 (0.34 to 2.42)	2.58 (0.14 to 13.12)	0.92 (0.33 to 2.06)	6.28 (0.89 to 24.85)
Placebo versus:								
Aripiprazole	0.54 (0.37 to 0.80)	0.81 (0.47 to 1.27)	0.54 (0.37 to 0.77)	0.81 (0.43 to 1.36)	0.54 (0.37 to 0.79)	0.80 (0.40 to 1.41)	0.54 (0.37 to 0.79)	0.81 (0.40 to 1.42)
Bupropion	1.00 (0.45 to 1.95)	0.73 (0.32 to 1.55)	0.78 (0.44 to 1.25)	1.12 (0.50 to 2.37)	0.85 (0.46 to 1.41)	1.18 (0.48 to 2.73)	0.78 (0.42 to 1.29)	1.24 (0.52 to 2.83)
Buspirone	0.68 (0.38 to 1.12)	1.56 (0.63 to 3.28)	0.81 (0.49 to 1.23)	0.93 (0.43 to 1.95)	0.95 (0.52 to 1.52)	1.00 (0.38 to 2.40)	0.81 (0.46 to 1.24)	1.10 (0.47 to 2.45)
Lamotrigine	1.20 (0.46 to 2.61)	1.54 (0.54 to 3.49)	0.92 (0.41 to 1.78)	1.41 (0.50 to 3.23)	0.91 (0.39 to 1.76)	1.42 (0.48 to 3.34)	0.89 (0.38 to 1.76)	1.42 (0.47 to 3.37)
Lithium	0.57 (0.33 to 0.87)	0.83 (0.43 to 1.61)	0.70 (0.44 to 1.03)	0.82 (0.40 to 1.57)	0.64 (0.38 to 0.95)	0.82 (0.39 to 1.60)	0.63 (0.36 to 0.97)	0.84 (0.39 to 1.68)
Methylphenidate	0.73 (0.33 to 1.38)	0.89 (0.29 to 2.13)	0.72 (0.34 to 1.35)	0.93 (0.28 to 2.34)	0.72 (0.33 to 1.34)	0.95 (0.27 to 2.45)	0.72 (0.33 to 1.35)	0.95 (0.27 to 2.47)
Olanzapine	0.71 (0.44 to 1.05)	0.86 (0.52 to 1.41)	0.71 (0.46 to 1.03)	0.89 (0.49 to 1.56)	0.71 (0.45 to 1.04)	0.90 (0.47 to 1.65)	0.71 (0.44 to 1.05)	0.91 (0.47 to 1.65)
Pindolol	1.03 (0.41 to 2.13)	2.80 (0.39 to 10.84)	1.05 (0.43 to 2.12)	2.91 (0.37 to 11.75)	1.06 (0.43 to 2.20)	2.83 (0.36 to 11.01)	1.04 (0.43 to 2.17)	2.97 (0.37 to 11.93)
Quetiapine	0.52 (0.32 to 0.72)	0.92 (0.58 to 1.54)	0.54 (0.34 to 0.74)	1.04 (0.61 to 1.84)	0.52 (0.32 to 0.72)	1.07 (0.61 to 1.94)	0.52 (0.31 to 0.72)	1.08 (0.61 to 1.96)
Risperidone	0.65 (0.38 to 1.03)	0.89 (0.45 to 1.62)	0.69 (0.41 to 1.10)	0.70 (0.32 to 1.37)	0.57 (0.31 to 0.96)	1.04 (0.43 to 2.25)	0.68 (0.40 to 1.09)	0.94 (0.42 to 1.92)
Thyroid hormone	0.50 (0.25 to 0.87)	3.29 (0.81 to 9.81)	0.57 (0.30 to 0.98)	2.56 (0.62 to 7.79)	0.54 (0.22 to 1.10)	2.26 (0.15 to 11.18)	0.61 (0.21 to 1.39)	5.63 (0.74 to 23.24)
SUCRA:								
Aripiprazole	0.26 (0.00 to 0.73)	0.32 (0.00 to 0.73)	0.19 (0.00 to 0.64)	0.33 (0.00 to 0.82)	0.24 (0.00 to 0.64)	0.32 (0.00 to 0.82)	0.23 (0.00 to 0.73)	0.29 (0.00 to 0.82)
Bupropion	0.74 (0.09 to 1.00)	0.22 (0.00 to 0.82)	0.56 (0.09 to 1.00)	0.56 (0.00 to 1.00)	0.64 (0.09 to 1.00)	0.57 (0.00 to 1.00)	0.57 (0.09 to 1.00)	0.57 (0.00 to 0.91)
Buspirone	0.46 (0.00 to 0.91)	0.73 (0.18 to 1.00)	0.63 (0.18 to 1.00)	0.41 (0.00 to 0.91)	0.75 (0.27 to 1.00)	0.42 (0.00 to 1.00)	0.63 (0.18 to 1.00)	0.47 (0.00 to 0.91)
Lamotrigine	0.81 (0.09 to 1.00)	0.69 (0.00 to 1.00)	0.67 (0.00 to 1.00)	0.67 (0.00 to 1.00)	0.66 (0.00 to 1.00)	0.66 (0.00 to 1.00)	0.65 (0.00 to 1.00)	0.62 (0.00 to 1.00)
Lithium	0.32 (0.00 to 0.73)	0.31 (0.00 to 0.82)	0.48 (0.09 to 0.91)	0.32 (0.00 to 0.82)	0.40 (0.09 to 0.82)	0.32 (0.00 to 0.82)	0.38 (0.00 to 0.82)	0.30 (0.00 to 0.82)
Methylphenidate	0.49 (0.00 to 1.00)	0.35 (0.00 to 0.91)	0.47 (0.00 to 1.00)	0.38 (0.00 to 1.00)	0.47 (0.00 to 1.00)	0.39 (0.00 to 1.00)	0.48 (0.00 to 1.00)	0.36 (0.00 to 0.91)
Olanzapine	0.53 (0.09 to 0.91)	0.37 (0.00 to 0.82)	0.49 (0.09 to 0.91)	0.40 (0.00 to 0.91)	0.50 (0.09 to 0.91)	0.41 (0.00 to 0.91)	0.51 (0.09 to 0.91)	0.37 (0.00 to 0.82)
Pindolol	0.73 (0.09 to 1.00)	0.75 (0.00 to 1.00)	0.75 (0.00 to 1.00)	0.77 (0.00 to 1.00)	0.75 (0.09 to 1.00)	0.77 (0.00 to 1.00)	0.74 (0.09 to 1.00)	0.73 (0.00 to 1.00)
Quetiapine	0.22 (0.00 to 0.55)	0.42 (0.09 to 0.82)	0.19 (0.00 to 0.55)	0.53 (0.09 to 0.91)	0.20 (0.00 to 0.55)	0.55 (0.09 to 0.91)	0.18 (0.00 to 0.55)	0.51 (0.09 to 0.91)
Risperidone	0.43 (0.00 to 0.82)	0.37 (0.00 to 0.82)	0.44 (0.00 to 0.91)	0.22 (0.00 to 0.82)	0.29 (0.00 to 0.82)	0.48 (0.00 to 1.00)	0.45 (0.00 to 0.91)	0.37 (0.00 to 0.91)
Thyroid hormone	0.19 (0.00 to 0.73)	0.90 (0.36 to 1.00)	0.24 (0.00 to 0.82)	0.85 (0.18 to 1.00)	0.24 (0.00 to 0.91)	0.55 (0.00 to 1.00)	0.31 (0.00 to 1.00)	0.91 (0.27 to 1.00)
Placebo	0.84 (0.64 to 1.00)	0.56 (0.27 to 0.82)	0.88 (0.64 to 1.00)	0.57 (0.27 to 0.82)	0.85 (0.64 to 1.00)	0.56 (0.27 to 0.82)	0.87 (0.64 to 1.00)	0.51 (0.18 to 0.82)

Abbreviations: SMD= standardized mean difference, OR=odds ratio, CrI= credibility interval.

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Supplementary eTable 5C. Sensitivity Analysis of Effect Sizes for Primary Efficacy and Acceptability Outcomes in the Network Meta-Analysis Model

	Exclusion of non-industry support		Publication year		Placebo response		Exclusion of TCAs	
	Efficacy	Acceptability	Efficacy	Acceptability	Efficacy	Acceptability	Efficacy	Acceptability
Comparison	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)
Aripiprazole versus:								
Bupropion	1.90 (0.83 to 3.67)	1.13 (0.30 to 3.53)	1.49 (0.70 to 2.66)	1.35 (0.44 to 3.85)	1.39 (0.61 to 2.56)	1.47 (0.56 to 3.67)	1.48 (0.73 to 2.57)	1.62 (0.56 to 4.27)
Buspirone	1.77 (0.79 to 3.39)	2.67 (0.60 to 7.99)	1.57 (0.65 to 2.97)	1.00 (0.27 to 3.28)	1.36 (0.59 to 2.43)	1.24 (0.44 to 3.23)	1.54 (0.77 to 2.54)	1.41 (0.49 to 3.68)
Lamotrigine	2.19 (0.66 to 5.42)	2.27 (0.43 to 7.29)	1.89 (0.76 to 3.90)	1.85 (0.52 to 4.90)	1.60 (0.60 to 3.38)	1.98 (0.61 to 4.97)	1.67 (0.58 to 3.67)	1.80 (0.42 to 5.16)
Lithium	1.31 (0.61 to 2.26)	1.02 (0.32 to 2.77)	1.81 (0.87 to 3.28)	0.89 (0.26 to 2.53)	0.90 (0.45 to 1.58)	1.64 (0.61 to 3.59)	1.52 (0.68 to 2.67)	0.90 (0.27 to 2.46)
Methylphenidate	1.39 (0.59 to 2.67)	1.30 (0.31 to 3.85)	1.40 (0.59 to 2.71)	1.28 (0.31 to 3.70)	1.38 (0.55 to 2.80)	1.22 (0.33 to 3.31)	1.70 (0.63 to 3.75)	0.55 (0.07 to 1.95)
Olanzapine	1.38 (0.75 to 2.19)	1.23 (0.49 to 2.91)	1.49 (0.84 to 2.40)	1.12 (0.44 to 2.48)	1.37 (0.69 to 2.27)	1.17 (0.53 to 2.45)	1.37 (0.74 to 2.19)	1.22 (0.50 to 2.73)
Pindolol	2.23 (0.56 to 6.04)	49.32 (0.03 to 72.41)	0.83 (0.11 to 2.83)	12.04 (0.42 to 63.31)	1.65 (0.55 to 3.70)	4.68 (0.44 to 20.51)	2.11 (0.49 to 5.77)	6.63 (0.42 to 32.99)
Quetiapine	1.09 (0.58 to 1.69)	1.39 (0.56 to 3.55)	1.14 (0.61 to 1.76)	1.31 (0.56 to 3.20)	0.59 (0.25 to 1.10)	2.90 (1.07 to 6.78)	1.07 (0.55 to 1.67)	1.34 (0.56 to 3.15)
Risperidone	1.10 (0.53 to 1.97)	1.39 (0.46 to 3.70)	1.31 (0.68 to 2.23)	1.09 (0.40 to 2.73)	1.20 (0.58 to 2.12)	1.12 (0.44 to 2.57)	1.29 (0.66 to 2.21)	1.21 (0.44 to 2.96)
Thyroid hormone	..	..	1.13 (0.45 to 2.31)	4.47 (0.60 to 18.23)	0.71 (0.29 to 1.40)	4.66 (0.84 to 16.72)	1.05 (0.41 to 2.07)	5.59 (0.80 to 22.13)
Bupropion versus:								
Buspirone	1.04 (0.37 to 2.33)	3.13 (0.46 to 10.39)	1.08 (0.59 to 1.72)	0.77 (0.31 to 1.78)	1.02 (0.52 to 1.67)	0.89 (0.41 to 1.81)	1.08 (0.61 to 1.69)	0.94 (0.40 to 2.01)
Lamotrigine	1.29 (0.33 to 3.54)	2.65 (0.34 to 9.13)	1.38 (0.49 to 3.13)	1.69 (0.34 to 4.70)	1.26 (0.42 to 2.92)	1.56 (0.39 to 4.03)	1.20 (0.39 to 2.78)	1.31 (0.24 to 3.86)
Lithium	0.76 (0.28 to 1.56)	1.19 (0.24 to 3.62)	1.32 (0.58 to 2.66)	0.80 (0.17 to 2.30)	0.71 (0.32 to 1.41)	1.30 (0.37 to 2.97)	1.09 (0.46 to 2.05)	0.66 (0.16 to 1.80)
Methylphenidate	0.81 (0.28 to 1.80)	1.52 (0.25 to 4.93)	1.02 (0.38 to 2.22)	1.16 (0.22 to 3.46)	1.09 (0.39 to 2.48)	0.96 (0.21 to 2.68)	1.23 (0.42 to 2.89)	0.40 (0.05 to 1.43)
Olanzapine	0.81 (0.34 to 1.58)	1.44 (0.35 to 3.91)	1.09 (0.52 to 2.08)	1.02 (0.27 to 2.37)	1.07 (0.48 to 2.08)	0.92 (0.32 to 1.98)	0.99 (0.49 to 1.78)	0.89 (0.28 to 2.03)
Pindolol	1.31 (0.29 to 3.87)	72.52 (0.03 to 88.71)	0.61 (0.07 to 2.15)	10.73 (0.33 to 57.42)	1.29 (0.41 to 3.11)	3.72 (0.30 to 16.57)	1.51 (0.34 to 4.25)	4.88 (0.27 to 24.20)
Quetiapine	0.64 (0.26 to 1.23)	1.62 (0.43 to 4.69)	0.83 (0.39 to 1.47)	1.18 (0.37 to 2.95)	0.46 (0.18 to 0.95)	2.28 (0.68 to 5.42)	0.77 (0.37 to 1.32)	0.97 (0.33 to 2.29)
Risperidone	0.65 (0.25 to 1.37)	1.61 (0.36 to 4.68)	0.94 (0.46 to 1.76)	0.95 (0.30 to 2.20)	0.93 (0.42 to 1.83)	0.86 (0.31 to 1.88)	0.93 (0.45 to 1.72)	0.86 (0.28 to 2.01)
Thyroid hormone	..	..	0.81 (0.33 to 1.68)	3.68 (0.55 to 13.95)	0.55 (0.22 to 1.16)	3.52 (0.64 to 12.20)	0.75 (0.29 to 1.52)	3.87 (0.57 to 14.91)
Buspirone versus:								
Lamotrigine	1.38 (0.35 to 3.74)	1.19 (0.15 to 4.50)	1.34 (0.45 to 3.24)	2.53 (0.41 to 7.38)	1.28 (0.45 to 3.00)	1.91 (0.44 to 5.02)	1.14 (0.39 to 2.62)	1.51 (0.28 to 4.37)
Lithium	0.82 (0.31 to 1.69)	0.53 (0.10 to 1.78)	1.27 (0.54 to 2.75)	1.19 (0.21 to 3.55)	0.72 (0.34 to 1.44)	1.59 (0.43 to 3.72)	1.03 (0.49 to 1.90)	0.75 (0.18 to 1.97)
Methylphenidate	0.87 (0.30 to 1.95)	0.68 (0.10 to 2.43)	0.99 (0.34 to 2.32)	1.73 (0.26 to 5.48)	1.11 (0.41 to 2.59)	1.17 (0.25 to 3.30)	1.17 (0.42 to 2.74)	0.46 (0.05 to 1.63)
Olanzapine	0.86 (0.38 to 1.69)	0.65 (0.14 to 1.96)	1.06 (0.47 to 2.24)	1.53 (0.32 to 3.85)	1.09 (0.52 to 2.17)	1.13 (0.36 to 2.43)	0.94 (0.50 to 1.66)	1.02 (0.32 to 2.24)
Pindolol	1.40 (0.31 to 4.14)	26.96 (0.01 to 36.74)	0.59 (0.07 to 2.16)	15.91 (0.42 to 86.18)	1.31 (0.44 to 3.13)	4.59 (0.35 to 20.92)	1.42 (0.34 to 3.93)	5.68 (0.31 to 27.88)
Quetiapine	0.68 (0.29 to 1.31)	0.73 (0.16 to 2.35)	0.80 (0.36 to 1.55)	1.75 (0.44 to 4.62)	0.47 (0.20 to 0.97)	2.77 (0.78 to 6.65)	0.73 (0.39 to 1.21)	1.10 (0.38 to 2.48)

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Risperidone	0.69 (0.27 to 1.47)	0.73 (0.14 to 2.40)	0.91 (0.43 to 1.76)	1.37 (0.40 to 3.20)	0.95 (0.47 to 1.82)	1.03 (0.38 to 2.15)	0.88 (0.48 to 1.55)	0.96 (0.35 to 2.06)
Thyroid hormone	..	..	0.77 (0.33 to 1.60)	5.08 (0.83 to 18.24)	0.56 (0.25 to 1.13)	4.14 (0.82 to 13.71)	0.70 (0.31 to 1.36)	4.25 (0.71 to 15.59)
Lamotrigine versus:								
Lithium	0.77 (0.21 to 1.98)	0.69 (0.11 to 2.49)	1.08 (0.43 to 2.28)	0.58 (0.14 to 1.73)	0.65 (0.26 to 1.38)	1.00 (0.29 to 2.51)	1.06 (0.38 to 2.34)	0.66 (0.14 to 2.02)
Methylphenidate	0.82 (0.20 to 2.21)	0.88 (0.12 to 3.30)	0.85 (0.27 to 2.02)	0.87 (0.16 to 2.85)	1.00 (0.31 to 2.49)	0.76 (0.15 to 2.35)	1.24 (0.32 to 3.40)	0.42 (0.04 to 1.71)
Olanzapine	0.81 (0.24 to 2.01)	0.83 (0.16 to 2.73)	0.91 (0.36 to 1.92)	0.77 (0.21 to 2.02)	0.99 (0.37 to 2.17)	0.73 (0.23 to 1.84)	0.99 (0.35 to 2.25)	0.94 (0.22 to 2.75)
Pindolol	1.32 (0.22 to 4.43)	37.64 (0.01 to 48.71)	0.51 (0.05 to 1.93)	7.98 (0.24 to 43.65)	1.20 (0.31 to 3.17)	2.92 (0.22 to 13.46)	1.52 (0.28 to 4.90)	5.10 (0.24 to 27.73)
Quetiapine	0.64 (0.19 to 1.58)	0.95 (0.19 to 3.31)	0.69 (0.28 to 1.37)	0.89 (0.27 to 2.46)	0.42 (0.15 to 0.96)	1.79 (0.50 to 4.80)	0.77 (0.28 to 1.66)	1.01 (0.26 to 3.02)
Risperidone	0.65 (0.17 to 1.72)	0.95 (0.16 to 3.34)	0.80 (0.30 to 1.76)	0.74 (0.19 to 2.16)	0.87 (0.32 to 1.96)	0.70 (0.20 to 1.88)	0.93 (0.32 to 2.19)	0.92 (0.20 to 2.91)
Thyroid hormone	..	..	0.68 (0.22 to 1.65)	3.06 (0.33 to 13.17)	0.51 (0.17 to 1.21)	2.90 (0.41 to 11.17)	0.75 (0.23 to 1.85)	4.27 (0.42 to 18.80)
Lithium versus:								
Methylphenidate	1.14 (0.45 to 2.51)	1.55 (0.29 to 4.76)	0.83 (0.31 to 1.79)	1.83 (0.32 to 5.76)	1.63 (0.62 to 3.50)	0.85 (0.20 to 2.48)	1.23 (0.41 to 3.01)	0.76 (0.08 to 2.83)
Olanzapine	1.13 (0.56 to 2.15)	1.48 (0.43 to 3.65)	0.89 (0.42 to 1.67)	1.61 (0.41 to 4.08)	1.61 (0.78 to 2.92)	0.81 (0.31 to 1.84)	0.98 (0.48 to 1.87)	1.69 (0.48 to 4.25)
Pindolol	1.86 (0.44 to 5.51)	40.37 (0.04 to 92.30)	0.50 (0.06 to 1.74)	17.30 (0.50 to 91.91)	1.95 (0.63 to 4.54)	3.28 (0.27 to 14.67)	1.51 (0.33 to 4.45)	9.23 (0.48 to 46.25)
Quetiapine	0.88 (0.53 to 1.39)	1.56 (0.66 to 3.49)	0.66 (0.36 to 1.03)	1.75 (0.70 to 3.99)	0.67 (0.36 to 1.08)	1.87 (0.91 to 3.78)	0.75 (0.43 to 1.17)	1.72 (0.71 to 3.79)
Risperidone	0.91 (0.40 to 1.87)	1.66 (0.43 to 4.54)	0.78 (0.36 to 1.46)	1.55 (0.40 to 4.32)	1.41 (0.67 to 2.59)	0.78 (0.26 to 1.92)	0.92 (0.44 to 1.78)	1.65 (0.44 to 4.46)
Thyroid hormone	..	..	0.65 (0.29 to 1.25)	6.25 (0.70 to 26.22)	0.82 (0.39 to 1.50)	3.18 (0.55 to 11.46)	0.72 (0.33 to 1.40)	7.53 (0.91 to 30.91)
Methylphenidate versus:								
Olanzapine	1.11 (0.48 to 2.23)	1.30 (0.31 to 3.75)	1.20 (0.51 to 2.47)	1.19 (0.28 to 3.33)	1.13 (0.44 to 2.34)	1.26 (0.34 to 3.40)	0.96 (0.34 to 2.10)	4.08 (0.59 to 15.49)
Pindolol	1.81 (0.40 to 5.45)	46.16 (0.03 to 76.47)	0.67 (0.07 to 2.44)	12.60 (0.34 to 69.46)	1.36 (0.38 to 3.48)	5.03 (0.35 to 23.29)	1.47 (0.27 to 4.83)	23.08 (0.69 to 127.10)
Quetiapine	0.88 (0.37 to 1.72)	1.46 (0.36 to 4.47)	0.91 (0.39 to 1.80)	1.38 (0.35 to 4.05)	0.49 (0.17 to 1.08)	3.12 (0.73 to 9.06)	0.75 (0.26 to 1.60)	4.48 (0.66 to 17.43)
Risperidone	0.89 (0.35 to 1.93)	1.47 (0.30 to 4.61)	1.05 (0.42 to 2.23)	1.15 (0.25 to 3.49)	0.99 (0.37 to 2.15)	1.20 (0.30 to 3.43)	0.90 (0.31 to 2.05)	4.03 (0.54 to 15.84)
Thyroid hormone	..	..	0.91 (0.30 to 2.17)	4.70 (0.44 to 20.66)	0.59 (0.19 to 1.37)	5.01 (0.64 to 19.50)	0.73 (0.21 to 1.81)	18.72 (1.21 to 93.06)
Olanzapine versus:								
Pindolol	1.70 (0.42 to 4.72)	36.92 (0.03 to 65.00)	0.58 (0.07 to 1.99)	11.88 (0.41 to 62.34)	1.27 (0.43 to 2.93)	4.31 (0.39 to 18.87)	1.60 (0.38 to 4.49)	5.95 (0.37 to 29.34)
Quetiapine	0.82 (0.45 to 1.32)	1.23 (0.50 to 2.89)	0.80 (0.42 to 1.27)	1.28 (0.54 to 3.08)	0.45 (0.20 to 0.87)	2.65 (0.98 to 5.97)	0.81 (0.44 to 1.29)	1.19 (0.50 to 2.63)
Risperidone	0.83 (0.41 to 1.55)	1.24 (0.40 to 3.07)	0.91 (0.46 to 1.60)	1.06 (0.38 to 2.63)	0.92 (0.45 to 1.71)	1.02 (0.41 to 2.24)	0.98 (0.51 to 1.75)	1.07 (0.39 to 2.51)
Thyroid hormone	..	..	0.79 (0.31 to 1.67)	4.37 (0.59 to 17.69)	0.55 (0.23 to 1.12)	4.25 (0.78 to 14.95)	0.79 (0.32 to 1.62)	4.97 (0.72 to 19.32)
Pindolol versus:								
Quetiapine	0.68 (0.17 to 1.85)	8.00 (0.02 to 38.24)	2.64 (0.39 to 10.38)	0.59 (0.02 to 2.90)	0.43 (0.13 to 1.06)	1.54 (0.12 to 6.60)	0.73 (0.17 to 2.04)	0.66 (0.04 to 2.98)
Risperidone	0.69 (0.16 to 1.96)	7.94 (0.02 to 37.79)	3.04 (0.44 to 12.2)	0.49 (0.02 to 2.43)	0.88 (0.29 to 2.10)	0.59 (0.05 to 2.49)	0.88 (0.21 to 2.51)	0.60 (0.03 to 2.70)

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Thyroid hormone	..	..	2.64 (0.33 to 11.1)	1.99 (0.03 to 11.80)	0.52 (0.16 to 1.35)	2.50 (0.12 to 12.72)	0.71 (0.14 to 2.14)	2.79 (0.08 to 15.16)
Quetiapine versus:								
Risperidone	1.05 (0.52 to 1.97)	1.10 (0.34 to 2.58)	1.19 (0.65 to 2.11)	0.90 (0.31 to 1.96)	2.22 (0.98 to 4.55)	0.44 (0.15 to 1.06)	1.25 (0.68 to 2.26)	0.98 (0.35 to 2.13)
Thyroid hormone	..	..	1.02 (0.45 to 2.05)	3.63 (0.50 to 13.89)	1.30 (0.54 to 2.72)	1.83 (0.30 to 6.59)	1.00 (0.45 to 1.99)	4.49 (0.66 to 16.99)
Risperidone versus:								
Thyroid hormone	..	..	0.89 (0.39 to 1.75)	4.23 (0.72 to 15.46)	0.62 (0.27 to 1.20)	4.42 (0.92 to 15.00)	0.84 (0.36 to 1.61)	4.88 (0.85 to 17.83)
Placebo versus:								
Aripiprazole	0.54 (0.38 to 0.76)	0.81 (0.40 to 1.41)	0.54 (0.38 to 0.76)	0.81 (0.42 to 1.38)	0.54 (0.37 to 0.80)	0.81 (0.44 to 1.32)	0.54 (0.37 to 0.77)	0.81 (0.42 to 1.38)
Bupropion	0.99 (0.49 to 1.81)	0.82 (0.27 to 2.21)	0.77 (0.41 to 1.29)	0.98 (0.40 to 2.40)	0.73 (0.37 to 1.23)	1.09 (0.52 to 2.34)	0.77 (0.44 to 1.23)	1.19 (0.52 to 2.64)
Buspirone	0.92 (0.46 to 1.65)	1.95 (0.53 to 5.25)	0.82 (0.38 to 1.45)	0.73 (0.24 to 2.10)	0.71 (0.36 to 1.16)	0.92 (0.40 to 2.06)	0.80 (0.47 to 1.20)	1.03 (0.45 to 2.26)
Lamotrigine	1.14 (0.37 to 2.71)	1.65 (0.38 to 4.77)	0.98 (0.44 to 1.93)	1.36 (0.47 to 3.16)	0.84 (0.36 to 1.65)	1.48 (0.54 to 3.28)	0.87 (0.33 to 1.81)	1.32 (0.37 to 3.40)
Lithium	0.68 (0.36 to 1.09)	0.74 (0.29 to 1.70)	0.94 (0.52 to 1.59)	0.65 (0.23 to 1.61)	0.47 (0.28 to 0.74)	1.23 (0.56 to 2.31)	0.79 (0.41 to 1.29)	0.66 (0.24 to 1.56)
Methylphenidate	0.72 (0.35 to 1.30)	0.95 (0.27 to 2.46)	0.73 (0.34 to 1.33)	0.94 (0.27 to 2.40)	0.72 (0.33 to 1.36)	0.91 (0.29 to 2.24)	0.89 (0.36 to 1.85)	0.41 (0.06 to 1.32)
Olanzapine	0.72 (0.46 to 1.02)	0.90 (0.48 to 1.67)	0.77 (0.51 to 1.13)	0.82 (0.43 to 1.46)	0.71 (0.44 to 1.05)	0.88 (0.51 to 1.49)	0.71 (0.46 to 1.02)	0.90 (0.49 to 1.60)
Pindolol	1.16 (0.32 to 3.08)	33.18 (0.02 to 53.48)	0.43 (0.06 to 1.42)	8.80 (0.35 to 45.46)	0.86 (0.32 to 1.83)	3.52 (0.36 to 14.84)	1.10 (0.28 to 2.92)	4.89 (0.36 to 23.52)
Quetiapine	0.57 (0.36 to 0.79)	1.01 (0.55 to 2.04)	0.59 (0.38 to 0.82)	0.96 (0.54 to 1.85)	0.31 (0.15 to 0.52)	2.17 (0.98 to 4.33)	0.56 (0.34 to 0.77)	0.98 (0.55 to 1.83)
Risperidone	0.57 (0.32 to 0.95)	1.02 (0.43 to 2.23)	0.68 (0.41 to 1.06)	0.80 (0.37 to 1.66)	0.63 (0.36 to 1.00)	0.83 (0.41 to 1.62)	0.67 (0.40 to 1.05)	0.88 (0.42 to 1.78)
Thyroid hormone	..	..	0.59 (0.26 to 1.13)	3.26 (0.51 to 12.48)	0.37 (0.18 to 0.68)	3.49 (0.72 to 11.73)	0.54 (0.24 to 1.01)	4.09 (0.70 to 15.25)
SUCRA:								
Aripiprazole	0.18 (0.00 to 0.60)	0.37 (0.00 to 0.90)	0.23 (0.00 to 0.64)	0.39 (0.00 to 0.82)	0.37 (0.09 to 0.82)	0.26 (0.00 to 0.73)	0.20 (0.00 to 0.64)	0.37 (0.00 to 0.82)
Bupropion	0.70 (0.10 to 1.00)	0.32 (0.00 to 0.90)	0.56 (0.09 to 1.00)	0.48 (0.09 to 0.91)	0.61 (0.18 to 1.00)	0.46 (0.00 to 0.91)	0.55 (0.09 to 1.00)	0.60 (0.09 to 0.91)
Buspirone	0.65 (0.10 to 1.00)	0.80 (0.10 to 1.00)	0.61 (0.09 to 1.00)	0.24 (0.00 to 0.82)	0.60 (0.18 to 1.00)	0.31 (0.00 to 0.82)	0.61 (0.18 to 1.00)	0.49 (0.09 to 0.91)
Lamotrigine	0.71 (0.00 to 1.00)	0.70 (0.00 to 1.00)	0.72 (0.09 to 1.00)	0.67 (0.09 to 1.00)	0.68 (0.09 to 1.00)	0.63 (0.00 to 1.00)	0.59 (0.00 to 1.00)	0.61 (0.09 to 1.00)
Lithium	0.41 (0.00 to 0.90)	0.28 (0.00 to 0.90)	0.75 (0.27 to 1.00)	0.21 (0.00 to 0.82)	0.27 (0.09 to 0.73)	0.54 (0.00 to 0.91)	0.58 (0.09 to 1.00)	0.23 (0.00 to 0.82)
Methylphenidate	0.44 (0.00 to 1.00)	0.43 (0.00 to 1.00)	0.49 (0.00 to 1.00)	0.43 (0.00 to 0.91)	0.58 (0.09 to 1.00)	0.31 (0.00 to 0.91)	0.61 (0.00 to 1.00)	0.09 (0.00 to 0.73)
Olanzapine	0.46 (0.10 to 0.80)	0.45 (0.00 to 0.90)	0.58 (0.18 to 1.00)	0.40 (0.00 to 0.82)	0.61 (0.18 to 0.91)	0.32 (0.00 to 0.73)	0.49 (0.09 to 0.91)	0.44 (0.09 to 0.91)
Pindolol	0.67 (0.00 to 1.00)	0.53 (0.00 to 1.00)	0.17 (0.00 to 1.00)	0.84 (0.00 to 1.00)	0.68 (0.09 to 1.00)	0.74 (0.00 to 1.00)	0.66 (0.00 to 1.00)	0.80 (0.09 to 1.00)
Quetiapine	0.23 (0.00 to 0.60)	0.52 (0.10 to 0.90)	0.31 (0.00 to 0.64)	0.50 (0.09 to 0.91)	0.05 (0.00 to 0.27)	0.84 (0.45 to 1.00)	0.23 (0.00 to 0.64)	0.50 (0.09 to 0.91)
Risperidone	0.25 (0.00 to 0.80)	0.51 (0.00 to 1.00)	0.44 (0.09 to 0.91)	0.35 (0.00 to 0.82)	0.49 (0.09 to 0.91)	0.27 (0.00 to 0.73)	0.41 (0.00 to 0.91)	0.40 (0.00 to 0.82)
Placebo	0.80 (0.60 to 1.00)	0.60 (0.30 to 0.90)	0.87 (0.64 to 1.00)	0.62 (0.27 to 0.91)	0.92 (0.73 to 1.00)	0.47 (0.18 to 0.73)	0.86 (0.64 to 1.00)	0.58 (0.27 to 0.82)
Thyroid hormone	..	..	0.30 (0.00 to 0.91)	0.84 (0.18 to 1.00)	0.13 (0.00 to 0.55)	0.86 (0.27 to 1.00)	0.22 (0.00 to 0.82)	0.90 (0.27 to 1.00)

Abbreviations: SMD= standardized mean difference, OR=odds ratio, CrI= credibility interval.

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Supplementary eTable 6A. Sensitivity Analysis of Surface Under the Cumulative Ranking Curve (SUCRA) for Primary Efficacy and Acceptability Outcomes

Agent	Therapy dose		Therapy duration		Exclusion of imputation		Exclusion of bipolar patients	
	Primary Efficacy (%)	Acceptability (%)	Primary Efficacy (%)	Acceptability (%)	Primary Efficacy (%)	Acceptability (%)	Primary Efficacy (%)	Acceptability (%)
Aripiprazole	81.00	35.00	75.00	32.00	78.00	33.00	79.00	32.00
Bupropion	39.00	56.00	38.00	59.00	42.00	57.00	45.00	56.00
Buspirone	35.00	44.00	29.00	50.00	37.00	42.00	41.00	41.00
Lamotrigine	51.00	58.00	28.00	65.00	34.00	67.00	33.00	65.00
Lithium	61.00	40.00	38.00	33.00	59.00	27.00	47.00	24.00
Methylphenidate	49.00	36.00	50.00	39.00	51.00	38.00	53.00	39.00
Olanzapine	47.00	38.00	47.00	41.00	49.00	40.00	51.00	40.00
Pindolol	24.00	75.00	100.00	44.00	25.00	78.00	26.00	76.00
Quetiapine	76.00	48.00	71.00	54.00	81.00	40.00	79.00	50.00
Risperidone	52.00	33.00	52.00	39.00	56.00	33.00	57.00	35.00
Thyroid hormone	75.00	86.00	61.00	90.00	77.00	87.00	76.00	86.00
Placebo	11.00	53.00	11.00	54.00	12.00	58.00	13.00	55.00

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Supplementary eTable 6B. Sensitivity Analysis of Surface Under the Cumulative Ranking Curve (SUCRA) for Primary Efficacy and Acceptability Outcomes

Agent	Blinding		Refractory duration		Thyroid hormone		Exclusion of triiodothyronine	
	Primary Efficacy (%)	Acceptability (%)	Primary Efficacy (%)	Acceptability (%)	Primary Efficacy (%)	Acceptability (%)	Primary Efficacy (%)	Acceptability (%)
Aripiprazole	74.00	32.00	81.00	33.00	76.00	30.00	77.00	29.00
Bupropion	26.00	22.00	44.00	56.00	36.00	57.00	43.00	57.00
Buspirone	54.00	73.00	37.00	41.00	25.00	42.00	37.00	47.00
Lamotrigine	19.00	69.00	33.00	67.00	34.00	66.00	35.00	62.00
Lithium	68.00	31.00	52.00	32.00	60.00	32.00	62.00	30.00
Methylphenidate	51.00	35.00	53.00	38.00	53.00	39.00	52.00	36.00
Olanzapine	47.00	37.00	51.00	40.00	50.00	41.00	49.00	37.00
Pindolol	27.00	75.00	25.00	77.00	25.00	77.00	26.00	73.00
Quetiapine	78.00	42.00	81.00	53.00	80.00	55.00	82.00	51.00
Risperidone	57.00	37.00	56.00	22.00	71.00	48.00	55.00	37.00
Thyroid hormone	81.00	90.00	76.00	85.00	76.00	55.00	69.00	91.00
Placebo	16.00	56.00	12.00	57.00	15.00	56.00	13.00	51.00

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Supplementary eTable 6C. Sensitivity Analysis of Surface Under the Cumulative Ranking Curve (SUCRA) for Primary Efficacy and Acceptability Outcomes

Agent	Exclusion of non-industry support		Publication year		Placebo response		Exclusion of TCAs	
	Primary Efficacy (%)	Acceptability (%)	Primary Efficacy (%)	Acceptability (%)	Primary Efficacy (%)	Acceptability (%)	Primary Efficacy (%)	Acceptability (%)
Aripiprazole	82.00	37.00	77.00	39.00	37.00	26.00	80.00	37.00
Bupropion	30.00	32.00	44.00	48.00	61.00	46.00	45.00	60.00
Buspirone	35.00	80.00	39.00	24.00	60.00	31.00	39.00	49.00
Lamotrigine	29.00	70.00	28.00	67.00	68.00	63.00	41.00	61.00
Lithium	59.00	28.00	25.00	21.00	27.00	54.00	42.00	23.00
Methylphenidate	56.00	43.00	51.00	43.00	58.00	31.00	39.00	9.00
Olanzapine	54.00	45.00	42.00	40.00	61.00	32.00	51.00	44.00
Pindolol	33.00	53.00	83.00	84.00	68.00	74.00	34.00	80.00
Quetiapine	77.00	52.00	69.00	50.00	5.00	84.00	77.00	50.00
Risperidone	75.00	51.00	56.00	35.00	49.00	27.00	59.00	40.00
Thyroid hormone	-	60.00	70.00	84.00	13.00	86.00	78.00	90.00
Placebo	20.00	60.00	13.00	62.00	92.00	47.00	14.00	58.00

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Supplementary eTable 7. Meta-Regression by Sample Size, Sponsorship, and Publication Year

Variable	Primary Efficacy		Primary Acceptability	
	Coefficient (95% CI)	***P***	**Coefficient (95% CI)**	***P***
Sponsorship	1.15 (0.97 to 1.35)	0.97	1.22 (1.00 to 1.47)	0.41

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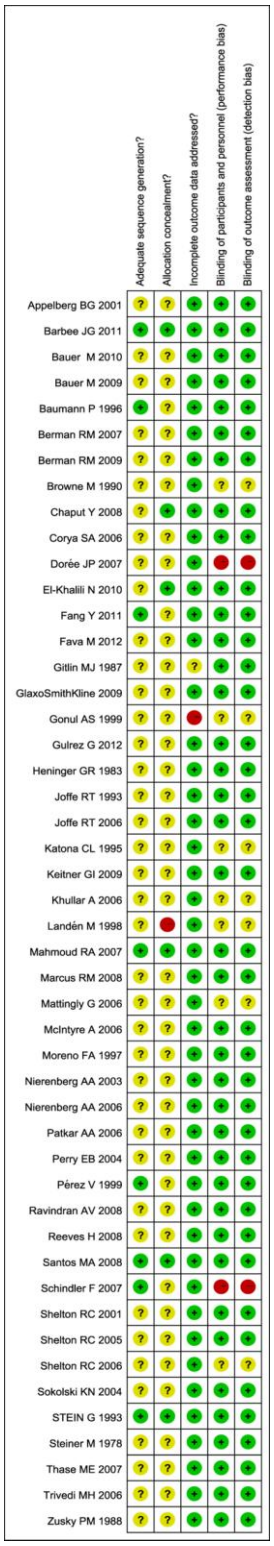
SUPPLEMENTARY FIGURES

Supplementary eFigure 1. Risk of Bias Analysis



Detailed risk of bias analysis across all included trials.

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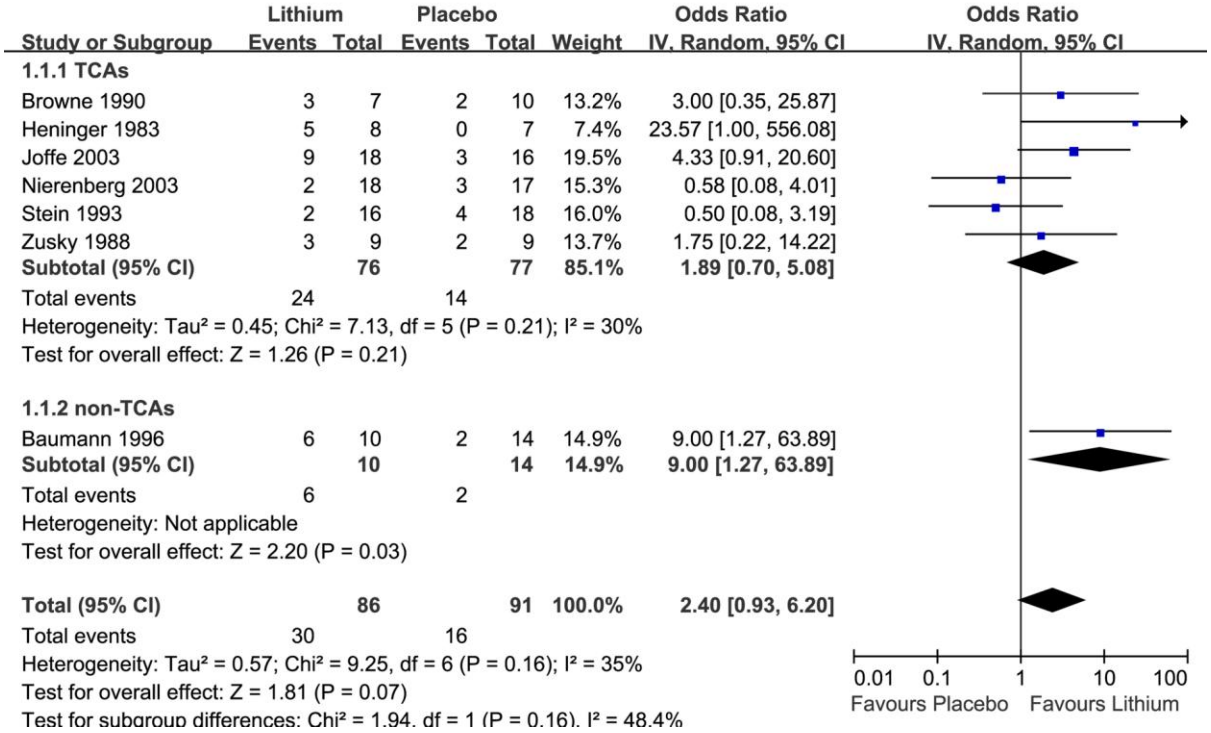
Supplementary eFigure 2. Subgroup Analysis of lithium augmentation studies with tricyclics and non-tricyclic antidepressants



Abbreviations: TCA= tricyclic antidepressants.

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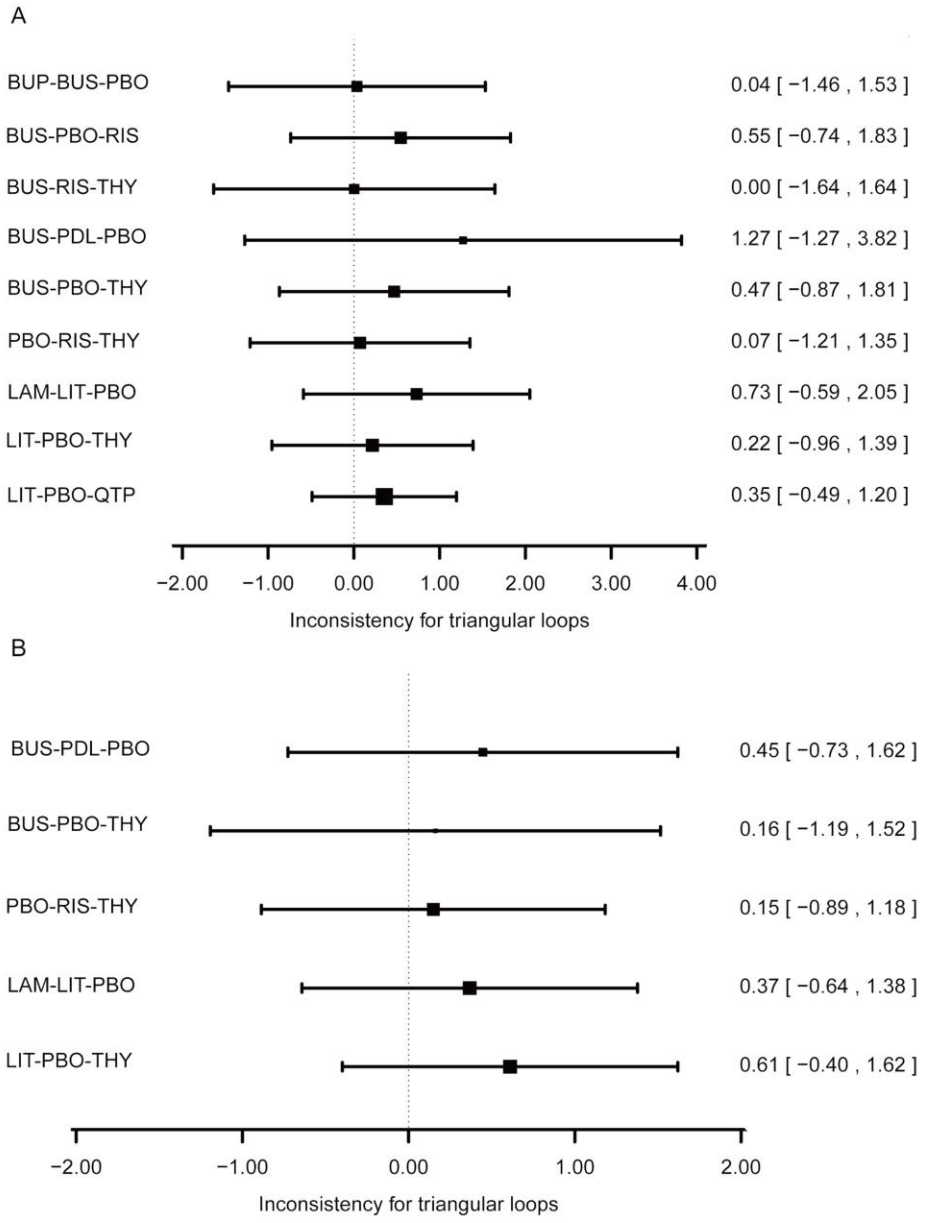
Supplementary eFigure 3. Consistency Analysis of the Primary Efficacy and Acceptability Outcomes



(A) Forest plots demonstrating consistency in loops (i.e., networks of three comparisons that arise when collating studies involving different selections of competing treatments) for the primary efficacy outcome. (B) Forest plots demonstrating the consistency in loops of the primary acceptability outcome. Abbreviations: ARI=Aripiprazole, BUP=Bupropion, BUS=Buspirone, LAM=Lamotrigine, LIT=Lithium, MPD=Methyl-phenidate, OLZ=Olanzapine, PDL=Pindolol, PBO=Placebo, QTP=Quetiapine, RIS=Risperidone, THY=thyroid hormone.

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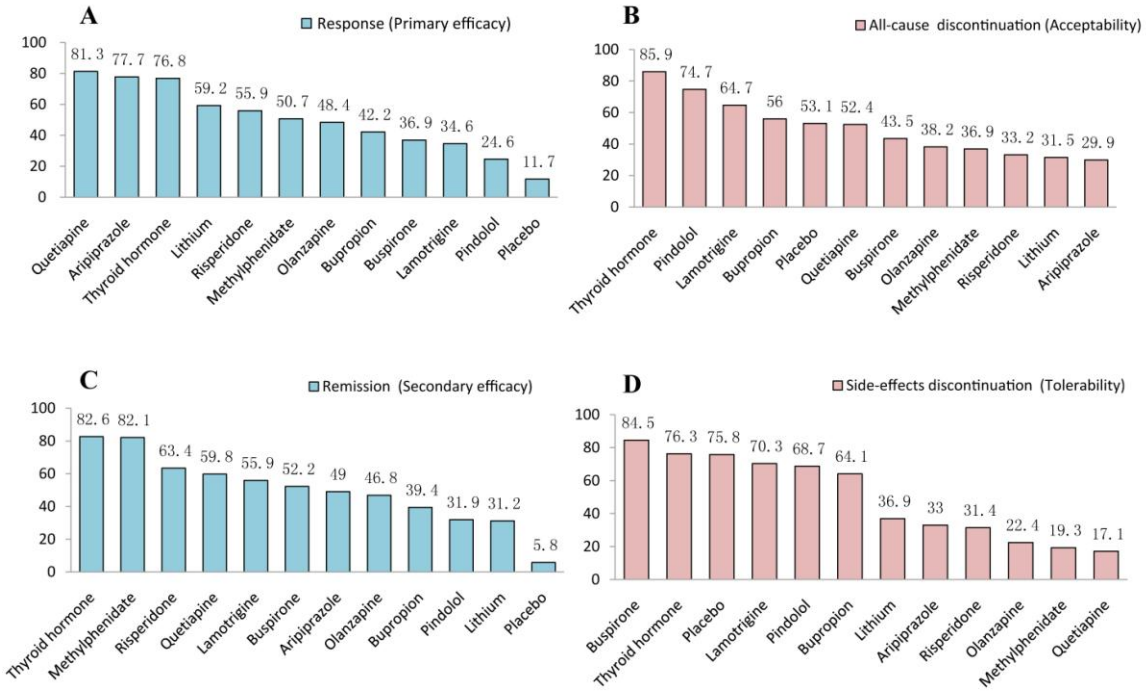
Supplementary eFigure 4. Ranking of Efficacy, Acceptability and Tolerability Based on Cumulative Probabilities of Being Most Effective Intervention



Drugs rank-ordered according to their overall probability of being the best treatment in terms of response, remission, all-cause discontinuation, or side-effects discontinuation. Every drug was scored on a scale of 1-100 from surface under the cumulative ranking curve (SUCRA) data.

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