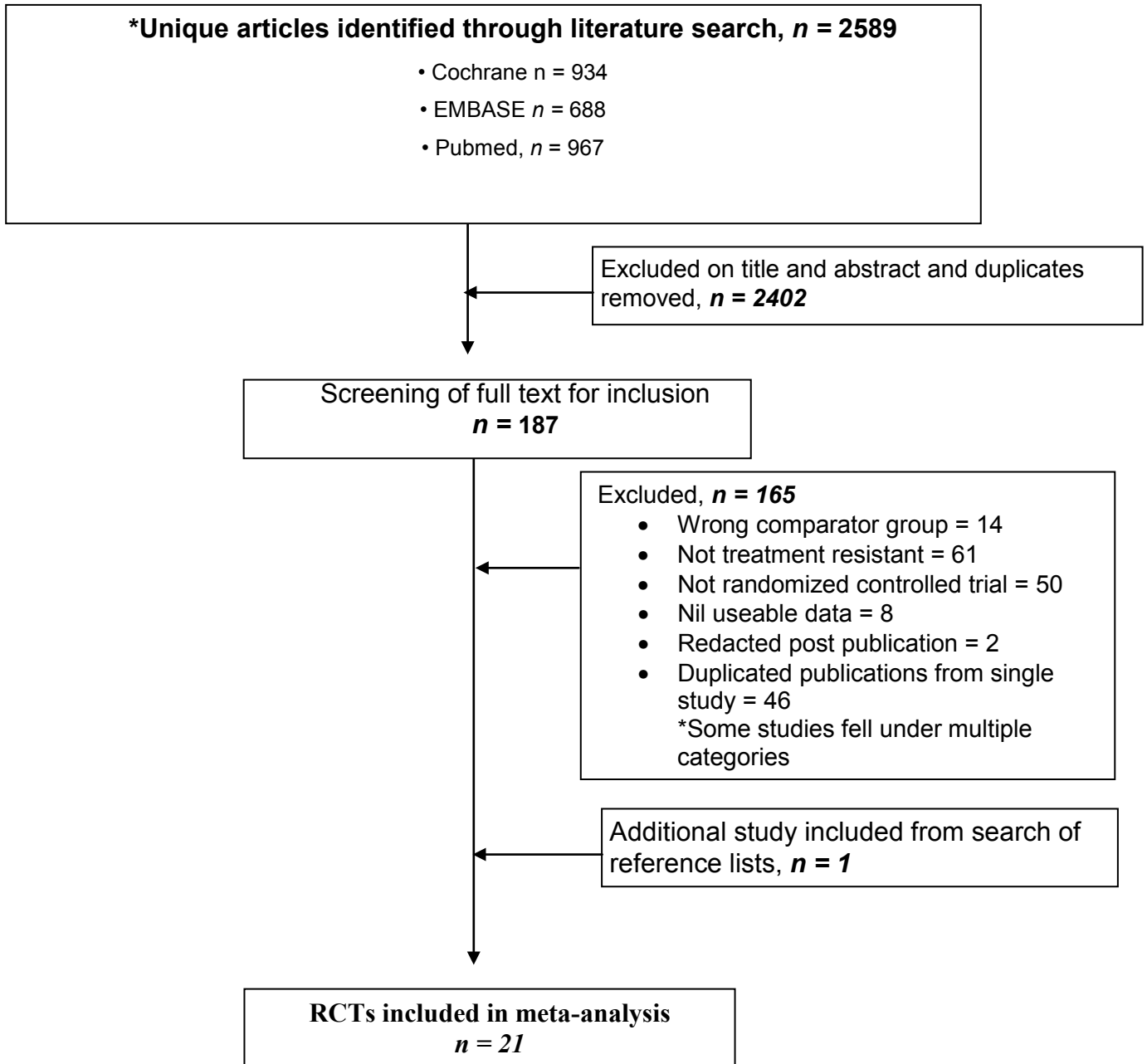


Data supplement to Siskind et al. Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. Br J Psychiatry doi: 10.1192/bjp.bp.115.177261

**Fig DS1** PRISMA diagram



**Table DS1** Included studies

Paper <sup>1</sup>	Duration <sup>2</sup>	Country	Setting <sup>3</sup>	Diagnostic tool <sup>4</sup>	TRS criteria deviation <sup>5</sup>	Control Medication <sup>6</sup>	Mean Age (SD) for Clozapine / Control <sup>7</sup>	Number of Participants Clozapine / Control	CPZ equivalent control (SD) <sup>8</sup>	CPZ equivalent clozapine (SD)	Allocation <sup>9</sup>	Blinding <sup>10</sup>	Randomisation <sup>11</sup>	Primary Outcome <sup>12</sup>	Reporting <sup>13</sup>	ITT <sup>14</sup>	Other Bias <sup>15</sup>
<b>Azorin et al 2001</b>	12 w	France & Canada	H+C	DSM-IV	One Trial, intolerance	Risperidone <sup>A</sup>	37.8 (10.4) / 39.5 (11.3)	138 / 135	NS	NS	NS	Double	Yes	Yes	Yes	Yes	Pharma clozapine
<b>Bitter et al 2004</b>	18 w	Hungary & South Africa	H	DSM-IV	One Trial, intolerance	Olanzapine <sup>A</sup>	37.6 *	72 / 72	441 (102)	224 (100)	NS	Double	Yes	Yes	Yes	Yes	Pharma control
<b>Bondolfi et al 1998</b>	8 w	Switzerland	C	DSM-III-R	No Dose, intolerance	Risperidone <sup>A</sup>	36.2 (12.2) / 38.3 (12.9)	43 / 43	NS	NS	NS	Double	Yes	Yes	Yes	Yes	Pharma control
<b>Buchanan et al 1998</b>	10 w	USA	C	DSM-III-R	No deviation	Haloperidol <sup>T</sup>	41.0 (6.4) / 40.1 (7.9)	38 / 37	1124 (334)	474 (50)	Yes	Double	Yes	Yes	Yes	Yes	Pharma clozapine & control
<b>Cao et al 2003</b>	12 w	China	H	ICD 10	No deviation	Risperidone <sup>A</sup>	36.9 (7.9) / 37.5 (8.7)	30 / 30	NS	NS	NS	Double	Yes	Yes	Yes	Yes	FNS
<b>Hong et al 1997</b>	12 w	China	H	DSM-IV	No deviation	Chlorpromazine <sup>T</sup>	39.7 (8.4) / 37.1 (8.7)	21 / 19	1163 (228)	641 (155)	Yes	Double	Yes	Yes	Yes	Yes	No
<b>Kane et al 1988</b>	6 w	USA	H	DSM-III	No deviation	Chlorpromazine <sup>T</sup>	35.7 (8.87)*	37 / 34	NS	NS	NS	Double	NS	Yes	Yes	Yes	Pharma clozapine
<b>Kane et al 2001</b>	29 w <sup>16</sup>	USA	H + C	DSM-III-R	No deviation	Haloperidol <sup>T</sup>	41 (10) / 40 (8)	126 / 141	900 (334)	523 (171)	Yes	Double	Yes	Yes	Yes	No	No
<b>Kumra et al 1996</b>	6 w	USA	H	DSM-III-R	No Dose or Duration, intolerance	Haloperidol <sup>T</sup>	14.4 (3.0) / 13.7 (1.6)	10 / 11	718 (378)	176 (145)	Yes	Double	Yes	Yes	Yes	Yes	No
<b>Kumra et al 2008</b>	12 w	USA	not stated	DSM-IV	No Dose or Duration	Olanzapine <sup>A</sup>	15.8 (2.2) / 15.5 (2.1)	18 / 21	716 (144)	461 (207)	Yes	Double	Yes	Yes	Yes	Yes	No
<b>McEvoy et al 2006</b>	78 w <sup>17</sup>	USA	C	DSM-IV	One Trial & no Dose, intolerance	Olanzapine <sup>A</sup> Risperidone <sup>A</sup> Quetiapine <sup>A</sup>	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
<b>Meltzer et al 2008</b>	26 w <sup>18</sup>	USA	C	DSM-IV	No Dose	Olanzapine <sup>A</sup>	37.2 (9.2) / 36.4 (11.1)	21 / 19	953 (270)	680 (256)	Yes	Double	NS	Yes	Yes	No	Pharma control
<b>Moresco et al 2004</b>	8 w	Italy	H	DSM-IV	No deviation	Olanzapine <sup>A</sup>	38.3 (9.1) / 34.1 (7.6)	12 / 11	474 (8)	359 (6)	Yes	Double	NS	Yes	Yes	No	Pharma control
<b>Naber et al 2005</b>	26 w	Germany	H+C	DSM-IV	One Trial & no Dose, intolerance	Olanzapine <sup>A</sup>	35.2 (10.8) / 32.9 (10.4)	57 / 57	412 (102)	215 (82)	NS	Double	Yes	Yes	Yes	Yes	Pharma control

<b>Rosenheck et al 1997</b>	52 w <sup>19</sup>	USA	H+C	DSM-III-R	Intolerance	Haloperidol <sup>T</sup>	43.2 (7.7) / 43.9 (8.3)	205 / 218	NS	NS	NS	Double	Yes	Yes	Yes	Yes	No
<b>Sacchetti et al 2009</b>	18 w	Italy	C	DSM-IV	Intolerance	Ziprasidone <sup>A</sup>	38.3 (11.2) / 41.6 (10.2)	74 / 73	450 (31)	386 (52)	NS	Double	Yes	Yes	Yes	No	Pharma control
<b>Shaw et al 2006</b>	8 w	USA	H	K-SADS §	<4 week Duration >100mg CPZ equivalent, intolerance	Olanzapine <sup>A</sup>	12.8 (2.4) / 11.7 (2.3)	12 / 13	468 (90)	362 (106)	Yes	Double	Yes	Yes	Yes	Yes	FNS
<b>Tollefson et al 2001</b>	18 w	Multiple <sup>20</sup>	C	DSM-IV	>500mg CPZ equivalent, intolerance	Olanzapine <sup>A</sup>	38.6 (10.6)*	90 / 90	450 (55)	332 (101)	NS	Double	NS	Yes	Yes	Yes	Pharma control
<b>Volavka et al 2002</b>	14 w <sup>21</sup>	USA	H	DSM-IV	One Trial	Olanzapine <sup>A</sup> Risperidone <sup>A</sup> Haloperidol <sup>T</sup>	40.8 (9.2)*	40 / 41 / 39 / 37	513 (39) 683 (163) 837 (157)	459 (158)	Yes	Double	Yes	Yes	Yes	Yes	Pharma control
<b>Wahlbeck et al 2000</b>	10 w	Finland	H+C	DSM-IV	Intolerance	Risperidone <sup>A</sup>	35.7 (9.8) / 36.8 (9.8)	11 / 9	673 (163)	437 (227)	Yes	Single	Yes	Yes	Yes	Yes	No
<b>Wang et al 2002</b>	12 w	China	H	CCMD-3	No Dose	Risperidone <sup>A</sup>	35.6 (7.5) / 36 (7.5)	35 / 35	NS	NS	NS	Single	Yes	Yes	Yes	Yes	FNS

NS=not stated

<sup>1</sup> Lead author and year of publication

<sup>2</sup> w=weeks

<sup>3</sup> H = Hospital, C = Community

<sup>4</sup> 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

<sup>5</sup> 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.

<sup>6</sup> A=Atypical antipsychotic, T=Typical antipsychotic

<sup>7</sup> SD= Standard Deviation, \* = mean age and SD not provided for both clozapine and control

<sup>8</sup> Mean chlorpromazine equivalent dose and standard deviation of control medication and clozapine using power transformation formula from Andreason et al (2010)

<sup>9</sup> Adequate allocation concealment

<sup>10</sup> Single is to assessor only

<sup>11</sup> Adequate Random Sequence Generation

<sup>12</sup> Primary Outcome Measures were pre-specified and reported

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<sup>13</sup> Completeness of outcome reporting

<sup>14</sup> ITT=Intention to Treat analysis

<sup>15</sup> Were other potential sources of bias present. Pharma=Pharmaceutical company sponsorship. FNS = funding source not specified

<sup>16</sup> Data reported at 5, 11, 17 and 29 weeks

<sup>17</sup> Data reported at 3 and 6 months

<sup>18</sup> Data reported at 6 weeks and 6 months

<sup>19</sup> Data reported at 6 weeks, 3 months, 6 months, 9 months and 12 months

<sup>20</sup> Belgium, Denmark, Finland, France, Germany, Italy, Norway, Portugal, South Africa, Spain, Sweden, Switzerland, Great Britain, and Ireland

<sup>21</sup> Data reported at 8 and 14 weeks



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