

## Supplement

Pharmacological and nonpharmacological augmentation treatments for clozapine-resistant schizophrenia: a systematic review and network meta-analysis

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eTable 1. The demographics of the included studies

Trial	Study design	Inclusion Criteria	Location	Definition of treatment failure	Primary outcome	Treatment	CZ dose (mg, mean±SD)	CZ treatment duration (day, mean±SD)	Sample size	Completed rate (%)	Age (year, Mean ± SD)	Male (%)	Dose (dose schedule)	Trial duration (weeks)	ROB*
Chang et al (2008) <sup>1</sup>	DB, RCT	Schizophrenia (DSM-IV)	H+C	BPRS ≥ 35 or>2 SANS global item rating scores of at least 3	BPRS	Aripiprazole Placebo	Aripiprazole = 304.3 ± 104.8 Placebo = 290.6 ± 101.9	Aripiprazole = 740.8 ± 590.7 Placebo = 290.6 ± 412.7	Aripiprazole = 29 Placebo = 32	Aripiprazole = 90 Placebo = 91	Aripiprazole = 33.2 ± 8.2 Placebo = 31.7 ± 7.4	Aripiprazole = 90 Placebo = 91	5 to 30 mg/d (flexible)	8	Low
Muscatello et al. (2011a) <sup>2</sup>	DB, RCT	Schizophrenia (DSM-IV)	Unclear	BPRS>25	BPRS SANS SAPS	Aripiprazole Placebo	Aripiprazole = 310.7 ± 73.1 Placebo = 341.2 ± 77.5	At least one year	Aripiprazole = 20 Placebo = 20	Aripiprazole = 70 Placebo = 85	Aripiprazole = 31.9 ± 3.9 Placebo = 30.7 ± 5.3	Aripiprazole = 57.14 Placebo = 52.94	10 to 15 mg/d (fixed)	24	Some concerns
Barnes et al (2017) <sup>3</sup>	DB, RCT	schizophrenia/Schizophreniform/Schizoaffective/Psychosis NOS (DSM-IV)	C	PANSS ≥ 80 CGI ≥ 4 SOFAS ≤ 40	PANSS	Amisulpride Placebo	≥ 400 mg†	at least 12 weeks	Amisulpride = 20 Placebo = 20	Amisulpride = 94 Placebo = 83	82.7 ± 7.7†	Amisulpride = 34 Placebo = 29	400 to 800 mg/d (flexible)	12	Some concerns
Genc et al (2007) <sup>4</sup>	SB, RCT	Schizophrenia (DSM-IV)	H+C	BPRS>45 or 2 of 4 BPRS positive symptom items moderately ill (≥ 2)	BPRS SANS SAPS	Amisulpride Quetiapine	Amisulpride = 550 ± 127.09 Quetiapine = 536.95 ± 125.42	at least 12 weeks	Amisulpride = 28 Quetiapine = 28	Amisulpride = 96 Quetiapine = 82	Amisulpride = 37.29 ± 8.17 Quetiapine = 37.3 ± 8.18	Amisulpride = 44.4 Quetiapine = 39.1	Amisulpride = 600 mg/d Quetiapine = 900 mg/d (flexible)	8	High
Friedman et al (2011) <sup>5</sup>	DB, RCT	Schizophrenia/Schizoaffective disorder (DSM-IV)	H+C	PANSS>60 CGI≥4	PANSS	Pimozide Placebo	Pimozide = 518.8 ± 117.3 Placebo = 478.1 ± 150.2	Pimozide = 470.4 ± 411.6 Placebo = 582.4 ± 705.6	Pimozide = 25 Placebo = 28	Pimozide = 82 Placebo = 88	Pimozide = 45.5 ± 10.2 Placebo = 44.4 ± 8.7	Pimozide = 71 Placebo = 84	2 to 8 mg/d (flexible)	12	Some concerns
Freudenreich et al (2007) <sup>6</sup>	DB, RCT	Schizophrenia (DSM-IV)	C	PANSS>60	PANSS	Risperidone Placebo	456 (range 200–700 mg/day) †	NA	Risperidone = 11 Placebo = 13	Risperidone = 100 Placebo = 100	42.3†	87.5†	4 mg/d (fixed)	6	Low
Honer et al. (2006) <sup>7</sup>	DB, RCT	Schizophrenia/Schizoaffective disorder (DSM-IV)	H+C	PANSS>80 CGI≥4 SOFAS<40	CGI PANSS	Risperidone Placebo	Risperidone = 494 ± 168 Placebo = 487 ± 135	Risperidone = 1463 ± 1582 Placebo = 777 ± 1127	Risperidone = 34 Placebo = 34	91†	Risperidone = 39.4 ± 11 Placebo = 34.9 ± 8.5	74†	1 to 3 mg/d (flexible)	8	Low
Weiner et al, (2010) <sup>8</sup>	DB, RCT	Schizophrenia/Schizoaffective disorder	H+C	BSRS ≥ 45 or CGI ≥ 4 BPRS positive	BPRS	Risperidone Placebo	NA	≥ 6 months	Risperidone = 33 Placebo = 36	84†	Risperidone = 48.3 ± 7.2 Placebo	64†	Up to 4 mg/d (flexible)	16	Some concerns

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		(DSM-IV)		symptom item total score ≥ 8, with one or more item ≥ 4.							=44.1 ± 9.3				
<b>Zink et al. (2009)</b> <sup>9</sup>	Open-label RCT	Schizophrenia/Schizoaffective disorder (DSM-IV)	H+C	PANSS ≥65	PANSS SANS	Risperidone Ziprasidone	Risperidone = 437.5 ± 140.4 Ziprasidone = 370.8 ± 150	≥ 3 months	Risperidone = 12 Ziprasidone = 12	100†	Risperidone = 31.83 ± 13.5 Ziprasidone = 37.25 ± 9.9	58†	Risperidone = 3.82 ± 1.8 Ziprasidone = 134 ± 34.4 (flexible)‡	6	High
<b>Nielsen et al. (2012)</b> <sup>10</sup>	DB, RCT	Schizophrenia (ICD-10)	H	PANSS>65	PANSS	Sertindole Placebo	Sertindole = 394 ±148.1 Placebo = 435 ± 197.8	≥ 6 months	Sertindole = 25 Placebo = 25	Sertindole = 88 Placebo = 92	Sertindole = 41.8 ± 11.7 Placebo = 42.7 ± 10.7	Sertindole = 60 Placebo = 60	Start with 4mg and increased by 4 mg every 4 days until 16 mg/d (fixed)	12	Low
<b>Shiloh et al (1997)</b> <sup>11</sup>	DB, RCT	Schizophrenia (DSM-IV)	H	BPRS>25	BPRS SANS SAPS	Sulpride Placebo	Sulpride = 403.1 ±137.2 Placebo = 445.8 ±132.2	Sulpride = 527.8 ±865.2 Placebo = 354.9 ± 257.6	Sulpride = 16 Placebo = 12	Sulpride = 100 Placebo = 100	Sulpride = 40.3 ± 10.8 Placebo = 37.1 ± 12.4	Sulpride = 69 Placebo = 75	100 to 600 mg/d (flexible)	10	High
<b>Mico et al. (2011)</b> <sup>12</sup>	DB, RCT	Schizophrenia (DSM-IV)	C	BPRS>25	PANSS BPRS	Duloxetine Placebo	Duloxetine = 503.3 ± 66.7 Placebo = 533.3 ± 67.2	≥ 1 year	Duloxetine = 20 Placebo = 20	Duloxetine = 85 Placebo = 80	Duloxetine = 35.9 ± 7.1 Placebo = 34 ± 6.8	Duloxetine = 65 Placebo = 55	60 mg/d (fixed)	16	Low
<b>Buchanan et al. (1996)</b> <sup>13</sup>	DB, RCT	Schizophrenia (DSM-III-R)	C	BPRS positive>8 or SANS>20	BPRS	Fluoxetine Placebo	Fluoxetine = 457.4 ± 89 Placebo = 522.7 ± 109.3	≥ 6 months	Fluoxetine = 18 Placebo = 16	Fluoxetine = 100 Placebo = 100	Fluoxetine = 36.8 ± 6.4 Placebo = 32.8 ± 5	Fluoxetine = 83 Placebo = 53	20 to 80 mg/d (flexible)	8	Some concerns
<b>Zoccali et al. (2004)</b> <sup>14</sup>	DB, RCT	Schizophrenia (DSM-IV)	C	Persistent negative symptoms	PANSS	Mirtazapine Placebo	Mirtazapine = 511.7 ± 109.3 Placebo = 320 ± 151.2	≥ 1 year	Mirtazapine = 12 Placebo = 12	MIR = 80 Placebo = 80	Mirtazapine = 30.7 ± 6.5 Placebo = 33.4 ± 9	Mirtazapine = 60 Placebo = 70	30 mg/d (fixed)	8	Some concerns
<b>Vayisoglu et al. (2013)</b> <sup>15</sup>	DB, RCT	Schizophrenia (DSM-IV)	C	PANSS>70 CGI>3	PANSS	Lamotrigine Placebo	Lamotrigine = 514.7 ± 201.3 Placebo = 426.4 ± 192.9	Lamotrigine = 1708 ± 1290.8 Placebo = 1736 ±1747.2	Lamotrigine =17 Placebo = 17	Lamotrigine = 94.1 Placebo = 100	Lamotrigine = 40.5 ± 9.9 Placebo = 41.2 ± 10.9	Lamotrigine = 58.8 Placebo = 76.5	25 to 200 mg/d (flexible)	12	Low
<b>Zoccali et al. (2007)</b> <sup>16</sup>	DB, RCT	Schizophrenia (DSM-IV)	C	BPRS>25	BPRS	Lamotrigine Placebo	Lamotrigine = 300 ± 128.1	≥ 1 year	Lamotrigine = 30 Placebo =	Lamotrigine = 86.7 Placebo =	Lamotrigine = 32.5 ± 6.9	Lamotrigine = 57.69	25 to 200 mg/d (flexible)	24	Low



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							Placebo = 335 ± 128.5		30	83.3	Placebo = 30.2 ± 7.8	Placebo = 52			
<b>Muscatello et al. (2011b)</b> <sup>17</sup>	DB, RCT	Schizophrenia (DSM-IV)	C	BPRS>25	BPRS SANS SAPS	Topiramate Placebo	Topiramate = 333.3 ± 61.2 Placebo = 327.3 ± 84.7	≥ 1 year	Topiramate = 30 Placebo = 30	Topiramate = 63 Placebo = 80	Topiramate = 32.3 ± 4.6 Placebo = 31.5 ± 4.9	Topiramate = 73.68 Placebo = 70.83	25 to 200 mg/d (flexible)	24	Some concerns
<b>De Lucena et al. (2009)</b> <sup>18</sup>	DB, RCT	Schizophrenia (DSM-IV)	C	partial remission of negative symptoms	BPRS	Memantine Placebo	Memantine = 540 ± 211.87 Placebo = 659.09 ±185.55	≥ 10 years	Memantine = 11 Placebo = 11	Memantine = 90.91 Placebo = 100	Memantine = 34.6 ± 9.99 Placebo = 34.73 ±8.57	Memantine = 80 Placebo = 100	5-20 mg/d (flexible)	12	Some concerns
<b>Evins et al. (2000)</b> <sup>19</sup>	DB, RCT	Schizophrenia (DSM-IV)	C	SANS ≥ 27	BPRS PANSS SANS	Glycine Placebo	455±116†	≥ 1 month	Glycine = 14 Placebo = 14	90†	39 ± 7†	80†	3000 mg/d (fixed)	8	Some concerns
<b>Lane et al. (2006)</b> <sup>20</sup>	DB, RCT	Schizophrenia (DSM-IV)	H	PANSS >70	PANSS	Glycine Placebo	Glycine = 306 ± 158 Placebo = 305 ± 55	≥ 3 months	Glycine = 10 Placebo = 10	100 <sup>b</sup>	Glycine = 33.2 ± 12.4 Placebo = 39.8 ± 7.7	Glycine = 44 Placebo = 58	2000 mg/d (fixed)	6	Low
<b>Kelly et al. (2015)</b> <sup>21</sup>	Open-label RCT	schizophrenia or schizoaffective disorder (DSM-IV-TR)	H+C	BPRS≥ 45 CGI≥ 4 BPRS-positive ≥ 8 and ≥4 at least one individual item	BPRS CGI	Minocycline Placebo	Minocycline = 423.1 ± 189.5 Placebo =433.7 ± 140.1	≥ 6 months	Minocycline = 29 Placebo =23	Minocycline = 98 Placebo =98	Minocycline = 42.9 ± 14.2 Placebo = 42.3 ± 11	Minocycline = 71 PLA = 78	200 mg/d (flexible)	10	Low
<b>Doruk et al. (2008)</b> <sup>22</sup>	DB, RCT	Schizophrenia (DSM-IV)	C	Remained symptomatic	BPRS SANS SAPS	Ginkgo Placebo	Ginkgo Biloba = 415 ± 72.7 Placebo =409.1 ± 54.9	Ginkgo Biloba = 839.5 ±328.5 Placebo = 1095 ± 584	Ginkgo Biloba = 23 Placebo = 23	Ginkgo Biloba = 100 Placebo = 100	Ginkgo Biloba = 20.6 ± 3.4 Placebo = 22.5 ± 4.4	Ginkgo Biloba = 55 Placebo = 72.7	120 mg/d (fixed)	12	Some concerns
<b>De Jesus et al. (2011)</b> <sup>23</sup>	DB, RCT	Schizophrenia (OPCRIT 4.0)	Unclear	Daily auditory hallucinations occurring at least five times per day BPRS ≥27	BPRS CGI	rTMS Placebo	rTMS= 700 ± 200 Placebo =650 ± 100	≥ 4 months	rTMS= 23 Placebo = 23	rTMS= 100 Placebo = 100	rTMS= 46 ± 9.84 Placebo = 36.5 ± 6.36	rTMS= 62.5 Placebo = 77.8	90% of the motor threshold 5 sessions/wk for 4 weeks (fixed)	4	Low
<b>Petrides et al. (2015)</b> <sup>24</sup>	SB, RCT	Schizophrenia (DSM-IV)	H	BPRS ≥4 on one of the four psychotic items or score ≥ 12	BPRS	ECT (bilateral, 50% above threshold)	ECT= 525 ± 224.3 Placebo =511.1 ± 171	≥ 4 months	ECT= 20 Placebo = 19	ECT= 85 Placebo = 84.2	ECT= 35.7 ± 2.27 Placebo = 42.78 ± 1.82	ECT= 75 Placebo = 68.4	three times per week for the first 4 weeks, then twice	8	Some concerns

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				on these four items combined CGI-S ≥ 4		Placebo							weekly for the next 4 weeks 50% above threshold (fixed)		
<b>Barretto et al. (2009)</b> <sup>25</sup>	Open-label RCT	Schizophrenia (DSM-IV)	C	at least one psychotic symptom of the BPRS ≥4	BPRS PANSS	CBT Placebo	NA	≥ 6 months	CBT= 12 Placebo = 10	CBT= 100 Placebo = 90	CBT= 39.8 ± 7.7 Placebo = 33.2 ± 12.4	CBT= 58.3 Placebo = 44.4	three times per week for the first 4 weeks, then twice weekly for the next 4 weeks (fixed)	21	High
<b>Fleischhacker et al. (2010)</b> <sup>26</sup>	DB, RCT	Schizophrenia (DSM-IV-TR)	C	not optimally controlled by clozapine	PANSS	Aripiprazole Placebo	Aripiprazole = 383.8 ± 158.2 Placebo = 362.6 ± 158.7	Aripiprazole = 1794.8 ± 1708 Placebo = 1772.4 ± 1635.2	Aripiprazole = 108 Placebo = 99	Aripiprazole = 89.81 Placebo = 93.93	Aripiprazole = 37.6 ± 10.9 Placebo = 40.5 ± 9.9	Aripiprazole = 63 Placebo = 66.7	200 mg/d (flexible)	16	Low
<b>Wagner et al. (2019)</b> <sup>27</sup>	DB, RCT	Schizophrenia (ICD-10)	H+C	PANSS negative subscale score >20 points, and at least one PANSS negative item ≥4	BPRS CGI PANSS	rTMS Placebo	NA	NA	rTMS= 12 Placebo = 14	rTMS= 100 Placebo = 100	rTMS= 36.6 ± 10 Placebo = 36.2 ± 9	rTMS = 72 Placebo = 85.7	10 Hz, five sessions/week for a 3-week treatment period (from day 0 to day 21) with an intensity of 110% of the individual resting motor threshold and 1000 stimuli (fixed)	3	Low
<b>Tiihonen et al. (2003)</b> <sup>28</sup>	DB, placebo-controlled crossover trial	Schizophrenia (DSM-IV)	H	Unsatisfactory response with clozapine treatment	PANSS	Lamotrigine Placebo	Lamotrigine = 508 ± 188 Placebo = 603 ± 125	≥ 6 months	Lamotrigine = 29 Placebo = 30	Lamotrigine = 82.75 Placebo = 83.3	Lamotrigine = 38.3 ± 8.4 Placebo = 38.3 ± 10	NA	25 to 200 mg/d (flexible)	14	Low

Trial	Study design	Inclusion Criteria	Location	Definition of treatment failure	Primary outcome	Treatment	CZ dose (mg, mean±SD)	CZ treatment duration (day, mean±SD)	Sample size	Completed rate (%)	Age (year, Mean ± SD)	Male (%)	Dose (dose schedule)	Trial duration (weeks)	ROB*
<b>Tsai et al. (1999)</b> <sup>29</sup>	DB, RCT	Schizophrenia (DSM-IV)	H	SANS ≥ 45	CGI PANSS SANS	D-Serine Placebo	D-Serine = 353 ± 128 Placebo =3315 ± 146	D-Serine =406 ± 201.6 Placebo =560 ± 59.6	D-Serine =10 Placebo =10	D-Serine =100 Placebo =100	D-Serine =42.6 ± 3.6 Placebo = 39.5 ± 5.5	D-Serine = 60 Placebo = 50	30 mg/kg per day (fixed)	6	Some concerns
<b>Goff et al. (1999)</b> <sup>30</sup>	DB, placebo-controlled crossover trial	Schizophrenia (DSM-IV)	C	SANS >30	GAF PANSS SANS	D-Cycloserine Placebo	490.9 ± 141.1	≥ 6 months	D-Cycloserine =11 Placebo =11	64.7†	36.6 6± 9.6†	88.2†	50 mg/day (fixed)	6	Some concerns
<b>Goff et al. (2001)</b> <sup>31</sup>	DB, RCT	Schizophrenia (DSM-IV)	H	NA	PANSS SANS	Ampakine Placebo	406.6 ±126.6†	≥ 6 months	Ampakine =12 Placebo =7	Ampakine =100 Placebo =85.7	39.8 ± 10.5	NA	300 -900 mg (fixed)	4	Some concerns
<b>Josiassen et al. (2005)</b> <sup>32</sup>	DB, RCT	schizophrenia or schizoaffective disorder (DSM-IV)	H+C	BPRS ≥45 or BPRS ≥4 on two of the four positive items	BPRS CGI SANS	Risperidone Placebo	Risperidone = 528.8 ± 166.7 Placebo =402.5±102.9	≥ 3 months	Risperidone =20 Placebo =20	Risperidone =100 Placebo =100	Risperidone = 40.8 ± 6.9 Placebo =39.9 ± 10.8	Risperidone =95 Placebo =80	1 to 6 mg/d (flexible)	12	Some concerns
<b>Yaycioglu et al. (2005)</b> <sup>33</sup>	DB, RCT	schizophrenia or schizoaffective disorder (DSM-IV)	H+C	PANSS ≥ 72 CGI-S ≥ 4 PANSS ≥3 on any of PANSS positive items	CGI PANSS GAF	Risperidone Placebo	Risperidone = 515.6 ± 138.7 Placebo =414.3 ± 96.9	Risperidone = 747.6 ± 803.6 Placebo =1061.2 ± 831.6	Risperidone =16 Placebo =14	Risperidone = 93.75 Placebo =100	Risperidone = 35.3 ± 10.8 Placebo =31.2 ± 6.9	Risperidone =56.2 Placebo =78.5	2 to 6 mg/d (flexible)	6	Some concerns
<b>Muscatello et al. (2014)</b> <sup>34</sup>	DB, RCT	Schizophrenia (DSM-IV)	H	BPRS≥ 25	BPRS PANSS	Ziprasidone Placebo	350 to 600 mg/d\$	≥ 1 year	Ziprasidone = 20 Placebo =20	Ziprasidone = 80 Placebo = 85	Ziprasidone = 36.5 ± 8.8 Placebo =33.6 ± 5.6	Ziprasidone =25 Placebo =40	80 mg/d (fixed)	16	Low
<b>Gunduz-Bruce et al. (2013)</b> <sup>35</sup>	DB, RCT	Schizophrenia (DSM-IV)	C	BPRS≥ 35 BPRS psychotic symptom cluster score of ≥8	BPRS CGI SANS	Pimozide Placebo	blood level ≥ 350 ng/ml¶	NA	Pimozide = 14 Placebo = 14	Pimozide = 92.8 Placebo = 100	Pimozide = 43.3 ± 2.0 Placebo = 41.5 ±2.8	Pimozide = 71.4 Placebo = 71.4	1 to 4 mg/d (flexible)	12	Some concerns

Abbreviation: BPRS: Brief psychiatric rating scale; C: Community; CBT: Cognitive behavioral therapy; CGI: Clinical global impression; DSM-IV: Diagnostic and statistical manual of mental disorders, fourth edition; DSM-IV-TR: Diagnostic and statistical manual of mental disorders, fourth edition-text revision; ECT: Electroconvulsive therapy; GAF: Global assessment of functioning; H: hospital; ICD-10: International classification of diseases, tenth revision; NA: Not available; OPCRIT: Operational criteria checklist for psychotic illness and affective illness; PANSS: Positive and negative syndrome scale; rTMS: Repetitive transcranial magnetic stimulation; SANS: Scale

for assessment of negative symptoms; SAPS: Scale for assessment of positive symptoms; SOFAS: Social and occupational functioning assessment scale.

\* Use Revised Cochrane risk of bias tool for randomized trials (RoB 2.0) to assess individual randomized parallel group trial or randomized cross-over trial

† Data is combined for both placebo and active treatment groups.

‡ Only mean and range of clozapine dose were provided.

§ Only range of clozapine dose was provided.

¶ Clozapine dose is not available so replaced by plasma level.

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**eTable 2. Definition of clozapine-resistant schizophrenia in the included studies**

<b>Trial</b>	<b>Clozapine-refractory/resistant schizophrenia or poor response to clozapine using standard scale</b>	<b>Treatment-resistant schizophrenia*</b>	<b>Ultra treatment-resistant schizophrenia†</b>
Chang 2008 (Aripiprazole vs Placebo)	Yes	Yes	Yes
Muscatello 2011a (Aripiprazole vs Placebo)	Yes		
Barnes 2017 (Amisulpride vs Placebo)	Yes	Yes	Yes
Genc 2007‡ (Amisulpride vs Quetiapine)	Yes	Yes	Yes
Friedman 2011 (Pimozide vs Placebo)	Yes		
Freudenreich 2007 <sup>c</sup> (Risperidone vs Placebo)	Yes	Yes	Yes
Honer 2006 (Risperidone vs Placebo)	Yes	Yes	Yes
Weiner 2010 (Risperidone vs Placebo)	Yes		
Zink 2009 (Risperidone vs Ziprasidone)	Yes		
Nielsen 2012 (Sertindole vs Placebo)	Yes		
Shiloh 1997 <sup>c</sup> (Sulpride vs Placebo)	Yes	Yes	Yes
Mico 2011 (Duloxetine vs Placebo)	Yes		
Buchanan 1996 (Fluoxetine vs Placebo)	Yes		
Zoccali 2004 (Mirtazapine vs Placebo)	Yes		
Vayisoglu 2013 (Lamotrigine vs Placebo)	Yes		
Zoccali 2007 (Lamotrigine vs Placebo)	Yes		
Muscatello 2011b (Topiramate vs Placebo)	Yes		
De Lucena 2009	Yes		

<b>Trial</b>	<b>Clozapine-refractory/resistant schizophrenia or poor response to clozapine using standard scale</b>	<b>Treatment-resistant schizophrenia*</b>	<b>Ultra treatment-resistant schizophrenia†</b>
(Memantine vs Placebo)			
Evins 2000 (Glycine vs Placebo)	Yes		
Lane 2006 (Glycine vs Placebo)	Yes		
Kelly 2015 (Minocycline vs Placebo)	Yes		
Doruk 2008 <sup>c</sup> (Ginkgo Biloba vs Placebo)	Yes	Yes	Yes
De Jesus 2011 (rTMS vs Placebo)	Yes		
Petrides 2015 (ECT vs Placebo)	Yes		
Barretto 2009 <sup>c</sup> (CBT vs Placebo)	Yes	Yes	Yes
Fleischhacker 2010 (Aripiprazole vs Placebo)	Yes		
Wagner 2019 <sup>S</sup> (rTMS vs Placebo )	Yes	Yes	Yes
Tiihonen 2003 (Lamotrigine vs Placebo)	Yes		
Tsai 1999 <sup>d</sup> (D-Serine vs Placebo)	Yes	Yes	Yes
Goff 1999 (D-Cycloserine vs Placebo)	Yes		
Goff 2001 (Ampakine vs Placebo)	Yes		
Josiassen 2005 (Risperidone vs Placebo)	Yes	Yes	Yes
Yaycioglu 2005 (Risperidone vs Placebo)	Yes	Yes	Yes
Muscatello 2014 (Ziprasidone vs Placebo)	Yes		
Gunduz-Bruce 2013 (Pimozide vs Placebo)	Yes		

Abbreviation: CBT: Cognitive behavioral therapy; ECT: Electroconvulsive therapy; rTMS: Repetitive transcranial magnetic stimulation

\*† Definitions of treatment resistant schizophrenia and ultra-treatment resistant schizophrenia were adapted from the minimum requirement of Treatment Response and Resistance in Psychosis (TRRIP) Working Group.



‡ Minimal clozapine dose and duration were obtained from demographic data.

§ Mean dose of clozapine was lower than 400mg per day.

**References:** Howes OD, McCutcheon R, Agid O, et al. Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology. *Am J Psychiatry*. 2017;174(3):216-229. doi:10.1176/appi.ajp.2016.16050503.

**eTable 3. Meta-regression analyses for all included studies**

Variables	Number of Studies	Z	P
Overall Symptoms			
PANSS	33	0.019	0.316
DDD	27	0.131	0.848
Clozapine Dose	27	-0.001	0.805
Illness Duration	26	0.002	0.537
DDD*PANSS	27	-0.015	0.796
DDD*Clozapine Dose	23	-0.009	0.856
Male	31	0.467	0.776
Age	33	0.032	0.445
Trial Duration	33	0.005	0.895
Positive symptoms			
PANSS	31	0.009	0.600
DDD	26	0.204	0.287
Clozapine Dose	27	-0.001	0.603
Illness Duration	26	-0.001	0.528
DDD*PANSS	25	-0.020	0.464
DDD*Clozapine Dose	23	-0.009	0.586
Male	30	-0.532	0.706
Age	32	-0.003	0.933
Trial Duration	32	-0.009	0.771
Negative symptoms			
PANSS	33	0.028	<b>0.039*</b>
DDD	28	0.305	0.485
Clozapine Dose	29	-0.002	0.418
Illness Duration	28	0.004	0.163
DDD*PANSS	27	0.018	0.724
DDD*Clozapine Dose	23	-0.009	0.586
Male	33	1.213	0.343
Age	35	0.054	0.110
Trial Duration	35	-0.050	0.072

Abbreviation: DDD, defined daily dose; PANSS, Positive and Negative Syndrome Scale.

\* Meta-regression analyses were conducted across treatments.

**eTable 4. Number of outliving moderators in each included study**

Year	Treatment	DDD	PANSS	Clozapine dose	Illness Duration (M)	Trial Duration (W)	Male	Age	Outlier of Modified Z Score	Outlier of Treatment Method
1995-2017	Amisulpride	2	95.3			12	0.654	39.5	1	0
2007	Amisulpride/Quetiapine	1.29	82.7	543.48	188	8	0.418	37.3	0	0
Aug 2008	Aripiprazole	1.03	80.1	297.1	151.2	8	0.787	32.4	0	0
Matello	Aripiprazole	1	57.7	326.4		24	0.523	31.3	0	0
Aschbacher	Aripiprazole	0.74	71.5	373.7	162.5	16	0.648	39	0	0
Edman 2011	Pimozide	1.62	87	497.3	313.1	12	0.779	44.9	0	0
Fuz-Bruce	Pimozide	1	73.7			12	0.714	42.5	0	0
Edenreich	Risperidone	1	75	456		6	0.875	42.3	0	0
Er 2006	Risperidone	0.735	100.1	490.4	178.7	8	0.74	37.1	0	0
Er 2010	Risperidone	0.99	82.6		321.3	16	0.64	46	0	0
2009	Risperidone/Ziprasidone	1.315	83	404.15	138.8	6	0.58	34.5	0	0
assen	Risperidone	1.108	79.9	456.7	265.2	12	0.875	40.4	0	0
ioğlu	Risperidone	1.275	77.4	468.3	147	6	0.666	33.4	0	0
sen 2012	Sertindole	1	79	414.5	154.8	12	0.6	42.3	0	0
oh 1997	Sulpiride	0.75	82.9	421.4	239.8	10	0.716	38.9	0	0
Matello	Ziprasidone	1	71.5			16	0.325	35.1	0	0
2011	Duloxetine	1	65.7	518.3	77.4	16	0.6	35	0	0
anan 1996	Fluoxetine	2.445		483	191	8	0.68	34.9	1	1
ali 2004	Mirtazapine	1	75.7	322.5	139	8	0.65	32.1	0	0
soglu	Lamotrigine	0.677	71.7	470.6	219	12	0.677	40.9	0	0
ali 2007	Lamotrigine	0.677	52.4	317.2	119	24	0.549	31.4	1	0
onen 2003	Lamotrigine	1	64.5	556.3	163.2	14		38.3	0	0
Matello	Topiramate	0.677	59.8	330.3	66	24	0.723	31.9	0	0
b 1999	D-Serine		81.4	339	243	6	0.45	41.1	0	0
1999	D-Serine			490.9	177.6	6	0.882	36.6	0	0
s 2000	Glycine	1.5	72.4	455	192	8		39	0	0
2006	Sarcosine	1	78	305.5	178.8	6	0.7	36.1	0	0
ucena	Memantine	1	67.1	602.4	214	12	0.905	34.7	0	0
2001	Ampakine		78.2	406.6	237.6	4	0.842	39.8	0	0
k 2008	Ginkgo_Biloba	1	99.4	412.1	113.4	12	0.639	21.5	1	0
y 2015	Minocycline	1	74.1	428	285.1	10	0.745	42.6	0	0
etto 2009	CBT		82.2		154.3	21	0.52	36.5	0	0
ides 2015	ECT		76.7	518.2		8	0.718	39.1	0	0
esus 2011	rTMS		57.6	673.5	242.8	4	0.706	41	0	0
er 2019	rTMS		78			3	0.789	36.4	0	0

Abbreviation: CBD, cognitive-behavioral therapy; DDD, defined daily dose; ECT, electroconvulsive therapy; PANSS, Positive and Negative Syndrome Scale; rTMS, repetitive transcranial magnetic therapy.

**eTable 5. Design-by treatment interaction and node-splitting models**

<b>Design-by-treatment</b>	<b>Q</b>	<b>Df</b>	<b>P</b>	<b>Tau-within</b>	<b>Tau<sup>2</sup>.within</b>
Overall symptoms	1.14	1	0.285	0.543	0.295
Positive symptoms	0.00	1	0.972	0.306	0.094
Negative symptoms	0.77	1	0.380	0.471	0.221
Acceptability	0.01	1	0.923	0	0
<b>Node-splitting</b>	<b>K</b>	<b>Direct</b>	<b>Indirect</b>	<b>Difference</b>	<b>p</b>
Overall symptoms					
Risperidone vs Placebo	5	0.057	-0.844	0.091	0.284
Ziprasidone vs Placebo	1	-0.523	0.378	-0.091	0.284
Ziprasidone	1	-0.321	0.580	-0.091	0.284
Positive symptoms					
Risperidone vs Placebo	5	-0.024	-0.007	-0.017	0.971
Ziprasidone vs Placebo	1	0.044	0.027	0.017	0.971
Ziprasidone	1	-0.051	-0.068	0.017	0.971
Negative symptoms					
Risperidone vs Placebo	5	-0.175	-0.806	0.631	0.379
Ziprasidone vs Placebo	1	-0.740	-0.109	-0.631	0.379
Ziprasidone	1	-0.066	0.565	-0.631	0.379
Acceptability					
Risperidone vs Placebo	3	1.176	1.364	0.862	0.923
Ziprasidone vs Placebo	1	1.364	1.176	1.160	0.923
Ziprasidone	1	1.000	0.862	1.160	0.923

**eTable 6. Outlier and influential detection measures for overall symptoms**

Treatment 1	Treatment 2	Raw residual	Standardized residual	Studentized residual	Mahalanobis distance	Leverage
Aripiprazole+Clozapine	Placebo+Clozapine	0.1653	0.3044	0.3162	0.0878	0.0729
Aripiprazole+Clozapine	Placebo+Clozapine	-0.3669	-0.6735	-0.6851	86.9017	0.0335
Amisulpride+Clozapine	Placebo+Clozapine	0	0	0	0	1
Amisulpride+Clozapine	Quetiapine+Clozapine	0	0	--	0	1
Pimozide+Clozapine	Placebo+Clozapine	-0.0152	-0.028	-0.066	0.0163	0.8202
Risperidone+Clozapine	Placebo+Clozapine	0.3646	0.6631	0.6874	4.9465	0.0693
Risperidone+Clozapine	Placebo+Clozapine	-0.1954	-0.3596	-0.436	64.5424	0.3197
Risperidone+Clozapine	Placebo+Clozapine	0.3578	0.6588	0.853	26.9799	0.4036
Risperidone+Clozapine	Ziprasidone+Clozapine	-0.4462	-0.7542	-0.7803	7.0519	0.0657
Sertindole+Clozapine	Placebo+Clozapine	0	0	0	0	1
Sulpiride+Clozapine	Placebo+Clozapine	0	0	--	0	1
Duloxetine+Clozapine	Placebo+Clozapine	0	0	0	0	1
Mirtazapine+Clozapine	Placebo+Clozapine	0	0	0	0	1
Lamotrigine+Clozapine	Placebo+Clozapine	1.3881	2.5346	2.7437	395.9457	0.1466
Lamotrigine+Clozapine	Placebo+Clozapine	-1.3078	-2.4011	-2.8599	366.2609	0.2951
Topiramate+Clozapine	Placebo+Clozapine	0	0	--	0	1
Memantine+Clozapine	Placebo+Clozapine	0	0	--	0	1
Glycine+Clozapine	Placebo+Clozapine	0	0	0	0	1
Sarcosine+Clozapine	Placebo+Clozapine	0	0	--	0	1
Minocycline+Clozapine	Placebo+Clozapine	0	0	0	0	1
Ginkgo_Biloba+Clozapine	Placebo+Clozapine	0	0	--	0	1
rTMS+Clozapine	Placebo+Clozapine	0	-0.0001	-0.0001	0	0.3947
ECT+Clozapine	Placebo+Clozapine	0	0	--	0	1
CBT+Clozapine	Placebo+Clozapine	0	0	0	0	1
Aripiprazole+Clozapine	Placebo+Clozapine	0.1984	0.3661	1.1224	3.5657	0.8936
rTMS+Clozapine	Placebo+Clozapine	0	0.0001	0.0001	0	0.6053
Lamotrigine+Clozapine	Placebo+Clozapine	-0.0648	-0.1192	-0.1794	13.8053	0.5583
D-Serine+Clozapine	Placebo+Clozapine	0	0	0	0	1
Ampakine+Clozapine	Placebo+Clozapine	0	0	0	0	1
Risperidone+Clozapine	Placebo+Clozapine	0.4457	0.8179	0.8988	23.6719	0.1719
Risperidone+Clozapine	Placebo+Clozapine	-1.4394	-2.5545	-2.5875	105.6281	0.0254
Placebo+Clozapine	Ziprasidone+Clozapine	0.3784	0.6946	2.9477	0.4191	0.9445
Pimozide+Clozapine	Placebo+Clozapine	0.0156	0.0283	0.0313	0.0745	0.1798

Abbreviation: CBT, cognitive behavioral treatment; ECT, electroconvulsive therapy; rTMS, repetitive

transcranial magnetic stimulation.

**eTable 7. Outlier and influential detection measures for positive symptoms**

Treatment 1	Treatment 2	Raw residual	Standardized residual	Studentized residual	Mahalanobis distance	Leverage
Aripiprazole+Clozapine	Placebo+Clozapine	0.3451	1.1356	1.1857	11.8324	0.0827
Aripiprazole+Clozapine	Placebo+Clozapine	-0.5995	-1.9489	-1.979	187.1	0.0301
Pimozide+Clozapine	Placebo+Clozapine	-0.2575	-0.8441	-2.0791	3.9261	0.8352
Risperidone+Clozapine	Placebo+Clozapine	0.0104	0.0331	0.0341	0.663	0.0586
Risperidone+Clozapine	Placebo+Clozapine	-0.1038	-0.3413	-0.4287	26.1274	0.3659
Risperidone+Clozapine	Placebo+Clozapine	0.2414	0.794	0.9941	17.3435	0.362
Risperidone+Clozapine	Ziprasidone+Clozapine	0.0083	0.0253	0.0277	0.4246	0.1667
Sertindole+Clozapine	Placebo+Clozapine	0	0	--	0	1
Sulpiride+Clozapine	Placebo+Clozapine	0	0	0	0	1
Duloxetine+Clozapine	Placebo+Clozapine	0	0	0	0	1
Fluoxetine+Clozapine	Placebo+Clozapine	0	0	--	0	1
Mirtazapine+Clozapine	Placebo+Clozapine	0	0	0	0	1
Lamotrigine+Clozapine	Placebo+Clozapine	0.2061	0.6642	0.72	11.685	0.1491
Lamotrigine+Clozapine	Placebo+Clozapine	-0.251	-0.8229	-1.0497	21.4501	0.3854
Topiramate+Clozapine	Placebo+Clozapine	0	0	--	0	1
Memantine+Clozapine	Placebo+Clozapine	0	0	0	0	1
Glycine+Clozapine	Placebo+Clozapine	0	0	--	0	1
Sarcosine+Clozapine	Placebo+Clozapine	0	0	--	0	1
Minocycline+Clozapine	Placebo+Clozapine	0	0	--	0	1
Ginkgo_Biloba+Clozapine	Placebo+Clozapine	0	0	--	0	1
rTMS+Clozapine	Placebo+Clozapine	-0.3672	-1.1132	-1.5344	8.2837	0.4736
ECT+Clozapine	Placebo+Clozapine	0	0	0	0	1
CBT+Clozapine	Placebo+Clozapine	0	0	--	0	1
Aripiprazole+Clozapine	Placebo+Clozapine	0.2369	0.7846	2.3357	2.1592	0.8872
rTMS+Clozapine	Placebo+Clozapine	0.3612	1.1041	1.6043	7.4536	0.5264
Lamotrigine+Clozapine	Placebo+Clozapine	0.0516	0.1696	0.232	5.198	0.4655
D-Serine+Clozapine	Placebo+Clozapine	0	0	0	0	1
Ampakine+Clozapine	Placebo+Clozapine	0	0	0	0	1
Risperidone+Clozapine	Placebo+Clozapine	0.4464	1.4519	1.57	37.2957	0.1448
Risperidone+Clozapine	Placebo+Clozapine	-0.639	-1.9968	-2.0426	46.1837	0.0443
Ziprasidone+Clozapine	Placebo+Clozapine	-0.0072	-0.0235	-0.0624	0.0726	0.8576
Pimozide+Clozapine	Placebo+Clozapine	0.28	0.8802	0.9632	19.8904	0.1648

Abbreviation: CBT, cognitive behavioral treatment; ECT, electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation.

**eTable 8. Outlier and influential detection measures for negative symptoms**

Treatment 1	Treatment 2	Raw residual	Standardized residual	Studentized residual	Mahalanobis distance	Leverage
Aripiprazole+Clozapine	Placebo+Clozapine	-0.2437	-0.5171	-0.5348	114.1151	0.065
Aripiprazole+Clozapine	Placebo+Clozapine	0.0182	0.0385	0.0391	9.3461	0.0348
Amisulpride+Clozapine	Placebo+Clozapine	0	0	--	0	1
Amisulpride+Clozapine	Quetiapine+Clozapine	0	0	--	0	1
Pimozide+Clozapine	Placebo+Clozapine	0.0571	0.1211	0.2589	0.3541	0.7812
Risperidone+Clozapine	Placebo+Clozapine	-0.0657	-0.1373	-0.1411	0.0025	0.0536
Risperidone+Clozapine	Placebo+Clozapine	-0.2539	-0.539	-0.6596	26.6629	0.3323
Risperidone+Clozapine	Placebo+Clozapine	-0.043	-0.0914	-0.1178	0.2775	0.398
Risperidone+Clozapine	Ziprasidone+Clozapine	-0.3014	-0.6083	-0.6528	12.6245	0.1318
Sertindole+Clozapine	Placebo+Clozapine	0	0	0	0	1
Sulpiride+Clozapine	Placebo+Clozapine	0	0	--	0	1
Duloxetine+Clozapine	Placebo+Clozapine	0	0	--	0	1
Fluoxetine+Clozapine	Placebo+Clozapine	0	0	--	0	1
*Mirtazapine+Clozapine	Placebo+Clozapine	0	0	Influential	0	1
Lamotrigine+Clozapine	Placebo+Clozapine	0.716	1.5101	1.6847	130.6702	0.1965
Lamotrigine+Clozapine	Placebo+Clozapine	-0.9129	-1.932	-2.3198	272.6994	0.3064
Topiramate+Clozapine	Placebo+Clozapine	0	0	--	0	1
Memantine+Clozapine	Placebo+Clozapine	0	0	--	0	1
Glycine+Clozapine	Placebo+Clozapine	0	0	0	0	1
Sarcosine+Clozapine	Placebo+Clozapine	0	0	0	0	1
Minocycline+Clozapine	Placebo+Clozapine	0	0	0	0	1
Ginkgo_Biloba+Clozapine	Placebo+Clozapine	0	0	0	0	1
rTMS+Clozapine	Placebo+Clozapine	0.7495	1.5085	2.1539	20.5668	0.5095
ECT+Clozapine	Placebo+Clozapine	0	0	--	0	1
CBT+Clozapine	Placebo+Clozapine	0	0	0	0	1
Aripiprazole+Clozapine	Placebo+Clozapine	0.2241	0.4771	1.5101	12.0581	0.9002
rTMS+Clozapine	Placebo+Clozapine	-0.7526	-1.5117	-2.1178	21.3632	0.4905
Lamotrigine+Clozapine	Placebo+Clozapine	0.2009	0.4261	0.6008	33.3773	0.4971
D-Serine+Clozapine	Placebo+Clozapine	-1.2414	-2.5722	-3.5084	142.0983	0.4625
D-Serine+Clozapine	Placebo+Clozapine	1.2321	2.5626	3.7683	122.2551	0.5375
Ampakine+Clozapine	Placebo+Clozapine	0	0	0	0	1
Risperidone+Clozapine	Placebo+Clozapine	0.3562	0.753	0.8128	53.1847	0.1416
Risperidone+Clozapine	Placebo+Clozapine	-0.2728	-0.5708	-0.5882	5.6278	0.0582



Ziprasidone+Clozapine	Placebo+Clozapine	0.2747	0.5808	1.7093	1.6786	0.8846
Pimozide+Clozapine	Placebo+Clozapine	-0.0583	-0.1223	-0.1384	1.2645	0.2188

Abbreviation: CBT, cognitive behavioral treatment; ECT, electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation.

\*: an influential study.

**eTable 9. Outlier and influential detection measures for acceptability**

Treatment 1	Treatment 2	Raw residual	Standardized residual	Studentized residual	Mahalanobis distance	Leverage
Aripiprazole+Clozapine	Placebo+Clozapine	-0.389	-0.5018	-0.5607	0.2518	0.199
Aripiprazole+Clozapine	Placebo+Clozapine	0.2057	0.3253	0.3885	0.1058	0.299
Amisulpride+Clozapine	Placebo+Clozapine	0	0	0	0	1
Pimozide+Clozapine	Placebo+Clozapine	-0.2293	-0.3389	-0.8658	0.1149	0.8468
Risperidone+Clozapine	Placebo+Clozapine	-0.4337	-0.5316	-0.6109	0.2826	0.2428
Risperidone+Clozapine	Placebo+Clozapine	-0.6149	-0.5126	-0.544	0.2627	0.1123
Risperidone+Clozapine	Placebo+Clozapine	0.3212	0.6059	0.9296	0.3671	0.5752
Risperidone+Clozapine	Ziprasidone+Clozapine	0.1178	0.087	0.1014	0.0076	0.2638
*Sertindole+Clozapine	Placebo+Clozapine	0	0	Influentia l	0	1
Duloxetine+Clozapine	Placebo+Clozapine	0	0	0	0	1
*Fluoxetine+Clozapine	Placebo+Clozapine	0	0	Influentia l	0	1
*Mirtazapine+Clozapine	Placebo+Clozapine	0	0	Influentia l	0	1
Lamotrigine+Clozapine	Placebo+Clozapine	0.8184	0.5123	0.5312	0.2624	0.07
Lamotrigine+Clozapine	Placebo+Clozapine	0.1914	0.2838	0.3641	0.0805	0.3925
*Topiramate+Clozapine	Placebo+Clozapine	0	0	Influentia l	0	1
Memantine+Clozapine	Placebo+Clozapine	0	0	0	0	1
Glycine+Clozapine	Placebo+Clozapine	0	0	--	0	1
Minocycline+Clozapine	Placebo+Clozapine	0	0	0	0	1
Ginkgo_Biloba+Clozapine	Placebo+Clozapine	0	0	--	0	1
*ECT+Clozapine	Placebo+Clozapine	0	0	Influentia l	0	1
CBT+Clozapine	Placebo+Clozapine	0	0	--	0	1
Aripiprazole+Clozapine	Placebo+Clozapine	0.0317	0.0649	0.092	0.0042	0.502
rTMS+Clozapine	rTMS+Clozapine	0	0	0	0	1
Lamotrigine+Clozapine	Placebo+Clozapine	-0.2463	-0.4273	-0.6284	0.1826	0.5375
D-Serine+Clozapine	Placebo+Clozapine	0	0	--	0	1
*Ampakine+Clozapine	Placebo+Clozapine	0	0	Influentia l	0	1
Ziprasidone+Clozapine	Placebo+Clozapine	-0.0311	-0.0447	-0.1014	0.002	0.8059
Pimozide+Clozapine	Placebo+Clozapine	1.2669	0.7967	0.8658	0.6347	0.1532

Abbreviation: CBT, cognitive behavioral treatment; ECT, electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation.

\*: an influential study.

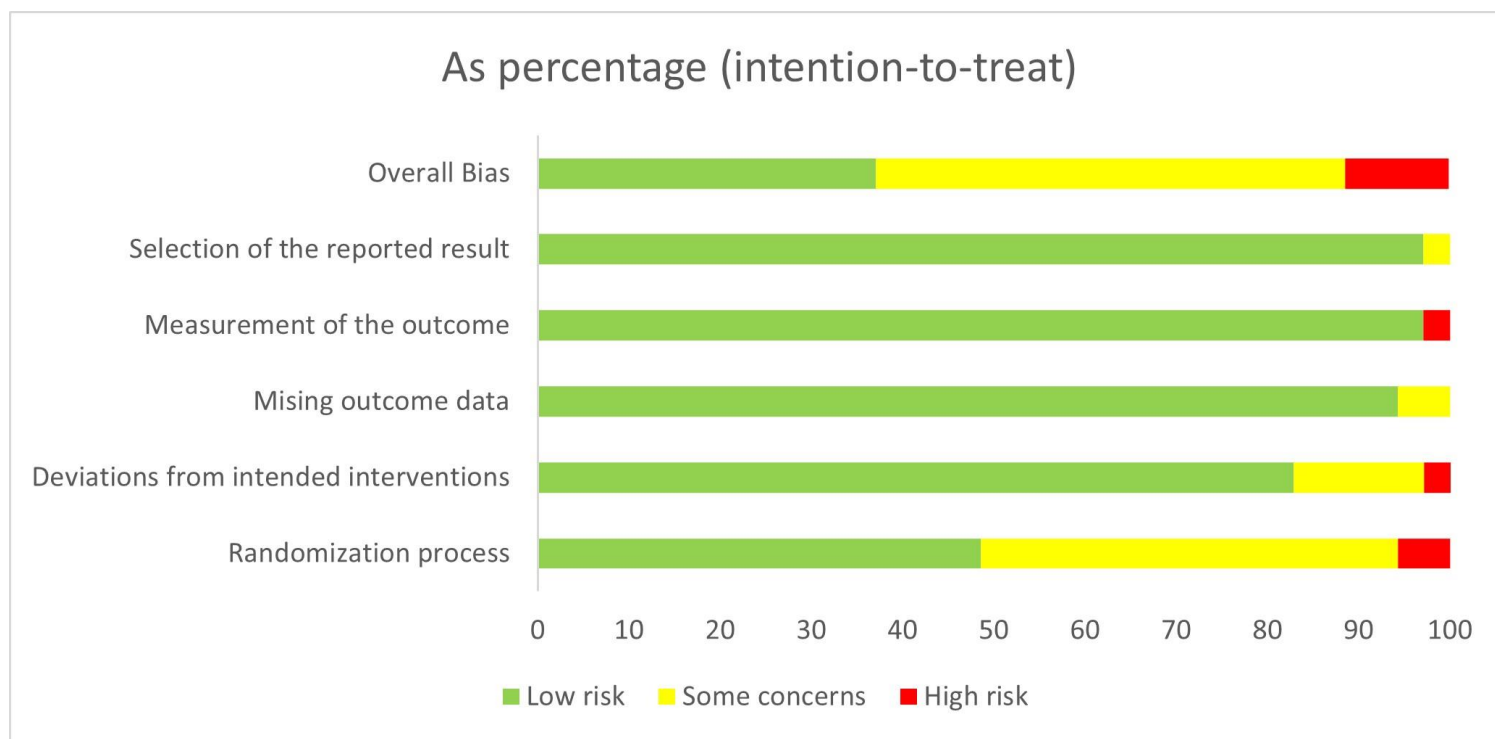
**eFigure 1. Risk of bias for all enrolled studies**

Study ID	Experimental	Comparator	Outcome	D1	D2	D3	D4	D5	Overall	
Chang 2008	Aripiprazole	PLA	Effectiveness	+	+	+	+	+	+	+
Muscatello 2011a	Aripiprazole	PLA	Effectiveness	+	!	+	+	+	!	!
Barnes 2017	Amisulpride	PLA	Effectiveness	+	+	+	+	!	!	+
Genc 2007	Amisulpride	Quetiapine	Effectiveness	!	-	+	+	+	-	-
Friedman 2011	Pimozide	PLA	Effectiveness	!	+	+	+	+	!	D1
Freudenreich 2007	Risperidone	PLA	Effectiveness	+	+	+	+	+	+	D2
Honer 2006	Risperidone	PLA	Effectiveness	+	+	+	+	+	+	D3
Weiner 2010	Risperidone	PLA	Effectiveness	!	+	+	+	+	!	D4
Zink 2009	Risperidone	Ziprasidone	Effectiveness	!	+	+	-	+	-	D5
Nielsen 2012	Sertindole	PLA	Effectiveness	+	+	+	+	+	+	
Shiloh 1997	Sulpiride	PLA	Effectiveness	-	+	+	+	+	-	
Mico 2011	Duloxetine	PLA	Effectiveness	+	+	+	+	+	+	
Buchanan 1996	Fluoxetine	PLA	Effectiveness	!	!	+	+	+	!	
Zoccali 2004	Mirtazapine	PLA	Effectiveness	!	!	+	+	+	!	
Vayisoglu 2013	Lamotrigine	PLA	Effectiveness	+	+	+	+	+	+	
Zoccali 2007	Lamotrigine	PLA	Effectiveness	+	+	+	+	+	+	
Muscatello 2011b	Topiramate	NA	Effectiveness	+	+	!	+	+	!	
Evins 2000	Glycine	PLA	Effectiveness	!	+	+	+	+	!	
De Lucena 2009	Memantine	PLA	Effectiveness	!	+	+	+	+	!	
Lane 2006	Sarcosine	PLA	Effectiveness	+	+	+	+	+	+	
Kelly 2015	Minocycline	PLA	Effectiveness	+	+	+	+	+	+	
Doruk 2008	Ginkgo biloba	PLA	Effectiveness	!	+	+	+	+	!	
De Jesus 2011	rTMS	PLA	Effectiveness	+	!	+	+	+	!	
Petrides 2015	ECT	PLA	Effectiveness	!	+	+	+	+	!	
Barretto 2009	CBT	OLA	Effectiveness	-	+	+	+	+	-	
Fleischhacker 2010	Aripiprazole	PLA	Effectiveness	+	+	+	+	+	+	
Wagner 2019	rTMS	PLA	Effectiveness	+	+	+	+	+	+	
Tiihonen 2003	Lamotrigine	PLA	Effectiveness	+	+	+	+	+	+	
Tsai 1999	D-Serine	PLA	Effectiveness	!	+	+	+	+	!	
Goff 1999	D-Serine	PLA	Effectiveness	!	+	!	+	+	!	
Goff 2001	Ampakine	PLA	Effectiveness	!	!	+	+	+	!	
Josiassen 2005	Risperidone	PLA	Effectiveness	!	+	+	+	+	!	
Yaycioglu 2005	Risperidone	PLA	Effectiveness	!	+	+	+	+	!	
Muscatello 2014	Ziprasidone	PLA	Effectiveness	+	+	+	+	+	+	
Gunduz-Bruce 2013	Pimozide	PLA	Effectiveness	!	+	+	+	+	!	

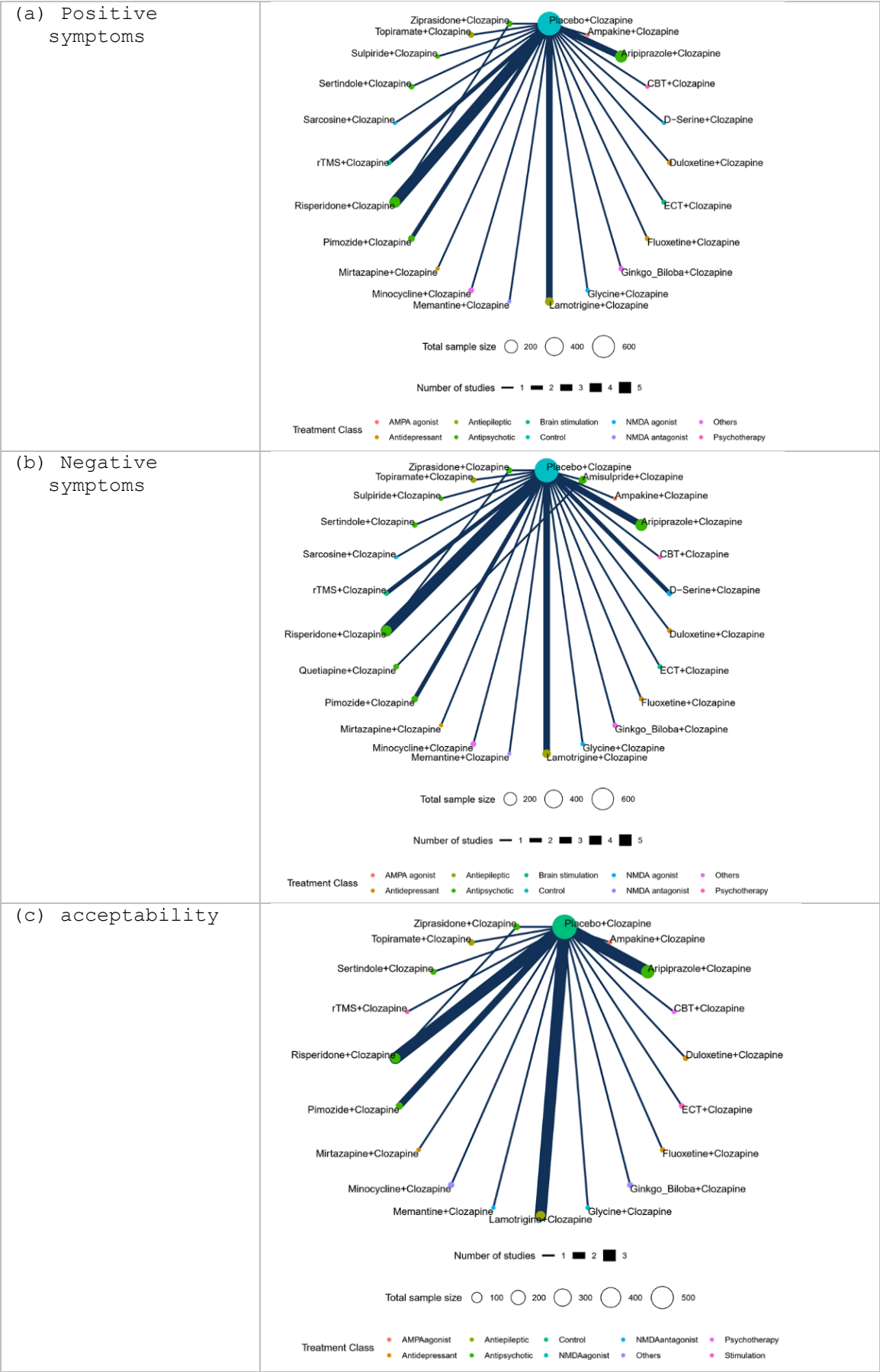
- + Low risk |
- ! Some concerns |
- High risk |

- D1 Randomisation process
- D2 Deviations from the intended interventions
- D3 Missing outcome data
- D4 Measurement of the outcome
- D5 Selection of the reported result

**eFigure 2. Summary of risk of bias**



**eFigure 3. Network diagram for positive and negative symptoms and acceptability**



Abbreviation: CBT, cognitive behavioral treatment; ECT, electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation

**eFigure 4. League table of positive symptoms of schizophrenia**

ECT + Clozapine	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.										
-4.38 [-5.32; -3.44]*	Memantine + Clozapine	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.										
-4.69 [-5.60; -3.78]*	-0.31 [-1.18; 0.57]	Topiramate + Clozapine	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.										
-4.69 [-5.62; -3.76]*	-0.31 [-1.21; 0.59]	-0.00 [-0.87; 0.87]	D-Serine + Clozapine	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.										
-4.82 [-5.73; -3.91]*	-0.44 [-1.31; 0.44]	-0.13 [-0.97; 0.72]	-0.13 [-1.00; 0.74]	Minocycline + Clozapine	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.										
-4.87 [-5.64; -4.10]*	-0.49 [-1.21; 0.24]	-0.18 [-0.87; 0.51]	-0.18 [-0.90; 0.54]	-0.05 [-0.74; 0.64]	Aripiprazole + Clozapine	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.										
-4.91 [-5.68; -4.14]*	-0.53 [-1.25; 0.20]	-0.22 [-0.91; 0.47]	-0.22 [-0.94; 0.50]	-0.09 [-0.78; 0.60]	-0.04 [-0.53; 0.45]	Lamotrigine + Clozapine	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.										
-4.93 [-5.85; -4.01]*	-0.55 [-1.44; 0.34]	-0.24 [-1.10; 0.62]	-0.24 [-1.12; 0.64]	-0.11 [-0.97; 0.75]	-0.06 [-0.77; 0.65]	-0.02 [-0.73; 0.68]	Mirtazapine + Clozapine	.	.	.	.	.	.	.	.	.	.	.	.	.	.										
-4.96 [-5.88; -4.04]*	-0.58 [-1.46; 0.31]	-0.27 [-1.13; 0.58]	-0.27 [-1.15; 0.61]	-0.14 [-1.00; 0.71]	-0.09 [-0.79; 0.61]	-0.05 [-0.76; 0.65]	-0.03 [-0.90; 0.84]	Sulpiride + Clozapine	.	.	.	.	.	.	.	.	.	.	.	.	.										
-4.97 [-5.88; -4.06]*	-0.59 [-1.47; 0.29]	-0.28 [-1.13; 0.56]	-0.28 [-1.15; 0.59]	-0.15 [-1.00; 0.69]	-0.10 [-0.79; 0.59]	-0.06 [-0.76; 0.63]	-0.04 [-0.90; 0.82]	-0.01 [-0.87; 0.85]	Duloxetine + Clozapine	.	.	.	.	.	.	.	.	.	.	.	.										
-5.06 [-5.98; -4.15]*	-0.68 [-1.56; 0.19]	-0.38 [-1.23; 0.47]	-0.38 [-1.25; 0.50]	-0.25 [-1.10; 0.60]	-0.20 [-0.89; 0.50]	-0.16 [-0.86; 0.54]	-0.13 [-1.00; 0.73]	-0.11 [-0.97; 0.75]	-0.09 [-0.95; 0.76]	Fluoxetine + Clozapine	.	.	.	.	.	.	.	.	.	.	.										
-5.07 [-5.89; -4.25]*	-0.69 [-1.47; 0.09]	-0.38 [-1.13; 0.37]	-0.38 [-1.16; 0.40]	-0.25 [-1.01; 0.50]	-0.20 [-0.77; 0.37]	-0.16 [-0.74; 0.41]	-0.14 [-0.91; 0.63]	-0.11 [-0.88; 0.65]	-0.10 [-0.85; 0.65]	-0.01 [-0.76; 0.75]	rTMS + Clozapine	.	.	.	.	.	.	.	.	.	.										
-5.09 [-6.03; -4.15]*	-0.71 [-1.62; 0.19]	-0.41 [-1.28; 0.47]	-0.40 [-1.30; 0.50]	-0.28 [-1.15; 0.60]	-0.22 [-0.95; 0.51]	-0.19 [-0.92; 0.54]	-0.16 [-1.05; 0.73]	-0.13 [-1.02; 0.75]	-0.12 [-1.00; 0.76]	-0.03 [-0.91; 0.86]	-0.02 [-0.81; 0.77]	Ampakine + Clozapine	.	.	.	.	.	.	.	.	.	.									
-5.14 [-6.07; -4.20]*	-0.76 [-1.66; 0.14]	-0.45 [-1.32; 0.42]	-0.45 [-1.34; 0.45]	-0.32 [-1.19; 0.55]	-0.27 [-0.99; 0.46]	-0.23 [-0.96; 0.49]	-0.21 [-1.09; 0.68]	-0.18 [-1.06; 0.71]	-0.17 [-1.04; 0.71]	-0.07 [-0.95; 0.81]	-0.07 [-0.85; 0.72]	-0.04 [-0.95; 0.86]	CBT + Clozapine	.	.	.	.	.	.	.	.	.	.								
-5.15 [-5.89; -4.42]*	-0.77 [-1.46; 0.09]*	-0.47 [-1.12; 0.18]	-0.47 [-1.15; 0.22]	-0.34 [-0.99; 0.31]	-0.29 [-0.72; 0.15]	-0.25 [-0.68; 0.18]	-0.22 [-0.89; 0.45]	-0.20 [-0.86; 0.47]	-0.18 [-0.84; 0.47]	-0.09 [-0.75; 0.57]	-0.08 [-0.61; 0.44]	-0.06 [-0.76; 0.63]	-0.02 [-0.71; 0.67]	Risperidone + Clozapine	.	.	.	.	.	.	.	.	.	.							
-5.18 [-5.86; -4.49]*	-0.80 [-1.43; 0.16]*	-0.49 [-1.09; 0.11]	-0.49 [-1.12; 0.14]	-0.36 [-0.96; 0.24]	-0.31 [-0.65; 0.04]	-0.27 [-0.62; 0.08]	-0.25 [-0.86; 0.37]	-0.22 [-0.83; 0.39]	-0.21 [-0.81; 0.39]	-0.11 [-0.72; 0.49]	-0.11 [-0.56; 0.35]	-0.08 [-0.73; 0.56]	-0.04 [-0.68; 0.60]	-0.02 [-0.28; 0.24]	Placebo + Clozapine	.	.	.	.	.	.	.	.	.	.						
-5.21 [-6.04; -4.39]*	-0.83 [-1.62; 0.05]*	-0.53 [-1.28; 0.22]	-0.52 [-1.30; 0.25]	-0.40 [-1.15; 0.35]	-0.34 [-0.92; 0.23]	-0.31 [-0.88; 0.27]	-0.28 [-1.05; 0.49]	-0.26 [-1.02; 0.51]	-0.24 [-1.00; 0.51]	-0.15 [-0.91; 0.61]	-0.14 [-0.79; 0.50]	-0.12 [-0.91; 0.67]	-0.08 [-0.86; 0.71]	-0.06 [-0.52; 0.40]	-0.04 [-0.49; 0.42]	Ziprasidone + Clozapine	.	.	.	.	.	.	.	.	.	.					
-5.28 [-6.21; -4.35]*	-0.90 [-1.80; 0.01]*	-0.59 [-1.46; 0.27]	-0.59 [-1.48; 0.30]	-0.46 [-1.33; 0.40]	-0.41 [-1.13; 0.31]	-0.38 [-1.09; 0.34]	-0.35 [-1.23; 0.53]	-0.32 [-1.20; 0.56]	-0.31 [-1.18; 0.56]	-0.22 [-1.09; 0.66]	-0.21 [-0.99; 0.57]	-0.19 [-1.09; 0.71]	-0.14 [-1.04; 0.75]	-0.13 [-0.81; 0.56]	-0.10 [-0.73; 0.53]	-0.07 [-0.84; 0.71]	Sarcosine+Cl ozapine	.	.	.	.	.	.	.	.	.	.				
-5.28 [-6.19; -4.37]*	-0.90 [-1.78; 0.03]*	-0.60 [-1.44; 0.25]	-0.59 [-1.46; 0.28]	-0.47 [-1.31; 0.38]	-0.41 [-1.10; 0.28]	-0.38 [-1.07; 0.32]	-0.35 [-1.21; 0.51]	-0.32 [-1.18; 0.53]	-0.31 [-1.16; 0.54]	-0.22 [-1.07; 0.63]	-0.21 [-0.96; 0.54]	-0.19 [-1.07; 0.69]	-0.15 [-1.02; 0.73]	-0.13 [-0.78; 0.53]	-0.11 [-0.70; 0.49]	-0.07 [-0.82; 0.68]	-0.00 [-0.87; 0.87]	Ginkgo + Clozapine	.	.	.	.	.	.	.	.	.	.			
-5.34 [-6.15; -4.53]*	-0.96 [-1.73; 0.19]*	-0.65 [-1.39; 0.08]	-0.65 [-1.41; 0.12]	-0.52 [-1.26; 0.21]	-0.47 [-1.02; 0.08]	-0.43 [-0.99; 0.12]	-0.41 [-1.16; 0.35]	-0.38 [-1.13; 0.37]	-0.37 [-1.11; 0.37]	-0.27 [-1.02; 0.47]	-0.27 [-0.90; 0.36]	-0.25 [-1.02; 0.53]	-0.20 [-0.97; 0.57]	-0.18 [-0.69; 0.32]	-0.16 [-0.59; 0.27]	-0.13 [-0.75; 0.50]	-0.06 [-0.82; 0.71]	-0.06 [-0.80; 0.68]	Pimozide + Clozapine	.	.	.	.	.	.	.	.	.	.		
-5.44 [-6.36; -4.53]*	-1.06 [-1.94; 0.19]*	-0.76 [-1.60; 0.09]	-0.75 [-1.63; 0.12]	-0.63 [-1.47; 0.22]	-0.57 [-1.27; 0.12]	-0.54 [-1.23; 0.16]	-0.51 [-1.37; 0.35]	-0.49 [-1.34; 0.37]	-0.47 [-1.32; 0.38]	-0.38 [-1.23; 0.47]	-0.37 [-1.13; 0.38]	-0.35 [-1.23; 0.53]	-0.31 [-1.18; 0.57]	-0.29 [-0.94; 0.36]	-0.27 [-0.87; 0.33]	-0.23 [-0.98; 0.52]	-0.16 [-1.03; 0.71]	-0.16 [-1.01; 0.69]	-0.10 [-0.84; 0.63]	Sertindole + Clozapine	.	.	.	.	.	.	.	.	.	.	
-5.64 [-6.57; -4.72]*	-1.26 [-2.15; 0.38]*	-0.96 [-1.82; 0.10]*	-0.95 [-1.84; 0.07]*	-0.83 [-1.69; 0.03]	-0.77 [-1.48; 0.07]*	-0.74 [-1.45; 0.03]*	-0.71 [-1.59; 0.16]	-0.69 [-1.56; 0.18]	-0.67 [-1.54; 0.19]	-0.58 [-1.44; 0.29]	-0.57 [-1.34; 0.19]	-0.55 [-1.44; 0.34]	-0.51 [-1.39; 0.38]	-0.49 [-1.16; 0.18]	-0.47 [-1.08; 0.15]	-0.43 [-1.20; 0.34]	-0.36 [-1.24; 0.52]	-0.36 [-1.22; 0.50]	-0.30 [-1.06; 0.45]	-0.20 [-1.06; 0.66]	Glycine + Clozapine	.	.	.	.	.	.	.	.	.	.

Data are SMDs (95% CrI) in the column-defining treatment compared with the row-defining treatment. Negative values favour the column-defining treatment (order by rank from high to low).

Abbreviation: CBT, cognitive behavioral treatment; CI, confidence interval; ECT, electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation; SMD, standardized mean difference; SUCRA, surface under the cumulative ranking curve.

eFigure 5. League table of negative symptoms of schizophrenia

Memantine + Clozapine	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			
-0.11 [-1.56; 1.34]	Duloxetine + Clozapine	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			
-1.65 [-3.11; -0.20]*	-1.54 [-2.89; -0.19]*	Mirtazapine + Clozapine	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			
-2.73 [-4.18; -1.29]*	-2.62 [-3.96; -1.28]*	0.27]	CBT + Clozapine	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			
-2.85 [-4.28; -1.42]*	-2.74 [-4.06; -1.41]*	-1.20 [-2.53; 0.14]	-0.12 [-1.44; 1.20]	Topiramate + Clozapine	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			
-2.91 [-4.21; -1.61]*	-2.80 [-3.98; -1.63]*	-1.26 [-2.44; -0.07]*	-0.18 [-1.35; 0.99]	-0.06 [-1.22; 1.09]	Ziprasidone + Clozapine	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			
-3.04 [-4.48; -1.61]*	-2.93 [-4.26; -1.61]*	-1.39 [-2.72; -0.06]*	-0.31 [-1.63; 1.01]	-0.20 [-1.50; 1.11]	-0.13 [-1.29; 1.03]	Ginkgo + Clozapine	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			
-3.10 [-4.53; -1.67]*	-2.99 [-4.31; -1.67]*	-1.45 [-2.78; -0.12]*	-0.37 [-1.69; 0.95]	-0.25 [-1.56; 1.05]	-0.19 [-1.34; 0.97]	-0.06 [-1.36; 1.25]	Minocycline + Clozapine	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			
-3.11 [-4.55; -1.67]*	-3.00 [-4.33; -1.67]*	-1.45 [-2.79; -0.12]*	-0.38 [-1.70; 0.95]	-0.26 [-1.57; 1.05]	-0.20 [-1.36; 0.97]	-0.06 [-1.38; 1.25]	-0.01 [-1.32; 1.31]	Sulpiride + Clozapine	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			
-3.11 [-4.55; -1.68]*	-3.00 [-4.33; -1.68]*	-1.46 [-2.79; -0.13]*	-0.38 [-1.70; 0.94]	-0.26 [-1.57; 1.04]	-0.20 [-1.36; 0.96]	-0.07 [-1.38; 1.24]	-0.01 [-1.32; 1.30]	-0.00 [-1.32; 1.31]	ECT + Clozapine	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			
-3.14 [-4.36; -1.92]*	-3.03 [-4.12; -1.94]*	-1.49 [-2.58; -0.39]*	-0.41 [-1.49; 0.68]	-0.29 [-1.36; 0.78]	-0.23 [-1.10; 0.65]	-0.09 [-1.16; 0.97]	-0.04 [-1.11; 1.03]	-0.03 [-1.11; 1.04]	Aripiprazole + Clozapine	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			
-3.15 [-4.31; -1.98]*	-3.04 [-4.07; -2.01]*	-1.50 [-2.53; -0.46]*	-0.42 [-1.44; 0.61]	-0.30 [-1.31; 0.71]	-0.24 [-0.94; 0.47]	-0.10 [-1.11; 0.90]	-0.05 [-1.05; 0.96]	-0.04 [-1.06; 0.97]	-0.04 [-1.04; 0.97]	-0.01 [-0.67; 0.66]	0.01 [-0.79; 0.80]	Risperidone + Clozapine	.	.	.	.	.	.	.	.	.	.	.	.				
-3.14 [-4.44; -1.85]*	-3.03 [-4.21; -1.86]*	-1.49 [-2.67; -0.31]*	-0.41 [-1.58; 0.76]	-0.29 [-1.45; 0.86]	-0.23 [-1.21; 0.75]	-0.10 [-1.25; 1.06]	-0.04 [-1.20; 1.11]	-0.03 [-1.20; 1.13]	-0.03 [-1.19; 1.12]	-0.00 [-0.87; 0.80]	0.80]	rTMS + Clozapine	.	.	.	.	.	.	.	.	.	.	.	.				
-3.15 [-4.37; -1.93]*	-3.04 [-4.13; -1.95]*	-1.50 [-2.59; -0.40]*	-0.42 [-1.50; 0.67]	-0.30 [-1.37; 0.77]	-0.24 [-1.11; 0.64]	-0.10 [-1.17; 0.97]	-0.05 [-1.12; 1.02]	-0.04 [-1.12; 1.04]	-0.04 [-1.11; 1.03]	-0.01 [-0.76; 0.75]	-0.00 [-0.67; 0.67]	-0.01 [-0.88; 0.87]	Lamotrigine + Clozapine	.	.	.	.	.	.	.	.	.	.	.				
-3.17 [-4.60; -1.73]*	-3.06 [-4.38; -1.73]*	-1.51 [-2.85; -0.18]*	-0.43 [-1.76; 0.89]	-0.32 [-1.63; 0.99]	-0.25 [-1.42; 0.91]	-0.12 [-1.43; 1.19]	-0.07 [-1.38; 1.24]	-0.06 [-1.38; 1.26]	-0.06 [-1.37; 1.26]	-0.03 [-1.10; 1.04]	-0.02 [-1.03; 0.99]	-0.02 [-1.18; 1.13]	-0.02 [-1.09; 1.05]	Fluoxetine + Clozapine	.	.	.	.	.	.	.	.	.	.				
-3.19 [-4.63; -1.75]*	-3.08 [-4.42; -1.75]*	-1.54 [-2.88; -0.20]*	-0.46 [-1.79; 0.87]	-0.35 [-1.66; 0.97]	-0.28 [-1.45; 0.88]	-0.15 [-1.46; 1.17]	-0.09 [-1.41; 1.22]	-0.09 [-1.41; 1.24]	-0.08 [-1.40; 1.23]	-0.05 [-1.13; 1.02]	-0.05 [-1.06; 0.97]	-0.05 [-1.21; 1.11]	-0.05 [-1.12; 1.03]	-0.03 [-1.34; 1.29]	Glycine + Clozapine	.	.	.	.	.	.	.	.	.				
-3.28 [-4.72; -1.85]*	-3.17 [-4.50; -1.85]*	-1.63 [-2.96; -0.30]*	-0.55 [-1.87; 0.77]	-0.43 [-1.74; 0.87]	-0.37 [-1.53; 0.79]	-0.24 [-1.55; 1.07]	-0.18 [-1.49; 1.12]	-0.17 [-1.49; 1.14]	-0.17 [-1.48; 1.14]	-0.14 [-1.21; 0.92]	-0.13 [-1.14; 0.87]	-0.14 [-1.29; 1.01]	-0.13 [-1.20; 0.93]	-0.12 [-1.43; 1.19]	-0.09 [-1.40; 1.22]	Amisulpride + Clozapine	.	.	.	.	.	.	.	.				
-3.42 [-4.87; -1.97]*	-3.31 [-4.65; -1.97]*	-1.77 [-3.12; -0.42]*	-0.69 [-2.03; 0.65]	-0.57 [-1.90; 0.75]	-0.51 [-1.69; 0.67]	-0.38 [-1.70; 0.95]	-0.32 [-1.65; 1.00]	-0.31 [-1.65; 1.02]	-0.31 [-1.64; 1.02]	-0.28 [-1.37; 0.81]	-0.27 [-1.30; 0.76]	-0.28 [-1.45; 0.89]	-0.27 [-1.36; 0.82]	-0.26 [-1.58; 1.07]	-0.23 [-1.56; 1.10]	-0.14 [-1.46; 1.19]	Sarcosine + Clozapine	.	.	.	.	.	.	.				
-3.38 [-4.47; -2.28]*	-3.27 [-4.22; -2.32]*	-1.73 [-2.68; -0.77]*	-0.65 [-1.59; 0.30]	-0.53 [-1.45; 0.39]	-0.47 [-1.16; 0.23]	-0.33 [-1.26; 0.59]	-0.28 [-1.20; 0.65]	-0.27 [-1.20; 0.66]	-0.27 [-1.19; 0.66]	-0.24 [-0.77; 0.29]	-0.23 [-0.63; 0.17]	-0.24 [-0.93; 0.45]	-0.23 [-0.76; 0.31]	-0.21 [-1.14; 0.72]	-0.18 [-1.12; 0.75]	-0.10 [-1.02; 0.83]	0.04 [-0.91; 0.99]	Placebo + Clozapine	.	.	.	.	.	.				
-3.51 [-4.94; -2.08]*	-3.40 [-4.73; -2.08]*	-1.86 [-3.19; -0.53]*	-0.78 [-2.10; 0.54]	-0.66 [-1.97; 0.64]	-0.60 [-1.76; 0.56]	-0.47 [-1.78; 0.84]	-0.41 [-1.72; 0.90]	-0.40 [-1.72; 0.91]	-0.40 [-1.71; 0.91]	-0.37 [-1.52; 0.70]	-0.36 [-1.37; 0.64]	-0.37 [-1.52; 0.78]	-0.36 [-1.43; 0.71]	-0.34 [-1.66; 0.97]	-0.32 [-1.63; 1.00]	-0.23 [-1.54; 1.08]	-0.09 [-1.41; 1.24]	-0.13 [-1.06; 0.79]	Sertindole + Clozapine	.	.	.	.	.				
-3.60 [-5.31; -1.90]*	-3.49 [-5.11; -1.88]*	-1.95 [-3.57; -0.33]*	-0.87 [-2.48; 0.74]	-0.75 [-2.35; 0.85]	-0.69 [-2.17; 0.79]	-0.56 [-2.16; 1.05]	-0.50 [-2.10; 1.10]	-0.49 [-2.10; 1.11]	-0.49 [-2.09; 1.11]	-0.46 [-1.87; 0.95]	-0.45 [-1.82; 0.91]	-0.46 [-1.94; 1.02]	-0.45 [-1.86; 0.96]	-0.43 [-2.04; 1.17]	-0.41 [-2.01; 1.20]	-0.32 [-1.24; 0.61]	-0.18 [-1.79; 1.44]	-0.22 [-1.53; 1.08]	-0.09 [-1.69; 1.51]	Quetiapine + Clozapine	.	.	.	.	.			
-3.73 [-5.00; -2.45]*	-3.62 [-4.77; -2.46]*	-2.07 [-3.23; -0.91]*	-0.99 [-2.14; 0.16]	-0.88 [-2.01; 0.26]	-0.81 [-1.77; 0.15]	-0.68 [-1.82; 0.45]	-0.63 [-1.76; 0.51]	-0.62 [-1.76; 0.52]	-0.61 [-1.75; 0.52]	-0.59 [-1.43; 0.26]	-0.58 [-1.34; 0.19]	-0.58 [-1.54; 0.37]	-0.58 [-1.42; 0.27]	-0.56 [-1.70; 0.58]	-0.53 [-1.67; 0.61]	-0.44 [-1.58; 0.69]	-0.30 [-1.46; 0.85]	-0.35 [-1.00; 0.31]	-0.21 [-1.35; 0.92]	-0.12 [-1.59; 1.34]	Pimozide + Clozapine	.	.	.	.	.		
-4.21 [-5.49; -2.92]*	-4.10 [-5.26; -2.94]*	-2.55 [-3.72; -1.39]*	-1.48 [-2.63; -0.32]*	-1.36 [-2.50; -0.22]*	-1.29 [-2.26; -0.33]*	-1.16 [-2.30; -0.02]*	-1.11 [-2.25; 0.03]	-1.10 [-2.25; 0.05]	-1.10 [-2.24; 0.05]	-1.07 [-1.92; -0.21]*	-1.06 [-1.84; -0.28]*	-1.07 [-2.02; -0.11]*	-1.06 [-1.91; -0.20]*	-1.04 [-2.18; 0.10]	-1.01 [-2.16; 0.13]	-0.92 [-2.06; 0.22]	-0.79 [-1.95; 0.37]	-0.83 [-1.50; -0.16]*	-0.70 [-1.84; 0.44]	-0.61 [-2.07; 0.86]	-0.48 [-1.42; 0.45]	D-Serine + Clozapine	.	.	.	.	.	
-4.37 [-5.85; -2.89]*	-4.26 [-5.63; -2.89]*	-2.72 [-4.10; -1.34]*	-1.64 [-3.01; -0.27]*	-1.52 [-2.88; -0.16]*	-1.46 [-2.67; -0.24]*	-1.32 [-2.68; 0.03]	-1.27 [-2.63; 0.09]	-1.26 [-2.62; 0.10]	-1.26 [-2.62; 0.10]	-1.23 [-2.36; -0.10]*	-1.22 [-2.29; -0.15]*	-1.23 [-2.44; -0.02]*	-1.22 [-2.35; -0.09]*	-1.20 [-2.56; 0.16]	-1.18 [-2.54; 0.19]	-1.09 [-2.44; 0.27]	-0.95 [-2.32; 0.43]	-0.99 [-1.98; 0.00]	-0.86 [-2.21; 0.50]	-0.77 [-2.41; 0.87]	-0.64 [-1.83; 0.55]	-0.16 [-1.36; 1.04]	Ampakine + Clozapine	.	.	.	.	.

Data are SMDs (95% CrI) in the column-defining treatment compared with the row-defining treatment. Negative values favour the column-defining treatment (order by rank from high to low).

Abbreviation: CBT, cognitive behavioral treatment; CI, confidence interval; ECT, electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation; SMD, standardized mean difference.

eFigure 6. League table of acceptability

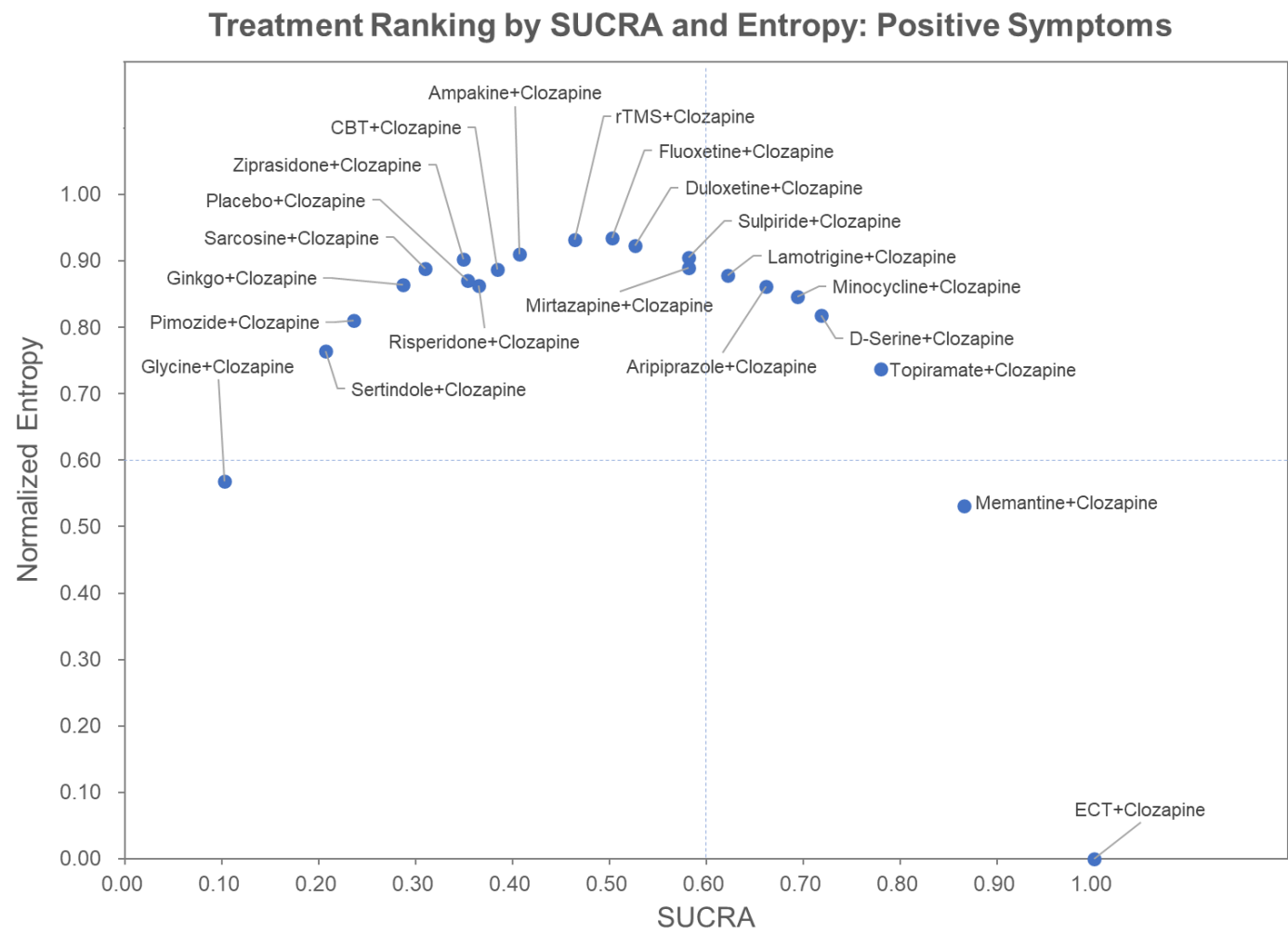
Amisulpride + Clozapine																							
1.07 [0.09; 13.15]	D-Serine + Clozapine																						
1.07 [0.04; 32.04]		Ampakine + Clozapine																					
0.76 [0.02; 23.38]	0.71 [0.02; 29.04]	0.71 [0.01; 55.81]	CBT + Clozapine																				
0.72 [0.02; 22.78]	0.67 [0.02; 28.22]	0.67 [0.01; 53.98]	0.94 [0.01; 76.84]	Fluoxetine + Clozapine																			
0.55 [0.04; 7.27]	0.51 [0.03; 9.80]	0.51 [0.01; 21.55]	0.72 [0.02; 30.76]	0.76 [0.02; 33.68]	rTMS + Clozapine																		
0.28 [0.04; 2.11]	0.27 [0.02; 3.10]	0.27 [0.01; 7.67]	0.37 [0.01; 10.97]	0.40 [0.01; 12.05]	6.49]	Duloxetine + Clozapine																	
0.28 [0.04; 2.15]	0.27 [0.02; 3.15]	0.27 [0.01; 7.76]	0.37 [0.01; 11.10]	0.40 [0.01; 12.19]	6.59]	1.00 [0.14; 7.01]	Sertindole + Clozapine																
0.25 [0.04; 1.70]	0.24 [0.02; 2.55]	0.24 [0.01; 6.44]	0.33 [0.01; 9.21]	0.35 [0.01; 10.13]	5.35]	0.46 [0.04; 5.35]	0.89 [0.14; 5.53]	0.89 [0.14; 5.64]	Pimozide + Clozapine														
0.21 [0.05; 0.93]*	0.20 [0.03; 1.54]	0.20 [0.01; 4.31]	0.28 [0.01; 6.18]	0.30 [0.01; 6.81]	3.27]	0.39 [0.05; 3.27]	0.75 [0.19; 2.93]	0.75 [0.19; 3.01]	0.85 [0.25; 2.86]	Placebo + Clozapine													
0.22 [0.03; 1.79]	0.21 [0.02; 2.60]	0.21 [0.01; 6.34]	0.29 [0.01; 9.06]	0.31 [0.01; 9.95]	5.44]	0.41 [0.03; 5.44]	0.79 [0.11; 5.87]	0.79 [0.10; 5.98]	0.89 [0.13; 6.02]	1.05 [0.24; 4.59]	ECT + Clozapine												
0.21 [0.02; 2.16]	0.20 [0.01; 3.01]	0.20 [0.01; 6.99]	0.28 [0.01; 9.98]	0.30 [0.01; 10.95]	6.27]	0.39 [0.02; 6.27]	0.75 [0.08; 7.11]	0.75 [0.08; 7.23]	0.85 [0.10; 7.37]	1.00 [0.17; 5.98]	0.95 [0.09; 9.64]	Mirtazapine + Clozapine											
0.19 [0.04; 0.98]*	0.17 [0.02; 1.55]	0.17 [0.01; 4.14]	0.24 [0.01; 5.93]	0.26 [0.01; 6.53]	3.27]	0.34 [0.04; 3.27]	0.65 [0.14; 3.15]	0.65 [0.13; 3.23]	0.74 [0.17; 3.14]	0.87 [0.17; 1.91]	0.83 [0.16; 4.39]	0.87 [0.12; 6.15]	Risperidone + Clozapine										
0.16 [0.02; 1.12]	0.15 [0.01; 1.67]	0.15 [0.01; 4.21]	0.22 [0.01; 6.03]	0.23 [0.01; 6.63]	3.50]	0.30 [0.03; 3.50]	0.58 [0.09; 3.62]	0.58 [0.09; 3.70]	0.65 [0.12; 3.68]	0.77 [0.23; 2.63]	0.73 [0.11; 4.98]	0.77 [0.09; 6.76]	0.89 [0.23; 3.47]	Ziprasidone + Clozapine									
0.16 [0.03; 0.87]*	0.15 [0.02; 1.37]	0.15 [0.01; 3.63]	0.21 [0.01; 5.20]	0.22 [0.01; 5.73]	2.88]	0.29 [0.03; 2.88]	0.57 [0.12; 2.79]	0.57 [0.11; 2.86]	0.64 [0.15; 2.79]	0.76 [0.33; 1.73]	0.72 [0.13; 3.89]	0.76 [0.11; 5.43]	0.87 [0.28; 2.72]	0.98 [0.22; 4.28]	Lamotrigine + Clozapine								
0.13 [0.03; 0.66]*	0.12 [0.01; 1.05]	0.12 [0.01; 2.85]	0.17 [0.01; 4.08]	0.18 [0.01; 4.50]	2.23]	0.24 [0.03; 2.23]	0.46 [0.10; 2.11]	0.46 [0.10; 2.16]	0.52 [0.13; 2.10]	0.61 [0.31; 1.21]	0.58 [0.12; 2.95]	0.61 [0.09; 4.16]	0.71 [0.25; 2.00]	0.79 [0.20; 3.21]	0.81 [0.28; 2.37]	Aripiprazole + Clozapine							
0.08 [0.00; 2.39]	0.07 [0.00; 2.96]	0.07 [0.00; 5.67]	0.10 [0.00; 8.08]	0.11 [0.00; 8.81]	6.05]	0.14 [0.00; 6.05]	0.27 [0.01; 8.04]	0.27 [0.01; 8.13]	0.30 [0.01; 8.57]	0.36 [0.02; 8.06]	0.34 [0.01; 10.65]	0.36 [0.01; 12.99]	0.41 [0.02; 10.21]	0.46 [0.02; 13.13]	0.47 [0.02; 11.88]	0.58 [0.02; 14.11]	Glycine + Clozapine						
0.12 [0.02; 0.64]*	0.11 [0.01; 1.00]	0.11 [0.00; 2.64]	0.15 [0.01; 3.78]	0.16 [0.01; 4.17]	2.10]	0.21 [0.02; 2.10]	0.41 [0.08; 2.05]	0.41 [0.08; 2.09]	0.46 [0.10; 2.05]	0.55 [0.23; 1.28]	0.52 [0.09; 2.84]	0.55 [0.08; 3.96]	0.63 [0.20; 2.01]	0.71 [0.16; 3.14]	0.72 [0.22; 2.38]	0.89 [0.30; 2.65]	1.52 [0.06; 38.48]	Topiramate + Clozapine					
0.06 [0.00; 1.98]	0.06 [0.00; 2.47]	0.06 [0.00; 4.74]	0.09 [0.00; 6.75]	0.09 [0.00; 7.36]	5.04]	0.12 [0.00; 5.04]	0.23 [0.01; 6.68]	0.23 [0.01; 6.76]	0.26 [0.01; 7.13]	0.30 [0.01; 6.68]	0.29 [0.01; 8.86]	0.30 [0.01; 10.81]	0.35 [0.01; 8.48]	0.39 [0.01; 10.91]	0.40 [0.02; 9.87]	0.50 [0.02; 11.71]	0.85 [0.01; 68.29]	0.56 [0.02; 13.77]	Memantine + Clozapine				
0.07 [0.01; 0.99]*	0.07 [0.00; 1.33]	0.07 [0.00; 2.89]	0.09 [0.00; 4.13]	0.10 [0.00; 4.52]	2.74]	0.13 [0.01; 2.74]	0.25 [0.02; 3.29]	0.25 [0.02; 3.34]	0.28 [0.02; 3.45]	0.33 [0.04; 2.97]	0.32 [0.02; 4.42]	0.33 [0.02; 5.63]	0.38 [0.04; 3.92]	0.43 [0.04; 5.28]	0.44 [0.04; 4.58]	0.54 [0.05; 5.36]	0.93 [0.02; 41.85]	0.61 [0.06; 6.41]	1.10 [0.02; 48.27]	Ginkgo + Clozapine			
0.05 [0.00; 1.39]	0.05 [0.00; 1.74]	0.05 [0.00; 3.39]	0.07 [0.00; 4.83]	0.07 [0.00; 5.27]	3.56]	0.09 [0.00; 3.56]	0.18 [0.01; 4.68]	0.18 [0.01; 4.73]	0.20 [0.01; 4.98]	0.23 [0.01; 4.64]	0.22 [0.01; 6.21]	0.23 [0.01; 7.60]	0.27 [0.01; 5.90]	0.30 [0.01; 7.62]	0.31 [0.01; 6.87]	0.38 [0.02; 8.14]	0.65 [0.01; 48.86]	0.43 [0.02; 9.59]	0.77 [0.01; 56.48]	0.70 [0.02; 28.45]	Minocycline + Clozapine		

Data are RRs (95% CrI) in the column-defining treatment compared with the row-defining treatment. For acceptability, RRs lower than 1 favour the column-defining treatment (order by rank from high to low).

Abbreviation: CBT, cognitive behavioral treatment; CI, confidence interval; ECT, electroconvulsive therapy; RR, risk ratio, rTMS, repetitive transcranial magnetic stimulation.



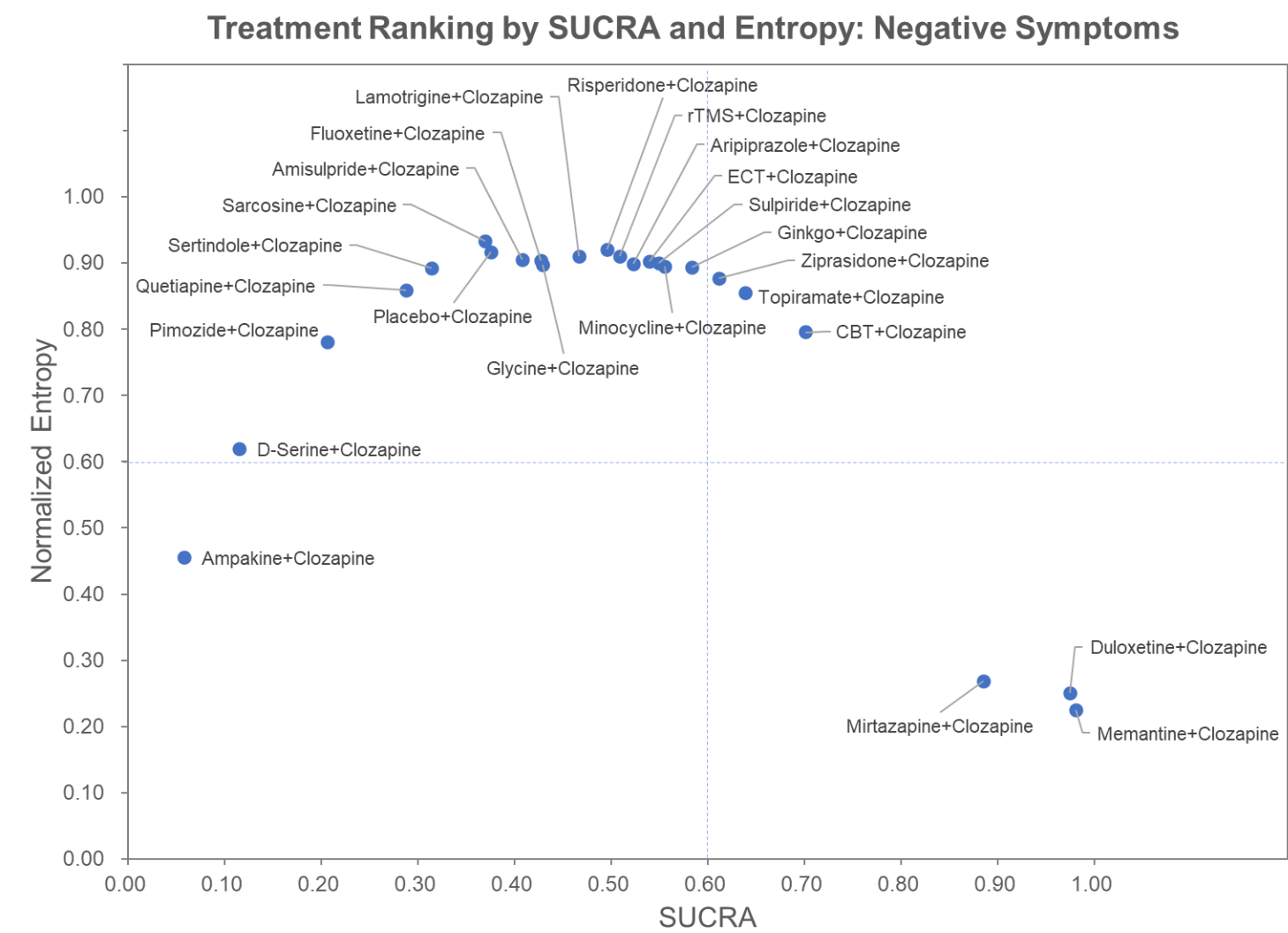
**eFigure 7. Scatter plot of SURA vs normalized entropy for the positive symptoms**



Abbreviation: CBT, cognitive behavioral treatment; ECT, electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation; SUCRA, surface under the cumulative ranking curve.

\* Higher value of SURCA indicates better ranking on acceptability, and lower value of normalized entropy indicates more certainty of treatment ranking by the value of SUCRA.

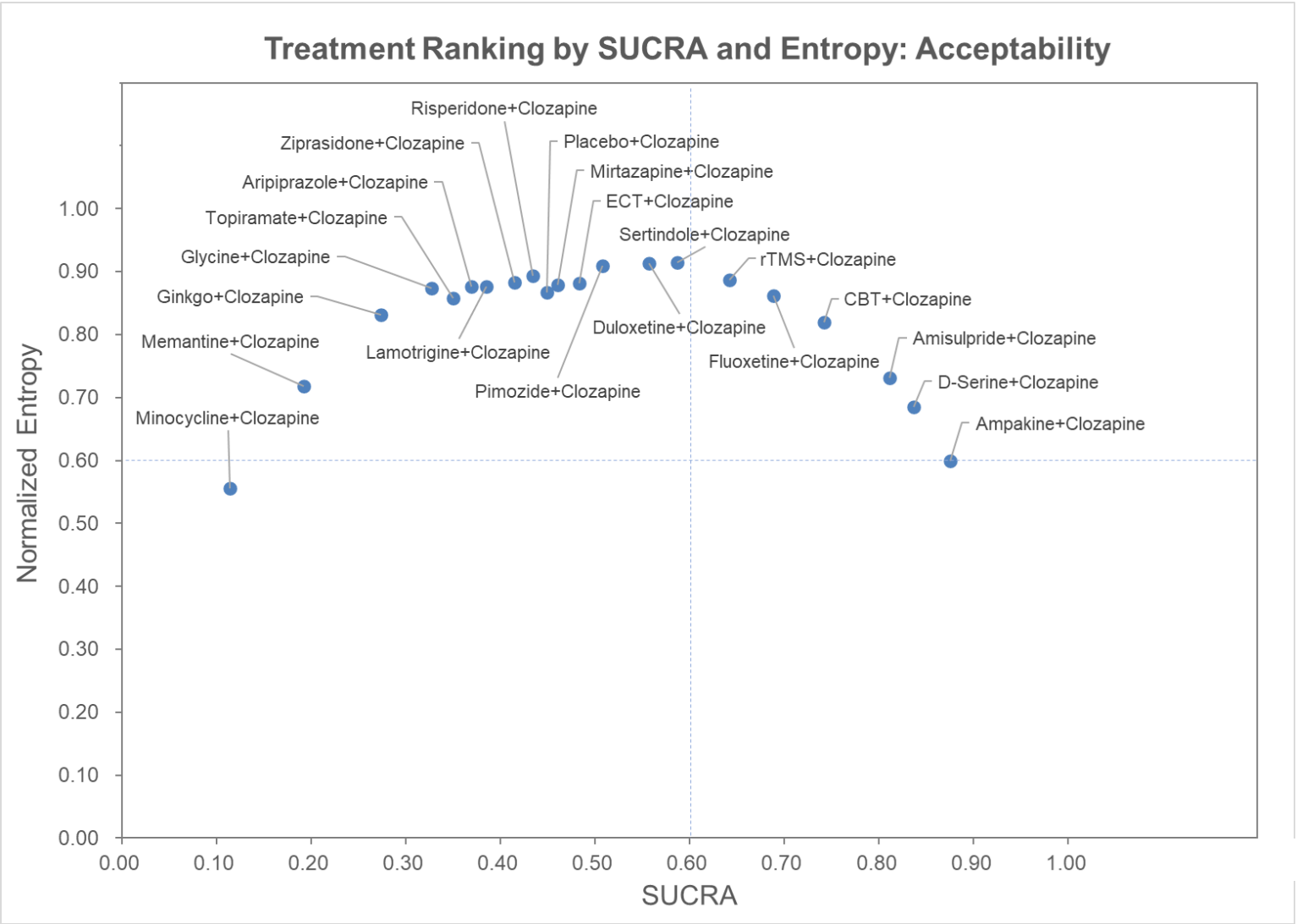
**eFigure 8. Scatter plot of SURA vs normalized entropy for the negative symptoms**



Abbreviation: CBT, cognitive behavioral treatment; ECT, electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation; SUCRA, surface under the cumulative ranking curve.

\* Higher value of SURCA indicates better ranking on acceptability, and lower value of normalized entropy indicates more certainty of treatment ranking by the value of SUCRA.

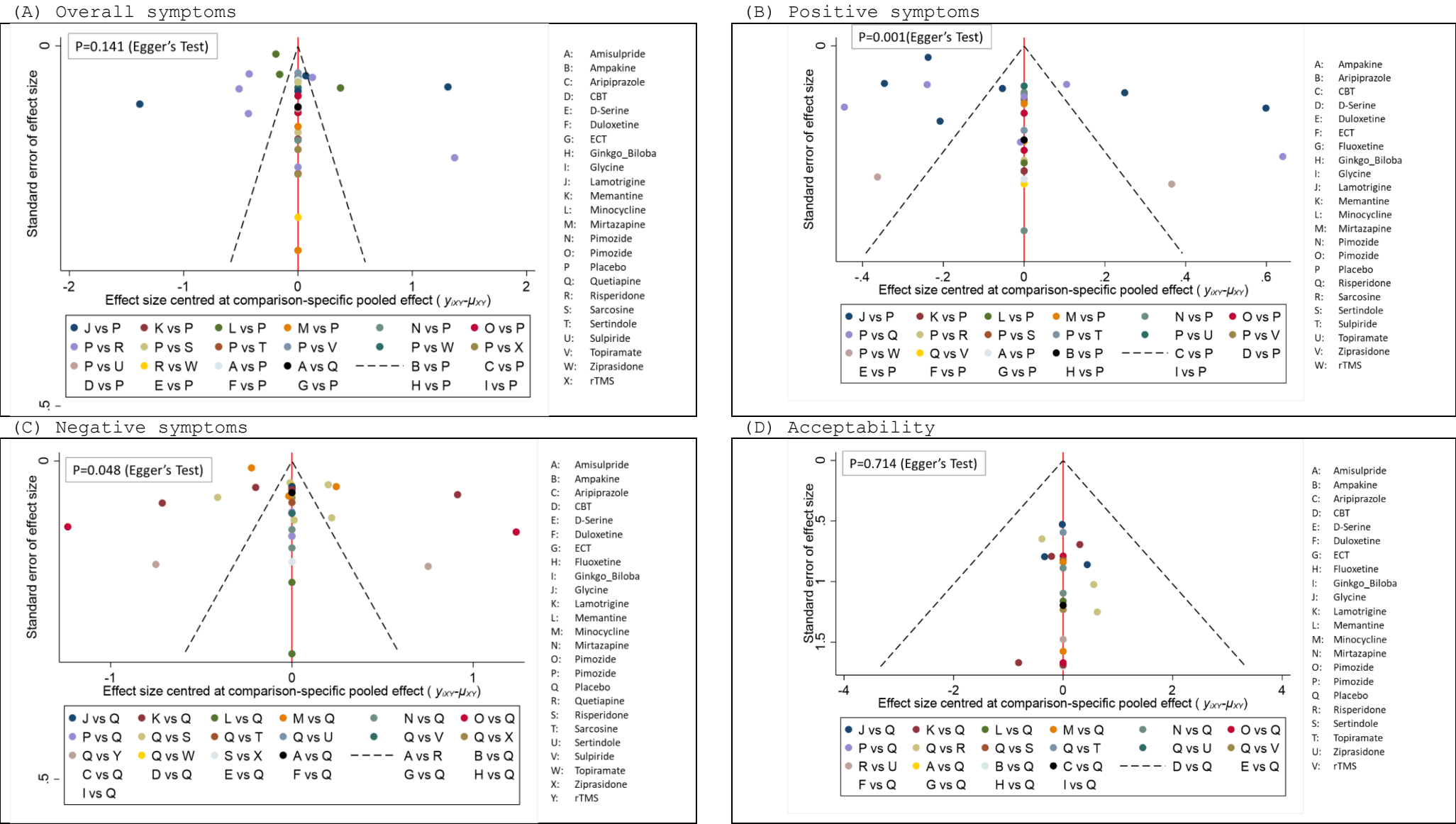
**eFigure 9. Scatter plot of SUCRA vs normalized entropy for the acceptability**



Abbreviation: CBT, cognitive behavioral treatment; ECT, electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation; SUCRA, surface under the cumulative ranking curve.

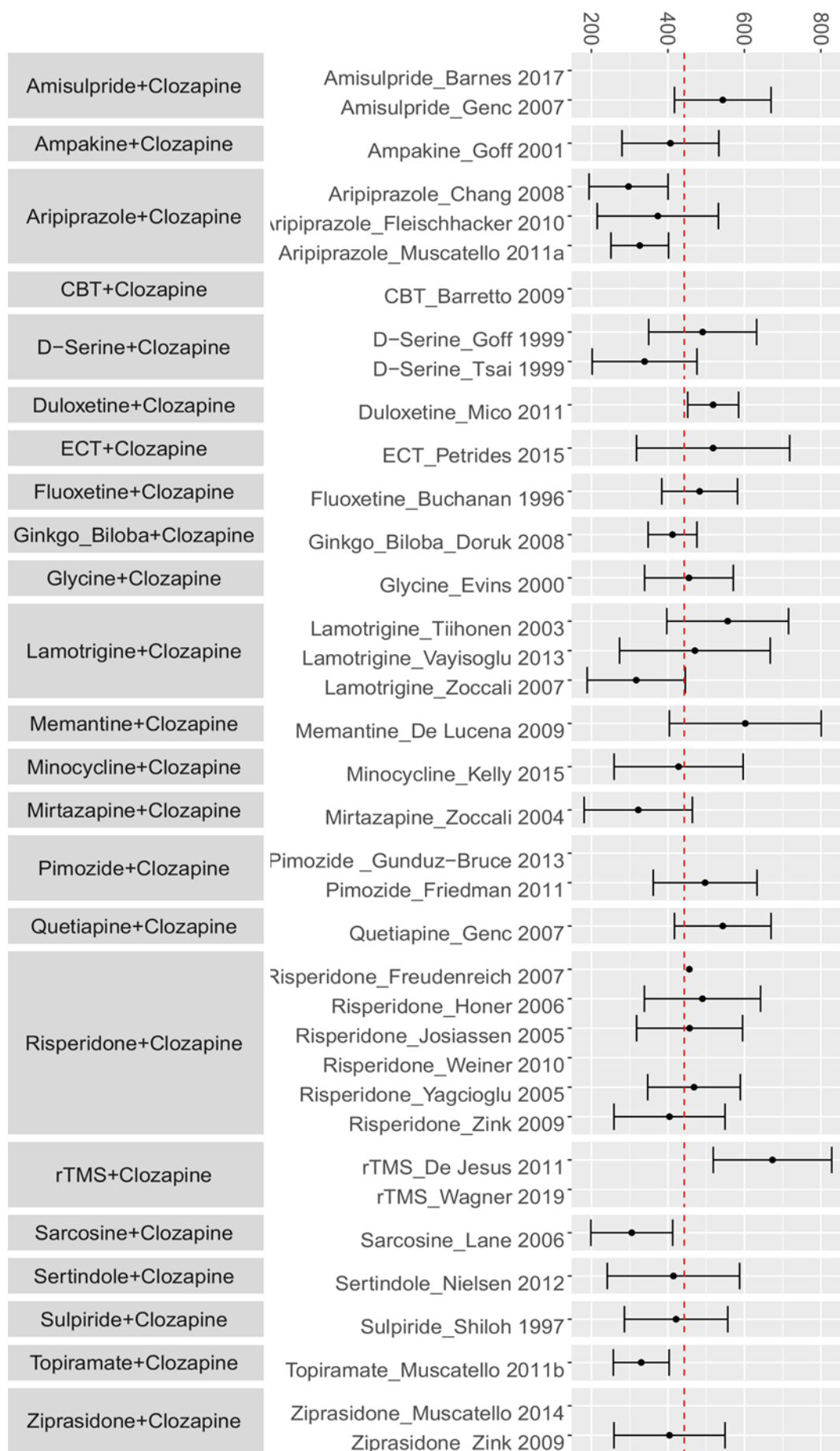
\* Higher value of SURCA indicates better ranking on acceptability, and lower value of normalized entropy indicates more certainty of treatment ranking by the value of SUCRA.

eFigure 10. Funnel plot and egger's test



Abbreviation: CBT, cognitive behavioral treatment; ECT, electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation

**eFigure 11. Distribution of daily dose of clozapine among the included studies**

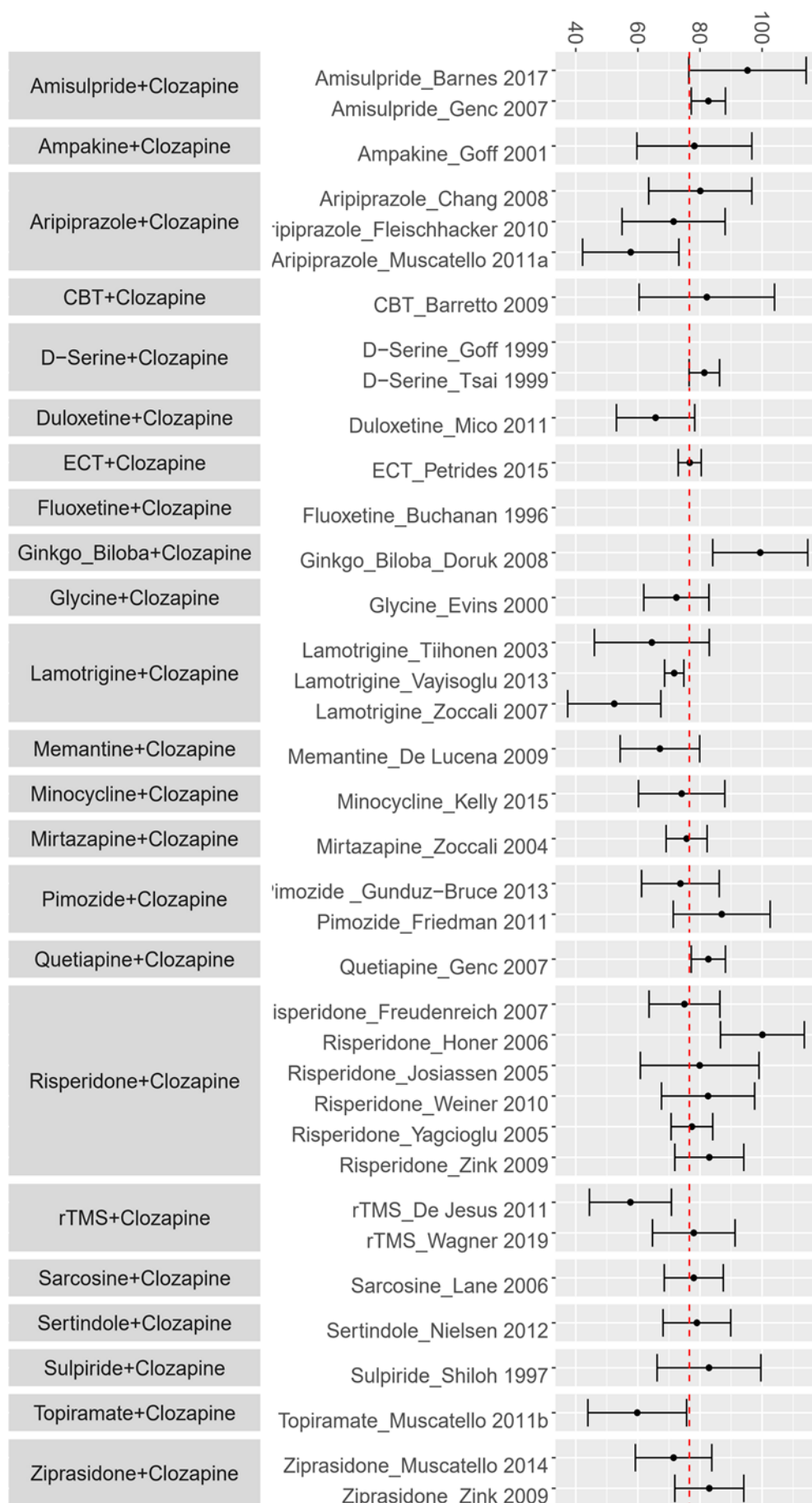


Daily dose: mg/per day

Abbreviation: CBT, cognitive behavioral treatment; ECT, electroconvulsive therapy; rTMS, repetitive

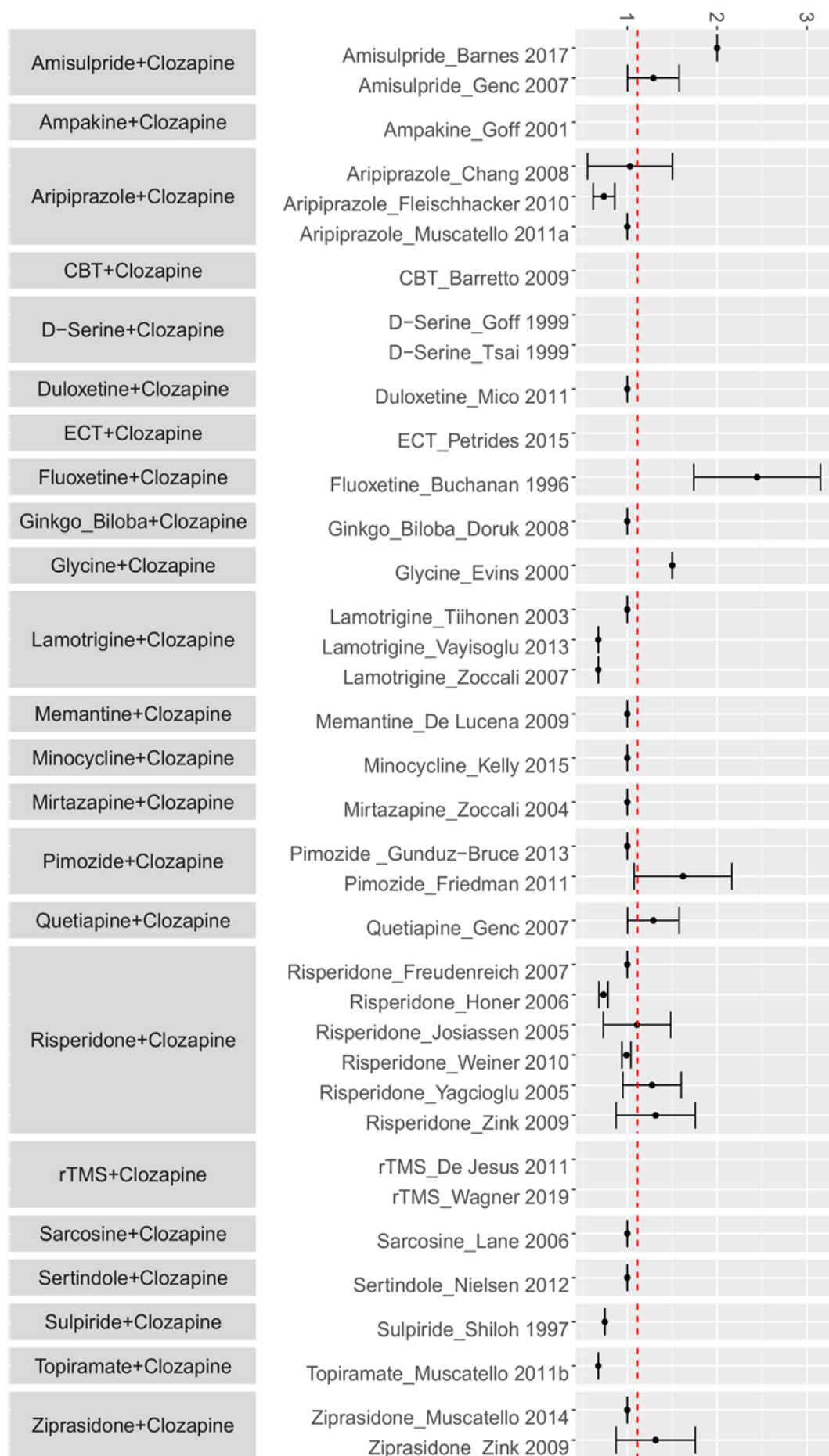
transcranial magnetic stimulation.

**eFigure 12. Distribution of baseline PANSS score among the included studies**



Abbreviation: CBT, cognitive behavioral treatment; ECT, electroconvulsive therapy; PANSS, positive and negative syndrome scale; rTMS, repetitive transcranial magnetic stimulation.

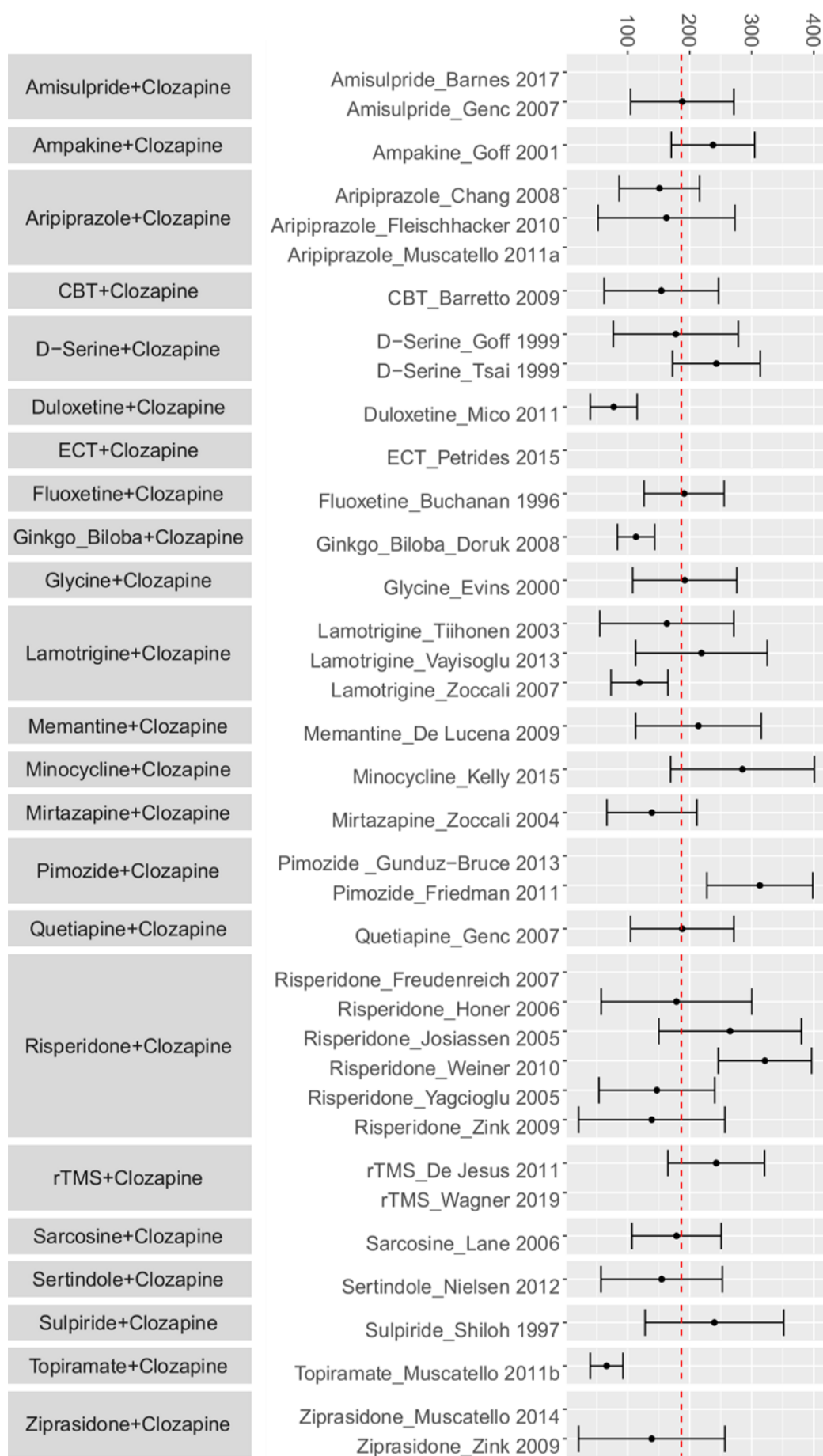
**eFigure 13. Distribution of daily defined dose of augmentation treatment among the included studies**



Abbreviation: CBT, cognitive behavioral treatment; ECT, electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation.



**eFigure 14. Distribution of illness duration among the included studies**

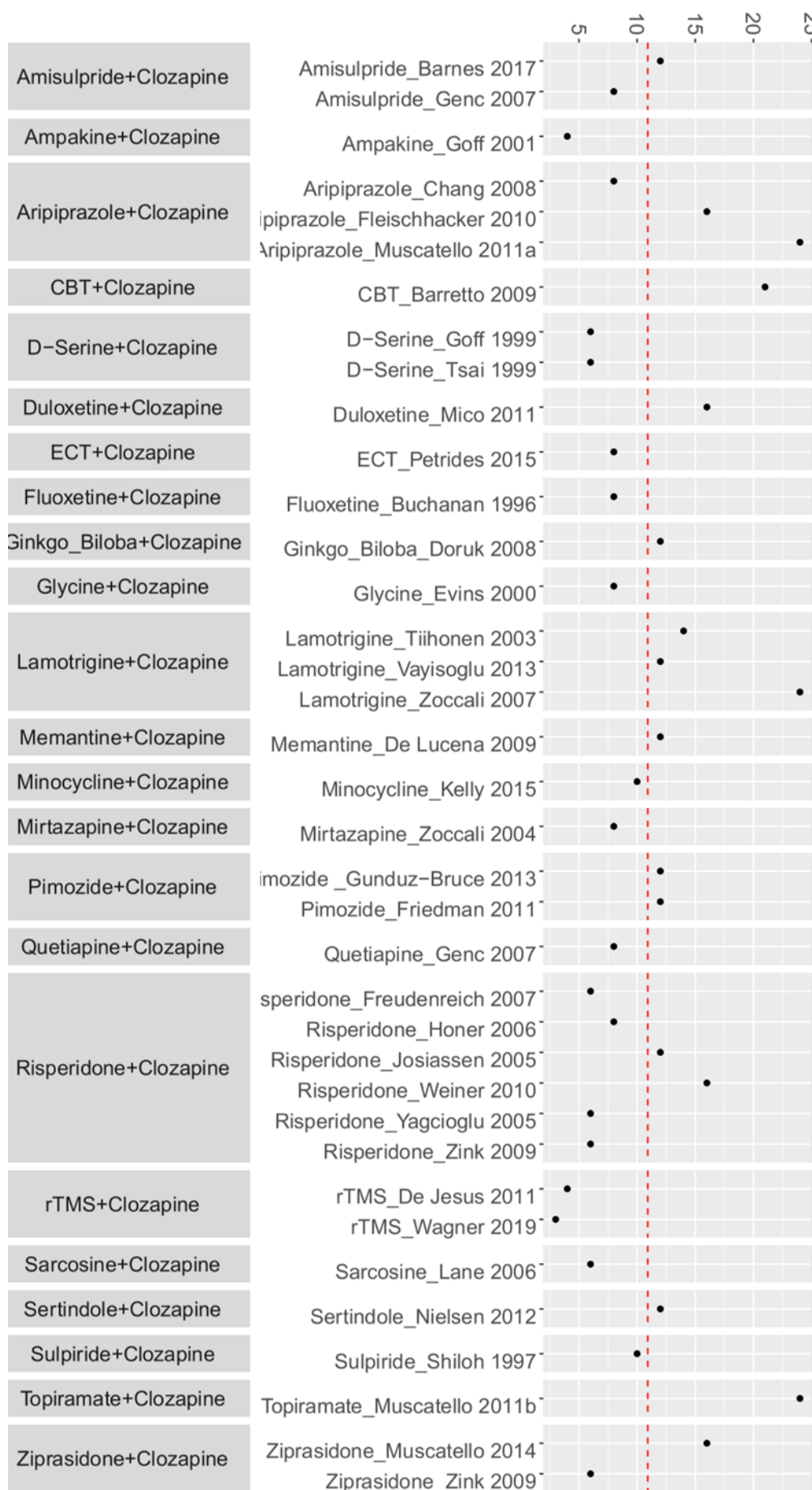


Illness duration: weeks

Abbreviation: CBT, cognitive behavioral treatment; ECT, electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation.



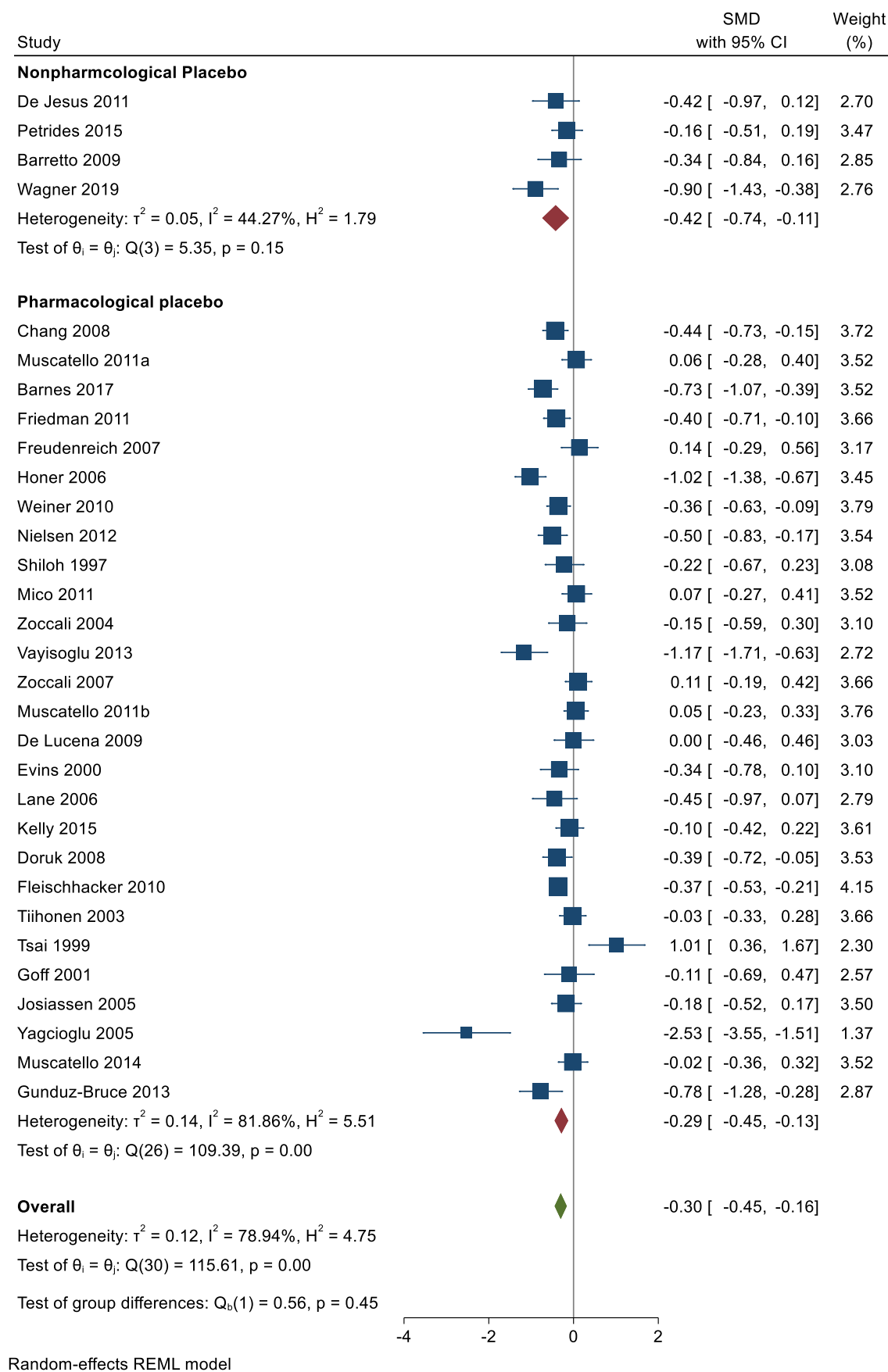
**eFigure 15. Distribution of trial duration among the included studies**



Trial duration: weeks

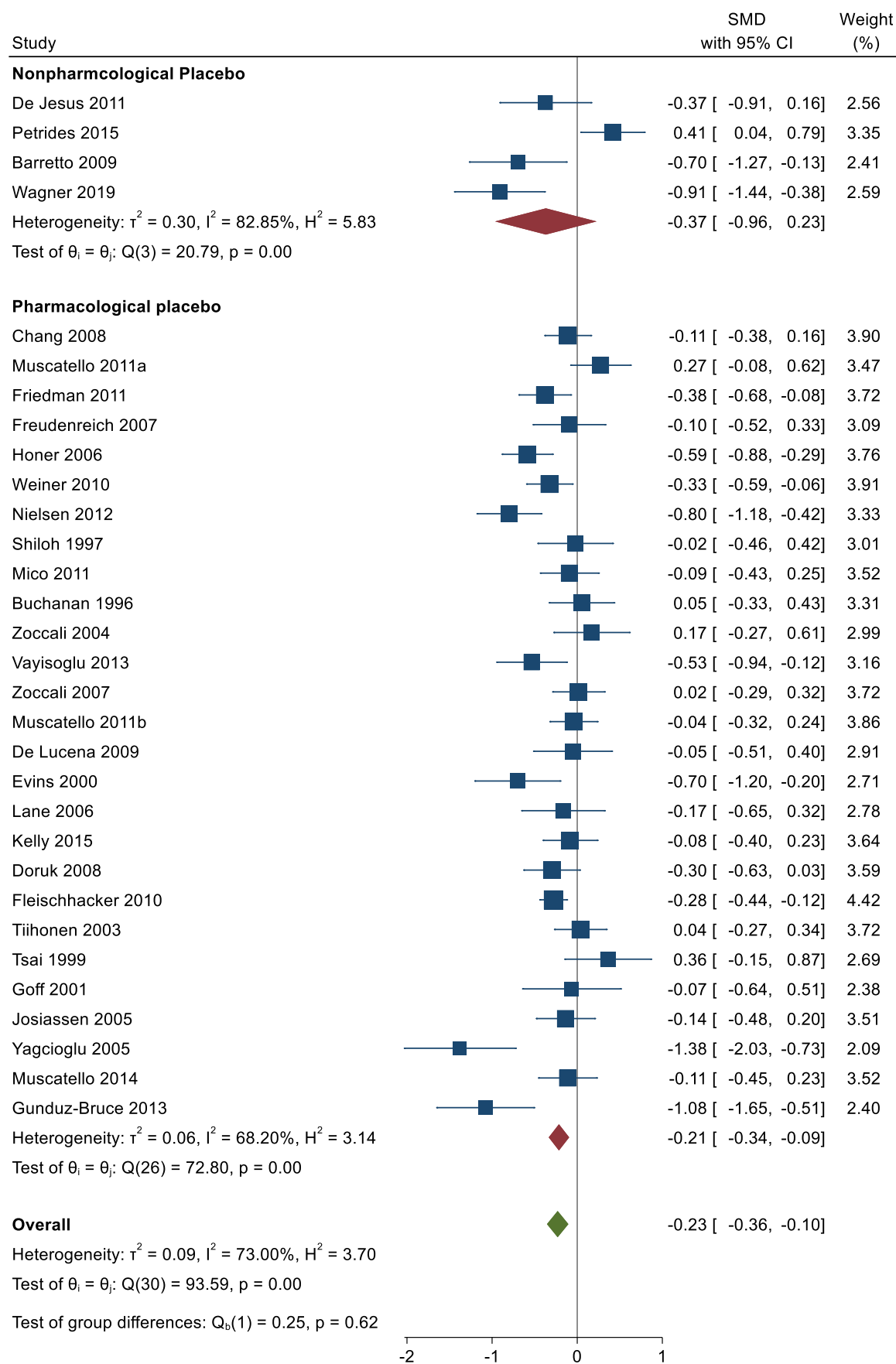
Abbreviation: CBT, cognitive behavioral treatment; ECT, electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation.

**eFigure 16. Nonpharmacological placebos vs pharmacological placebos on overall symptoms**



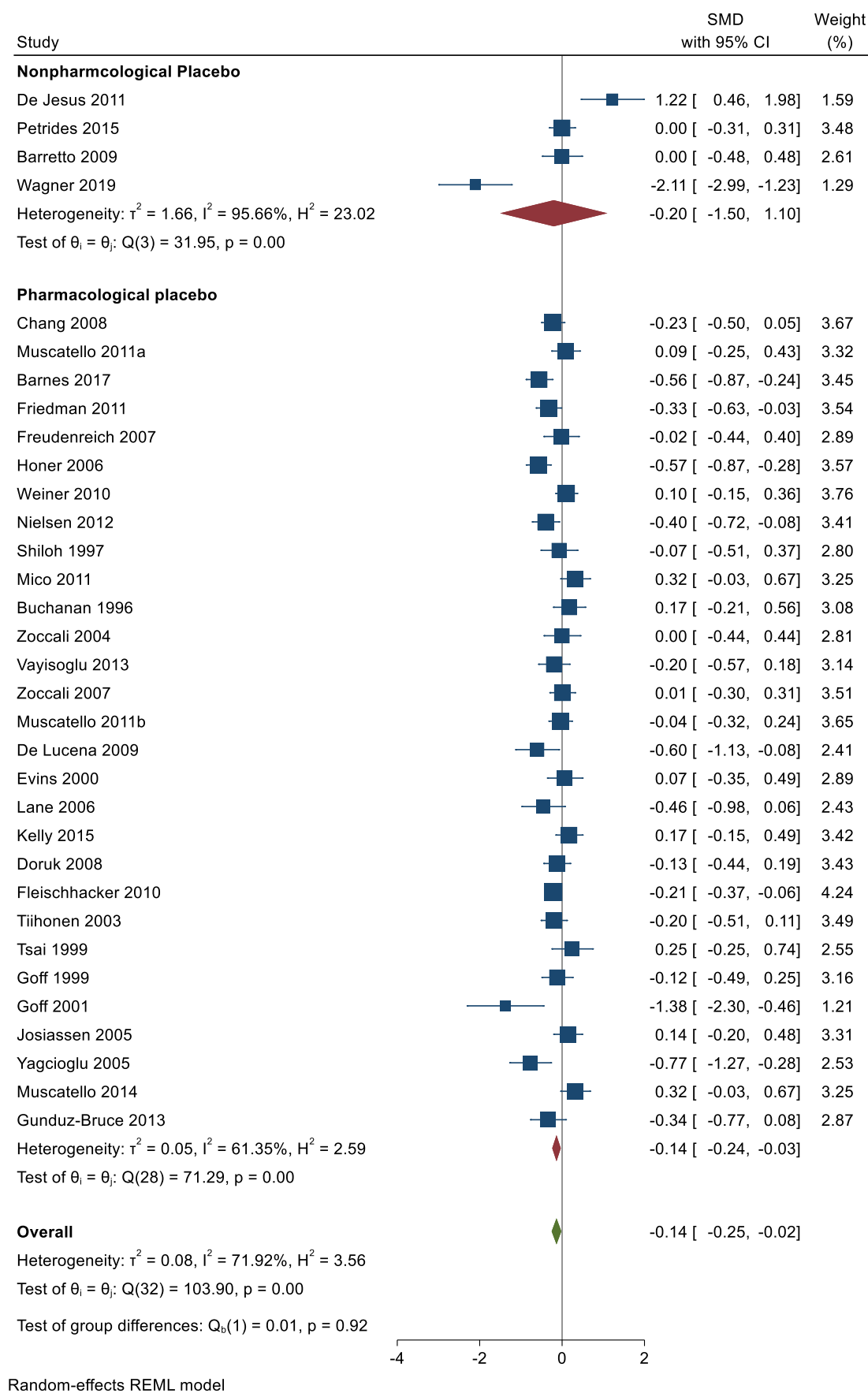
Abbreviation: CI, confidence interval; SMD, standardized mean difference.

**eFigure 17. Nonpharmacological placebos vs pharmacological placebos on positive symptoms**



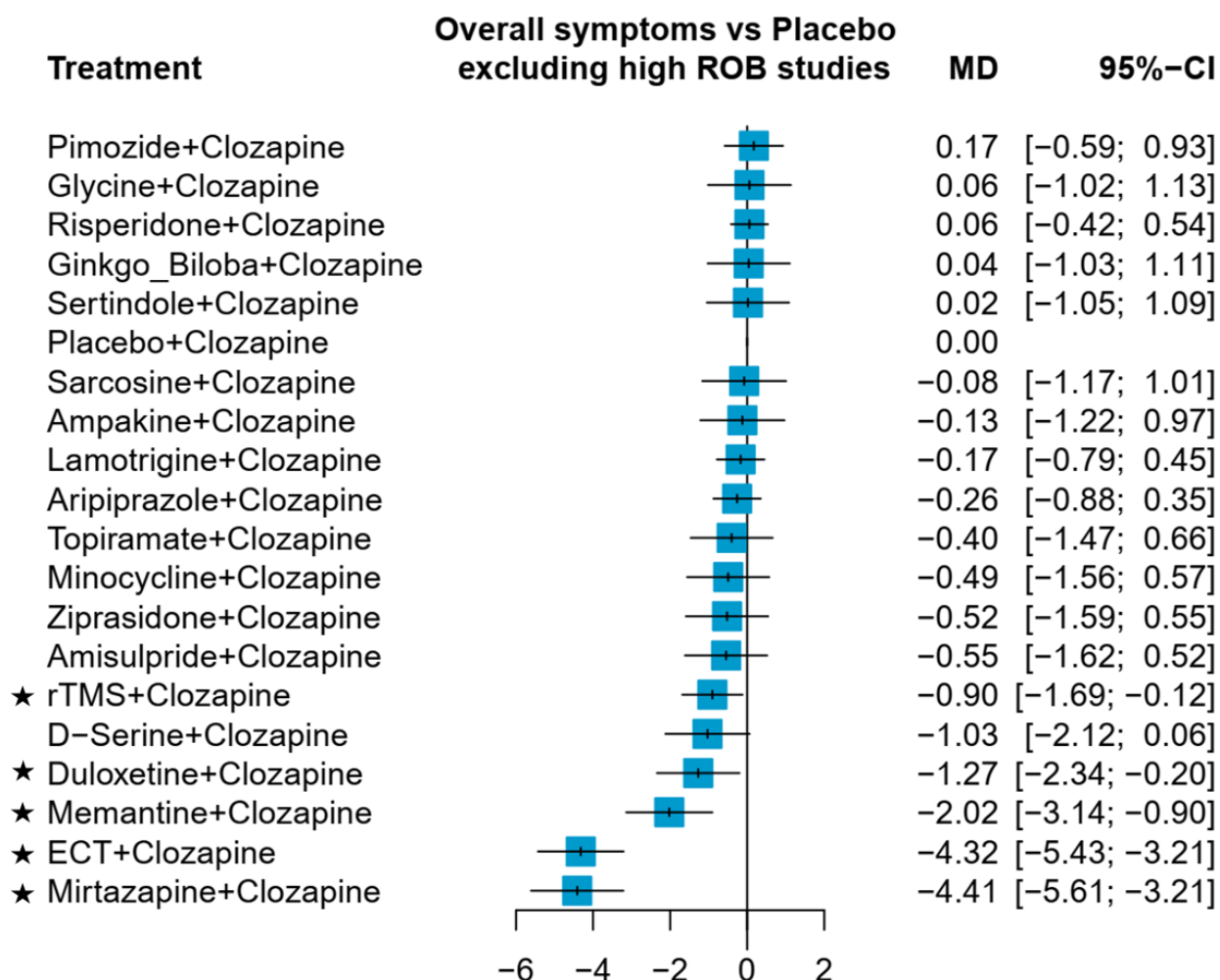
Abbreviation: CI, confidence interval; SMD, standardized mean difference.

**eFigure 18. Nonpharmacological placebos vs pharmacological placebos on negative symptoms**



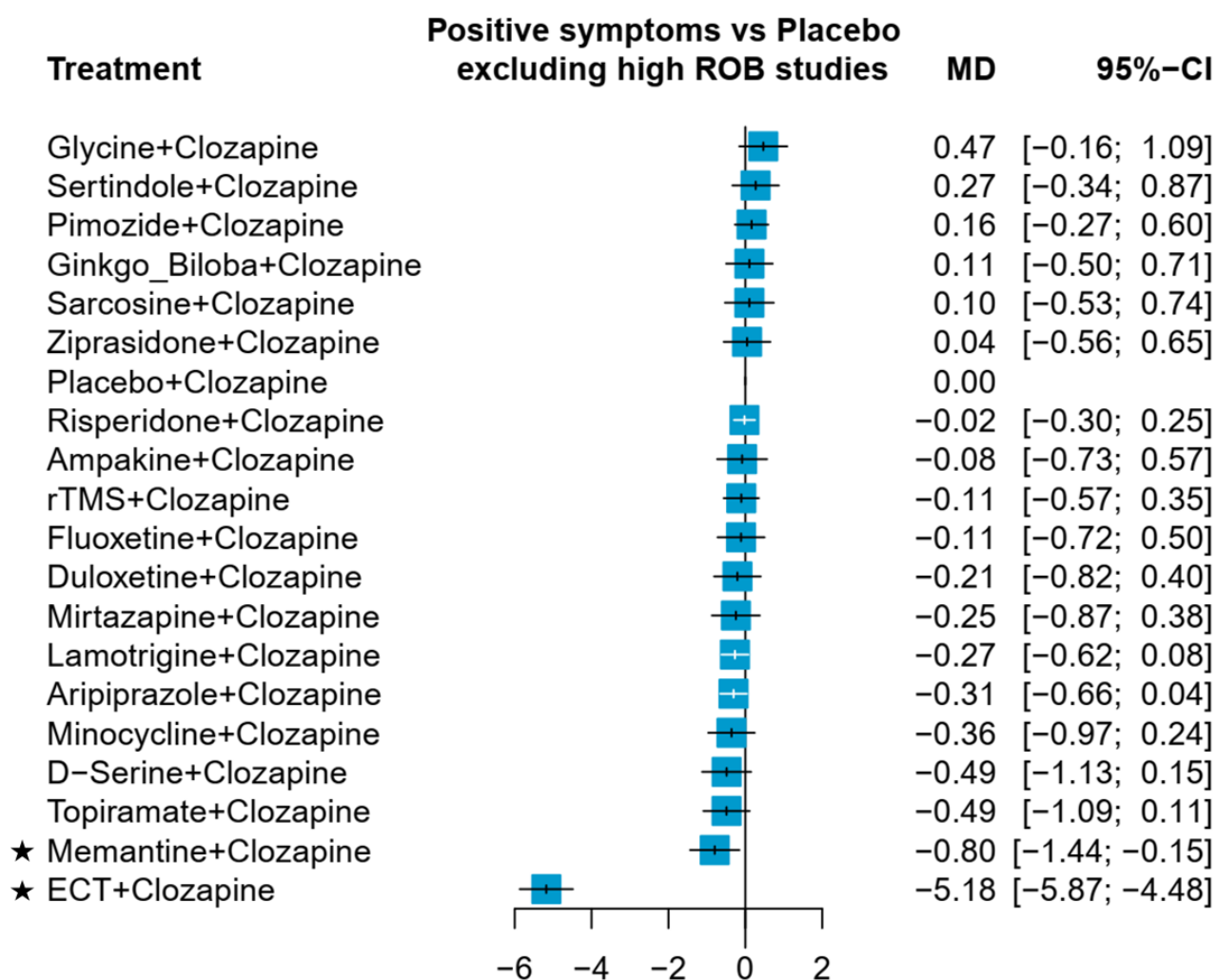
Abbreviation: CI, confidence interval; SMD, standardized mean difference.

**eFigure 19. Sensitivity analysis for excluding studies with high risk of bias: overall symptoms**



Abbreviation: CBT, cognitive behavioral treatment; CI, confidence interval; ECT, electroconvulsive therapy rTMS, repetitive transcranial magnetic stimulation. MD, mean difference.

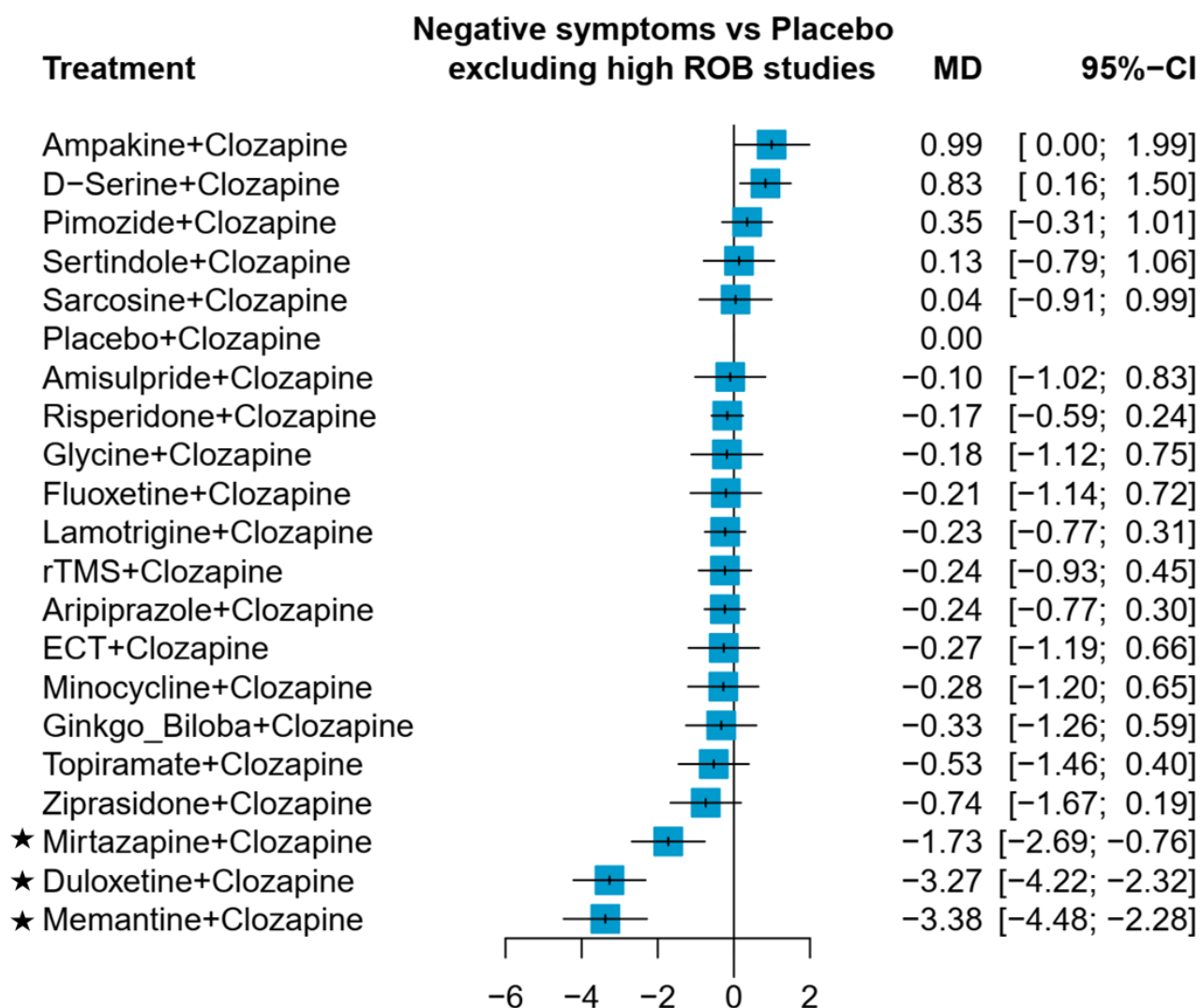
**eFigure 20. Sensitivity analysis for excluding studies with high risk of bias: positive symptoms**



Abbreviation: CBT, cognitive behavioral treatment; CI, confidence interval; ECT, electroconvulsive therapy rTMS, repetitive transcranial magnetic stimulation. MD, mean difference.

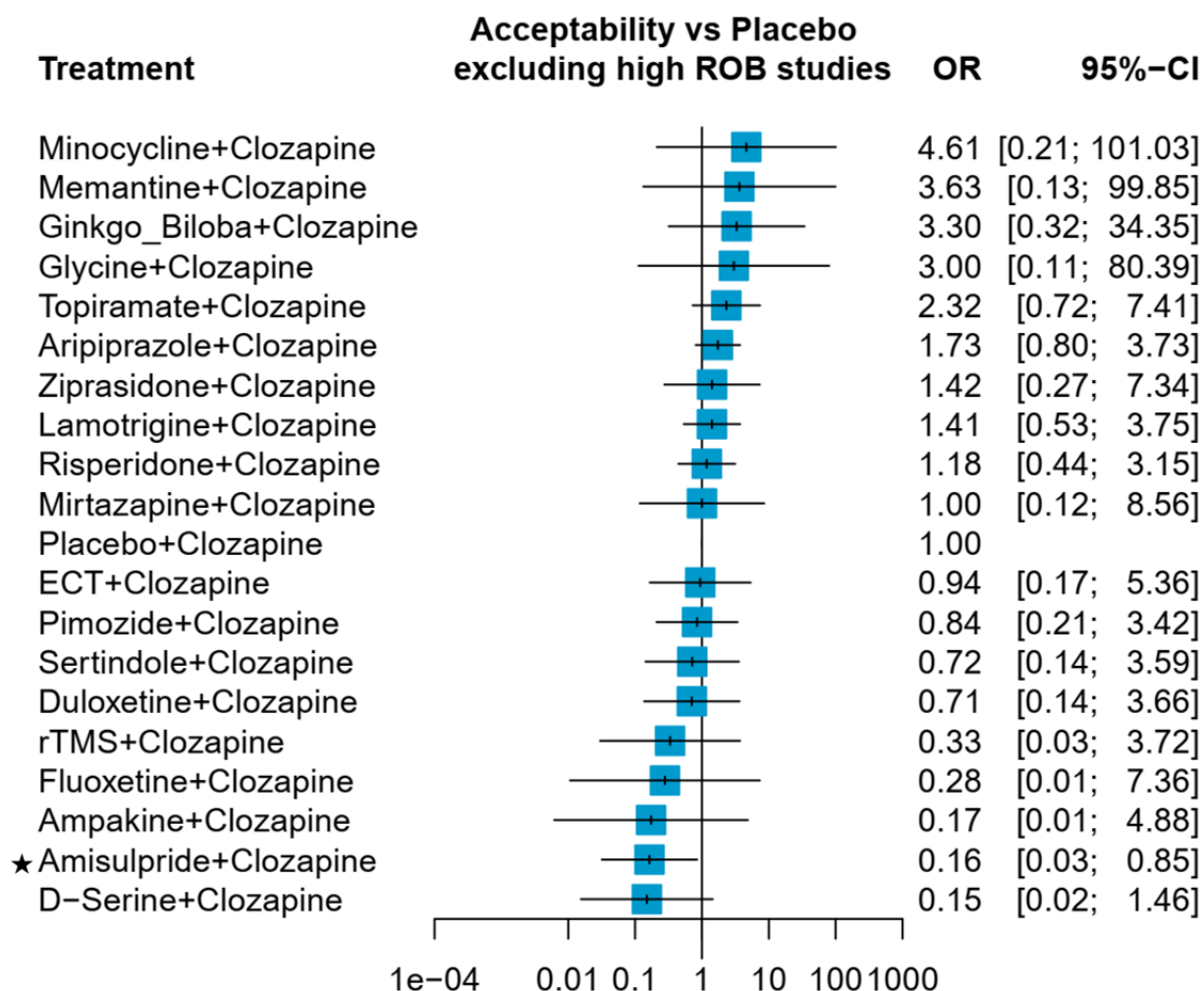


**eFigure 21. Sensitivity analysis for excluding studies with high risk of bias: negative symptoms**



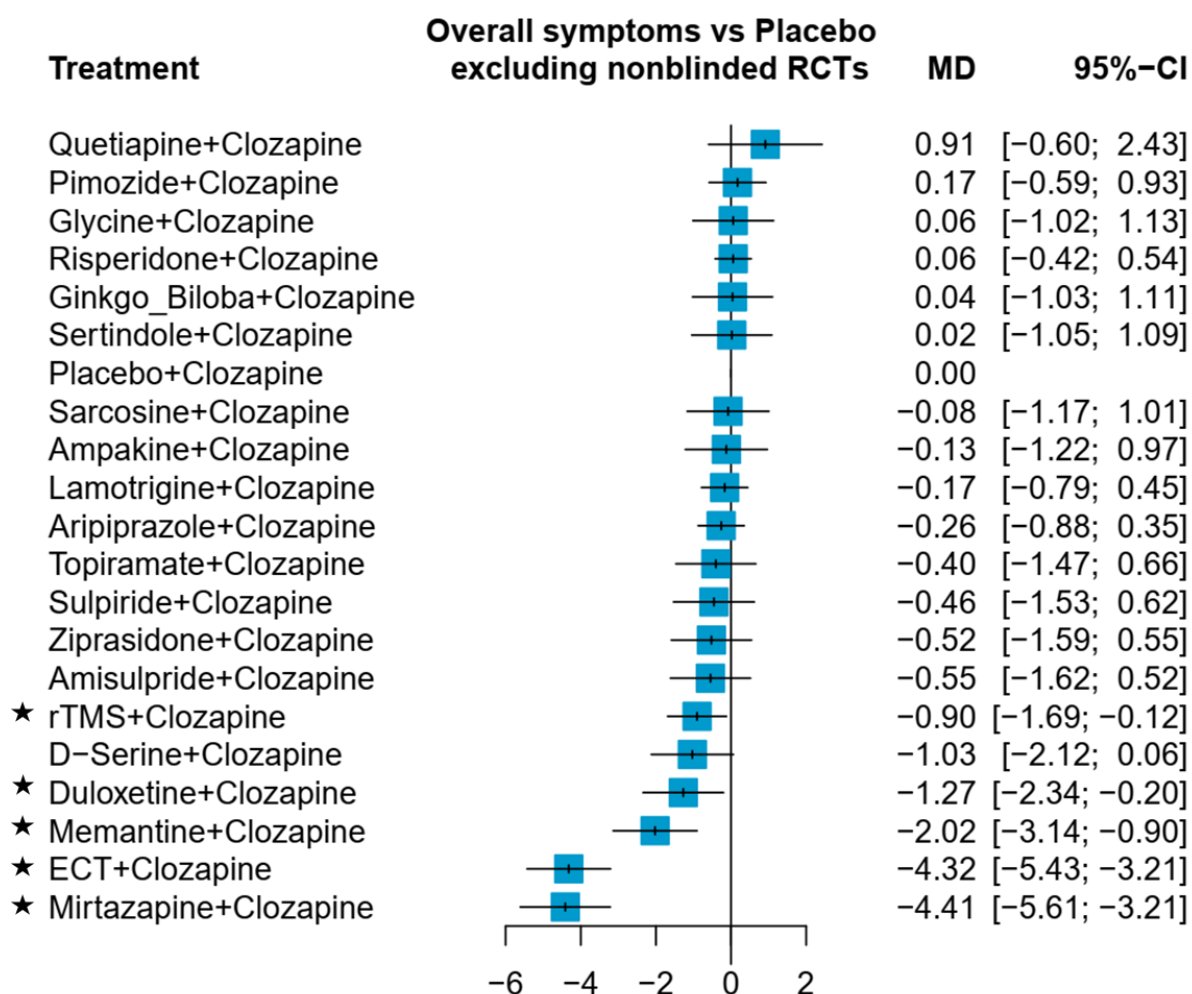
Abbreviation: CBT, cognitive behavioral treatment; CI, confidence interval; ECT, electroconvulsive therapy rTMS, repetitive transcranial magnetic stimulation. MD, mean difference.

**eFigure 22. Sensitivity analysis for excluding studies with high risk of bias: acceptability**



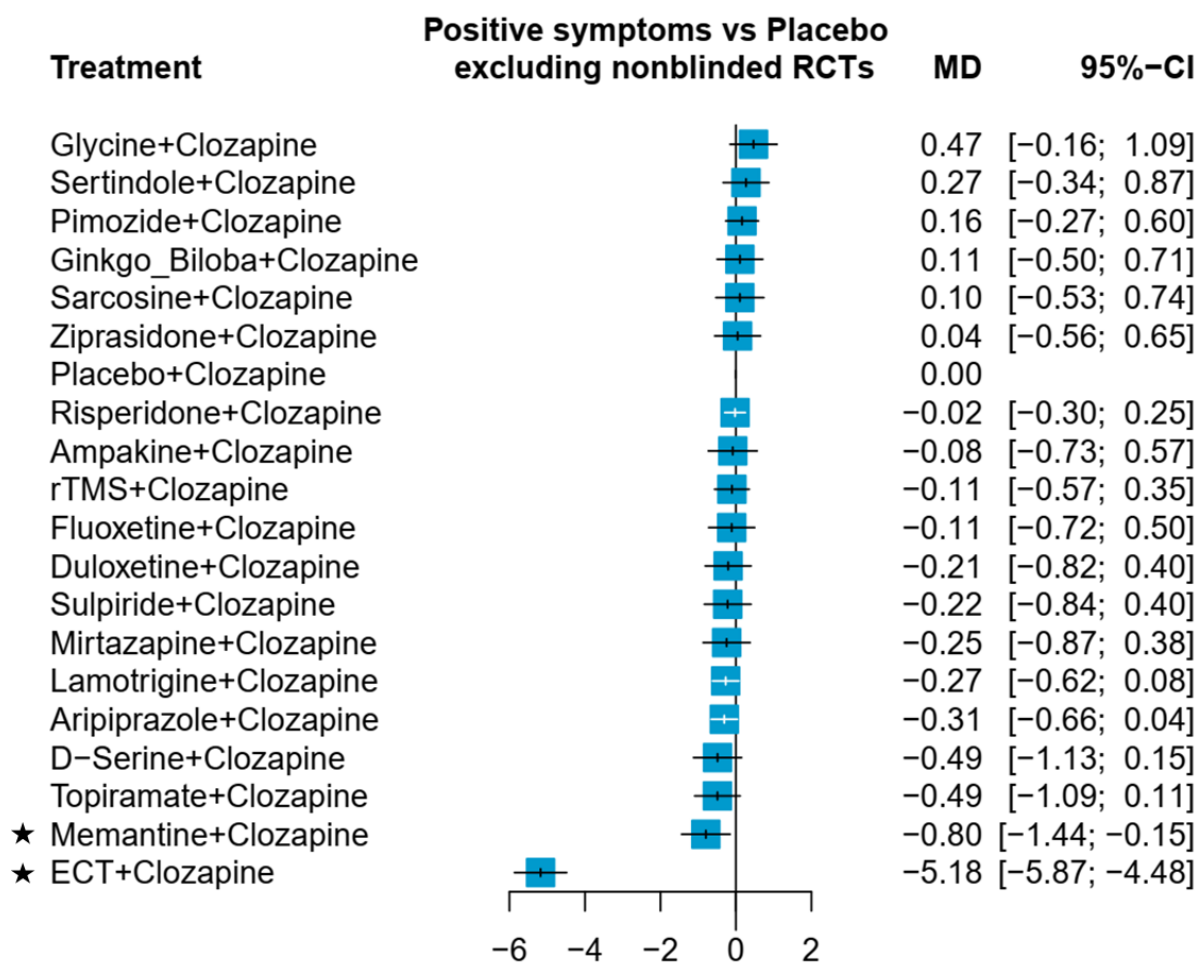
Abbreviation: CBT, cognitive behavioral treatment; CI, confidence interval; ECT, electroconvulsive therapy rTMS, repetitive transcranial magnetic stimulation. MD, mean difference.

**eFigure 23. Sensitivity analysis for excluding nonblinded randomized controlled trials: overall symptoms**



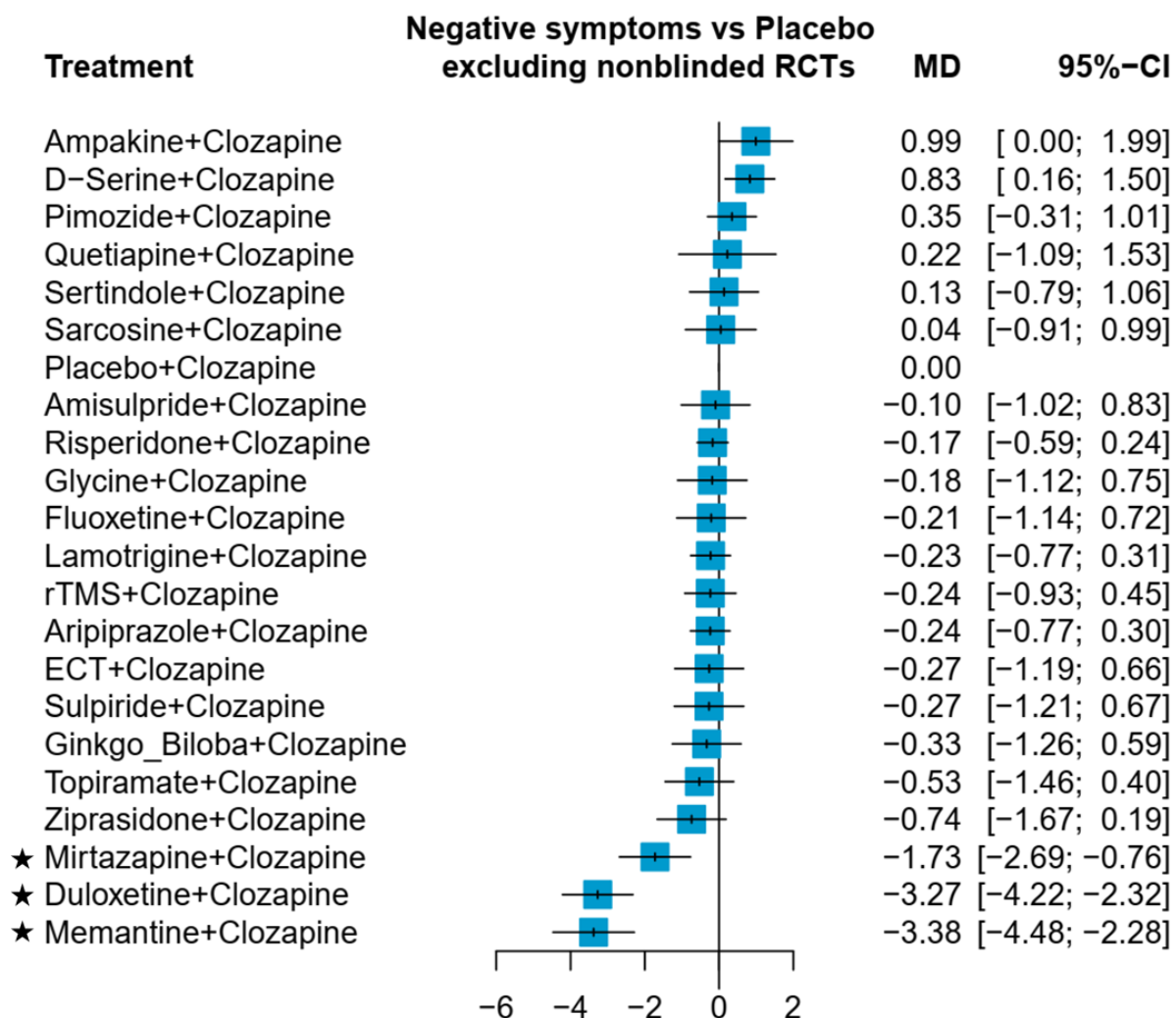
Abbreviation: CBT, cognitive behavioral treatment; CI, confidence interval; ECT, electroconvulsive therapy rTMS, repetitive transcranial magnetic stimulation. MD, mean difference.

**eFigure 24. Sensitivity analysis for excluding nonblinded randomized controlled trials: positive symptoms**



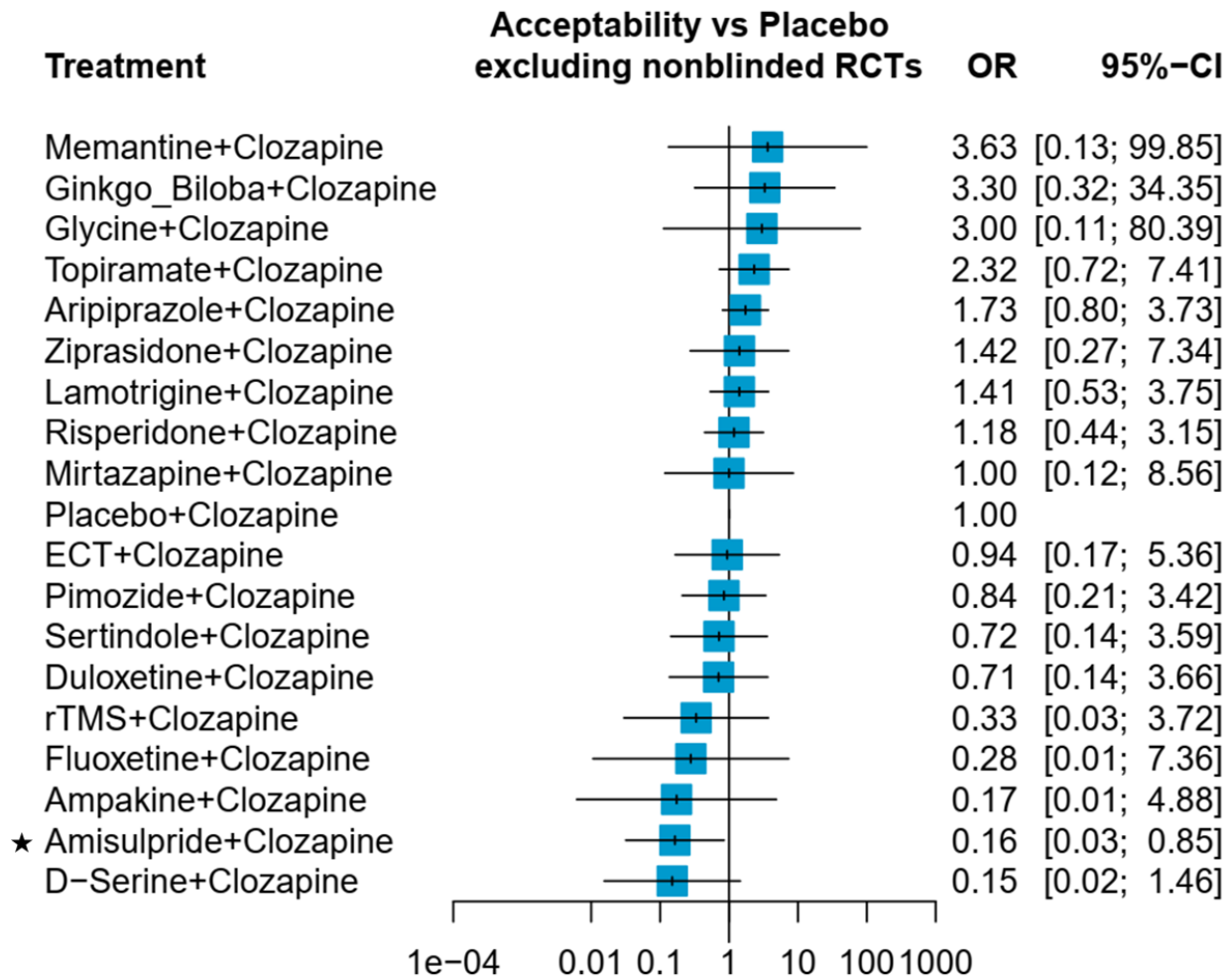
Abbreviation: CBT, cognitive behavioral treatment; CI, confidence interval; ECT, electroconvulsive therapy rTMS, repetitive transcranial magnetic stimulation. MD, mean difference.

**eFigure 25. Sensitivity analysis for excluding nonblinded randomized controlled trials: negative symptoms**



Abbreviation: CBT, cognitive behavioral treatment; CI, confidence interval; ECT, electroconvulsive therapy rTMS, repetitive transcranial magnetic stimulation. MD, mean difference.

**eFigure 26. Sensitivity analysis for excluding nonblinded randomized controlled trials: acceptability**



Abbreviation: CBT, cognitive behavioral treatment; CI, confidence interval; ECT, electroconvulsive therapy OR, odds ratio; rTMS, repetitive transcranial magnetic stimulation.

## eAppendix 1. Rationale for any changes in the PROSPERO (CRD42021262197)

Item	Changes in Protocol	Rationale
28	Analysis for surface under the cumulative ranking curve and normalized entropy	We ranked treatments using the surface under the cumulative ranking curve (SUCRA), which could be interpreted as the probability of being among the best option in the network. SUCRA ranges from 0 to 1; the greater the SUCRA value of a treatment, the better its performance is.
29	Normalized Entropy to Measure Uncertainty of Rankings	Normalized entropy is an alternative tool for measuring the uncertainty of treatment ranking by improving the translation of results from NMAs to clinical practice and avoiding naïve interpretation of treatment ranking. If the SUCRA value of a treatment is associated with a large value of normalized entropy, the ranking of this treatment is more likely to be affected by minor modifications to the current evidence or the addition of new evidence. <sup>1,2</sup> Normalized entropy ranges from 0 to 1 and is independent of the number of treatments, it can be used to compare the uncertainty of treatment ranking within a NMA and between different NMAs. <sup>3</sup>
30	Additional analysis for the outlying study and outlying moderators	We conducted several analyses to confirm that differences in treatment effect sizes were not due to differences in potential moderators. We calculated each study's potential outlying moderators according to the modified Z scores and Tukey methods. We also conducted several statistical measures to examine the potential outlying and influential studies, including raw residuals, standardized residuals, studentized residuals, Mahalanobis distances, and leverage.

### References

1. Trinquart L, Attiche N, Bafeta A, Porcher R, Ravaud P. Uncertainty in Treatment Rankings: Reanalysis of Network Meta-analyses of Randomized Trials. *Ann Intern Med*. 2016; 164(10): 666-673. doi:10.7326/M15-2521
2. Faltinsen EG, Storebo OJ, Jakobsen JC, Boesen K, Lange T, Gluud C. Network meta-analysis: the highest level of medical evidence? *BMJ Evid Based Med*. 2018; 23(2): 56-59. doi:10.1136/bmjebm-2017-110887
3. Wu YC, Shih MC, Tu YK. Using Normalized Entropy to Measure Uncertainty of Rankings for Network Meta-analyses. *Med Decis Making*. 2021;41(6):706-713. doi:10.1177/0272989X21999023.



## eAppendix 2. PRISMA Check list

Section and Topic	Item #	Checklist item	Location where item is reported
<b>TITLE</b>			
Title	1	Identify the report as a systematic review.	1
<b>ABSTRACT</b>			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	3
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	6
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	7
<b>METHODS</b>			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	8
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	8
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	8
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	9
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	9-10
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	9
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7,9
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	9,10
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	7,8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	9,10
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	9,10
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	9–11
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	10,11
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	11
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	10,11
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	9,10
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	12
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	12(Figure1),17
Study characteristics	17	Cite each included study and present its characteristics.	11,12 eTable 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	12 eFigure 1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	13,14
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	15
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	13,14
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	13,14
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	13,14
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	13,14
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	16,17
<b>DISCUSSION</b>			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	17–20
	23b	Discuss any limitations of the evidence included in the review.	21
	23c	Discuss any limitations of the review processes used.	21
	23d	Discuss implications of the results for practice, policy, and future research.	21
<b>OTHER INFORMATION</b>			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	7
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	7
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	eAppendix 1.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	2
Competing interests	26	Declare any competing interests of review authors.	2
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	7–9

#Location numbers correspond to page number.

References: 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.





## eAppendix 3. AMSTAR2

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

<b>1. Did the research questions and inclusion criteria for the review include the components of PICO?</b>		
For Yes: <input type="checkbox"/> Population <input type="checkbox"/> Intervention <input type="checkbox"/> Comparator group <input type="checkbox"/> Outcome	Optional (recommended) <input type="checkbox"/> Timeframe for follow-up	<input type="checkbox"/> Yes <input type="checkbox"/> No
<b>2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?</b>		
For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following:  <input type="checkbox"/> review question(s) <input type="checkbox"/> a search strategy <input type="checkbox"/> inclusion/exclusion criteria <input type="checkbox"/> a risk of bias assessment	For Yes: As for partial yes, plus the protocol should be registered and should also have specified:  <input type="checkbox"/> a meta-analysis/synthesis plan, if appropriate, <i>and</i> <input type="checkbox"/> a plan for investigating causes of heterogeneity <input type="checkbox"/> justification for any deviations from the protocol	<input type="checkbox"/> Yes <input type="checkbox"/> Partial Yes <input type="checkbox"/> No
<b>3. Did the review authors explain their selection of the study designs for inclusion in the review?</b>		
For Yes, the review should satisfy ONE of the following: <input type="checkbox"/> <i>Explanation for</i> including only RCTs <input type="checkbox"/> OR <i>Explanation for</i> including only NRSI <input type="checkbox"/> OR <i>Explanation for</i> including both RCTs and NRSI		<input type="checkbox"/> Yes <input type="checkbox"/> No
<b>4. Did the review authors use a comprehensive literature search strategy?</b>		
For Partial Yes (all the following):  <input type="checkbox"/> searched at least 2 databases (relevant to research question) <input type="checkbox"/> provided key word and/or search strategy <input type="checkbox"/> justified publication restrictions (e.g. language)	For Yes, should also have (all the following):  <input type="checkbox"/> searched the reference lists / bibliographies of included studies <input type="checkbox"/> searched trial/study registries <input type="checkbox"/> included/consulted content experts in the field <input type="checkbox"/> where relevant, searched for grey literature <input type="checkbox"/> conducted search within 24 months of completion of the review	<input type="checkbox"/> Yes <input type="checkbox"/> Partial Yes <input type="checkbox"/> No
<b>5. Did the review authors perform study selection in duplicate?</b>		
For Yes, either ONE of the following: <input type="checkbox"/> at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include <input type="checkbox"/> OR two reviewers selected a sample of eligible studies <u>and</u> achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.		<input type="checkbox"/> Yes <input type="checkbox"/> No

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

<p><b>6. Did the review authors perform data extraction in duplicate?</b></p> <p>For Yes, either ONE of the following:</p> <div> <input checked="" type="checkbox"/> at least two reviewers achieved consensus on which data to extract from included studies         <input type="checkbox"/> OR two reviewers extracted data from a sample of eligible studies <u>and</u> achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.       </div> <div> <input checked="" type="checkbox"/> Yes  <input type="checkbox"/> No       </div>		
<p><b>7. Did the review authors provide a list of excluded studies and justify the exclusions?</b></p> <div> <div> <p>For Partial Yes:</p> <input type="checkbox"/> provided a list of all potentially relevant studies that were read in full-text form but excluded from the review         </div> <div> <p>For Yes, must also have:</p> <input checked="" type="checkbox"/> Justified the exclusion from the review of each potentially relevant study         </div> <div> <input checked="" type="checkbox"/> Yes  <input type="checkbox"/> Partial Yes  <input type="checkbox"/> No         </div> </div>		
<p><b>8. Did the review authors describe the included studies in adequate detail?</b></p> <div> <div> <p>For Partial Yes (ALL the following):</p> <input type="checkbox"/> described populations  <input type="checkbox"/> described interventions  <input type="checkbox"/> described comparators  <input type="checkbox"/> described outcomes  <input type="checkbox"/> described research designs         </div> <div> <p>For Yes, should also have ALL the following:</p> <input checked="" type="checkbox"/> described population in detail  <input checked="" type="checkbox"/> described intervention in detail (including doses where relevant)  <input checked="" type="checkbox"/> described comparator in detail (including doses where relevant)  <input checked="" type="checkbox"/> described study's setting  <input checked="" type="checkbox"/> timeframe for follow-up         </div> <div> <input checked="" type="checkbox"/> Yes  <input type="checkbox"/> Partial Yes  <input type="checkbox"/> No         </div> </div>		
<p><b>9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?</b></p> <div> <div> <p><b>RCTs</b></p> <p>For Partial Yes, must have assessed RoB from</p> <input type="checkbox"/> unconcealed allocation, <i>and</i>  <input type="checkbox"/> lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)         </div> <div> <p>For Yes, must also have assessed RoB from:</p> <input checked="" type="checkbox"/> allocation sequence that was not truly random, <i>and</i>  <input checked="" type="checkbox"/> selection of the reported result from among multiple measurements or analyses of a specified outcome         </div> <div> <input checked="" type="checkbox"/> Yes  <input type="checkbox"/> Partial Yes  <input type="checkbox"/> No  <input type="checkbox"/> Includes only NRSI         </div> </div> <div> <div> <p><b>NRSI</b></p> <p>For Partial Yes, must have assessed RoB:</p> <input type="checkbox"/> from confounding, <i>and</i>  <input type="checkbox"/> from selection bias         </div> <div> <p>For Yes, must also have assessed RoB:</p> <input type="checkbox"/> methods used to ascertain exposures and outcomes, <i>and</i>  <input type="checkbox"/> selection of the reported result from among multiple measurements or analyses of a specified outcome         </div> <div> <input type="checkbox"/> Yes  <input type="checkbox"/> Partial Yes  <input type="checkbox"/> No  <input checked="" type="checkbox"/> Includes only RCTs         </div> </div>		
<p><b>10. Did the review authors report on the sources of funding for the studies included in the review?</b></p> <p>For Yes</p> <div> <input type="checkbox"/> Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies         </div> <div> <input checked="" type="checkbox"/> Yes  <input type="checkbox"/> No         </div>		

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

<p><b>11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?</b></p>	
<p><b>RCTs</b> For Yes:</p> <div style="display: flex; justify-content: space-between;"> <div> <p><input checked="" type="checkbox"/> The authors justified combining the data in a meta-analysis</p> <p><input type="checkbox"/> AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.</p> <p><input type="checkbox"/> AND investigated the causes of any heterogeneity</p> </div> <div> <p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> No meta-analysis conducted</p> </div> </div>	
<p><b>For NRSI</b> For Yes:</p> <div style="display: flex; justify-content: space-between;"> <div> <p><input type="checkbox"/> The authors justified combining the data in a meta-analysis</p> <p><input type="checkbox"/> AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present</p> <p><input type="checkbox"/> AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available</p> <p><input type="checkbox"/> AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review</p> </div> <div> <p><input type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> No meta-analysis conducted</p> </div> </div>	
<p><b>12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?</b></p>	
<p>For Yes:</p> <div style="display: flex; justify-content: space-between;"> <div> <p><input type="checkbox"/> included only low risk of bias RCTs</p> <p><input checked="" type="checkbox"/> OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.</p> </div> <div> <p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> No meta-analysis conducted</p> </div> </div>	
<p><b>13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?</b></p>	
<p>For Yes:</p> <div style="display: flex; justify-content: space-between;"> <div> <p><input type="checkbox"/> included only low risk of bias RCTs</p> <p><input checked="" type="checkbox"/> OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results</p> </div> <div> <p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> </div> </div>	
<p><b>14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?</b></p>	
<p>For Yes:</p> <div style="display: flex; justify-content: space-between;"> <div> <p><input type="checkbox"/> There was no significant heterogeneity in the results</p> <p><input checked="" type="checkbox"/> OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review</p> </div> <div> <p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> </div> </div>	
<p><b>15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?</b></p>	
<p>For Yes:</p> <div style="display: flex; justify-content: space-between;"> <div> <p><input checked="" type="checkbox"/> performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias</p> </div> <div> <p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> No meta-analysis conducted</p> </div> </div>	

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

**16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?**

For Yes:

- |  |   |
|--|---|
| <input type="checkbox"/> The authors reported no competing interests OR  | <input checked="" type="checkbox"/> Yes |
| <input checked="" type="checkbox"/> The authors described their funding sources and how they managed potential conflicts of interest | <input type="checkbox"/> No             |

**To cite this tool:** Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017 Sep 21;358:j4008.

## **eAppendix 4. Search details**

### **Database searches**

Date through July 10<sup>th</sup>, 2021

Total: **9,456**

#### ● **Pubmed: 5,381**

(Schizophrenia or "Schizophrenia Spectrum and Other Psychotic Disorders"[Mesh]) AND (Clozapine) AND (resistant or refractory or augmentation or "Psychotropic Drugs"[Mesh] or "Psychiatric Somatic Therapies"[Mesh])

limited to human and English

#### ● **Medline: 141**

(Schizophrenia or schizophrenic disorder) AND (Clozapine) AND (resistant or refractory or augmentation AND (Psychotropic medication or Psychiatric Therapy)

limited to human and English and Clinical Study

#### ● **Embase: 543**

(Schizophrenia or schizophrenic disorder) AND (Clozapine) AND (resistant or refractory or augmentation AND (Psychotropic medication or Psychiatric Therapy)

#### ● **Cochrane library: 2,908**

(Schizophrenia or schizophrenic disorder) AND (Clozapine) AND (resistant or refractory or augmentation AND ('psychotropic agent' or 'psychiatric treatment'))

Use Emtree terms

#### ● **APA PsycInfo: 483**

(Schizophrenia or schizophrenic disorder) AND (Clozapine) AND (resistant or refractory or augmentation AND (Psychotropic medication or Psychiatric Therapy)

limited to human and English

### **Clinical trial registry**

Date through July 10<sup>th</sup>, 2021

Total: **70**

#### ● **ClinicalTrials.gov: 25**

#### ● **ICTRP Search Portal: 55**

-including Chinese Clinical Trial Registry (ChiCTR), The Netherlands National Trial Register (NTR), German Clinical Trials Register (DRKS), Japan Primary Registries Network (JPRN), Clinical Research Information Service (CRiS), Republic of Korea, Iranian Registry of Clinical Trials (IRCT), Peruvian Clinical Trial Registry (REPEC)

## Excluded studies with reasons

### Total=45

Review/Meta-analysis/comment: 9

Wrong outcome: 7

Case report: 10

Conference paper: 7

Not CRS: 3

Open label study: 7

Same population: 2

### Review/Meta-analysis/comment

Bartoli F, Crocamo C, Di Brita C, Esposito G, Tabacchi TI, Verrengia E, Clerici M, Carrà G: **Adjunctive second-generation antipsychotics for specific symptom domains of schizophrenia resistant to clozapine: A meta-analysis.** *J Psychiatr Res* 2019, **108**:24-33.

Bogers J, Cohen D: **Clozapine resistance: What is a rational pharmacotherapeutic next step?** *European archives of psychiatry and clinical neuroscience* 2015, **265**(1):S27.

Chiu YH, Hsu CY, Lu ML, Chen CH: **Augmentation Strategies for Clozapine-Resistant Patients with Schizophrenia.** *Curr Pharm Des* 2020, **26**(2):218-227.

Englisch S, Zink M: **Combined antipsychotic treatment involving clozapine and aripiprazole.** *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 2008, **32**(6):1386-1392.

Grover S, Hazari N, Kate N: **Combined use of clozapine and ECT: a review.** *Acta Neuropsychiatr* 2015, **27**(3):131-142.

Harrison PJ: **D-Amino Acid Oxidase Inhibition: A New Glutamate Twist for Clozapine Augmentation in Schizophrenia?** *Biol Psychiatry* 2018, **84**(6):396-398.

Kittsteiner Manubens L, Lobos Urbina D, Aceituno D: **Is electroconvulsive therapy effective as augmentation in clozapine-resistant schizophrenia?** *Medwave* 2016, **16**(Suppl5):e6577.

Tiihonen J, Wahlbeck K, Kiviniemi V: **The efficacy of lamotrigine in clozapine-resistant schizophrenia: a systematic review and meta-analysis.** *Schizophr Res* 2009, **109**(1-3):10-14.

Zheng W, Xiang YT, Yang XH, Xiang YQ, de Leon J: **Clozapine Augmentation With Antiepileptic Drugs for Treatment-Resistant Schizophrenia: A Meta-Analysis of Randomized Controlled Trials.** *J Clin Psychiatry* 2017, **78**(5):e498-e505.

### Wrong outcome:

Akdede BB, Anil Yağcıoğlu AE, Alptekin K, Turgut TI, Tümüklü M, Yazici MK, Jayathilake K, Tunca Z, Göğüş A, Meltzer HY: **A double-blind study of combination of clozapine with risperidone in patients with schizophrenia: effects on cognition.** *J Clin Psychiatry* 2006, **67**(12):1912-1919.

Angersbach D: **Refractory schizophrenia: Aripiprazole for augmentation of a treatment with clozapine.** *Psychopharmakotherapie* 2008, **15**(4):182-183.

Augustin M, Schoretsanitis G, Pfeifer P, Gründer G, Liebe C, Paulzen M: **Effect of**

**fluvoxamine augmentation and smoking on clozapine serum concentrations.** *Schizophr Res* 2019, **210**:143-148.

De Risio A, Pancheri A, Simonetti G, Giannarelli D, Stefanutto L, Gentile B: **Add-on of aripiprazole improves outcome in clozapine-resistant schizophrenia.** *Prog Neuropsychopharmacol Biol Psychiatry* 2011, **35**(4):1112-1116.

Delle Chiaie R, Salviati M, Fiorentini S, Biondi M: **Add-on mirtazapine enhances effects on cognition in schizophrenic patients under stabilized treatment with clozapine.** *Exp Clin Psychopharmacol* 2007, **15**(6):563-568.

Frilling L, Fuller M, Roche J, Jaskiw G: **Augmentation of clozapine with an additional antipsychotic in treatment resistant schizophrenia at the louis stokes cleveland vamc.** *Journal of Pharmacy Practice* 2013, **26**(3):321.

Karunakaran K, Tungaraza TE, Harborne GC: **Is clozapine-aripiprazole combination a useful regime in the management of treatment-resistant schizophrenia?** *J Psychopharmacol* 2007, **21**(4):453-456.

#### **Case report:**

Abu-Tair F, Kopitz J, Bergemann N: **Clozapine augmented with aripiprazole in 5 patients with schizophrenia.** *J Clin Psychopharmacol* 2006, **26**(6):669-671.

Ashton AK: **Aripiprazole augmentation of clozapine: in refractory schizophrenia.** *Psychiatry (Edgmont)* 2005, **2**(2):18-19.

Balcioğlu YH, Gokcay H, Yesilkaya UH: **One Plus One Sometimes Equals More Than Two: Long-acting Injectable Aripiprazole Adjunction in Clozapine-Resistant Schizophrenia.** *Clin Neuropharmacol* 2020, **43**(5):166-168.

Chiu HW, Ku YC, Li TC, Huang HT: **Amisulpride augmentation of clozapine in refractory schizophrenia.** *Journal of Neuropsychiatry and Clinical Neurosciences* 2011, **23**(3):E15.

Esslinger C, Inta D, Englisch S, Esser A, Zink M: **Clozapine combined with paliperidone observations in schizophrenic patients with insufficient responses to clozapine monotherapy.** *German Journal of Psychiatry* 2010, **13**(1):37-40.

Kim HS, Kim SH, Lee NY, Youn T, Lee JH, Chung S, Kim YS, Chung IW: **Effectiveness of Electroconvulsive Therapy Augmentation on Clozapine-Resistant Schizophrenia.** *Psychiatry Investig* 2017, **14**(1):58-62.

Leising J, Barr AM, Procyshyn RM, Ainsworth NJ, White RF, Honer W, Vila-Rodriguez F: **High-Dose Fluvoxamine Augmentation to Clozapine in Treatment-Resistant Psychosis.** *J Clin Psychopharmacol* 2021, **41**(2):186-190.

Masopust J: **Aripiprazole augmentantion of clozapine in schizophrenia patients.** *Psychiatrie* 2018, **22**(3):147-150.

Pavlovic ZM: **Augmentation of clozapine's antiaggressive properties with lamotrigine in a patient with chronic disorganized schizophrenia.** *J Clin Psychopharmacol* 2008, **28**(1):119-120.

Qurashi I, Collins JD, Chaudhry IB, Husain N: **Promising use of minocycline augmentation with clozapine in treatment-resistant schizophrenia.** *J Psychopharmacol* 2014, **28**(7):707-708.



#### **Conference paper:**

**Maintenance electroconvulsive therapy in clozapine resistant schizophrenia.** *Indian Journal of Psychiatry* 2020, **62**(7):S132.

Bise S, Sulejmanpasic-Arslanagic G, Semalovic O: **Efficacy, safety and tolerability of aripiprazole-clozapine combination therapy.** *European Neuropsychopharmacology* 2015, **25**:S513.

Chung IW, Kim HS, Kim SH, Youn T, Kim YS: **Effectiveness of electroconvulsive therapy on clozapine-resistant schizophrenia.** *Journal of ECT* 2016, **32**(3):216-217.

Chung IW, Youn T, Kim S, Lee NY, Kim YS: **Electroconvulsive therapy augmentation on clozapine in treatment-resistant schizophrenia.** *Journal of ECT* 2017, **33**(3):213.

Dardennes RM, Al Anbar NN, Rouillon F: **Successful augmentation of clozapine-resistant treatment of schizophrenia with clonidine.** *Prog Neuropsychopharmacol Biol Psychiatry* 2010, **34**(4):724-725.

Schulte P, Veerman S, Smith J, De Haan L: **Memantine augmentation in clozapine refractory schizophrenia: A randomized, double-blind, placebo-controlled crossover study.** *European Archives of Psychiatry and Clinical Neuroscience* 2015, **265**(1):S66.

Sulejmanpasic G, Bise S: **Clozapine augmented with amisulpride in treatment-resistant schizophrenia.** *European Neuropsychopharmacology* 2019, **29**:S121-S122.

#### **Not CRS:**

Assion HJ, Reinbold H, Lemanski S, Basilowski M, Juckel G: **Amisulpride augmentation in patients with schizophrenia partially responsive or unresponsive to clozapine. A randomized, double-blind, placebo-controlled trial.** *Pharmacopsychiatry* 2008, **41**(1):24-28.

Lin CH, Lin CH, Chang YC, Huang YJ, Chen PW, Yang HT, Lane HY: **Sodium Benzoate, a D-Amino Acid Oxidase Inhibitor, Added to Clozapine for the Treatment of Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled Trial.** *Biol Psychiatry* 2018, **84**(6):422-432.

Behdani F, Hebrani P, Rezaei Ardani A, Rafee E: **Effect of topiramate augmentation in chronic schizophrenia: a placebo-controlled trial.** *Archives of Iranian medicine* 2011, **14**(4):270-275.

#### **Open label study:**

Barbui C, Accordini S, Nose M, Stroup S, Purgato M, Girlanda F, Esposito E, Veronese A, Tansella M, Cipriani A: **Aripiprazole versus haloperidol in combination with Clozapine for treatment-resistant schizophrenia in routine clinical care a randomized, controlled trial.** *Journal of Clinical Psychopharmacology* 2011, **31**(3):266-273.

Bruno A, Pandolfo G, Crucitti M, Lorusso S, Zoccali RA, Muscatello MR: **Acetyl-L-Carnitine Augmentation of Clozapine in Partial-Responder Schizophrenia: A 12-Week, Open-Label Uncontrolled Preliminary Study.** *Clin Neuropharmacol* 2016, **39**(6):277-280.

Bruno A, Zoccali R, Bellinghieri PM, Pandolfo G, De Fazio P, Spina E, Muscatello MR: **Reboxetine adjuvant therapy in patients with schizophrenia showing a suboptimal response to clozapine: a 12-week, open-label, pilot study.** *J Clin Psychopharmacol* 2014, **34**(5):620-623.

Bruno A, Zoccali RA, Abenavoli E, Pandolfo G, Scimeca G, Spina E, Muscatello MR: **Augmentation of clozapine with agomelatine in partial-responder schizophrenia: a 16-week, open-label, uncontrolled pilot study.** *J Clin Psychopharmacol* 2014, **34**(4):491-494.

Grimminck R, Oluboka O, Sihota M, Rutherford DL, Yeung H: **Combination of Clozapine With Long-Acting Injectable Antipsychotics in Treatment-Resistant Schizophrenia: Preliminary Evidence From Health Care Utilization Indices.** *Prim Care Companion CNS Disord* 2020, **22**(4).

Grover S, Hazari N, Chakrabarti S, Avasthi A: **Augmentation of Clozapine With ECT: Observations From India.** *Am J Psychiatry* 2015, **172**(5):487.

Leung JG, Chengappa KN, Ivanov E, Gandotra G, Kahn CE, Weber JS, Fabian TJ: **Antipsychotic agents used to augment clozapine during long-term inpatient hospitalizations.** *Pharmacopsychiatry* 2014, **47**(7):263-267.

**Same population:**

Braga RJ, John M, Schooler NR, Bailine SH, Malur C, Mendelowitz A, Petrides G: **Continuation Electroconvulsive Therapy for Patients With Clozapine-Resistant Schizophrenia: A Pilot Study.** *J ect* 2019, **35**(3):156-160.

Melzer-Ribeiro DL, Rigonatti SP, Kayo M, Avrichir BS, Ribeiro RB, Dos Santos B, Fortes M, Elkis H: **Efficacy of electroconvulsive therapy augmentation for partial response to clozapine: A pilot randomized ECT - sham controlled trial.** *Revista de Psiquiatria Clinica* 2017, **44**(2):45-50.