

Variability and efficacy in treatment effects on manic symptoms with lithium, anticonvulsants, and antipsychotics in acute bipolar mania: A systematic review and meta-analysis

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Summary

Background Acute mania is a psychiatric emergency requiring rapid management. However, randomised controlled trials (RCTs) have shown considerable individual differences in treatment effects on manic symptoms with antimanic drugs.

Methods We searched the MEDLINE, CENTRAL, EMBASE, PsycINFO, and ClinicalTrials.gov to identify RCTs without language restrictions from inception to April 19, 2022. We included double-blind RCTs of oral antimanic monotherapy versus placebo in adult patients. The primary outcome was variability in improvement of manic symptoms (assessed using the coefficient of variation ratio [CVR]). The secondary outcomes were overall improvement of manic symptoms and acceptability (i.e., discontinuation for any reason). The pooled effects of outcomes were calculated by random-effects meta-analyses using restricted maximum likelihood methods. The quality of the included studies was assessed using the Cochrane Risk of Bias (ROB) Assessment Tool. This study was registered with OSF (DOI:10.17605/OSF.IO/G4JNY).

Findings We included 39 RCTs (N=12150; mean age=39.9 years, interquartile range [IQR]=38.7-41.1; mean proportion of female=48.6%, IQR=42.3%-52.3%) and investigated 14 antimanic drugs. We found that eight antimanic drugs compared to placebo were associated with lower CVRs (95% confidence interval [CI]; I²), including risperidone (0.51; 0.37-0.70; 0%), haloperidol (0.54; 0.44-0.67; 4%), olanzapine (0.59; 0.44-0.79; 47%), ziprasidone (0.61; 0.53-0.71; 0%), lithium (0.63; 0.52-0.76; 0%), quetiapine (0.65; 0.48-0.87; 2%), aripiprazole (0.68; 0.56-0.84; 25%), and

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cariprazine (0.70; 0.49-0.99; 28%). There were nine antimanic drugs associated with greater efficacy than placebo, including risperidone (reported as standardised mean difference; 95% CI; I^2 : 0.64; 0.31-0.97; 15%), haloperidol (0.57; 0.29-0.85; 64%), cariprazine (0.51; 0.24-0.78; 0%), olanzapine (0.44; 0.30-0.58; 0%), lithium (0.42; 0.29-0.55; 0%), ziprasidone (0.42; 0.26-0.58; 0%), quetiapine (0.40; 0.13-0.67; 0%), asenapine (0.40; 0.13-0.67; 0%), and aripiprazole (0.32; 0.14-0.49; 53%). Ziprasidone (reported as risk ratio; 95% CI; I^2 : 0.83; 0.79-0.89; 0%) and olanzapine (0.63; 0.49-0.80; 35%) were associated with better acceptability relative to placebo. Among the 39 RCTs, none had a high ROB.

Interpretation We demonstrated that eight antimanic drugs were associated with lower variability and better efficacy than placebo, suggesting that these antimanic drugs were associated with more homogenous and predictable improvements of manic symptoms in patients with acute mania.

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Keywords: Bipolar mania; Variability in improvement of manic symptoms; Meta-analysis; Antipsychotics; Mood stabilisers; Anticonvulsants

Research in context

Evidence before this study

We searched the MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, PsycINFO, and ClinicalTrials.gov databases without language restriction from database inception to April 19, 2022. We aimed to identify studies reporting variability in improvement of manic symptoms with antimanic drugs in patients with acute mania. However, so far no studies have addressed this issue.

Added value of this study

We provided data of variability and efficacy in improvement of manic symptoms for 14 antimanic drugs. Among the investigated antimanic drugs, eight antimanic drugs compared with placebo were associated with lower variability and better efficacy in improvement of manic symptoms, suggesting that these antimanic drugs were associated with more homogenous and predictable improvements of manic symptoms in patients with acute mania.

Implications of all the available evidence

Our study findings may assist the decision-making process in selecting a first-line treatment for acute bipolar mania. Future research can examine the variability of maintenance treatment for bipolar disorder, which are important for long-term management.

Introduction

Bipolar disorder is a complex and severe mental disorder affecting approximately 2.4% of the general population.¹⁻³ Acute bipolar mania is a psychiatric emergency. Patients in acute manic states often present with elevated mood, impulsivity, agitation, aggression, risky behaviours, and psychotic features.^{2,4} These symptoms may be severe, leading to marked functional impairment, hospitalisation, burden, and societal costs.^{4,5}

Pharmacological treatment is a cornerstone strategy for the management of acute mania.⁶ Both the National Institute for Health and Care Excellence (NICE) and the British Association for Psychopharmacology (BAP) guidelines suggest antipsychotic monotherapy as a first-line treatment for acute mania,^{7,8} while the most recent version of the Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines⁶ recommends different first-line treatment options for acute mania, namely (i) monotherapy with lithium, valproate, or atypical antipsychotics or (ii) a combination of an atypical antipsychotic with a mood stabiliser. The decision to treat patients with mania with either monotherapy or combination therapy may depend on symptom severity and the need for a rapid therapeutic response, previous history of response to monotherapy, tolerability concerns related to combination therapy relative to monotherapy, and the willingness of the patient.^{2,6} A recent network meta-analysis of randomised controlled trials (RCTs) reported that risperidone, quetiapine, aripiprazole, and olanzapine outperformed other antimanic

drugs in terms of overall improvement of manic symptoms and acceptability.⁹

Across distinct RCTs, participants varied considerably in their response to the same antimanic drug, dose, and treatment period,^{9–11} although the evidence generally points to uniform efficacy for every patient. A previous meta-analysis examined moderators of treatment response in participants with acute bipolar mania.¹² When considering antimanic drugs as a whole, this meta-analysis reported that younger age, male sex, and psychotic features were associated with greater drug-related improvement.¹² However, it remains unclear whether any individual antimanic drug is associated with either (i) a higher variability in improvement of manic symptoms, suggesting the possible existence of a subgroup of patients with a greater response to this drug, or (ii) a lower variability in improvement of manic symptoms, suggesting a more homogenous response to this drug irrespective of subtle individual differences. From a clinical perspective, if an antimanic drug has better efficacy coupled with lower variability in improvement of manic symptoms for acute mania, it could produce a more stable therapeutic response, and thus be favoured for managing acute bipolar mania.

The aim of the current study was to examine the variability in improvement of manic symptoms for individual antimanic drug compared to placebo in patients with an acute manic episode. We focused on improvement of manic symptoms in the acute phase because rapid management of an acute manic episode is important to ensure patient safety and prevent serious consequences. We also examined the efficacy and acceptability of the included antimanic drugs. We hypothesised that certain antimanic drugs, compared to placebo, could be associated with either higher or lower variability in improvement of manic symptoms.

Methods

The protocol of the current systematic review and meta-analysis was a priori, registered in OSF (10.17605/OSF.IO/G4JNY), and conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 statement (Appendix 1).¹³ Ethical approval is waived in this meta-analytic study.

Search strategy and selection criteria

The MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, PsycINFO, and Clinicaltrials.gov databases were systematically searched to identify RCTs testing different antimanic agents without language restriction, from database inception to April 19, 2022. The full details of the search strategies and the reasons of exclusions are provided in the Supplement (Appendix 2). The PICO (population, intervention, comparison, outcome) settings of the current

meta-analysis were (i) P: adult patients with bipolar I disorder experiencing an acute manic episode; (ii) I: monotherapy with an antimanic drug (e.g., lithium, valproate, topiramate, and antipsychotics); (iii) C: a placebo; and (iv) O: changes in manic symptoms. To compare the variability of responses between the active treatment and placebo groups, we only included double-blind RCTs of oral monotherapy versus placebo and reported the necessary information (i.e., standard deviations [SDs], means, and sample sizes). We excluded (i) trials involving add-on or combination treatments, (ii) head-to-head trials without a placebo group, (iii) studies that enrolled participants with schizoaffective disorder, and (iv) relapse prevention studies. Studies without available data on SDs of changes in manic symptoms were excluded. Screening and selection of studies were performed independently by four of the authors, with each study assessed by a minimum of two authors. Disagreements were resolved by consulting with the corresponding author.

Outcome definition and data extraction

The primary outcome was the variability in improvement of manic symptoms in patients with acute bipolar mania receiving an antimanic drug. The secondary outcomes were overall improvement of manic symptoms (i.e., efficacy) and acceptability (i.e., discontinuation for any reason). We extracted both SD (or variance, standard error) and means of changes in manic symptoms at week 3 from each study for both active treatment and placebo groups, as measured with the Young Mania Rating Scale or the Mania Rating Scale from the Schedule for Affective Disorders and Schizophrenia, Change Version. If there were two measures meeting the criteria, we will extract the measure with the lower p-value. Intention-to-treat datasets were used when available. For RCTs that compared different dosages of antimanic drugs versus placebo, we calculated the aggregated SDs and means across all active arms, leaving only one SD and one mean per study. At least two authors double-checked the data-transfer accuracy and calculations.

Data analysis

The Cochrane Risk of Bias Assessment Tool was used to rate the quality of the included studies by two independent authors.¹⁴ The included studies were classified as having high, low, or unclear risk of bias (ROB) according to the following domains: selection biases (randomisation and allocation concealment), detection bias, performance bias, attrition bias, reporting bias, and other bias. In case of discrepancies, another author was consulted to obtain a consensus.

Data analyses were conducted using R-Project (V.4.0.3, R Foundation). Across biological systems, variance often scales with the mean; most commonly, the

higher the mean, the higher the variance.¹⁵ Therefore, between-group differences in variability may, at least partly, be due to between-group differences across the mean. We used coefficient of variation ratios (CVRs) to adjust for mean-variance relationships.¹⁵ The use of CVRs for meta-analysis requires the following assumptions: (i) the data are expressed in ratio scales, and (ii) Taylor's law does not hold.¹⁶ According to Taylor's law, the natural logarithmic mean has a linear relationship with the natural logarithmic variance. The calculation of CVR and justification for using CVR is shown in the Supplement (Appendix 3).

All the effect sizes were calculated using random-effects meta-analysis with restricted maximum likelihood methods. The pooled CVR was calculated using a random-effects model. A CVR of 1 indicates equal variability in antimanic treatment and placebo. A CVR greater than 1 indicates higher variability in antimanic treatment compared to placebo, whereas a CVR smaller than 1 indicates less variability in antimanic treatments relative to placebo. The detailed formulae for CVR can be found elsewhere.¹⁵ In addition, we performed meta-analyses of group differences in overall improvements of manic symptoms, and standardised mean differences (SMDs) with respective 95% confidence intervals (CIs) were calculated. We also performed meta-analyses of group differences in acceptability (i.e., all-cause discontinuation), and the risk ratios (RRs) with 95% CIs were calculated.

The Cochran's Q test and I^2 statistics were used to assess heterogeneity, and $I^2 > 50\%$ indicated that the included studies were heterogeneous. Meta-regression and assessment of possible publication bias (Egger's test and visual inspection of funnel plots) analyses were conducted when individual antimanic drugs were investigated across ten or more studies.¹⁷ Subgroup analysis was performed when $I^2 > 50\%$ was identified and at least ten or more studies were included.¹⁷ Sensitivity analyses included: (i) excluding studies with a high risk of bias (ROB); (ii) using a random-slope mixed-effects model (RSMM) if the data did not satisfy the criteria for the use of CVR, or if the CVR of baseline manic symptoms between the treatment and control groups was significantly larger or smaller than 1 (i.e., baseline imbalance),¹⁶ and (ii) in 3-arm RCTs, dividing the sample size of the placebo arm equally to the two active drugs for calculating their corresponding CVR.

Role of the funding source

The funder has no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication. All authors confirmed that they had full access to all the data in the study and accept responsibility to submit for publication.

Results

The selection process and resulting number of RCTs included are shown in Figure 1. The current study included 39 RCTs (from 34 studies) comprising 12150 participants experiencing acute manic episodes. The sample size of the 39 RCTs ranged from 36 to 497, with a mean of 311.5 (SD: 128.8). The mean age was 39.9 (SD: 2.0; IQR [interquartile range]: 38.7-41.1) years, with 48.6% (SD: 7.3%; IQR: 42.3%-52.3%) being female. Among the 39 included RCTs, 38 (97.4%) provided data at week three (week 3: 38; week 4: 1). The follow-up periods of the included studies were 35 RCTs for three weeks, one for four weeks, one for six weeks, and two for eight weeks. The mean follow-up period was 3.4 week [IQR: 3-3]. The investigated antimanic drugs included lithium (k=5, four in the USA, and the other one across Eastern Europe, South Africa, South America, and India), valproate (k=5, all in the USA), topiramate (k=4, two in the USA, the other two across Europe, South Africa, Asia, and South America), eslicarbazepine (k=2, both in Europe), haloperidol (k=5, one in Japan, one in the USA, one in India, one in Russia, and the other one across Russia, India, and the USA), risperidone (k=3, one in the USA, one in India, and the other one in Russia), paliperidone (k=2, both across Europe, Asia, and the USA), ziprasidone (k=3, one in the USA and Brazil, one in the USA, Mexico, and Brazil, and the other one in the USA, Russia, and India), quetiapine (k=4, two in the USA, one in South America, and the other one across Europe, Asia, and the USA), olanzapine (k=6, three in the USA, one in Japan, and two across Europe, Asia, and the USA), asenapine (k=3, two across Europe, Asia, and the USA, and the other one in Europe and the USA), cariprazine (k=3, one in India, one in the USA, Russia, and India, and the other one across Europe and the USA), aripiprazole (k=6, five in the USA, and the other one in Asia), and brexpiprazole (k=2, both across Europe and the USA). One of four quetiapine studies used extended-released form, and two of five valproate studies used extended-released form. Details of the study characteristics and the head-to-head comparisons in 3-arm RCTs are provided in the Supplement (eTable 1 and eFigure 1).

Methodological quality of the included studies

The overall ROB are shown in the Supplement (eFigure 2 and eFigure 3). Among the included trials, none was rated as high overall ROB. The percentage of studies with high, unclear, and low ROB for the individual items was: 0%, 64.1%, and 35.9% for randomisation, 0%, 74.4%, and 25.6% for allocation concealment, 0%, 51.3%, and 48.7% for blinding of participants and personnel, 0%, 74.4%, and 25.6% for blinding of outcome assessment, 0%, 2.6%, and 97.4% for missing outcome, 0%, 30.8%, and 69.2% for selective reporting, and 0%, 100%, and 0% for other biases.

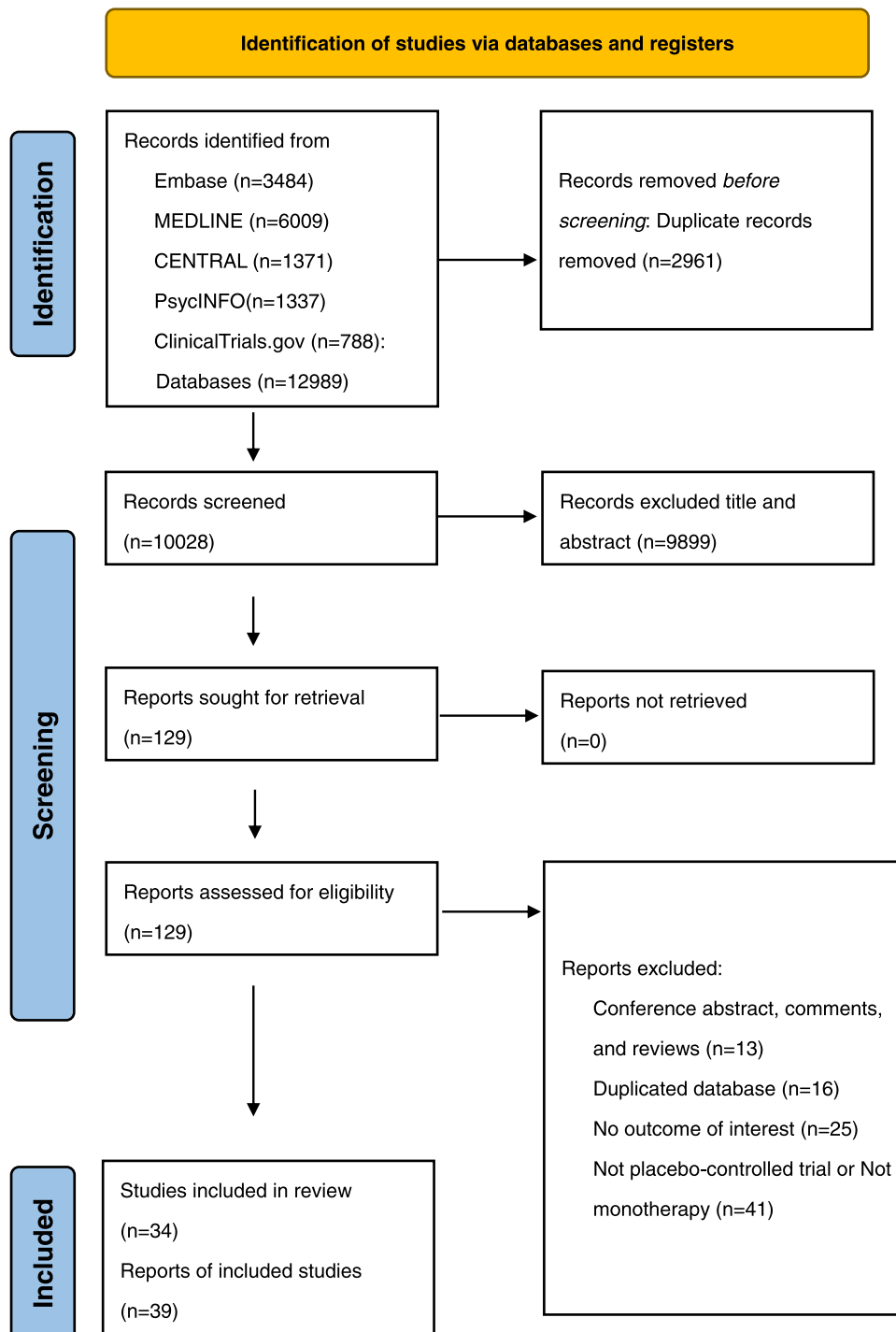


Figure 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

Variability in improvement of manic symptoms of individual antimanic drugs vs. placebo

Based on the value of CVR (from low to high), the antimanic drugs showing significantly lower variability in improvement of manic symptoms than placebo were risperidone (reported as CVR with 95% CI: 0.51; 0.38-0.70; $I^2=0\%$; $k=3$), haloperidol (0.54; 0.44-0.67; $I^2=4\%$; $k=5$), olanzapine (0.59; 0.44-0.79; $I^2=47\%$; $k=6$), ziprasidone (0.61; 0.53-0.71; $I^2=0\%$; $k=3$), lithium (0.63; 0.52-0.76; $I^2=0\%$; $k=5$), quetiapine (0.65; 0.48-0.87; $I^2=2\%$; $k=4$), aripiprazole (0.68; 0.56-0.84; $I^2=25\%$; $k=6$), and cariprazine (0.70; 0.49-0.99; $I^2=28\%$; $k=3$) (Figure 2). The other six antimanic drugs, namely paliperidone, valproate, asenapine, eslicarbazepine, brexpiprazole, and topiramate did not reach statistical significance in their variability of improvement of manic symptoms compared to placebo. Forest plots of individual antimanic drugs are provided in the Supplement (eFigure 4 to eFigure 17).

Improvement of manic symptoms of individual antimanic drugs vs. placebo

Ordered by the SMD value (from high to low), the antimanic drugs showing significantly greater efficacy in improvement of manic symptoms than placebo were risperidone (reported as SMD with 95% CI: 0.64; 0.31-0.97; $I^2=15\%$; $k=3$), haloperidol (0.57; 0.29-0.85; $I^2=64\%$; $k=5$), cariprazine (0.51; 0.24-0.78; $I^2=0\%$; $k=3$), olanzapine (0.44; 0.30-0.58; $I^2=0\%$; $k=6$), lithium (0.

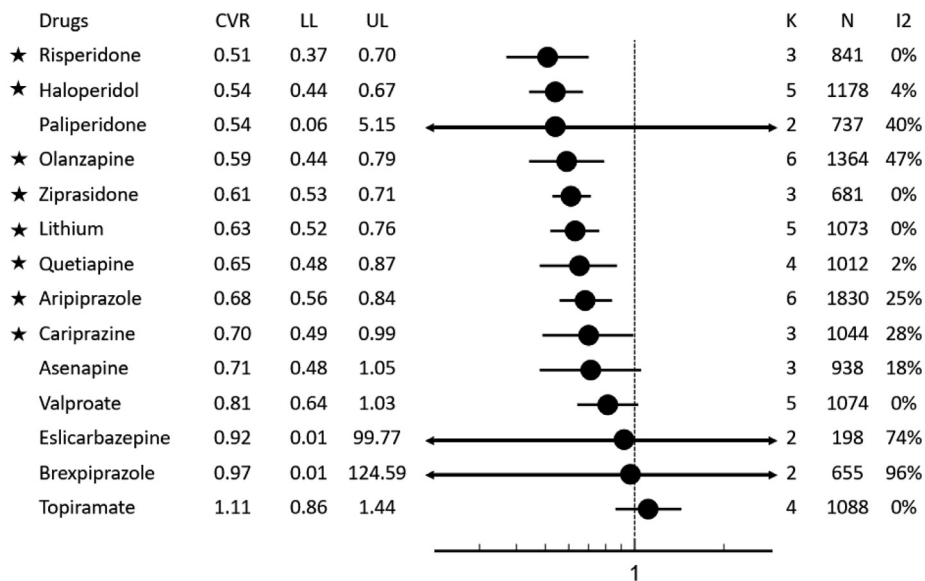
42; 0.29-0.55; $I^2=0\%$; $k=5$), ziprasidone (0.42; 0.26-0.58; $I^2=0\%$; $k=3$), quetiapine (0.40; 0.25-0.54; $I^2=0\%$; $k=4$), asenapine (0.40; 0.13-0.67; $I^2=0\%$; $k=3$), and aripiprazole (0.32; 0.14-0.49; $I^2=53\%$; $k=6$) (Figure 3). The other five antimanic drugs did not reach statistical significance in their efficacy of antimanic treatment compared to placebo, namely paliperidone, valproate, eslicarbazepine, brexpiprazole, and topiramate. Forest plots of individual antimanic drugs can be found in the Supplement (eFigure 18 to eFigure 31).

Acceptability

Forest plots of all-cause discontinuation for all investigated antimanic drugs can be found in the Supplement (eFigure 32 to eFigure 45). There were two antimanic drugs compared to placebo showing higher acceptability, namely ziprasidone (reported as RR with 95% CI: 0.83; 0.70-0.98; $I^2=0\%$; $k=3$) and olanzapine (0.63; 0.49-0.80; $I^2=35\%$; $k=6$). The other antimanic drugs did not reach statistical significance in the risk of all-cause discontinuation compared to placebo (eTable 2).

Two-dimensional graph of efficacy and variability in improvement of manic symptoms

Figure 4 illustrates a two-dimensional graph depicting both the efficacy and variability in improvement of manic symptoms across all investigated agents. Among



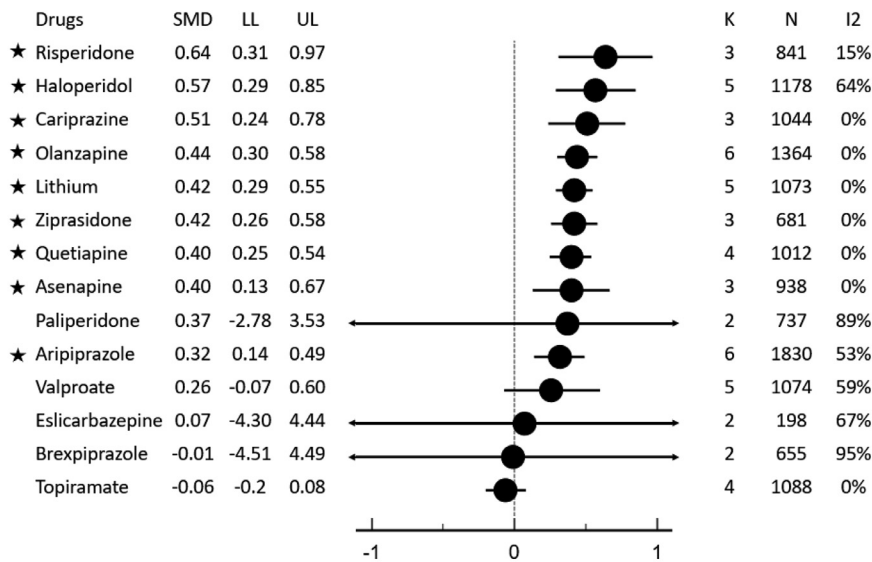
Asterisks indicate statistical significance.

Abbreviation: CI, confidence interval; CVR, coefficient of variation ratio; K, number of study; N, number of participant.

Figure 2. Variability in improvement of manic symptoms for individual antimanic drug compared with placebo.

Asterisks indicate statistical significance.

Abbreviation: CI, confidence interval; CVR, coefficient of variation ratio; K, number of study; N, number of participant.



Asterisks indicate statistical significance.

Abbreviation: CI, confidence interval; K, number of study; N, number of participants; SMD, standardised mean difference.

Figure 3. Efficacy in improvement of manic symptoms for individual antimanic drug compared with placebo.

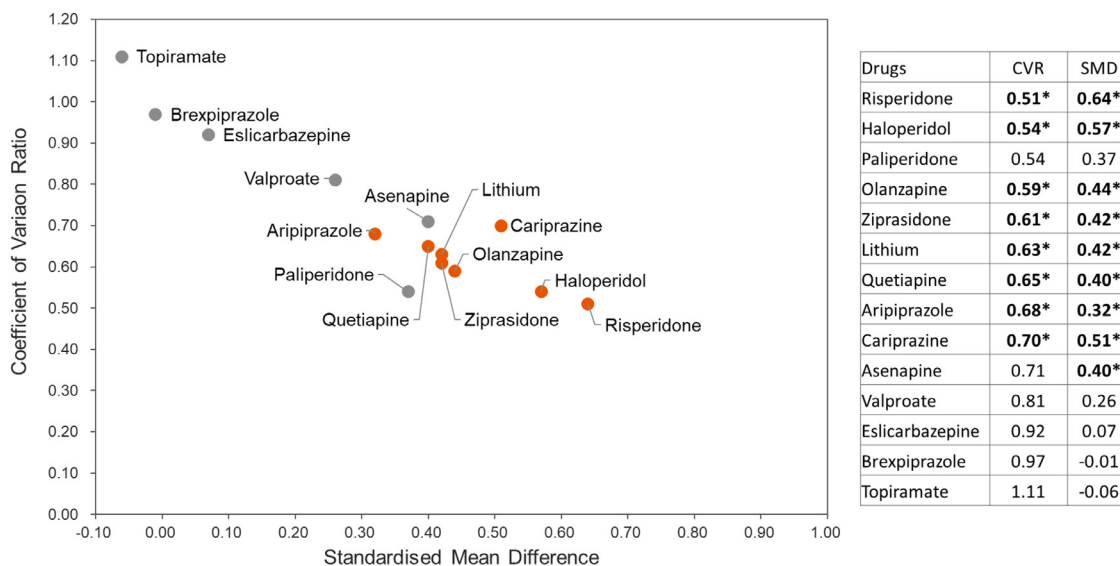
Asterisks indicate statistical significance.

Abbreviation: CI, confidence interval; K, number of study; N, number of participants; SMD, standard mean difference.

all the assessed antimanic drugs, eight antimanic drugs compared to placebo were associated with significantly lower variability and better efficacy in the improvement of manic symptoms.

Publication bias, meta-regression analyses, and sensitivity analyses

Publication bias and meta-regression analyses were not performed because none of the investigated antimanic



*: indicates statistical significance.

° Orange dots indicates statistical significance on both coefficient of variation ratio and standardised mean difference.

Figure 4. Two-dimension graph for variability and efficacy in improvement of manic symptoms.

*: indicates statistical significance, and orange dot indicates statistical significance on both CVR and SMD.

Abbreviation: CVR, coefficient of variation ratio; SMD, standardised mean difference.

drugs had data from at least ten individual studies. Sensitivity analyses showed that: (i) no antimanic drugs had a CVR of baseline manic symptoms significantly higher or lower than 1 (i.e., no baseline imbalance for CVR of manic symptoms) (eFigure 46 to eFigure 58); (ii) no antimanic drugs showed a linear relationship between the natural logarithmic mean and natural logarithmic variance (Appendix 3; thus, RSMM was not used); and (iii) consistent findings when splitting the sample size of the placebo arm in the 3-arm RCTs (eTable 3 and eTable 4).

Discussion

The current study assessed the variability and efficacy in improvement of manic symptoms to oral antimanic monotherapy options for individuals presenting with acute bipolar mania across RCTs. The main findings of this study are as follows: First, eight antimanic drugs compared to placebo were associated with significantly lower variability in the improvement of manic symptoms, namely (ordered from lower to higher CVR) risperidone, haloperidol, olanzapine, ziprasidone, lithium, quetiapine, aripiprazole, and cariprazine. Second, nine antimanic drugs compared to placebo were associated with better efficacy in the improvement of manic symptoms, namely (ordered from larger to smaller SMD) risperidone, haloperidol, cariprazine, olanzapine, lithium, ziprasidone, quetiapine, asenapine, and aripiprazole. Third, most of the investigated antimanic drugs were not associated with worse acceptability than placebo, while ziprasidone and olanzapine were associated with better acceptability than placebo.

Our study suggests that antimanic drugs with lower variability and greater efficacy in improvement of manic symptoms may show promising outcomes in patients with acute mania. Among the 14 antimanic drugs, eight antimanic drugs were associated with both lower variability and better efficacy than placebo in antimanic outcomes. Patients with acute mania may respond more homogeneously to the eight antimanic drugs irrespective of individual baseline differences in clinical or biological factors. The most recent CANMAT guidelines recommend risperidone, lithium, quetiapine, aripiprazole, and cariprazine as first-line treatments for acute mania,⁶ which is consistent with the findings of our study. The CANMAT guidelines also recommend olanzapine, ziprasidone, and haloperidol as second-line treatments due to their adverse effect profiles, although our study found ziprasidone and olanzapine to be associated with better acceptability (i.e., lower all-cause discontinuation) relative to placebo.⁶ The BAP guidelines⁸ and the Royal Australian and New Zealand College of Psychiatrists clinical practise guidelines¹⁸ recommend risperidone and quetiapine as first-line treatments for acute mania. However, the NICE guidelines recommend risperidone, quetiapine, olanzapine, and

haloperidol as first-line treatments for acute mania.⁷ Importantly, although our results showed better acceptability for ziprasidone and olanzapine compared to placebo, the concerns of QT prolongation on EKGs related to ziprasidone and metabolic adverse effects associated with olanzapine may influence the hierarchy of treatment choices for acute bipolar mania in some guidelines.^{19,20}

The recommendations of the aforementioned guidelines are principally based on evidence of efficacy, tolerability, and acceptability from RCTs and meta-analyses.^{6-9,11} Our study focused on individual differences in acute antimanic treatment by assessing variability in improvement of manic symptoms, providing another clinically relevant aspect for selecting first-line antimanic treatments. Importantly, a previous meta-analysis considering all antimanic drugs as a whole reported that younger age, male sex, and the presence of psychotic features were associated with greater efficacy across antimanic treatments relative to placebo.¹² However, the pharmacological profiles varied across different antimanic drugs. Therefore, we assessed the variability in the antimanic outcomes of individual antimanic drugs. We found that, compared to placebo, eight antimanic drugs were associated with lower variability in antimanic outcomes. Moreover, among the eight antimanic drugs, higher efficacy may not be consistently associated with lower variability (e.g., cariprazine).

Previous studies have assessed variability in treatment response in other fields of psychiatry, including antidepressants for major depression and antipsychotics for schizophrenia.^{21,22} When looking at variability in antidepressant outcomes, the study by Maslej et al. did not find a significantly lower variability in treatment response in all antidepressants as a whole compared to placebo.²¹ Conversely, when examining variability in treatment response to antipsychotic drugs in schizophrenia, the study by Winkelbeiner et al. found a slightly lower variability in treatment response to all antipsychotics as a whole compared to placebo (variability ratio of 0.97).²² The current study addressed response to individual antimanic drugs, and we found that eight antimanic drugs were associated with lower variability in treatment response, while this same pattern was not observed for the other six antimanic drugs.

Several limitations should be considered when interpreting our findings. First, there were relatively few trials for paliperidone, eslicarbazepine, and brexpiprazole. The statistical power of these drugs are limited. Second, we focused on acute antimanic outcomes (week 3); therefore, our study findings cannot be generalised to the maintenance treatment phase of bipolar disorder²³ and rapid cycling bipolar disorder.²⁴ Third, we examined the variability in improvement of manic symptoms of active treatments to control; therefore, we only included placebo-controlled trials. Head-to-head RCTs

were not included. In addition, we were unable to identify any RCTs addressing combination therapies compared to placebo alone. Therefore, we could not compare combination therapy versus monotherapy in terms of variability in improvement of manic symptoms, although the CANMAT guideline recommends combination therapy with two antimanic drugs as putative first-line treatments for acute mania.⁶ Fourth, the included studies showed high non-response rates (active arms: median=47.5%, IQR=43.4%-53.6%; placebo arms: median=65.6%, IQR=61.0%-72.6%) and high all-cause discontinuation rates (active arms: median=34.8%, IQR=21.5%-45.5%; placebo arms: median=40.4%, IQR=27.1%-57.1%), which were different from the discontinuation rates due to a lack of efficacy (active arms: median=8.8%, IQR=4.9%-15.9%; placebo arms: median=16.3%, IQR=9.4%-31.3%) or due to adverse events (active arms: median=7.4%, IQR=3.8%-10.0%; placebo arms: median=4.9%, IQR=2.7%-7.1%). The interpretation of variability in improvement of manic symptoms needs to consider these findings. Fifth, publication bias and meta-regression analyses could not be performed, because no single antimanic drug had data from 10 or more studies. Sixth, the variability in treatment response was based on the total scores of manic symptoms. Patients with the same total manic symptoms may present with different clinical manifestations. Thus, quantitative variability may not translate into qualitative variability in improving manic symptoms. For example, a recent study reported that the variability in lithium response is not just about symptoms of mania but overall clinical stability.²⁵ Moreover, clinical decisions should not exclusively rely on antimanic efficacy and acceptability outcomes. The individual history of each patient is also a paramount piece in clinical decision-making, and as we face the emergence of precision psychiatry,²⁶ the choice of particular drugs may be guided by other variables beyond the information gained from clinical trials. Seventh, we identified obvious heterogeneity for eslicarbazepine ($k=2$) and brexpiprazole ($k=2$) in CVR and haloperidol ($k=5$), paliperidone ($k=2$), eslicarbazepine ($k=2$), aripiprazole ($k=6$), and brexpiprazole ($k=2$) in SMD. The pooled estimates for these antimanic drugs may be unreliable, although only aripiprazole in SMD was statistically significant. However, subgroup analyses were not performed for these drugs, because the statistical power and validity are limited in subgroup analysis with insufficient number of studies.¹⁷

In conclusion, to the best of our knowledge, this study provides the first empirical examination of the variability in improvement of manic symptoms in participants with acute mania. We demonstrated that eight antimanic drugs were associated with lower variability and better efficacy than placebo, suggesting that these antimanic drugs were associated with more homogeneous and predictable antimanic outcomes in patients

with acute mania. When selecting an antimanic drug as the first-line treatment for acute mania, clinicians should consider each one's efficacy, acceptability, variability, and adverse effect profile in their decision-making process.

Contributors

CSL, FCY, YKT, and CKT conceived and designed the study. TWH, CWH, CLY, and PTT selected the articles and extracted the data. TWH and CSL wrote the first draft of the manuscript. TT, MS, EV, AFC, FCY, PTT, CWH, YKT, and CKT interpreted the data and contributed to the writing of the final version of the manuscript. CSL and TWH have accessed and verified the data. CSL and CKT were responsible for the decision to submit the manuscript. All authors confirmed that they had full access to all the data in the study and accept responsibility to submit for publication.

Data sharing statement

The data that support the findings of this study are available from the corresponding author (CSL) upon reasonable request.

Editor note

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Declaration of interests

All authors declared no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.eclinm.2022.101690](https://doi.org/10.1016/j.eclinm.2022.101690).

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