Supplemental material

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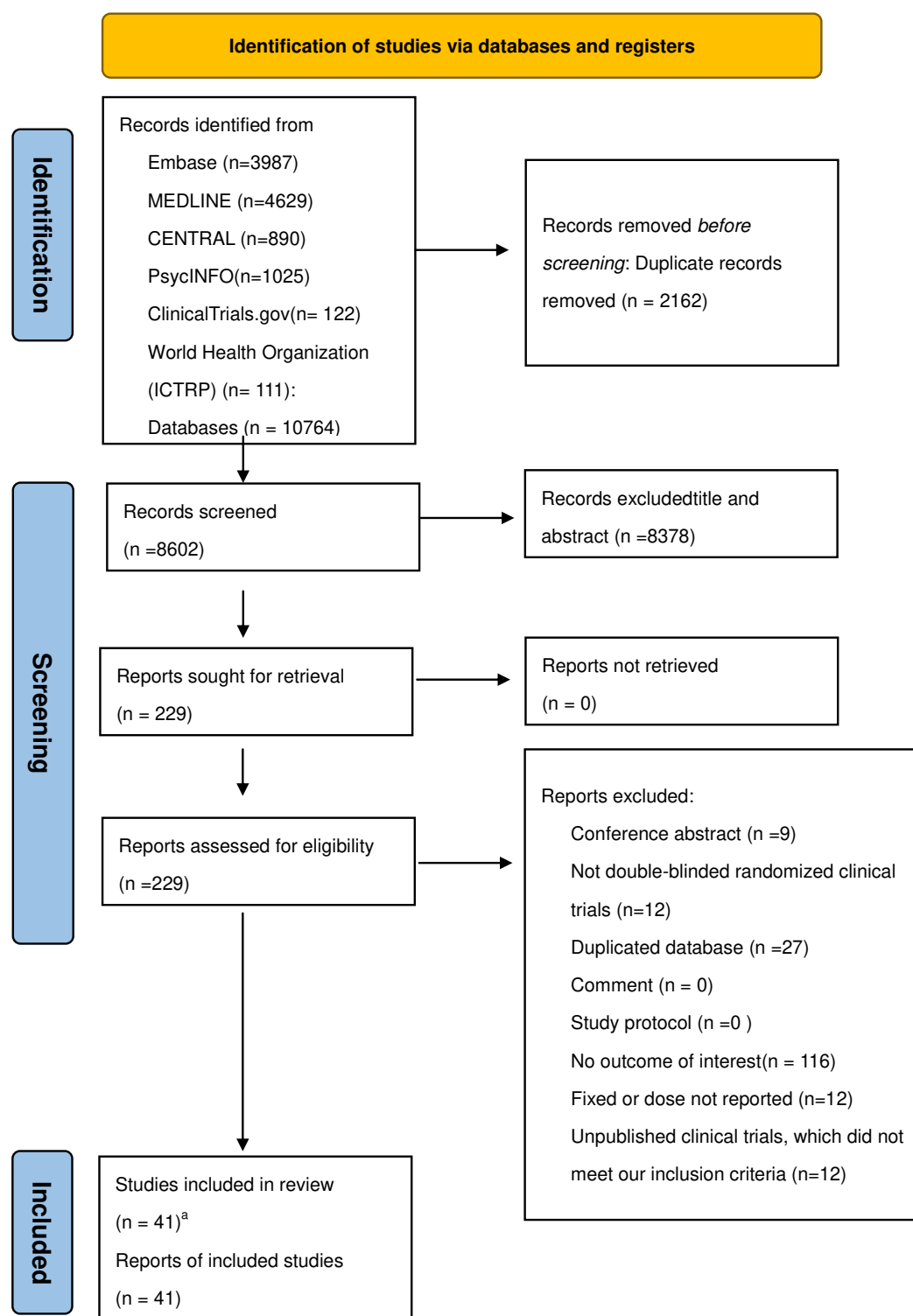
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eFigure 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.

Identification of studies via databases and registers

Identification

Records identified from
  Embase (n=3987)
  MEDLINE (n=4629)
  CENTRAL (n=890)
  PsycINFO(n=1025)
  ClinicalTrials.gov(n= 122)
  World Health Organization
  (ICTRP) (n= 111):
  Databases (n = 10764)

Records removed *before screening*: Duplicate records removed (n = 2162)

Screening

Records screened
(n =8602)

Records excludedtitle and abstract (n =8378)

Reports sought for retrieval
(n = 229)

Reports not retrieved
(n = 0)

Reports assessed for eligibility
(n =229)

Reports excluded:
  Conference abstract (n =9)
  Not double-blinded randomized clinical trials (n=12)
  Duplicated database (n =27)
  Comment (n = 0)
  Study protocol (n =0)
  No outcome of interest(n = 116)
  Fixed or dose not reported (n=12)
  Unpublished clinical trials, which did not meet our inclusion criteria (n=12)

Included

Studies included in review
(n = 41)[a]
Reports of included studies
(n = 41)

From: 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. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

[a.] There are 42 randomized-controlled trials in these 41 studies.
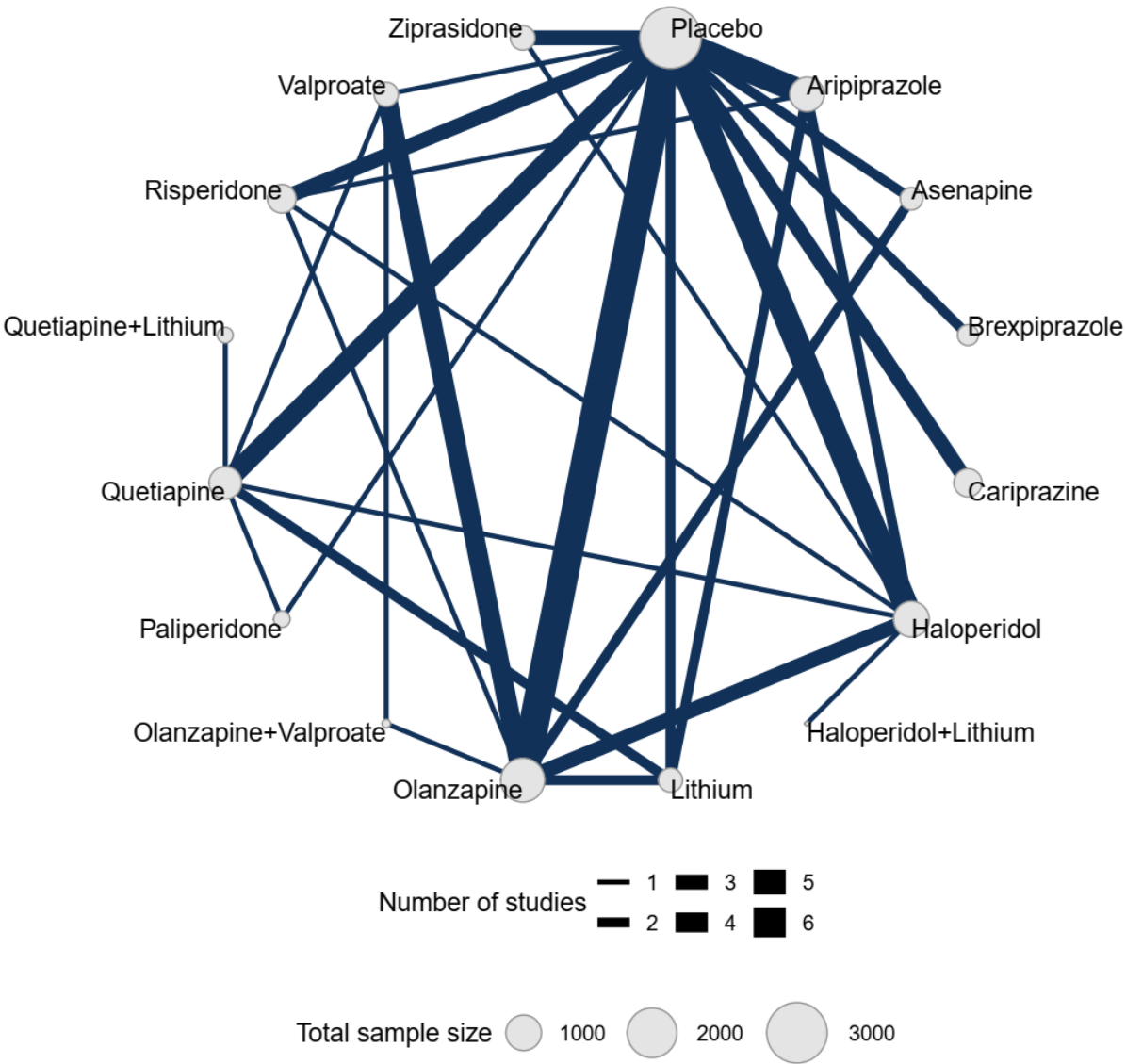
eFigure2. Risk of bias graph across the included 41 studies
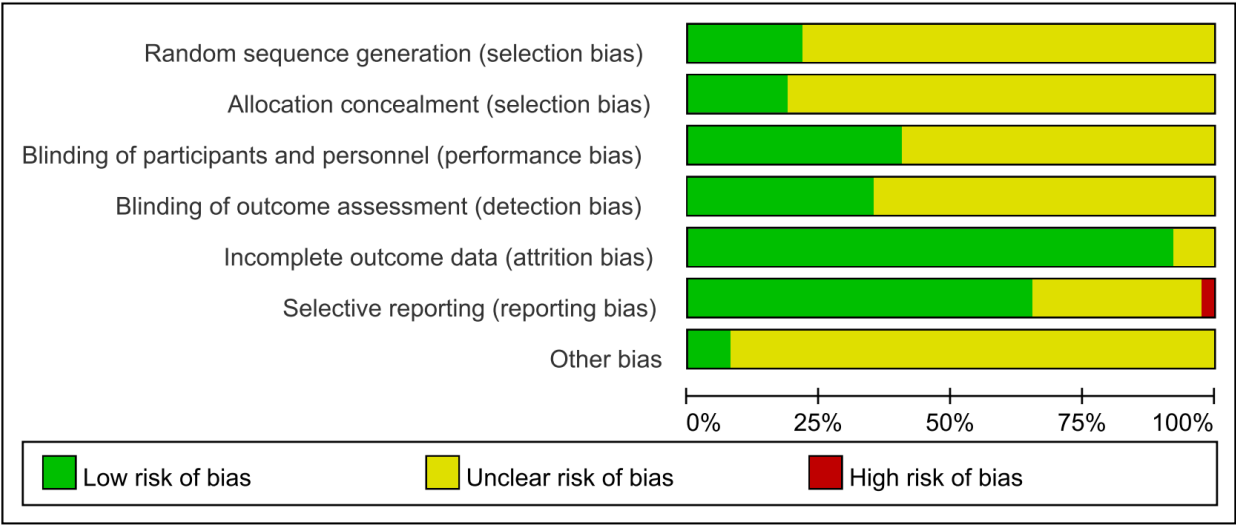
eFigure3. Summary of risk of bias on improvement of manic symptoms of the 41 included studies
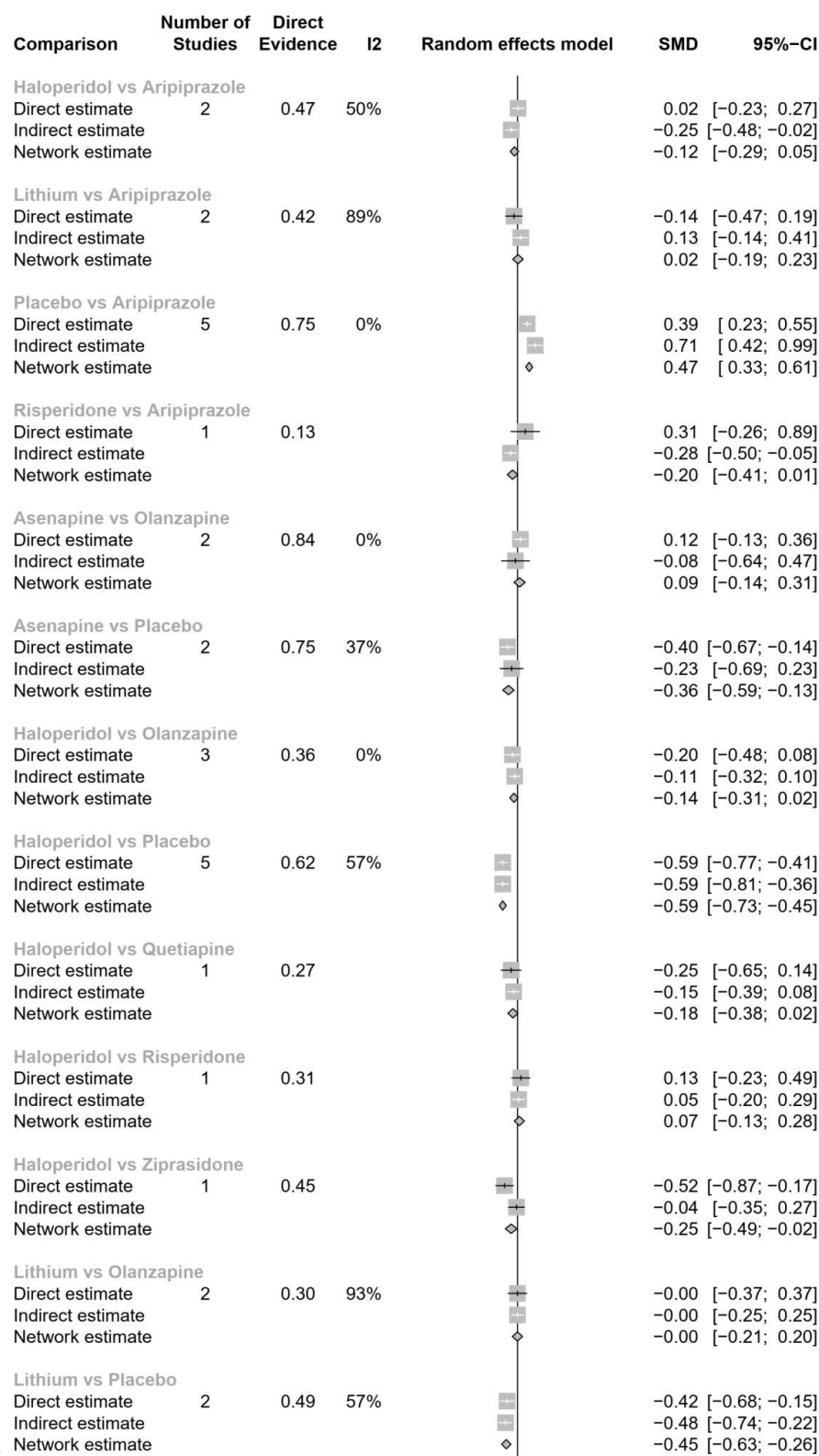
eFigure 4. Network plot

The size of the nodes corresponds to the number of participants assigned to each treatment, and the width of the lines corresponds to the number of trials evaluating the comparisons.

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eFigure 5. Forest plot for local inconsistency test by node-splitting method

Comparison	Number of Studies	Direct Evidence	I2	Random effects model	SMD	95%−CI
Haloperidol vs Aripiprazole						
Direct estimate	2	0.47	50%		0.02	[−0.23; 0.27]
Indirect estimate					−0.25	[−0.48; −0.02]
Network estimate					−0.12	[−0.29; 0.05]
Lithium vs Aripiprazole						
Direct estimate	2	0.42	89%		−0.14	[−0.47; 0.19]
Indirect estimate					0.13	[−0.14; 0.41]
Network estimate					0.02	[−0.19; 0.23]
Placebo vs Aripiprazole						
Direct estimate	5	0.75	0%		0.39	[0.23; 0.55]
Indirect estimate					0.71	[0.42; 0.99]
Network estimate					0.47	[0.33; 0.61]
Risperidone vs Aripiprazole						
Direct estimate	1	0.13			0.31	[−0.26; 0.89]
Indirect estimate					−0.28	[−0.50; −0.05]
Network estimate					−0.20	[−0.41; 0.01]
Asenapine vs Olanzapine						
Direct estimate	2	0.84	0%		0.12	[−0.13; 0.36]
Indirect estimate					−0.08	[−0.64; 0.47]
Network estimate					0.09	[−0.14; 0.31]
Asenapine vs Placebo						
Direct estimate	2	0.75	37%		−0.40	[−0.67; −0.14]
Indirect estimate					−0.23	[−0.69; 0.23]
Network estimate					−0.36	[−0.59; −0.13]
Haloperidol vs Olanzapine						
Direct estimate	3	0.36	0%		−0.20	[−0.48; 0.08]
Indirect estimate					−0.11	[−0.32; 0.10]
Network estimate					−0.14	[−0.31; 0.02]
Haloperidol vs Placebo						
Direct estimate	5	0.62	57%		−0.59	[−0.77; −0.41]
Indirect estimate					−0.59	[−0.81; −0.36]
Network estimate					−0.59	[−0.73; −0.45]
Haloperidol vs Quetiapine						
Direct estimate	1	0.27			−0.25	[−0.65; 0.14]
Indirect estimate					−0.15	[−0.39; 0.08]
Network estimate					−0.18	[−0.38; 0.02]
Haloperidol vs Risperidone						
Direct estimate	1	0.31			0.13	[−0.23; 0.49]
Indirect estimate					0.05	[−0.20; 0.29]
Network estimate					0.07	[−0.13; 0.28]
Haloperidol vs Ziprasidone						
Direct estimate	1	0.45			−0.52	[−0.87; −0.17]
Indirect estimate					−0.04	[−0.35; 0.27]
Network estimate					−0.25	[−0.49; −0.02]
Lithium vs Olanzapine						
Direct estimate	2	0.30	93%		−0.00	[−0.37; 0.37]
Indirect estimate					−0.00	[−0.25; 0.25]
Network estimate					−0.00	[−0.21; 0.20]
Lithium vs Placebo						
Direct estimate	2	0.49	57%		−0.42	[−0.68; −0.15]
Indirect estimate					−0.48	[−0.74; −0.22]
Network estimate					−0.45	[−0.63; −0.26]

eFigure 5

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Lithium vs Quetiapine
Direct estimate	2	0.54	33%		0.06 [−0.22; 0.35]
Indirect estimate					−0.16 [−0.47; 0.15]
Network estimate					−0.04 [−0.25; 0.17]

Olanzapine vs Olanzapine+Valproate
Direct estimate	1	0.86			0.65 [0.12; 1.17]
Indirect estimate					3.80 [2.52; 5.08]
Network estimate					1.10 [0.62; 1.59]

Olanzapine vs Placebo
Direct estimate	6	0.65	0%		−0.44 [−0.61; −0.28]
Indirect estimate					−0.45 [−0.67; −0.23]
Network estimate					−0.45 [−0.58; −0.32]

Olanzapine vs Risperidone
Direct estimate	1	0.30			0.32 [−0.04; 0.67]
Indirect estimate					0.17 [−0.06; 0.41]
Network estimate					0.22 [0.02; 0.41]

Olanzapine vs Valproate
Direct estimate	4	0.88	90%		−0.41 [−0.62; −0.21]
Indirect estimate					−0.25 [−0.80; 0.31]
Network estimate					−0.39 [−0.59; −0.20]

Olanzapine+Valproate vs Valproate
Direct estimate	1	0.70			−2.23 [−2.82; −1.64]
Indirect estimate					0.23 [−0.68; 1.14]
Network estimate					−1.50 [−1.99; −1.00]

Paliperidone vs Placebo
Direct estimate	1	0.75			−0.63 [−1.00; −0.26]
Indirect estimate					−0.49 [−1.12; 0.14]
Network estimate					−0.60 [−0.91; −0.28]

Paliperidone vs Quetiapine
Direct estimate	1	0.83			−0.16 [−0.50; 0.18]
Indirect estimate					−0.32 [−1.08; 0.44]
Network estimate					−0.19 [−0.50; 0.13]

Placebo vs Quetiapine
Direct estimate	4	0.78	0%		0.41 [0.22; 0.59]
Indirect estimate					0.42 [0.06; 0.78]
Network estimate					0.41 [0.24; 0.58]

Placebo vs Risperidone
Direct estimate	3	0.66	0%		0.68 [0.47; 0.89]
Indirect estimate					0.63 [0.34; 0.93]
Network estimate					0.66 [0.49; 0.84]

Placebo vs Valproate
Direct estimate	1	0.35			0.09 [−0.27; 0.46]
Indirect estimate					0.03 [−0.23; 0.30]
Network estimate					0.05 [−0.16; 0.27]

Placebo vs Ziprasidone
Direct estimate	3	0.87	0%		0.43 [0.20; 0.66]
Indirect estimate					−0.28 [−0.88; 0.31]
Network estimate					0.34 [0.12; 0.55]

Quetiapine vs Valproate
Direct estimate	1	0.11			0.22 [−0.58; 1.01]
Indirect estimate					−0.42 [−0.70; −0.15]
Network estimate					−0.36 [−0.62; −0.10]

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         -4   -2    0    2    4
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eFigure 6. Funnel plot with Egger's test