Are All Antidepressants Really the Same? The Case of Fluoxetine: A Systematic Review

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Objective: To systematically review the efficacy and tolerability of fluoxetine, the most widely studied of newer antidepressants, in comparison with all other antidepressants in the acute treatment of depression in patients aged more than 18 years.

Data Sources: Studies were identified through electronic searches of the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register and the Cochrane Central Register of Controlled Trials up to March 2004. The terms FLUOXETIN* OR *adofen* or *docutrix* or *erocap* or *fluctin* or *fluctine* or *fluoxeren* or *fontex* or *ladose* or *lorien* or *lovan* or *mutan* or *prozac* or *prozyn* or *reneuron* or *sanzur* or *saurat* or *zactin* were used. MEDLINE (1966–2004) and EMBASE (1974–2004) were searched using *fluoxetine* and *randomized controlled trial* or *random allocation* or *double-blind method*. No language restrictions were applied. Reference lists of relevant papers and previous systematic reviews were hand-searched for published reports up to March 2004.

Study Selection: Only randomized controlled trials (either blind or nonblind) were included.

Data Synthesis: 131 randomized controlled trials were eligible. A p value less than .01 was chosen to test the null hypothesis, and a 99% confidence interval was calculated to detect statistically significant differences with a high degree of confidence. Fixed- and random-effects relative risks, odds ratios (ORs), and Peto ORs were routinely calculated for each outcome measure. In terms of efficacy, we found a statistically significant difference favoring sertraline and venlafaxine over fluoxetine. In terms of tolerability, patients allocated to fluoxetine were less likely to leave the study early only in comparison with those allocated to amitriptyline and pramipexole.

Conclusions: This systematic review highlighted that there are differences between fluoxetine and specific comparator antidepressants. Several of the differences met a prespecified criterion for clinical significance. The statistical approach adopted in this systematic review could represent a useful tool for putting clinical trial data into practice.

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Evidence from randomized trials has shown similar efficacy between selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) in the pharmacologic treatment of depression.[1] Debate continues about the more favorable tolerability profile of the SSRIs[2–5]; similarly, emerging data on newer antidepressants are still inconclusive.[6]

The evidence of similar efficacy of *classes* of old and new agents is still controversial[7–11] and, additionally, may not be the most relevant question from a clinical viewpoint. Prescribers need to know whether there are differences between specific agents and the magnitude of these differences.[12] Pooling individual trials using meta-analysis is necessary to detect differences between antidepressants, because it is extremely unlikely that significant differences between active antidepressants could be detected in individual trials.[13]

Fluoxetine, the most widely studied of the newer antidepressants, has progressively replaced amitriptyline and imipramine as the standard of comparison for newer medications.[14] We previously reported the results of fluoxetine in comparison with classes of antidepressants[15] and the analysis of fluoxetine side effects.[16] In this systematic review, we compared fluoxetine with each individual antidepressant. Instead of using a standard

hypothesis-testing approach, in this analysis we also used a more appropriate and conservative approach based on noninferiority and estimated relative efficacy with 99% confidence intervals. This method can provide a robust evidence base that should guide physicians in reaching a decision about optimal care.

METHOD

Trial Inclusion Criteria

Only randomized controlled trials (RCTs) comparing fluoxetine with any other antidepressant agent, including St. John's wort, in the acute treatment of major depression in patients aged more than 18 years were included. Both blind and nonblind RCTs were eligible. Crossover studies and trials in depressed patients with a concurrent medical illness were excluded.

Data Sources

RCTs were identified by searching the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register (CCDANCTR) and the Cochrane Central Register of Controlled Trials (CENTRAL). The following terms were used: FLUOXETIN* OR *adofen* or *docutrix* or *erocap* or *fluctin* or *fluctine* or *fluoxeren* or *fontex* or *ladose* or *lorien* or *lovan* or *mutan* or *prozac* or *prozyn* or *reneuron* or *sanzur* or *saurat* or *zactin*. MEDLINE (1966–2004) and EMBASE (1974–2004) were searched using the terms *fluoxetine* and *randomized controlled trial* or *random allocation* or *double-blind method*. Non–English language publications were included. Reference lists of relevant papers and previous systematic reviews were hand-searched for published reports up to March 2004.

Outcome Measures

Efficacy was evaluated using the following outcome measures: decrease of at least 50% in Hamilton Rating Scale for Depression (HAM-D) score, mean HAM-D or Montgomery-Asberg Depression Rating Scale (MADRS) scores at the end of the trial, and response according to the authors' definition. Tolerability was evaluated according to patient dropout during the trial.

Validity Assessment

The quality of trials was assessed according to the criteria of the Cochrane Collaboration Handbook.[17]

Data Extraction

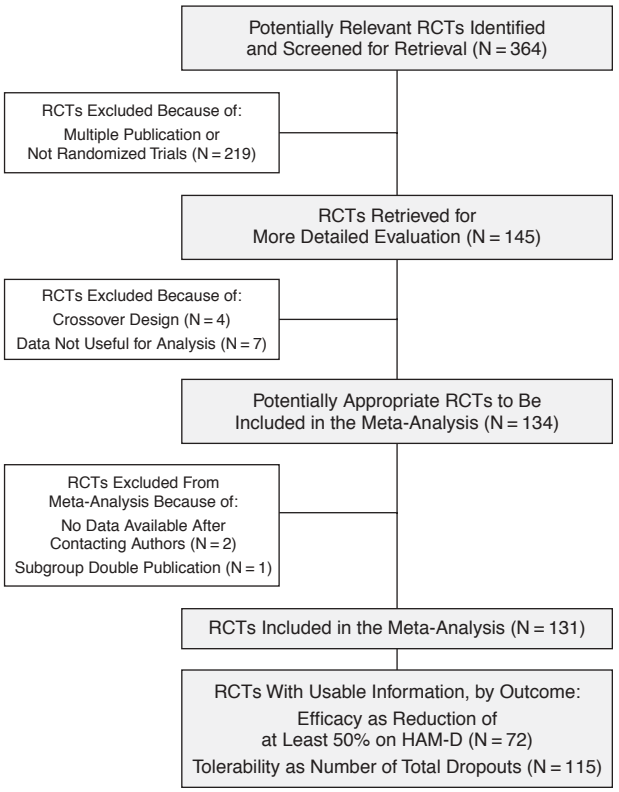
Two reviewers independently extracted data; any disagreement was solved by discussion and consensus with a third member of the team.

Statistical Analysis

Data were analyzed with Review Manager Version 4.2 (Cochrane Collaboration; Copenhagen, Denmark) and Stata 7.0 (StataCorp; College Station, Tex.). Responders were calculated including dropouts in the analysis. When data on dropouts were carried forward and included in the intention-to-treat efficacy analysis (last observation carried forward [LOCF]), they were analyzed in the same way as in the study report. When dropouts were excluded from any assessment in the primary studies, they were considered as drug failures (in both the fluoxetine and comparator arms).[18] Scores from continuous outcomes were analyzed including patients with a final assessment or with an LOCF to the final assessment. Tolerability data were analyzed by calculating the proportion of patients who failed to complete the study and who experienced adverse reactions out of the total number of randomized patients.

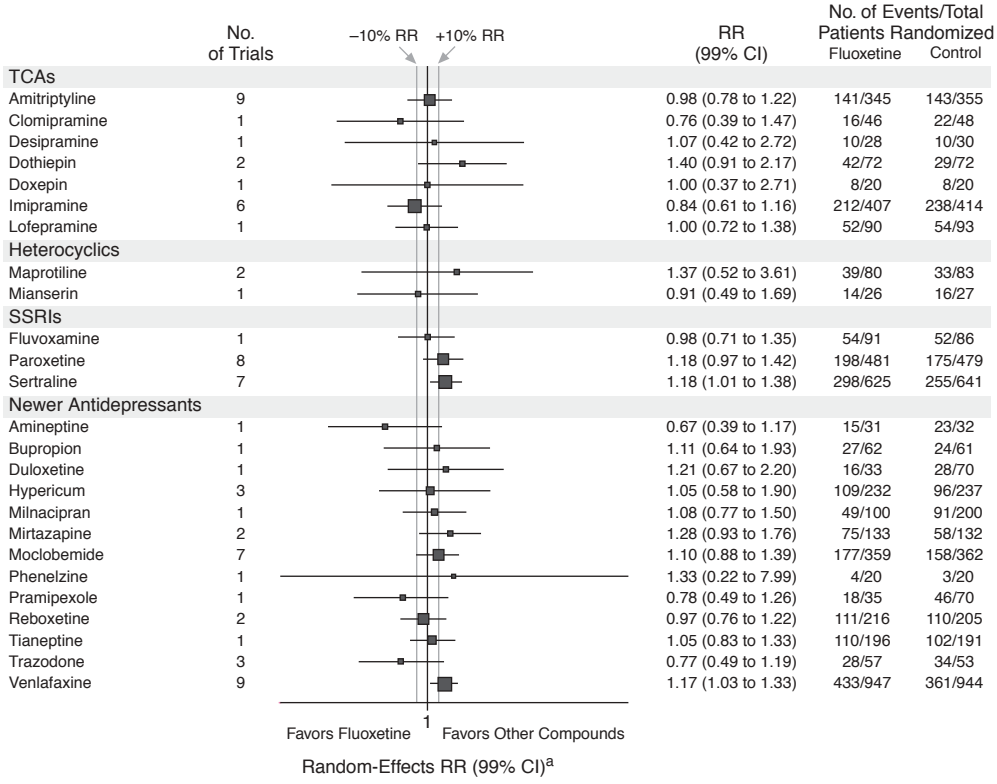
Dichotomous outcomes were analyzed by calculating the relative risk (RR) and the numbers needed to treat (NNTs). A standardized mean difference (SMD) was estimated for continuous outcomes. This measure provides the effect size of the intervention in units of standard deviations (SDs): scores from different outcome scales can be summarized in an overall SMD. Heterogeneity be-

Figure 1. Included and Excluded Studies With Reasons: The QUOROM[a] Flow Diagram



[a]Described in Moher et al.[34]
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, RCT = randomized controlled trial.

Figure 2. Efficacy Measured as Failure to Respond Considering Total Number of Participants With a Reduction of at Least 50% in HAM-D Score Between Baseline and Endpoint



[a]Box size variation indicates variation in total numbers of patients.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, RR = relative risk, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

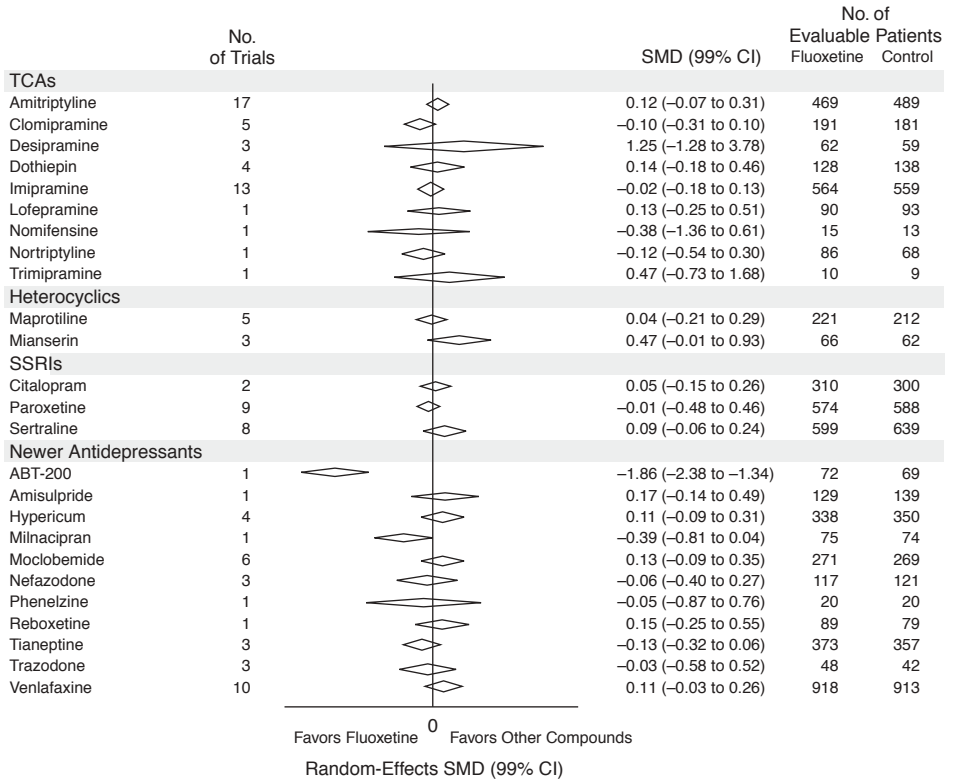
tween studies was assessed using the χ^2 test for heterogeneity. If significant heterogeneity was identified, potential sources were considered. Fixed- and random-effects RR, odds ratio (OR), and Peto OR were routinely calculated for each outcome measure to investigate the effect of different methods on treatment estimates and to take into account not only the observed heterogeneity but also the sampling error in the observed differences.[19]

Three-arm placebo trials were converted into 2-arm trials. Three-arm trials comparing different fixed doses of the same agent were converted into 2-arm trials by summing samples and averaging doses. When mean scores were reported with the standard error (SE), it was converted into an SD according to Altman.[20] When mean scores were reported without SDs and SEs, the mean value of known SDs was calculated from the group of included studies comparing the same drugs.[21]

A p value less than .01 was chosen to test the null hypothesis, and a 99% CI was calculated to highlight statistically significant differences with a high degree of confidence. This approach was adopted to have the widest estimate of likely true effect. We set the level of significance at .01, as we were making multiple comparisons and we reasoned that only robust differences between treatments should inform clinical practice. In fact, it was more important to avoid the possibility of showing a difference in the absence of a true difference than to avoid the possibility of not showing a difference in the presence of a true difference. In other words, we gave priority to avoiding a type I over a type II error. Furthermore, to be as conservative as possible, significant differences were defined as only those differences that were statistically significant in all the above-mentioned analyses (RR, OR, and Peto OR), applying for both fixed- and random-effects models (full dataset is available from authors).

To assess effectiveness, we considered, a priori, that a difference in RR of at least 10% was a clinically significant difference in efficacy. Adopting this cutoff value, estimates were classified into 1 of the following 5 groups. Group A: fluoxetine is clinically better than the other compound (both RR and upper limit of 99% CI are below 0.90). Group B: fluoxetine is certainly clinically not worse and probably better than the other compound (RR < 1 and the upper limit of 99% CI is within the range

Figure 3. Rating Scale Scores at Endpoint in Randomized Controlled Trials Comparing Fluoxetine With TCAs, Heterocyclics, SSRIs, and Newer Antidepressants



Abbreviations: SMD = standardized mean difference, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

0.90–1.10). Group C: uncertain if there is a clinically significant difference between compounds (RR < 1 and upper limit of 99% CI > 1.10, or RR > 1 and the lower limit of 99% CI < 0.90. Group D: fluoxetine is certainly clinically not better and probably worse than the other compound (RR > 1 and the lower limit of 99% CI is within the range 0.90–1.10). Group E: fluoxetine is clinically worse than the other compound (both RR and 99% CI > 1.10).

RESULTS

Study Characteristics

The search yielded 883 studies: after abstracts were read, 364 papers were considered potentially relevant (Figure 1), but only 131 RCTs meeting the inclusion criteria were included (for full description of study characteristics and references of included studies, see Appendix 1). The majority of the studies (69 RCTs) recruited fewer than 100 participants, and almost all (130 RCTs) were reported to be double-blind trials. The mean length of follow-up was 8 weeks (SD = 5.1). Twelve trials enrolled inpatients, and 24 enrolled both inpatients and outpatients, while the remaining studies were conducted in outpatient facilities. The majority of studies (74%) enrolled patients suffering from major depression according to DSM-III-R, DSM-IV, or ICD-10 criteria. Elderly subjects (over 65 years) were included in 58 studies.

A total of 57 studies compared fluoxetine with TCAs; 8, with heterocyclics; 21, with SSRIs; 44, with other newer antidepressants; and 1, with both a TCA and a newer antidepressant. The great majority of studies (N = 123) used the HAM-D as primary or secondary outcome measure, while a minority of studies used the MADRS and the Clinical Global Impressions scale. Around half of included trials (N = 73) reported the total number of patients experiencing any side effects, while the remaining studies reported the number of patients experiencing individual side effects only. Only 27 studies used interview-based scales to detect side effects.

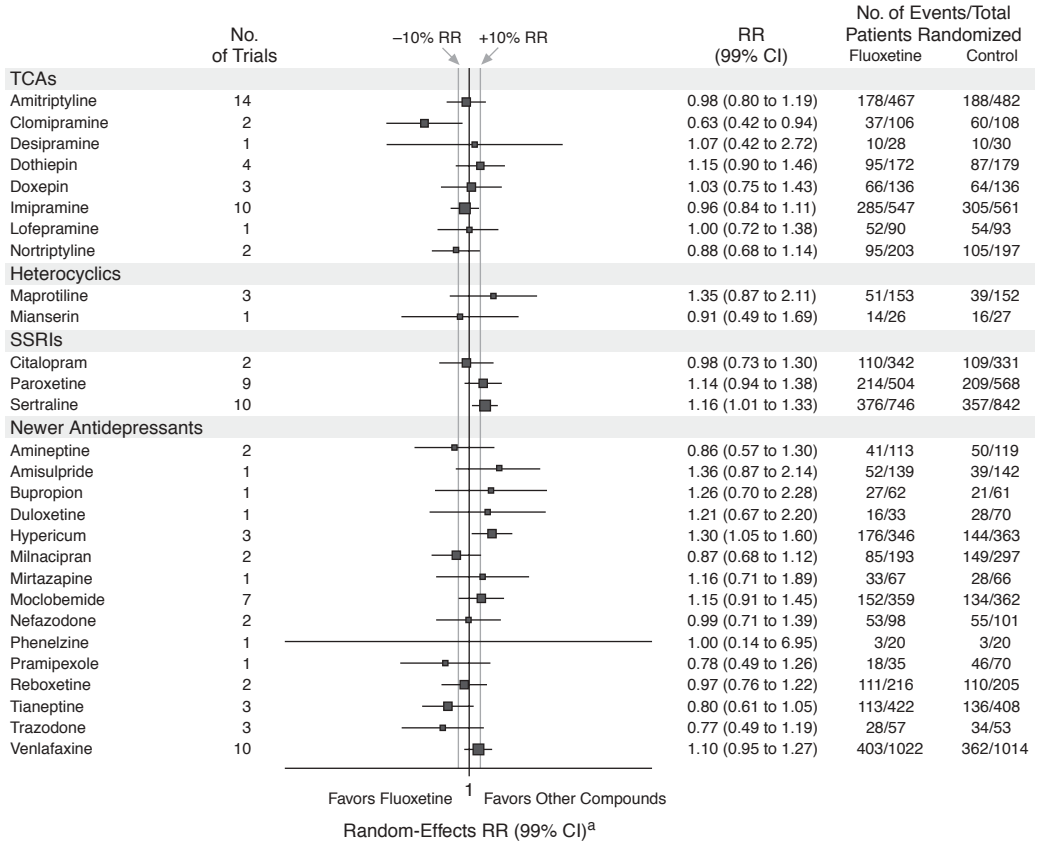
Publication Bias

Funnel plots did not suggest evidence of publication bias (figures not shown, but available from authors).

Quantitative Data Synthesis: Efficacy

Analysis of efficacy was based on 4494 patients treated with fluoxetine and 4817 with an alternative anti-

Figure 4. Efficacy Measured as Failure to Respond Considering Total Number of Participants Who Responded According to Authors' Definition



[a]Box size variation indicates variation in total numbers of patients.
Abbreviations: RR = relative risk, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

depressant (Figures 2–4). Considering dichotomous and continuous outcomes, we found no statistically significant difference between fluoxetine and individual TCAs or between fluoxetine and individual heterocyclics (mianserin, maprotiline). When fluoxetine was compared with SSRIs, there was a statistically significant difference favoring sertraline over fluoxetine on a dichotomous (RR random-effects: 1.18, 99% CI = 1.01 to 1.38; NNT = 14, 99% CI = 8 to 100) but not on a continuous outcome (SMD random-effects: 0.09, 99% CI = –0.06 to 0.24). Similarly, among newer antidepressants, venlafaxine was significantly more effective than fluoxetine on a dichotomous outcome (RR random-effects: 1.17, 99% CI = 1.03 to 1.33; NNT = 15, 99% CI = 9 to 50) but failed to reach statistical significance on a continuous outcome (SMD random-effects: 0.11, 99% CI = –0.03 to 0.26).

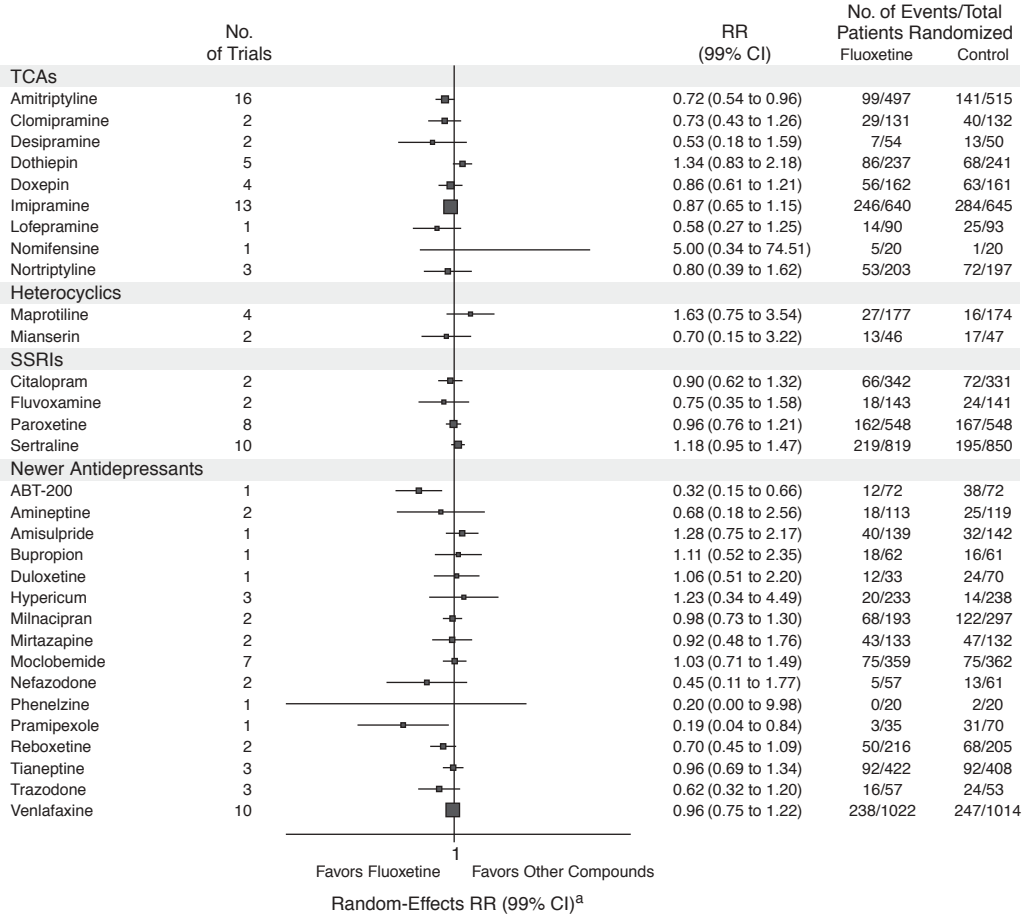
Quantitative Data Synthesis: Tolerability

Analysis of safety was based upon 7034 patients treated with fluoxetine and 7357 with an alternative antidepressant (Figure 5). Referring to TCAs, patients allocated to fluoxetine were less likely to be withdrawn for any cause from treatment than those allocated to amitriptyline (RR random-effects: 0.72, 99% CI = 0.54 to 0.96; NNT = 13, 99% CI = 8 to 100). The comparison between fluoxetine and individual heterocyclics or SSRIs did not reveal statistically significant differences, and among newer antidepressants only pramipexole was less well tolerated than fluoxetine in terms of failure to complete the trial for any reason (RR random-effects: 0.19, 99% CI = 0.04 to 0.84; NNT = 3, 99% CI = 2 to 7).

Clinically Significant Differences in Efficacy

Considering a difference in RR of more than 10% a reasonable estimate of difference in efficacy and referring to primary outcome, dothiepin, mirtazapine, paroxetine, sertraline, and venlafaxine belonged to group D (Figures 2 and 6). All the other antidepressants belonged to group C. Considering only a fixed-effects RR, imipramine would be in group B and moclobemide in group D (Figure 6).

Figure 5. Tolerability Measured as Failure to Complete Study Considering Total Number of Participants Who Withdrew Because of Any Cause



[a]Box size variation indicates variation in total numbers of patients.
Abbreviations: RR = relative risk, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Figure 6. Efficacy Measured as at Least 50% Reduction on HAM-D, Considering Relative Risk (RR) With Both Fixed- and Random-Effects Models

Clinical Efficacy				
Group A	Group B	Group C	Group D	Group E
Fluoxetine is clinically better than	Fluoxetine is certainly clinically not worse and probably better than	Uncertain whether there is a clinically significant difference between fluoxetine and	Fluoxetine is certainly clinically not better and probably worse than	Fluoxetine is clinically worse than
None	None	Amitriptyline Clomipramine Desipramine Doxepin Imipramine[a] Lofepramine Maprotiline Mianserin Amineptine Bupropion Duloxetine Hypericum Milnacipran Moclobemide[a] Phenelzine Pramipexole Reboxetine Tianeptine Trazodone	Dothiepin Mirtazapine Paroxetine Sertraline Venlafaxine	None

[a]Considering only RR fixed-effects model, imipramine would be in group B and moclobemide would be in group D.
Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

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DISCUSSION

The main finding of the present study is that there are statistically significant differences in terms of efficacy between fluoxetine and certain antidepressants, such as sertraline and venlafaxine. These data are consistent with previous evidence[6,10,11] but differ from results reported by Feiger and colleagues,[22] who performed a nonsystematic pooled analysis of RCTs comparing fluoxetine with sertraline. Additionally, in our meta-analysis fluoxetine was found to be clinically not better, and possibly worse, than dothiepin, mirtazapine, and paroxetine. With regard to tolerability, fluoxetine was similarly tolerated in comparison with other SSRIs and better tolerated than amitriptyline in terms of total dropout rate.

In this systematic review, individual antidepressants were compared against fluoxetine. Fluoxetine was chosen because it has been a market leader since its introduction almost 20 years ago and has been frequently used as a reference compound for newer antidepressants. However, the analysis of fluoxetine trials requires caution: looking at all trials comparing fluoxetine with other antidepressants and categorizing them according to whether fluoxetine was the new agent or the comparator, fluoxetine appeared slightly more effective when it was the new agent, therefore suggesting evidence of the so-called "wish bias" in which, possibly due to observer bias or to publication bias, the drug performed better when it was new than when it was old.[23] A second caution is that despite the large number of comparative trials included, the total number of randomized patients was under 15,000, and, apart from some drugs (amitriptyline, venlafaxine, imipramine, sertraline, and paroxetine), the number of studies involving specific antidepressants was quite small for a powerful use of meta-analysis. Studies were short—usually 6 to 8 weeks or less—and the mean size of each trial was around 110 participants, indicating that they were generally underpowered for demonstrating clinically meaningful differences.

A limitation of this analysis is that studies with different designs were pooled together and this might have biased the external validity of findings.[24] To address this problem, a non-conventional approach to data analysis was employed, comparing fluoxetine against individual antidepressants as opposed to classes of antidepressants and allowing us to gain more clinically relevant information. However, by making multiple comparisons we might have committed type I error—that is, reporting a spurious association. We countered this by using a conservative approach and setting our level of significance at .01 together with a 99% CI and by emphasizing effect sizes as well as statistical significance.

Another limitation is that, for many of the comparisons, many more trials presenting data on dropouts than on efficacy were found (a difference of 33 RCTs). This is because not all used 50% decrease in HAM-D score as their main outcome and therefore many data from our primary outcome were lost, which could have led to bias. Although this is a well-known limitation of secondary analyses of data extracted from RCTs,[25] we attempted to control this potential source of bias by extracting efficacy data according to each study's definition of responders. This secondary analysis included many more subjects than the primary analysis, and results did not differ substantially. Most likely, therefore, the overall comparison was not hampered by the exclusion of these trials.

We included only published RCTs in this systematic review. The great majority of these RCTs have been sponsored by pharmaceutical industry, and data have shown a relationship between industry sponsorship and trial outcomes.[26–28] In a post hoc sensitivity analysis, we investigated whether sponsorship influenced estimates of efficacy outcome when a statistical significant difference emerged. We found that results from RCTs funded by a sertraline manufacturer were in line with the overall pooled results (RR random-effects: 1.16, 99% CI = 0.99 to 1.36, 5 trials, 1000 participants, p = .02; SMD random-effects: 0.07, 99% CI = –0.11 to 0.25, 5 trials, 888 participants, p = .31). We could not run the same kind of sensitivity analysis with venlafaxine because all the RCTs included in this review were funded by a venlafaxine manufacturer. Additionally, even if the funnel plots did not show any evidence of publication bias, this possibility cannot be ruled out.[29] Funnel plots work on the assumption that researchers are less likely to leave unpublished the results of large trials than small trials. For the meta-analyses of TCAs and SSRIs, the funnel plots have generally been symmetrical,[25] suggesting publication bias is absent. However, recent evidence regarding data on children and adolescents with major depression suggested that publication bias may remain a very serious limitation to the entire literature comparing SSRIs and TCAs.[30] If important information is concealed, the funnel plot (and other formal statistical tests that work on the same principle) will not be able to detect publication bias under these circumstances. We therefore need further analyses investigating the possible confounding role of sponsorship and new methodological tools for improving the quality of evidence.

To give clinicians a practical tool to interpret results, we used an arbitrary cutoff value in terms of RR of 10% above or below 1 to signify clinical significance. This system could be a reasonable estimate of the worst-case scenario of expected improvement, guiding physicians in reaching a decision about optimal care. Obviously, it is likely that evidence coming from many trials and many patients (e.g., venlafaxine) is more robust and consistent than findings coming from a few RCTs with small sample sizes (e.g., dothiepin). To address this problem,

NNTs were reported when statistical significance was found. NNTs are a clinically useful measure, but some caution is needed when they are used. Systematic reviews tend to combine trials of varying follow-up periods, which could make it difficult to interpret NNTs: NNTs are specific to a particular length of follow-up, since they are based on the number of people who will benefit within a certain period of time and who otherwise would not benefit.[19]

In comparison with SSRIs and newer antidepressants, sertraline and venlafaxine were found statistically more effective than fluoxetine when efficacy was measured as a binary outcome but not when efficacy was measured on a continuous outcome. This could have occurred because continuous data analysis is usually more statistically efficient, especially when a 99% CI is chosen. However, other possible explanations should be considered. First, the discrepancies could be the result of differences in the numbers of studies included, reducing statistical power. Second, the LOCF method could have played a role inflating the SD of the continuous variables. Third, for studies in which SDs were not available, we averaged the mean SD values of other studies belonging to the same group, thus rounding up or down the real value and lowering statistical power. In future studies, more reliable data from RCTs and more powerful statistical devices to supply this kind of missing information are needed.

Although the better effectiveness profiles of sertraline and venlafaxine over fluoxetine seem clinically meaningful, they need further investigation, for example by systematically reviewing RCTs comparing these agents with all other antidepressants, because in these trials fluoxetine was used as the comparator antidepressant. Despite these limitations, the statistically significant and clinically relevant differences in efficacy that were calculated could represent a pragmatic way of putting clinical trial data into practice.[31] Hopefully, our analytic approach will in addition be seen as a methodological contribution in the evaluation of treatment effectiveness.[32,33]

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), doxepin (Sinequan and others), duloxetine (Cymbalta), fluoxetine (Prozac and others), imipramine (Tofranil and others), mirtazapine (Remeron), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil), pramipexole (Mirapex), sertraline (Zoloft), trazodone (Desyrel and others), trimipramine (Surmontil), venlafaxine (Effexor).

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Appendix 1. Summary of Included Studies

Randomized Controlled Trial	Comparator	Follow-Up (wk)	Inpatient/ Outpatient Setting	Diagnostic Criteria	Sample Size		Baseline HAM-D Score (SD)		Dose (mg)		Funded by	Quality[a]
					Fluoxetine	Comparator	Fluoxetine	Comparator	Fluoxetine	Comparator		
Altamura et al, 1989[4]	Amitriptyline	5	In	DSM-III	13	15	27 (4.3)	27 (6.9)	20	75	Unclear	B
Chouinard, 1985[20]	Amitriptyline	5	Out	Other criteria	23	28	27.6 (n/s)	25.9 (n/s)	40–80	100–300	Unclear	A
Demyttenaere et al, 1998[35]	Amitriptyline	9	Out	DSM-III-R	35	31	24.9 (4.1)	23.9 (3.7)	20	150	Industry	B
De Ronchi et al, 1998[32]	Amitriptyline	10	In and out	DSM-III-R	32	33	25.6 (5.9)	26.5 (5.67)	20	50–100	Unclear	B
Fawcett et al, 1989[46]	Amitriptyline	6	Out	DSM-III	20	20	23.6 (3)	23.5 (3.1)	20–60	50–200	Industry	B
Feighner, 1985[48]	Amitriptyline	5	Out	Other criteria	22	22	27 (n/s)	26 (n/s)	20–80	75–300	Unclear	B
Judd et al, 1993[65]	Amitriptyline	6	Unclear	DSM-III-R	30	28	24.4 (4.7)	23.7 (3.7)	20	50–200	Industry	B
Keegan et al, 1991[66]	Amitriptyline	6	Out	DSM-III	20	22	25 (2.5)	27.5 (2.5)	20–80	100–250	Industry	B
Kerkhofs et al, 1990[67]	Amitriptyline	6	In	Other criteria	16	18	21.9 (8.4)	21.8 (4.4)	40–60	100–150	Industry	A
Laakmann et al, 1988[70]	Amitriptyline	5	Out	ICD-9	63	65	24.8 (6.1)	24.9 (7.4)	20–60	50–150	Unclear	B
Marchesi et al, 1998[78]	Amitriptyline	10	Out	DSM-III-R	67	75	25.5 (5.2)	25.3 (5.7)	20	75–225	Industry	B
Masco and Sheetz, 1985[80]	Amitriptyline	6	Out	Implicit criteria	20	21	n/s	n/s	40–80	150–300	Industry	B
Ontiveros et al, 1998[89]	Amitriptyline	6	Out	DSM-III-R	21	21	23.5 (3.9)	23.1 (4.8)	20	50–250	Industry	B
Peters et al, 1990[93]	Amitriptyline	5	Out	ICD-9	51	51	27 (5)	27 (4)	20	100	Unclear	B
Preskorn et al, 1991[95]	Amitriptyline	6	Out	DSM-III	30	31	23.8 (2.6)	23.5 (2.9)	20–60	50–200	Industry	B
Suleman et al, 1997[115]	Amitriptyline	6	Out	DSM-IV	15	15	25.4 (2.2)	22.9 (3.5)	20	100	Industry	A
	Moclobemide					15		25.4 (3.6)		240		
Upward et al, 1988[124]	Amitriptyline	4	Out	Unclear	11	12	n/s	n/s	60–80	150–200	Industry	B
Versiani et al, 1999[126]	Amitriptyline	8	Unclear	DSM-IV	77	80	28.4 (4.8)	27.8 (4.8)	20	50–250	Industry	B
Young et al, 1987[130]	Amitriptyline	6	Out	Other criteria	25	25	n/s	n/s	40–80	50–150	Unclear	B
Yu et al, 1997[131]	Amitriptyline	6	Unclear	Unclear	8	8	Unclear	Unclear	20	150	Unclear	B
Ginestet, 1989[57]	Clomipramine	8	In	DSM-III	28	26	33.1 (5.2)	33.7 (5)	20–80	50–200	Unclear	B
Manna et al, 1989[77]	Clomipramine	5	In	DSM-III	15	15	25 (3.5)	24.5 (3.5)	20	75	Unclear	B
Noguera et al, 1991[86]	Clomipramine	6	Unclear	DSM-III	60	60	24.3 (4.9)	24.6 (5.15)	20–40	100	Industry	B
Pakesch and Dossenbach, 1991[90]	Clomipramine	4	Out	Other criteria	46	48	26.4 (6.02)	22.5 (6.12)	40	50	Industry	B
Ropert, 1989[101]	Clomipramine	6	Out	DSM-III	71	72	23 (4.4)	23 (3.8)	20	75	Unclear	B
Bowden et al, 1993[14]	Desipramine	6	In and out	DSM-III-R	28	30	25.4 (3.9)	25.7 (4.6)	20–60	150–250	Industry	B
Levkovitz et al, 2002[73]	Desipramine	6	Out	DSM-IV	8	9	25.6 (1.84)	25.3 (2.26)	20	125–200	Unclear	B
Remick et al, 1993[98]	Desipramine	6	In and out	DSM-III-R	26	20	24.8 (n/s)	24.1 (n/s)	20–60	150–300	Industry	B
Corne and Hall, 1989[25]	Dothiepin	6	GP	Other criteria	49	51	24.4 (4.19)	23.9 (3.95)	20–60	50–100	Industry	B
Dowling et al, 1990[38]	Dothiepin	6	In and out	DSM-III	30	30	23.3 (n/s)	21.5 (n/s)	20–40	100–200	Industry	B
Fairweather et al, 1999[41]	Dothiepin	6	GP	DSM-III-R	42	42	18.4 (3.5)	23.7 (11.9)	20	75–150	Industry	B
South Wales Antidepressant Drug Trial Group, 1988[110]	Dothiepin	6	In and out	DSM-III	31	28	24.5 (5.56)	23.5 (5.29)	60–80	150–225	Industry	B
Stephenson et al, 2000[113]	Dothiepin	6	Unclear	DSM-III-R	51	56	19.8 (4.6)	21 (5.7)	20	75–150	Industry	B
Thompson et al, 2000[119]	Dothiepin	12	GP	DSM-III-R	76	76	n/s	n/s	20	75–150	Industry	B
Feighner and Cohn, 1985[47]	Doxepin	6	Out	DSM-III	78	79	25.1 (n/s)	25.8 (n/s)	20–80	50–250	Industry	B
Remick et al, 1989[97]	Doxepin	6	In and out	DSM-III	38	37	26.1 (n/s)	25.5 (n/s)	20–60	100–200	Industry	B
Sandor et al, 1998[104]	Doxepin	6	Out	DSM-III-R	20	20	25.3 (4.2)	26.2 (4.4)	20–60	75–225	Industry	B
Tamminen and Lehtinen, 1989[117]	Doxepin	5	In and out	Other criteria	26	25	27 (n/s)	27.8 (n/s)	40–80	50–150	Unclear	B
Beasley et al, 1993[8]	Imipramine	6	In	DSM-III	56	62	28 (5.3)	27 (5.8)	40–80	150–300	Industry	B
Bremner, 1984[16]	Imipramine	5	Out	Other criteria	20	20	n/s	n/s	60–80	125–300	Academy	B
Bressa et al, 1989[17]	Imipramine	5	Out	DSM-III	18	12	31 (n/s)	22 (n/s)	20–60	75–175	Unclear	A
Byerley et al, 1988[18]	Imipramine	6	Out	DSM-III	32	34	27.2 (4.9)	28.3 (4.2)	40–80	150–300	Industry	A
Cohn and Wilcox, 1985[23]	Imipramine	6	Out	DSM-III	54	54	27.7 (n/s)	25.9 (n/s)	20–80	75–300	Unclear	B

continued

Appendix 1. Summary of Included Studies (cont.)

Randomized Controlled Trial	Comparator	Follow-Up (wk)	Inpatient/ Outpatient Setting	Diagnostic Criteria	Sample Size		Baseline HAM-D Score (SD)		Dose (mg)		Funded by	Quality[a]
					Fluoxetine	Comparator	Fluoxetine	Comparator	Fluoxetine	Comparator		
Cohn et al, 1989[24]	Imipramine	6	Out	DSM-III	30	30	27.7 (n/s)	26 (n/s)	20–80	75–300	Industry	B
Feighner et al, 1989[49]	Imipramine	6	Out	DSM-III	61	58	25.6 (5.22)	25.9 (4.46)	80	150	Industry	B
Levine et al, 1989[72]	Imipramine	6	In and out	Other criteria	30	30	26.5 (n/s)	28.8 (n/s)	40–60	75–150	Unclear	B
Loeb et al, 1989[74]	Imipramine	5	Unclear	DSM-III	15	15	23.4 (3.25)	23.4 (2.25)	20	100–150	Unclear	B
McGrath et al, 2000[82]	Imipramine	10	Unclear	DSM-IV	49	53	n/s	n/s	20–60	50–300	Industry	B
Nielsen et al, 1993[85]	Imipramine	8	Out	DSM-III	29	30	24.5 (n/s)	24 (n/s)	20	75–150	Industry	B
Stark and Hardison, 1985[112]	Imipramine	6	Out	DSM-III	185	186	27.5 (5.3)	28.2 (5.8)	20–80	75–300	Industry	B
Stratta et al, 1991[114]	Imipramine	5	Unclear	Other criteria	14	14	15.1 (8)	16.2 (7.7)	20	75–125	Unclear	B
Tollefson et al, 1994[121]	Imipramine	8	Out	DSM-III-R	62	62	21.6 (3.9)	21.3 (3.8)	20–80	50–300	Industry	B
Robertson et al, 1994[100]	Lofepramine	6	In and out	DSM-III-R	90	93	23.8 (4)	23.5 (3.8)	20	140–210	Industry	B
De Jonghe et al, 1991[30]	Maprotiline	6	In	DSM-III	30	35	25.25 (4.73)	24.5 (4.38)	40–80	50–150	Industry	B
Jakovljevic et al, 1996[63]	Maprotiline	6	In and out	DSM-IV	50	48	22.45 (4.06)	22.5 (3.65)	20–40	75–150	Industry	B
Kuha et al, 1991[68]	Maprotiline	5	In and out	Other criteria	24	22	25.83 (n/s)	24.92 (n/s)	20–60	50–150	Unclear	B
Martenyi et al, 2001[79]	Maprotiline	6	In	DSM-III-R	59	46	26.2 (5.5)	24.3 (4.8)	20	100–200	Industry	B
Poelinger and Haber, 1989[94]	Maprotiline	4	Out	Other criteria	73	69	22.5 (6)	22 (6)	40	75	Unclear	B
Besancon et al, 1993[11]	Mianserin	8	Out	DSM-III	33	32	35.1 (5.7)	35.9 (5.6)	20–40	60–90	Industry	B
La Pia et al, 1992[69]	Mianserin	6	In and out	DSM-III-R	20	20	24.1 (5.19)	22.2 (3.89)	20	40	Unclear	B
Muijen et al, 1988[83]	Mianserin	6	Out	Other criteria	26	27	26 (3.6)	25.9 (4.7)	20–80	20–80	Unclear	B
Taneri and Kohler, 1989[118]	Nomifensine	5	Out	ICD-9	20	20	19.2 (6)	20.8 (4.2)	40	150	Unclear	B
Fabre et al, 1991[40]	Nortriptyline	5	Out	DSM-III-R	103	102	22 (n/s)	23 (n/s)	20–40	50–100	Unclear	B
Joyce et al, 2002[64]	Nortriptyline	6	Out	DSM-IV	100	95	19.9 (4.4)	19.9 (4.4)	10–80	50–175	Industry	B
Akhondzadeh et al, 2003[2]	Nortriptyline	6	Out	DSM-IV	24	24	n/s	n/s	60	150	Unclear	B
Wolf et al, 2001[129]	Trimipramine	6	In and out	DSM-III-R	10	9	28.1 (5.8)	29.4 (7)	20	150	Industry	B
Bougerol et al, 1997[13]	Citalopram	8	Out	DSM-III-R	184	173	n/s	n/s	20	20	Industry	B
Bougerol et al, 1997[13]	Citalopram	8	In and out	DSM-III-R	158	158	n/s	n/s	20	20–40	Industry	B
Dalery and Honig, 2003[29]	Fluvoxamine	6	Out	DSM-III-R	94	90	22.2 (n/s)	22.3 (n/s)	20	100	Industry	B
Rapaport et al, 1996[96]	Fluvoxamine	7	Out	DSM-III-R	49	51	25.6 (n/s)	25.2 (n/s)	20–80	100–150	Industry	B
Cassano et al, 2002[19]	Paroxetine	52	Out	ICD-10	119	123	23.5 (n/s)	23 (n/s)	20–60	20–40	Industry	B
Chouinard et al, 1999[21]	Paroxetine	12	Unclear	DSM-III-R	101	102	25.45 (0.46)	25.9 (0.46)	20–80	20–50	Industry	B
De Wilde et al, 1993[33]	Paroxetine	6	Unclear	DSM-III	41	37	28.2 (5.3)	27 (4.8)	20–60	20–40	Industry	B
Fava et al, 1998[43]	Paroxetine	12	Out	DSM-III-R	54	55	23.9 (3.8)	23.1 (3.4)	20–80	20–50	Industry	B
Fava et al, 2000[44]	Paroxetine	16	Out	DSM-IV	35	30	23.6 (3.9)	25 (3.8)	20–60	20–60	Industry	B
	Sertraline					43		23.9 (3.4)		50–200		
Fava et al, 2002[45]	Paroxetine	10	Out	DSM-IV	92	96	20.5 (4.3)	20.6 (4.4)	20–60	20–60	Industry	B
	Sertraline					96		21 (4.4)		50–200		
Gagiano, 1993[53]	Paroxetine	6	Out	DSM-III-R	45	45	25 (4.7)	24.5 (5)	20–60	20–40	Unclear	B
Ontiveros and Garcia-Barriga, 1997[88]	Paroxetine	6	Out	DSM-III-R	61	60	26.4 (5.2)	26.2 (6.2)	20	20	Industry	B
Schoene and Ludwig, 1993[105]	Paroxetine	6	Out	DSM-III-R	52	54	28 (n/s)	29 (n/s)	20–60	20–40	Industry	B
Tignol, 1993[120]	Paroxetine	6	In	DSM-III-R	87	89	n/s	n/s	20	20	Industry	B
Aguglia et al, 1993[1]	Sertraline	8	Out	DSM-III-R	56	52	25.1 (6.9)	24.8 (5.3)	20–60	50–150	Unclear	B
Bennie et al, 1995[9]	Sertraline	6	Out	DSM-III-R	144	142	23.4 (n/s)	23.2 (n/s)	20–40	50–100	Industry	B
Boyer et al, 1998[15]	Sertraline	26	GP	DSM-IV	120	122	n/s	n/s	20–60	50–150	Industry	B
Newhouse et al, 2000[84]	Sertraline	12	Out	DSM-III-R	119	117	25 (4.7)	25.1 (4.2)	20–40	50–100	Industry	B
Sechter et al, 1999[107]	Sertraline	24	Out	DSM-III-R	120	118	24.9 (3.6)	24.5 (2.9)	20–60	50–150	Industry	B
Suri et al, 2000[116]	Sertraline	6	Out	DSM-IV	18	35	20.6 (4.53)	20.6 (2.79)	20	50–100	Industry	B

continued

Appendix 1. Summary of Included Studies (cont.)

Randomized Controlled Trial	Comparator	Follow-Up (wk)	Inpatient/ Outpatient Setting	Diagnostic Criteria	Sample Size		Baseline HAM-D Score (SD)		Dose (mg)		Funded by	Quality[a]
					Fluoxetine	Comparator	Fluoxetine	Comparator	Fluoxetine	Comparator		
Van Moffaert et al, 1995[125]	Sertraline	8	In and out	DSM-III-R	82	83	23.1 (n/s)	24.5 (n/s)	20–40	50–100	Industry	B
Sramek et al, 1995[111]	ABT-200	20	Out	DSM-III-R	72	72	28.2 (4.1)	27.3 (4)	20	220	Industry	B
Dalery et al, 1997[28]	Amineptine	12	Unclear	DSM-III-R	82	87	n/s	n/s	20	200	Unclear	B
Ferreri, 1989[51]	Amineptine	6	Out	DSM-III	31	32	25.1 (3.9)	23.6 (3.2)	20	200	Unclear	B
Smeraldi, 1998[109]	Amisulpride	12	Out	DSM-III-R	139	142	21.6 (2.9)	21.2 (2.8)	20	50	Industry	B
Feighner et al, 1991[50]	Bupropion	6	Out	DSM-III-R	62	61	26.1 (n/s)	25.3 (n/s)	20–80	225–450	Industry	B
Goldstein et al, 2002[58]	Duloxetine	8	Out	DSM-IV	33	70	17.9 (4.3)	18.4 (4)	20	40–120	Industry	A
Behnke et al, 2002[12]	Hypericum	6	Unclear	ICD-10	35	35	20.7 (2.9)	20 (3.2)	40	300	Industry	B
Harrer et al, 1999[61]	Hypericum	6	GP	ICD-10	84	77	17.18 (n/s)	16.6 (n/s)	20	800	Industry	A
Schrader, 2000[106]	Hypericum	6	Out	ICD-10	114	126	19.5 (n/s)	19.7 (n/s)	20	500	Industry	B
Ansseau et al, 1994[7]	Milnacipram	6	Out	DSM-III-R	93	97	32.4 (6.2)	30.6 (5.7)	20	100	Industry	B
Guelfi et al, 1998[59]	Milnacipram	12	In	DSM-III-R	100	200	27.4 (4)	27.9 (3.8)	20	100–200	Industry	B
Hong et al, 2003[62]	Mirtazapine	6	Out	DSM-IV	66	66	24.3 (5.2)	23.1 (5.1)	20–40	30–45	Unclear	B
Wheatley et al, 1998[127]	Mirtazapine	6	In and out	DSM-III-R	67	66	26.1 (4.3)	29.2 (4.5)	20–40	15–60	Industry	A
Duarte et al, 1996[39]	Moclobemide	6	Out	DSM-III-R	21	21	24 (3.15)	24 (3.11)	20	300	Industry	B
Gattaz et al, 1995[54]	Moclobemide	4	In	DSM-III-R	34	35	28 (5.3)	26.9 (5.3)	20–40	300–600	Unclear	B
Geerts et al, 1994[55]	Moclobemide	6	In and out	DSM-III-R	25	24	26.5 (5.8)	22 (4.6)	20–40	300–600	Industry	A
Lapierre et al, 1997[71]	Moclobemide	6	Out	DSM-III-R	62	66	25 (3)	31 (4)	20–40	200–600	Industry	B
Lonnqvist et al, 1994[75]	Moclobemide	6	In and out	DSM-III-R	107	102	22.2 (4.3)	22 (3.9)	20–40	300–450	Industry	B
Reynaert et al, 1995[99]	Moclobemide	6	In and out	DSM-III-R	50	51	23 (5.1)	24 (4.4)	20–40	300–600	Industry	A
Williams et al, 1993[128]	Moclobemide	6	In and out	DSM-III	60	62	24.6 (4.9)	24.4 (4.3)	20–40	300–600	Unclear	B
Berlanga et al, 1997[10]	Nefazodone	8	Out	DSM-III-R	37	37	23.7 (n/s)	25.1 (n/s)	20–40	400–500	Industry	B
Gillin et al, 1997[56]	Nefazodone	8	Out	DSM-III-R	20	24	23.2 (2.95)	22.9 (3.03)	20–40	200–500	Industry	B
Rush et al, 1998[103]	Nefazodone	8	Out	DSM-III-R	61	64	23.3 (2.7)	22.9 (2.9)	20–40	200–500	Industry	B
Pande et al, 1996[91]	Phenelzine	6	Out	DSM-III-R	20	20	13.9 (2.05)	13.1 (2.81)	20–60	45–90	Industry	B
Corrigan et al, 2000[26]	Pramipexole	8	Unclear	DSM-III-R	35	70	22 (n/s)	22 (n/s)	20	1–5	Industry	B
Andreoli et al, 2002[6]	Reboxetine	8	In and out	DSM-III-R	127	126	26.9 (3.6)	26.8 (3.4)	20–40	8–10	Unclear	B
Massana et al, 1999[81]	Reboxetine	8	In and out	DSM-III-R	89	79	27.4 (4.1)	28.6 (5.3)	20–40	8–10	Unclear	B
Alby et al, 1993[3]	Tianeptine	13	Out	DSM-III-R	104	102	32.8 (7.13)	33.4 (7.06)	20	37.5	Academy	B
Guelfi et al, 1999[60]	Tianeptine	12	GP	DSM-III-R	122	115	n/s	n/s	20	25–37.5	Industry	B
Loo et al, 1999[76]	Tianeptine	6	In and out	ICD-10	196	191	n/s	n/s	20	37.5	Unclear	B
Novotny and Faltus, 2002[87]	Tianeptine	6	In and out	DSM-IV	91	87	n/s	n/s	20	37.5	Industry	B
Debus et al, 1988[34]	Trazodone	6	Out	DSM-III	22	21	23.4 (3.8)	25.2 (4.3)	20–60	50–400	Industry	B
Falk et al, 1989[42]	Trazodone	6	Out	DSM-III	14	13	23.77 (4.28)	26.2 (6.67)	20–60	50–400	Industry	B
Perry et al, 1989[92]	Trazodone	6	Out	DSM-III	21	19	23.2 (2.8)	23.6 (3)	20–60	50–400	Unclear	B
Alves et al, 1999[5]	Venlafaxine	12	Out	DSM-IV	47	40	26.9 (3.9)	27.9 (5.2)	20–40	75–150	Industry	A
Clerc et al, 1994[22]	Venlafaxine	6	In	DSM-III-R	34	34	29.7 (4.2)	29.1 (5.2)	40	200	Industry	B
Costa e Silva, 1998[27]	Venlafaxine	8	Out	DSM-III-R	186	196	29.7 (5.3)	30.4 (6.2)	20–40	75–150	Industry	B
De Nayer et al, 2002[31]	Venlafaxine	12	Out	Implicit criteria	73	73	23.1 (n/s)	23 (n/s)	20–40	75–150	Industry	B
Diaz Martinez et al, 1998[36]	Venlafaxine	8	Out	DSM-III-R	75	70	29.4 (4.5)	27.8 (5)	20–40	75–150	Industry	B
Dierick et al, 1996[37]	Venlafaxine	8	Out	DSM-III-R	161	153	26.6 (4.1)	27 (4.2)	20	75–150	Industry	B
Rudolph and Feiger, 1999[102]	Venlafaxine	8	Out	DSM-IV	103	100	26 (n/s)	25 (n/s)	20–60	75–225	Industry	A
Silverstone and Ravindran, 1999[108]	Venlafaxine	12	Out	DSM-IV	119	122	27 (4.6)	27.6 (5.1)	20–60	75–225	Industry	B
Tylee et al, 1997[122]	Venlafaxine	12	GP	DSM-IV	170	171	22.5 (4.4)	22.4 (5)	20	75	Industry	A
Tzanakaki et al, 2000[123]	Venlafaxine	6	In	DSM-IV	54	55	27.1 (5.6)	27.8 (5.6)	60	225	Industry	B

continued

Appendix 1. Summary of Included Studies (cont.)

[a]Cochrane criteria for quality in Sackett[132] were used; these place particular emphasis on the adequacy of the randomization procedure. On this basis, studies were given a quality rating of A (adequate), B (unclear), or C (inadequate).
Abbreviations: GP = general practice, HAM-D = Hamilton Rating Scale for Depression, n/s = not stated.

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Appendix 1. Summary of Included Studies (cont.)

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Appendix 1. Summary of Included Studies (cont.)

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