
**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
<p>| Paper1 | Duration2 | Country | Setting 3 | Diagnostic tool4 | TRS criteria deviation5 | Control Medication6 | Mean Age (SD) for Clozapine / Control7 | Number of Participants Clozapine / Control8 | CPZ equivalent Control (SD)9 | CPZ equivalent clozapine (SD)10 | Allocation11 | Blinding12 | Randomisation13 | Primary Outcome14 | Repor15 | ITT16 | Other Bias17 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Azorin et al 2001 | 12 w | France &amp; Canada | H+C | DSM-IV | One Trial, intolerance | Risperidone a | 37.8 (10.4) / 39.5 (11.3) | 138 / 135 | NS | NS | NS | Double | Yes | Yes | Yes | Yes | Pharma clozapine |
| Bitter et al 2004 | 18 w | Hungary &amp; South Africa | H | DSM-IV | One Trial, intolerance | Olanzapine a | 37.6 * | 72 / 72 | 441 (102) | 224 (100) | NS | Double | Yes | Yes | Yes | Yes | Pharma control |
| Bondolfi et al 1998 | 8 w | Switzerland | C | DSM-III-R | No Dose, intolerance | Risperidone a | 36.2 (12.2) / 38.3 (12.9) | 43 / 43 | NS | NS | NS | Double | Yes | Yes | Yes | Yes | Pharma control |
| Buchanan et al 1998 | 10 w | USA | C | DSM-III-R | No deviation | Haloperidol a | 41.0 (6.4) / 40.1 (7.9) | 38 / 37 | 1124 (334) | 474 (50) | Yes | Double | Yes | Yes | Yes | Yes | Pharma clozapine &amp; control |
| Cao et al 2003 | 12 w | China | H | ICD-10 | No deviation | Risperidone a | 36.9 (7.9) / 37.5 (8.7) | 30 / 30 | NS | NS | NS | Double | Yes | Yes | Yes | Yes | FNS |
| Hong et al 1997 | 12 w | China | H | DSM-IV | No deviation | Chlorpromazine a | 39.7 (8.4) / 37.1 (8.7) | 21 / 19 | 1163 (228) | 641 (155) | Yes | Double | Yes | Yes | Yes | Yes | No |
| Kane et al 1988 | 6 w | USA | H | DSM-III | No deviation | Chlorpromazine a | 35.7 (8.87) | 37 / 34 | NS | NS | NS | Double | NS | Yes | Yes | Yes | Pharma clozapine |
| Kane et al 2001 | 29 w16 | USA | H + C | DSM-III-R | No deviation | Haloperidol a | 41 (10) / 40 (8) | 126 / 141 | 900 (334) | 523 (171) | Yes | Double | Yes | Yes | No | No |
| Kumra et al 1996 | 6 w | USA | H | DSM-III-R | No Dose or Duration, intolerance | Haloperidol a | 14.4 (3.0) / 13.7 (1.6) | 10 / 11 | 718 (378) | 176 (145) | Yes | Double | Yes | Yes | Yes | Yes | No |
| Kumra et al 2008 | 12 w | USA | not stated | DSM-IV | No Dose or Duration | Olanzapine a | 15.8 (2.2) / 15.5 (2.1) | 18 / 21 | 716 (144) | 461 (207) | Yes | Double | Yes | Yes | Yes | No |
| McEvoy et al 2006 | 78 w17 | USA | C | DSM-IV | One Trial &amp; no Dose, intolerance | Olanzapine a | 39.4 (9.9) / 44.3 (10.5) / 37.1 (11.8) / 39.7 (10.4) | 43 / 17 / 14 / 14 | 629 (180) / 398 (97) / 589 (145) | 368 (154) | NS | Clozapine single, control double | Yes | Yes | Yes | Yes | No |
| Meltzer et al 2008 | 26 w18 | USA | C | DSM-IV | No Dose | Olanzapine a | 37.2 (9.2) / 36.4 (11.1) | 21 / 19 | 953 (270) | 680 (256) | Yes | Double | NS | Yes | Yes | No | Pharma control |
| Morecbo et al 2004 | 8 w | Italy | H | DSM-IV | No deviation | Olanzapine a | 38.3 (9.1) / 34.1 (7.4) | 12 / 11 | 474 (8) | 359 (6) | Yes | Double | NS | Yes | Yes | No | Pharma control |
| Naber et al 2005 | 26 w | Germany | H+C | DSM-IV | One Trial &amp; no Dose, intolerance | Olanzapine a | 35.2 (10.8) / 32.9 (10.4) | 57 / 57 | 412 (102) | 215 (82) | NS | Double | Yes | Yes | Yes | Yes | Pharma control |</p>
<table>
<thead>
<tr>
<th>Name of Study</th>
<th>Lead Author and Year of Publication</th>
<th>Country</th>
<th>Setting</th>
<th>DSM Classification</th>
<th>Intolerance</th>
<th>Treatment</th>
<th>Mean Age ± SD (Clozapine ± Control)</th>
<th>N (Clozapine ± Control)</th>
<th>Side Effects</th>
<th>Random Sequence Generation</th>
<th>Allocation Concealment</th>
<th>Primary Outcome Measures</th>
<th>Adequate Random Sequence Generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenheck et al 1997</td>
<td>S2 w19 USA H+C DSM-III-R Intolerance Haloperidol</td>
<td>43.2 (7.7) / 43.9 (8.3)</td>
<td>205 / 218</td>
<td>NS NS NS NS Double Yes Yes Yes Yes No</td>
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<td>Sacchetti et al 2009</td>
<td>18 w Italy C DSM-IV Intolerance Ziprasidone</td>
<td>38.3 (11.2) / 41.6 (10.2)</td>
<td>74 / 73</td>
<td>450 (31) 386 (52) NS Double Yes Yes Yes Yes No Pharma control</td>
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<td>Shaw et al 2006</td>
<td>8 w USA H K-SADS § ≤4 week Duration &gt;100mg CPZ equivalent, intolerance Olanzapine</td>
<td>12.8 (2.4) / 11.7 (2.3)</td>
<td>12 / 13</td>
<td>468 (90) 362 (106) Yes Double Yes Yes Yes Yes FNS Pharma control</td>
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<td>Tollefson et al 2001</td>
<td>18 w Multiple20 C DSM-IV ≤500mg CPZ equivalent, intolerance Olanzapine</td>
<td>38.6 (10.6)*</td>
<td>90 / 90</td>
<td>450 (55) 332 (101) NS Double NS Yes Yes Yes Yes Pharma control</td>
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<td>Volavka et al 2002</td>
<td>14 w21 USA H DSM-IV One Trial Olanzapine Risperidone Haloperidol</td>
<td>40.8 (9.2)*</td>
<td>40 / 41 / 39</td>
<td>513 (39) 683 (163) 837 (157) 459 (158) Yes Double Yes Yes Yes Yes Pharma control</td>
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<td>Wahlbeck et al 2000</td>
<td>10 w Finland H+C DSM-IV Intolerance Risperidone</td>
<td>35.7 (9.8) / 36.8 (9.8)</td>
<td>11 / 9</td>
<td>673 (163) 437 (227) Yes Single Yes Yes Yes Yes No</td>
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<td>Wang et al 2002</td>
<td>12 w China H CCMD-3 No Dose Risperidone</td>
<td>35.6 (7.5) / 36 (7.5)</td>
<td>35 / 35</td>
<td>NS NS NS Single Yes Yes Yes Yes FNS</td>
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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  
5 CCMD-3 = Chinese classification of mental disorder  
6 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.  
7 A=Atypical antipsychotic, T=Typical antipsychotic  
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
References


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-


