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How to disseminate reviews with network meta-analysis

Andrea Cipriani

Cochrane webinar – May 4th 2020

Disclosure

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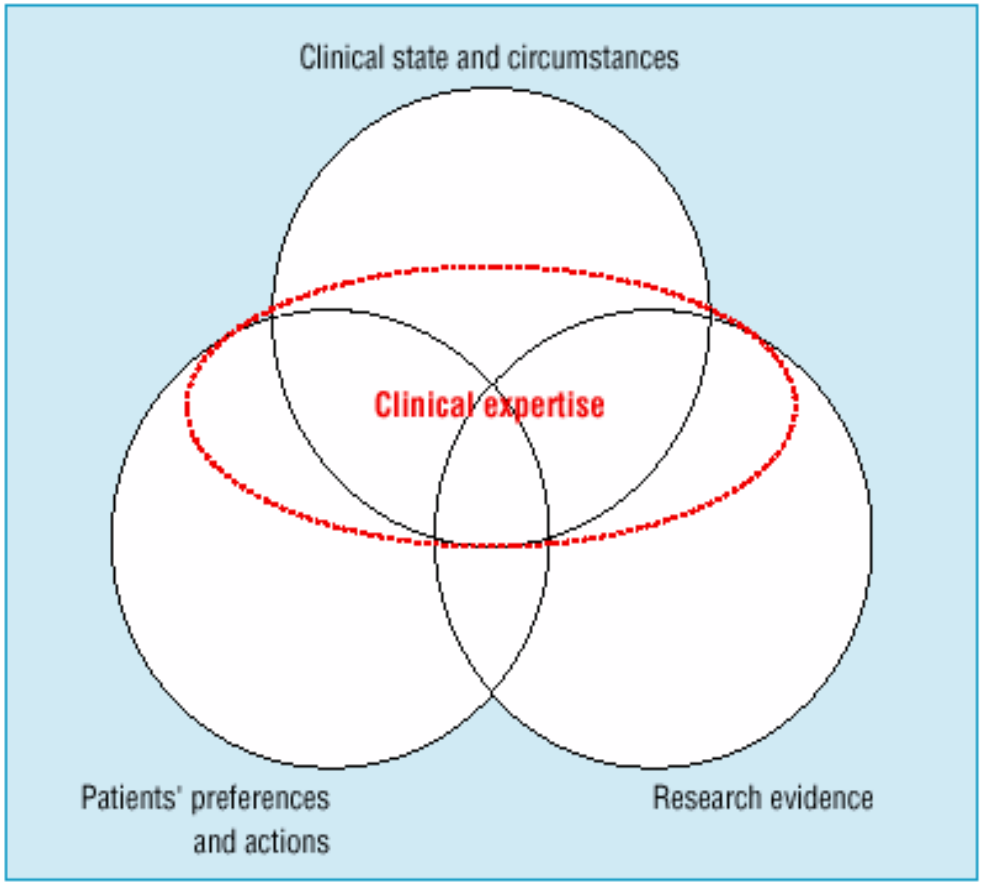
Conflict of interest

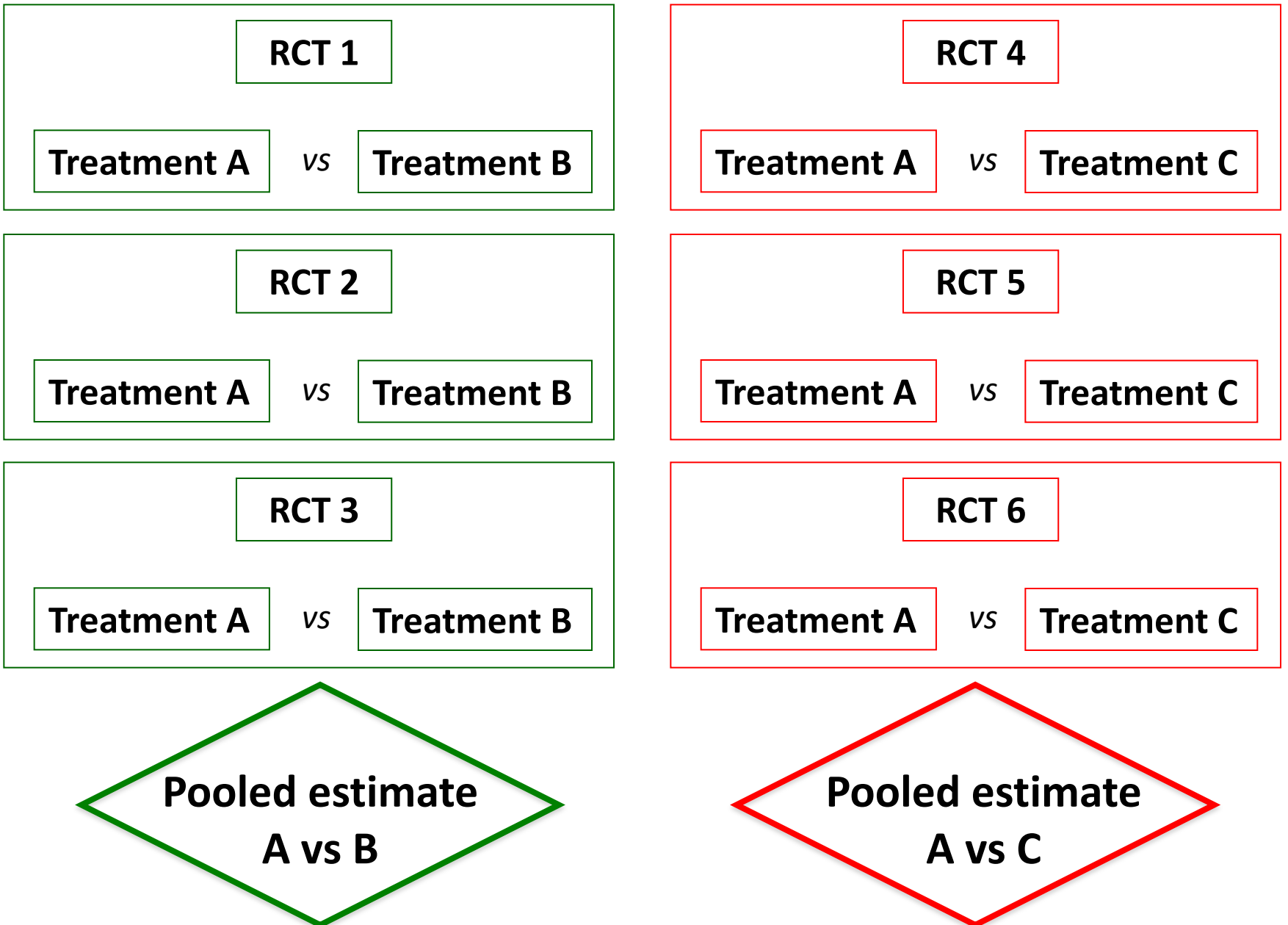
Andrea Cipriani has received research and consultancy fees from INCiPiT (Italian Network for Paediatric Trials), CARIPLO Foundation and Angelini Pharma.

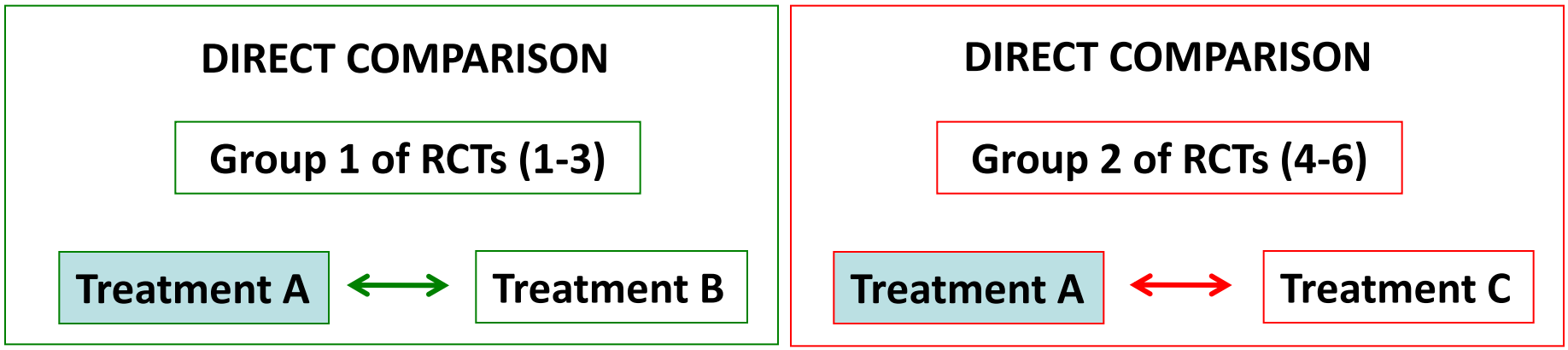


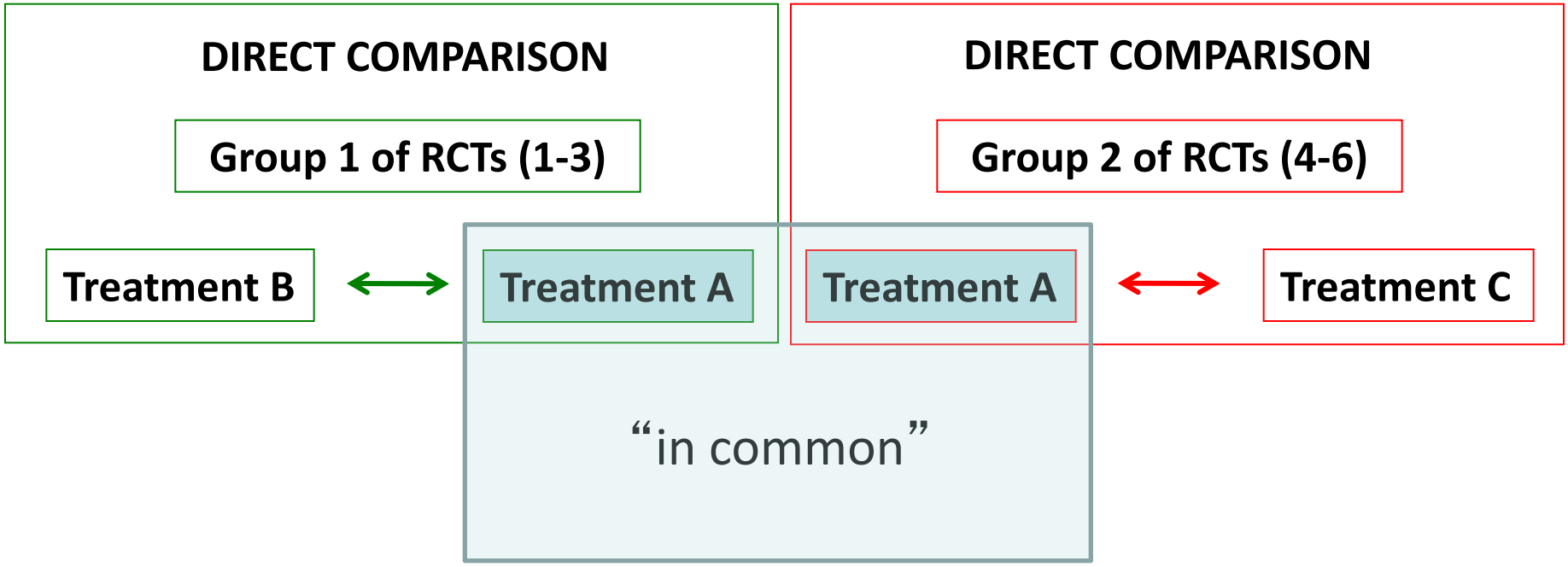
An updated model for evidence based clinical decisions[1]

BMJ 2002;324:1350

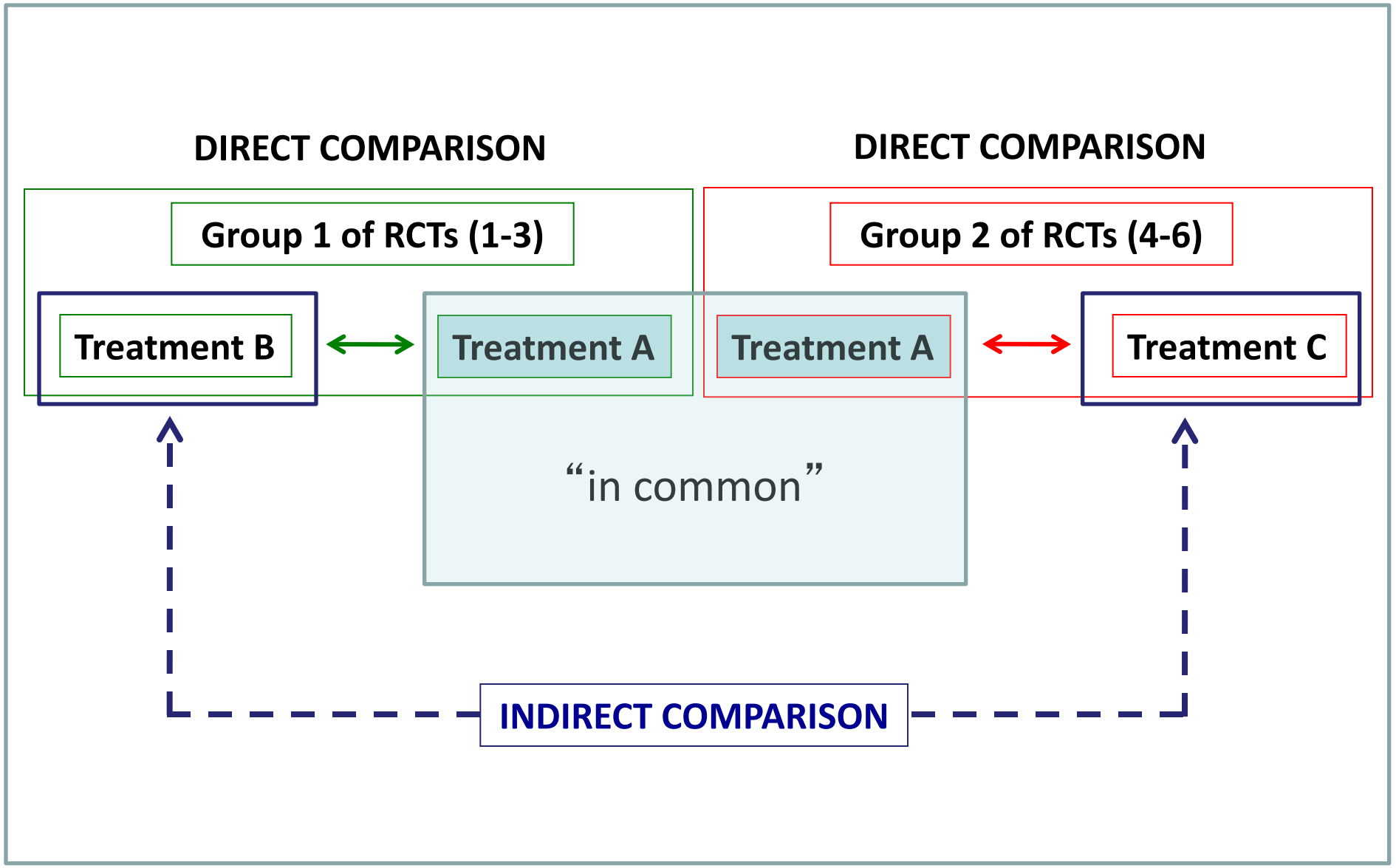
Standard (or pair-wise) meta-analysis



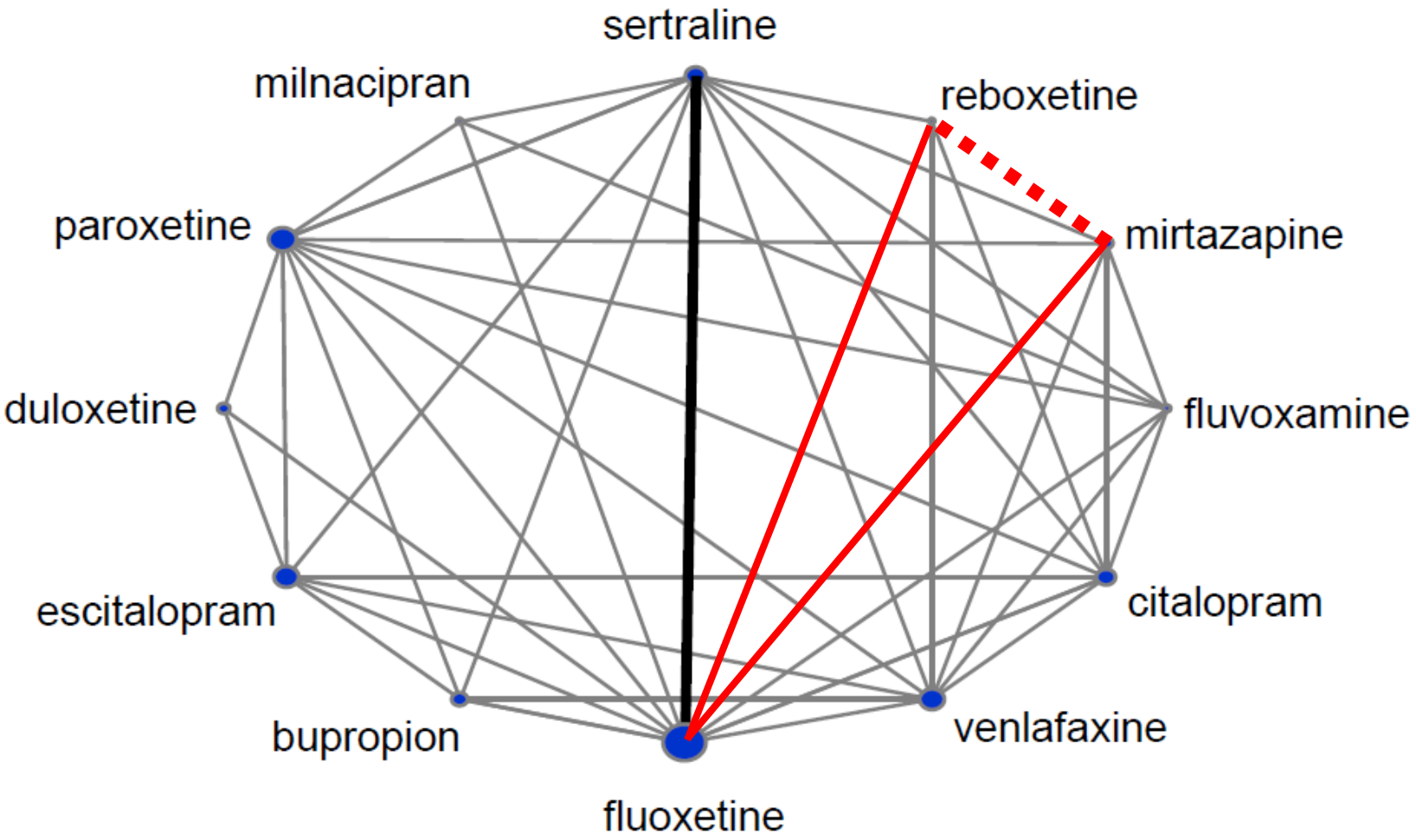

DIRECT COMPARISON
Group 1 of RCTs (1-3)
Treatment A
Treatment B
DIRECT COMPARISON
Group 2 of RCTs (4-6)
Treatment A
Treatment C


DIRECT COMPARISON
Group 1 of RCTs (1-3)
Treatment B
Treatment A
DIRECT COMPARISON
Group 2 of RCTs (4-6)
Treatment A
Treatment C
"in common"

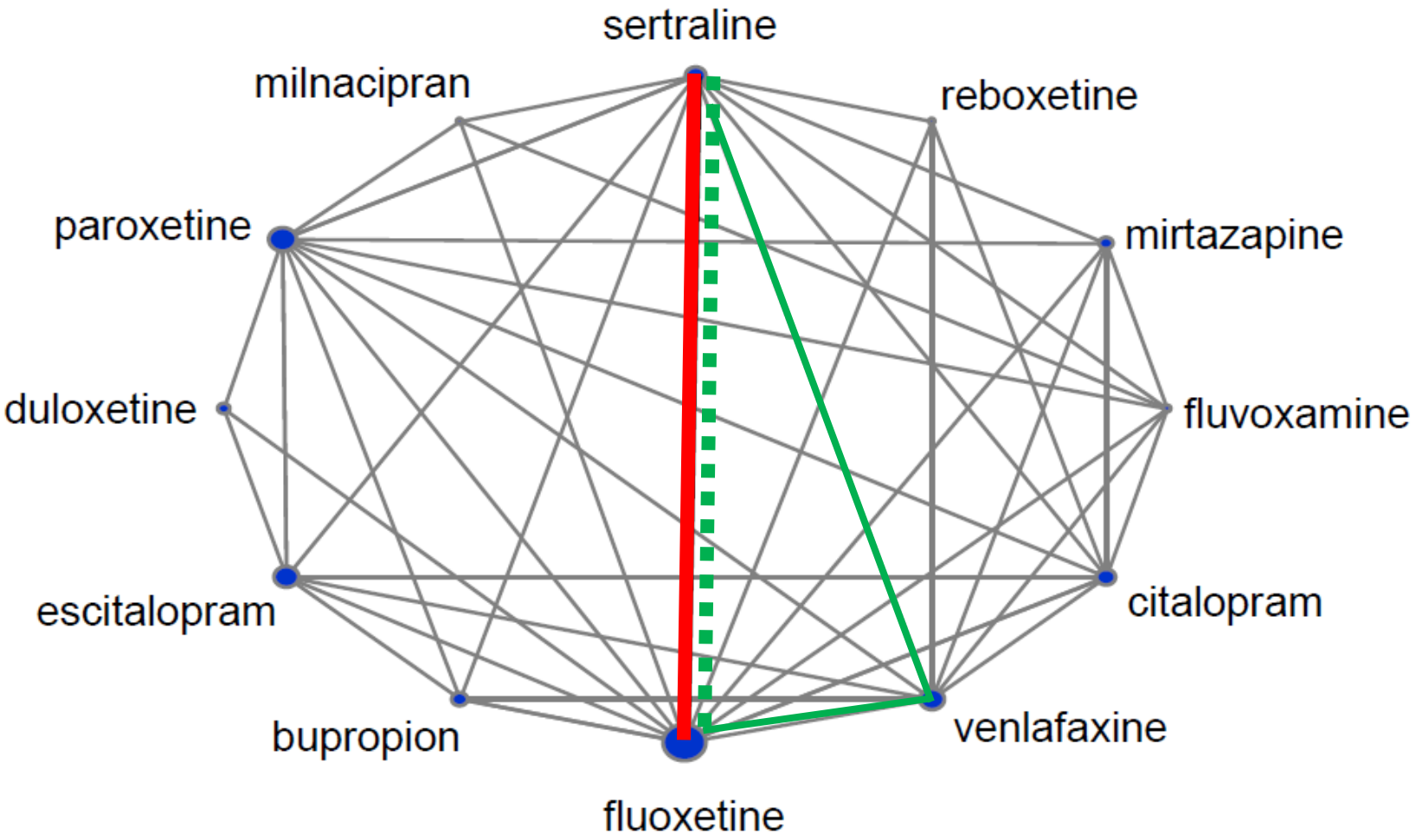
NETWORK (or multiple-treatment) META-ANALYSIS



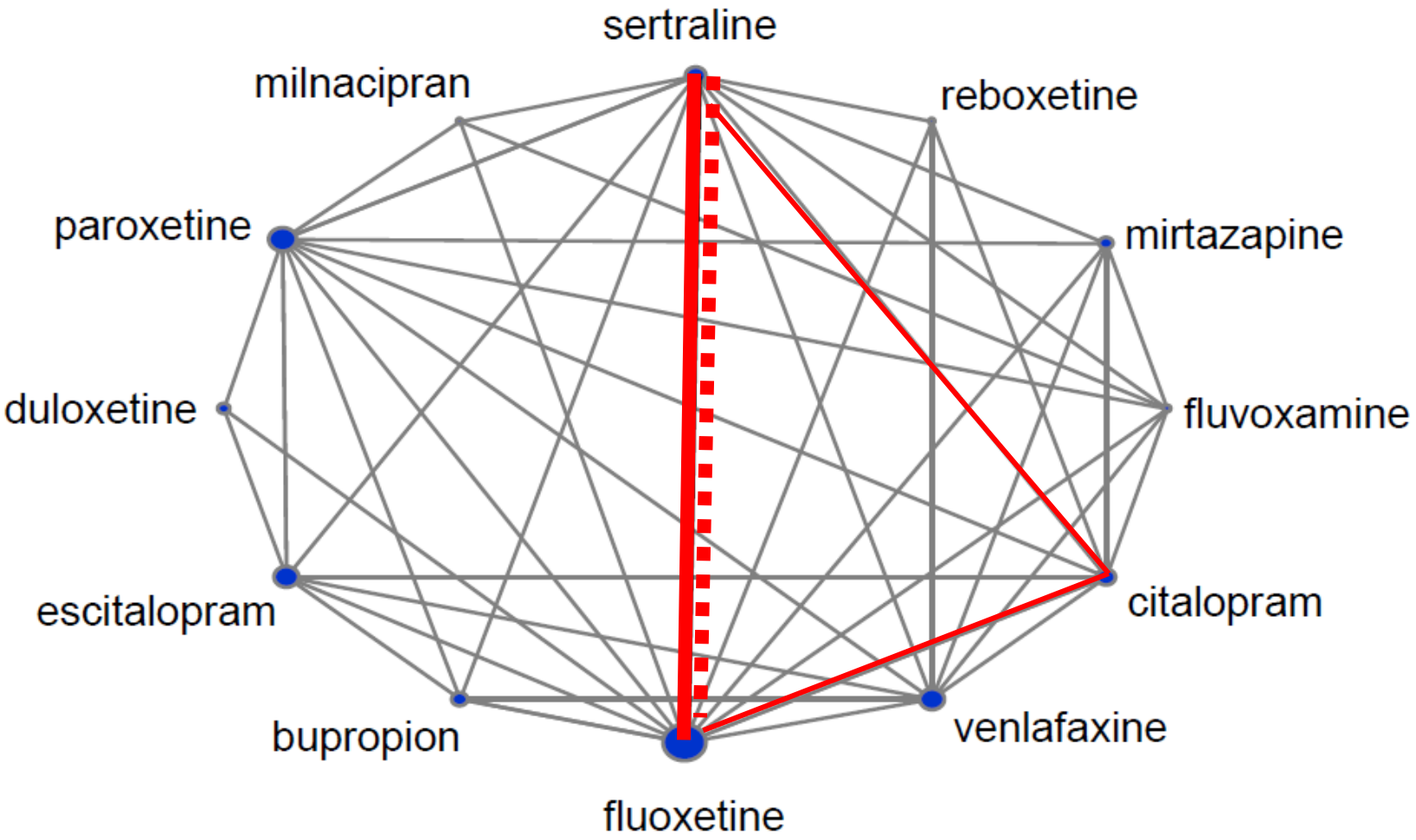
Network of experimental comparisons



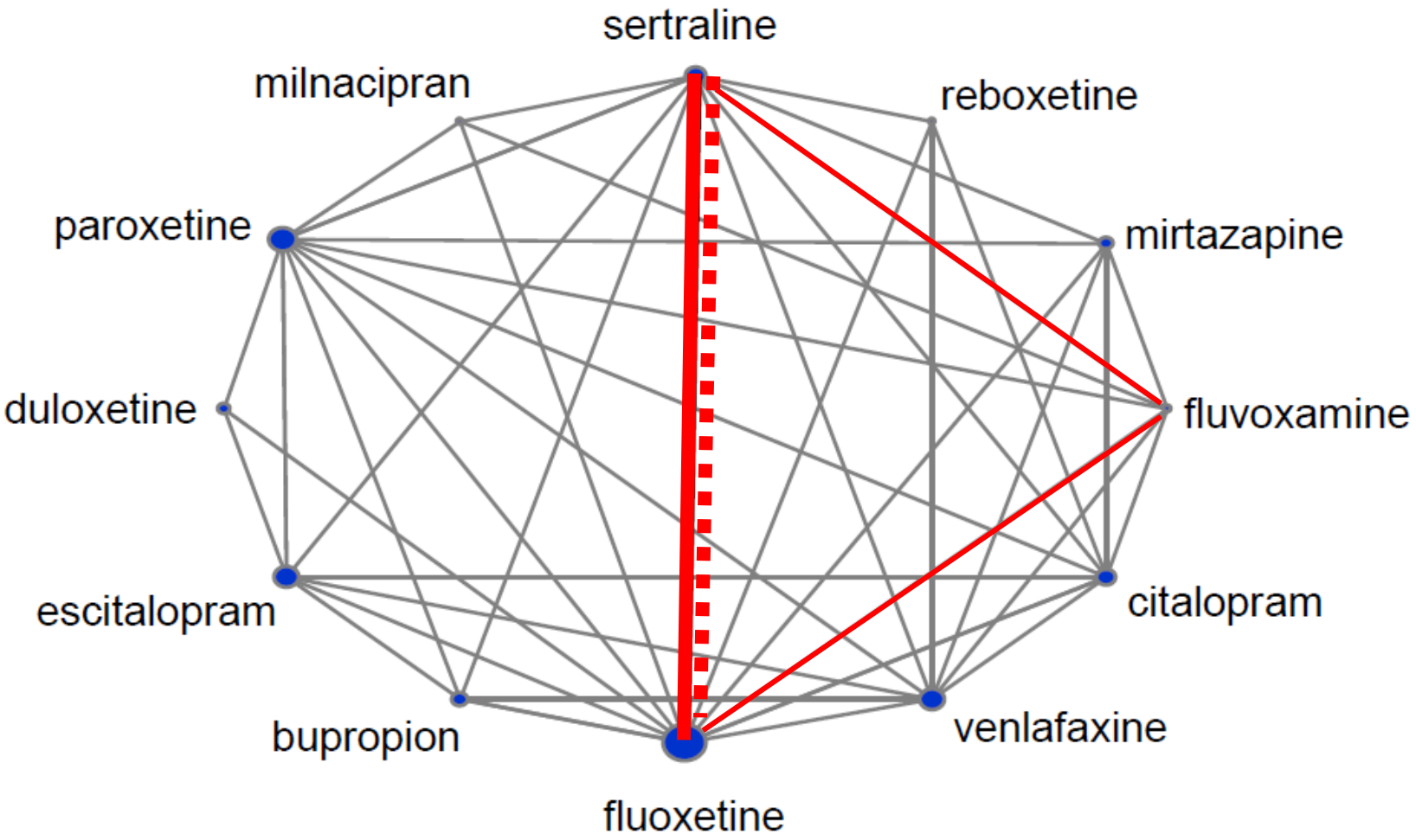
Network of experimental comparisons



Network of experimental comparisons



Network of experimental comparisons



Advantages of NMA

- Comprehensive use of all available data (direct evidence + indirect evidence)
- Comparison of interventions which haven't been directly compared in any trial
- Improved precision for each comparison
- Ranking of many treatments for the same condition

Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis

Andrea Cipriani, Toshiaki A Furukawa, Georgia Salanti, John R Geddes, Julian P T Higgins, Rachel Churchill, Norio Watanabe, Atsuo Nakagawa, Ichiro M Omori, Hugh McGuire, Michele Tansella, Corrado Barbui

Summary

Background Conventional meta-analyses have shown inconsistent results for efficacy of second-generation antidepressants. We therefore did a multiple-treatments meta-analysis, which accounts for both direct and indirect comparisons, to assess the effects of 12 new-generation antidepressants on major depression.

Methods We systematically reviewed 117 randomised controlled trials (25 928 participants) from 1991 up to Nov 30, 2007, which compared any of the following antidepressants at therapeutic dose range for the acute treatment of unipolar major depression in adults: bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, and venlafaxine. The main outcomes were the proportion of patients who responded to or dropped out of the allocated treatment. Analysis was done on an intention-to-treat basis.

Findings Mirtazapine, escitalopram, venlafaxine, and sertraline were significantly more efficacious than duloxetine (odds ratios [OR] 1·39, 1·33, 1·30 and 1·27, respectively), fluoxetine (1·37, 1·32, 1·28, and 1·25, respectively), fluvoxamine (1·41, 1·35, 1·30, and 1·27, respectively), paroxetine (1·35, 1·30, 1·27, and 1·22, respectively), and reboxetine (2·03, 1·95, 1·89, and 1·85, respectively). Reboxetine was significantly less efficacious than all the other antidepressants tested. Escitalopram and sertraline showed the best profile of acceptability, leading to significantly fewer discontinuations than did duloxetine, fluvoxamine, paroxetine, reboxetine, and venlafaxine.

Interpretation Clinically important differences exist between commonly prescribed antidepressants for both efficacy and acceptability in favour of escitalopram and sertraline. Sertraline might be the best choice when starting treatment for moderate to severe major depression in adults because it has the most favourable balance between benefits, acceptability, and acquisition cost.

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Correspondence to:
Dr Andrea Cipriani, Department of Medicine and Public Health, Section of Psychiatry and Clinical Psychology, University of Verona, Policlinico "G B Rossi", Piazzale L A Scuro, 10, 37134, Verona, Italy
andrea.cipriani@univr.it

	Number of studies	Number of patients	Efficacy		Acceptability	
			Response rate (responders/ total randomised)	OR (95% CI)	Dropout rate (dropouts/ total randomised)	OR (95% CI)
Bupropion *vs*						
Escitalopram	3	842	163/279 *vs* 172/287	0·93 (0·60–1·45)	105/417 *vs* 109/425	0·98 (0·72–1·34)
Fluoxetine	3	740	187/369 *vs* 206/371	0·82 (0·62–1·10)	134/369 *vs* 134/371	1·01 (0·75–1·36)
Paroxetine	2	240	34/48 *vs* 40/52	0·73 (0·30–1·79)	22/117 *vs* 26/123	0·86 (0·45–1·63)
Sertraline	3	727	237/364 *vs* 231/363	1·07 (0·79–1·45)	63/242 *vs* 82/237	0·66 (0·38–1·16)
Venlafaxine	3	1127	307/563 *vs* 329/564	0·85 (0·63–1·16)	150/563 *vs* 152/564	0·99 (0·76–1·31)
Duloxetine *vs*						
Escitalopram	3	1120	260/562 *vs* 286/558	0·77 (0·52–1·13)	131/411 *vs* 87/414	1·93 (0·99–3·77)
Fluoxetine	1	103	32/70 *vs* 15/33	1·01 (0·44–2·32)	24/70 *vs* 12/33	0·91 (0·38–2·16)
Paroxetine	4	1095	398/736 *vs* 200/359	0·91 (0·61–1·35)	171/736 *vs* 90/359	0·91 (0·67–1·24)
Fluoxetine* *vs*						
Bupropion	3	740	206/371 *vs* 187/369	1·21 (0·91–1·62)	134/371 *vs* 134/369	0·99 (0·73–1·34)
Citalopram	3	740	219/376 *vs* 216/364	0·95 (0·70–1·29)	68/376 *vs* 75/364	0·86 (0·59–1·25)
Duloxetine	1	103	15/33 *vs* 32/70	0·99 (0·43–2·27)	12/33 *vs* 24/70	1·09 (0·46–2·60)
Escitalopram	2	543	126/267 *vs* 143/276	0·81 (0·57–1·15)	68/267 *vs* 66/276	1·02 (0·39–2·67)
Fluvoxamine	2	284	83/143 *vs* 83/141	0·97 (0·60–1·55)	28/143 *vs* 31/141	0·85 (0·48–1·52)
Milnacipran	3	560	106/224 *vs* 156/336	1·15 (0·72–1·85)	83/224 *vs* 138/336	0·98 (0·68–1·42)
Mirtazapine	5	622	176/316 *vs* 200/306	0·65 (0·45–0·93)	48/164 *vs* 50/159	0·92 (0·56–1·49)
Paroxetine*	13	2806	771/1287 *vs* 740/1277	1·01 (0·82–1·24)	447/1406 *vs* 468/1400	0·93 (0·79–1·09)
Reboxetine	4	764	204/387 *vs* 168/377	1·39 (0·93–2·09)	98/387 *vs* 126/377	0·68 (0·49–0·94)
Sertraline*	8	1352	344/666 *vs* 406/686	0·70 (0·56–0·88)	151/546 *vs* 135/568	1·25 (0·88–1·77)
Venlafaxine	12	2446	607/1126 *vs* 679/1116	0·74 (0·62–0·88)	290/1226 *vs* 302/1220	0·94 (0·78–1·13)

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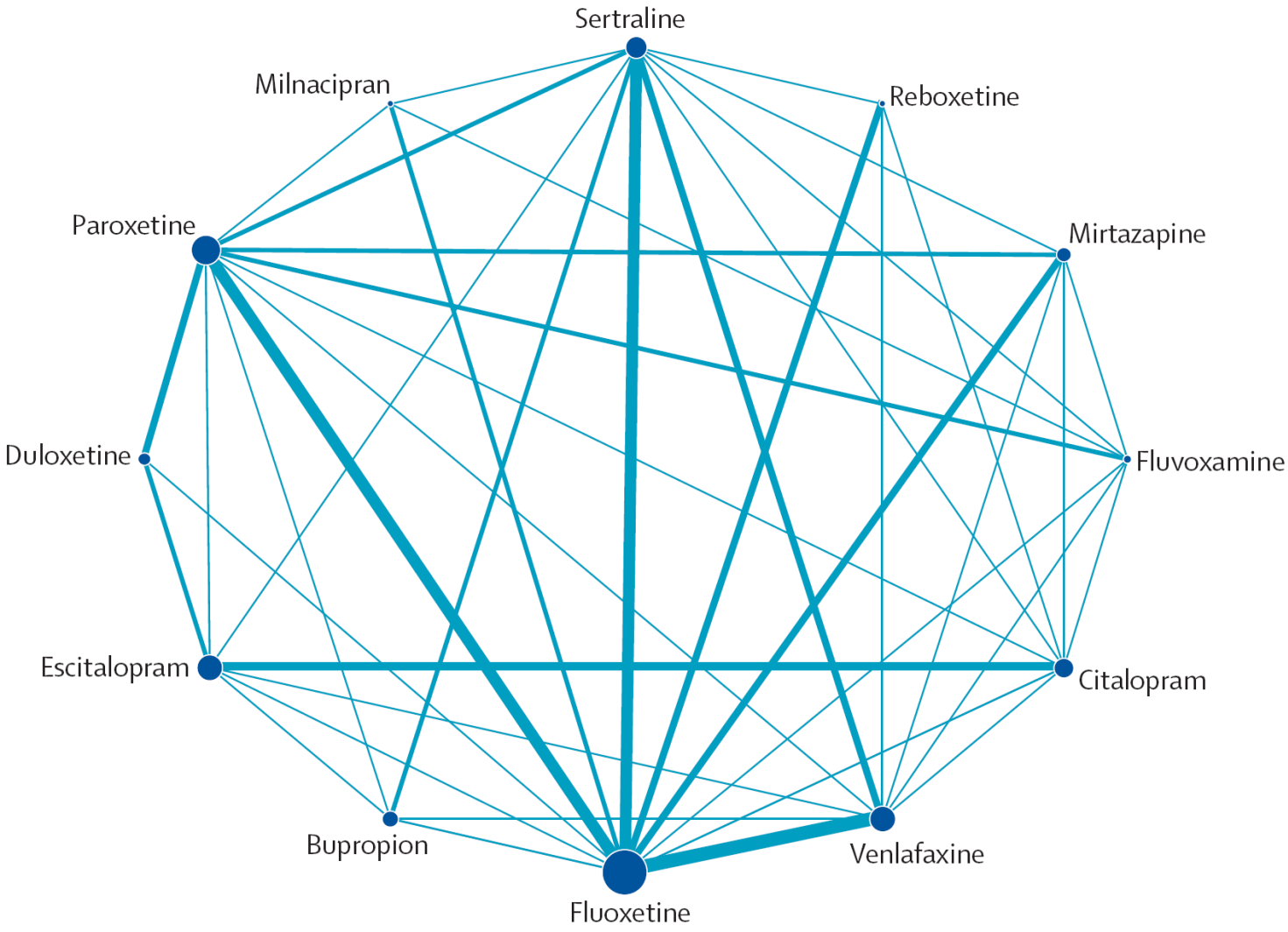


Figure 2: **Network of eligible comparisons for the multiple-treatment meta-analysis for efficacy (response rate)**
The width of the lines is proportional to the number of trials comparing each pair of treatments, and the size of each node is proportional to the number of randomised participants (sample size). The network of eligible comparisons for acceptability (dropout rate) analysis is similar.

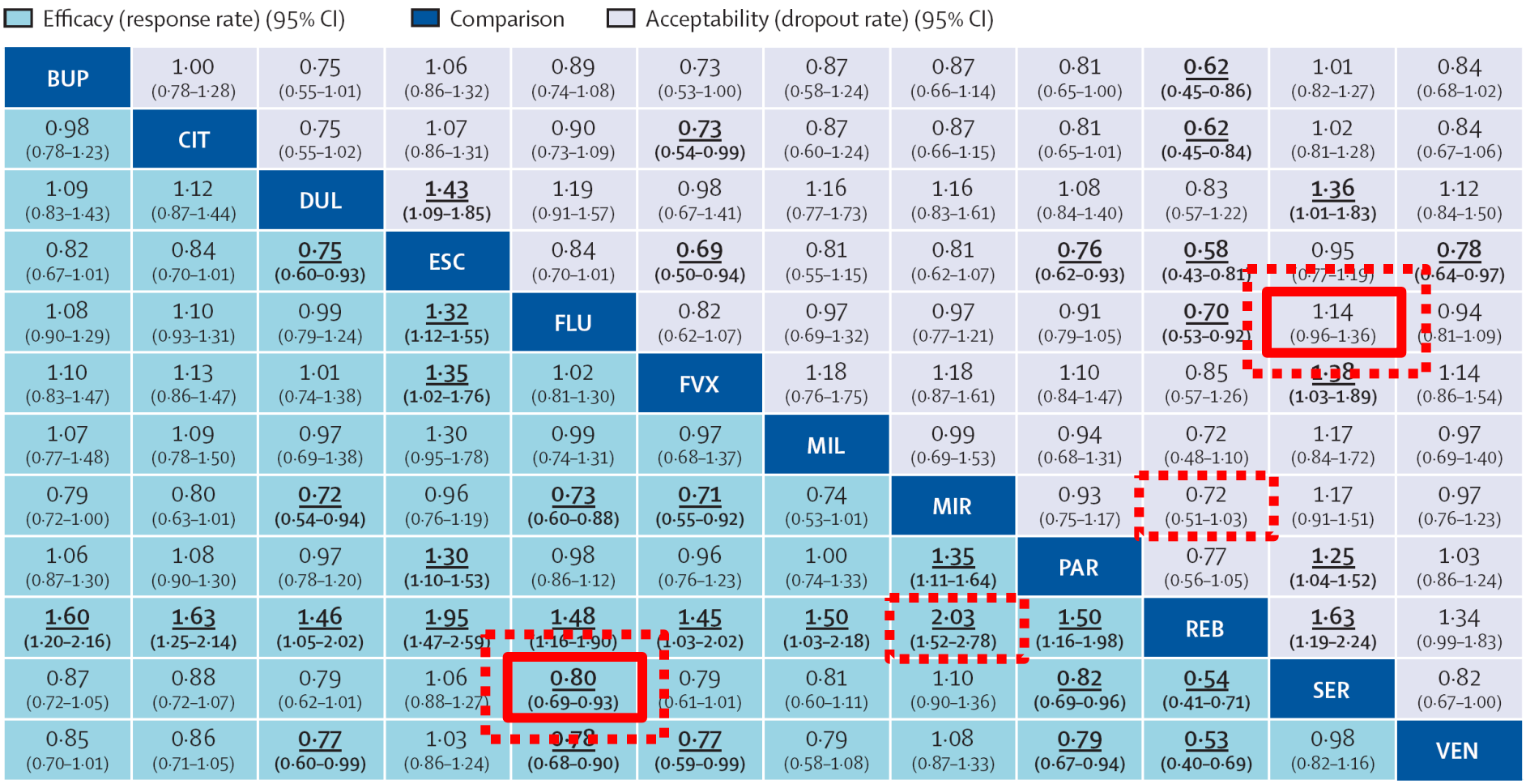


***Figure 3*: Efficacy and acceptability of the 12 antidepressants**

Drugs are reported in alphabetical order. Results are the ORs in the column-defining treatment compared with the ORs in the row-defining treatment. For efficacy, ORs higher than 1 favour the column-defining treatment (ie, the first in alphabetical order). For acceptability, ORs lower than 1 favour the first drug in alphabetical order. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken (eg, the OR for FLU compared with CIT is 1/1·10=0·91). Significant results are in bold and underscored. BUP=bupropion. CIT=citalopram. DUL=duloxetine. ESC=escitalopram. FLU=fluoxetine. FVX=fluvoxamine. MIL=milnacipran. MIR=mirtazapine. PAR=paroxetine. REB=reboxetine. SER=sertraline. VEN=venlafaxine. MTM=multiple-treatments meta-analysis. OR=Odds ratio. CI=credibility interval.

Ranking measures from MTM

- Estimate for each treatment the probability to be the best

% probability	A	B	C	D
j=1	0.25	0.50	0.25	0.00
j=2	0.25	0.25	0.50	0.00
j=3	0.25	0.25	0.25	0.25
j=4	0.25	0	0	0.75

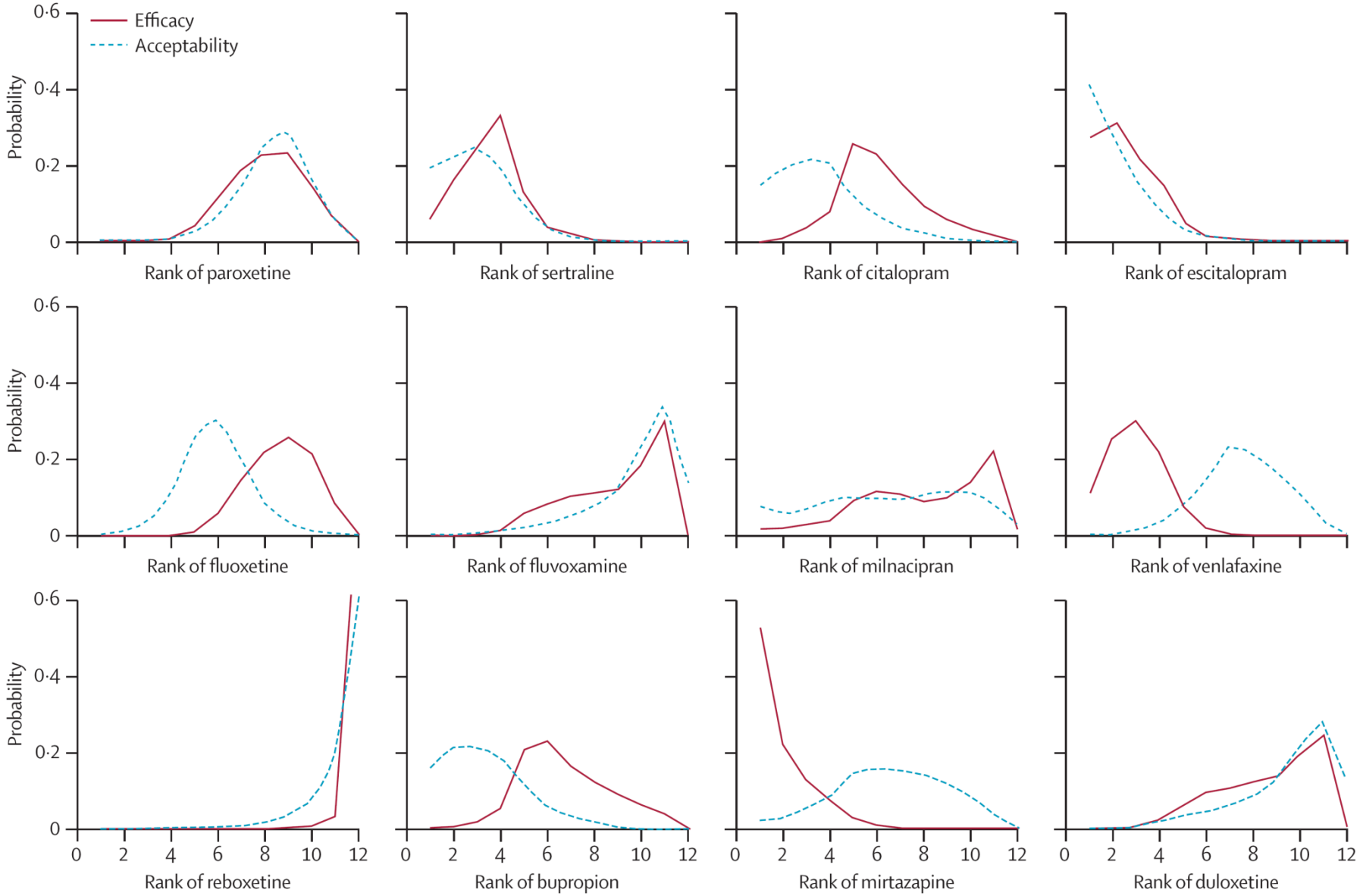


Figure 4: **Ranking for efficacy (solid line) and acceptability (dotted line)**
Ranking indicates the probability to be the best treatment, the second best, the third best, and so on, among the 12 antidepressants.

The cumulative probabilities of being among the four most efficacious treatments and among the four best treatments in terms of acceptability

	Efficacy		Acceptability	
Rank	**Drug**	**%**	**Drug**	**%**
1.	Mirtazapine	*24·4*	Escitalopram	*27·6*
2.	Escitalopram	*23·7*	Sertraline	*21·3*
3.	Venlafaxine	*22·3*	Bupropion	*19·3*
4.	Sertraline	*20·3*	Citalopram	*18·7*
5.	Citalopram	*3·4*	Milnacipran	*7·1*
6.	Milnacipran	*2·7*	Mirtazapine	*4·4*
7.	Bupropion	*2·0*	Fluoxetine	*3·4*
8.	Duloxetine	*0·9*	Venlafaxine	*0·9*
9.	Fluvoxamine	*0·7*	Duloxetine	*0·7*
10.	Paroxetine	*0·1*	Fluvoxamine	*0·4*
11.	Fluoxetine	*0·0*	Paroxetine	*0·2*
12.	Reboxetine	*0·0*	Reboxetine	*0·1*

Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis

Andrea Cipriani, Corrado Barbui, Georgia Salanti, Jennifer Rendell, Rachel Brown, Sarah Stockton, Marianna Purgato, Loukia M Spineli, Guy M Goodwin, John R Geddes

Department of Public Health and Community Medicine, Section of Psychiatry and Clinical Psychology, University of Verona, Verona, Italy (A Cipriani PhD, Prof C Barbui MD, M Purgato PsyD); **Department of Hygiene and Epidemiology University of Ioannina School of Medicine, Ioannina, Greece** (Prof G Salanti PhD, L M Spineli MSc); **and Department of Psychiatry, University of Oxford, Oxford, UK** (J Rendell PhD, S Stockton BA (Hons), R Brown BPharm, Prof G M Goodwin FMedSci, Prof J R Geddes MD)

Correspondence to: Dr Andrea Cipriani, WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation, Policlinico "G.B. Rossi", Piazzale LA Scuro, 10, 37134 Verona, Italy
andrea.cipriani@univr.it

Lancet 2011; 378: 1306–15

Summary

Background Conventional meta-analyses have shown inconsistent results for efficacy of pharmacological treatments for acute mania. We did a multiple-treatments meta-analysis, which accounted for both direct and indirect comparisons, to assess the effects of all antimanic drugs.

Methods We systematically reviewed 68 randomised controlled trials (16 073 participants) from Jan 1, 1980, to Nov 25, 2010, which compared any of the following pharmacological drugs at therapeutic dose range for the treatment of acute mania in adults: aripiprazole, asenapine, carbamazepine, valproate, gabapentin, haloperidol, lamotrigine, lithium, olanzapine, quetiapine, risperidone, topiramate, and ziprasidone. The main outcomes were the mean change on mania rating scales and the number of patients who dropped out of the allocated treatment at 3 weeks. Analysis was done by intention to treat.

Findings Haloperidol (standardised mean difference [SMD] –0·56 [95% CI –0·69 to –0·43]), risperidone (–0·50 [–0·63 to –0·38]), olanzapine (–0·43 [–0·54 to –0·32], lithium (–0·37 [–0·63 to –0·11]), quetiapine (–0·37 [–0·51 to –0·23]), aripiprazole (–0·37 [–0·51 to –0·23]), carbamazepine (–0·36 [–0·60 to –0·11], asenapine (–0·30 [–0·53 to –0·07]), valproate (–0·20 [–0·37 to –0·04]), and ziprasidone (–0·20 [–0·37 to –0·03]) were significantly more effective than placebo, whereas gabapentin, lamotrigine, and topiramate were not. Haloperidol had the highest number of significant differences and was significantly more effective than lithium (SMD –0·19 [95% CI –0·36 to –0·01]), quetiapine (–0·19 [–0·37 to 0·01]), aripiprazole (–0·19 [–0·36 to –0·02]), carbamazepine (–0·20 [–0·36 to –0·01]), asenapine (–0·26 [–0·52 to 0·01]), valproate (–0·36 [–0·56 to –0·15]), ziprasidone (–0·36 [–0·56 to –0·15]), lamotrigine (–0·48 [–0·77 to –0·19]), topiramate (–0·63 [–0·84 to –0·43]), and gabapentin (–0·88 [–1·40 to –0·36]). Risperidone and olanzapine had a very similar profile of comparative efficacy, being more effective than valproate, ziprasidone, lamotrigine, topiramate, and gabapentin. Olanzapine, risperidone, and quetiapine led to significantly fewer discontinuations than did lithium, lamotrigine, placebo, topiramate, and gabapentin.

Interpretation Overall, antipsychotic drugs were significantly more effective than mood stabilisers. Risperidone, olanzapine, and haloperidol should be considered as among the best of the available options for the treatment of manic episodes. These results should be considered in the development of clinical practice guidelines.

	Number of studies	Overall number of patients	Efficacy		Acceptability
			Standardised mean difference (95% CI)	Response rate OR (95% CI)	Dropout rate OR (95% CI)
Aripiprazole *vs*					
Haloperidol	2	679	0·05 (–0·10 to 0·20)	1·16 (0·76 to 1·77)	0·58 (0·25 to 1·35)
Lithium	1	315	–0·06 (–0·28 to 0·16)	1·09 (0·70 to 1·70)	1·07 (0·69 to 1·66)
Placebo	6	1959	–0·31 (–0·42 to –0·20)	1·75 (1·37 to 2·24)	0·86 (0·62 to 1·19)
Asenapine *vs*					
Olanzapine	2	774	0·22 (0·08 to 0·37)	0·68 (0·46 to 1·03)	2·04 (1·49 to 2·86)
Placebo	2	582	–0·42 (–0·59 to –0·24)	2·04 (1·20 to 3·45)	0·80 (0·56 to 1·14)
Carbamazepine *vs*					
Valproate	1	30	0·85 (0·10 to 1·60)	0·41 (0·09 to 1·92)	1·00 (0·16 to 5·88)
Haloperidol	3	70	–0·09 (–0·56 to 0·38)	0·80 (0·12 to 5·56)	0·81 (0·06 to 10·00)
Lithium	2	67	0·23 (–0·30 to 0·76)	..	0·81 (0·08 to 8·33)
Placebo	1	443	–0·50 (–0·69 to –0·30)	3·12 (2·08 to 4·76)	0·71 (0·49 to 1·04)
Gabapentin *vs*					
Placebo	1	118	0·32 (–0·08 to 0·72)	..	1·75 (0·83 to 3·70)
Haloperidol *vs*					
Aripiprazole	2	679	–0·05 (–0·20 to 0·10)	0·86 (0·56 to 1·32)	1·72 (0·74 to 4·00)
Carbamazepine	3	70	0·09 (–0·38 to 0·56)	1·25 (0·18 to 8·44)	1·23 (0·10 to 15·43)
Lithium	2	44	–1·11 (–1·89 to –0·33)	..	0·98 (0·09 to 11·11)
Olanzapine	2	578	–0·15 (–0·32 to 0·03)	1·14 (0·76 to 1·70)	1·86 (0·81 to 4·30)
Placebo	6	1285	–0·58 (–0·77 to –0·39)	2·27(1·54 to 3·33)	0·72 (0·50 to 1·06)
Quetiapine	1	201	–0·42 (–0·71 to –0·14)	1·71 (0·98 to 3·00)	0·52 (0·28 to 0·98)
Risperidone	3	433	0·02 (–0·17 to 0·21)	0·95 (0·60 to 1·51)	1·36 (0·72 to 2·57)
Ziprasidone	1	350	–0·51 (–0·72 to –0·29)	2·05 (1·33 to 3·14)	0·83 (0·55 to 1·28)
Lamotrigine *vs*					
Lithium	3	303	0·21 (–0·02 to 0·50)	0·76 (0·18 to 3·23)	1·01 (0·26 to 3·85)

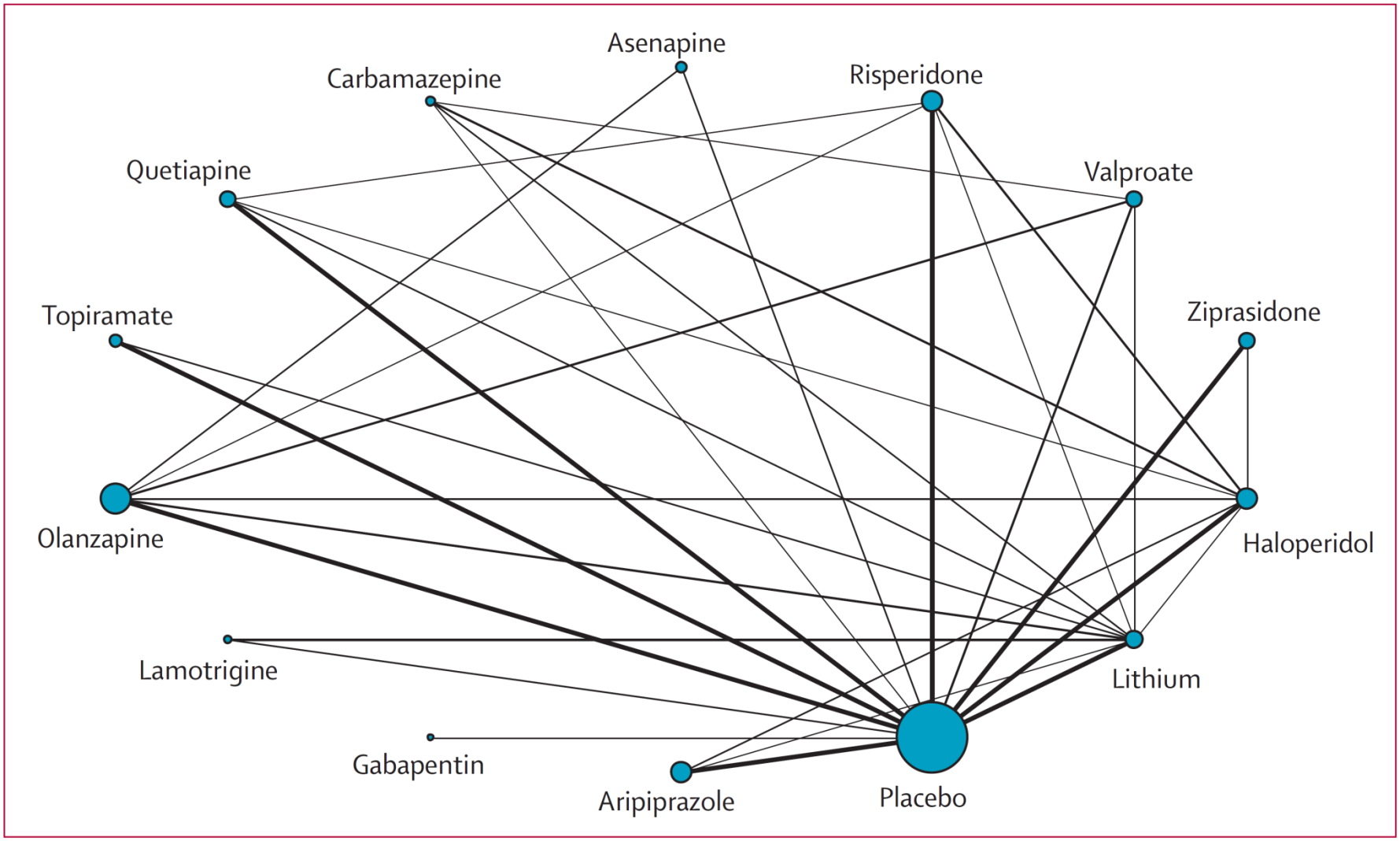


Figure 2: **Network of eligible comparisons for the multiple-treatments meta-analysis for efficacy**
The width of the lines is proportional to the number of trials comparing every pair of treatments, and the size of every node is proportional to the number of randomised participants (sample size). The networks of eligible comparisons for acceptability analysis dropout rate) and for efficacy as binary outcome are similar (webappendix pp 26–27).

HAL	1·40 (0·93 to 2·11)	**1·49 (1·03 to 2·15)**	0·81 (0·53 to 1·22)	1·32 (0·85 to 2·06)	1·11 (0·75 to 1·66)	1·16 (0·63 to 2·14)	0·86 (0·46 to 1·60)	1·16 (0·73 to 1·86)	0·93 (0·59 to 1·49)	0·69 (0·36 to 1·36)	0·85 (0·62 to 1·15)	**0·56 (0·34 to 0·93)**	0·48 (0·16 to 1·44)
−0·06 (−0·22 to 0·11)	**RIS**	1·06 (0·72 to 1·56)	**0·58 (0·37 to 0·88)**	0·94 (0·60 to 1·47)	0·80 (0·51 to 1·25)	0·83 (0·44 to 1·57)	0·62 (0·33 to 1·16)	0·83 (0·51 to 1·34)	0·67 (0·41 to 1·10)	**0·50 (0·25 to 0·98)**	**0·61 (0·44 to 0·83)**	**0·40 (0·24 to 0·68)**	0·34 (0·11 to 1·03)
−0·12 (−0·28 to 0·02)	−0·07 (−0·22 to 0·08)	**OLZ**	**0·54 (0·37 to 0·79)**	0·88 (0·58 to 1·36)	0·75 (0·49 to 1·13)	0·78 (0·43 to 1·44)	0·58 (0·33 to 1·00)	0·78 (0·52 to 1·17)	0·63 (0·40 to 1·00)	**0·47 (0·24 to 0·89)**	**0·57 (0·44 to 0·74)**	**0·38 (0·23 to 0·61)**	**0·32 (0·11 to 0·95)**
−0·19 (−0·36 to −0·01)	−0·13 (−0·30 to 0·04)	−0·06 (−0·22 to 0·10)	**LIT**	**1·63 (1·06 to 2·54)**	1·38 (0·91 to 2·12)	1·44 (0·81 to 2·60)	1·07 (0·57 to 2·00)	1·44 (0·92 to 2·28)	1·15 (0·71 to 1·91)	0·86 (0·47 to 1·59)	1·05 (0·78 to 1·43)	0·70 (0·44 to 1·11)	0·60 (0·20 to 1·77)
−0·19 (−0·37 to −0·01)	−0·13 (−0·31 to 0·04)	−0·07 (−0·24 to 0·11)	−0·01 (−0·18 to 0·17)	**QTP**	0·85 (0·52 to 1·35)	0·88 (0·46 to 1·70)	0·66 (0·34 to 1·25)	0·88 (0·53 to 1·46)	0·71 (0·42 to 1·20)	0·53 (0·27 to 1·05)	**0·64 (0·45 to 0·91)**	**0·43 (0·25 to 0·73)**	0·36 (0·12 to 1·10)
−0·19 (−0·36 to −0·02)	−0·13 (−0·31 to 0·05)	−0·06 (−0·23 to 0·11)	−0·01 (−0·18 to 0·17)	0·00 (−0·19 to 0·20)	**ARI**	1·04 (0·55 to 1·98)	0·77 (0·41 to 1·47)	1·05 (0·64 to 1·70)	0·84 (0·51 to 1·39	0·62 (0·32 to 1·24)	0·76 (0·55 to 1·06)	**0·50 (0·30 to 0·85)**	0·43 (0·14 to 1·29)
−0·20 (−0·36 to −0·01)	−0·14 (−0·42 to 0·12)	−0·08 (−0·34 to 0·18)	−0·02 (−0·28 to 0·24)	−0·01 (−0·30 to 0·26)	−0·01 (−0·29 to 0·26)	**CBZ**	0·74 (0·34 to 1·62)	1·00 (0·52 to 1·91)	0·80 (0·41 to 1·59)	0·60 (0·27 to 1·33)	0·73 (0·42 to 1·28)	**0·48 (0·25 to 0·96)**	0·41 (0·13 to 1·37)
−0·26 (−0·52 to −0·01)	−0·20 (−0·46 to 0·05)	−0·14 (−0·36 to 0·10)	−0·08 (−0·41 to 0·27)	−0·07 (−0·34 to 0·20)	−0·07 (−0·34 to 0·20)	−0·06 (−0·39 to 0·28)	**ASE**	1·35 (0·71 to 2·58)	1·08 (0·56 to 2·14)	0·81 (0·36 to 1·83)	0·98 (0·57 to 1·72)	0·65 (0·33 to 1·30)	0·56 (0·17 to 1·82)
−0·36 (−0·56 to −0·15)	**−0·30 (−0·50 to −0·10)**	**−0·23 (−0·40 to −0·06)**	−0·10 (−0·41 to 0·23)	−0·17 (−0·38 to 0·05)	−0·17 (−0·38 to 0·05)	−0·15 (−0·44 to 0·13)	−0·10 (−0·37 to 0·18)	**VAL**	0·80 (0·47 to 1·37)	0·60 (0·30 to 1·20)	0·73 (0·51 to 1·05)	**0·48 (0·28 to 0·83)**	0·41 (0·13 to 1·25)
−0·36 (−0·56 to −0·15)	**−0·31 (−0·51 to −0·10)**	**−0·24 (−0·43 to −0·03)**	−0·15 (−0·44 to 0·16)	−0·17 (−0·39 to 0·05)	−0·18 (−0·39 to 0·04)	−0·16 (−0·45 to 0·14)	−0·10 (−0·39 to 0·18)	−0·01 (−0·24 to 0·23)	**ZIP**	0·75 (0·37 to 1·51)	0·91 (0·61 to 1·34)	0·61 (0 34 to 1 06)	0·52 (0 17 to 1 58)
−0·48 (−0·77 to −0·19)	**−0·43 (−0·71 to −0·14)**	**−0·36 (−0·64 to −0·08)**	−0·32 (−0·67 to 0·06)	−0·29 (−0·58 to 0·00)	−0·29 (−0·58 to 0·00)	−0·28 (−0·63 to 0·08)	−0·22 (−0·57 to 0·12)	−0·13 (−0·43 to 0·18)	−0·12 (−0·43 to 0·19)	**LAM**	1·22 (0·67 to 2·21)	0·81 (0·40 to 1·65)	0·69 (0·21 to 2·30)
−0·56 (−0·69 to −0·43)	**−0·50 (−0·63 to −0·38)**	**−0·43 (−0·54 to −0·32)**	**−0·37 (−0·63 to −0·11)**	**−0·37 (−0·51 to −0·23)**	**−0·37 (−0·51 to −0·23)**	**−0·36 (−0·60 to −0·11)**	**−0·30 (−0·53 to −0·07)**	**−0·20 (−0·37 to −0·04)**	**−0·20 (−0·37 to −0·03)**	−0·08 (−0·34 to 0·18)	**PBO**	0·66 (0·44 to 1·00)	0·57 (0·20 to 1·62)
−0·63 (−0·84 to −0·43)	**−0·58 (−0·78 to −0·37)**	**−0·51 (−0·70 to −0·31)**	**−0·45 (−0·75 to −0·14)**	**−0·44 (−0·66 to −0·23)**	**−0·45 (−0·66 to −0·23)**	**−0·43 (−0·72 to −0·14)**	**−0·38 (−0·66 to −0·09)**	**−0·28 (−0·52 to −0·04)**	**−0·27 (−0·51 to −0·04)**	−0·15 (−0·46 to 0·15)	−0·07 (−0·24 to 0·09)	**TOP**	0·85 (0·28 to 2·63)
−0·88 (−1·40 to −0·36)	**−0·83 (−1·34 to −0·31)**	**−0·76 (−1·27 to −0·24)**	**−0·70 (−1·21 to −0·18)**	**−0·69 (−1·21 to −0·17)**	**−0·69 (−1·21 to −0·17)**	**−0·68 (−1·23 to −0·12)**	**−0·62 (−1·17 to −0·07)**	−0·53 (−1·05 to 0·01)	−0·52 (−1·05 to 0·01)	−0·40 (−0·96 to 0·16)	−0·32 (−0·82 to 0·18)	−0·25 (−0·77 to 0·28)	**GBT**

Treatment Efficacy (SMD with 95% CrI) Dropout rate (OR with 95% CrI)

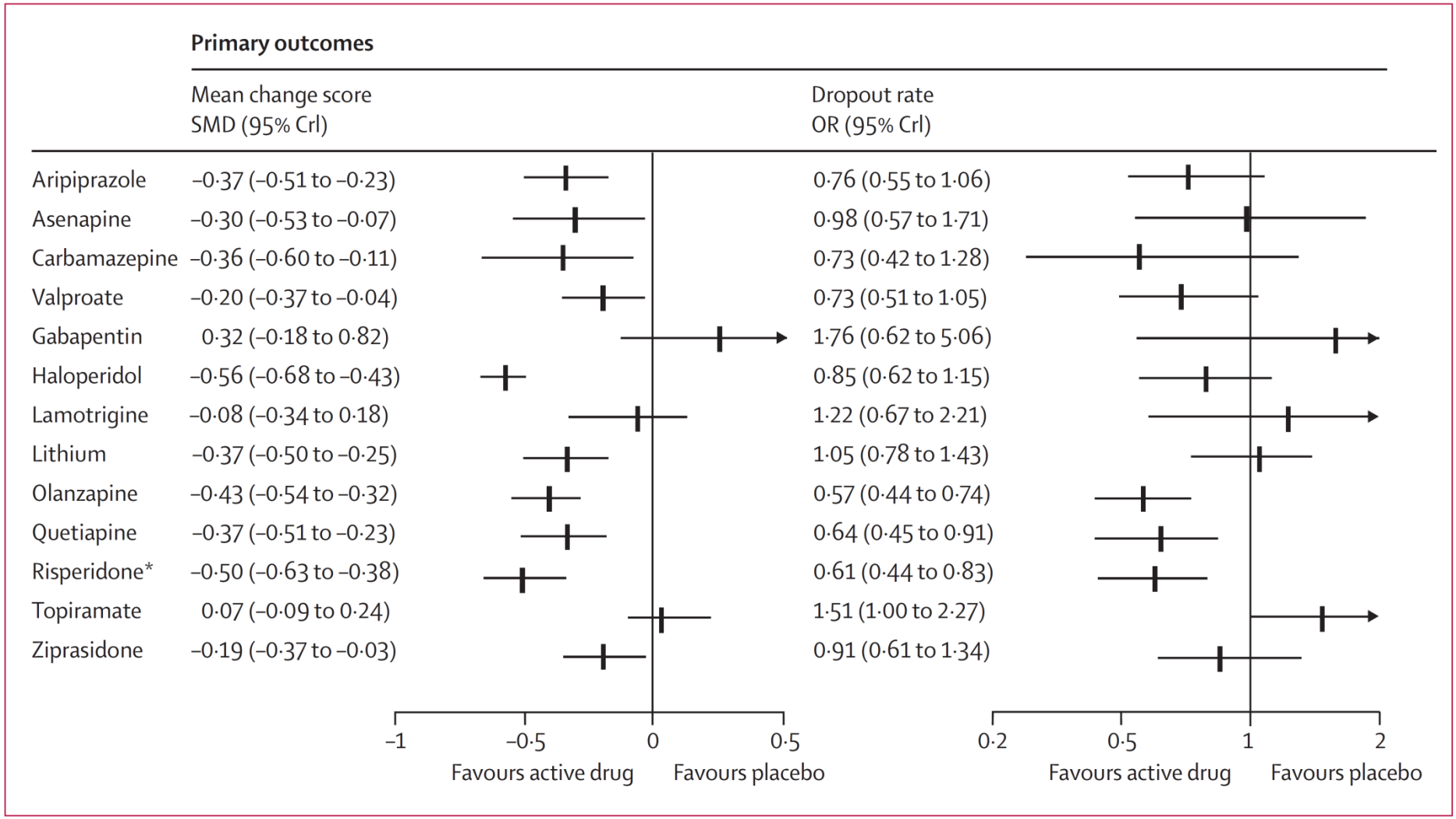


Figure 3: **Forest plots of MTM results for efficacy outcomes and dropout rate with placebo as reference compound**

Standardised mean differences lower than 0 and ORs lower than 1 favour active compound. *As stated in the protocol, data from risperidone and paliperidone were merged. MTM= multiple-treatments meta-analysis. OR=odds ratio. CrI=credibilty interval.

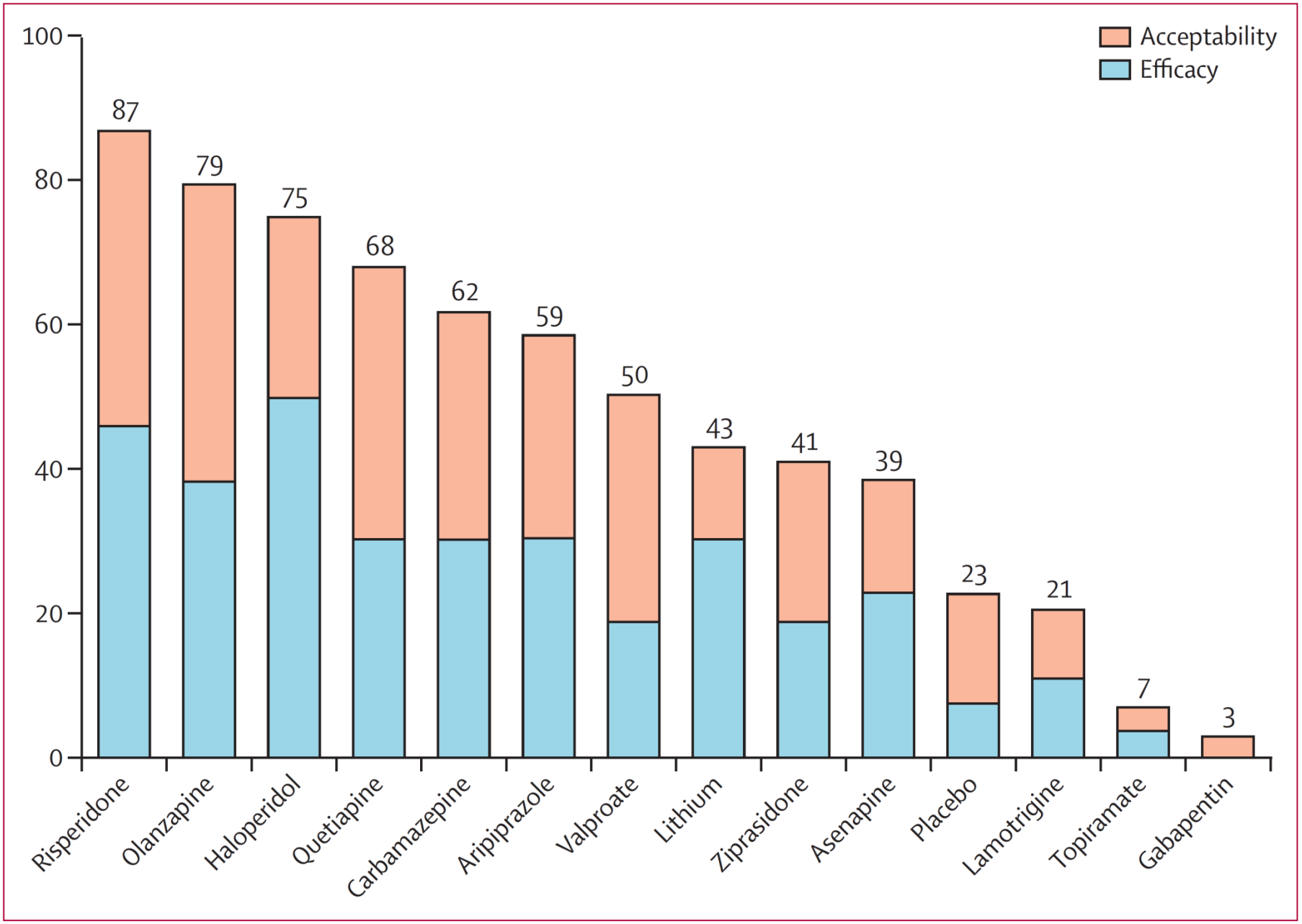


Figure 5: **Drugs ordered by their overall probability to be the best treatment in terms of both efficacy and dropout rate, showing the separate contributions to the overall scores of efficacy and dropout**

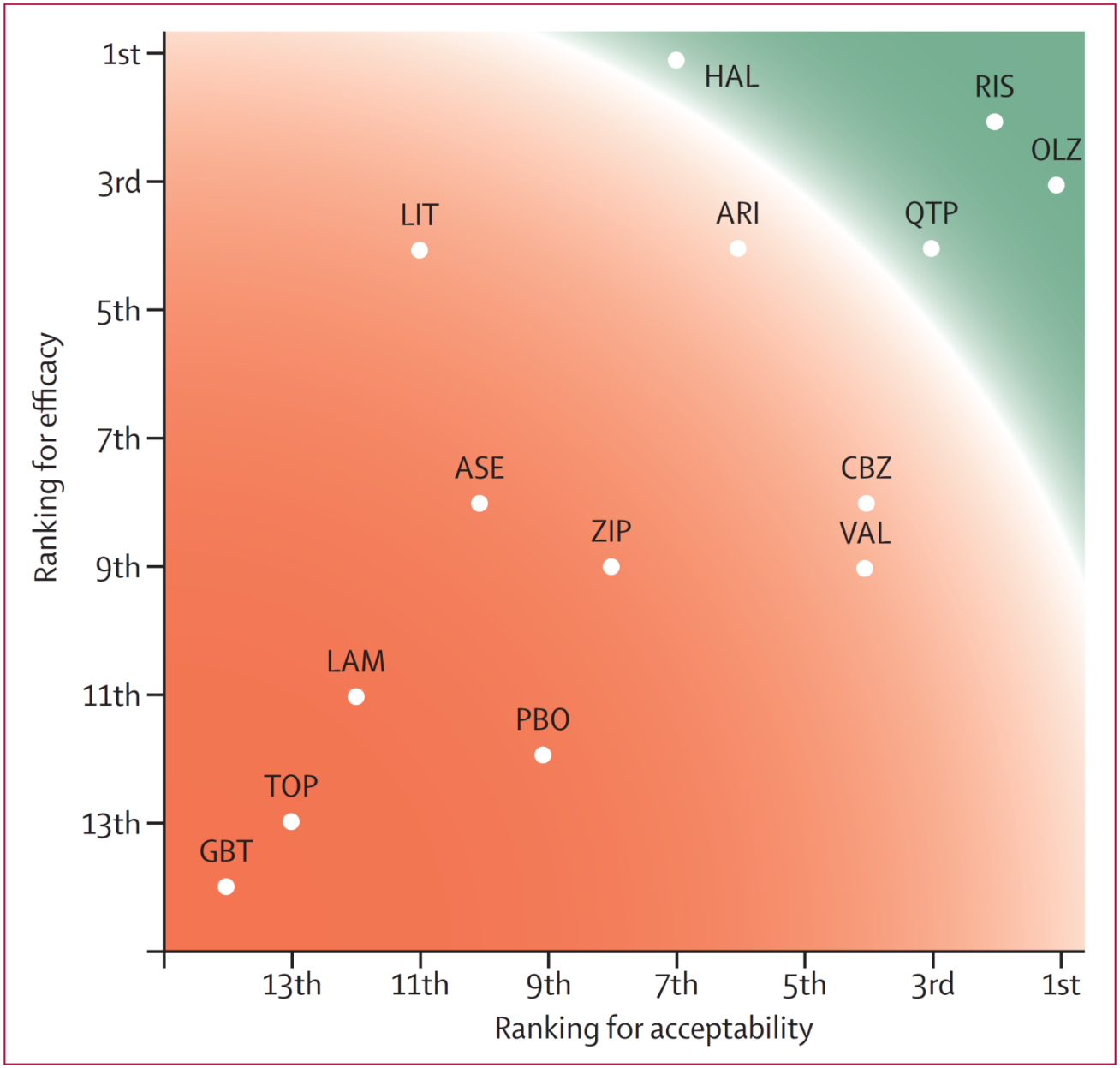
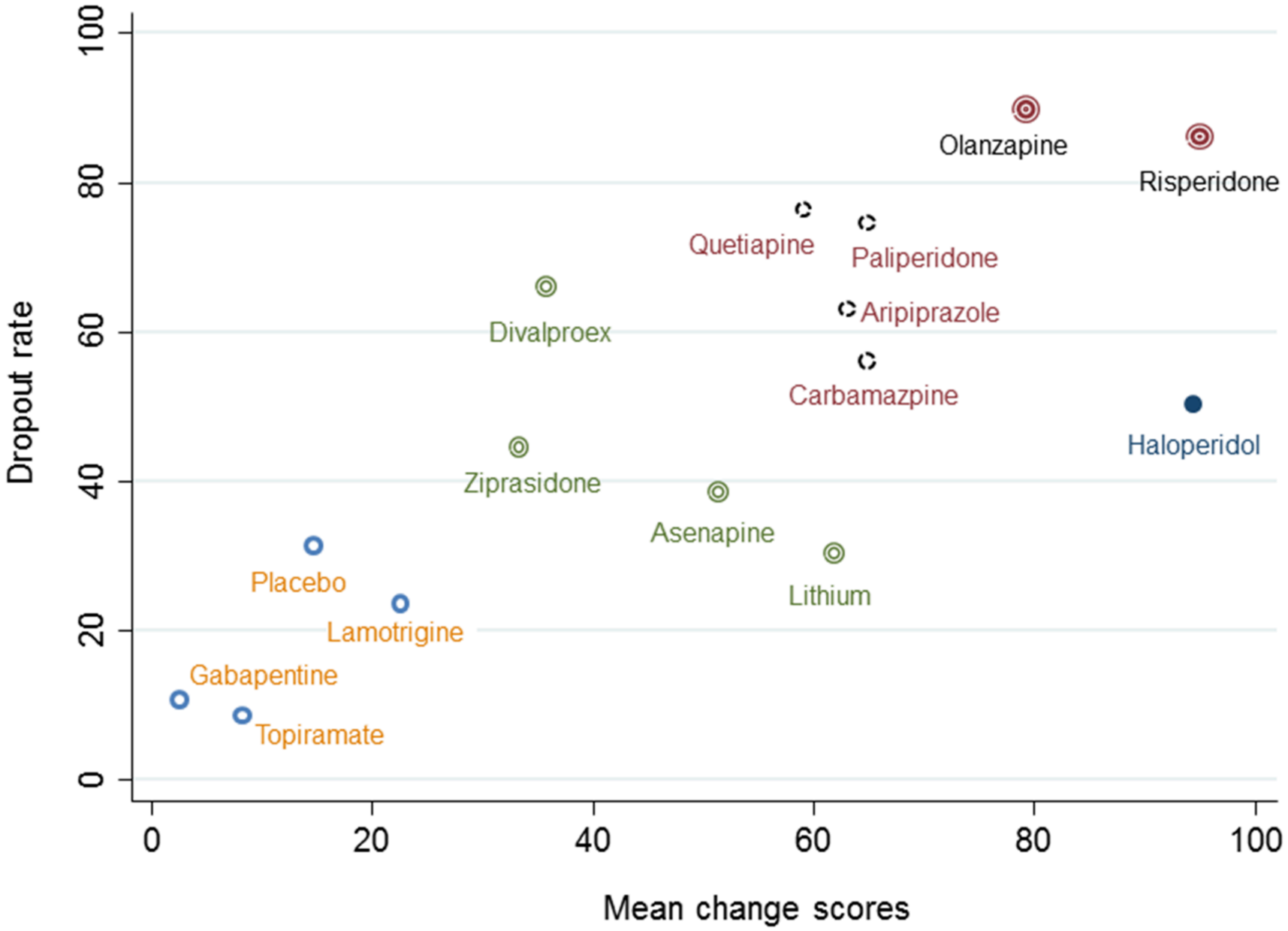


Figure 6: **Ranking of antimanic drugs according to primary outcomes: efficacy (as continuous outcome) and dropout rate**



Mavridis et al., *Evid Based Mental Health* 2015;18:40-46

A primer on network meta-analysis with emphasis on mental health

Dimitris Mavridis,[1,2] Myrsini Giannatsi,[1] Andrea Cipriani,[3] Georgia Salanti[1]

[1]Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece; [2]Department of Primary Education, University of Ioannina, Ioannina, Greece; [3]Department of Psychiatry, University of Oxford, Oxford, UK
Correspondence to Dr Dimitris Mavridis, dimi.mavridis@googlemail.com

ABSTRACT

Objective A quantitative synthesis of evidence via standard pair-wise meta-analysis lies on the top of the hierarchy for evaluating the relative effectiveness or safety between two interventions. In most healthcare problems, however, there is a plethora of competing interventions. Network meta-analysis allows to rank competing interventions and evaluate their relative effectiveness even if they have not been compared in an individual trial. The aim of this paper is to explain and discuss the main features of this statistical technique.

Methods We present the key assumptions underlying network meta-analysis and the graphical methods to visualise results and information in the network. We used one illustrative example that compared the relative effectiveness of 15 antimanic drugs and placebo in acute mania.

Results A network plot allows to visualise how information flows in the network and reveals important information about network geometry. Discrepancies between direct and indirect evidence can be detected using inconsistency plots. Relative effectiveness or safety of competing interventions can be presented in a league table. A contribution plot reveals the contribution of each direct comparison to each network estimate. A comparison-adjusted funnel plot is an extension of simple funnel plot to network meta-analysis. A rank probability matrix can be estimated to present the probabilities of all interventions assuming each rank and can be represented using rankograms and cumulative probability plots.

Conclusions Network meta-analysis is very helpful in comparing the relative effectiveness and acceptability of competing treatments. Several issues, however, still need to be addressed when conducting a network meta-analysis for the results to be valid and correctly interpreted.

INTRODUCTION

Evidence-based practices are crucial in informing healthcare decisions as they provide evidence on the effectiveness and adverse effects of the available treatment options. A quantitative synthesis of research findings from randomised controlled trials (RCTs) via meta-analysis lies at the top of evidence based methods.[1] The benefits from meta-analysis are well established and include increased power, more precise effect estimates, and ability to generalise research findings and identify factors that modify the effect of an intervention (effect modifiers). In mental health, several meta-analyses have identified interventions that help people with mental disorders to attain better outcomes assess the comparative efficacy and tolerability of competing treatments for various disorders.[11–14]

BASIC CONCEPTS AND ASSUMPTIONS IN NMA

A fundamental concept in NMA is that of an indirect comparison. If two treatments, A and B, have both been compared with a common treatment, say C, in two different sets of trials (A vs C and B vs C), then the relative effectiveness between A and B can be estimated indirectly via the common comparator C.[15] For illustrative purposes, we will consider three active antipsychotics, namely haloperidol (H), olanzapine (O) and risperidone (R). If there are only studies comparing risperidone

Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis

Tomofumi Miura, Hisashi Noma, Toshi A Furukawa, Hiroshi Mitsuyasu, Shiro Tanaka, Sarah Stockton, Georgia Salanti, Keisuke Motomura, Satomi Shimano-Katsuki, Stefan Leucht, Andrea Cipriani, John R Geddes, Shigenobu Kanba

Summary

Background Lithium is the established standard in the long-term treatment of bipolar disorder, but several new drugs have been assessed for this indication. We did a network meta-analysis to investigate the comparative efficacy and tolerability of available pharmacological treatment strategies for bipolar disorder.

Methods We systematically searched Embase, Medline, PreMedline, PsycINFO, and the Cochrane Central Register of Controlled Trials for randomised controlled trials published before June 28, 2013, that compared active treatments for bipolar disorder (or placebo), either as monotherapy or as add-on treatment, for at least 12 weeks. The primary outcomes were the number of participants with recurrence of any mood episode, and the number of participants who discontinued the trial because of adverse events. We assessed efficacy and tolerability of bipolar treatments using a random-effects network meta-analysis within a Bayesian framework.

Findings We screened 114 potentially eligible studies and identified 33 randomised controlled trials, published between 1970 and 2012, that examined 17 treatments for bipolar disorder (or placebo) in 6846 participants. Participants assigned to all assessed treatments had a significantly lower risk of any mood relapse or recurrence compared with placebo, except for those assigned to aripiprazole (risk ratio [RR] 0·62, 95% credible interval [CrI] 0·38–1·03), carbamazepine (RR 0·68, 0·44–1·06), imipramine (RR 0·95, 0·66–1·36), and paliperidone (RR 0·84, 0·56–1·24). Lamotrigine and placebo were significantly better tolerated than carbamazepine (lamotrigine, RR 5·24, 1·07–26·32; placebo, RR 3·60, 1·04–12·94), lithium (RR 3·76, 1·13–12·66; RR 2·58, 1·33–5·39), or lithium plus valproate (RR 5·95, 1·02–33·33; RR 4·09, 1·01–16·96).

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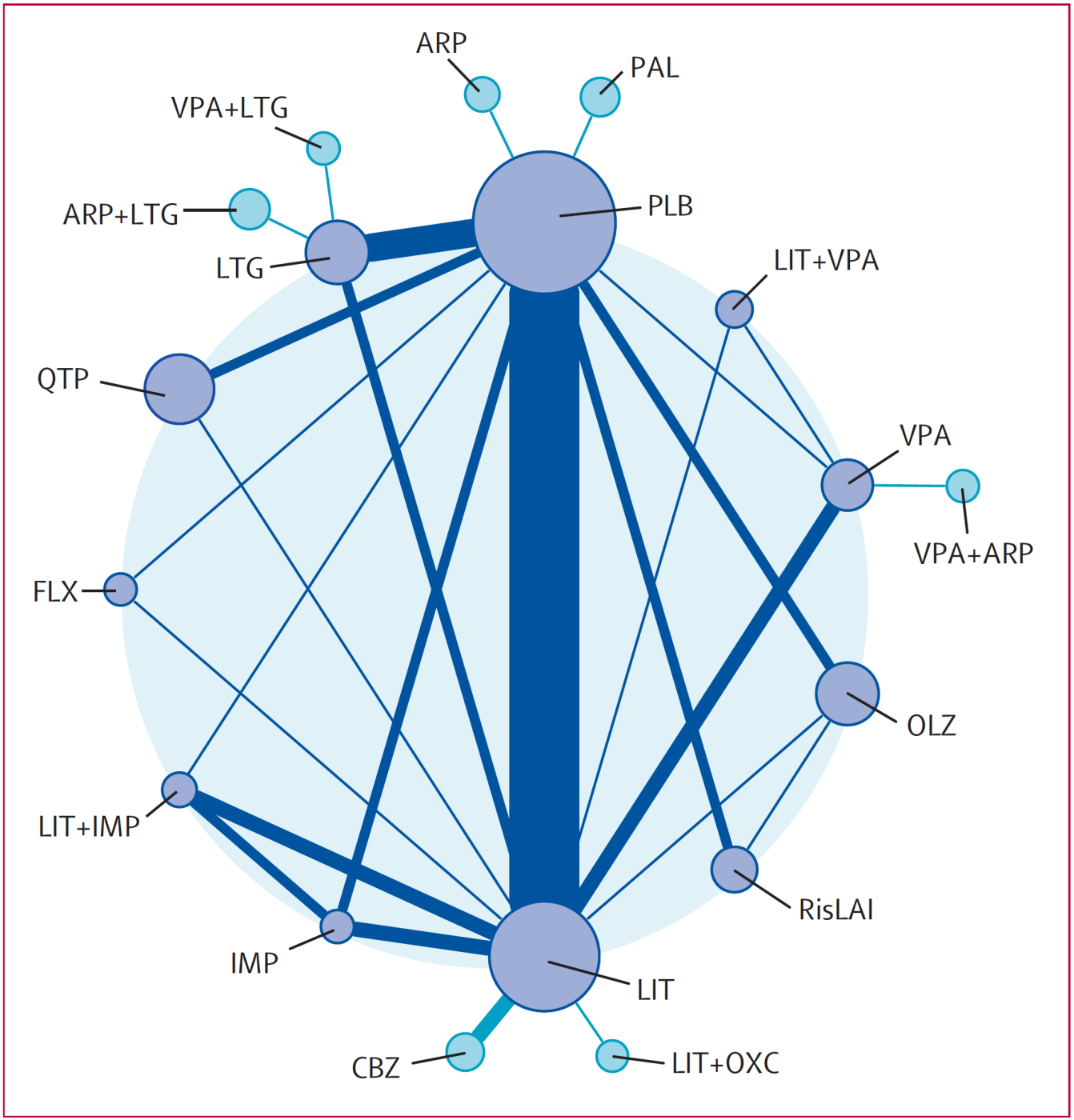
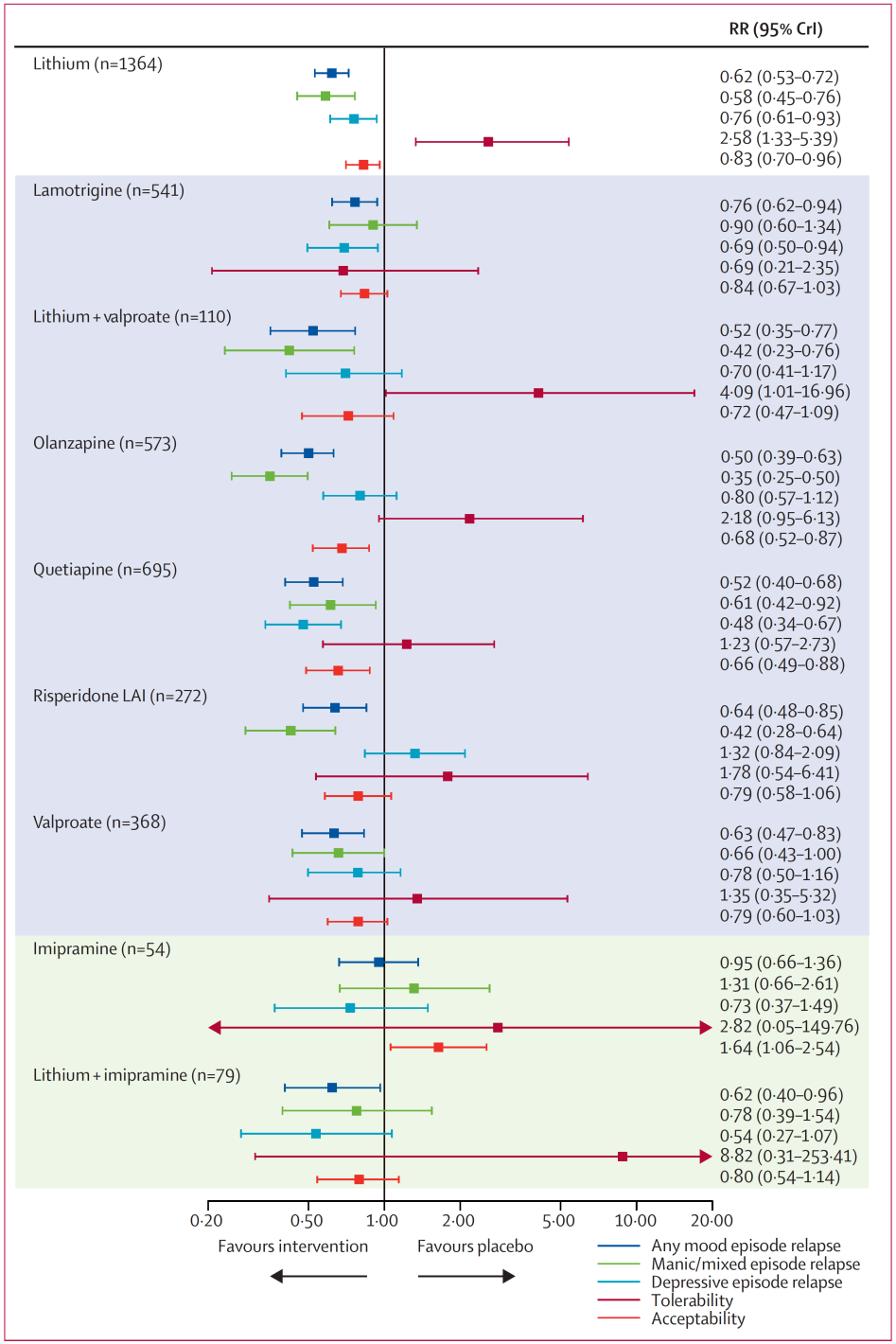
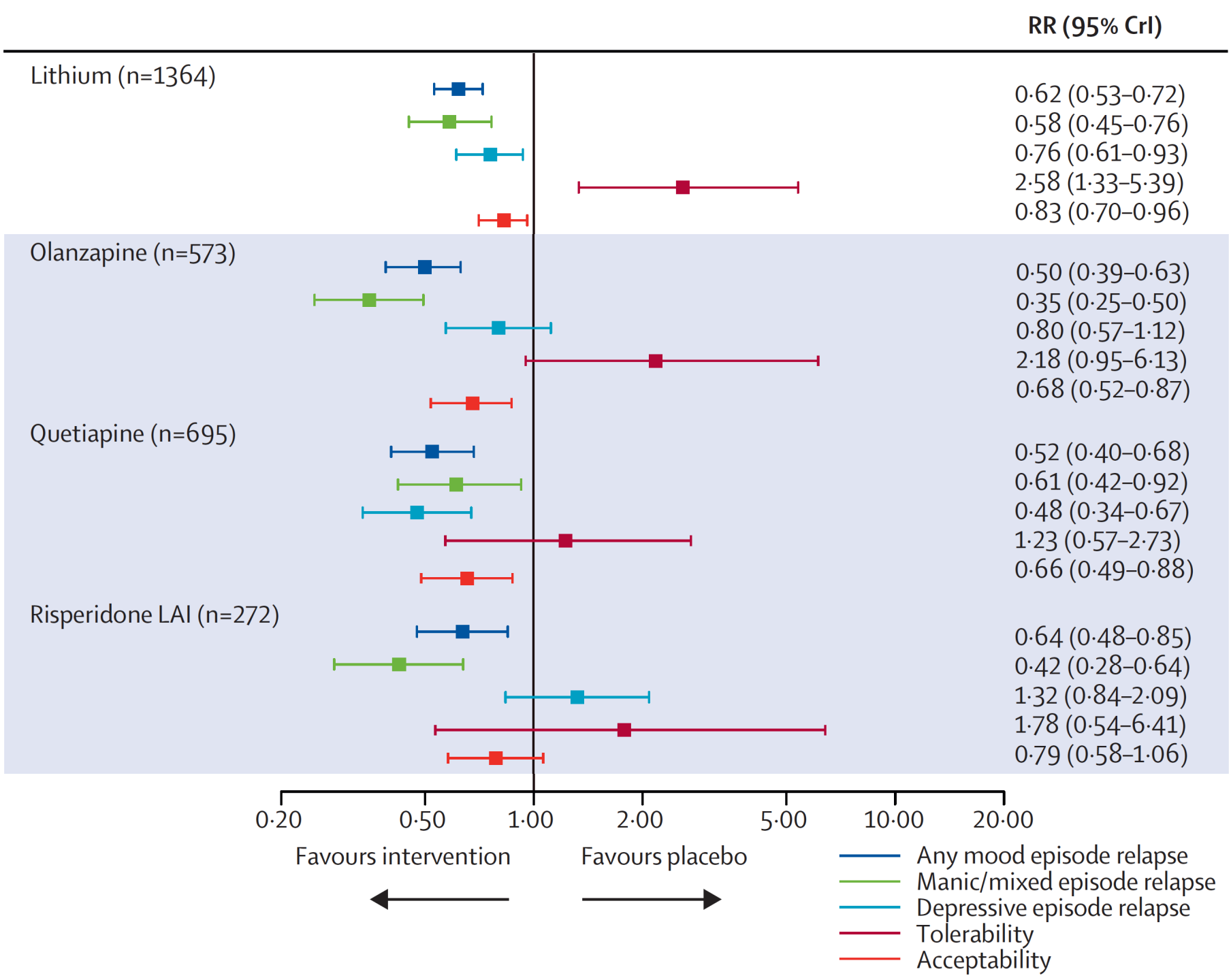
Department of Neuropsychiatry Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan (T Miura MD, H Mitsuyasu MD, K Motomura MD, S Shimano-Katsuki MD, Prof S Kanba MD); **Department of Data Science, The Institute of Statistical Mathematics, Tokyo, Japan** (H Noma PhD); **Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine**


ARP
PAL
VPA+LTG
ARP+LTG
PLB
LTG
LIT+VPA
QTP
VPA
VPA+ARP
FLX
OLZ
LIT+IMP
RisLAI
IMP
LIT
CBZ
LIT+OXC


RR (95% CrI)
Lithium (n=1364)
0·62 (0·53–0·72)
0·58 (0·45–0·76)
0·76 (0·61–0·93)
2·58 (1·33–5·39)
0·83 (0·70–0·96)
Lamotrigine (n=541)
0·76 (0·62–0·94)
0·90 (0·60–1·34)
0·69 (0·50–0·94)
0·69 (0·21–2·35)
0·84 (0·67–1·03)
Lithium + valproate (n=110)
0·52 (0·35–0·77)
0·42 (0·23–0·76)
0·70 (0·41–1·17)
4·09 (1·01–16·96)
0·72 (0·47–1·09)
Olanzapine (n=573)
0·50 (0·39–0·63)
0·35 (0·25–0·50)
0·80 (0·57–1·12)
2·18 (0·95–6·13)
0·68 (0·52–0·87)
Quetiapine (n=695)
0·52 (0·40–0·68)
0·61 (0·42–0·92)
0·48 (0·34–0·67)
1·23 (0·57–2·73)
0·66 (0·49–0·88)
Risperidone LAI (n=272)
0·64 (0·48–0·85)
0·42 (0·28–0·64)
1·32 (0·84–2·09)
1·78 (0·54–6·41)
0·79 (0·58–1·06)
Valproate (n=368)
0·63 (0·47–0·83)
0·66 (0·43–1·00)
0·78 (0·50–1·16)
1·35 (0·35–5·32)
0·79 (0·60–1·03)
Imipramine (n=54)
0·95 (0·66–1·36)
1·31 (0·66–2·61)
0·73 (0·37–1·49)
2·82 (0·05–149·76)
1·64 (1·06–2·54)
Lithium + imipramine (n=79)
0·62 (0·40–0·96)
0·78 (0·39–1·54)
0·54 (0·27–1·07)
8·82 (0·31–253·41)
0·80 (0·54–1·14)
0·20
0·50
1·00
2·00
5·00
10·00
20·00
Favours intervention
Favours placebo
Any mood episode relapse
Manic/mixed episode relapse
Depressive episode relapse
Tolerability
Acceptability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2·00
5·00
10·00
20·00
Favours intervention
Favours placebo
Any mood episode relapse
Manic/mixed episode relapse
Depressive episode relapse
Tolerability
Acceptability

The contribution matrix – Any mood relapse

	Comparisons	Number of comparisons	PLB vs LIT	PLB vs VPA	PLB vs LTG	PLB vs IMP	PLB vs LIT+IMP	PLB vs ARP	PLB vs OLZ	PLB vs QTP	LIT vs LIT+VPA	LIT vs LIT+OXC	LIT vs OLZ	LIT vs QTP
Mixed Comparison	PLB vs LIT	10	27.2	5.3	13.7	2.3	0.2	0	4.9	5.7	2.2	0	6.9	5.7
	PLB vs VPA	1	14.2	13	7.1	1.2	0.1	0	2.5	3	12.2	0	3.6	3
	PLB vs LTG	4	9.9	1.9	56.5	0.8	0.1	0	1.8	2	0.8	0	2.5	2
	PLB vs IMP	2	14.8	2.9	7.4	8.1	0.5	0	2.6	3.1	1.2	0	3.7	3.1
	PLB vs LIT+IMP	1	14.3	2.8	7.1	4.3	1	0	2.5	3	1.2	0	3.6	3
	PLB vs ARP	1	0	0	0	0	0	100	0	0	0	0	0	0
	PLB vs OLZ	2	11.5	2.2	5.8	1	0.1	0	22.5	2.4	0.9	0	23	2.4
	PLB vs QTP	2	14.4	2.8	7.2	1.2	0.1	0	2.6	23.6	1.2	0	3.7	29.4
	PLB vs RisLAI	2	4.6	0.9	2.3	0.4	0	0	9	1	0.4	0	9.2	1
	PLB vs PAL	1	0	0	0	0	0	0	0	0	0	0	0	0
	LIT vs VPA	3	6.5	13.3	3.2	0.5	0.1	0	1.2	1.3	19.5	0	1.6	1.3
	LIT vs CBZ	3	0	0	0	0	0	0	0	0	0	0	0	0
	LIT vs LTG	2	17	3.3	29.7	1.4	0.1	0	3	3.5	1.4	0	4.3	3.5
	LIT vs IMP	3	5.3	1	2.7	10.9	0.5	0	0.9	1.1	0.4	0	1.3	1.1
	LIT vs LIT+IMP	3	3.1	0.6	1.5	5.2	1.4	0	0.6	0.6	0.3	0	0.8	0.6
	LIT vs LIT+VPA	1	3.8	7.7	1.9	0.3	0	0	0.7	0.8	40.8	0	1	0.8
	LIT vs LIT+OXC	1	0	0	0	0	0	0	0	0	0	100	0	0
	LIT vs OLZ	1	12.6	2.4	6.3	1.1	0.1	0	17.7	2.6	1	0	28.4	2.6
	LIT vs QTP	1	11.1	2.1	5.5	0.9	0.1	0	2	22.6	0.9	0	2.8	41.4
	VPA vs LIT+VPA	1	3.4	6.9	1.7	0.3	0	0	0.6	0.7	21	0	0.9	0.7
	VPA vs VPA+ARP	1	0	0	0	0	0	0	0	0	0	0	0	0
	LTG vs ARP+LTG	1	0	0	0	0	0	0	0	0	0	0	0	0
	IMP vs LIT+IMP	2	2	0.4	1	5.4	1	0	0.4	0.4	0.2	0	0.5	0.4
	OLZ vs RisLAI	1	7.1	1.4	3.6	0.6	0.1	0	13.8	1.5	0.6	0	14.1	1.5
	PLB vs CBZ		16.9	3.3	8.5	1.4	0.1	0	3	3.5	1.4	0	4.3	3.5
	PLB vs LIT+VPA		14.6	7.8	7.3	1.2	0.1	0	2.6	3	22.6	0	3.7	3
	PLB vs LIT+OXC		16.9	3.3	8.5	1.4	0.1	0	3	3.5	1.4	38	4.3	3.5
	PLB vs VPA+ARP		10	9.1	5	0.8	0.1	0	1.8	2.1	8.6	0	2.5	2.1
	PLB vs ARP+LTG		5.7	1.1	32.5	0.5	0	0	1	1.2	0.5	0	1.4	1.2
	LIT vs ARP		16.9	3.3	8.5	1.4	0.1	38	3	3.5	1.4	0	4.3	3.5
	LIT vs RisLAI		15.3	3	7.7	1.3	0.1	0	2.2	3.2	1.2	0	10.1	3.2
	LIT vs PAL		16.9	3.3	8.5	1.4	0.1	0	3	3.5	1.4	0	4.3	3.5

Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis

Andrea Cipriani, Xinyu Zhou*, Cinzia Del Giovane, Sarah E Hetrick, Bin Qin, Craig Whittington, David Coghill, Yuqing Zhang, Philip Hazell, Stefan Leucht, Pim Cuijpers, Juncai Pu, David Cohen, Arun V Ravindran, Yiyun Liu, Kurt D Michael, Lining Yang, Lanxiang Liu, Peng Xie*

Summary

Background Major depressive disorder is one of the most common mental disorders in children and adolescents. However, whether to use pharmacological interventions in this population and which drug should be preferred are still matters of controversy. Consequently, we aimed to compare and rank antidepressants and placebo for major depressive disorder in young people.

Methods We did a network meta-analysis to identify both direct and indirect evidence from relevant trials. We searched PubMed, the Cochrane Library, Web of Science, Embase, CINAHL, PsycINFO, LiLACS, regulatory agencies' websites, and international registers for published and unpublished, double-blind randomised controlled trials up to May 31, 2015, for the acute treatment of major depressive disorder in children and adolescents. We included trials of amitriptyline, citalopram, clomipramine, desipramine, duloxetine, escitalopram, fluoxetine, imipramine, mirtazapine, nefazodone, nortriptyline, paroxetine, sertraline, and venlafaxine. Trials recruiting participants with treatment-resistant depression, treatment duration of less than 4 weeks, or an overall sample size of less than ten patients were excluded. We extracted the relevant information from the published reports with a predefined data extraction sheet, and assessed the risk of bias with the Cochrane risk of bias tool. The primary outcomes were efficacy (change in depressive symptoms) and tolerability (discontinuations due to adverse events). We did pair-wise meta-analyses using the random-effects model and then did a random-effects network meta-analysis within a Bayesian framework. We assessed the quality of evidence contributing to each network estimate using the GRADE framework. This study is registered with PROSPERO, number CRD42015016023.

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See **Comment** page 844

*Contributed equally

Department of Psychiatry, University of Oxford, Oxford, UK (A Cipriani PhD); **Department of Neurology and Psychiatry, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China** (X Zhou PhD, B Qin MD, Y Zhang MD, J Pu MD, Y Liu MD, L Yang MD, L Liu MD, Prof P Xie MD); **Institute of Neuroscience and the Collaborative Innovation Center for Brain Science, Chongqing Medical University,**

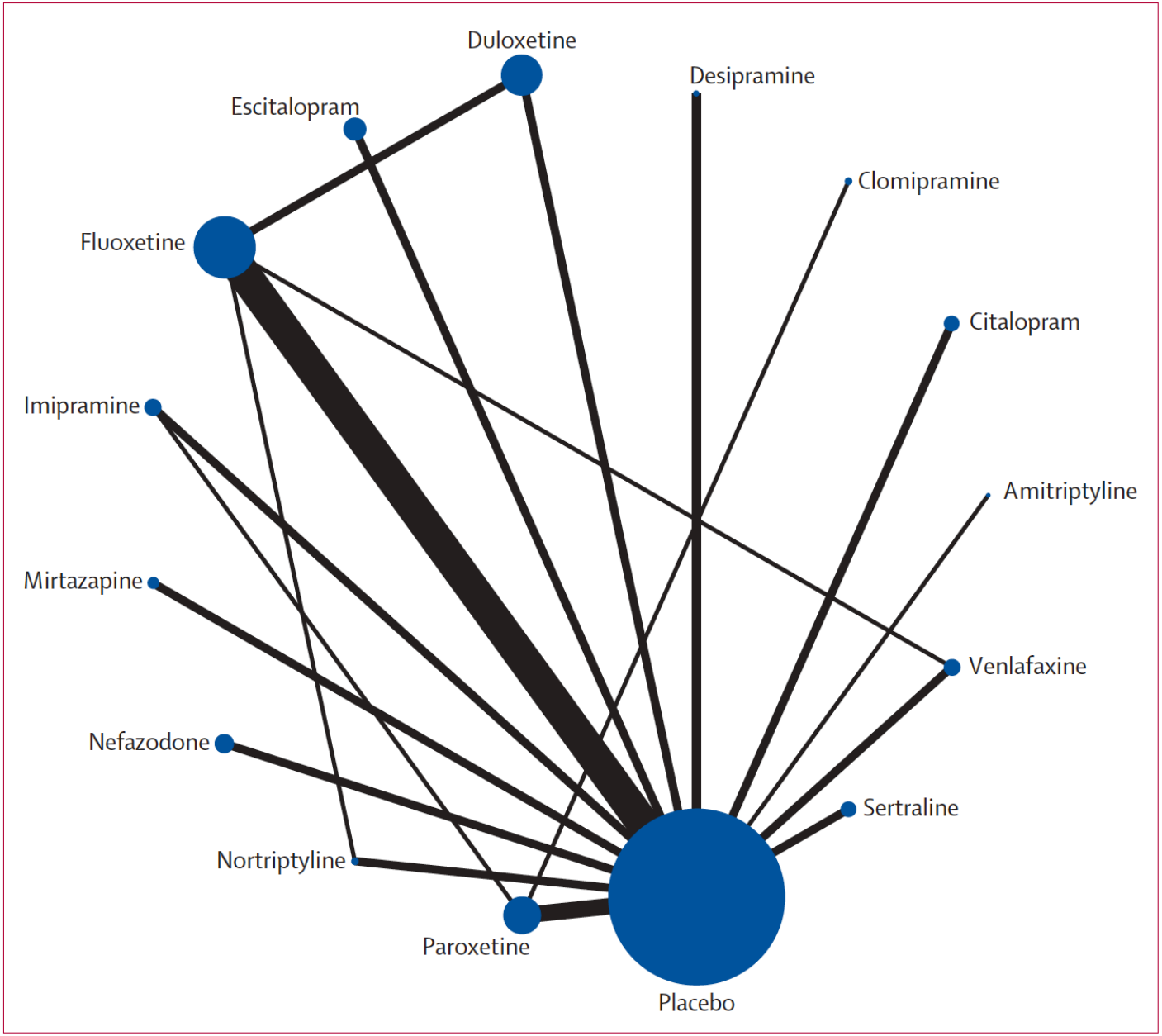


Figure 2: **Network of eligible comparisons for efficacy**
The width of the lines is proportional to the number of trials comparing every pair of treatments, and the size of every circle is proportional to the number of randomly assigned participants (sample size).

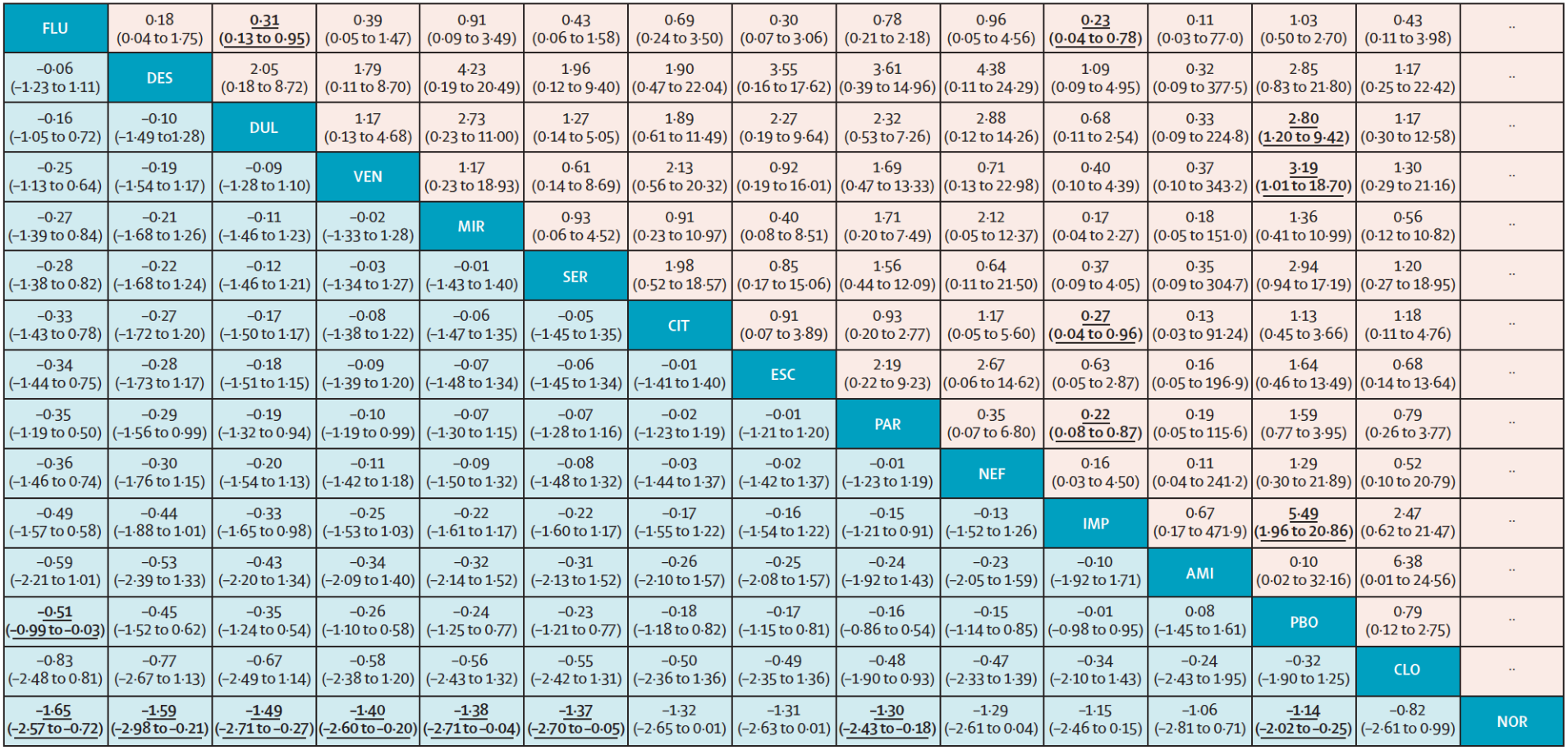
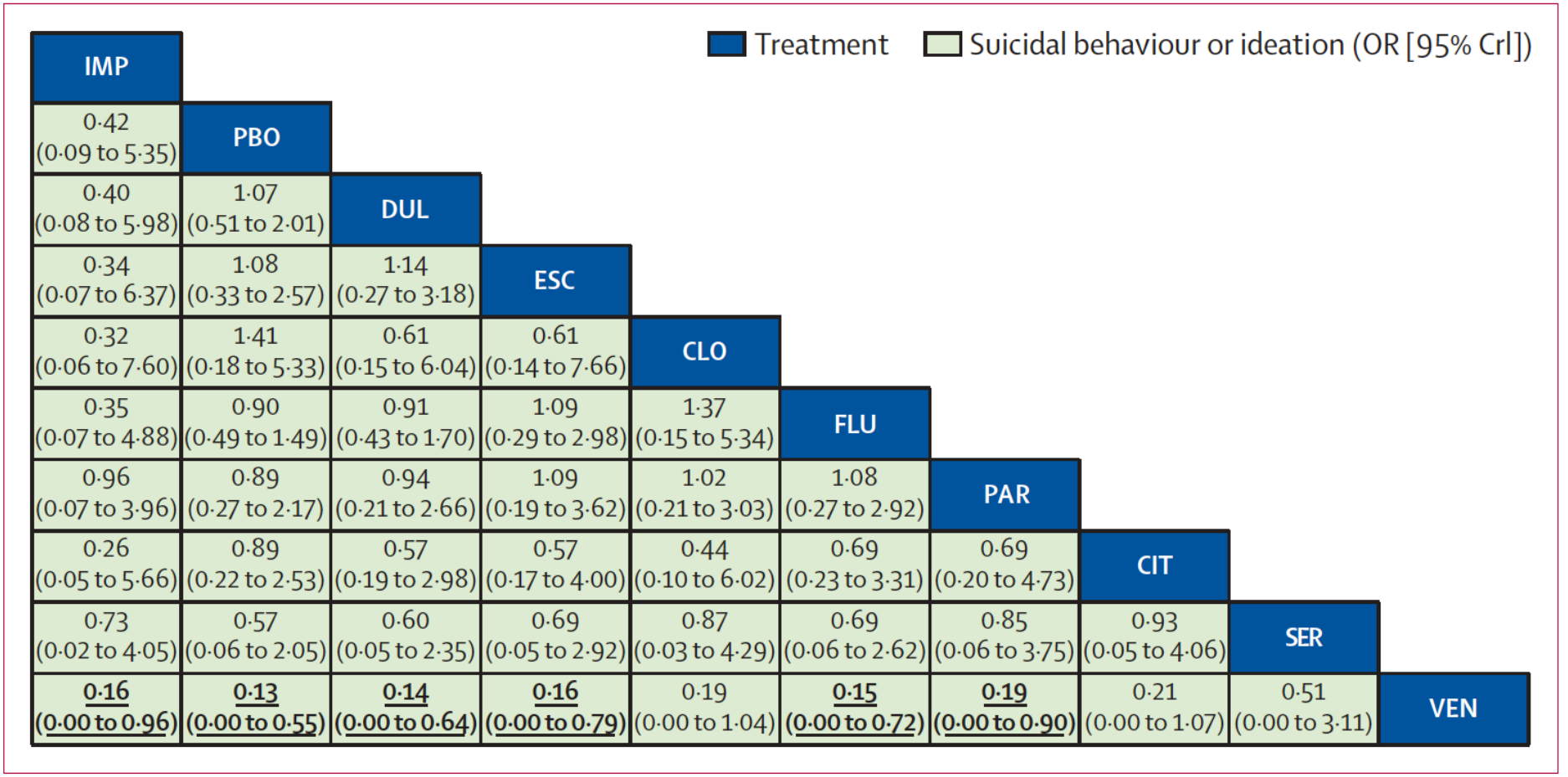


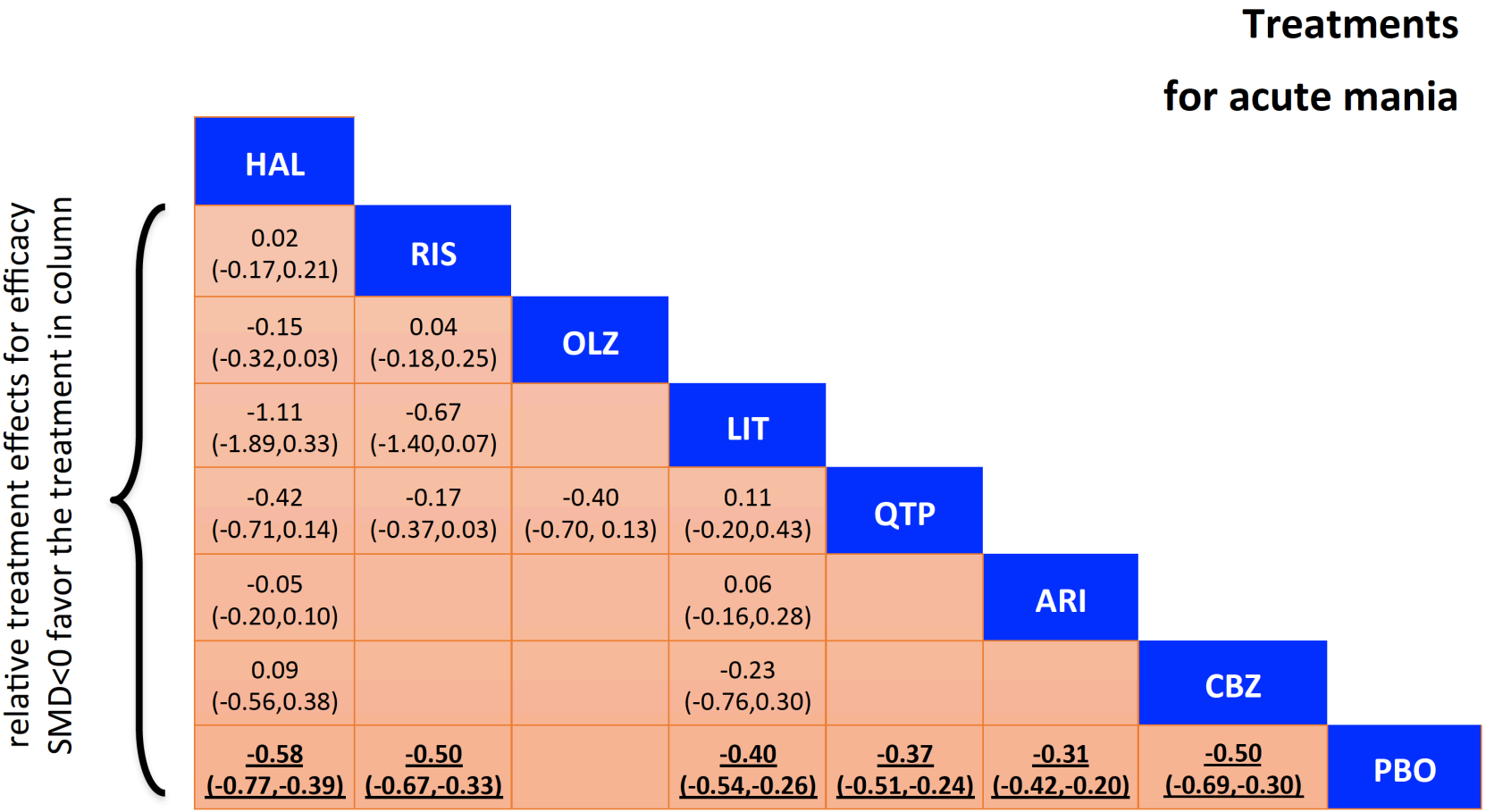
Figure 3: **Network meta-analysis of efficacy and tolerability**

Drugs are reported in order of efficacy ranking according to SUCRAs. Comparisons should be read from left to right. The efficacy and tolerability estimate is located at the intersection of the column-defining treatment and the row-defining treatment. For efficacy (mean overall change in symptoms), an SMD below 0 favours the column-defining treatment. For tolerability (discontinuation due to adverse events), an OR below 1 favours the row-defining treatment. To obtain SMDs for comparisons in the opposing direction, negative values should be converted into positive values and vice versa. To obtain ORs for comparisons in the opposing direction, reciprocals should be taken. Significant results are in bold and underlined. AMI=amitriptyline. CIT=citalopram. CLO=clomipramine. CrI=credibility interval. DES=desipramine. DUL=duloxetine. ESC=escitalopram. FLU=fluoxetine. IMP=imipramine. MIR=mirtazapine. NEF=nefazodone. NOR=nortriptyline. OR=odds ratio. PAR=paroxetine. PBO=placebo. SER=sertraline. SMD=standardised mean difference. SUCRA=surface under the cumulative ranking curve. VEN=venlafaxine.



IMP									
0·42 (0·09 to 5·35)	PBO								
0·40 (0·08 to 5·98)	1·07 (0·51 to 2·01)	DUL							
0·34 (0·07 to 6·37)	1·08 (0·33 to 2·57)	1·14 (0·27 to 3·18)	ESC						
0·32 (0·06 to 7·60)	1·41 (0·18 to 5·33)	0·61 (0·15 to 6·04)	0·61 (0·14 to 7·66)	CLO					
0·35 (0·07 to 4·88)	0·90 (0·49 to 1·49)	0·91 (0·43 to 1·70)	1·09 (0·29 to 2·98)	1·37 (0·15 to 5·34)	FLU				
0·96 (0·07 to 3·96)	0·89 (0·27 to 2·17)	0·94 (0·21 to 2·66)	1·09 (0·19 to 3·62)	1·02 (0·21 to 3·03)	1·08 (0·27 to 2·92)	PAR			
0·26 (0·05 to 5·66)	0·89 (0·22 to 2·53)	0·57 (0·19 to 2·98)	0·57 (0·17 to 4·00)	0·44 (0·10 to 6·02)	0·69 (0·23 to 3·31)	0·69 (0·20 to 4·73)	CIT		
0·73 (0·02 to 4·05)	0·57 (0·06 to 2·05)	0·60 (0·05 to 2·35)	0·69 (0·05 to 2·92)	0·87 (0·03 to 4·29)	0·69 (0·06 to 2·62)	0·85 (0·06 to 3·75)	0·93 (0·05 to 4·06)	SER	
0·16 (0·00 to 0·96)	**0·13 (0·00 to 0·55)**	**0·14 (0·00 to 0·64)**	**0·16 (0·00 to 0·79)**	0·19 (0·00 to 1·04)	**0·15 (0·00 to 0·72)**	**0·19 (0·00 to 0·90)**	0·21 (0·00 to 1·07)	0·51 (0·00 to 3·11)	VEN

Direct relative treatment effects



NMA relative treatment effects

Treatments

for acute mania

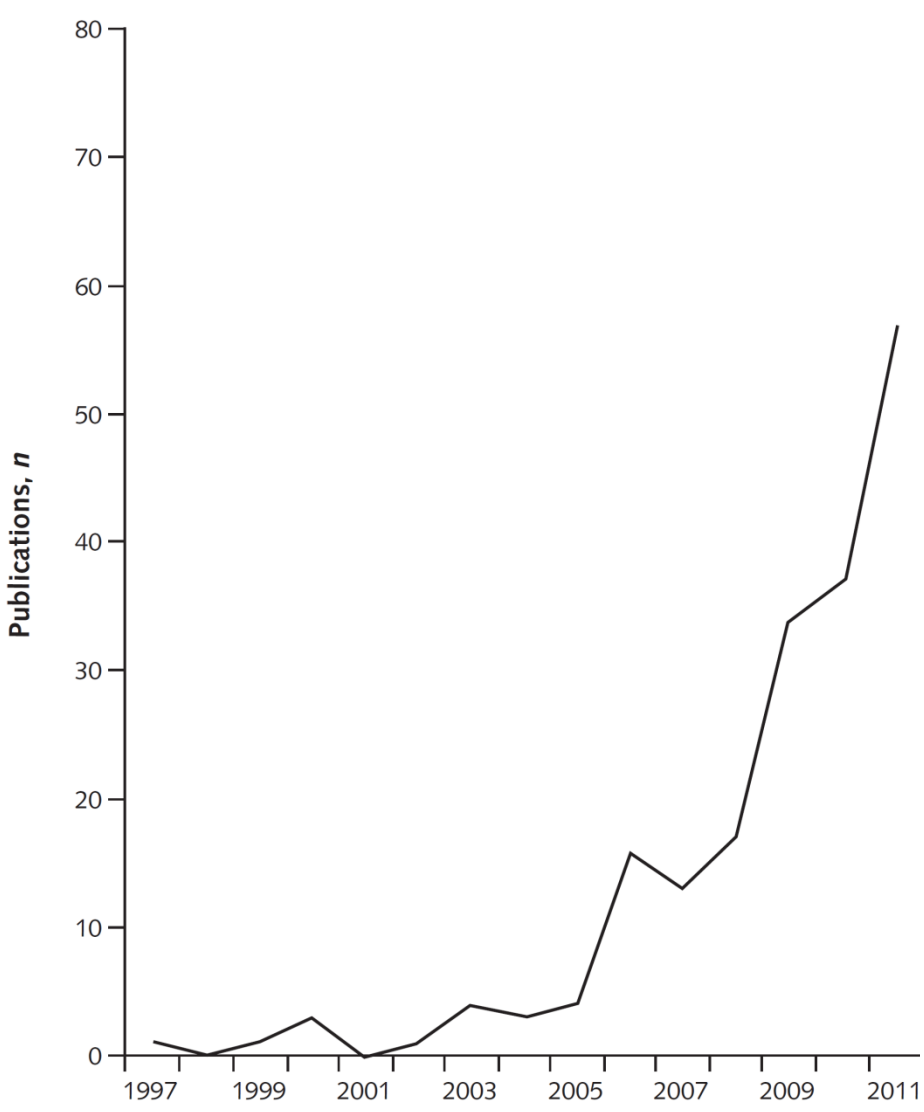
Network estimates

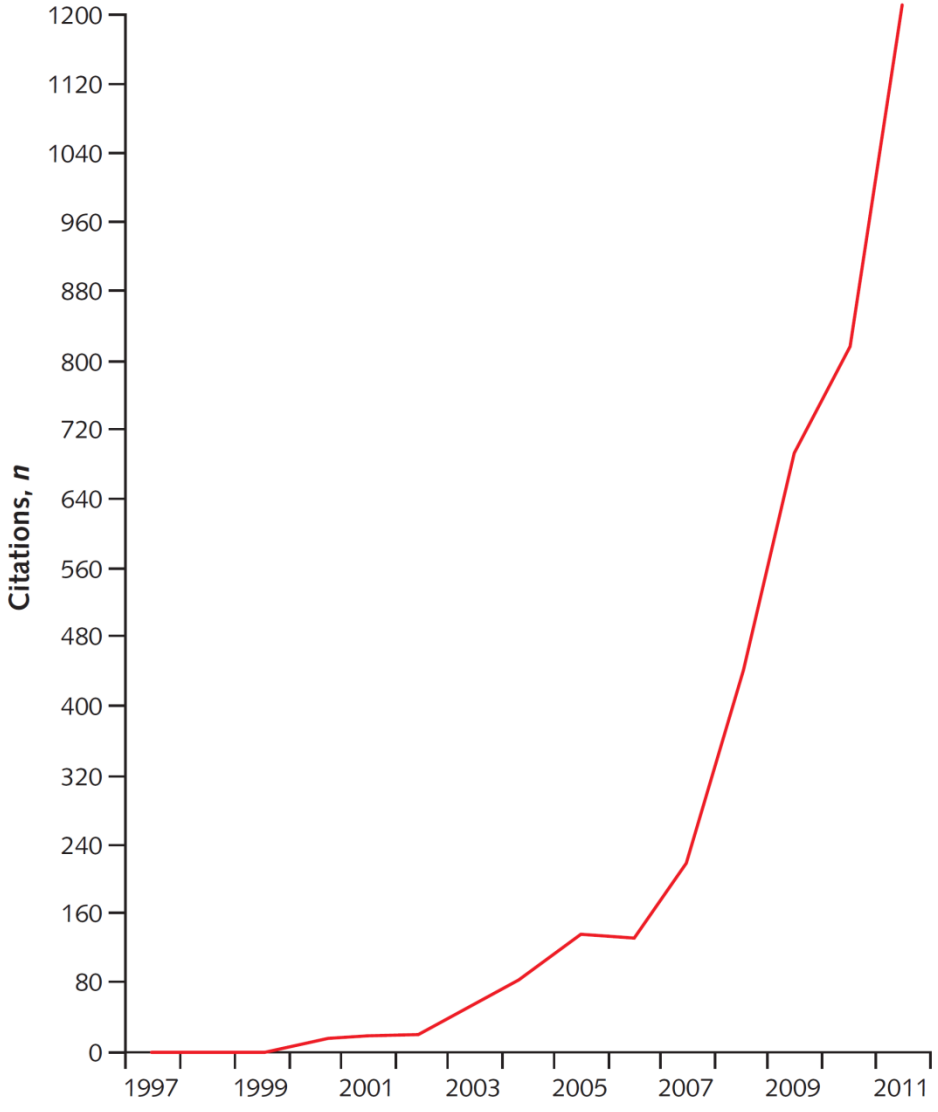
relative treatment effects for efficacy
SMD<0 favor the treatment in column

HAL							
-0.06 (-0.22,0.11)	RIS						
-0.12 (-0.28,0.02)	-0.07 (-0.22,0.08)	OLZ					
-0.19 (-0.36,-0.01)	-0.13 (-0.30,0.04)	-0.06 (-0.22,0.10)	LIT				
-0.19 (-0.37,-0.01)	-0.13 (-0.31,0.04)	-0.07 (-0.24,0.11)	-0.01 (-0.18,0.17)	QTP			
-0.19 (-0.36,-0.02)	-0.13 (-0.31,0.05)	-0.06 (-0.23,0.11)	-0.01 (-0.18,0.17)	0.00 (-0.19,0.20)	ARI		
-0.20 (-0.36,-0.01)	-0.14 (-0.42,0.12)	-0.08 (-0.34,0.18)	-0.02 (-0.28,0.24)	-0.01 (-0.30,0.26)	-0.01 (-0.29,0.26)	CBZ	
-0.56 (-0.69,-0.43)	**-0.50 (-0.63,-0.38)**	**-0.43 (-0.54,-0.32)**	**-0.37 (-0.63,-0.11)**	**-0.37 (-0.51,-0.23)**	**-0.37 (-0.51,-0.23)**	**-0.36 (-0.60,-0.11)**	PBO

Appendix Figure 1. **Number of network meta-analyses published in the scientific literature and their citations since 1997.**

We defined a network meta-analysis as any meta-analysis that used a form of valid indirect relative treatment estimates.





BMJ Open

Comparative efficacy and acceptability of first-generation and second-generation antidepressants in the acute treatment of major depression: protocol for a network meta-analysis

Toshi A Furukawa,[1] Georgia Salanti,[2,3,4] Lauren Z Atkinson,[5] Stefan Leucht,[6] Henricus G Ruhe,[7,8] Erick H Turner,[9,10] Anna Chaimani,[4] Yusuke Ogawa,[1] Nozomi Takeshima,[1] Yu Hayasaka,[1] Hissei Imai,[1] Kiyomi Shinohara,[1] Aya Suganuma,[1] Norio Watanabe,[1] Sarah Stockton,[5] John R Geddes,[5,11] Andrea Cipriani[5,11]

For numbered affiliations see end of article.

Correspondence to
Professor Andrea Cipriani;
andrea.cipriani@psych.ox.ac.uk

ABSTRACT

Introduction: Many antidepressants are indicated for the treatment of major depression. Two network meta-analyses have provided the most comprehensive assessments to date, accounting for both direct and indirect comparisons; however, these reported conflicting interpretation of results. Here, we present a protocol for a systematic review and network meta-analysis aimed at updating the evidence base and comparing all second-generation as well as selected first-generation antidepressants in terms of efficacy and acceptability in the acute treatment of major

Strengths and limitations of this study

- We will conduct a random effects network meta-analysis to synthesise all available evidence (either published or unpublished) for each pre-specified outcome, and obtain a comprehensive ranking of all treatments.
- We will employ local as well as global methods to evaluate consistency and we will explore whether treatment effects are robust in network meta-regression.
- This will be the largest network meta-analysis (in

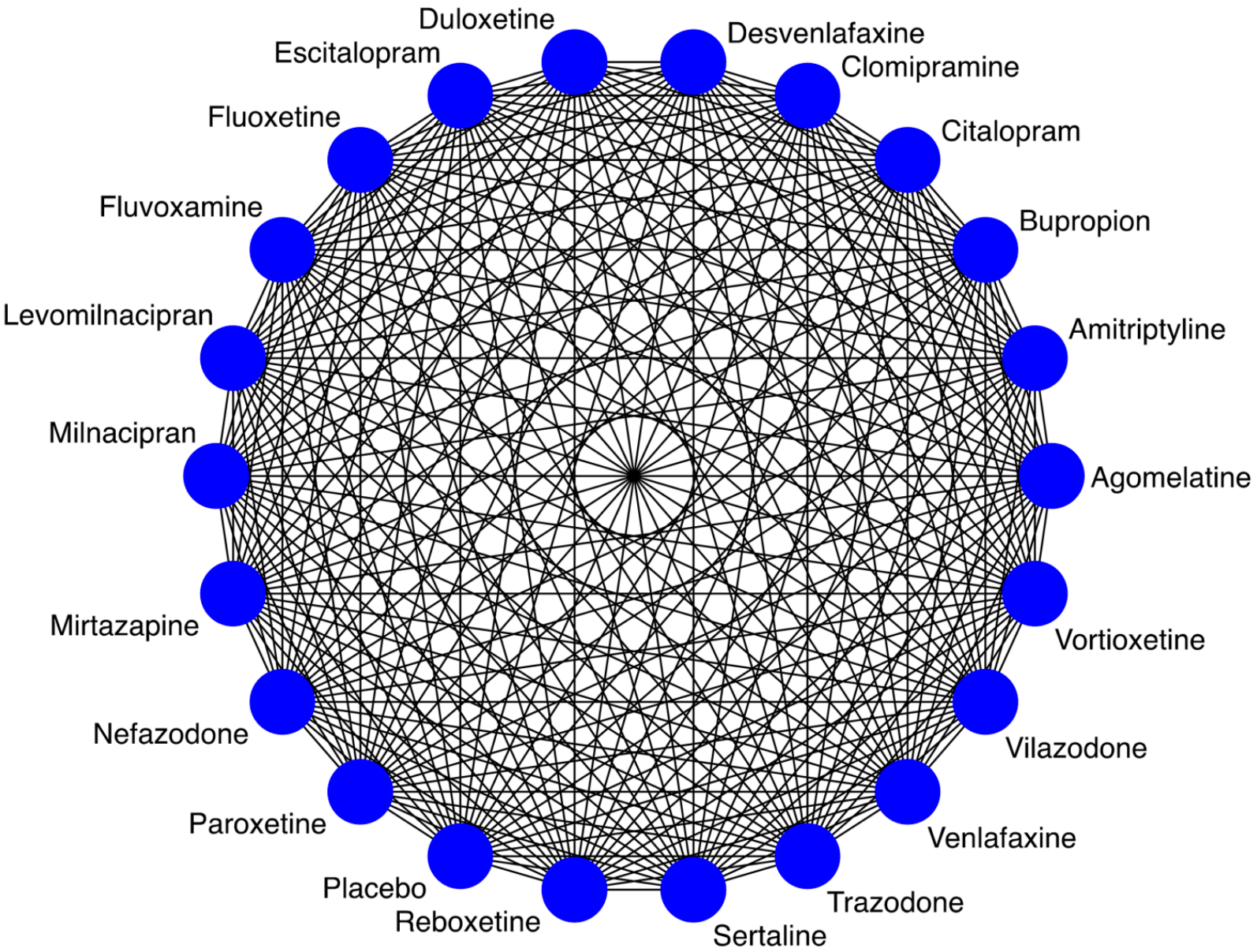


Figure 1 Network of all possible pairwise comparisons between the eligible interventions.

Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis

Andrea Cipriani, Toshi A Furukawa, Georgia Salanti*, Anna Chaimani, Lauren Z Atkinson, Yusuke Ogawa, Stefan Leucht, Henricus G Ruhe, Erick H Turner, Julian P T Higgins, Matthias Egger, Nozomi Takeshima, Yu Hayasaka, Hissei Imai, Kiyomi Shinohara, Aran Tajika, John P A Ioannidis, John R Geddes*

Summary

Background Major depressive disorder is one of the most common, burdensome, and costly psychiatric disorders worldwide in adults. Pharmacological and non-pharmacological treatments are available; however, because of inadequate resources, antidepressants are used more frequently than psychological interventions. Prescription of these agents should be informed by the best available evidence. Therefore, we aimed to update and expand our previous work to compare and rank antidepressants for the acute treatment of adults with unipolar major depressive disorder.

Methods We did a systematic review and network meta-analysis. We searched Cochrane Central Register of Controlled Trials, CINAHL, Embase, LILACS database, MEDLINE, MEDLINE In-Process, PsycINFO, the websites of regulatory agencies, and international registers for published and unpublished, double-blind, randomised controlled trials from their inception to Jan 8, 2016. We included placebo-controlled and head-to-head trials of 21 antidepressants used for the acute treatment of adults (≥18 years old and of both sexes) with major depressive disorder diagnosed according to standard operationalised criteria. We excluded quasi-randomised trials and trials that were incomplete or included 20% or more of participants with bipolar disorder, psychotic depression, or treatment-resistant depression; or patients with a serious concomitant medical illness. We extracted data following a predefined hierarchy. In network meta-analysis, we used group-level data. We assessed the studies' risk of bias in accordance to the Cochrane Handbook for Systematic Reviews of Interventions, and certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation framework. Primary outcomes were efficacy (response rate) and acceptability (treatment discontinuations due to any cause). We estimated summary

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See **Online/Comment**
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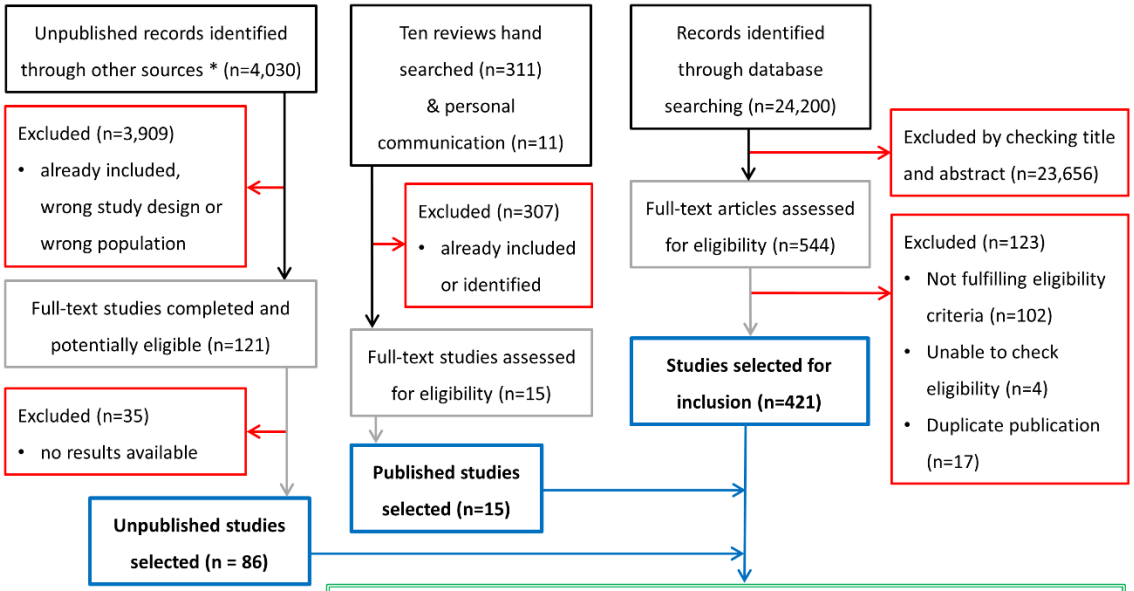
*Joint first authors

Department of Psychiatry, University of Oxford, Oxford, UK (A Cipriani MD, L Z Atkinson MSc, H G Ruhe PhD, Prof J R Geddes MD); **Oxford Health NHS Foundation Trust** (A Cipriani, Prof J R Geddes) **and Oxford Centre for Human Brain Activity, Department of Psychiatry** (L Z Atkinson), **Warneford Hospital, Oxford, UK; Department of Health Promotion and Human**



Total number of DB RCTs included in the network meta-analysis (n=522, N=116,477)

- Agomelatine vs placebo or another active comparison (n = 23)
- Amitriptyline vs placebo or another active comparison (n = 96)
- Bupropion vs placebo or another active comparison (n = 33)
- Citalopram vs placebo or another active comparison (n = 38)
- Clomipramine vs placebo or another active comparison (n = 20)
- Desvenlafaxine vs placebo or another active comparison (n = 9)
- Duloxetine vs placebo or another active comparison (n = 30)
- Escitalopram vs placebo or another active comparison (n = 42)
- Fluoxetine vs placebo or another active comparison (n = 117)
- Fluvoxamine vs placebo or another active comparison (n = 32)
- Levomilnacipran vs placebo or another active comparison (n = 6)
- Milnacipran vs placebo or another active comparison (n = 10)
- Mirtazapine vs placebo or another active comparison (n = 34)
- Nefazodone vs placebo or another active comparison (n = 21)
- Paroxetine vs placebo or another active comparison (n = 114)
- Reboxetine vs placebo or another active comparison (n = 17)
- Sertraline vs placebo or another active comparison (n = 54)
- Trazodone vs placebo or another active comparison (n = 26)
- Venlafaxine vs placebo or another active comparison (n = 68)
- Vilazodone vs placebo or another active comparison (n = 9)
- Vortioxetine vs placebo or another active comparison (n = 15)

Figure 1: Selection of included and excluded studies (with reasons). Black boxes present screened references; red boxes present excluded studies (with reasons); blue boxes present selected studies, and green boxes present studies included in the network meta-analysis. DB: double blind; RCTs: randomized controlled trials. * Industry websites, contact with authors and trial registries. Clinicaltrials.gov was searched by 'drug name' AND 'major depressive disorder' as the major heading. The total number of unpublished records is the total number of results doing this for each drug and on each unpublished database source. The main reasons for exclusion included open label/single blind studies, studies including patients with comorbid disorders and combination therapy trials. Searches were only conducted on completed trials, which also removed many ongoing/terminated results, especially from clinicaltrials.gov.

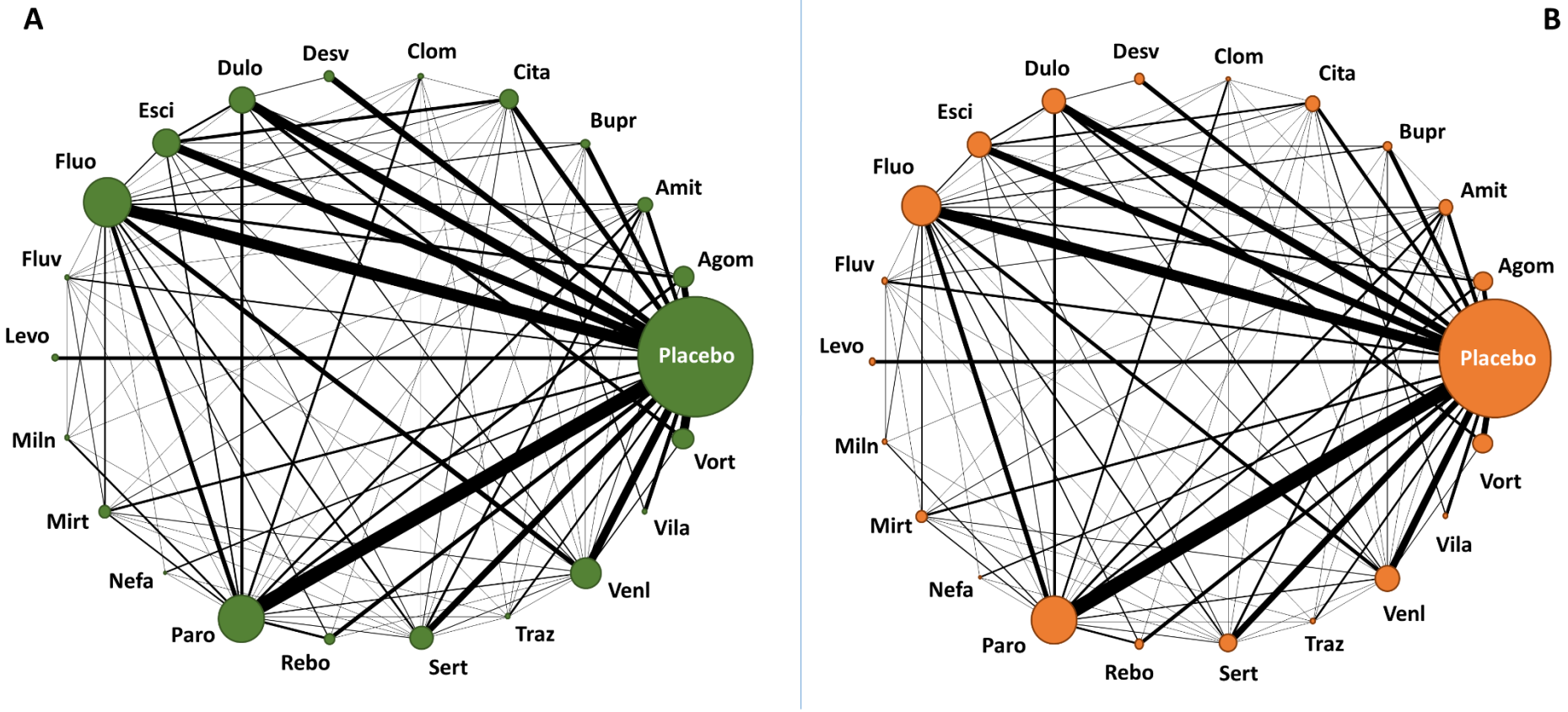
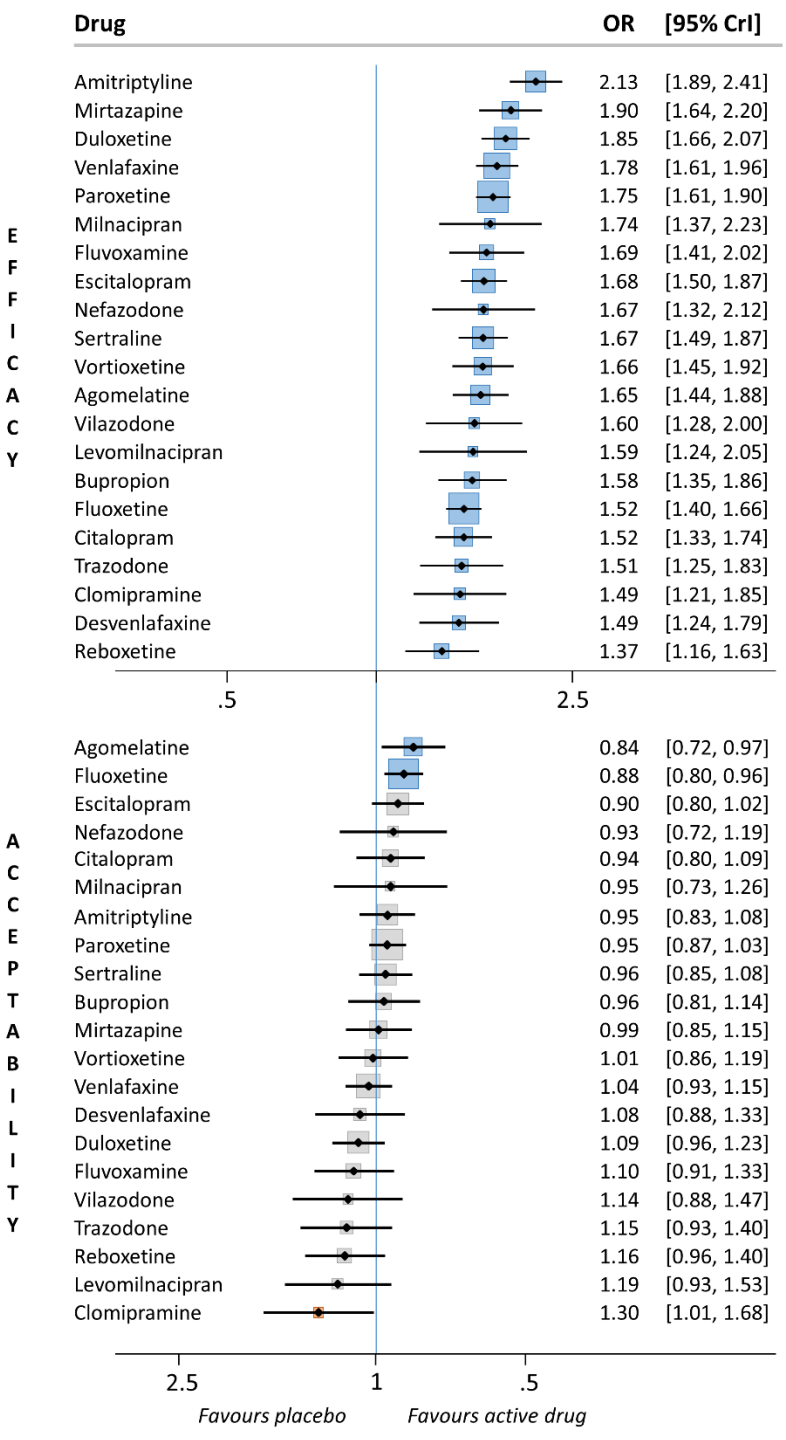
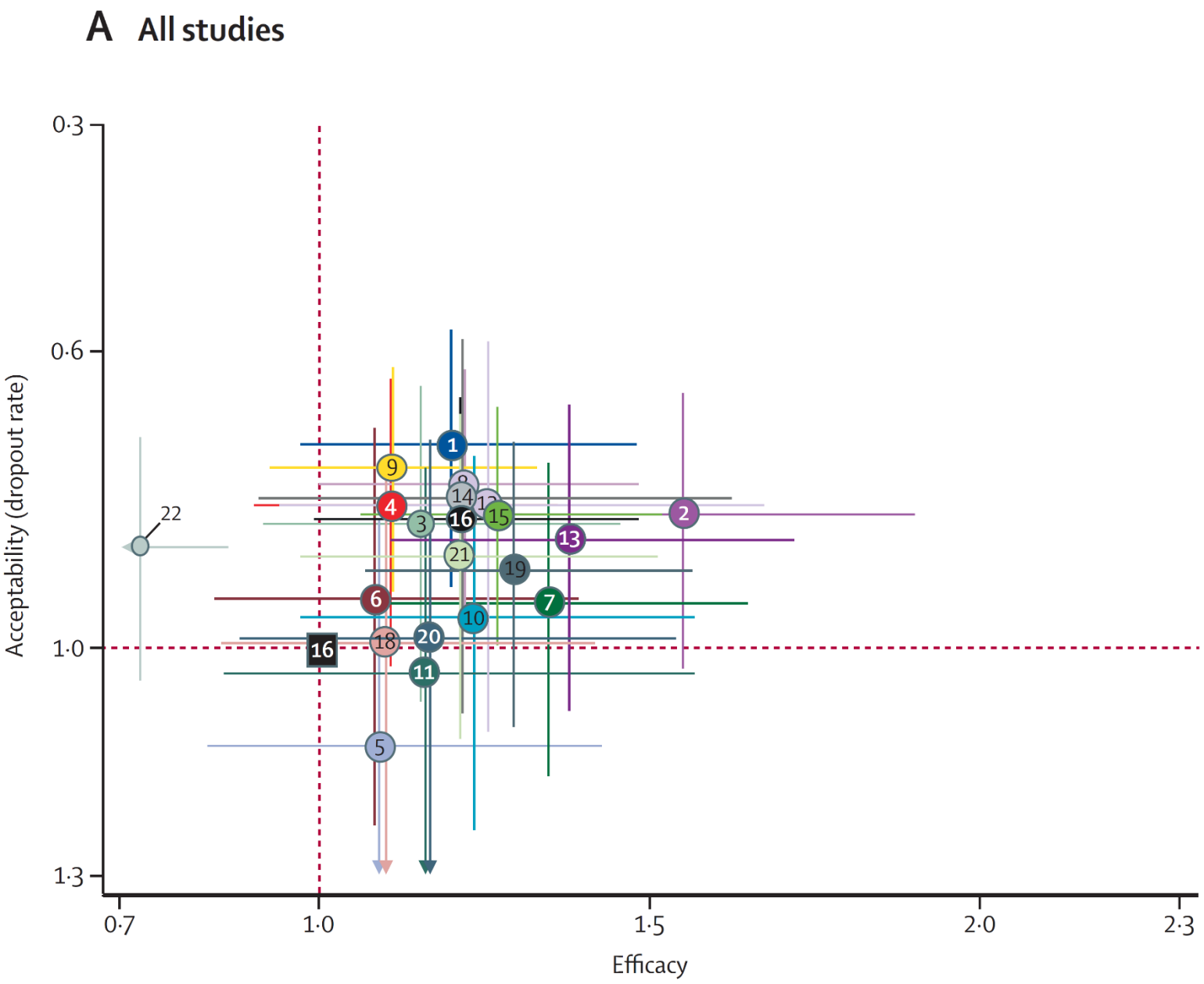


Figure 2: Network of eligible comparisons for efficacy (A) and acceptability (B). The width of the lines is proportional to the number of trials comparing every pair of treatments, and the size of every circle is proportional to the number of randomly assigned participants (sample size). Legend: Agom: agomelatine; Amit: amitriptyline; Bupr: bupropion; Cita: citalopram; Clom: clomipramine; Desv: desvenlafaxine; Dulo: duloxetine; Esci: escitalopram; Fluo: fluoxetine; Fluv: fluvoxamine; Levo: levomilnacipran; Miln: milnacipran; Mirt: mirtazapine; Nefa: nefazodone; Paro: paroxetine; Rebo: reboxetine; Sert: sertraline; Traz: trazodone; Venl: venlafaxine; Vila: vilazodone; Vort: vortioxetine.


Drug
OR
[95% CrI]
EFFICACY
Amitriptyline 2.13 [1.89, 2.41]
Mirtazapine 1.90 [1.64, 2.20]
Duloxetine 1.85 [1.66, 2.07]
Venlafaxine 1.78 [1.61, 1.96]
Paroxetine 1.75 [1.61, 1.90]
Milnacipran 1.74 [1.37, 2.23]
Fluvoxamine 1.69 [1.41, 2.02]
Escitalopram 1.68 [1.50, 1.87]
Nefazodone 1.67 [1.32, 2.12]
Sertraline 1.67 [1.49, 1.87]
Vortioxetine 1.66 [1.45, 1.92]
Agomelatine 1.65 [1.44, 1.88]
Vilazodone 1.60 [1.28, 2.00]
Levomilnacipran 1.59 [1.24, 2.05]
Bupropion 1.58 [1.35, 1.86]
Fluoxetine 1.52 [1.40, 1.66]
Citalopram 1.52 [1.33, 1.74]
Trazodone 1.51 [1.25, 1.83]
Clomipramine 1.49 [1.21, 1.85]
Desvenlafaxine 1.49 [1.24, 1.79]
Reboxetine 1.37 [1.16, 1.63]
.5
2.5
ACCEPTABILITY
Agomelatine 0.84 [0.72, 0.97]
Fluoxetine 0.88 [0.80, 0.96]
Escitalopram 0.90 [0.80, 1.02]
Nefazodone 0.93 [0.72, 1.19]
Citalopram 0.94 [0.80, 1.09]
Milnacipran 0.95 [0.73, 1.26]
Amitriptyline 0.95 [0.83, 1.08]
Paroxetine 0.95 [0.87, 1.03]
Sertraline 0.96 [0.85, 1.08]
Bupropion 0.96 [0.81, 1.14]
Mirtazapine 0.99 [0.85, 1.15]
Vortioxetine 1.01 [0.86, 1.19]
Venlafaxine 1.04 [0.93, 1.15]
Desvenlafaxine 1.08 [0.88, 1.33]
Duloxetine 1.09 [0.96, 1.23]
Fluvoxamine 1.10 [0.91, 1.33]
Vilazodone 1.14 [0.88, 1.47]
Trazodone 1.15 [0.93, 1.40]
Reboxetine 1.16 [0.96, 1.40]
Levomilnacipran 1.19 [0.93, 1.53]
Clomipramine 1.30 [1.01, 1.68]
2.5
1
.5
Favours placebo
Favours active drug


A All studies
0·3
0·6
1·0
1·3
Acceptability (dropout rate)
0·7
1·0
1·5
2·0
2·3
Efficacy
22
1
9
4
3
16
15
2
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21
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6
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16
18
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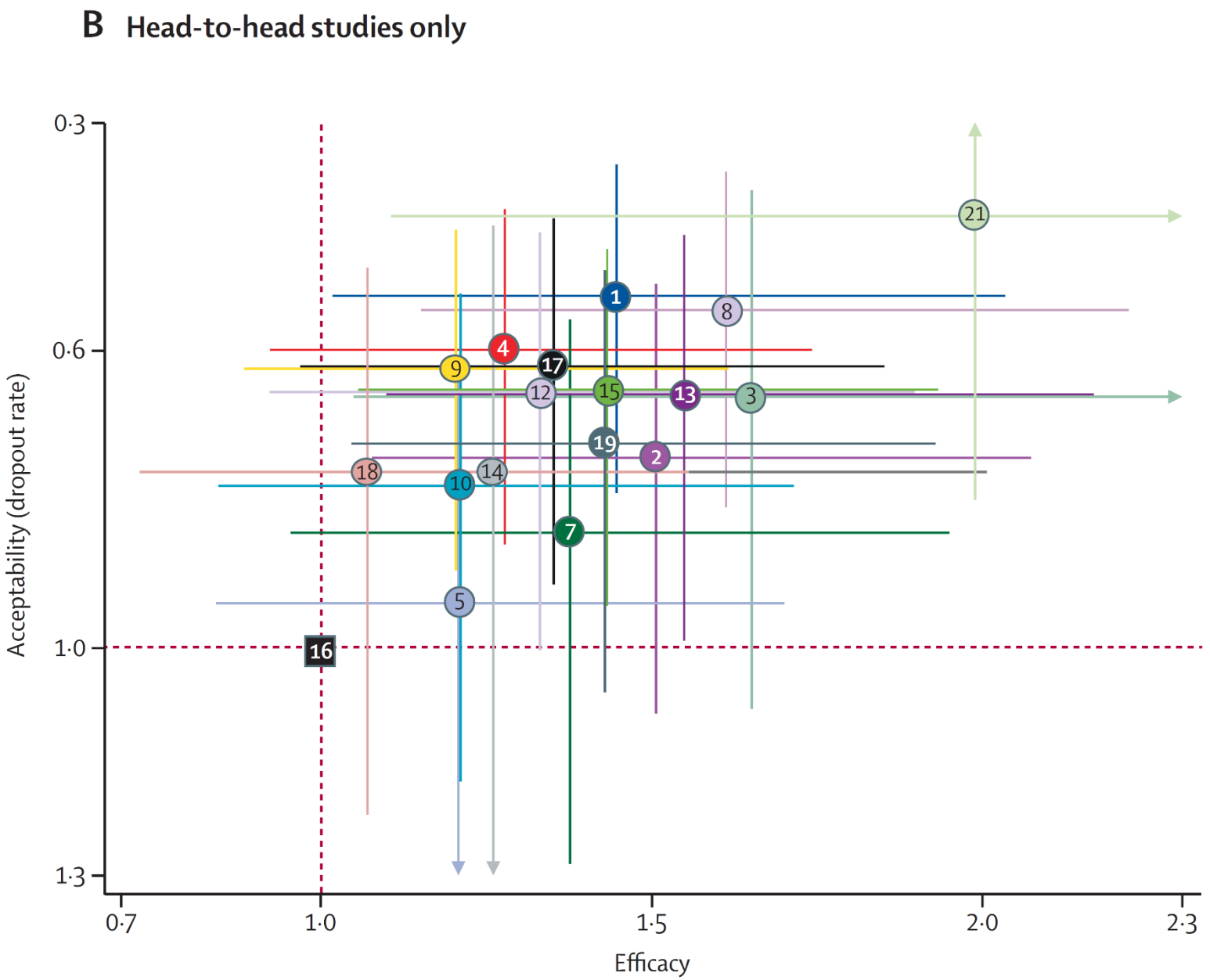
11
5


B Head-to-head studies only
0·3
0·6
1·0
1·3
Acceptability (dropout rate)
0·7
1·0
1·5
2·0
2·3
Efficacy
1
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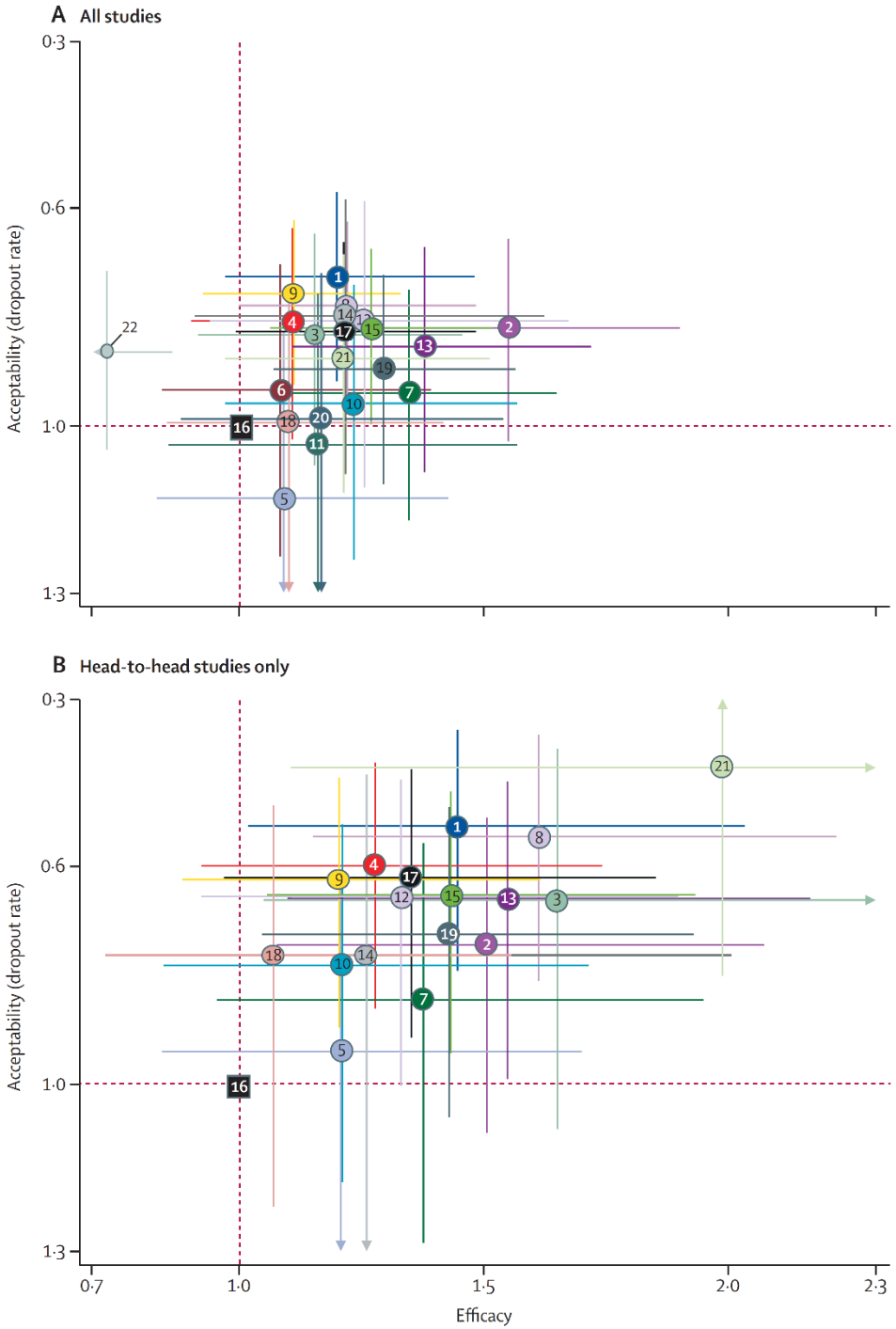
A All studies
0·3
0·6
1·0
1·3
Acceptability (dropout rate)
22
B Head-to-head studies only
0·3
0·6
1·0
1·3
Acceptability (dropout rate)
0·7
1·0
1·5
2·0
2·3
Efficacy

BMJ

RESEARCH

Efficacy of drug treatments for generalised anxiety disorder: systematic review and meta-analysis

David Baldwin, professor of psychiatry and honorary consultant psychiatrist,[1] Robert Woods, senior research executive,[2] Richard Lawson, statistician,[2] David Taylor, professor of psychopharmacology[3]

[1]University of Southampton Faculty of Medicine, University Department of Psychiatry, Academic Centre, Southampton SO14 3DT, UK

[2]Complete Medical Group, Macclesfield SK10 1AQ

[3]King's College London, London SE1 9NH

Correspondence to: D Baldwin
D.S.Baldwin@soton.ac.uk

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doi:10.1136/bmj.d1199

ABSTRACT

Objective To appraise the evidence for comparative efficacy and tolerability of drug treatments in patients with generalised anxiety disorder.

Design Systematic review of randomised controlled trials. Primary Bayesian probabilistic mixed treatment meta-analyses allowed pharmacological treatments to be ranked for effectiveness for each outcome measure, given as percentage probability of being the most effective treatment. Secondary frequentist mixed treatment meta-analyses conducted with random effects model; effect meta-analyses, fluoxetine was ranked first for response and remission (probability of 62.9% and 60.6%, respectively) and sertraline was ranked first for tolerability (49.3%). In a subanalysis ranking treatments for generalised anxiety disorder currently licensed in the United Kingdom, duloxetine was ranked first for response (third across all treatments; 2.7%), escitalopram was ranked first for remission (second across all treatments; 26.7%), and pregabalin was ranked first for tolerability (second across all treatments; 7.7%).

Conclusions Though the frequentist analysis was

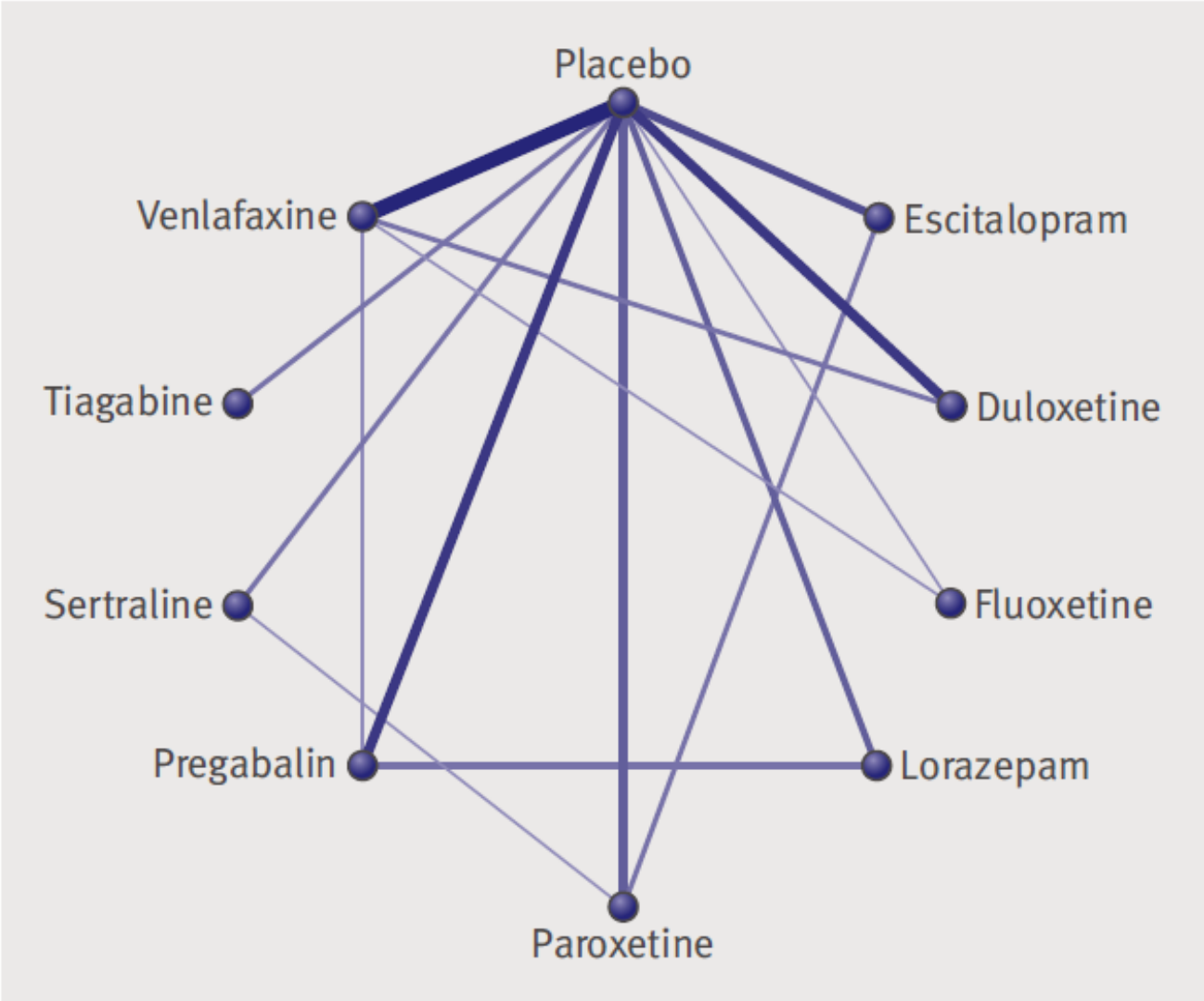

Fig 1 | Eligible network comparisons between all treatments, with increasing thickness of lines indicating increasing number of direct comparisons

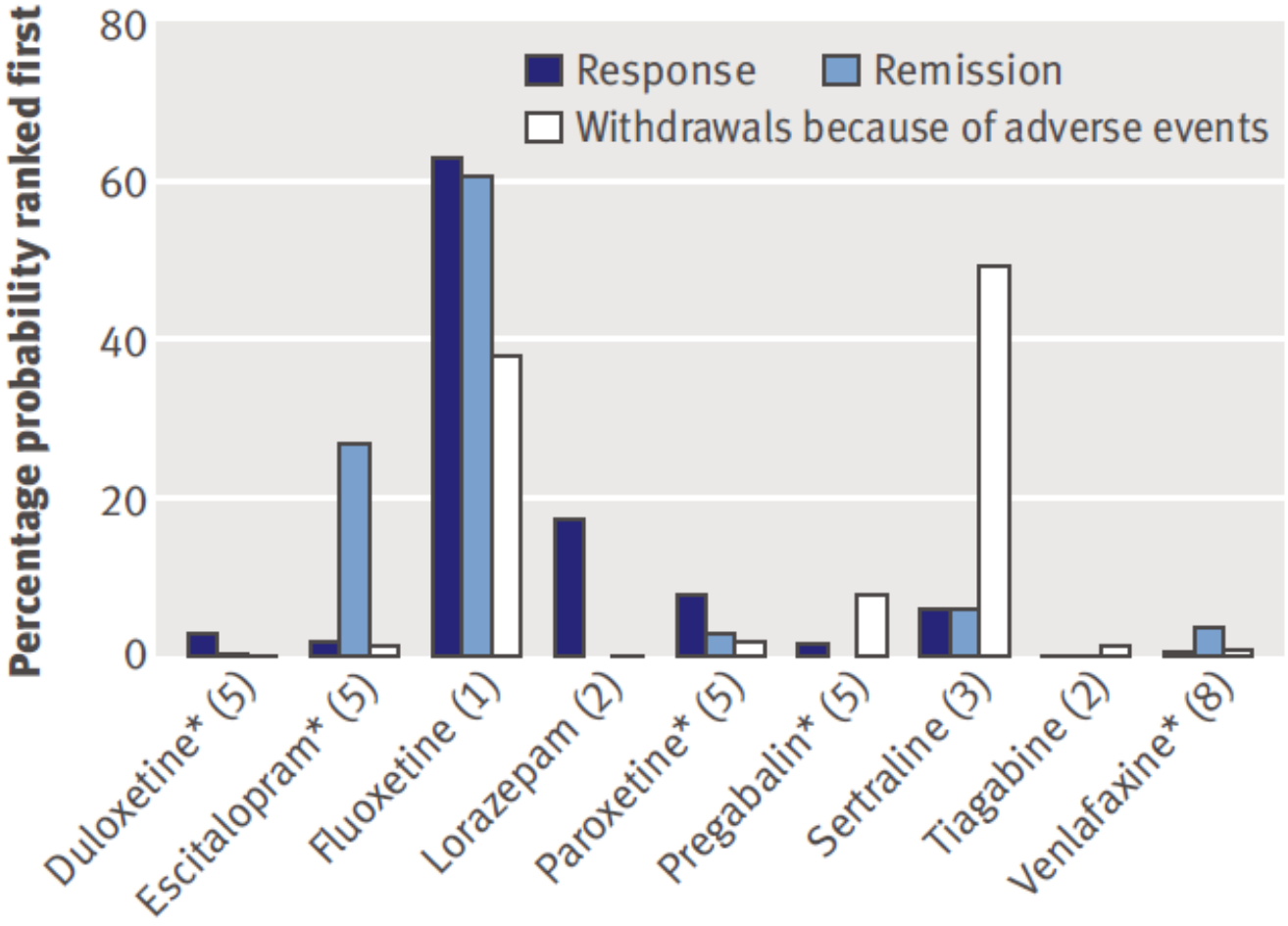

Fig 4 | Probabilistic analysis showing percentage probability of each treatment being ranked first by outcome measure. Numbers in parentheses indicate number of trials analysed for each treatment. Remission data were not available for lorazepam and pregabalin. *Drug licensed in UK

	Duloxetine	Escitalopram	Fluoxetine	Lorazepam	Paroxetine	Placebo	Pregabalin	Sertraline	Tiagabine	Venlafaxine
Duloxetine		–	–	–	–	5	–	–	–	2
Escitalopram			–	–	2	4	–	–	–	–
Fluoxetine				–	–	1	–	–	–	1
Lorazepam					–	3	2	–	–	–
Paroxetine						3	–	1	–	–
Placebo							5	2	2	8
Pregabalin								–	–	1
Sertraline									–	–
Tiagabine										–
Venlafaxine										

Fig 3 | Number of direct comparisons between treatments (or placebo) for generalised anxiety

33 Silverstone PH, Salinas E. Efficacy of venlafaxine extended release in patients with major depressive disorder and comorbid generalized anxiety disorder. *J Clin Psychiatry* 2001;62:523-9.

Efficacy of Venlafaxine Extended Release in Patients With Major Depressive Disorder and Comorbid Generalized Anxiety Disorder

Peter H. Silverstone, M.D., F.R.C.P.C., and Eliseo Salinas, M.D.

Method: From a total of 368 patients, 92 patients meeting DSM-IV criteria for major depressive disorder who also had comorbid GAD were identified. The comparison group comprised 276 evaluable noncomorbid patients. Patients received venlafaxine XR (75–225 mg/day), fluoxetine (20–60 mg/day), or placebo for 12 weeks. Efficacy evaluations included Hamilton Rating Scale for Depression (HAM-D), Hamilton Rating Scale for Anxiety (HAM-A), and Clinical Global Impressions (CGI) scale.

Table 2. Adjusted Mean Scores and Between-Group Comparisons Versus Placebo in Patients With Major Depressive Disorder and Comorbid GAD[a]

	Fluoxetine (N = 33)			Venlafaxine XR (N = 32)	
Scale	Placebo (N = 25)	Adjusted Mean Score	Adjusted Mean Different From Placebo (95% CL)	Adjusted Mean Score	Adjusted Mean Different From Placebo (95% CL)
HAM-A total					
Baseline	25.7	25.7		25.7	
Week 1	22.4	21.8	0.6 (–1.9, 3.1)	23.6	–1.2 (–3.8, 1.3)
Week 2	20.6	20.0	0.5 (–2.5, 3.6)	20.4	0.2 (–2.9, 3.3)
Week 3	20.2	18.6	1.6 (–1.6, 4.8)	19.2	1.0 (–2.2, 4.3)
Week 4	19.4	17.2	2.3 (–1.3, 5.8)	17.0	2.4 (–1.2, 6.1)
Week 6	17.5	17.6	–0.1 (–3.8, 3.6)	15.6	1.9 (–1.8, 5.6)
Week 8	16.1	15.9	0.2 (–4.1, 4.5)	14.4	1.7 (–2.6, 6.0)
Week 12	16.9	14.4	2.5 (–1.7, 6.7)	12.5*	4.5 (0.2, 8.7)

[a]Based on data from Silverstone and Ravindran.[14] Analysis based on last observation carried forward. Abbreviations: CL = confidence limits, GAD = generalized anxiety disorder, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, XR = extended release.
*Significant difference vs. placebo ($p < .05$).

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Statistics in practice

Common pitfalls and mistakes in the set-up, analysis and interpretation of results in network meta-analysis: what clinicians should look for in a published article

Anna Chaimani,[1] Georgia Salanti,[1,2] Stefan Leucht,[3] John R Geddes,[4,5] Andrea Cipriani[4,5]

Correspondence to Professor Andrea Cipriani, Department of Psychiatry, University of Oxford, Warneford Hospital, OX3 7JX, Oxford, UK; andrea.cipriani@psych.ox.ac.uk

ABSTRACT

Objective Several tools have been developed to evaluate the extent to which the findings from a network meta-analysis would be valid; however, applying these tools is a time-consuming task and often requires specific expertise. Clinicians have little time for critical appraisal, and they need to understand the key elements that help them select network meta-analyses that deserve further attention, optimising time and resources. This paper is aimed at providing a practical framework to assess the methodological robustness and reliability of results from network meta-analysis.

Methods As a working example, we selected a network meta-analysis about drug treatments for generalised anxiety disorder, which was published in 2011 in the British Medical Journal. The same network meta-analysis was previously used to illustrate the potential of this methodology in a methodological paper published in JAMA.

Results We reanalysed the 27 studies included in this network following the methods reported in the original article and compared our findings with the published results. We showed how different methodological approaches and the presentation of results can affect conclusions from network meta-analysis. We divided our results into three sections, according to the specific issues that should always be addressed in network meta-analysis: (1) understanding the evidence base, (2) checking the statistical analysis and (3) checking the reporting of findings.

Conclusions The validity of the results from network meta-analysis depends on the plausibility of the transitivity assumption. The risk of bias introduced by limitations of individual studies must be considered first and judgement should be used to infer about the plausibility of transitivity. Inconsistency exists when treatment effects from direct and indirect evidence are in disagreement. Unlike transitivity, inconsistency can be always evaluated statistically, and it should be specifically investigated and reported in the published paper. Network meta-analysis allows researchers to list treatments in preferential order; however, in this paper we demonstrated that rankings could be misleading if based on the probability of being the best. Clinicians should always be interested in the effect sizes rather than the naive rankings.

Thank you

andrea.cipriani@psych.ox.ac.uk

@And_Cipriani