Comparison of antipsychotic dose equivalents for acute bipolar mania and schizophrenia

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ABSTRACT

Question Are antipsychotic dose equivalents between acute mania and schizophrenia the same?

Study selection and analysis Six databases were systematically searched (from inception to 17 September 2022) to identify blinded randomised controlled trials (RCTs) that used a flexible-dose oral antipsychotic drug for patients with acute mania. The mean and SD of the effective dose and the pre–post changes in manic symptoms were extracted. A network meta-analysis (NMA) under a frequentist framework was performed to examine the comparative efficacy between the antipsychotics. A classic mean dose method (sample size weighted) was used to calculate each antipsychotic dose equivalent to 1 mg/day olanzapine for acute mania. The antipsychotic dose equivalents of acute mania were compared with published data for schizophrenia.

Findings We included 42 RCTs which enrolled 11396 participants with acute mania. The NMA showed that risperidone was superior to olanzapine (reported standardised mean difference: −0.02, 95% CI −0.41 to −0.02), while brexpiprazole was inferior to olanzapine (standardised mean difference: 0.36, 95% CI 0.08 to 0.64). The dose equivalents to olanzapine (with SD) were 0.68 (0.23) for haloperidol, 0.32 (0.07) for risperidone, 0.60 (0.11) for paliperidone, 8.00 (1.41) for ziprasidone, 41.46 (5.98) for quetiapine, 1.65 (0.32) for aripiprazole, 1.23 (0.20) for asenapine, 0.53 (0.14) for cariprazine and 0.22 (0.03) for brexpiprazole. Compared with the olanzapine dose equivalents for schizophrenia, those of acute mania were higher for quetiapine (p<0.001, 28.5%) and aripiprazole (p<0.001, 17.0%), but lower for haloperidol (p<0.001, −8.1%) and risperidone (p<0.001, −15.8%).

Conclusions Antipsychotic drugs have been considered first-line treatment for acute mania, warranting specific dose equivalence for scientific and clinical purposes.

BACKGROUND

Substantial evidence has confirmed the efficacy of antipsychotic drugs for treatment of acute bipolar mania. A recent meta-analysis reported that several antipsychotic drugs were associated with greater efficacy in acute bipolar mania, including haloperidol, aripiprazole, asenapine, cariprazine, olanzapine, paliperidone, quetiapine, risperidone and ziprasidone, than placebo.1 The meta-analytic evidence also suggests that some antipsychotics showed greater efficacy than mood stabilisers, such as haloperidol versus lithium (reported standardised mean difference (SMD): −0.26, 95% CI −0.44 to −0.07) and risperidone versus valproate (SMD: −0.38, 95% CI −0.60 to −0.16).1 Several guidelines have recommended atypical antipsychotics as the first-line therapeutic option for acute mania. The Canadian Network for Mood and Anxiety Treatments guideline recommends that quetiapine,
asenapine, aripiprazole, paliperidone, risperidone and cariprazine can be used as first-line treatment for patients with acute mania. The National Institute for Health and Care Excellence guideline and the Royal Australian and New Zealand College of Psychiatrists clinical practice guideline recommend antipsychotic monotherapy as the first-line treatment for acute mania, and its combination with lithium or valproate as the next step if insufficient efficacy ensues.

The dose equivalence of antipsychotics is important for both clinical and research purposes. When switching antipsychotic drugs or comparing/combining different antipsychotic drugs in clinical trials or meta-analyses, knowledge of dose equivalence for comparable efficacy is needed. Davis’ used data from double-blind, flexible-dose, randomised controlled trials (RCTs) on schizophrenia and estimated the antipsychotic dose equivalents to chlorpromazine 100 mg/day. This method assumed that physicians would adjust the dosages of the experimental drug to obtain the maximum clinical response in these flexible-dose RCTs. Therefore, the reported mean doses could be applied to estimate the clinical equivalent doses between antipsychotics. The equivalence dose reference reported by Davis has been widely applied for decades. Leucht et al. employed the same method and extended the dose equivalence to atypical antipsychotics and shifted the comparator to olanzapine 1 mg/day. Importantly, the antipsychotic drugs have been considered as first-line treatment for bipolar mania; however, there are so far no specific antipsychotic dose equivalents for treatment of bipolar mania. It is unknown that simply borrowing the dose equivalence from RCTs conducted among participants with schizophrenia could be directly translated to patients with acute bipolar mania. According to the results of network meta-analysis (NMA) studies, the efficacy of antipsychotics may differ between schizophrenia and acute mania. For example, risperidone was associated with better efficacy than quetiapine in the treatment of schizophrenia (SMD: −0.13, 95% CI −0.23 to −0.04) ; however, risperidone was not associated with better efficacy compared with quetiapine in alleviating acute mania (SMD: 0.22, 95% CI 0.01 to 0.46). Therefore, we hypothesised that the equivalent dose of antipsychotics may differ between schizophrenia and bipolar mania.

Objective
We systematically reviewed the RCTs on oral antipsychotic drugs for treatment of acute mania. We first conducted an NMA to compare the efficacy of the included antipsychotics for acute mania and then calculated dose equivalence using the classic mean dose method by Leucht et al. Finally, we compared the antipsychotic dose equivalents between acute bipolar mania and schizophrenia.

METHODS
Search strategy and inclusion criteria
We followed the classic mean dose method by Leucht et al. to calculate the antipsychotic dose equivalence. The NMA was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guideline for NMA (online supplemental appendix 1). The study protocol was registered on the Open Science Framework (doi: 10.17605/OSF.IO/CYPV6). Two authors reviewed the literature search, data transfer accuracy and statistical analyses, and discrepancies were resolved by discussing with a third author.

The MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE, PsycINFO, ClinicalTrials.gov and WHO ICTRP databases were systematically searched without language restrictions from database inception to 17 September 2022 (online supplemental appendix 2). We included blinded, flexible-dose RCTs (placebo-controlled, head-to-head or multiple arms) that had used an oral antipsychotic drug for treatment of patients with bipolar I disorder who experienced an acute manic or mixed episode. We also included RCTs that used fixed-dose design initially but allowed investigators to titrate the dose according to patients’ clinical conditions. The following were the PICO (population, intervention, comparison, outcome) settings of the current study: (1) P: adult patients with bipolar I disorder experiencing an acute manic episode; (2) I: monotherapy with an antipsychotic drug; (3) C: a placebo or another antimanic drug; and (4) O: changes in manic symptoms. We excluded (1) RCTs that used the dose lower than the recommended target range; (2) studies that enrolled participants with schizoaffective disorder or bipolar II disorder; (3) relapse prevention studies; (4) open-label studies; (5) studies in special populations such as children, adolescents, elderly or patients with treatment resistance; and (6) RCTs with augmentation or combined treatment but without any antipsychotic monotherapy (eg, quetiapine + lithium vs lithium).

Outcome measures and target population
We extracted the bibliographic and background information. We collected data on the changes in manic symptoms at week 3, measured with the Young Mania Rating Scale (YMRS), the Mania Rating Scale from the Schedule for Affective Disorders and Schizophrenia (MRS), or the Manic State Rating Scale. For studies without data on week 3, we used data at the points closest to 3 weeks (2 weeks to 6 weeks). If there were two measures meeting the criteria, we will extract the measure with the lower P value. Intention-to-treat data sets were used when available. We collected the mean daily dose and their SD after consulting with the corresponding author.

The primary outcome was weighted mean dose equivalence, and the secondary outcomes were direct ratios and direct and indirect ratio dose equivalences. The Cochrane Risk of Bias Assessment Tool was used to rate the quality of the included studies by two independent authors. 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 analysis
We performed NMA under a frequentist framework using a multivariate random-effects NMA model with the statistical package
netmeta in R statistical software V4.0.2 (R Project for Statistical Computing). We estimated the antimanic outcomes using SMD with 95% CI. The restricted maximum likelihood estimation method was used to estimate the heterogeneity, assuming a common estimate for heterogeneity variance among different comparisons. The transitivity assumption was supported by evaluating the distribution of potential effect modifiers (publication year, sample size, baseline severity, mean age and female percentage). Heterogeneity among the included studies was evaluated by $\tau$ statistic. Inconsistency between direct and indirect comparisons was examined using the design-by-treatment and the node-splitting methods. Publication bias was investigated using Egger's tests and comparison-adjusted funnel plots. The certainty of evidence for the results of NMA was evaluated using the CINeMA (Confidence in Network Meta-Analysis).

The classic mean dose method included three analyses: (1) weighted mean, (2) direct ratios, and (3) direct and indirect ratios. The dose equivalent to olanzapine was calculated from the sample size weighted mean dose of each antipsychotic drug divided by the weighted mean dose of olanzapine. The direct ratio analysis was calculated from the mean dose ratio of each antipsychotic drug to olanzapine in RCTs with head-to-head comparisons (vs olanzapine). The calculated direct ratios were then weighted by sample size, producing average weighted direct ratios. The direct and indirect ratio analyses used all ratios in head-to-head comparisons (any comparisons) and then obtained indirect ratio of any antipsychotic to olanzapine. For example, we had a ratio of olanzapine to haloperidol and a direct ratio of aripiprazole to haloperidol; we obtained an indirect ratio of aripiprazole to olanzapine by dividing aripiprazole/haloperidol by olanzapine/haloperidol. We compared the dose equivalents of acute mania with those of schizophrenia obtained from the study by Leucht et al. using the independent samples t-test. If the efficacy of an antipsychotic drug significantly differed from that of olanzapine, we provided efficacy-adjusted dose equivalents to olanzapine to those antipsychotic drugs by using the formula shown in online supplemental appendix 3. A two-sided $p<0.05$ was considered statistically significant. We used GRADE (Grading of Recommendations, Assessment, Development and Evaluation) assessment to evaluate the certainty of evidence of antipsychotic dose equivalents to olanzapine. The GRADE assessment was rated by two independent authors. The certainty of evidence was then reported as very low, low, moderate and high.

Findings

The selection process and the number of included RCTs are shown in online supplemental efigure 1. The current study included 41 studies (42 RCTs) with 11 396 participants experiencing an acute manic episode (online supplemental etable 1). The sample size of the 42 RCTs ranged from 12 to 521, with a mean of 117.61 (59.35). The mean age was 39.32 (13.10) years, 48.77% of whom were female. Among the 42 RCTs, 35 (83.3%) provided data at week 3 (week 3: 35; week 4: 5; week 6: 3). The antimanic drugs investigated included haloperidol (k=9), risperidone (k=6), paliperidone (k=1), ziprasidone (k=3), quetiapine (k=7), olanzapine (k=14), asenapine (k=2), cariprazine (k=3), aripiprazole (k=8) and brexpiprazole (k=2) (online supplemental etable 1). Among the 42 RCTs, only one study had a high ROB (online supplemental efigures 2 and 3).

The network plot is highly connected (online supplemental efigure 4). The size of the nodes corresponds to the number of participants assigned to each treatment, and the width of the lines corresponds to the number of trials evaluating the comparisons. Figure 1 shows the comparative efficacy of the

<table>
<thead>
<tr>
<th>Risperidone (0.82)</th>
<th>-0.13 [-0.49: 0.23]</th>
<th>0.31 [-0.26: 0.89]</th>
<th>-0.32 [-0.67: 0.04]</th>
<th>-0.68 [-0.89: -0.47]</th>
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<td>-0.20 [-0.48: 0.08]</td>
<td>-0.25 [-0.69: 0.14]</td>
<td>-0.59 [-0.77: -0.41]</td>
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<tr>
<td>Paliperidone (0.71)</td>
<td>-0.16 [-0.59: 0.18]</td>
<td>-0.52 [-0.87: -0.17]</td>
<td>0.01 [-0.34: 0.35]</td>
<td>0.00 [-0.36: 0.36]</td>
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<tr>
<td>Paliperidone (0.71)</td>
<td>-0.16 [-0.59: 0.18]</td>
<td>-0.52 [-0.87: -0.17]</td>
<td>0.01 [-0.34: 0.35]</td>
<td>0.00 [-0.36: 0.36]</td>
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<tr>
<td>Cariprazine (0.57)</td>
<td>-0.03 [-0.28: 0.22]</td>
<td>0.00 [-0.29: 0.19]</td>
<td>-0.05 [-0.49: 0.19]</td>
<td>-0.14 [-0.31: 0.02]</td>
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<tr>
<td>Aripiprazole (0.53)</td>
<td>-0.03 [-0.28: 0.22]</td>
<td>0.00 [-0.29: 0.19]</td>
<td>-0.05 [-0.49: 0.19]</td>
<td>-0.14 [-0.31: 0.02]</td>
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</table>

Figure 1  Comparative efficacy (standardised mean difference) in antimanic outcome of the included antipsychotic drugs. Antipsychotics are shown in grey and reported in order of surface under the curve cumulative ranking (given in parentheses). The results of the pairwise meta-analyses are presented in the upper right half and the results of the network meta-analyses in the left lower half. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. In the left lower half, standard mean differences lower than 0 favour the column-defining treatment, and in the upper right half those lower than 0 favour the row-defining treatment. Cells in blue and bold print indicate significant results. Bold type indicates statistical significance.


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Table 1  Weighted mean analyses for dose equivalents to olanzapine 1 mg

<table>
<thead>
<tr>
<th>Drug</th>
<th>Group</th>
<th>n</th>
<th>Dose</th>
<th>Upper</th>
<th>Lower</th>
<th>t</th>
<th>P value</th>
<th>Change (%)</th>
<th>Certainty*</th>
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<td>1.67</td>
<td>1.63</td>
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</table>

*The certainty of evidence for antipsychotic dose equivalence was according to the data in online supplemental etables 7–15.

The certainty of evidence for antipsychotic dose equivalence was according to the data in online supplemental etables 7–15.

Table 1 presents the antipsychotic dose equivalents to olanzapine (1 mg/day) for acute mania using weighted mean analyses. For patients with acute mania, the dose equivalents to olanzapine (1 mg/day) were 0.68 for haloperidol, 0.32 for risperidone, 0.61 for paliperidone, 8.00 for ziprasidone, 41.46 for quetiapine, 1.65 for aripiprazole, 1.23 for asenapine, 0.53 for cariprazine and 0.22 for brexpiprazole. The comparisons between acute mania and schizophrenia were significant for haloperidol, risperidone, quetiapine and aripiprazole (all p<0.001). The percentage change in olanzapine equivalent dose from schizophrenia to acute mania ranged from −15.8% to 38.2%. The olanzapine equivalent dose for bipolar mania decreased 15.8% in risperidone and 8.1% in haloperidol, and increased 1.0% in ziprasidone, 17.0% in aripiprazole, 28.5% in quetiapine and 38.20% in asenapine. The efficacy-adjusted dose equivalents to olanzapine (1 mg/day) were 0.19 for risperidone and 0.50 for brexpiprazole. Using weighted mean analyses, all of the certainty of evidence for antipsychotic dose equivalence were moderate, except for haloperidol (low) and brexpiprazole (low).

Table 2 presents the antipsychotic dose equivalents to olanzapine 1 mg/day using the direct and indirect ratio analyses. For patients with acute mania, the dose equivalents to olanzapine (1 mg/day) were 0.47 for haloperidol, 0.25 for risperidone, 3.41 for ziprasidone, 1.10 for aripiprazole and 1.15 for asenapine. The comparisons between acute mania and schizophrenia were significant for haloperidol, risperidone, ziprasidone and aripiprazole (all p<0.001). The percentage change ranged from −48.9% to 16.2% for acute mania relative to those for schizophrenia. The olanzapine equivalent dose for acute mania decreased 48.88% in ziprasidone, 38.2% in haloperidol, 12.7% in aripiprazole and 7.4% in risperidone, and increased 16.2% in asenapine. Using direct and indirect ratio analyses, all of the certainty of evidence for antipsychotic dose equivalence were low, except for haloperidol (very low). The results of direct ratio analyses are shown in online supplemental etable 6. The details of GRADE assessment for antipsychotic dose equivalence are shown in online supplemental etables 7–15.

**DISCUSSION**

To date, there has been no evidence-based approach to examine the dose equivalents of antipsychotic drugs for acute bipolar mania. Clinicians and researchers still borrowed the dose equivalence derived from schizophrenia for acute bipolar mania. In the current study, we used the approach by Leucht et al. estimating the antipsychotic dose equivalents to olanzapine 1 mg/day for acute mania. We also found that the differences in dose equivalence between acute mania and schizophrenia were statistically significant. Substantial evidence has confirmed the efficacy of antipsychotic drugs for patients with acute bipolar mania, and antipsychotic drugs are recommended in several treatment guidelines as first-line treatment for acute bipolar mania. Therefore, our study findings may provide rational and useful...
antipsychotic dose equivalents for acute bipolar mania in clinical and research settings.

The classic mean method by Davis and Leucht et al. assumes that physicians would adjust the dosages of the experimental drug to obtain the maximum clinical response in the flexible-dose RCTs, and this assumption was translated to therapeutic equivalence among all antipsychotic drugs for schizophrenia. However, the assumed therapeutic equivalence in the classic mean dose method was not subject to statistical analyses. In the current study, we conducted NMA to examine comparable efficacy in reducing manic symptoms among all antipsychotic drugs. The NMA results supported therapeutic equivalence among the investigated antipsychotic drugs, except for risperidone and brexipiprazole relative to olanzapine. Global inconsistency was statistically significant, while local inconsistency was only observed in ziprasidone relative to haloperidol and placebo. Notably, we included three RCTs of ziprasidone and these three RCTs used the MRS as their measurement for the antimanic outcome. However, most of the included studies used the YMRS as their measurement. The inconsistency of ziprasidone relative to haloperidol and placebo might be related to the use of a different rating scale for manic symptoms.

For acute bipolar mania, we found that the results of olanzapine equivalent dose may differ between the weighted mean analyses and the direct and indirect ratio analyses. For example, 1.00 mg of olanzapine was equal to 8.00 mg of ziprasidone in the weighted mean method, while it was equal to 3.41 mg of ziprasidone in the direct and indirect ratio methods. One of the explanations is that olanzapine has been directly compared with ziprasidone in the direct and indirect ratio methods. The accuracy of the estimated dose–response curve, some dose equivalents estimated by this method are far from clinical practice or estimation by other methods. For example, it is reported that 1.84 mg/day aripiprazole is equivalent to 1 mg/day risperidone for schizophrenia. Moreover, the near-maximum effective doses method requires (1) antipsychotic dose equivalence to convert all antipsychotic drugs and (2) an adequate number of multiple fixed-dose RCTs for dose–response curve on low doses. These two requirements are still lacking in acute bipolar mania.

**Limitations**

There were some limitations to the current study. First, the dose–response curve was not a linear model, but a sigmoid model, and it can differ from drug to drug. The weighted mean dose of olanzapine was 14.90 mg/day, and thereby antipsychotic conversion around olanzapine 14.90 mg/day may be more applicable than those far from 14.90 mg/day. Second, the number of patients and head-to-head RCTs was relatively small for some antipsychotic drugs such as paliperidone, limiting the statistical power of these drugs. Third, we focused on the acute antimanic outcomes (week 3); therefore, our findings cannot be generalised to other time scale far from acute manic phase. Fourth, we also calculated efficacy-adjusted dose equivalence for risperidone and brexipiprazole; however, such adjustment was based on the assumption that the mean dose in the included RCT provided the maximum clinical response. Therefore, the

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**Table 2**  Direct and indirect ratio analyses for dose equivalents to olanzapine 1 mg

<table>
<thead>
<tr>
<th>Drug</th>
<th>Group</th>
<th>n</th>
<th>Dose</th>
<th>Upper</th>
<th>Lower</th>
<th>t</th>
<th>P value</th>
<th>Change (%)</th>
<th>Certainty*</th>
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<td>Aripiprazole†</td>
<td>Mania</td>
<td>679</td>
<td>1.10</td>
<td>1.12</td>
<td>1.08</td>
<td>12.09</td>
<td>&lt;0.001</td>
<td>−12.7</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Schizophrenia</td>
<td>1013</td>
<td>1.26</td>
<td>1.28</td>
<td>1.24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asenapine</td>
<td>Mania</td>
<td>770</td>
<td>1.15</td>
<td>1.16</td>
<td>1.14</td>
<td></td>
<td></td>
<td>16.2</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Schizophrenia</td>
<td>913</td>
<td>0.99</td>
<td>na</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P value < 0.05, na, not available.

†P value < 0.05

dose equivalence for brexpiprazole is limited. Fifth, the certainty of evidence was low to very low for direct and indirect ratio methods. Sixth, we only took antipsychotic monotherapy into account; however, augmentation treatments with mood stabilisers play an important role in clinical scenarios. Our study findings cannot be applied to antipsychotic dose equivalence when using augmentation treatment. Finally, our results were derived from population-level data. When applying the dose equivalents, physicians need to consider patient characteristics such as age, body mass index or stage of illness (eg, treatment resistance).

Clinical implications
To our knowledge, this is the first study to assess the antipsychotic dose equivalence for treatment of acute bipolar mania. We found that the antipsychotic dose equivalence for acute bipolar mania is different from schizophrenia. We believe acute bipolar mania warrants its own antipsychotic dose equivalence, and our findings are useful for both clinical practice and future research.

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Contributors C-SL developed the study concept and design. Testing and data collection were supervised by C-LY and T-WH. Data were analysed and interpreted by C-SL and C-LY. The paper was drafted by T-WH and C-SL. AFC, TT and P-IT provided advice on statistical analysis and provided important intellectual content. AFC, TT and C-WH assisted with the preparation and proof-reading of the manuscript. C-SL accept full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish. All authors approved the final version of the paper for submission.

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