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

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For the **study protocol** see http://www.psychiatry.univr.it/docs/Research%20Activities/MTM_Protocol.pdf

For the **data set** see http://www.psychiatry.univr.it/docs/Research%20Activities/MTM_Analysis.pdf

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.

Funding None.

Introduction

In the past 20 years, several new drugs have been introduced for the treatment of depression, many of which are structurally related and share similar putative mechanisms of action. As with statins for the prevention of coronary events,[1] the extent to which these agents vary in terms of efficacy and acceptability is unclear. Moreover, some of the new drugs are so-called me-too drugs[2]—ie, chemically similar to existing drugs with expiring patents rather than genuine advances in treatment. Systematic reviews have already highlighted some differences in efficacy between second-generation antidepressants.[3–9]

We report an overview of all randomised controlled trials that compared 12 new-generation antidepressants in terms of efficacy and acceptability in the acute-phase treatment of major depression. We used multiple-treatments meta-analysis,[10] also known as mixed-treatment comparisons meta-analysis or network meta-analysis, which allows the integration of data from direct (when treatments are compared within a randomised trial) and indirect comparisons (when treatments are compared between trials by combining results on how effective they are compared with a common comparator treatment).[11] We aimed to provide a clinically useful summary of the results of the multiple-treatments meta-analysis that can be used to guide treatment decisions.

Methods

Study selection and data collection

At the beginning of this project, we drafted a study protocol and subsequently made it freely available to the public on our institutional website before carrying out the final analyses. Furthermore, with the publication of this paper the overall data set will be in the public domain.

For our analysis, we included only randomised controlled trials that compared any of the following 12 new-generation antidepressants (bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, and venlafaxine) as monotherapy in the acute-phase treatment of adults with unipolar major depression. We excluded placebo groups where present and randomised controlled trials of women with post-partum depression.[12]

To identify the relevant studies, we reviewed the Cochrane collaboration depression, anxiety, and neurosis review group controlled trials registers (CCDANDTR-studies and CCDANCTR-references) up to Nov 30, 2007.

We asked pharmaceutical companies, regulatory agencies, and study investigators to supply all available information.

Two persons within the reviewing team independently reviewed references and abstracts retrieved by the search, assessed the completeness of data abstraction, and confirmed quality rating. We used a structured data-abstraction form to ensure consistency of appraisal for each study. Investigators were contacted and asked to provide data to supplement the incomplete reporting of the original articles.

We gave studies a quality rating of adequate, unclear, or inadequate, according to the adequacy of the random allocation concealment and blinding.[13] Studies that scored adequate or unclear on these criteria were included in the final list.

Outcome measures

We defined acute treatment as 8-week treatment for both efficacy and acceptability analyses.[14] If 8-week data were not available, we used data ranging between 6 and 12 weeks (we gave preference to the timepoint given in the original study as the study endpoint). Response and dropout rates were chosen as primary outcomes, being the most consistently reported estimates of acute-treatment efficacy and acceptability. We defined response as the proportion of patients who had a reduction of at least 50% from the baseline score on the Hamilton depression rating scale (HDRS) or Montgomery–Åsberg depression rating scale (MADRS), or who scored much improved or very much improved on the clinical global impression (CGI) at 8 weeks. When trials reported results from all three rating scales, we used the HDRS results. Finally, we defined treatment discontinuation (acceptability) as the number of patients who terminated the study early for any reason during the first 8 weeks of treatment (dropouts).

Comparability of dosages

In addition to internal and external validity, we assessed the comparability of dosages. Because we could not find any clear definitions about equivalence of dosages among new-generation antidepressants in the published literature, we used a modified version of a previously published classification described by Gartlehner and colleagues[8] (table 1). We employed this information to detect inequalities in dosing that could affect comparative efficacy, and used it in a sensitivity analysis by defining within the therapeutic dose only those studies that used comparable dosages within the predefined range.

Statistical analysis

We chose a dichotomous primary outcome mainly for clinical reasons. We used both the number of patients who responded and the number of patients who dropped out to have hard outcome measures of both treatment efficacy and acceptability. We used response rate instead of a continuous symptom score for efficacy analysis to make the interpretation of results easier for clinicians.[15] When dichotomous efficacy outcomes were not reported, but baseline scores, endpoint means, and standard deviations (SD) of the depression rating scales (such as HDRS or MADRS) were provided, we estimated the number of patients responding to treatment at 8 weeks (range 6–12 weeks)

	Range (mg/day)	Low	Medium	High
Bupropion	150–450	<337·5	337·5–412·5	>412·5
Citalopram	20–60	<30	30–50	>50
Duloxetine	60–100	<70	70–90	>90
Escitalopram	10–30	<15	15–25	>25
Fluoxetine	20–60	<30	30–50	>50
Fluvoxamine	50–300	<75	75–125	>125
Milnacipran	50–300	<75	75–125	>125
Mirtazapine	15–45	<22·5	22·5–37·5	>37·5
Paroxetine	20–60	<30	30–50	>50
Reboxetine	4–12	<5	5–9	>9
Sertraline	50–200	<75	75–125	>125
Venlafaxine	75–250	<156·3	156·25–218·7	>218·75

Table 1: **Dosing classification based on lower and upper dosing range quartiles**

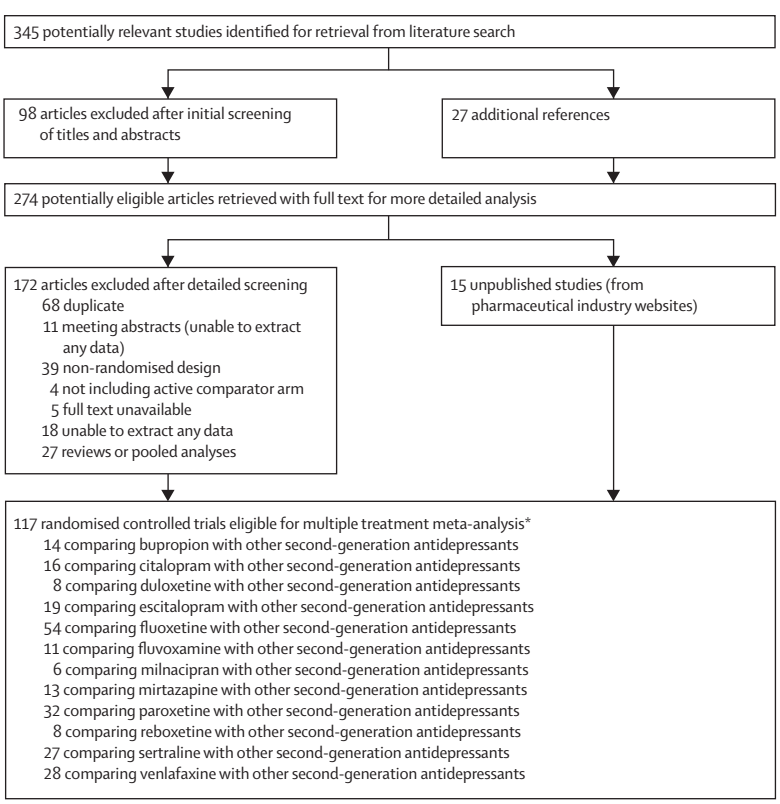

Figure 1: **Study selection process**

*117 randomised controlled trials correspond to 236 arms because two three-arm studies comparing fluoxetine with paroxetine and sertraline were included in this multiple-treatments meta-analysis.

	Number of trials	Year of publication			Country				
		Earliest	Median	Latest	Europe	North America	Africa	Asia	Multiple countries
Bupropion	14	1991	2003	2007	1	10	0	0	2
Citalopram	16	1993	2002	2007	4	4	0	1	4
Duloxetine	8	2002	2006	2007	2	5	0	0	1
Escitalopram	19	2000	2005	2007	5	11	0	0	2
Fluoxetine	54	1991	2000	2007	15	13	1	3	6
Fluvoxamine	11	1993	1998	2006	3	2	0	1	2
Milnacipran	6	1994	2000	2003	2	1	0	2	0
Mirtazapine	13	1997	2002	2005	3	3	1	1	5
Paroxetine	32	1993	2001	2007	12	13	1	1	2
Reboxetine	8	1997	2003	2006	2	2	0	0	1
Sertraline	27	1993	2000	2007	10	9	0	2	1
Venlafaxine	28	1994	2002	2007	7	5	0	1	6

The number of studies across countries in this table does not match the number of trials included in the review. Missing studies scored as other or not known. *Two three-arm studies comparing fluoxetine with paroxetine and sertraline were included in the systematic review (the total number of arms is 236 and it corresponds to 115 two-arm and two three-arm studies).

Table 2: **Studies included in the multiple-treatments meta-analysis**

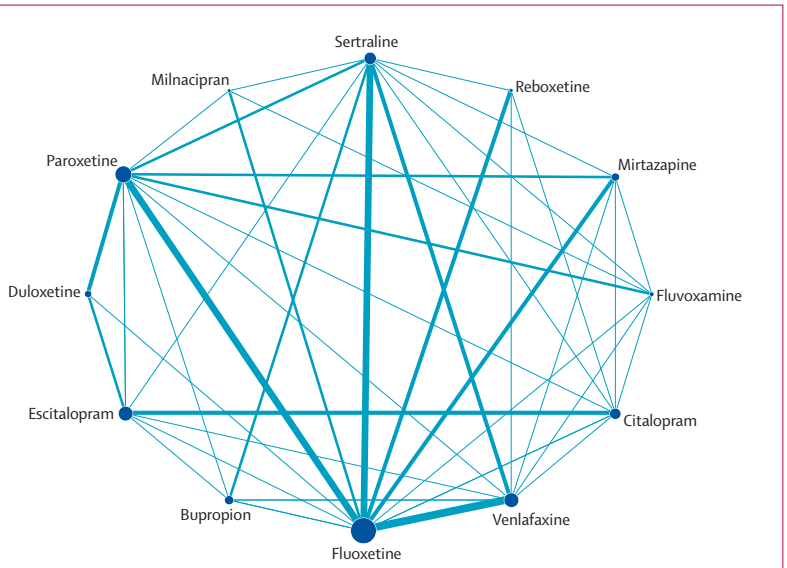

Figure 2: **Network of eligible comparisons for the multiple-treatment meta-analysis for efficacy (response rate)**
The width of the lines is proportional to the number of trials comparing each pair of treatments, and the size of each node is proportional to the number of randomised participants (sample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

with a validated imputation method.[16] Responders to treatment were calculated on an intention-to-treat basis: the analysis was based on the total number of randomly assigned participants, irrespective of how the original study investigators analysed the data. To carry out a clinically sound analysis, we used a conservative approach and imputed outcomes for the missing participants assuming that they did not respond to treatment.

First, we did pair-wise meta-analyses by synthesising[17] studies that compared the same interventions with a random-effects model[18] to incorporate the assumption that different studies assessed different, yet related, treatment effects.[17] We used visual inspection of the forest plots to investigate the possibility of statistical heterogeneity, and the I^2 statistic.[19] We did the analyses using Stata version 9.

Second, we did a random-effects model within a Bayesian framework using Markov chain Monte Carlo methods in WinBUGS (MRC Biostatistics Unit, Cambridge, UK).[11] We modelled the binary outcomes in every treatment group of every study, and specified the relations among the odds ratios (ORs) across studies making different comparisons.[10] This method combines direct and indirect evidence for any given pair of treatments. We used p values less than 0·05 and 95% CIs (according to whether the CI included the null value) to assess significance, and looked at a plausible range for the magnitude of the population difference.[20] We also assessed the probability that each antidepressant drug was the most efficacious regimen, the second best, the third best, and so on, by calculating the OR for each drug compared with an arbitrary common control group, and counting the proportion of iterations of the Markov chain in which each drug had the highest OR, the second highest, and so on. We ranked treatments in terms of acceptability with the same methods.

A key assumption behind multiple-treatments meta-analysis is that the analysed network is coherent—ie, that direct and indirect evidence on the same comparisons do not disagree beyond chance. To estimate incoherence, we calculated the ratio of odds ratios for indirect versus direct evidence whenever indirect estimates could be constructed with a single common comparator. We defined incoherence as the disagreement between direct and indirect evidence with a 95% CI excluding 1.

Finally, we looked at comparative efficacy among the 12 antidepressant drugs. We expressed these using fluoxetine as reference drug, because it was the first among these 12 antidepressants to be marketed in Europe and the USA, and it has been consistently used as reference drug among the different pair-wise comparisons.

We did sensitivity analyses according to the following variables: dose (including only studies within the therapeutic range) and imputation (including only studies without imputation). To investigate the effect of sponsorship on outcome estimate, we carried out a meta-regression analysis.

Role of the funding source

No drug manufacturing company was involved in the study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit the report for publication. All authors saw and

	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)
Citalopram *vs*						
Escitalopram	5	1604	319/622 *vs* 426/725	0·68 (0·53–0·87)	127/750 *vs* 141/854	1·17 (0·83–1·64)
Fluoxetine	3	740	216/364 *vs* 219/376	1·05 (0·77–1·43)	75/364 *vs* 68/376	1·17 (0·80–1·70)
Fluvoxamine	1	217	33/108 *vs* 31/109	1·11 (0·62–1·98)	22/108 *vs* 29/109	0·71 (0·37–1·33)
Mirtazapine	1	270	117/133 *vs* 116/137	1·32 (0·66–2·66)	8/133 *vs* 18/137	0·42 (0·18–1·01)
Paroxetine	1	406	77/199 *vs* 102/207	1·54 (1·04–2·28)	41/199 *vs* 43/207	1·01 (0·62–1·63)
Reboxetine	2	451	145/227 *vs* 110/224	1·72 (1·01–2·93)	51/227 *vs* 73/224	0·86 (0·22–3·46)
Sertraline	2	615	139/200 *vs* 136/200	0·93 (0·61–1·42)	60/307 *vs* 82/308	0·67 (0·46–0·98)
Venlafaxine	1	151	50/75 *vs* 49/76	1·10 (0·56–2·16)	..	..
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)
Escitalopram *vs*						
Bupropion	3	842	172/287 *vs* 163/279	1·07 (0·69–1·67)	109/425 *vs* 105/417	1·02 (0·75–1·39)
Citalopram	5	1604	426/725 *vs* 319/622	1·47 (1·15–1·90)	141/854 *vs* 127/750	0·86 (0·61–1·20)
Duloxetine	3	1120	286/558 *vs* 260/562	1·30 (0·88–1·91)	87/414 *vs* 131/411	0·52 (0·26–1·01)
Fluoxetine	2	543	143/276 *vs* 126/267	1·23 (0·87–1·74)	66/276 *vs* 68/267	0·98 (0·37–2·56)
Paroxetine	2	784	274/398 *vs* 255/386	1·12 (0·76–1·65)	40/398 *vs* 50/386	0·75 (0·48–1·17)
Sertraline	2	489	144/243 *vs* 152/246	0·90 (0·62–1·30)	47/243 *vs* 40/246	1·24 (0·77–1·97)
Venlafaxine	2	495	172/249 *vs* 160/246	1·21 (0·69–2·11)	52/249 *vs* 56/246	0·90 (0·58–1·39)
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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approved the final version of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The electronic searches yielded 345 potentially relevant studies, of which 274 potentially eligible articles were analysed. We excluded 172 reports that did not meet eligibility criteria (figure 1). We identified a further 15 unpublished trials eligible for our meta-analysis from pharmaceutical industry websites. Overall, we used 117 trials from 1991 to 2007 for the multiple-treatments meta-analysis.[21–137] Most trials (63%) were carried out in North America and Europe (table 2). Overall, 25 928 individuals were randomly assigned to one of the 12 antidepressant drugs and were included in the multiple-treatments meta-analysis. About two-thirds of

	Number of studies	Number of patients	Efficacy		Acceptability	
			Response rate (responders/total randomised)	OR (95% CI)	Dropout rate (dropouts/total randomised)	OR (95% CI)
(Continued from previous page)						
Fluvoxamine *vs*						
Citalopram	1	217	31/109 *vs* 33/108	0·90 (0·50–1·62)	29/109 *vs* 22/108	1·42 (0·75–2·66)
Fluoxetine	2	284	83/141 *vs* 83/143	1·03 (0·64–1·66)	31/141 *vs* 28/143	1·17 (0·66–2·09)
Milnacipran	1	113	32/56 *vs* 40/57	0·57 (0·26–1·23)	17/56 *vs* 15/57	1·22 (0·54–2·77)
Mirtazapine	1	412	127/207 *vs* 132/205	0·88 (0·59–1·31)	41/207 *vs* 47/205	0·83 (0·52–1·33)
Paroxetine	3	281	72/143 *vs* 77/138	0·83 (0·51–1·34)	42/143 *vs* 38/138	1·08 (0·62–1·85)
Sertraline	2	185	48/89 *vs* 49/96	1·21 (0·53–2·75)	22/89 *vs* 12/96	1·47 (0·19–11·11)
Venlafaxine	1	111	14/34 *vs* 48/77	0·42 (0·19–0·96)	13/34 *vs* 18/77	2·03 (0·85–4·84)
Milnacipran *vs*						
Fluoxetine	3	560	156/336 *vs* 106/224	0·87 (0·54–1·39)	138/336 *vs* 83/224	1·02 (0·71–1·46)
Fluvoxamine	1	113	40/57 *vs* 32/56	1·76 (0·81–3·83)	15/57 *vs* 17/56	0·82 (0·36–1·86)
Paroxetine	1	302	74/149 *vs* 78/153	0·95 (0·60–1·49)	29/149 *vs* 33/153	0·88 (0·50–1·54)
Sertraline	1	53	4/27 *vs* 2/26	2·08 (0·35–12·5)	15/27 *vs* 11/26	1·70 (0·57–5·05)
Mirtazapine *vs*						
Citalopram	1	270	116/137 *vs* 117/133	0·76 (0·38–1·52)	18/137 *vs* 8/133	2·36 (0·99–5·65)
Fluoxetine	5	622	200/306 *vs* 176/316	1·55 (1·07–2·23)	50/159 *vs* 48/164	1·09 (0·67–1·78)
Fluvoxamine	1	412	132/205 *vs* 127/207	1·14 (0·76–1·70)	47/205 *vs* 41/207	1·20 (0·75–1·93)
Paroxetine	3	726	184/366 *vs* 160/360	1·27 (0·94–1·70)	99/366 *vs* 110/360	0·84 (0·60–1·16)
Sertraline	1	346	117/176 *vs* 114/170	0·97 (0·62–1·52)	41/176 *vs* 32/170	1·31 (0·78–2·20)
Venlafaxine	2	415	113/208 *vs* 91/207	1·53 (1·03–2·25)	57/208 *vs* 75/207	0·66 (0·44–1·01)
Paroxetine* *vs*						
Bupropion	2	240	40/52 *vs* 34/48	1·37 (0·56–3·36)	26/123 *vs* 22/117	1·16 (0·61–2·20)
Citalopram	1	406	77/199 *vs* 102/207	0·65 (0·44–0·96)	41/199 *vs* 43/207	0·99 (0·61–1·60)
Duloxetine	4	1095	200/359 *vs* 398/736	1·10 (0·74–1·63)	90/359 *vs* 171/736	1·10 (0·81–1·50)
Escitalopram	2	784	255/386 *vs* 274/398	0·89 (0·61–1·32)	50/386 *vs* 40/398	1·33 (0·85–2·07)
Fluoxetine*	13	2806	740/1277 *vs* 771/1287	0·99 (0·85–1·22)	468/1400 *vs* 447/1406	1·08 (0·92–1·26)
Fluvoxamine	3	281	77/138 *vs* 72/143	1·20 (0·74–1·96)	38/138 *vs* 42/143	0·93 (0·54–1·60)
Milnacipran	1	302	78/153 *vs* 74/149	1·05 (0·67–1·65)	33/153 *vs* 29/149	1·14 (0·65–1·99)
Mirtazapine	3	726	160/360 *vs* 184/366	0·79 (0·59–1·06)	110/360 *vs* 99/366	1·19 (0·86–1·65)
Sertraline*	4	664	204/325 *vs* 241/339	0·57 (0·30–1·07)	75/325 *vs* 69/339	1·47 (0·65–3·33)
Venlafaxine	1	361	105/178 *vs* 113/183	0·89 (0·58–1·36)	52/178 *vs* 47/183	1·19 (0·75–1·90)
Reboxetine *vs*						
Citalopram	2	451	110/224 *vs* 145/227	0·58 (0·34–0·99)	73/224 *vs* 51/227	1·16 (0·29–4·63)
Fluoxetine	4	764	168/377 *vs* 204/387	0·72 (0·48–1·08)	126/377 *vs* 98/387	1·47 (1·07–2·02)
Sertraline	1	48	16/25 *vs* 17/24	0·73 (0·22–2·43)	5/25 *vs* 3/24	1·75 (0·37–8·33)
Venlafaxine	1	107	32/57 *vs* 37/50	0·45 (0·20–1·02)	7/57 *vs* 7/50	0·86 (0·28–2·65)

(Continues on next page)

participants (64%) were women. 24595 were included in the efficacy analysis (111 studies) and 24693 in the acceptability analysis (112 studies). The mean duration of the studies was 8·1 weeks and the mean sample size was 109·8 participants per group (range 9–357), 62 trials having at least 100 participants per group. 85 studies were two-arm trials; 23 were three-arm trials involving two different active comparisons and placebo; seven were multi-arm trials involving two active compounds at various fixed dosages and placebo; and two were three-arm trials with three different active comparisons.[61,62]

Only 14 studies (comparing all included antidepressants except fluvoxamine and milnacipran) had a follow-up longer than 12 weeks. We obtained supplementary information about outcome data from the investigators for 42 of the included studies. In terms of clinical characteristics, 53 studies (9321 participants) included individuals aged 65 years or younger (eight recruited only individuals older than 65, n=1583), and 87 were carried out in outpatient clinics (seven in primary care). The overall mean baseline score at study entry was 23·47 (SD 4·27) for HDRS-17, 25·72 (4·62) for HDRS-21,

	Number of studies	Number of patients	Efficacy		Acceptability	
			Response rate (responders/ total randomised)	OR (95% CI)	Dropout rate (dropouts/ total randomised)	OR (95% CI)
(Continued from previous page)						
Sertraline* *vs*						
Bupropion	3	727	231/363 *vs* 237/364	0·93 (0·69–1·27)	82/237 *vs* 63/242	1·51 (0·86–2·64)
Citalopram	2	615	139/200 *vs* 136/200	1·07 (0·70–1·64)	82/308 *vs* 60/307	1·49 (1·02–2·18)
Escitalopram	2	489	152/246 *vs* 144/243	1·12 (0·77–1·61)	40/246 *vs* 47/243	0·81 (0·51–1·29)
Fluoxetine*	8	1352	406/686 *vs* 344/666	1·42 (1·13–1·78)	135/568 *vs* 151/546	0·80 (0·56–1·14)
Fluvoxamine	2	185	49/96 *vs* 48/89	0·83 (0·36–1·88)	12/96 *vs* 22/89	0·68 (0·09–5·15)
Milnacipran	1	53	2/26 *vs* 4/27	0·48 (0·08–2·87)	11/26 *vs* 15/27	0·59 (0·20–1·74)
Mirtazapine	1	346	114/170 *vs* 117/176	1·03 (0·66–1·61)	32/170 *vs* 41/176	0·76 (0·45–1·28)
Paroxetine*	4	664	241/339 *vs* 204/325	1·76 (0·93–3·32)	69/339 *vs* 75/325	0·68 (0·30–1·54)
Reboxetine	1	48	17/24 *vs* 16/25	1·37 (0·41–4·54)	3/24 *vs* 5/25	0·57 (0·12–2·71)
Venlafaxine	5	611	177/303 *vs* 190/308	0·87 (0·59–1·29)	49/303 *vs* 70/308	0·56 (0·24–1·33)
Venlafaxine *vs*						
Bupropion	3	1127	329/564 *vs* 307/563	1·17 (0·86–1·59)	152/564 *vs* 150/563	1·00 (0·76–1·32)
Citalopram	1	151	49/76 *vs* 50/75	0·91 (0·46–1·78)	..	..
Escitalopram	2	495	160/246 *vs* 172/249	0·82 (0·47–1·44)	56/246 *vs* 52/249	1·12 (0·72–1·73)
Fluoxetine	12	2446	679/1116 *vs* 607/1126	1·36 (1·14–1·62)	302/1220 *vs* 290/1226	1·07 (0·88–1·29)
Fluvoxamine	1	111	48/77 *vs* 14/34	2·36 (1·04–5·38)	18/77 *vs* 13/34	0·49 (0·21–1·18)
Mirtazapine	2	415	91/207*vs* 113/208	0·65 (0·44–0·97)	75/207 *vs* 57/208	1·50 (0·99–2·29)
Paroxetine	1	361	113/183 *vs* 105/178	1·12 (0·74–1·71)	47/183 *vs* 52/178	0·84 (0·53–1·33)
Reboxetine	1	107	37/50 *vs* 32/57	2·22 (0·98–5·05)	7/50 *vs* 7/57	1·16 (0·39–3·58)
Sertraline	5	611	190/308 *vs* 177/303	1·15 (0·78–1·69)	70/308 *vs* 49/303	1·78 (0·75–4·18)

OR=odds ratio. Vs=versus. CI=confidence interval. *Two three-arm studies comparing fluoxetine with paroxetine and sertraline were included in the systematic review.

Table 3: **Response and dropout rates for efficacy and acceptability in meta-analyses of direct comparisons between each pair of antidepressants**

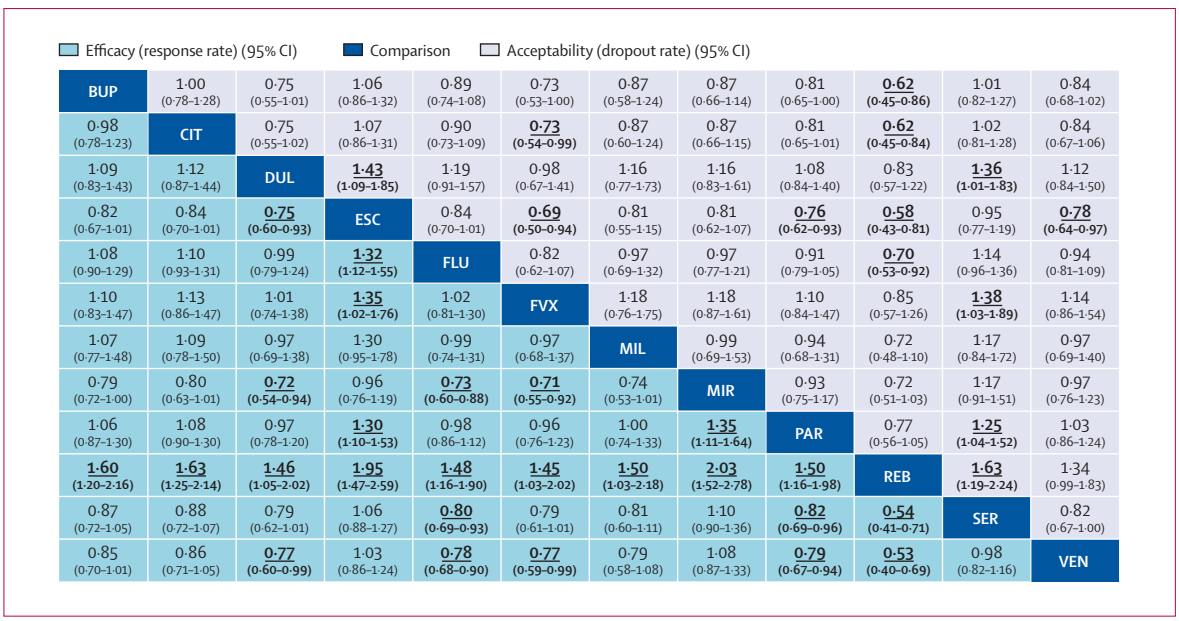
and 30·09 (4·64) for MADRS. Most trials were rated as unclear according to our quality assessment and only 12 were rated as adequate. Figure 2 shows the network of eligible comparisons for the multiple-treatments meta-analysis. Of the 66 possible pair-wise comparisons between the 12 treatments, 42 have been studied directly in one or more trials for efficacy and 41 for acceptability.

We did direct comparisons (table 3), showing that efficacy favours escitalopram over citalopram; citalopram over reboxetine and paroxetine; mirtazapine over fluoxetine and venlafaxine; sertraline over fluoxetine; and venlafaxine over fluoxetine and fluvoxamine. These results arise from 42 independent analyses without adjustment for multiple testing (ie, about two CIs would be expected to exclude 1 by chance alone). For dropouts, fluoxetine was better tolerated than reboxetine, and citalopram than sertraline.

Overall, heterogeneity was moderate, although for most comparisons the 95% CI included values that showed very high or no heterogeneity, reflecting the small number of included studies for each pair-wise comparison. In the meta-analyses of direct comparisons, we found I^2 values higher than 75% for the comparisons citalopram and reboxetine (I^2=85·0%), and escitalopram and fluoxetine (I^2=82·7%). In both cases, only two studies were included in the meta-analysis.

Figure 3 summarises the results of the multiple-treatments meta-analysis. Escitalopram, mirtazapine, sertraline, and venlafaxine were significantly more efficacious than duloxetine, fluoxetine, fluvoxamine, paroxetine, and reboxetine (even though less clear benefits were noted with sertraline than with escitalopram, venlafaxine, and mirtazapine when comparing with duloxetine and fluvoxamine, with the credibility interval for OR slightly more than 1). Reboxetine was significantly less efficacious than all the other 11 antidepressants. These findings arise from 66 simultaneous comparisons and about three statistically significant findings might be expected by chance alone. In terms of acceptability, duloxetine and paroxetine were less well tolerated than escitalopram and sertraline; fluvoxamine less well tolerated than citalopram, escitalopram, and sertraline; venlafaxine less well tolerated than escitalopram; reboxetine less well tolerated than many other antidepressants, such as bupropion, citalopram, escitalopram, fluoxetine, and sertraline; and escitalopram and sertraline were better tolerated than duloxetine, fluvoxamine, paroxetine, and reboxetine (figure 3).

Mirtazapine, escitalopram, venlafaxine, and sertraline were more efficacious than fluoxetine, and fluoxetine was



BUP	1·00 (0·78–1·28)	0·75 (0·55–1·01)	1·06 (0·86–1·32)	0·89 (0·74–1·08)	0·73 (0·53–1·00)	0·87 (0·58–1·24)	0·87 (0·66–1·14)	0·81 (0·65–1·00)	**0·62 (0·45–0·86)**	1·01 (0·82–1·27)	0·84 (0·68–1·02)
0·98 (0·78–1·23)	CIT	0·75 (0·55–1·02)	1·07 (0·86–1·31)	0·90 (0·73–1·09)	**0·73 (0·54–0·99)**	0·87 (0·60–1·24)	0·87 (0·66–1·15)	0·81 (0·65–1·01)	**0·62 (0·45–0·84)**	1·02 (0·81–1·28)	0·84 (0·67–1·06)
1·09 (0·83–1·43)	1·12 (0·87–1·44)	DUL	**1·43 (1·09–1·85)**	1·19 (0·91–1·57)	0·98 (0·67–1·41)	1·16 (0·77–1·73)	1·16 (0·83–1·61)	1·08 (0·84–1·40)	0·83 (0·57–1·22)	**1·36 (1·01–1·83)**	1·12 (0·84–1·50)
0·82 (0·67–1·01)	0·84 (0·70–1·01)	**0·75 (0·60–0·93)**	ESC	0·84 (0·70–1·01)	**0·69 (0·50–0·94)**	0·81 (0·55–1·15)	0·81 (0·62–1·07)	**0·76 (0·62–0·93)**	**0·58 (0·43–0·81)**	0·95 (0·77–1·19)	**0·78 (0·64–0·97)**
1·08 (0·90–1·29)	1·10 (0·93–1·31)	0·99 (0·79–1·24)	**1·32 (1·12–1·55)**	FLU	0·82 (0·62–1·07)	0·97 (0·69–1·32)	0·97 (0·77–1·21)	0·91 (0·79–1·05)	**0·70 (0·53–0·92)**	1·14 (0·96–1·36)	0·94 (0·81–1·09)
1·10 (0·83–1·47)	1·13 (0·86–1·47)	1·01 (0·74–1·38)	**1·35 (1·02–1·76)**	1·02 (0·81–1·30)	FVX	1·18 (0·76–1·75)	1·18 (0·87–1·61)	1·10 (0·84–1·47)	0·85 (0·57–1·26)	**1·38 (1·03–1·89)**	1·14 (0·86–1·54)
1·07 (0·77–1·48)	1·09 (0·78–1·50)	0·97 (0·69–1·38)	1·30 (0·95–1·78)	0·99 (0·74–1·31)	0·97 (0·68–1·37)	MIL	0·99 (0·69–1·53)	0·94 (0·68–1·31)	0·72 (0·48–1·10)	1·17 (0·84–1·72)	0·97 (0·69–1·40)
0·79 (0·72–1·00)	0·80 (0·63–1·01)	**0·72 (0·54–0·94)**	0·96 (0·76–1·19)	**0·73 (0·60–0·88)**	**0·71 (0·55–0·92)**	0·74 (0·53–1·01)	MIR	0·93 (0·75–1·17)	0·72 (0·51–1·03)	1·17 (0·91–1·51)	0·97 (0·76–1·23)
1·06 (0·87–1·30)	1·08 (0·90–1·30)	0·97 (0·78–1·20)	**1·30 (1·10–1·53)**	0·98 (0·86–1·12)	0·96 (0·76–1·23)	1·00 (0·74–1·33)	**1·35 (1·11–1·64)**	PAR	0·77 (0·56–1·05)	**1·25 (1·04–1·52)**	1·03 (0·86–1·24)
1·60 (1·20–2·16)	**1·63 (1·25–2·14)**	**1·46 (1·05–2·02)**	**1·95 (1·47–2·59)**	**1·48 (1·16–1·90)**	**1·45 (1·03–2·02)**	**1·50 (1·03–2·18)**	**2·03 (1·52–2·78)**	**1·50 (1·16–1·98)**	REB	**1·63 (1·19–2·24)**	1·34 (0·99–1·83)
0·87 (0·72–1·05)	0·88 (0·72–1·07)	0·79 (0·62–1·01)	1·06 (0·88–1·27)	**0·80 (0·69–0·93)**	0·79 (0·61–1·01)	0·81 (0·60–1·11)	1·10 (0·90–1·36)	**0·82 (0·69–0·96)**	**0·54 (0·41–0·71)**	SER	0·82 (0·67–1·00)
0·85 (0·70–1·01)	0·86 (0·71–1·05)	**0·77 (0·60–0·99)**	1·03 (0·86–1·24)	**0·78 (0·68–0·90)**	**0·77 (0·59–0·99)**	0·79 (0·58–1·08)	1·08 (0·87–1·33)	**0·79 (0·67–0·94)**	**0·53 (0·40–0·69)**	0·98 (0·82–1·16)	VEN

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.

more efficacious than reboxetine (table 4). In terms of acceptability, fluoxetine was better than reboxetine (table 4).

Analysis indicated statistical incoherence in three out of 70 comparisons of direct with indirect evidence for response rate (paroxetine–citalopram–escitalopram; fluvoxamine–venlafaxine–mirtazapine; and sertraline–fluoxetine–bupropion) and three out of 63 comparisons for dropout rate (sertraline–citalopram–escitalopram; fluvoxamine–venlafaxine–mirtazapine; and sertraline–citalopram–fluoxetine). These numbers are compatible with chance because about six significant findings would be expected out of 133 statistical tests. Data extraction and data entering were correct, and we could not identify any important variable that differed across comparisons in those loops; however, the number of included studies was small.

Exclusion of studies with any treatment dosage outside the defined therapeutic range and without imputed data resulted in 109 and 90 trials, respectively. The multiple-treatments meta-analysis model was refitted accordingly and no differences in conclusions were observed in either set of ORs.

Figure 4 shows the distribution of probabilities of each treatment being ranked at each of the possible 12 positions. Mirtazapine, escitalopram, venlafaxine, and sertraline were among the most efficacious treatments, and escitalopram, sertraline, bupropion, and citalopram were better tolerated than the other remaining antidepressants (figure 4). The cumulative probabilities of being among the four most efficacious treatments were: mirtazapine (24·4%), escitalopram (23·7%), venlafaxine (22·3%), sertraline (20·3%), citalopram (3·4%), milnacipran (2·7%), bupropion (2·0%), duloxetine (0·9%), fluvoxamine (0·7%), paroxetine (0·1%), fluoxetine (0·0%), and reboxetine (0·0%). The cumulative probabilities of being among the four best treatments in terms of acceptability were: escitalopram (27·6%), sertraline (21·3%), bupropion (19·3%), citalopram (18·7%), milnacipran (7·1%), mirtazapine (4·4%), fluoxetine (3·4%), venlafaxine (0·9%), duloxetine (0·7%), fluvoxamine (0·4%), paroxetine (0·2%), and reboxetine (0·1%).

	Efficacy (response rate) OR (95% CI)	Acceptability (dropout rate) OR (95% CI)
Bupropion	0·93 (0·77–1·11)	1·12 (0·92–1·36)
Citalopram	0·91 (0·76–1·08)	1·11 (0·91–1·37)
Duloxetine	1·01 (0·81–1·27)	0·84 (0·64–1·10)
Escitalopram	0·76 (0·65–0·89)*	1·19 (0·99–1·44)
Fluvoxamine	1·02 (0·81–1·30)	0·82 (0·62–1·07)
Milnacipran	0·99 (0·74–1·31)	0·97 (0·69–1·32)
Mirtazapine	0·73 (0·60–0·88)*	0·97 (0·77–1·21)
Paroxetine	0·98 (0·86–1·12)	0·91 (0·79–1·05)
Reboxetine	1·48 (1·16–1·90)*	0·70 (0·53–0·92)*
Sertraline	0·80 (0·69–0·93)*	1·14 (0·96–1·36)
Venlafaxine	0·78 (0·68–0·90)*	0·94 (0·81–1·09)

OR=odds ratio. CI=credibilty interval. *p<0·05. For efficacy, OR higher than 1 favours fluoxetine. For acceptability, OR lower than 1 favours fluoxetine.

Table 4: **Efficacy and acceptability using fluoxetine as reference compound**

In a meta-regression analysis to assess potential sponsorship bias, ORs and final rankings did not substantially change. The cumulative probability of being among the four best treatments became slightly smaller for those drugs in trials which were sponsored by the marketing company, with the comparators moving up the ranking slightly.

Discussion

Our analysis was based on 117 studies including 25 928 individuals randomly assigned to 12 different new-generation antidepressants. Our findings might help to choose among new-generation antidepressants for acute treatment of major depression. Some antidepressants differed both statistically and clinically. In terms of response, mirtazapine, escitalopram, venlafaxine, and sertraline were more efficacious than duloxetine, fluoxetine, fluvoxamine, paroxetine, and reboxetine. In terms of acceptability, escitalopram, sertraline, citalopram, and bupropion were better tolerated than other new-generation antidepressants. These results indicate that two of the most efficacious treatments (mirtazapine and venlafaxine) might not be the best for overall acceptability.

Here, we did not investigate important outcomes, such as side-effects, toxic effects, discontinuation symptoms, and social functioning. However, the most important clinical implication of the results is that escitalopram and sertraline might be the best choice when starting a treatment for moderate to severe major depression because they have the best possible balance between efficacy and acceptability.

We did not do a formal cost-effectiveness analysis; however, because some new antidepressants are now off patent and available in generic form, their acquisition cost is reduced. Indeed, only two of the 12 antidepressants (escitalopram and duloxetine) are still on patent in the USA and in Europe. Sertraline seems to be better than escitalopram because of its lower cost in most countries. However, in the absence of a full economic model, this recommendation cannot be made unequivocally because several other costs are associated with the use of antidepressants.[138]

Reboxetine, fluvoxamine, paroxetine, and duloxetine were the least efficacious and acceptable drugs, making them less favourable options when prescribing an acute treatment for major depression. Furthermore, in terms of acceptability, reboxetine was the least tolerated agent among the 12 antidepressants and was significantly less effective than all the other 11 drugs. Therefore, reboxetine should not be used as a routine first-line acute treatment for major depression.

Findings from this analysis apply only to acute-phase treatment (8 weeks) of depression. Clinicians need to

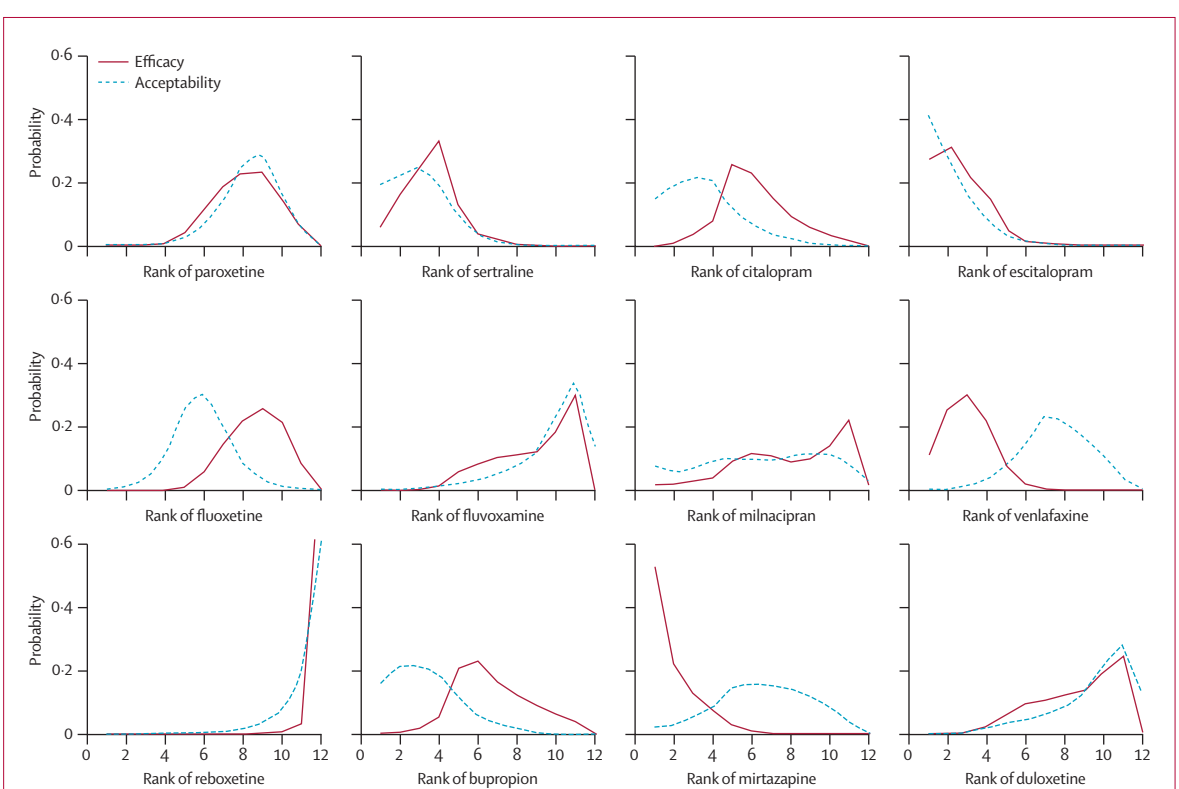


Figure 4: **Ranking for efficacy (solid line) and acceptability (dotted line)**
Ranking indicates the probability to be the best treatment, the second best, the third best, and so on, among the 12 antidepressants.

know whether (and to what extent) treatments work within a clinically reasonable period. Clinically, the assessment of efficacy after 6 weeks of treatment or after 16–24 weeks or more might lead to wide differences in treatment outcome. In many systematic reviews, the ability to provide valid estimates of treatment effect is limited because trials with different durations of follow-up have been combined.[139] A systematic review of clinical-trial data[140] that investigated early response to antidepressants employed a common definition of early response across all included studies. Apart from this study, however, no systematic review has investigated the comparative efficacy of antidepressants in individuals with major depression employing a common definition of acute response that includes a predefined follow-up duration.

Most trials included in our analysis did not report adequate information about randomisation and allocation concealment, and this might undermine the validity of overall findings. Nonetheless, all studies on antidepressants included in this meta-analysis were very similar in terms of design and conduct, and the scant information in terms of quality assessment could be more an issue of reporting in the text than real defects in study design, as it has been commonly found in other systematic reviews.[141]

Evidence exists of presence of sponsorship bias (ie, the bias associated with the commercial interests of industrial sponsors) in medicine,[142] and there is concern about the potential effect of financial interests on medical publications. Because most studies comparing the newest antidepressants (mirtazapine, escitalopram, buproprion, and duloxetine) were done by the pharmaceutical companies marketing these compounds, this might be a source of bias.[143] Some discrepancies existed between some of the results of the multiple-treatments meta-analysis and those in the direct comparisons (escitalopram *vs* citalopram and mirtazapine *vs* venlafaxine). These findings emphasise a potential advantage of this analysis that incorporates indirect and direct comparisons, decreasing the risk for possible sponsorship bias. However, limitations of the primary trials and potential confounders (such as dose issues) can affect the validity of the findings. Readers cannot fully appreciate the meaning of a study without acknowledging the biases in the design and interpretation that can arise when a sponsor might benefit from a study publication.[144] Such associations should be made clear to let anyone judge the relevance of findings.

Placebo-controlled trials are required to adequately assess the efficacy of novel antidepressant drugs.[145] In both the USA and Europe, regulatory authorities require placebo-controlled studies for marketing authorisation. The selective publication of placebo-controlled antidepressant trials and its effect on apparent efficacy is well recognised[146] and there is currently controversy on this topic [147] Placebo-controlled trials are mainly designed for regulatory approval purposes; to meet both ethical and safety requirements, they tend to recruit patients with a mild form of disease.[148] Although placebo-controlled trials can be efficient because they need smaller sample sizes than non-placebo-controlled trials, difficulties in carrying out these trials when effective treatments are known to exist can introduce artifacts into clinical trials.[149]

Response to placebo across antidepressant trials has been shown to vary and has clearly increased in the past two decades, with a similar increase occurring in the fraction of patients responding to active medication as well.[150] The issue of changes in trial outcomes over time is still under debate;[151] however, the change in placebo response does not seem to be directly explained by changes in study characteristics.[150] Inflation of baseline severity, for example, is likely to be a cause for the temporal rise in placebo response rates, which increases the proportion of failed trials.[150] As placebo-controlled trials of antidepressants become increasingly difficult to do, it is perhaps time to reconsider the standard requirements. Our analysis suggests that sertraline is better than other new-generation drugs in terms of efficacy and acceptability, and could be used as a standard comparator in phase III and also in pragmatic (or effectiveness) trials to increase the real-world applicability of the results. Although the sample-size requirements might be larger than in the ideal placebo-controlled trial, the increased real-world applicability of the results would, in our opinion, offset this disadvantage. Furthermore, the need of new treatments to show either greater efficacy or acceptability than an existing standard therapy would serve as a disincentive to the development of me-too agents that offer little to patients other than increased costs.

Contributors

AC, CB, TAF, RC, and JRG conceived and designed the meta-analysis, and GS and JPTH provided supervision. AC, CB, AN, TAF, IMO, NW, and HM identified and acquired reports of trials, and extracted data. AC, AN, IMO, NW, and HM contacted authors of trials and pharmaceutical industries for additional information. AC, CB, TAF, JRG, GS, and JPTH analysed and interpreted the data. GS and JPTH provided statistical advice and input. RC, AN, IMO, NW, MT, and HM contributed to the interpretation of the data. AC drafted the manuscript. CB, JRG, TAF, GS, JPTH, and MT critically reviewed the manuscript.

Conflict of interest statement

JRG has received research funding from GlaxoSmithKline, Sanofi-Aventis, the UK Department of Health and Medical Research Council, the Stanley Medical Research Institute, and advisory committee payments from Bristol Myers Squibb. TAF has received research funds and speaking fees from Asahi Kasei, Astellas, Dai-Nippon Sumitomo, Eisai, Eli Lilly, GlaxoSmithKline, Janssen, Kyowa Hakko, Meiji, Nikken Kagaku, Organon, Otsuka, Pfizer, and Yoshitomi. The Japanese Ministry of Education, Science and Technology, and the Japanese Ministry of Health, Labour and Welfare have also funded TAF's research. NW has received speaking fees from GlaxoSmithKline for evidence-based medicine. JPTH has received fees for consultancy from Roche and for teaching from Novartis. All other authors declare that they have no conflict of interest.

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