Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis

Dan Siskind, Lara McCartney, Romi Goldschlager and Steve Kisely

Background
Although clozapine is the ‘gold standard’ for treatment-refractory schizophrenia, meta-analyses of clozapine for this condition are lacking.

Aims
We conducted a systematic review and meta-analysis of clozapine treatment for people with treatment-refractory schizophrenia.

Method
We searched the Cochrane Schizophrenia Group’s trial register, PubMed and EMBASE and hand-searched key papers for randomised controlled trials of clozapine for treatment-refractory schizophrenia.

Results
Twenty-one papers with 25 comparisons were included. The number needed to treat was 9. Clozapine was superior for positive symptoms in both the short and long term. In the short term only clozapine was superior for total and negative symptoms, with higher response rates. Both funding source and dosage affected results. Higher baseline psychosis scores predicted better outcomes for clozapine in a meta-regression.

Conclusions
Clozapine is superior for treatment-refractory disorder but if there is no response by 6 months medications with lower adverse reactions should be considered.

Declaration of interest
None.

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**Study selection**

Studies were included if they were randomised and double- or rater-blinded. Diagnoses included schizophrenia, schizoaffective disorder or schizophreniform disorder. Participants had to have demonstrated a resistance to treatment as defined by a failure to respond to at least one trial (and preferably two) of a first- or second-generation antipsychotic of at least 6 weeks’ duration at dosage equivalents greater than 600 mg chlorpromazine. Studies were included if they compared clozapine with any other first- or second-generation antipsychotic medication. Studies were excluded if there was extensive crossover between the clozapine and control groups. All identified studies were screened at the title and abstract level by two authors (L.M. and R.G.). Studies that met the inclusion criteria on title and abstract review, or that could not be excluded on the basis of information provided in the abstract, were reviewed at full-text level. Snowball searches of key papers and the included studies’ reference lists were conducted. Narrative and systematic reviews, posters, conference abstracts, case reports, letters to editors and other articles that did not meet the inclusion criteria were cross-referenced for additional potential sources of RCTs. Attempts were made to contact first authors of included studies in cases where information was missing.

**Data collection**

Data extraction was conducted by two independent researchers (L.M. and R.G.). All discrepancies during each stage of study selection, data extraction and quality assessment were resolved by re-checking source papers. Extracted data were validated by D.S. Data analysis was conducted by two authors (D.S. and S.K.). We extracted data on the following: study duration, setting, diagnostic tool and type of interventions (e.g. control medication, first- or second-generation antipsychotic, mean age and standard deviation, number commenced in study arm, mean dose of clozapine or control medication, and dose of clozapine or control medication). Doses of clozapine and control medications were converted to chlorpromazine and olanzapine equivalents. These were used in separate meta-analyses comparing dose equivalents for clozapine and the control medication for each study. Where data in studies were missing or unclear, attempts were made to contact the study’s corresponding author.

**Outcomes**

Where possible, end-points were measured from commencement of intervention. Data from studies were divided into short term (less than 3 months) and long term (3 months or more). These time frames were selected after data were extracted, based on an approach used in a previous meta-analysis. Where multiple outcome time points were reported in the same study, the data for the last outcome time point in each period (short or long term) were used. Analysis was also conducted for all time points, with the data for the last outcome time point in each study included.

The primary outcome was a change in overall psychotic symptoms measured by the Brief Psychiatric Rating Scale (BPRS) or the Positive and Negative Syndrome Scale (PANSS). Where standard deviations for change in psychotic symptoms were not reported, the change score was calculated from baseline and end-point scores and the standard deviation imputed. Secondary outcomes included changes in positive and negative symptom scales. For changes in positive symptoms we used scores from the Scale for the Assessment of Positive Symptoms (SAPS), and the positive subscales of the PANSS and BPRS. For changes in negative symptoms, scores for the PANSS negative symptom subscale and the Scale for the Assessment of Negative Symptoms (SANS) were used.

**Study quality**

We assessed the quality of included studies using the following criteria adapted from Cochrane Collaboration guidelines:

(a) adequate generation of allocation sequence;
(b) masking of allocation to conditions to participant and/or assessor;
(c) adequate random sequence generation;
(d) pre-specified primary outcome measures;
(e) appropriate reporting on missing data;
(f) use of intention-to-treat analysis;
(g) other sources of potential bias including pharmaceutical company funding.

**Statistical analysis**

We used Review Manager version 5.3 for Mac for the meta-analyses and Comprehensive Meta-Analysis version 3.3 for the meta-regression. We calculated the standardised mean difference (SMD) for continuous data that used different scales. We reported the risk ratio (RR) for any dichotomous outcome. Where possible, intention-to-treat analyses were used. We conducted sensitivity analyses for the effect of dosages, use of first- or second-generation control medications, pharmaceutical company sponsorship and community or hospital study settings. We used meta-regression to assess the effect of baseline psychosis score as a continuous variable. We assessed heterogeneity using the I² statistic, a measure that does not depend on the number of studies in the meta-analysis and hence has greater power to detect heterogeneity when the number of studies is small; it provides an estimate of the percentage of variability due to heterogeneity rather than chance alone. An estimate of 50% or greater indicates possible heterogeneity, and scores of 75–100% indicate considerable heterogeneity. The I² estimate is calculated using the chi-squared statistic (Q) and its degrees of freedom. The random effects model was used for all the analyses as we could not definitely exclude between-study variation even in the absence of statistical heterogeneity, given the range of medications under review. We tested for publication bias using funnel plot asymmetry where low P values suggest publication bias.

**Results**

A total of 2589 articles were identified in the initial search of the electronic databases. Of these, 2402 were excluded at the title and abstract level and a further 167 were excluded after review of the full text (see online Fig. DS1). One additional paper was included after a review of reference lists of key articles. Twenty-one papers were included for the review. The sum of enrolled patients was 1131 commenced on clozapine and 1233 on control medications with 801 clozapine and 799 control participants at final follow-up.
Study characteristics

Study quality was fair (see online Table DS1). Seventeen papers reported adequate allocation concealment, 18 were double-blind and 3 were blinded only to assessor. Adequate random sequence generation was reported in 18 papers. All papers reported the primary outcome measures and adequately described missing data. Seventeen papers reported intention-to-treat data. Three papers did not provide any information about the funding source. Eleven papers reported financial support from a pharmaceutical company (8 were funded by the manufacturer of the control medication, 2 by the manufacturer of clozapine and 1 by a manufacturer of both clozapine and the control medication). Among long-term studies, all pharmaceutical funding was from the manufacturers of control medications.

Twenty-one papers were included in the meta-analysis. They provided data on comparisons with 25 control groups, hereafter referred to as studies. In papers where clozapine was compared with more than one control medication, the number of participants in the clozapine group was divided by the number of control medications, rounded down to the nearest integer, and used as the number of clozapine participants in analyses comparing clozapine with each control medication. This was done to avoid double-counting the individuals taking clozapine. Papers were published between 1988 and 2009. Studies reported data at time points ranging from 6 weeks to 78 weeks. Seventeen papers reported data on 21 short-term studies. Nine papers reported data on 13 long-term studies.

Six papers had strict adherence to our definition of treatment-refractory schizophrenia. Five papers included participants with only one failed trial of an antipsychotic, three papers had trial durations less than 6 weeks or did not report on trial duration, and nine papers reported that previous antipsychotic trials had a chlorpromazine-equivalent dose of less than 600 mg or did not report a dose. Eleven papers included some participants who had left previous antipsychotic trials owing to treatment intolerance rather than specifically treatment failure (online Table DS1).

Control medications comprised first-generation antipsychotics including chlorpromazine and haloperidol and second-generation antipsychotics including olanzapine, risperidone, quetiapine and ziprasidone (Table DS1). There was no statistically significant difference between clozapine and control groups in terms of age or baseline psychosis score in any of the included studies.

Psychotic symptoms

Twenty short-term studies had usable data for change in total psychotic symptoms for 604 people given clozapine and 708 people given a control medication. The standardised mean difference (SMD) favoured clozapine (Fig. 1). Eleven long-term studies had usable data with 368 people given clozapine and 451 people given a control medication. In contrast to the short-term results, there was no statistically significant difference in SMD between the groups (Fig. 1). However, clozapine was associated with a greater improvement in score when all time frames were combined, using the last reported time point in each study (SMD = −0.29, 95% CI −0.49 to −0.09, P < 0.005; 24 studies, \( n = 1858 \)). Clozapine had a greater effect on positive symptoms with statistically superior outcomes at all time points (Fig. 2) compared with negative symptoms where benefits were only seen in the short term (Fig. 3).

Sensitivity analyses

In studies that were restricted to in-patients or had not received pharmaceutical company funding, clozapine had significantly better outcomes in both the short and long term. For instance, the SMD for long-term studies without pharmaceutical company funding was −0.67 (95% CI −1.15 to −0.19, \( P = 0.006; 4 \) studies, \( n = 142 \)). We also investigated the effect of dosing. Overall, patients on clozapine were given 228 mg less of chlorpromazine equivalents per day than controls (95% CI 188 to 267, \( P < 0.0001 \)) and 9.8 mg less of olanzapine equivalents per day (95% CI 8.4 to 11.1, \( P < 0.0001 \)). When studies were ranked on degree of equivalence of dose and the half with the greatest difference excluded, the SMD more strongly favoured clozapine in each time frame, becoming significantly superior in the long term (SMD = −0.42, 95% CI −0.85 to −0.01, \( P = 0.05; 6 \) studies, \( n = 201 \)). When studies that had included any treatment-intolerant participants were excluded, there was no difference in the overall results, with clozapine showing superior outcomes in the short term but not in the long term. Similarly, a sensitivity analysis on whether the study was single-blinded made no difference to the results.

There was no difference in results for studies that used first- or second-generation comparator antipsychotics, with clozapine showing superior outcomes in the short term but not in the long term. We examined clozapine against specific comparator medications for which there were two or more studies in each time frame. Clozapine was significantly superior to olanzapine, haloperidol and chlorpromazine in the short term; however, there was no significant difference between clozapine and risperidone in the short or long term, nor against olanzapine in the long term.

Three short-term studies looked specifically at people under age 18 years.29,30,37 When only these studies were included, the SMD more strongly favoured clozapine, whereas when the studies specifically looking at children and adolescents were excluded, the SMD less strongly favoured clozapine. Finally, we explored the effect of baseline mean psychosis score using meta-regression: higher scores predicted greater response for clozapine in the long term (regression coefficient 0.03, s.e. = 0.01, \( P = 0.0034, \tau^2 = 0.0008 \)) but not the short term.

Response

Six studies defined response using the criteria outlined by Kane et al of a greater than 20% reduction in BPRS from baseline in the presence of a post-treatment CGI Scale score of 3 or less or a BPRS of 35 or less (online Table DS1).2,22,23,27,37,38 A further five studies defined response as an improvement on the BPRS or PANSS of greater than 20%.24,28,35,36,40 A final study defined response as a greater than 30% reduction in the BPRS plus a post-treatment CGI score of 2 or less.98 Eight short-term studies had usable data for 598 participants taking clozapine and 620 control group participants. People taking clozapine were significantly more likely to respond in the short term (risk ratio (RR) = 1.17, 95% CI 1.07 to 2.73, \( P = 0.03; 8 \) studies, \( n = 1218 \)). The absolute risk reduction was 12.48% (95% CI 7.52 to 17.43). Based on this response rate, the number needed to treat was 9. Five long-term studies had usable data for 479 participants in the clozapine group and 489 in the control group, with no significant difference between clozapine and control. For all time frames combined, results just failed to reach statistical significance (RR = 1.31, 95% CI 0.98 to 1.70, \( P = 0.07; 11 \) studies, \( n = 1692 \)).

Sensitivity analyses

There were insufficient studies to do meaningful sensitivity analyses for the short- and long-term periods separately. Sensitivity analyses are limited to the data for all time frames combined. Sensitivity analysis on strictness of criteria of response or
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The number of participants at the completion of the study time frame was compared with the number of participants commencing the studies. For both the short- and long-term analyses there was no statistically significant difference between clozapine and control antipsychotics on study completion.

Adverse drug reactions

Meta-analyses on adverse reactions were conducted for any results reported by two or more studies. The data for the last time-point in each study was used. It was not feasible to separate adverse reactions into time groups as only two papers reported long-term data. Participants taking clozapine reported significantly greater rates of sialorrhoea, tachycardia, seizures, fever, dizziness, sedation, constipation, and nausea and vomiting (Table 1). The number needed to harm ranged from 4 for sialorrhoea to 19 for nausea and vomiting. Participants taking clozapine reported significantly lower rates of insomnia and dry mouth. There was no significant difference for hypotension, headache or weight gain.

Publication bias

There were sufficient short-term studies to test for publication bias for the primary outcome of change in total psychosis scores.

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### Table 1

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Weight (%)</th>
<th>SMD IV, random, 95% CI</th>
<th>SMD IV, random, 95% CI</th>
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<tr>
<td><strong>Short term</strong></td>
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<tr>
<td>Azorin et al (2001)22</td>
<td>7.5</td>
<td>-0.41 (-0.66, -0.16)</td>
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<tr>
<td>Bondolfi et al (1998)24</td>
<td>6.4</td>
<td>0.18 (-0.24, 0.61)</td>
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<tr>
<td>Buchanan et al (1998)25</td>
<td>6.2</td>
<td>-0.05 (-0.50, 0.40)</td>
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<td>Cao et al (2003)26</td>
<td>5.8</td>
<td>0.08 (-0.43, 0.58)</td>
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<tr>
<td>Hong et al (1997)27</td>
<td>4.7</td>
<td>-0.92 (-1.59, -0.25)</td>
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<tr>
<td>Kane et al (1988)2</td>
<td>7.5</td>
<td>-1.10 (-1.36, -0.84)</td>
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<td>Kane et al (2001)28</td>
<td>6.0</td>
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<td>Kumra et al (1996)29</td>
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<td>-1.08 (-2.01, -0.15)</td>
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<tr>
<td>Kumra et al (2008)30</td>
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<td>-0.32 (-0.96, 0.31)</td>
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<td>McEvoy et al (2006) Olanzapine31</td>
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<td>-0.53 (-1.25, 0.19)</td>
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<td>4.1</td>
<td>-0.71 (-1.50, 0.07)</td>
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<td>McEvoy et al (2006) Risperidone31</td>
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<td>-0.98 (-1.77, -0.19)</td>
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<td>Meltzer et al (2008)32</td>
<td>4.5</td>
<td>-0.10 (-0.80, 0.61)</td>
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<td>Moreasco et al (2004)33</td>
<td>2.7</td>
<td>-0.85 (-1.94, 0.24)</td>
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<tr>
<td>Shaw et al (2006)34</td>
<td>3.9</td>
<td>-0.73 (-1.54, 0.09)</td>
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<td>Volavka et al (2002) Haloperidol35</td>
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<td>-0.12 (-0.74, 0.51)</td>
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<td>Volavka et al (2002) Risperidone35</td>
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<td>Wahlbeck et al (2000)36</td>
<td>3.2</td>
<td>0.69 (-0.26, 1.65)</td>
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<tr>
<td>Wang et al (2002)37</td>
<td>4.1</td>
<td>0.04 (-0.43, 0.51)</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>100.0</td>
<td>-0.39 (-0.61, -0.17)</td>
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</tbody>
</table>

### Fig. 1 Change in total psychotic symptoms. SMD, standardised mean difference.

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equivalence of dose did not alter the absence of statistically significant difference between the groups. When only studies using first-generation antipsychotics as the comparator were included, clozapine was statistically significantly more likely to lead to a response (RR = 1.77, 95% CI 1.19 to 2.64, P = 0.008; 4 studies, n = 164). There was no statistically significant difference between the groups when only second-generation antipsychotics were included. When studies with pharmaceutical funding were excluded, response statistically significantly favoured clozapine (RR = 1.68, 95% CI 1.20 to 2.35, P = 0.002; 6 studies, n = 208).

Publication bias

There were sufficient short-term studies to test for publication bias for the primary outcome of change in total psychosis scores.
### Short term

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Weight (%)</th>
<th>SMD IV, random, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Azorin et al (2001)(^{22})</td>
<td>26.3</td>
<td>−0.30 (−0.54, −0.05)</td>
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<td>Bondolfi et al (1998)(^{24})</td>
<td>14.5</td>
<td>0.17 (−0.25, 0.60)</td>
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<tr>
<td>McEvoy et al (2006) Olanzapine(^{21})</td>
<td>6.4</td>
<td>−0.43 (−1.15, 0.29)</td>
</tr>
<tr>
<td>McEvoy et al (2006) Quetiapine(^{27})</td>
<td>5.6</td>
<td>−0.65 (−1.43, 0.13)</td>
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<td>McEvoy et al (2006) Risperidone(^{27})</td>
<td>5.5</td>
<td>−0.87 (−1.66, −0.09)</td>
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<tr>
<td>Meltzer et al (2008)(^{22})</td>
<td>6.5</td>
<td>−0.37 (−1.09, 0.34)</td>
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<tr>
<td>Rosenheck et al (1997)(^{25})</td>
<td>30.1</td>
<td>−0.15 (−0.35, 0.06)</td>
</tr>
<tr>
<td>Shaw et al (2006)(^{27})</td>
<td>5.1</td>
<td>−0.77 (−1.59, 0.05)</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>100.0</td>
<td>−0.27 (−0.47, −0.08)</td>
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</table>

**Heterogeneity.** \( t^2 = 0.02; \chi^2 = 10.29, \text{d.f.} = 7 (P = 0.017); I^2 = 32\%

**Test for overall effect:** \( Z = 2.73 (P = 0.006) \)

### Long term

<table>
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<th>Weight (%)</th>
<th>SMD IV, random, 95% CI</th>
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<tr>
<td>Kane et al (2001)(^{20})</td>
<td>5.9</td>
<td>−0.61 (−1.35, 0.12)</td>
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<td>McEvoy et al (2006) Olanzapine(^{21})</td>
<td>4.3</td>
<td>−0.36 (−1.22, 0.51)</td>
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<tr>
<td>McEvoy et al (2006) Quetiapine(^{27})</td>
<td>3.5</td>
<td>−0.85 (−1.81, 0.11)</td>
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<tr>
<td>McEvoy et al (2006) Risperidone(^{27})</td>
<td>3.0</td>
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<td>Meltzer et al (2008)(^{22})</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>100.0</td>
<td>−0.25 (−0.43, −0.07)</td>
</tr>
</tbody>
</table>

**Heterogeneity.** \( t^2 = 0.00; \chi^2 = 4.67, \text{d.f.} = 6 (P = 0.59); I^2 = 0\%

**Test for overall effect:** \( Z = 2.77 (P = 0.006) \)

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**Fig. 2** Change in positive symptoms. SMD, standardised mean difference.

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### Short term

<table>
<thead>
<tr>
<th>Study or subgroup</th>
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<td>Azorin et al (2001)(^{22})</td>
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<td>McEvoy et al (2006) Olanzapine(^{21})</td>
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<td>McEvoy et al (2006) Quetiapine(^{27})</td>
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<td><strong>Subtotal (95% CI)</strong></td>
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<td>−0.25 (−0.40, −0.10)</td>
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**Heterogeneity.** \( t^2 = 0.000; \chi^2 = 6.38, \text{d.f.} = 6 (P = 0.381); I^2 = 6\%

**Test for overall effect:** \( Z = 3.3 (P = 0.00091) \)

### Long term

<table>
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<th>Study or subgroup</th>
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<td>McEvoy et al (2006) Olanzapine(^{21})</td>
<td>6.6</td>
<td>−0.96 (−1.87, −0.04)</td>
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<tr>
<td>McEvoy et al (2006) Quetiapine(^{27})</td>
<td>6.3</td>
<td>−0.65 (−1.59, 0.29)</td>
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<tr>
<td>McEvoy et al (2006) Risperidone(^{27})</td>
<td>5.4</td>
<td>−0.88 (−1.93, 0.17)</td>
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<td>Meltzer et al (2008)(^{22})</td>
<td>7.7</td>
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<td>Rosenheck et al (1997)(^{25})</td>
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<td>−0.34 (−0.60, −0.09)</td>
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<td>Sacchetti et al (2009)(^{26})</td>
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<td>0.23 (−0.10, 0.55)</td>
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<tr>
<td>Tollefson et al (2001)(^{28})</td>
<td>18.7</td>
<td>0.21 (−0.09, 0.50)</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>100.0</td>
<td>−0.11 (−0.39, 0.16)</td>
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</table>

**Heterogeneity.** \( t^2 = 0.08; \chi^2 = 19.55, \text{d.f.} = 6 (P = 0.007); I^2 = 64\%

**Test for overall effect:** \( Z = 0.81 (P = 0.42) \)

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**Fig. 3** Change in negative symptoms. SMD, standardised mean difference.
Pharmaceutical industry funding is a known source of systematic bias either through suppression of non-favourable results or inappropriate comparator medications.42,43 Sensitivity analyses for first- or second-generation comparator antipsychotic group did not appear to affect change in psychotic symptoms. With the exception of risperidone, clozapine was superior in the short term to individual second-generation antipsychotics but failed to reach statistical significance in long-term studies. However, this finding in the long term may be confounded by pharmaceutical industry funding of more recent comparisons with second-generation antipsychotics. When the five second-generation antipsychotic studies without pharmaceutical funding were examined, there was a trend favouring clozapine, but it failed to reach statistical significance. When dosage equivalents were compared, people taking clozapine were receiving significantly lower doses of medication. We attempted to validate this discrepancy using two different dosage equivalence formulas, and both demonstrated that clozapine doses were significantly lower than those of control group medication. It is therefore possible that lower clozapine doses may have biased the data against clozapine, although this is difficult to validate in the absence of reported serum clozapine levels in most of the included studies. Levels were reported in only three studies and ranged from 281 ng/ml to 715 ng/ml;24,30,37 clozapine is therapeutic at levels above 350 ng/ml.44,45 Reporting of serum clozapine levels in future RCTs would assist in confirming whether therapeutic doses were used.

The Egger’s regression asymmetry test did not suggest publication bias (intercept −0.81, 90% CI −2.11 to 0.49, P = 0.420).

Discussion

This study is the first systematic review and meta-analysis to look specifically at the pharmacotherapy of treatment-refractory schizophrenia with clozapine compared with all antipsychotics, not solely first-generation agents. We were able to include 21 studies with 2364 participants. These included 14 papers (n = 1379) published since the data collection periods of the previous meta-analysis,10 all of which used a second-generation antipsychotic as a comparator. We also used a tighter definition of treatment-refractory schizophrenia than previous meta-analyses, based on the criteria described by Kane et al.7 We found that clozapine was superior to other antipsychotics in reducing positive psychotic symptoms in both the short and long term for people with treatment-refractory disorder. In contrast, clozapine was not superior for negative symptoms in the long term although it was in the short term. This, in turn, may explain the lack of any difference in both total psychotic symptoms and response in the long term. It is unclear why the long-term advantages of clozapine are restricted to positive symptoms. Of the two previous meta-analyses of the effect of study duration on outcome, one reported that clozapine was superior in long-term studies,15 whereas the other reported that clozapine was superior in short-term studies.10 Clozapine was particularly effective for more severe baseline symptoms.

The source of funding did appear to have an effect on our results. Studies without pharmaceutical industry funding favoured clozapine more strongly and were statistically significant for all time frames, whereas those with such support favoured the comparator medication. This is in contrast to earlier findings that pharmaceutical industry funding either did not alter rates of improvement,15 or actually increased the likelihood of a study favouring clozapine.10 One explanation is that the earlier meta-analyses included comparisons with first-generation antipsychotics that were funded by manufacturers of clozapine. In contrast, all but two of the additional 14 papers included in this review were comparisons with second-generation antipsychotics that were funded by the manufacturers of the second-generation agents.

Study limitations

There were several limitations of this study. Many of our results showed heterogeneity. Although we attempted to explore this further with sensitivity analyses and meta-regression as well as using a random effects model throughout to incorporate heterogeneity into our analysis, our results should still be treated with caution. As noted above, there are potential biases associated with pharmaceutical industry funding, class of control antipsychotic and comparative doses of clozapine and control medications. We attempted to address these by conducting sensitivity analyses and meta-regression. It is important to note the difficulty of masking in studies where clozapine is a comparator, given the significant adverse drug reactions associated with clozapine. It is possible that this may have systematically biased the overall results. Several studies included participants who had been intolerant to previous antipsychotic trials, as opposed to a strict definition of two or more failed adequate trials. A sensitivity analysis of studies with strict inclusion criteria did not alter the results. We were unable to report on relapse, as the included studies did not provide usable data on this variable. Although we attempted to locate unpublished findings, it is possible that there are unpublished data that we were unable to include.

Clinical implications

Our results suggest that clozapine should remain the treatment of choice for refractory schizophrenia, at least in the short term. Clozapine demonstrated superiority for positive symptoms across all time frames. Given the challenges associated with treating people with refractory disorder, our finding of a number needed to treat of 9 is moderately good.46 However, this must be balanced against numbers needed to harm that ranged from 4 for sialorrhoea to 19 for fever. In addition, if there is no meaningful improvement of symptoms or function at 6 months, our findings suggest clozapine should be stopped and consideration given to an antipsychotic with a more favourable adverse reaction profile.
Pharmacological treatment should always be provided in concert with evidence-based psychosocial interventions.27

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**Fig DS1** PRISMA diagram

*Unique articles identified through literature search, n = 2589*
- Cochrane n = 934
- EMBASE n = 688
- PubMed, n = 967

Excluded on title and abstract and duplicates removed, n = 2402

Screening of full text for inclusion
n = 187

Excluded, n = 165
- Wrong comparator group = 14
- Not treatment resistant = 61
- Not randomized controlled trial = 50
- Nil useable data = 8
- Redacted post publication = 2
- Duplicated publications from single study = 46
  *Some studies fell under multiple categories*

Additional study included from search of reference lists, n = 1

RCTs included in meta-analysis
n = 21
<table>
<thead>
<tr>
<th>Paper</th>
<th>Duration</th>
<th>Country</th>
<th>Setting</th>
<th>Diagnostic tool</th>
<th>TRS criteria deviation</th>
<th>Control Medication</th>
<th>Mean Age (SD) for Clozapine / Control</th>
<th>Number of Participants</th>
<th>CPZ equivalent control (SD)</th>
<th>CPZ equivalent control (SD)</th>
<th>Allocation</th>
<th>Blinding</th>
<th>Randomisation</th>
<th>Primary Outcome</th>
<th>Reporting</th>
<th>ITT</th>
<th>Other Bias</th>
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<tr>
<td>Azorin et al 2001</td>
<td>12 w</td>
<td>France &amp; Canada</td>
<td>H+C</td>
<td>DSM-IV</td>
<td>One Trial, intolerance</td>
<td>Risperidone</td>
<td>37.8 (10.4) / 39.5 (11.3)</td>
<td>138 / 135</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>Double</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>18 w</td>
<td>Hungary &amp; South Africa</td>
<td>H</td>
<td>DSM-IV</td>
<td>One Trial, intolerance</td>
<td>Olanzapine</td>
<td>37.6 *</td>
<td>72 / 72</td>
<td>441 (102)</td>
<td>224 (100)</td>
<td>NS</td>
<td>Double</td>
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<td>8 w</td>
<td>Switzerland</td>
<td>C</td>
<td>DSM-III-R</td>
<td>No Dose, intolerance</td>
<td>Risperidone</td>
<td>36.2 (12.2) / 38.3 (12.9)</td>
<td>43 / 43</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>Double</td>
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<td>Yes</td>
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<td>USA</td>
<td>C</td>
<td>DSM-III-R</td>
<td>No deviation</td>
<td>Haloperidol</td>
<td>41.0 (6.4) / 40.1 (7.9)</td>
<td>38 / 37</td>
<td>1124 (334)</td>
<td>474 (50)</td>
<td>Yes</td>
<td>Double</td>
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<td>12 w</td>
<td>China</td>
<td>H</td>
<td>ICD 10</td>
<td>No deviation</td>
<td>Risperidone</td>
<td>36.9 (7.9) / 37.5 (8.7)</td>
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<td>Yes</td>
<td>Yes</td>
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<td>China</td>
<td>H</td>
<td>DSM-IV</td>
<td>No deviation</td>
<td>Chlorpromazine</td>
<td>39.7 (8.4) / 37.1 (8.7)</td>
<td>21 / 19</td>
<td>1163 (228)</td>
<td>641 (155)</td>
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<td>Double</td>
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<tr>
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<td>6 w</td>
<td>USA</td>
<td>H</td>
<td>DSM-III</td>
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<td>35.7 (8.87)</td>
<td>37 / 34</td>
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<td>Haloperidol</td>
<td>41 (10) / 40 (8)</td>
<td>126 / 141</td>
<td>900 (334)</td>
<td>523 (171)</td>
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<td>Yes</td>
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<td>Haloperidol</td>
<td>14.4 (3.0) / 13.7 (1.6)</td>
<td>10 / 11</td>
<td>718 (378)</td>
<td>176 (145)</td>
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<td>15.8 (2.2) / 15.5 (2.1)</td>
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<td>Olanzapine</td>
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<td>43 / 17 / 14 / 14</td>
<td>629 (180) / 368 (97) / 589 (145)</td>
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<td>C</td>
<td>DSM-IV</td>
<td>No Dose</td>
<td>Olanzapine</td>
<td>37.2 (9.2) / 36.4 (11.1)</td>
<td>21 / 19</td>
<td>953 (270)</td>
<td>680 (256)</td>
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<td>Double</td>
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<td>Yes</td>
<td>No</td>
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<td>8 w</td>
<td>Italy</td>
<td>H</td>
<td>DSM-IV</td>
<td>No deviation</td>
<td>Olanzapine</td>
<td>38.3 (9.1) / 34.1 (7.6)</td>
<td>12 / 11</td>
<td>474 (8)</td>
<td>359 (6)</td>
<td>Yes</td>
<td>Double</td>
<td>NS</td>
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<td>26 w</td>
<td>Germany</td>
<td>H+C</td>
<td>DSM-IV</td>
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<td>Olanzapine</td>
<td>35.2 (10.8) / 32.9 (10.4)</td>
<td>57 / 57</td>
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<td>215 (82)</td>
<td>NS</td>
<td>Double</td>
<td>Yes</td>
<td>Yes</td>
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<td>Pharma control</td>
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<td>Duration</td>
<td>Country</td>
<td>Setting</td>
<td>DSM</td>
<td>Primary Outcome</td>
<td>Intolerance</td>
<td>Treatment</td>
<td>Mean Chlorpromazine Equivalent Dose and Standard Deviation</td>
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<td>Adequate Allocation Concealment</td>
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<td>Adequate Blinding of Outcome Reporter</td>
<td>Adequate Masking of Control Medication</td>
<td>Primary Outcome Measures Were Pre-specified and Reported</td>
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<td>USA</td>
<td>H+C</td>
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<td>Intolerance</td>
<td>Haloperidol</td>
<td>43.2 (7.7) / 43.9 (8.3)</td>
<td>205 / 218</td>
<td>NS</td>
<td>NS</td>
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<td>18 w</td>
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<td>C</td>
<td>DSM-IV</td>
<td>Intolerance</td>
<td>Ziprasidone</td>
<td>38.3 (11.2) / 41.6 (10.2)</td>
<td>74 / 73</td>
<td>450 (31)</td>
<td>386 (52)</td>
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<td>USA</td>
<td>H</td>
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<td>&lt;4 week Duration &gt;100mg CPZ equivalent, intolerance</td>
<td>Olanzapine</td>
<td>12.8 (2.4) / 11.7 (2.3)</td>
<td>12 / 13</td>
<td>468 (90)</td>
<td>362 (106)</td>
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<td>Double</td>
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<td>Multiple</td>
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<td>DSM-IV</td>
<td>&lt;500mg CPZ equivalent, intolerance</td>
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<td>14 w</td>
<td>USA</td>
<td>H</td>
<td>DSM-IV</td>
<td>One Trial</td>
<td>Olanzapine, Risperidone, Haloperidol</td>
<td>40.8 (9.2) *</td>
<td>40 / 41 / 39 / 37</td>
<td>513 (39) / 653 (163) / 837 (157)</td>
<td>459 (158)</td>
<td>Yes</td>
<td>Double</td>
<td>Yes</td>
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<td>Yes</td>
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<td>10 w</td>
<td>Finland</td>
<td>H+C</td>
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<td>Intolerance</td>
<td>Risperidone</td>
<td>35.7 (9.8) / 36.8 (9.8)</td>
<td>11 / 9</td>
<td>673 (163)</td>
<td>437 (227)</td>
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<td>Single</td>
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<td>Yes</td>
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<td>12 w</td>
<td>China</td>
<td>H</td>
<td>CCMD-3</td>
<td>No Dose</td>
<td>Risperidone</td>
<td>35.6 (7.5) / 36 (7.5)</td>
<td>35 / 35</td>
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<td>NS</td>
<td>NS</td>
<td>Single</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>FNS</td>
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NS=not stated

1. Lead author and year of publication
2. w=weeks
3. H = Hospital, C = Community
4. DSM = Diagnostic and Statistical Manual, ICD = International Classification of Diseases, K-SADS = Schedule for Affective Disorders and Schizophrenia for School-Age Children CCMD-3 = Chinese classification of mental disorder
5. TRS= Treatment Refractory Schizophrenia. Table lists areas in which study varied from definition of TRS criteria of failed treatment: Trial of ≥2 antipsychotics; Duration ≥ 6 weeks each; Dose over 600mg/day chlorpromazine (CPZ) equivalents; trials not shortened because of intolerable side effects.
6. A=Atypical antipsychotic, T=Typical antipsychotic
7. SD= Standard Deviation, * = mean age and SD not provided for both clozapine and control
8. Mean chlorpromazine equivalent dose and standard deviation of control medication and clozapine using power transformation formula from Andreason et al (2010)
9. Adequate allocation concealment
10. Single is to assessor only
11. Adequate Random Sequence Generation
12. Primary Outcome Measures were pre-specified and reported
Completeness of outcome reporting

ITT=Intention to Treat analysis

Were other potential sources of bias present. Pharma=Pharmaceutical company sponsorship. FNS = funding source not specified

Data reported at 5, 11, 17 and 29 weeks

Data reported at 3 and 6 months

Data reported at 6 weeks and 6 months

Data reported at 6 weeks, 3 months, 6 months, 9 months and 12 months

Belgium, Denmark, Finland, France, Germany, Italy, Norway, Portugal, South Africa, Spain, Sweden, Switzerland, Great Britain, and Ireland

Data reported at 8 and 14 weeks
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Cao HJ, You HF, Fan FL, Zhang J. The control study of risperidone and clozapine for the treatment-resistant schizophrenia 2003(4):316-9

Hong CJ, Chen JY, Chiu HJ, Sim CB. A double-blind comparative study of clozapine versus chlorpromazine on chinese patients with treatment-refractory schizophrenia 1997(3):123-30

Kane JM, Marder SR, Schooler NR, Wirshing WC, Umbricht D, Baker RW, et al. Clozapine and haloperidol in moderately refractory schizophrenia: A 6-


Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis

Dan Siskind, Lara McCartney, Romi Goldschlager and Steve Kisely

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