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REVIEW ARTICLE

Comparison of the efficacy and safety of quetiapine and lithium for bipolar depression: A systematic review and meta-analysis of randomized controlled trials

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Abstract

Aim: Pharmacological treatments recommended for bipolar depression are inconsistent across guidelines. We compared the efficacy and safety of antipsychotics and mood stabilizers for bipolar depression.

Methods: A systemic review and meta-analysis of randomized controlled trials comparing antipsychotics and mood stabilizers for bipolar depression was conducted based on a literature search of major electronic databases.

Results: Three studies comparing quetiapine with lithium were identified and analyzed; no other antipsychotic-mood stabilizer combinations were found. The meta-analysis revealed no significant differences between quetiapine and lithium for the following outcomes: (1) remission from depressive episodes (risk ratio [RR]: 1.80, 95% CI: 0.51-6.40, $P = 0.36$), (2) changes in depressive symptom (standardized mean difference: −0.22, 95% CI: −0.52-0.08, $P = 0.15$), (3) changes in social function (standardized mean difference: −0.00, 95% CI: −0.19-0.18, $P = 0.98$), (4) suicide-related events (odds ratio [OR]: 2.35, 95% CI: 0.40-13.65, $P = 0.34$), (5) severe adverse events (OR: 1.63, 95% CI: 0.51-5.20, $P = 0.41$), (6) dropouts due to adverse events (RR: 1.19, 95% CI: 0.76-1.87, $P = 0.45$, 7) dropout for any reasons (RR: 0.95, 95% CI: 0.74-1.22, $P = 0.70$).

Conclusion: Although this study found no differences in the efficacy and safety of quetiapine and lithium for bipolar depression, a comprehensive comparison of antipsychotics and mood stabilizers was not performed. Further studies are needed to clarify which of these, not just quetiapine and lithium, is more useful for bipolar depression.

KEYWORDS
antipsychotics: clinical, bipolar disorders: basic/clinical, mood stabilizers: clinical, psychopharmacology: clinical

1 | INTRODUCTION

Bipolar disorder is a severe persistent mood disorder with a lifetime prevalence of approximately 1% in a mental health survey worldwide.[1] Major depressive episodes are the most common abnormal mood states in patients with bipolar disorder,[2,3,4] and are associated with suicidal ideations and attempts,[5,6] cognitive impairment,[7,8,9] worse social and occupational functioning,[10,11] reduced quality of life,[12] and greater caregiver burden.[13] The diagnosis of bipolar disorder is often delayed and has social and economic consequences for the patients.[14,15] Therefore, diagnosing it early and providing prompt and appropriate therapeutic intervention considering the effects of therapeutic agents, adverse events, and adherence in patients with bipolar depression is crucial.[16]

The recommended pharmacological treatments for bipolar depression are inconsistent across guidelines. Monotherapy with atypical antipsychotics is recommended as the first-line treatment in major guidelines, while monotherapy with mood stabilizers, such as lithium, lamotrigine, valproate, or carbamazepine, is recommended to varying degrees in each guideline; the Canadian Network for Mood and Anxiety Treatments and International Society for Bipolar Disorders 2018 guidelines and the Japanese Society of Mood Disorders (2020) guidelines recommend monotherapy with lithium or lamotrigine as the first-line treatment.[17,18] The International College of Neuro-Psychopharmacology (CINP) Treatment Guidelines for Bipolar Disorder in Adults (CINP-BD-2017) recommend monotherapy with lithium or valproate as the second-line treatment,[19] while the British Association for Psychopharmacology guidelines recommend lithium as the third-line treatment.[20] In a network meta-analysis conducted by Taylor et al. in 2014, no difference in antidepressant effects for bipolar depression was observed between individual antipsychotics and individual mood stabilizers.[21] However, of the 29 randomized controlled trials (RCTs) included in the network meta-analysis, only one RCT directly compared antipsychotics and mood stabilizers (quetiapine vs lithium), so most differences in antidepressant effects between individual antipsychotics and individual mood stabilizers were derived from indirect comparisons.[21] Furthermore, the network meta-analysis conducted by Bahji et al. in 2020 did not compare individual antipsychotics with individual mood stabilizers, and of the 46 RCTs included in both Bahji's and Taylor's network meta-analyses, only one study directly compared antipsychotics with mood stabilizers.[22] Although a network meta-analysis has the advantage of increased statistical power and more reliable effect estimates than a paired comparison meta-analysis, it has the disadvantage of increased risk of heterogeneity and inconsistency compared with paired a comparison meta-analysis. Moreover, double-blind RCTs of antipsychotics and mood stabilizers may not be blinded because of their side effect profiles; therefore, it is worthwhile to incorporate more pragmatic open-label or single-blind RCTs to examine effect sizes with larger sample sizes.[23,24]

In this systematic review and meta-analysis of RCTs, we compared the efficacy and safety of antipsychotics and mood stabilizers in patients with bipolar depression.

2 | METHODS

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations for reporting systematic reviews and meta-analyses[25] and registered with PROSPERO (https://www.crd.york.ac.uk/PROSPERO/#searchadvanced, CRD 42021250410).[26]

2.1 | Search strategy

We searched the PubMed electronic databases (search date: March 3, 2021), Cochrane Central Register of Controlled Trials (CENTRAL; search date: March 4, 2021), Embase (search date: March 4, 2021), and ClinicalTrials.gov (search date: March 4, 2021) for reports of RCTs, using appropriate subject headings and search syntaxes that were relevant to each resource (e.g., bipolar depression, individual antipsychotic drug name, lithium, lamotrigine, valproic acid, and carbamazepine; Table S1). In a network meta-analysis conducted by Bahji et al. in 2020 examining the efficacy and tolerability of psychotropic drugs for bipolar depression, only one double-blind RCT directly compared antipsychotics and mood stabilizers.[22] Therefore, we decided to include single-blind and open-label RCTs as well as double-blind RCTs in this study. When necessary, we contacted the authors of the specific studies to clarify additional points. There may have been few RCTs that included only patients during the depression phase of bipolar disorder. Consequently, we contacted individual authors of studies that included patients with bipolar disorder to ask for additional information regarding their participants during the depression phase of bipolar disorder, which was incorporated here.

2.2 | Inclusion criteria

Studies in any language that met the following criteria were included in the final review: participants were diagnosed with a depressive episode of bipolar spectrum disorder and at least 90% of the participants were diagnosed with bipolar I or II depression according to diagnostic criteria (DSM-III, DSM-III-R, DSM-IV, DSM-IV-TR, DSM-5, and ICD-10); participants were aged ≥18 years; interventions involved the use of any type of antipsychotic; treatment for control groups comprised mood stabilizers such as lithium, lamotrigine, valproate, and carbamazepine; studies were conducted as RCTs. Cross-over studies were included if they reported results for the first period (i.e., before crossover) as a carry-over effect of treatment may be present in subsequent periods; and the research period was ≤16 weeks.

2.3 | Article selection process

Author Y.A removed the duplicates. Subsequently, two groups to which two authors belonged were created (group 1: M.T. and M.O.,

group 2: Y.E. and Y.K.). In each group, the two authors independently screened the titles and abstracts of the identified references to exclude irrelevant studies. The full texts of these references were evaluated, and ineligible reports were excluded according to the above criteria. Reasons for exclusion were registered by the authors of each group. Any disagreement was resolved by a systematic and thorough discussion with another author (M.S.).

2.4 | Outcome measures

The primary outcome measures were (1) the remission rate from depressive episodes (from baseline to up to 4 months of follow-up). The study period was set according to a previous study.[21] Remission was defined as scores on the Montgomery–Asberg Depression Rating Scale (MADRS)[27] ≤12 or the 17-item Hamilton Depression Rating Scale (HAM-D17)[28] ≤7, which was used by the author. Remission rates from depressive episodes were calculated by dividing the number of participants who achieved remission in a group by the total number of participants in that group.

The secondary outcome measures included the following: (2) changes in depressive symptom scores; (3) changes in social function; (4) suicide-related events; (5) serious adverse events; (6) dropouts due to adverse events; and (7) dropouts due to any reason. Depressive symptoms were evaluated using the MADRS[27] or HAM-D17.[28] Social function was evaluated using the Sheehan Disability Scale (SDS).[29]

When a three or more arm study included different groups administered with the same antipsychotics or mood stabilizers with different doses, we merged the two different dose groups into one group. When standard deviation (SD) was not examined in the study, the SD from other similar studies was substituted, and similar studies were selected in the following priority order: (1) studies using the same rating scale, (2) studies with similar baseline diagnoses and severity, (3) studies with the same intervention and control, (4) studies with similar intervention and control doses, and (5) studies with similar sample sizes.

2.5 | Data extraction, study quality, and risk of bias assessment

Four authors were divided into two groups (group 1: M.T. and M.O., group 2: Y.E. and Y.K.) to evaluate the quality of the studies and assess their risk of bias. The authors in each group carefully and independently extracted the relevant data. Author M.S. performed checks to ensure the quality and consistency of the assessment.

The following variables were extracted from each study: demographics of the participants (e.g., age, sex, education, employment status, and marital status); diagnostic criteria for bipolar depression; details on the participants' bipolar depression history (type, rapid cycler, age of onset, family history, and the number of mood episodes); details of psychotropic drug use (e.g., mood stabilizers, antipsychotics, antidepressants, and benzodiazepines), concurrent psychiatric disorders, the country in which the study was performed, measure for depressive symptoms, and measure for a social function. The following additional variables were also recorded: RCT type, study settings (primary or secondary care), inclusion and exclusion criteria of participant recruitment, contents of the intervention and control group (maximum dose, protocol), lithium concentration, and funding source.

The quality of the included studies was evaluated by the same four authors, divided into the same two groups, using the Cochrane risk of bias assessment.[30] The assessment evaluates the risk of bias of RCTs in seven domains: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective outcome reporting, and (7) other sources of bias. The rating for each domain can be "yes" (low risk of bias), "no" (high risk of bias), or "unclear" (unclear risk). Any disagreement was resolved through systematic and thorough discussions with M.S. Other biases were defined as baseline differences in the severity of depressive symptoms between the two groups. The rating of each domain can be "yes" (low risk of bias), "no" (high risk of bias), or "unclear" (uncertain risk). Disagreements were resolved through systematic and thorough discussions with M.S.

2.6 | Statistical analyses

The Cochrane Collaboration Review Manager software (RevMan 5.4.1) was used for the statistical analysis. Continuous outcome data were summarized using effect size, with "standardized mean differences (SMD)" and 95% confidence intervals (CIs); for dichotomous outcomes, risk ratios (RRs) with 95% CIs were used. In addition, because suicide-related events and serious adverse events are considered rare, odds ratios (ORs) with 95% CIs were used for their analysis. We used random-effects models for the data analyses. Publication bias was evaluated using a funnel plot of the treatment effect against a standard error and Egger's test when at least 10 studies were available.[30]

A sensitivity analysis on primary outcome remission rates from depressive episodes was performed as follows. We removed the studies that targeted all phases of analysis of bipolar disorder and were not stratified according to the phase of the disorder. Subgroup analysis was planned based on the type of bipolar disorder (types I and II).

3 | RESULTS

3.1 | Description of the Included Studies

Figure 1 shows the study selection flowchart. The initial literature search yielded 3520 unique entries published up to March 2021 (PubMed = 939, CENTRAL = 1111, EMBASE = 1470). Two ongoing

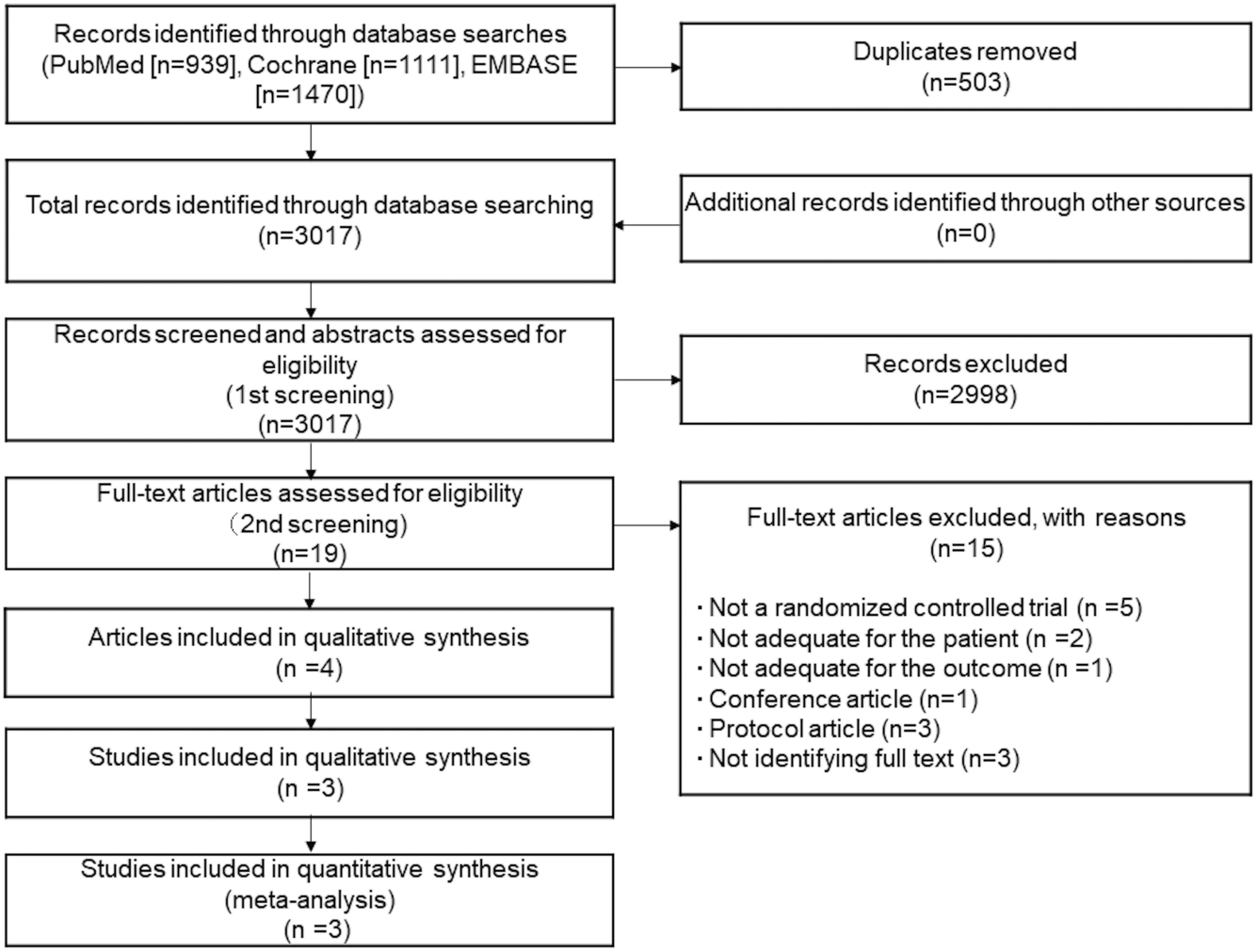

FIGURE 1 Flowchart of the study selection process

studies were identified on ClinicalTrials.gov up to March 2021, although they had already been identified in a systematic literature search. After screening the titles and abstracts of the identified reports, the full-text versions of a total of 19 articles were reviewed. Of the 19 articles, 15 articles were excluded for various reasons (Table S2). Finally, four articles comprising three studies were included in this study.

3.2 | Study characteristics

Three studies comprising four articles published between 2010 and 2019 were included in this review.[23,24,31,32] Two studies included only patients with bipolar disorder in major depressive episodes.[23,24,31] One study included 42 patients with bipolar spectrum disorder (25: bipolar I, 15: bipolar II, and 2: subthreshold bipolar disorder) in any phase (35: depressive episode, 4: manic/hypomanic/mixed episode, and 3: euthymic episode).[32] The sample size ranged from 35 to 669, with a total of 740 participants (Table 1). Of all the participants, 60.0% were female, and the mean age was 42.1 years. The criteria used for the diagnosis of bipolar spectrum disorders vary across studies. One study used the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV)[31] and another study used the Structured Clinical Interview for DSM-IV for the diagnosis of bipolar disorder.[23,24] Another study used the DSM-IV for the diagnosis of bipolar disorder and the National Comorbidity Survey–Replication subthreshold bipolar disorder for the diagnosis of subthreshold bipolar disorder.[32,33] The inclusion criteria for severity of depressive symptoms included a HAM-D score of ≥20 points and a HAM-D item 1 score of ≥2 points in one study,[31] a HAM-D of ≥20 points in one study,[23,24] and none in the other study.[32]

All studies were individual RCTs conducted at a secondary care facility.[23,24,31,32] One study was conducted in the USA,[32] one in Korea,[23,24] and the other in various countries (Europe, Canada, and Asia).[31] Two studies received financial support from AstraZeneca Pharmaceutics related to antipsychotics,[23,24,32] one study received financial support from funder-related or not related to antipsychotics.[31] There were two two-arm studies[23,24,32] and one four-arm study.[31]

All studies compared quetiapine with lithium. Of the three resultant studies, two assigned quetiapine or lithium after the washout of prior medication,[23,31] while one assigned these during the washout

TABLE 1 Characteristics of the study participants

Study (y)	Study design, duration, blinding	Duration	Blinding	Number of patients randomized	Age (Mean)	Female (%)	Bipolar I (%)	Rapid cycler (%)	Number of mood episodes (Mean)
Gao (2018) (Gao et al., 2018)	RCT (two-arm)	16 wk	single-blind (participants)	QTP (N = 20)	ND	ND	ND	ND	ND
				Li (N = 15)	ND	ND	ND	ND	ND
Kim (2014) (Kim et al., 2014)	RCT (two-arm)	8 wk	open-labeled	QTP (N = 18)	39.2	75% (9/12)	16.7% (2/12)	ND	3.8
				Li (N = 18)	33.9	41.2% (7/17)	5.9% (1/17)	ND	2.8
Young (2010) (Young et al., 2010)	RCT (four-arm)	8 wk	double-blind	QTP (N = 533)	42.6	60.4% (313/518)	62.2% (322/518)	6.2% (32/518)	ND
				Li (N = 136)	41.4	59.6% (81/136)	64.0% (87/136)	5.9% (8/136)	ND

Abbreviations: Li, lithium; ND, not described; QTP, quetiapine; SD, standard deviation.

period for up to 4 weeks[32] (Table 2). All studies did not provide details of prior medications before taking the study medications.[23,24,31,32] In the quetiapine group, the dosage (i.e., 300 mg/day or 600 mg/day) and duration (i.e., 8 weeks or 16 weeks) varied. In the lithium group, the initial dosage (i.e., 300 mg/day or 600 mg/day) and target lithium concentration (i.e., ≥0.6 mEq/L, 0.6–1.2 mEq/L, or 0.8–1.2 mEq/L) varied (Table 2).

3.3 | Risk of bias assessment

The risk of bias evaluation (Figure 2) showed the following: one RCT had adequate randomization methods,[31] one RCT has reported a sufficient allocation concealment procedure;[31] two RCTs had a high risk of bias in the participant and personnel blinding domain,[23,24,32] and one RCT was judged to have a high risk of bias in the blinding of the outcome assessment domain.[23,24] Regarding incomplete outcome data, two RCTs had a high risk of bias due to a high dropout rate.[23,24,32] One RCT had an unclear reporting bias because it was unable to obtain the research registration.[23,24] One RCT had a low risk of other bias.[31]

3.4 | Treatment outcome assessment

The outcomes are summarized in Table 3. Two RCTs have reported remission rates from depressive episodes after mood stabilizer/antipsychotic treatment.[23,24,31] Change scores in depressive symptoms (MADRS = 2, HAM-D17 = 1) have been reported in three studies.[23,2431,32] One study lacked the SD of the change in depressive symptoms from baseline to endpoint.[23] Therefore, we substituted SDs from studies with the same intervention and control medications and depressive symptom rating scales.[31] Two RCTs evaluated social function using the SDS.[31,32] Two studies have reported the rate of suicide-related events after the intervention.[23,24,31] One study defined suicide-related events as the incidence of patients with a HAM-D item 3 (suicide) score ≥3 or an adverse event of suicidality, suicidal ideation, suicide attempt, or suicide completion,[31] and the other study did not define suicide-related events.[23,24] Three studies have reported the rate of serious adverse events, dropout due to adverse events, and dropout for any reason.[23,24,31,32]

No significant differences were observed in the remission rates from depressive episodes (RR: 1.80, 95% CI: 0.51-6.40, $P = 0.36$; 683 participants, two studies)[23,24,31] (Figure 3) or in change scores for depressive symptoms (SMD: −0.22, 95% CI: −0.52–0.08, $P = 0.15$; 718 participants, three studies) between the quetiapine and lithium groups (Figure 4).[23,24,31,32] Moreover, no significant difference was observed in the changes in social function between the two groups (SMD: −0.00, 95% CI: −0.19-0.18, $P = 0.98$; 658 participants, two studies) (Figure 5).[31,32] No significant differences were observed in suicide-related events (OR: 2.35, 95% CI: 0.40-13.65, $P = 0.34$; 699 participants, two studies) (Figure 6),[23,24,31] serious adverse events (OR: 1.63, 95% CI: 0.51-5.20, $P = 0.41$; 734 participants, three

TABLE 2 Study protocol and washout of previous and concomitant psychotropic medications

Study (y)	Number of patients randomized	Study protocol	Washout of previous and concomitant psychotropic medications
Gao (2018) (Gao et al., 2018)	QTP (N = 20) Li (N = 15)	300 mg/day li was initiated at 300 mg/day for 3 d and subsequently increased to 600 mg/day. After a minimum of 5 d of administering 600 mg/day of Li, the serum Li level was checked. Subsequently, 300-mg increments every 7 d were titrated up as tolerated to a serum Li level of ≥0.6 mEq/L. those who were unable to tolerate 600 mg/day could discontinue the study.	sedatives and hypnotics were allowed as rescue medications during the first 8 wk of the study. Benzodiazepine and hypnotics were discontinued after 8 wk of study participation. no other concomitant psychiatric medications were allowed after week 4.
Kim (2014) (Kim et al., 2014)	QTP (N = 18) Li (N = 18)	300 mg/day li was initiated at 600 mg/day and adjusted to a serum level of 0.8–1.2 mEq/L for 2 wk. Serum Li level was monitored at weeks 1 and 8, and the level was checked at week 2 only when it was not within 0.8–1.2 mEq/L at week 1.	Before taking the study drugs, washout of all previous psychotropic medications for a period of at least four half-lives was done. The use of cytochrome P450 3A4 inhibitors or inducers was not permitted within 14 d prior to enrollment and during the study.
Young (2010) (Young et al., 2010)	QTP (N = 533) Li (N = 136)	300 mg/day (N = 265), 600 mg/day (N = 268) li was initiated at 600 mg/day and subsequently increased to 900 mg/day from day 4 until day 8. it was administered thereafter in a balanced manner at 600 to 1800 mg/day to maintain a serum Li level between 0.6 and 1.2 mEq/L.	once enrolled, patients underwent a washout period of at least 5-28 d during which prior psychotropic medications were discontinued.

Abbreviations: Li, lithium; ND, not described; QTP, quetiapine; SD, standard deviation.

studies) (Figure 7),[23,24,31,32] dropouts due to adverse events (risk ratio [RR]: 1.19, 95% CI: 0.76-1.87, $P = 0.45$; 734 participants, three studies) (Figure 8),[23,24,31,32] and dropouts for any reasons (risk ratio [RR]: 0.95, 95% CI: 0.74-1.22, $P = 0.70$; 740 participants, three studies) (Figure 9).[23,24,30,31] No patients completed suicide. Concerning serious adverse events, Kim et al. have reported one suicide attempt in the quetiapine group.[23,24] Young et al. 2010 and Gao et al. 2018 have not reported any serious adverse events.[31,32]

A subgroup analysis could not be performed because data on remission rates for bipolar disorder types I and II were not available. We did not perform additional sensitivity analyses because the studies for which remission rates were available randomized the use of quetiapine and lithium in patients with bipolar depression.[23,24,31]

4 | DISCUSSION

To the best of our knowledge, this is the first systematic review and meta-analysis to compare the efficacy and safety between antipsychotics and mood stabilizers in patients with bipolar depression. All three studies included in the meta-analysis compared quetiapine with lithium for bipolar depression. Hence, this study is a meta-analysis of RCTs directly comparing quetiapine and lithium. The study did not show any difference in efficacy between quetiapine and lithium for patients with bipolar depression, nor did it show any difference in safety. We could not perform a subgroup analysis to compare remission rates from depressive episodes for bipolar I and II depression between quetiapine and lithium.

Here, no significant difference was observed in the antidepressant effects of quetiapine and lithium for bipolar depression. This result is consistent with the results of a network meta-analysis of double-blind RCTs conducted by Taylor et al. in 2014.[21] The efficacy of quetiapine for bipolar depression has been supported by placebo-controlled RCTs and their combined MAs,[21,34] and quetiapine is the first-line treatment for bipolar depression according to various guidelines.[17,18,19,20] However, the effect of lithium on bipolar depression is controversial, and the recommendations for lithium vary widely among guidelines, ranging from the first-line treatment to no recommendation.[17,18,19,20] Small RCTs conducted in the 1970s have reported the efficacy of lithium,[35,36] whereas a relatively large placebo-controlled RCT conducted in the 2000s found no significant difference in antidepressant effects between lithium and placebo for bipolar depression.[31] Kelly has reported that guidelines favoring lithium for bipolar depression suffer from the Woozle effect (evidence by citation), reference inflation (overreporting the findings of cited studies), and belief perseverance (maintaining a

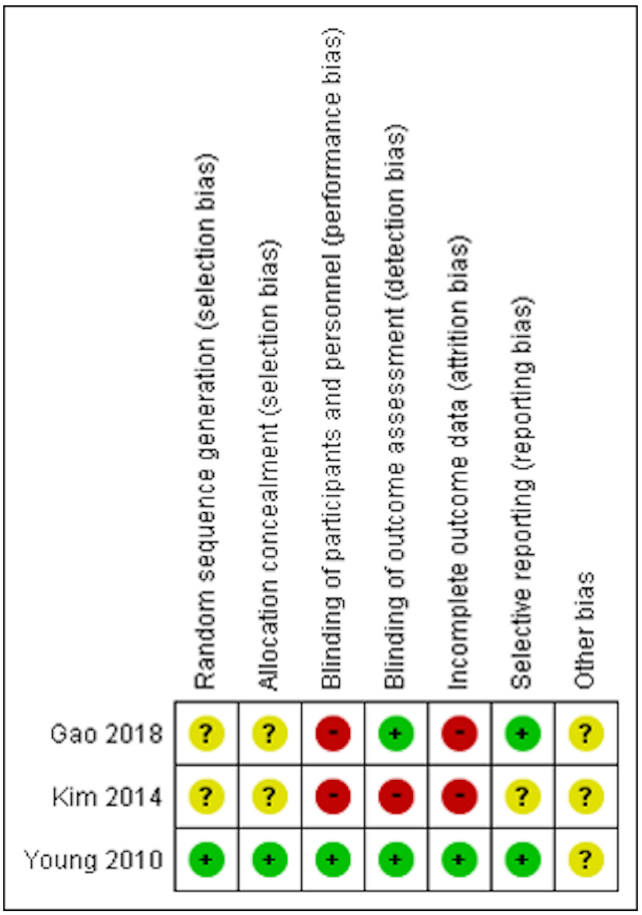

FIGURE 2 Risk of bias assessment. Green indicates a low risk of bias, yellow indicates an unclear risk of bias, and red indicates a high risk of bias

belief despite new contradictory evidence) as possible causes for these discrepancies.[37] Although this study included RCTs that were not double-blind, only three RCTs directly compared quetiapine and lithium, and the sample size was small; thus, this study could not detect a difference between the antidepressant effects of quetiapine and lithium on bipolar depression due to insufficient statistical power. Since there is currently insufficient evidence for the use of lithium for bipolar depression, the position of lithium in treating bipolar depression might be determined after the accumulation of well-designed, large-scale RCTs.

Social dysfunction is common in patients with bipolar disorder, especially in patients with bipolar depression.[38] Here, no significant difference was observed in the improvement of social functioning between patients on quetiapine and lithium. Since previous meta-analyses and network meta-analyses have focused mainly on antidepressant effects and not on improving social functioning,[21,22,34,39,40] this study is valuable in that it examined improvements in social functioning. However, considering that the functional recovery was delayed by symptomatic remission[41,42] and that this study reviewed the RCTs for a relatively short period (8–16 weeks), the effect of the improvement in social functioning should be evaluated over a longer period.

Patients with bipolar disorder are at a higher risk of suicide, and depressive episodes are the most likely mood states associated with suicide risk among them.[16,43] However, the short-term preventive effects of pharmacotherapy on suicide remain unclear.[43] Although this study did not show a difference between the effects of quetiapine and lithium on suicide-related events, it would be meaningful to investigate the effects of pharmacotherapy on suicide-related events in this study, which were not discussed in previous studies.[21,22,13] This study also evaluated serious adverse events that were not investigated in previous studies, although no significant differences were identified between the two groups.[21,22,44] However, due to the study's small sample size and a small number of suicide-related and serious adverse events, the confidence intervals for the risk ratios were very wide. Thus, our results on suicide-related events and serious adverse events may be imprecise. Since only a few RCTs have compared quetiapine and lithium, it would be appropriate to judge whether quetiapine or lithium is superior for suicide-related events and serious adverse events by considering not only RCTs but also observational studies based on existing evidence.

Our study has several limitations. First, since all the included RCTs compared quetiapine with lithium, this meta-analysis could not compare the usefulness of antipsychotics and mood stabilizers (such as lurasidone and lamotrigine), including studies other than quetiapine and lithium. Thus, further studies are needed to investigate the comprehensive efficacy and safety of antipsychotics and mood stabilizers in patients with bipolar depression. Second, we only included three RCTs with a total of 740 patients, leading to a relatively low statistical power. A previous network meta-analysis included only one double-blind RCT that directly compared antipsychotics and mood stabilizers; accordingly, the present study also included open-label and single-blind RCTs to analyze a larger sample size. However, only three RCTs could be identified that directly compared quetiapine and lithium. Therefore, further RCTs with more participants are needed to clarify whether antipsychotics or mood stabilizers are more useful for treating bipolar depression. Third, the target dose and blood level of lithium were different across the RCTs, and some patients did not reach the target lithium blood concentration, which may have influenced our results.[23,31,32] Although there is no consensus on the optimal blood level of lithium for the acute treatment of bipolar depression, the Japanese Society of Mood Disorders and NICE guidelines suggest that increasing the blood level of lithium may enhance the antidepressant effect in treating bipolar depression.[18,45] Moreover, higher doses and blood levels of lithium may contribute to higher rates of adverse events and dropout rates. Therefore, the true usefulness of lithium in bipolar depression should be examined with strict control of lithium blood levels in the future.

In conclusion, this meta-analysis did not demonstrate any difference in the efficacy or safety between quetiapine and lithium for bipolar depression. Further studies, especially comparing antipsychotics and mood stabilizers other than quetiapine with lithium, are needed to clarify whether antipsychotics or mood stabilizers are more useful for bipolar depression.

TABLE 3 Summary of depressive symptoms and social function outcomes

Study (year)	Intervention and control	Remission from depressive episode (percent and number)	Change in depressive symptoms (mean (SD) and number)	Change in social function (mean (SD) and number)
Gao (2018) (Gao et al., 2018)[a]	QTP	ND	at 8 wk • −9.50 (14.40) [N = 20] at 16 wk • −13.09 (17.89) [N = 20]	at 8 wk • −4.56 (14.18) [N = 20] at 16 wk • −5.85 (13.1) [N = 20]
	Li	ND	at 8 wk • −10.17 (15.49) [N = 15] at 16 wk • −11.76 (20.10) [N = 15]	at 8 wk • −3.40 (13.32) [N = 15] at 16 wk • −8.62 (14.72) [N = 15]
Kim (2014) (Kim et al., 2014)[b]	QTP	at 8 wk • 50.0% (6/12)	at 8 wk • −16.3 (12.46) [N = 12]	ND
	Li	at 8 wk • 11.8% (2/17)	at 8 wk • −7.0 (10.5) [N = 17]	ND
Young (2010) (Young et al., 2010)[b]	QTP	at 8 wk • 70.1% (363/518)	at 8 wk • −15.74 (14.88) [N = 518]	at 8 wk • −7.22 (12.22) [N = 492]
	Li	at 8 wk • 62.5% (85/136)	at 8 wk • −13.6 (12.59) [N = 136]	at 8 wk • −7.00 (10.07) [N = 131]

Abbreviations: Li, lithium; ND, not described; QTP, quetiapine; SD, standard deviation.

[a]A mixed model for repeated measures was used to handle missing data.

[b]The last observation carried forward method was used to handle missing data.

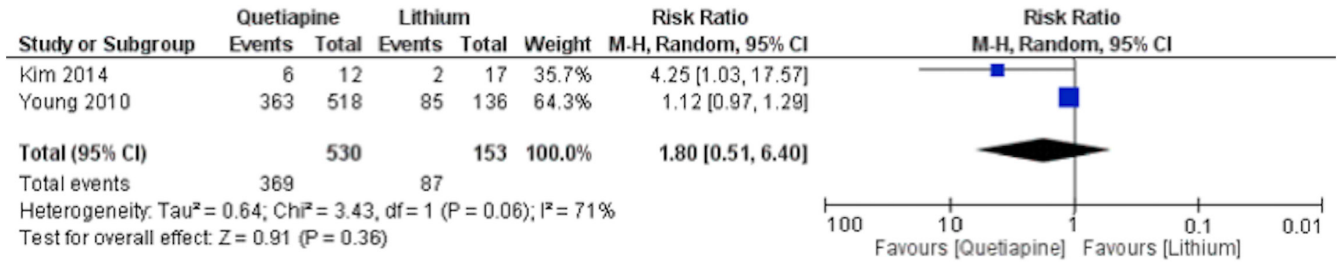

FIGURE 3 Forest plot of post-intervention treatment effect sizes for remission rates from depressive episodes. CI, confidence interval; SD, standard deviation

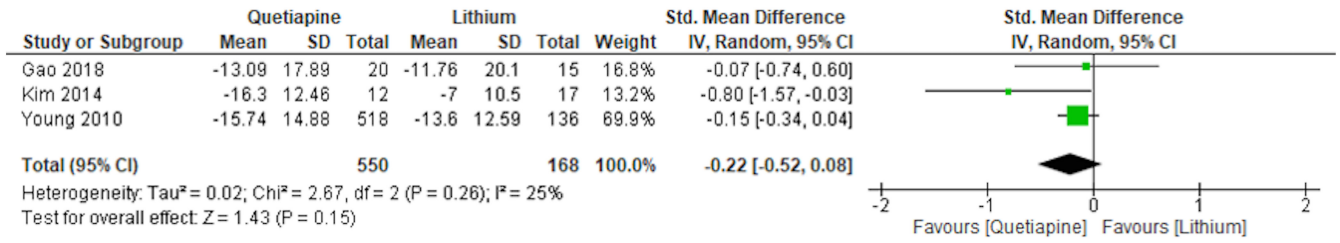

FIGURE 4 Forest plot of post-intervention treatment effect sizes for changes in depressive symptoms. CI, confidence interval; SD, standard deviation

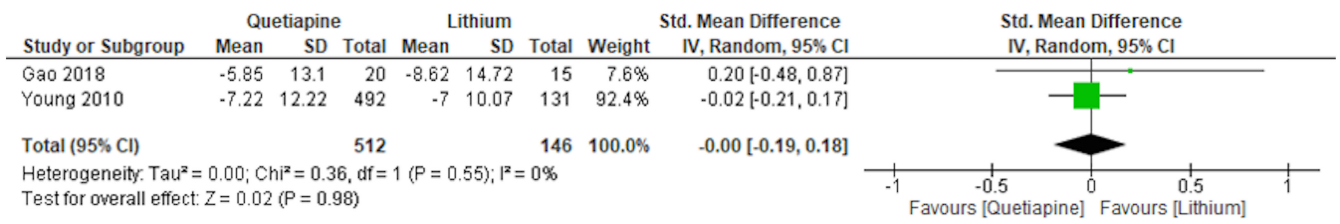

FIGURE 5 Forest plot of post-intervention treatment effect sizes for changes in social function. CI, confidence interval; SD, standard deviation

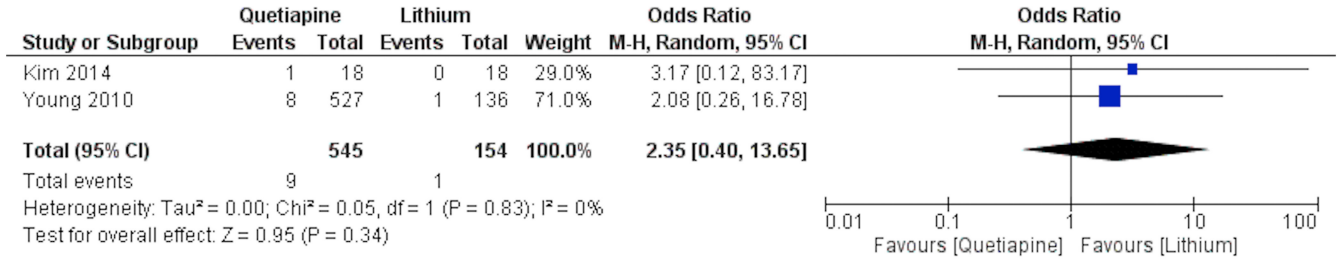

FIGURE 6 Forest plot of post-intervention treatment effect sizes for suicide-related events. CI, confidence interval; SD, standard deviation

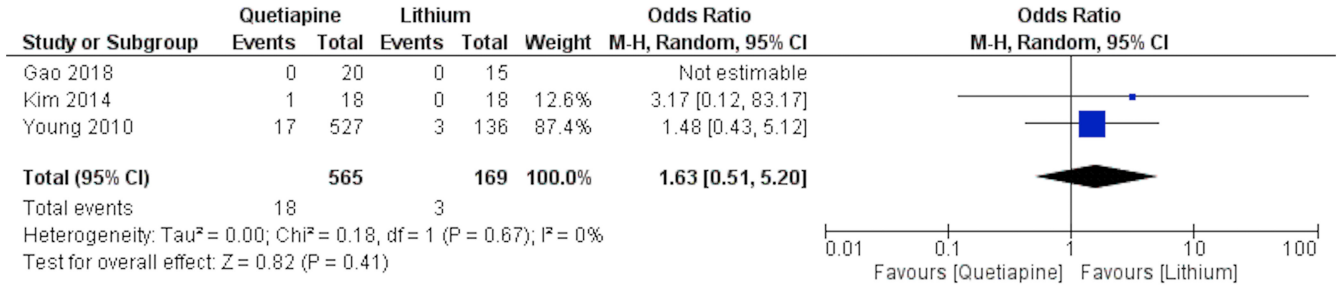

FIGURE 7 Forest plot of post-intervention treatment effect sizes for serious adverse events. CI, confidence interval; SD, standard deviation

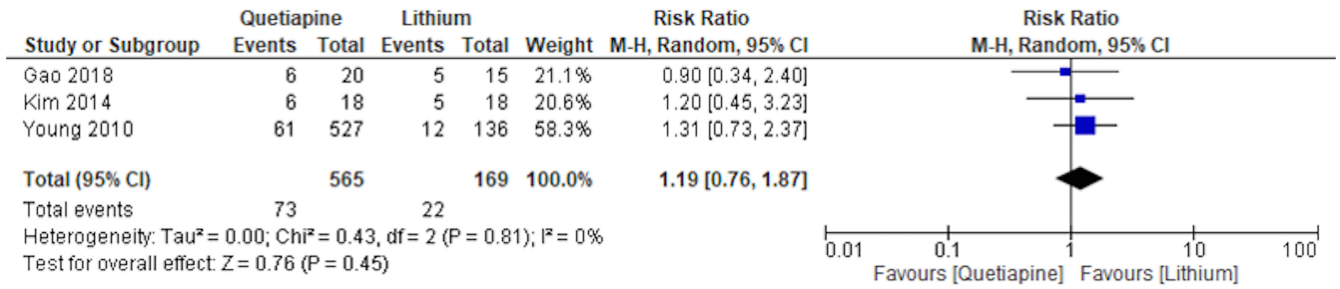

FIGURE 8 Forest plot of post-intervention treatment effect sizes for dropouts due to adverse events. CI, confidence interval; SD, standard deviation

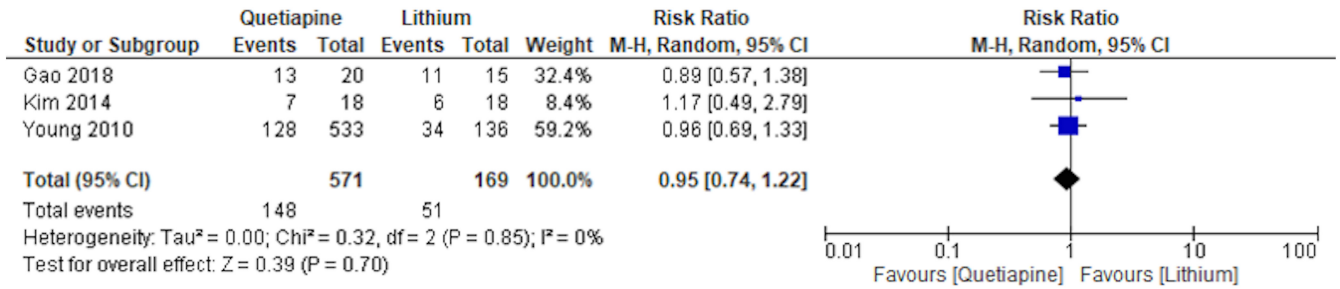

FIGURE 9 Forest plot of post-intervention treatment effect sizes for dropouts for any reasons

AUTHOR CONTRIBUTIONS

Masahiro Takeshima; Conceptualization, Role/writing original draft, Methodology: Masaya Ogasawara, Yuichi Esaki, Yoshiyuki Kaneko, and Yumi Aoki; Investigation; Tomohiro Utsumi; Dats analyses: Norio Watanabe, Masahiro Suzuki and Yoshikazu Takaesu; supervision.

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CONFLICT OF INTEREST

Conflict of interest disclosure: Masahiro Takeshima has received lecture fees from Daiichi Sankyo Company, Sumitomo Dainippon Pharma, Meiji Seika Pharma, Viatris Pharmaceuticals Japan, Yoshitomi Pharmaceutical, and Daiichi Sankyo Company; and research grants from Otsuka Pharmaceutical, EISAI, and Shionogi, outside the submitted work. Yuichi Esaki has received manuscript fees from Dainippon Sumitomo, outside the submitted work. Yoshiyuki Kaneko has received lecture fees from Meiji Seika Pharma, Mochida Pharmaceutical, and Otsuka Pharmaceutical; and a grant from Idorsia Pharmaceuticals Japan, outside the submitted work. Tomohiro Utsumi has received lecture fees from EISAI, outside the submitted work. Masahiro Suzuki has received speaker's honoraria from Dainippon Sumitomo, EA Pharma, Meiji Seika Pharma, Mochida Pharmaceutical, MSD, Otsuka Pharmaceutical, Pfizer, Shionogi Pharma, Takeda Pharmaceutical, Yoshitomi Pharmaceutical, and Viatris; and research grants from Dainippon Sumitomo, Eisai, Mochida Pharmaceutical, Otsuka Pharmaceutical, Shionogi Pharma, and Takeda Pharmaceutical, outside the submitted work. Yoshikazu Takaesu has received lecture fees from Takeda Pharmaceutical, Sumitomo Dainippon Pharma, Otsuka Pharmaceutical, Meiji Seika Pharma, Eli Lilly, EISAI, MSD, and Yoshitomiyakuhin; and research funding from Otsuka Pharmaceutical, Meiji Seika Pharma, MSD, and EISAI, outside the submitted work. Masaya Ogasawara, Yumi Aoki, and Norio Watanabe have nothing relevant to declare.

DATA AVAILABILITY STATEMENT

The data used in this meta-analysis are openly available in the three published studies that were cited in this paper.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

n/a

INFORMED CONSENT

n/a

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

This study was registered with PROSPERO (https://www.crd.york.ac.uk/PROSPERO/#searchadvanced, CRD 42021250410).

ANIMAL STUDIES

n/a

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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