Paroxetine Versus Placebo and Other Agents for Depressive Disorders: A Systematic Review and Meta-Analysis

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Objective: To compare paroxetine with placebo and other antidepressants across multiple efficacy and tolerability outcomes.

Data sources: Searches were conducted in MEDLINE (1966–2004), EMBASE (1980–2004), CINAHL (1982–2004), all Evidence-Based Medicine Reviews (1991–2004), HealthSTAR (1975–2004), BIOSIS (1980–2004), and PsycINFO (1840–2004). Medical Subject Headings (MeSH) included "paroxetine" OR "Paxil" exploded. The searches were not restricted by language, publication type, or study design.

Study selection: A study report was included if it described a randomized trial of paroxetine versus placebo or other antidepressants for patients with depressive disorders. Records were screened independently by 2 reviewers under the supervision of another reviewer.

Data extraction: Three investigators abstracted data, including study design, trial characteristics, and psychiatric assessment tools, using a prespecified form. Two investigators assessed quality of reporting using Jadad's scale.

Data synthesis: We included 62 unique randomized controlled trials. Paroxetine yielded consistently and significantly better remission (rate difference [RD]: 10% [95% CI = 6 to 14]), clinical response (RD: 17% [95% CI = 7 to 27]), and symptom reduction (effect size: 0.2 [95% CI = 0.1 to 0.3]) than placebo. Such consistency in the evidence base was not observed between paroxetine and other antidepressants. Pairwise comparisons of paroxetine and venlafaxine, mirtazapine, mianserin, or fluoxetine yielded inconsistent results across efficacy outcomes. Controlled-release paroxetine was the only antidepressant with significantly fewer dropouts due to adverse events than immediate-release paroxetine (RD: 5% [95% CI = 0.1 to 11]).

Conclusions: There were no significant and valid differences between paroxetine and other antidepressants to suggest that multiple modes of action improve clinical outcomes.

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Depression is a major medical and social problem.[1–3] For the past 50 years, treatment of depression has primarily been with antidepressants.[4,5] A variety of antidepressants have selective effects on the serotonin system, while other agents act on multiple receptor systems, with effects on the monoamine neurotransmitters norepinephrine, serotonin (5-HT), and dopamine.[6] Previous meta-analyses suggest greater efficacy for multiaction agents in the treatment of patients with depressive disorders.[7–9] However, uncertainty regarding the relative efficacy and tolerability between these agents remains, especially with respect to evidence consistency when agents of different modes of action are evaluated using multiple outcome measures.[10,11] We aimed to determine whether differences in therapeutic efficacy and tolerability are apparent between paroxetine, placebo, and other agents for patients with depressive disorders. Furthermore, we aimed to determine whether real differences exist in efficacy and tolerability, using multiple measures (e.g., remission, clinical response, symptom reduction),

between agents with different modes of action, using the totality of evidence on paroxetine as a case example.

METHOD

Search Strategy

Literature searches were conducted in MEDLINE (Jan. 1966–Feb. 2004), EMBASE (Jan. 1980–Feb. 2004), CINAHL (Jan. 1982–Feb. 2004), all Evidence-Based Medicine Reviews (Jan. 1991–Feb. 2004), HealthSTAR (Jan. 1975–Feb. 2004), BIOSIS (Jan. 1980–Feb. 2004), and PsycINFO (Jan. 1840–Feb. 2004). Medical Subject Headings (MeSH) were kept broad and included "paroxetine" exploded OR "Paxil" exploded. The searches were not restricted by language, publication type, or study design.

In order to ensure saturation of the literature, the reference lists of potentially relevant reports were scanned. Furthermore, the full-text articles from potentially relevant conference abstracts were obtained. Experts in the psychiatry domain were contacted to identify further literature.

Eligibility Criteria

A study report was included if it described a randomized trial of paroxetine versus placebo or other antidepressants for patients with depressive disorders. A study report was excluded if it examined clinically heterogeneous populations. Excluded reports included those that (1) examined bipolar disorder, (2) used electroconvulsive therapy as a comparator, (3) studied the efficacy of the off-label use of antidepressants (e.g., in adolescent populations), and (4) investigated depression in medically ill patients (e.g., those with HIV or cancer).

Screening

Citations and abstracts were initially screened independently by 2 reviewers (A.C.T., B.P.). The full-text articles of potentially relevant material were obtained and reviewed independently (A.C.T., B.P.) under the supervision of another reviewer (M.A.K.). Disagreements were resolved through discussion.

Data Abstraction

Three investigators (M.A.K., A.C.T., B.P.) abstracted data independently using a prespecified form. The abstracted data included study design, trial characteristics, psychiatric assessment tools, subject characteristics at baseline, and baseline assessment. Two investigators (A.C.T., B.P.) independently assessed quality of reporting using a validated quality scale.[12] Dimensions of quality included randomization, double-blinding, dropouts, and allocation concealment. Discrepancies among independent assessments were resolved through discussion.

Outcome data included remission (e.g., a score of less than 8 on the Hamilton Rating Scale for Depression [HAM-D]), clinical response (e.g., 50% reduction in HAM-D score from baseline), and symptom reduction (i.e., change score from baseline). As a surrogate marker for tolerability, total dropouts and dropouts due to adverse events were examined, but a detailed comparison of specific adverse events was not undertaken. Definitions of response and remission (e.g., based upon the HAM-D, Clinical Global Impressions-Improvement [CGI-I] scale, and the Montgomery-Asberg Depression Rating Scale [MADRS]) reported in the original trial reports were used. Outcome data were abstracted, including the assessment scale and definitions of remission and response. Data were abstracted and analyzed according to both the intention-to-treat and observed-case analysis principles, using the *Cochrane Handbook for Systematic Reviews of Interventions* as a guide.[13]

Data Analysis

Percent differences in remission, clinical response, and dropouts were derived between paroxetine and its comparators (i.e., placebo and other antidepressants). Effect sizes (i.e., the difference in change scores from baseline between the 2 treatments divided by the combined standard deviation) were derived for symptom reduction.[14]

Pooled estimates of treatment effect for the above outcomes were derived using a random-effects model with a χ^2 test for heterogeneity.[15] The effect size (ES) estimates were plotted against their precision to assist in the assessment of publication bias.[16]

RESULTS

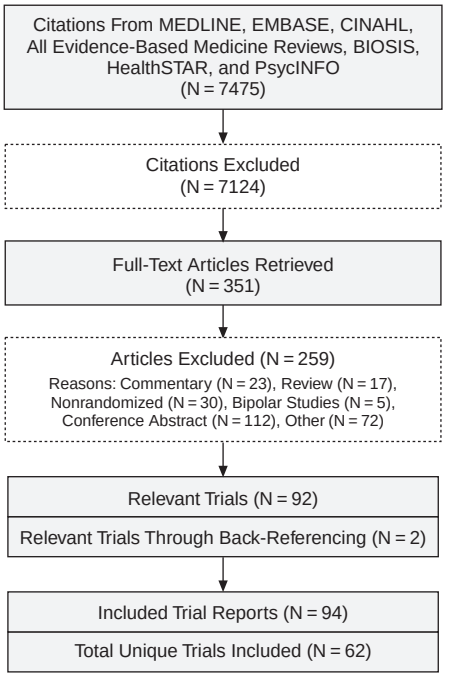
Literature Review

A total of 7475 potentially relevant records (abstracts and titles) were screened (Figure 1). Of these, 351 full-text reports were obtained and reviewed, yielding 94 trial reports describing 62 unique trials that passed the eligibility criteria and were therefore included (Appendix 1).[17–110]

Study Characteristics

The 62 trials compared paroxetine with placebo (N = 11) and other antidepressants (N = 51) (Table 1). Comparative antidepressants included amitriptyline (N = 13), fluoxetine (N = 12), mirtazapine (N = 4), imipramine (N = 4), clomipramine (N = 3), sertraline (N = 3), and venlafaxine (N = 3), among others (Table 1 and Appendix 1). The design of the included trials was either 2-arm (N = 55) or 3-arm (N = 7) (Table 1). The median sample size was 122 (range, 24–953). The quality of reporting of included trials was above average with a median score of 3.0 (range, 2.0–5.0). Allocation concealment was adequately reported in only 8% of included trial reports (N = 5) and was unclear in 92% (N = 57).

Figure 1. Results of the Literature Search



Patient Population

The median age of patients who participated in the included trials was 44 (range, 29–87; Table 1). In total, 38 trials (61%) included outpatient participants, 8 (13%) included inpatient participants, and 8 (13%) included both (8 [13%] were not reported). The majority of these trials were conducted in Europe (N = 38; 61%) and North America (N = 16; 26%). The primary diagnosis was major depressive disorder in 46 trials (74%), depressive disorders in 12 trials (19%), and other diagnoses in 4 trials (7%) (e.g., depressive disorder or dysthymia; Appendix 1).

Intervention, Outcome Measures, and Reporting of Outcomes

The median duration of treatment was 6 weeks (range, 4–52 weeks; Table 1). Psychiatric assessment was conducted via the HAM-D (N = 55 of the 62 included trials, 89%), CGI (N = 44, 71%), and MADRS (N = 24, 39%). On average, the included trials used 3 assessment scales per trial. Treatment effect was reported as change score (N = 47, 76%), clinical response (N = 37, 60%), and remission (N = 31, 50%), among others (Table 1).

Consistency of Treatment Effect

According to the intention-to-treat analysis, paroxetine was consistently and significantly more efficacious than placebo with respect to remission (rate difference [RD]: 10% [95% CI = 6 to 14]; Table 2 and Figure 2), clinical response (RD: 17% [95% CI = 7 to 27]; Table 2 and

Table 1. Characteristics of Included Trial Reports (N = 62)

Characteristic	Value
Study design	
Active trial, N (%)[a]	51 (82)
Amitriptyline, N	13
Fluoxetine, N	12
Mirtazapine, N	4
Imipramine, N	4
Clomipramine, N	3
Sertraline, N	3
Venlafaxine, N	3
Maprotiline, N	2
Nefazodone, N	2
Paroxetine controlled-release, N	2
Placebo-controlled trial, N (%)	11 (18)
3-Arm trial, N (%)	7 (11)
2-Arm trial, N (%)	55 (89)
Sample size, median (min, max), N	122 (24, 953)
Quality score, median (min, max)	3.0 (2.0, 5.0)
Allocation concealment, N (%)	
Adequate	5 (8)
Inadequate	0 (0)
Unclear	57 (92)
Patient population	
Mean age, median (min, max), y	44.4 (29.0, 87.9)
Percent male, median (min, max)	35.0 (12.0, 58.0)
Setting, N (%)	
Outpatient	38 (61)
Inpatient	8 (13)
Outpatient and inpatient	8 (13)
Not reported	8 (13)
Location, N (%)	
Europe	38 (61)
North America	16 (26)
Other	8 (13)
Primary diagnosis, N (%)	
Major depressive disorder	46 (74)
Depressive disorder	12 (19)
Other[b]	4 (7)
Intervention	
Treatment duration, median (min, max), wk	6.0 (4.0, 52.0)
Outcome measures	
Psychiatric assessment, N (%)	
HAM-D	55 (89)
CGI	44 (71)
MADRS	24 (39)
No. of psychiatric assessment tools, median (min, max)	3.0 (1.0, 7.0)
Reporting outcomes, N (%)	
Change score	47 (76)
Clinical response	37 (60)
Remission	31 (50)
All dropouts	51 (82)
Dropouts due to adverse events	51 (82)

[a]Antidepressants with more than 1 trial were displayed. For a complete listing of evaluated antidepressants, refer to Appendix 1.
[b]Includes depressive disorder and dysthymia, major depressive disorder and dysthymia, and minor depressive disorder and dysthymia.
Abbreviations: CGI = Clinical Global Impressions scale, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale.

Table 2. Remission, Clinical Response, Change Score, and Dropout Differences Between Paroxetine IR and Controlled Treatments

Controlled Treatment	No. Trials/ No. Patients	Remission Difference,[a] % (95% CI)	No. Trials/ No. Patients	Response Difference,[a] % (95% CI)	No. Trials/ No. Patients	Change Score,[a] Effect Size (95% CI)	No. Trials/ No. Patients	Total Dropouts,[b] % (95% CI)	No. Trials/ No. Patients	Dropouts Due to Adverse Events,[b] % (95% CI)
Placebo	6/1822	10.1 (5.9 to 14.4)[c]	5/1330	16.9 (7.0 to 26.8)[c]	9/2009	0.21 (0.10 to 0.30)[c]	8/1495	–0.2 (–7.4 to 6.7)	8/1882	8.2 (3.8 to 12.6)[c]
TCA	12/2330	–1.7 (–6.9 to 3.5)	14/3218	0.2 (–3.7 to 4.0)	19/3655	0.002 (–0.11 to 0.11)	21/3665	–4.7 (–8.5 to –0.9)[c]	23/3755	–4.8 (–7.3 to –2.3)[c]
Amitriptyline	5/844	–0.5 (–8.8 to 7.9)	6/973	–4.5 (–11.0 to 2.0)	9/999	–0.01 (–0.22 to 0.20)	10/1493	–3.7 (–10.6 to 3.3)	12/1583	–1.6 (–4.0 to 0.8)
Imipramine	2/534	–1.7 (–9.2 to 5.8)	3/574	1.0 (–7.0 to 9.0)	2/507	0.16 (–0.28 to 0.60)	4/605	–7.2 (–15.6 to 1.3)	4/605	–7.9 (–17.0 to 1.2)
Clomipramine	NR	NR	2/1032	1.6 (–4.2 to 7.3)	2/1055	–0.18 (–0.77 to 0.40)	3/1201	–8.3 (–13.1 to –3.4)[c]	3/1201	–8.0 (–14.2 to –1.8)[c]
Mianserin	NR	NR	2/127	14.6 (–16.3 to 45.6)	2/124	0.43 (0.07 to 0.80)[c]	2/128	–0.2 (–13.7 to 13.4)	2/128	–6.0 (–23.2 to 11.2)
SSRI	9/2200	0.7 (–3.3 to 4.8)	10/1653	3.2 (–1.6 to 8.0)	10/1489	0.04 (–0.06 to 0.14)	14/2645	1.2 (–2.3 to 4.6)	11/1832	1.4 (–1.9 to 4.8)
Fluoxetine	6/1275	3.4 (–2.2 to 8.9)	7/988	6.6 (0.7 to 12.5)[c]	6/769	0.10 (–0.05 to 0.24)	10/1600	1.5 (–2.8 to 5.8)	8/1140	1.6 (–2.2 to 5.3)
Fluvoxamine	NR	NR	NR	NR	2/178	0.02 (–0.28 to 0.32)	NR	NR	NR	NR
Sertraline	3/925	–2.8 (–9.1 to 3.5)	2/545	–3.6 (–11.2 to 4.7)	2/542	–0.03 (–0.20 to 0.14)	3/925	1.7 (–4.5 to 7.8)	2/572	5.4 (–0.6 to 11.3)
SNRI (venlafaxine)	3/567	–12.1 (–28.8 to 4.6)	2/206	–21.0 (–34.0 to –8.0)[c]	3/543	–0.07 (–0.24 to 0.10)	2/445	–2.6 (–18.6 to 13.4)	3/567	–0.9 (–7.8 to 5.9)
Paroxetine CR	2/627	–4.8 (–13.6 to 3.9)	1/417	–4.3 (–14.2 to 5.7)	2/627	–0.10 (–0.29 to 0.10)	1/210	6.2 (–6.5 to 18.9)	2/639	5.4 (0.1 to 10.7)[c]
Other	4/796	–4.9 (–14.1 to 4.4)	10/1769	0.3 (–5.5 to 6.0)	9/1607	0.003 (–0.16 to 0.17)	10/2323	1.1 (–2.4 to 4.5)	10/2285	0.9 (–1.8 to 3.5)
Mirtazapine	3/673	–8.9 (–16.0 to –1.8)[c]	3/673	–6.6 (–14.1 to 0.9)	3/673	–0.24 (–0.40 to –0.09)[c]	4/793	3.6 (–2.3 to 9.4)	3/726	3.8 (–4.0 to 11.7)
Bupropion	NR	NR	2/200	1.2 (–11.6 to 14.0)	NR	NR	NR	NR	1/100	–2.6 (–14.6 to 9.5)
Nefazodone	NR	NR	2/236	10.3 (–10.8 to 31.4)	NR	NR	NR	NR	2/246	–4.0 (–20.5 to 12.6)

[a]Intention-to-treat analysis. A positive value in the response-difference estimate indicates paroxetine is more effective compared to the controlled treatment.
[b]Intention-to-treat analysis. A positive value indicates paroxetine with more dropouts.
[c]Statistically significant difference ($p < .05$). Random-effect model estimates were used for remission differences.
Abbreviations: CR = controlled release, NR = not reported, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Figure 3), and change score (ES: 0.2 [95% CI = 0.1 to 0.3]; Table 2 and Figure 4).

Consistency of clinical evidence across all efficacy outcomes was not observed in comparisons between paroxetine and other antidepressants, including those with different modes of action (Table 2 and Figures 2–4). Clinical response with paroxetine was significantly lower than with venlafaxine (RD: –21% [95% CI = –34 to –8]); the 2 drugs, however, were not different with respect to remission (RD: –12% [95% CI = –29 to 5]) and change score (ES: –0.07 [95% CI = –0.24 to 0.10]). Remission and change score with paroxetine were significantly lower than those with mirtazapine (RD: –9% [95% CI = –16 to –2]; ES: –0.24 [95% CI = –0.40 to –0.09], respectively); the 2 drugs, however, were not different with respect to clinical response (RD: –7% [95% CI = –14 to 1]). The change score with paroxetine was significantly higher than with mianserin (ES: 0.43 [95% CI = 0.07 to 0.80]); the 2 drugs, however, were not different with respect to clinical response (RD: 15% [95% CI = –16 to 46]). Clinical response with paroxetine was significantly higher than with fluoxetine (RD: 7% [95% CI = 0.7 to 13]); the 2 drugs, however, were not different with respect to change score (ES: 0.10 [95% CI = –0.05 to 0.24]) and remission (RD: 3% [95% CI = –2 to 9]).

Paroxetine treatment was associated with significantly more dropouts due to adverse events than treatment with placebo (RD: 8% [95% CI = 4 to 13]; Table 2). Compared with tricyclic antidepressants, paroxetine was associated with fewer dropouts (RD: –5% [95% CI = –9 to –1]) and fewer dropouts due to adverse events (RD: –5% [95% CI = –7 to –2]). Controlled-release paroxetine was the only antidepressant associated with significantly fewer dropouts due to adverse events than immediate-release paroxetine (RD: 5% [95% CI = 0.1 to 11]), although the estimated difference was based on limited data from 2 trials (Table 2).

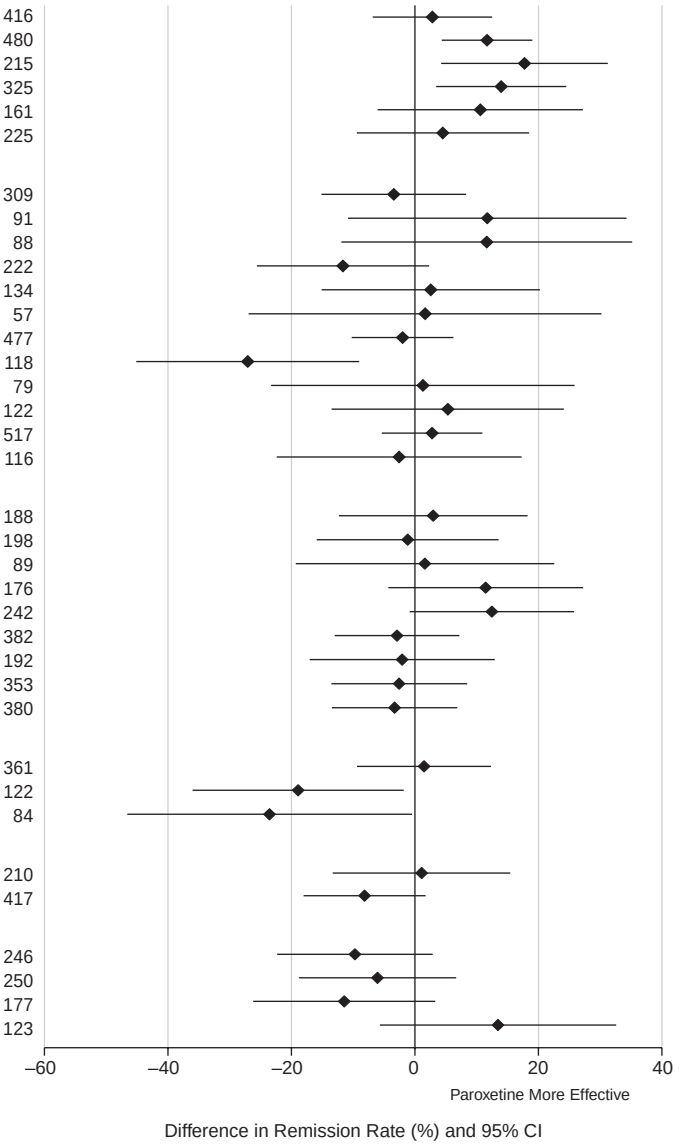
Results from the observed-case analysis were similar to those from the intention-to-treat analysis discussed above (data not shown). Furthermore, the funnel plot suggested a lack of publication bias among trials comparing paroxetine and other antidepressants, with respect to change score (Figure 5).

DISCUSSION

The current systematic review and meta-analysis included a large number of randomized controlled trials evaluating paroxetine, one of the most commonly prescribed selective serotonin reuptake inhibitors (SSRIs).[111] Most of the included trials directly compared paroxetine with other antidepressants, although a smaller number of placebo-controlled trials were also included. This systematic review included a broad population base and a range of clinical outcomes. Using this broad set of clinical data,

Figure 2. Summary of Remission Rate Differences Between Paroxetine IR and Alternative Treatments

Trial	Diagnosis	Definition of Remission	Control	N
			Placebo	
Golden et al (2002)[69]	MDD	HAM-D ≤ 7	PL	416
Feighner et al (1993)[52]	MD	HAM-D ≤ 10	PL	480
Rapaport et al (2003)[94]	MD	HAM-D ≤ 7	PL	215
Claghorn (1992)[36]	MD	HAM-D ≤ 10	PL	325
Barrett et al (2001)[24]	DYS/minor DD	HAM-D ≤ 6	PL	161
Williams et al (2000)[108]	DYS/minor DD	HAM-D ≤ 7	PL	225
			TCA	
Bignamini and Rapisarda (1992)[29]	MD	HAM-D ≤ 12	AM	309
Geretsegger et al (1995)[68]	MD	HAM-D ≤ 14	AM	91
Hutchinson et al (1992)[73]	MD	HAM-D ≤ 14	AM	88
Moeller et al (1993)[81]	MD	HAM-D ≤ 14	AM	222
Stuppaeck et al (1994)[100]	MD	HAM-D ≤ 14	AM	134
Arminen et al (1994)[20]	MD	HAM-D ≤ 7	IM	57
Feighner et al (1993)[52]	MD	HAM-D ≤ 10	IM	477
DUAG (1990)[44]	MD	HAM-D ≤ 7	CL	118
Guillibert et al (1989)[70]	MD	HAM-D ≤ 14	CL	79
Moon and Vince (1996)[82]	MD	MADRS ≤ 12	LO	122
Szegedi et al (1997)[101]	MD/minor DD	HAM-D ≤ 9	MP	517
Mulsant et al (2001)[83]	MD/MEL	HAM-D ≤ 10	NO	116
			SSRI	
Fava et al (2002)[50]	MDD/AMDD	HAM-D ≤ 7	FL	188
Chouinard et al (1999)[34]	MD	HAM-D ≤ 10	FL	198
Gagiano (1993)[66]	MD	HAM-D ≤ 14	FL	89
Tignol (1993)[104]	MD	MADRS ≤ 7	FL	176
Cassano et al (2002)[31]	DD	HAM-D ≤ 10	FL	242
Kroenke et al (2001)[75]	DD	MCS ≥ 40	FL	382
Fava et al (2002)[50]	MDD/AMDD	HAM-D ≤ 7	SE	192
Aberg-Wistedt et al (2000)[17]	MD	MADRS ≤ 7	SE	353
Kroenke et al (2001)[75]	DD	MCS ≥ 40	SE	380
			SNRI	
McPartlin et al (1998)[78]	MD	HAM-D ≤ 7	VN	361
Poirier and Boyer (1999)[93]	MD	HAM-D ≤ 10	VN	122
Ballús et al (2000)[23]	DD/DYS	HAM-D ≤ 8	VN	84
			PR CR	
Rapaport et al (2003)[94]	MD	HAM-D ≤ 7	PR CR	210
Golden et al (2002)[69]	MDD	HAM-D ≤ 7	PR CR	417
			Other	
Schatzberg et al (2002)[88]	MD	HAM-D ≤ 7	MI	246
Szegedi et al (2003)[28]	MD	HAM-D ≤ 7	MI	250
Wade et al (2003)[105]	DD	HAM-D ≤ 18	MI	177
Pini et al (2003)[92]	MD/DYS/A	CGI = 1 or 2	MO	123



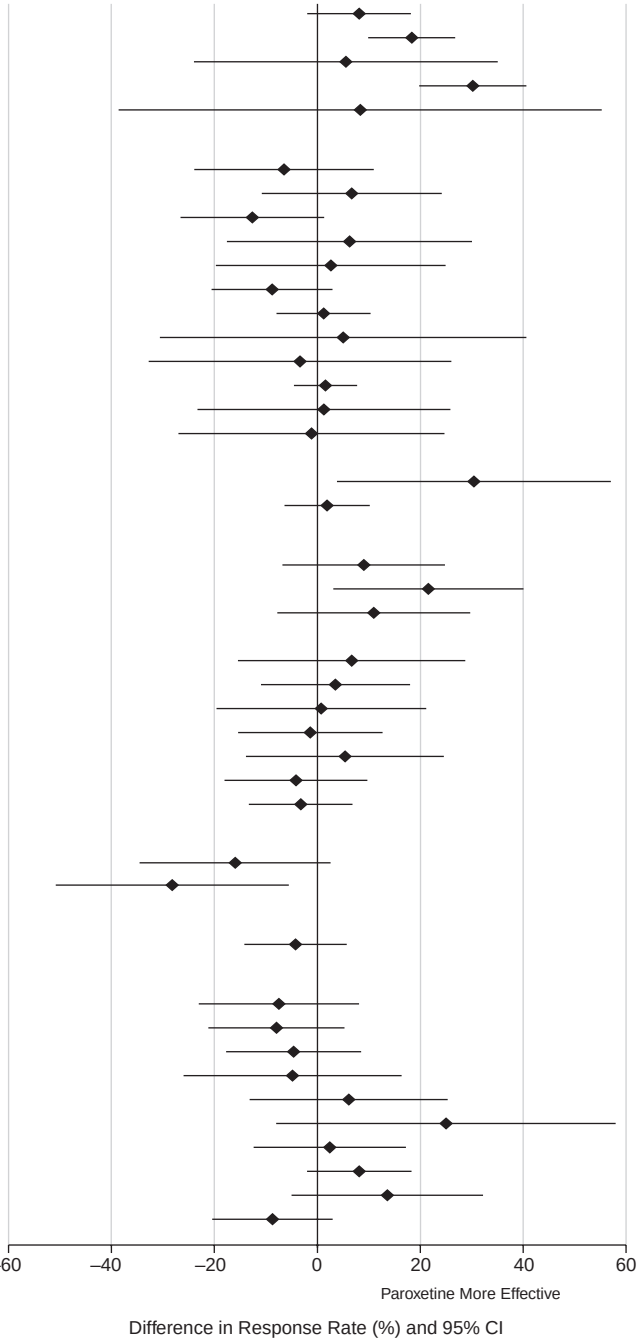
Abbreviations: A = anxiety, AM = amitriptyline, AMDD = atypical major depressive disorder, CGI = Clinical Global Impressions scale, CL = clomipramine, DD = depressive disorder, DUAG = Danish University Antidepressant Group, DYS = dysthymia, FL = fluoxetine, HAM-D = Hamilton Rating Scale for Depression, IM = imipramine, IR = immediate-release, LO = lofepramine, MADRS = Montgomery-Asberg Depression Rating Scale, MCS = Mental Component Summary of the Medical Outcomes Study 36-Item Short-Form Health Survey, MD = major depression, MDD = major depressive disorder, MEL = melancholic disorder, MI = mirtazapine, MO = moclobemide, MP = maprotiline, NO = nortriptyline, PL = placebo, PR CR = paroxetine controlled-release, SE = sertraline, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant, VN = venlafaxine.

the relative efficacy and tolerability of paroxetine and other antidepressants were examined.

The first result from the current meta-analysis was predictable. Paroxetine was consistently better than placebo across a range of patient populations and clinical outcomes. The latter included symptom reduction, clinical response, and remission. The observed consistency across multiple studies, especially with respect to different clinical outcomes, indicated that a true difference in efficacy exists between this SSRI and placebo. Our results suggest that in practical terms, one needs to treat, on average, 10 patients with depressive disorders in order to observe 1 patient achieving remission (i.e., a remission difference of 10%). The number needed to treat to achieve a clinical response is approximately 6 (i.e., a response difference of 17%).[112,113]

Figure 3. Summary of Response Rate Differences Between Paroxetine IR and Alternative Treatments

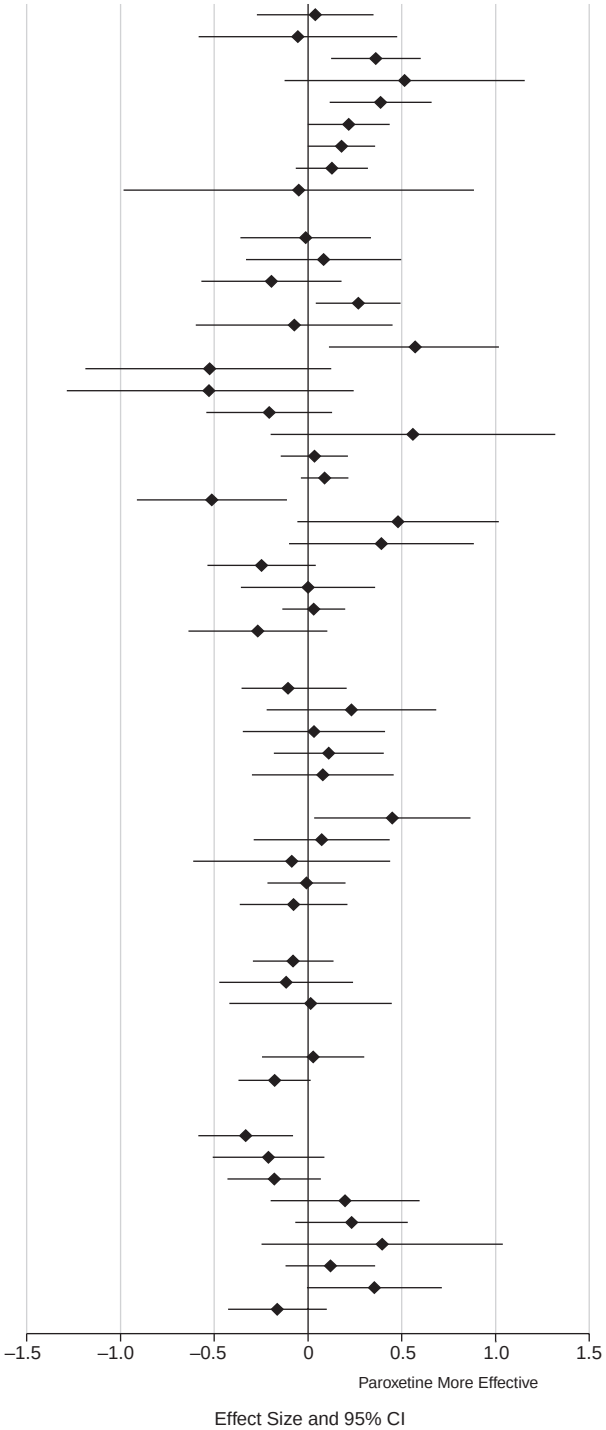
Trial	Diagnosis	Definition of Response	Control	N
			Placebo	
Golden et al (2002)[69]	MDD	HAM-D	PL	416
Feighner et al (1993)[52]	MD	HAM-D	PL	480
Fava et al (1998)[49]	MD	HAM-D	PL	74
Claghorn (1992)[36]	MD	HAM-D	PL	336
Burrows and Salzman (2002)[30]	Minor DD	CGI	PL	24
			TCA	
Stuppaeck et al (1994)[100]	MD	HAM-D	AM	134
Sacchetti et al (2002)[96]	MD	HAM-D	AM	129
Moeller et al (1993)[81]	MD	HAM-D	AM	222
Hutchinson et al (1992)[73]	MD	HAM-D	AM	88
Geretsegger et al (1995)[68]	MD	HAM-D	AM	91
Bignamini and Rapisarda (1992)[29]	MD	HAM-D	AM	309
Feighner et al (1993)[52]	MD	HAM-D	IM	477
Chiu et al (1996)[33]	MD	HAM-D	IM	40
Arminen et al (1994)[20]	MD	HAM-D	IM	57
Ravindran et al (1997)[95]	DD/A	MADRS	CL	953
Guillibert et al (1989)[70]	MD	HAM-D	CL	79
Schnyder and Koller-Leiser (1996)[97]	MD	HAM-D	MP	70
Dorman (1992)[46]	DD	HAM-D	MA	57
Szegedi et al (1997)[101]	MD/minor DD	HAM-D	MP	512
			SSRI	
Tignol (1993)[104]	MD	MADRS	FL	176
Schoene and Ludwig (1993)[98]	MD	HAM-D	FL	106
Ontiveros and Garcia-Barriga (1997)[91]	MD	HAM-D	FL	121
Gagiano (1993)[66]	MD	HAM-D	FL	90
Fava et al (2002)[50]	MDD/AMDD	HAM-D	FL	188
Fava et al (1998)[49]	MD	HAM-D	FL	109
Chouinard et al (1999)[34]	MD	HAM-D	FL	198
Ansseau et al (1994)[19]	MD	HAM-D	FV	120
Fava et al (2002)[50]	MDD/AMDD	HAM-D	SE	192
Aberg-Wistedt et al (2000)[17]	MD	MADRS/CGI	SE	353
			SNRI	
Poirier and Boyer (1999)[93]	MD	HAM-D/CGI	VN	122
Ballús et al (2000)[23]	DD/DYS	HAM-D/CGI	VN	84
			PR CR	
Golden et al (2002)[69]	MDD	HAM-D	PR CR	417
			Other	
Wade et al (2003)[105]	DD	HAM-D	MI	177
Schatzberg et al (2002)[88]	MD	HAM-D	MI	246
Benkert et al (2000)[27]	MD	HAM-D	MI	250
Weihs et al (2000)[107]	MD	CGI	BU	100
Weihs et al (2000)[107]	MD	HAM-D	BU	100
Hicks et al (2002)[71]	DD	HAM-D	NE	40
Baldwin et al (1996)[21]	MD	CGI	NE	196
Cassano and Jori (2002)[32]	MD	HAM-D	AI	275
Pini et al (2003)[92]	MD/DYS/A	HAM-D	MO	123
Waintraub et al (2002)[106]	MD	HAM-D	TI	262



Abbreviations: A = anxiety, AI = amisulpride, AM = amitriptyline, AMDD = atypical major depressive disorder, BU = bupropion, CGI = Clinical Global Impressions scale, CL = clomipramine, DD = depressive disorder, DYS = dysthymia, FL = fluoxetine, FV = fluvoxamine, HAM-D = Hamilton Rating Scale for Depression, IM = imipramine, IR = immediate-release, MA = mianserin, MADRS = Montgomery-Asberg Depression Rating Scale, MD = major depression, MDD = major depressive disorder, MI = mirtazapine, MO = moclobemide, MP = maprotiline, NE = nefazodone, PL = placebo, PR CR = paroxetine controlled-release, SE = sertraline, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant, TI = tianeptine, VN = venlafaxine.

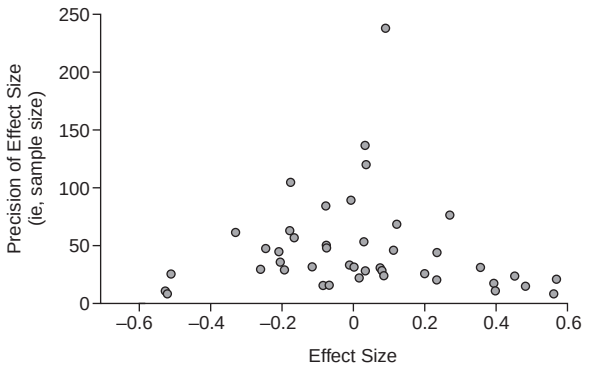
Figure 4. Summary of Effect Sizes Derived From Change Scores Between Paroxetine IR and Alternative Treatments

Trial	Diagnosis	Measure of Severity	Control	N
			Placebo	
Barrett et al (2001)[24]	DYS/minor DD	HSCL-D-20	PL	161
Fava et al (1998)[49]	MD	HAM-D-21	PL	74
Williams et al (2000)[108]	DYS/minor DD	HSCL-D-20	PL	277
Edwards and Goldie (1993)[48]	MD	HAM-D	PL	41
Rapaport et al (2003)[94]	MD	HAM-D	PL	215
Claghorn (1992)[36]	MD	HAM-D	PL	325
Feighner et al (1993)[52]	MD	HAM-D	PL	480
Golden et al (2002)[69]	MDD	HAM-D	PL	416
Burrows and Salzman (2002)[30]	Minor DD	HAM-D	PL	20
			TCA	
Sacchetti et al (2002)[96]	MD	HAM-D	AM	129
Stuppaeck et al (1994)[100]	MD	HAM-D	AM	92
Christiansen and Behnke (1996)[35]	DD	HAM-D	AM	113
Freed et al (1999)[64]	DD	MADRS	AM	306
Geretsegger et al (1995)[68]	MD	HAM-D	AM	59
Hutchinson et al (1991)[72]	MD	HAM-D	AM	90
Staner et al (1995)[99]	MD	HAM-D	AM	40
Laursen et al (1985)[77]	DD/DYS	HAM-D	AM	30
Moeller et al (1993)[81]	MD	HAM-D	AM	140
Chiu et al (1996)[33]	MD	HAM-D	IM	30
Feighner et al (1993)[52]	MD	HAM-D	IM	477
Ravindran et al (1997)[95]	DD/A	MADRS	CL	953
DUAG (1990)[44]	MD	HAM-D-17	CL	102
Dorman (1992)[46]	DD	HAM-D	MA	57
Mertens and Pintens (1988)[79]	DD	HAM-D	MA	67
Dunner et al (1992)[47]	MD	HAM-D	DO	188
Moon and Vince (1996)[82]	MD	MADRS	LO	122
Szegedi et al (1997)[101]	MD/minor DD	MADRS	MP	544
Mulsant et al (2001)[83]	MD/MEL	HAM-D	NO	116
			SSRI	
Chouinard et al (1999)[34]	MD	HAM-D	FL	198
De Wilde et al (1993)[45]	MD	HAM-D	FL	78
Fava et al (1998)[49]	MD	HAM-D-21	FL	109
Fava et al (2002)[50]	MDD/AMDD	HAM-D	FL	181
Ontiveros and Garcia-Barriga (1997)[91]	MD	HAM-D	FL	110
Geretsegger et al (1994)[67]	MD	HAM-D	FL	93
Ansseau et al (1994)[19]	MD	HAM-D	FV	120
Kiev and Feiger (1997)[74]	MD	HAM-D	FV	58
Aberg-Wistedt et al (2000)[17]	MD	MADRS	SE	353
Fava et al (2002)[50]	MDD/AMDD	HAM-D	SE	189
			SNRI	
McPartlin et al (1998)[78]	MD	HAM-D	VN	336
Poirier and Boyer (1999)[93]	MD	HAM-D	VN	123
Ballús et al (2000)[23]	DD/DYS	HAM-D	VN	84
			PR CR	
Rapaport et al (2003)[94]	MD	HAM-D	PR CR	210
Golden et al (2002)[69]	MDD	HAM-D	PR CR	417
			Other	
Schatzberg et al (2002)[88]	MD	HAM-D-17	MI	246
Wade et al (2003)[105]	DD	HAM-D-17	MI	177
Benkert et al (2000)[27]	MD	HAM-D	MI	250
Weihs et al (2000)[107]	MD	HAM-D	BU	100
Baldwin et al (1996)[21]	MD	MADRS	NE	174
Hicks et al (2002)[71]	DD	HAM-D	NE	40
Cassano and Jori (2002)[32]	MD	HAM-D	AI	272
Pini et al (2003)[92]	MD/DYS/A	HAM-D	MO	123
Waintraub et al (2002)[106]	MD	HAM-D	TI	225



Abbreviations: A = anxiety, AI = amisulpride, AM = amitriptyline, AMDD = atypical major depressive disorder, BU = bupropion, CL = clomipramine, DD = depressive disorder, DO = doxepin, DUAG = Danish University Antidepressant Group, DYS = dysthymia, FL = fluoxetine, FV = fluvoxamine, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, HSCL-D-20 = 20-item Hopkins Symptom Checklist Depression Scale, IM = imipramine, IR = immediate-release, LO = lofepramine, MA = mianserin, MADRS = Montgomery-Asberg Depression Rating Scale, MD = major depression, MDD = major depressive disorder, MEL = melancholic disorder, MI = mirtazapine, MO = moclobemide, MP = maprotiline, NE = nefazodone, NO = nortriptyline, PL = placebo, PR CR = paroxetine controlled-release, SE = sertraline, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant, TI = tianeptine, VN = venlafaxine.

Figure 5. Funnel Plot of Effect Sizes Versus Their Precision to Assess for Publication Bias Among Trials of Paroxetine IR Versus Active Treatments



Substantial uncertainty remained regarding the true difference between paroxetine and other antidepressants. One interpretation would be that multi-action drugs are better than paroxetine on some clinical outcomes in some cases (e.g., using data from 2 trials, venlafaxine was superior on clinical response, and, using data from another 3 trials, mirtazapine was superior on remission and symptom reduction). However, if the level of consistency across the evidence base observed above was used as a threshold to discern a true difference, there were no consistent data to suggest a true difference in efficacy between paroxetine and other antidepressants.[10,11] In the large number of active comparator trials, there were no drugs that were consistently shown to be better than paroxetine by more than 1 clinical outcome, nor did paroxetine differ from any other agent, except in special cases, which will be described below.

As a class, dual agents did not seem to provide consistently better efficacy than paroxetine. For example, venlafaxine was shown to achieve a better remission rate than paroxetine in 2 relatively small trials,[23,93] but this finding was not confirmed in a larger trial.[78] Venlafaxine was also shown to have a better response rate than paroxetine, a finding that was consistent with results from previous meta-analyses.[7] However, the pooled response rate difference was based upon data from 3 trials.[23,78,93] One of these trials was a study designed to compare venlafaxine and paroxetine in patients who were SSRI nonrespondents, many of whom had previously failed paroxetine.[93] This fact obviously predisposed an outcome favorable toward venlafaxine but did not support a true difference in efficacy between venlafaxine and paroxetine for major depressive disorder. Overall, no consistent difference was shown between the 2 agents across all clinical outcomes (i.e., remission and symptom reduction did not differ).

Compared to paroxetine, mirtazapine was better in symptom reduction and remission. It was, however, not better with respect to clinical response or tolerability. These observations could be explained in part by the sedating effect of mirtazapine as measured by the 3 sleep questions in the HAM-D questionnaire.[114] For example, mirtazapine has been shown to improve sleep continuity in major depressive disorder (MDD) patients with poor sleep quality.[115,116] Other inconsistent findings across different outcomes were observed in the pairwise comparisons between paroxetine and mianserin and paroxetine and fluoxetine in favor of paroxetine. Once again it becomes apparent that choosing 1 criterion that shows a difference between 2 agents when all other criteria do not very likely results in the reader's falsely believing that there is a clinically significant difference between the medications.

Similarly, in a systematic review of head-to-head studies comparing 1 second-generation antidepressant (i.e., SSRI, serotonin-norepinephrine reuptake inhibitor, dopamine reuptake inhibitor, or 5-HT_2 receptor antagonist) with another in the treatment of MDD, Hansen et al.[117] concluded that the efficacy and safety profiles of these antidepressants did not differ substantially. Similarly, Gartlehner et al.,[118] in another systematic review, reported no difference in discontinuation rates between SSRIs as a class and other second-generation antidepressants.

Compared to the immediate-release formulation of paroxetine, the controlled-release formulation seemed to be better tolerated, as suggested by its smaller number of early terminations. On average, one would need to switch 20 trial participants from the immediate-release to the controlled-release formulation to prevent an early termination due to adverse events (i.e., an absolute difference of 5.4%). This difference is consistent with other evaluative studies that suggest a longer median time to discontinuation with the controlled-release formulation.[119,120] This finding, however, needs to be interpreted cautiously, as it was based upon a relatively limited amount of data from 2 studies.[69,94]

This systematic review has several limitations. Unpublished trials involving paroxetine were not included, although there was no clear indication of publication bias. Dose-response assessment was not feasible due to the dose titration design in the majority of the included trials. An analysis of sustained response was not feasible with the current data, although the placebo-subtracted responses observed with paroxetine might have to be interpreted in light of treatment expectation and the episodic duration of depressive symptoms.[121] In some instances, heterogeneity was noted for the pooled results. Reasons for this heterogeneity included different depression classification systems (i.e., other than DSM-III criteria), patient settings, and inclusion criteria.[122–124] These limitations were evaluated by conducting several sensitivity analyses. The findings reported here were unchanged when smaller studies and those with differing diagnostic criteria were removed.

Our results suggest that symptom reduction captured by a variety of outcome measures must be consistently

different for a valid and reliable suggestion of differences between 2 antidepressants. Based on this principle, there were no consistent and valid differences between paroxetine and other antidepressants to suggest that multiple modes of action improve clinical outcomes. Taking this into account, our findings suggest that clinicians must focus on improving adherence to treatment regimens, past response rates, and other practical considerations when choosing an antidepressant that is appropriate for a given patient.

Drug names: bupropion (Wellbutrin and others), clomipramine (Anafranil and others), doxepin (Sinequan and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

Author contributions: All the authors conceived the research question, interpreted the data, revised the article, and approved this version of the article for publication. Dr. Katzman and Mr. Pham designed the study with the help of Ms. Tricco. Mr. Pham conducted the meta-analysis. Dr. Katzman drafted the article with the help of Ms. Tricco and Mr. Pham.

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Appendix 1. Study and Participant Characteristics for All Trials (N = 94)

Reference	Same Trial	Country	Primary Diagnosis; Diagnostic Criteria; Severity Criteria	Treatment Setting	Weeks of Treatment	Treatment/Dose, mg	Age, Mean	% Male	Patient Assessment Tools
Aberg-Wistedt et al (2000)[17]	1	Sweden	MD; DSM-III-R; MADRS-10 ≥ 21	O	24	PR/20–40, SE/50–150	43.0	32	MADRS, CGI
Stain-Malmgren et al (2001)[18]	1	Sweden	MD; DSM-III-R; MADRS-10 ≥ 21	O	24	PR/NR, SE/NR	39.0	27	MADRS
Ansseau et al (1994)[19]		Belgium	MD; DSM-III-R; HAM-D-21 ≥ 18	I/O	6	PR/20–30, FV/50–200	43.7	54	HAM-D, HAM-A, CGI
Arminen et al (1994)[20]		Turkey	MD; DSM-III-R; HAM-D ≥ 18 on first 17 items	I	12	PR/20–40, IM/100–200	NR	46	HAM-D, MADRS, BDI
Baldwin et al (1996)[21]	2	UK and Ireland	MD; DSM-III-R; HAM-D ≥ 18 on first 17 items, moderately ill on CGI	O	8	PR/20–40, NE/200–600	38.1	45	HAM-D, HAM-A, CGI, MADRS, PGA
Baldwin et al (2001)[22]	2	UK and Ireland	MD; DSM-III-R; HAM-D ≥ 18 on first 17 items, moderately ill on CGI	O	16	PR/20–40, NE/200–600	38.8	47	HAM-D, CGI, PGA, HAM-A, MADRS
Ballús et al (2000)[23]		Spain	DD or DYS; ICD-10; HAM-D-21 ≥ 17	O	24	PR/20–40, VN/75–150	44.6	12	HAM-D, MADRS, CGI
Barrett et al (2001)[24]	3	US	DD or DYS; DSM-III-R; HAM-D-17 ≥ 10	O	11	PR/10–40, PL	43.9	38	HAM-D, HSCL-D
Sullivan et al (2003)[25]	3	US	DD or DYS; DSM-IV; HAM-D-17 ≥ 10	O	11	PR/NR, PL	NR	48	HAM-D, HSCL
Bascara (1989)[26]		Philippines	MD; DSM-III; HAM-D-21 ≥ 18	NR	6	PR/20–30, AM/50–75	34.0	48	HAM-D, PGA, SCL-24
Benkert et al (2000)[27]	4	Germany	MD; DSM-IV; HAM-D-17 ≥ 18	O	6	PR/20–40, MI/15–45	47.2	36	HAM-D, HAM-A, CGI
Szegedi et al (2003)[28]	4	Germany	MD; DSM-IV; HAM-D-17 ≥ 18	O	6	PR/20–40, MI/15–45	47.2	36	HAM-D
Bignamini and Rapisarda (1992)[29]		Italy	MD; DSM-III; HAM-D-21 ≥ 18	O	6	PR/20–30, AM/75–150	NR	NR	HAM-D, CGI
Burrows and Salzman (2002)[30]		US	Minor DD; NR; NR	I	8	PR/10–30, PL	87.9	25	HAM-D, CGI, CS
Cassano et al (2002)[31]		Italy	DD; ICD-10; MMSE ≥ 22, HAM-D ≥ 18, RDS > CAS	O	52	PR/20–40, FL/20–60	75.2	44	HAM-D, CAS
Cassano and Jori (2002)[32]		Italy	MD; DSM-IV; HAM-D ≥ 18	O	8	PR/20, AI/50	51.2	28	HAM-D, MADRS, CGI
Chiu et al (1996)[33]		Taiwan	MD; DSM-III-R; HAM-D > 18	O	6	PR/20–30, IM/100–125	29.0	38	HAM-D, CGI
Chouinard et al (1999)[34]		Canada	MD; DSM-III-R; HAM-D-21 ≥ 20, HAM-D ≥ 2 on first item	O	12	PR/20–50, FL/20–80	40.9	38	HAM-D, CGI, CAS, STAI
Christiansen and Behnke (1996)[35]		Denmark	DD; NR; HAM-D ≥ 15 on first 17 items	O	8	PR/20–40, AM/50–150	NR	NR	HAM-D, CGI, VAS
Claghorn (1992)[36]	5	UK	MD; DSM-III; HAM-D-21 ≥ 18 on first 21 items, RDS > CAS	O	6	PR/10–50, PL	41.7	48	HAM-D, MADRS, CGI, CAS
Dunbar et al (1993)[37]	5	UK	MD; DSM-III; HAM-D-21 ≥ 18 on first 21 items, RDS > CAS	O	6	PR/10–50, PL	41.0	67	HAM-D, MADRS, CGI, CAS, PGE
Claghorn (1992)[38]	5	US	MD; DSM-III; HAM-D ≥ 18 on first 17 items, RDS > CAS	O	6	PR/10–50, PL	NR	NR	HAM-D, MADRS, CGI, CAS
Claghorn et al (1992)[39]	5	US	MD; DSM-III; HAM-D-21 ≥ 18 on first 17 items, RDS ≥ 8, RDS > CAS	O	6	PR/10–50, PL	35.0	60	HAM-D, MADRS, CGI, RDS, CAS, HSCL, PGE
Kiev (1992)[40]	5	US	MD; DSM-III; HAM-D ≥ 18 on first 17 items, RDS ≥ 8, RDS > CAS	O	6	PR/10–50, PL	37.5	55	HAM-D-21, MADRS, CGI, RDS, SCL, PGE
Rickels et al (1992)[41]	5	US	MD; DSM-III; HAM-D-21 ≥ 18 on first 17 items, RDS > CAS	O	6	PR/10–50, PL	44.8	36	HAM-D-21, MADRS, CGI, RDS, SCL, PGE
Rickels et al (1989)[42]	5	US	MD; DSM-III; HAM-D-21 ≥ 18 on first 17 items, RDS ≥ 8, RDS > CAS	O	6	PR/10–50, PL	44.0	38	HAM-D-21, MADRS, CGI, HSCL

(continued)

Appendix 1 (continued). Study and Participant Characteristics for All Trials (N = 94)

Reference	Same Trial	Country	Primary Diagnosis; Diagnostic Criteria; Severity Criteria	Treatment Setting	Weeks of Treatment	Treatment/Dose, mg	Age, Mean	% Male	Patient Assessment Tools
Smith and Glaudin (1992)[43]	5	US	MD; DSM-III; HAM-D ≥ 18 on first 17 items, RDS ≥ 8, RDS > CAS	NR	6	PR/10–50, PL	44.8	50	HAM-D, MADRS, CGI, HSCL
DUAG (1990)[44]		Denmark	MD; DSM-III; HAM-D-17 ≥ 18	I	6	PR/30, CL/150	NR	32	HAM-D-17, HAM-D subscale, BRMS
De Wilde et al (1993)[45]		Belgium	MD; DSM-III; HAM-D-21 ≥ 18	NR	6	PR/30–40, FL/40–60	44.3	38	HAM-D, MADRS, CGI
Dorman (1992)[46]		UK	DD; DSM-III; HAM-D-17 ≥ 17 on first 17 items	NR	6	PR/15–30, MA/30–60	NR	NR	HAM-D-17, CGI
Dunner et al (1992)[47]		US	MD; DSM-III; NR	O	6	PR/10–40, DO/NR–200	68.0	46	HAM-D, MADRS, CGI, SCL
Edwards and Goldie (1993)[48]		UK	MD; DSM-III; HAM-D-17 ≥ 18	O	6	PR/30, PL	44.2	44	HAM-D, Leeds Scale, EPI
Fava et al (1998)[49]		US	MD; NR; HAM-D ≥ 18 on first 17 items, RDS > 8, RDS > CAS	O	12	PR/20–50, FL/20–80, PL	41.3	49	HAM-D-21, CAS
Fava et al (2002)[50]	6	US	MDD/AMDD; DSM-IV; HAM-D-28 ≥ 16 on first 17 items	O	10–16	PR/20–60, FL/20–60, SE/50–200	42.9	41	HAM-D-17, CGI
Fava et al (2000)[51]	6	US	MD; DSM-IV; HAM-D-28 ≥ 16 on first 17 items	O	10–16	PR/20–60, FL/20–60, SE/50–200	40.9	34	HAM-D, HAM-D anxiety score
Feighner et al (1993)[52]	7	US	MD; DSM-III; HAM-D ≥ 18 on first 17 items, RDS > CAS	O	6	PR/10–50, IM/65–145, PL	39.7	49	HAM-D, MADRS, CGI, CAS, PGE
Feighner (1992)[53]	7	US	MD; DSM-III; HAM-D ≥ 18 on first 17 items, RDS > CAS	O	6	PR/10–40, IM/65–145, PL	40.0	NR	HAM-D, MADRS, CGI, PGE
Claghorn and Feighner (1993)[54]	7	US	MD; DSM-III; HAM-D-21 ≥ 18 on first 17 items, RDS > CAS	O	54	PR/10–50, IM/65–145, PL	41.3	39	HAM-D, CGI
Cohn et al (1990)[55]	7	US	MD; DSM-III; HAM-D ≥ 18 on first 17 items, RDS ≥ 8, RDS > CAS	O	6	PR/10–50, IM/65–275, PL	NR	NR	HAM-D, MADRS, CGI, SCL-56, PGE, RDS, CAS
Cohn and Wilcox (1992)[56]	7	US	MD; DSM-III; HAM-D ≥ 18 on first 17 items	O	6	PR/10–50, IM/65–275, PL	41.8	41	HAM-D, MADRS, CGI, SCL-56, PGE, RDS, CAS
Dunbar et al (1991)[57]	7	US	MD; DSM-III; HAM-D ≥ 18 on first 17 items, RDS > CAS	O	6	PR/10–50, IM/65–275, PL	39.7	49	HAM-D, MADRS, CGI, SCL-56, PGE, CAS
Fabre (1992)[58]	7	US	MD; DSM-III; HAM-D ≥ 18 on first 17 items, RDS ≥ 8, RDS > CAS	O	6	PR/10–50, IM/65–275, PL	35.5	14	HAM-D-21, MADRS, CGI, RDS, SCL-56, PGE
Feighner and Boyer (1989)[59]	7	US	MD; DSM-III; HAM-D ≥ 18, RDS ≥ 8, RDS > CAS	O	6	PR/NR–50, IM/NR–275, PL	NR	NR	HAM-D, MADRS, CGI, RDS, SCL-56, CAS
Feighner and Boyer (1992)[60]	7	US	MD; DSM-III; HAM-D ≥ 18, RDS ≥ 8, RDS > CAS	O	6	PR/10–50, IM/65–275, PL	NR	NR	HAM-D-21, MADRS, CGI, RDS, CAS, SCL-56
Shrivastava et al (1992)[61]	7	US	MD; DSM-III; HAM-D-21 ≥ 18 on first 17 items, RDS ≥ 8, RDS > CAS	O	6	PR/10–50, IM/65–275, PL	34.7	22	HAM-D, MADRS, CGI, SCL-56, PGE, RDS
Peselow et al (1989)[62]	7	US	MD; DSM-III; HAM-D-21 ≥ 18, RDS ≥ 9, RDS > CAS	O	6	PR/20–50, IM/65–275, PL	NR	NR	HAM-D, MADRS, CGI
Peselow et al (1989)[110]	7	US	MD; DSM-III; HAM-D-21 ≥ 18 on first 17 items	O	6	PR/10–50, IM/65–275, PL	44.6	64	HAM-D, MADRS, CGI, RDS, BDI, CGI
Ferguson et al (2003)[63]		US	MD; DSM-IV; HAM-D-17 ≥ 20	NR	8	PR/20–40, RE/8–10, PL	NR	NR	HAM-D, MADRS
Freed et al (1999)[64]		Australia	DD; NR; MADRS ≥ 20	O	9	PR/20, AM/50–100	48.0	35	MADRS, CGI

(continued)

Appendix 1 (continued). Study and Participant Characteristics for All Trials (N = 94)

Reference	Same Trial	Country	Primary Diagnosis; Diagnostic Criteria; Severity Criteria	Treatment Setting	Weeks of Treatment	Treatment/Dose, mg	Age, Mean	% Male	Patient Assessment Tools
Gagiano et al (1989)[65]		S. Africa	MD; NR; HAM-D-21 ≥ 18	O	6	PR/30, AM/75	NR	NR	HAM-D
Gagiano (1993)[66]		S. Africa	MD; DSM-III-R; HAM-D-21 ≥ 18	O	6	PR/20–40, FL/40–60	38.7	20	HAM-D, MADRS, CGI, HAM-A
Geretsegger et al (1994)[67]		Germany	MD; DSM-III-R; HAM-D-21 ≥ 18	I/O	6	PR/20–40, FL/20–60	74.0	14	HAM-D, CGI, MADRS, SECL
Geretsegger et al (1995)[68]		Austria and Germany	MD; DSM-III; HAM-D ≥ 18 on first 17 items	I	6	PR/20–30, AM/50–150	71.2	14	HAM-D, MADRS, CGI
Golden et al (2002)[69]		US and Canada	MDD; DSM-IV; HAM-D-17 ≥ 20	NR	12	PR IR/20–50, PR CR/25–62.5, PL	40.1	40	HAM-D-17
Guillibert et al (1989)[70]		France	MD; DSM-III; HAM-D-21 ≥ 20, Newcastle Scale ≥ 6	NR	6	PR/20–30, CL/25–75	68.7	31	HAM-D, Wang Anxiety Scale, Widlocher Scale, CGI
Hicks et al (2002)[71]		UK	DD; DSM-IV; HAM-D ≥ 18	O	8	PR/20–40, NE/400–600	42.9	43	HAM-D, MADRS, CGI
Hutchinson et al (1991)[72]	8	UK	MD; DSM-III; HAM-D ≥ 18	O	6	PR/20–30, AM/50–100	71.8	25	HAM-D, CGI
Hutchinson et al (1992)[73]	8	UK	MD; DSM-III; HAM-D ≥ 18	O	6	PR/20–30, AM/50–100	71.8	23	HAM-D, CGI
Kiev and Feiger (1997)[74]		US	MD; DSM-III-R; HAM-D-21 ≥ 20, depressed mood item ≥ 2	O	7	PR/20–50, FV/50–150	41.3	47	HAM-D, CGI, HAM-A, SCL-56
Kroenke et al (2001)[75]		US	DD; NR; NR	O	36	PR/20–NR, FL/20–NR, SE/50–NR	46.1	21	SF-36, SCL-20
Kuhs and Rudolf (1989)[76]		Germany	MD; DSM-III; HAM-D-21 ≥ 18	NR	6	PR/30, AM/150	NR	NR	HAM-D, CGI, VAMS, CGI
Laursen et al (1985)[77]		Denmark	DD; ICD-8; HAM-D-17 ≥ 15	I/O	6	PR/30–NR, AM/50–NR	62.5	30	HAM-D
McPartlin et al (1998)[78]		UK	MD; DSM-IV; MADRS ≥ 19	O	12	PR/20, VN/75	44.5	39	HAM-D-17, MADRS, CGI, QOL
Mertens and Pintens (1988)[79]		Belgium	DD; DSM-III; HAM-D-21 ≥ 18	I/O	6	PR/30, MA/60	51.2	30	HAM-D, PGA, SCL-24
Miller et al (1989)[80]		UK	DD; NR; HAM-D-21 ≥ 18	O	4	PR/30, PL	42.3	32	HAM-D-21, CGI , BDI, VAS
Moeller et al (1993)[81]		Germany and Hungary	MD; DSM-III; HAM-D-21 ≥ 18	I	6	PR/30, AM/150	NR	NR	HAM-D, CGI
Moon and Vince (1996)[82]		UK	MD; DSM-III; MADRS ≥ 18	O	6	PR/20–30, LO/140–210	43.7	29	MADRS, CGI
Mulsant et al (2001)[83]	9	US	MD; DSM-IV; HAM-D-17 ≥ 15, MMSE ≥ 15	I/O	12	PR/10–20, NO/25–50	72.1	28	HAM-D
Mulsant et al (1999)[84]	9	US	MD; DSM-IV; HAM-D ≥ 15, MMSE ≥ 18	I/O	6	PR/10–20, NO/25–50	75.1	27	HAM-D
Bump et al (2001)[85]	9	US	MD; NR; NR	I	12	PR/NR, NO/NR	70.5	29	HAM-D
Weber et al (2000)[86]	9	US	MD; DSM-IV Axis I Disorders; HAM-D-17 ≥ 15, MMSE ≥ 18	I	12	PR/NR, NO/NR	74.0	23	HAM-D
Murphy et al (2003)[87]	10	US	MD; DSM-IV; MMSE > 25th percentile for age, HAM-D-17 ≥ 18	O	8	PR/20–40, MI/15–45	72.0	50	HAM-D-17, CGI, GDS
Schatzberg et al (2002)[88]	10	US	MD; DSM-IV; MMSE > 25th percentile for age, HAM-D-17 ≥ 18	O	8	PR/20–40, MI/15–45	72.0	49	HAM-D-17, CGI, MMSE
Nielsen et al (1991)[89]	11	Denmark	MD; DSM-III; HAM-D ≥ 18	I/O	12	PR/30, IM/150	NR	46	HAM-D-17, BRMS, DUAGDS
Skausig et al (1992)[90]	11	Denmark	MD; DSM-III; HAM-D ≥ 18	NR	12	PR/30, IM/150	NR	36	HAM-D-17, BRMS, DUAGDS
Ontiveros and Garcia-Barriga (1997)[91]		Mexico	MD; DSM-III-R; HAM-D-21 ≥ 18	O	6	PR/20, FL/20	40.8	27	HAM-D-21
Pini et al (2003)[92]		Italy	MD/DYS + comorbid anxiety disorder; DSM-III-R; NR	O	17	PR/20–40, MO/300–600	45.8	31	HAM-D-21, CGI, HAM-A

(continued)

Appendix 1 (continued). Study and Participant Characteristics for All Trials (N = 94)

Reference	Same Trial	Country	Primary Diagnosis; Diagnostic Criteria; Severity Criteria	Treatment Setting	Weeks of Treatment	Treatment/Dose, mg	Age, Mean	% Male	Patient Assessment Tools
Poirier and Boyer (1999)[93]		France	MD; DSM-III-R; HAM-D-17 ≥ 18	I/O	4	PR/30–40, VN/200–300	43.3	28	HAM-D-17, CGI
Rapaport et al (2003)[94]		US and Canada	MD; DSM-IV; HAM-D-17 ≥ 18	NR	12	PR IR/10–40, PR CR/ 12.5–50, PL	70.0	44	HAM-D-17, CGI
Ravindran et al (1997)[95]		10 Intl Countries	DD + anxiety; NR; MADRS ≥ 20, CAS ≥ 11	O	12	PR/20–40, CL/75–150	42.6	27	MADRS, CGI, CAS
Sacchetti et al (2002)[96]		Italy	RMD; DSM-III-R; HAM-D-21 ≥ 18, HAM-D depressed mood, suicide, insomnia, and retardation ≥ 1	O	12	PR/20–50, AM/50–250	49.6	35	HAM-D-21, CGI
Schnyder and Koller-Leiser (1996)[97]		Switzerland	MD; DSM-III-R; HAM-D-21 ≥ 18	I/O	6	PR/20–40, MP/50–150	44.6	35	HAM-D-21, MADRS, CGI
Schoene and Ludwig (1993)[98]		Austria and Germany	MD; DSM-III-R; HAM-D-21 ≥ 18 on first 21 items	O	6	PR/20–40, FL/20–60	74.0	14	HAM-D, MADRS, CGI, SCAG, MMSE, SCL-23
Staner et al (1995)[99]		Belgium	MD; RDC; HAM-D-21 ≥ 18	I	5	PR/20–30, AM/100–150	42.1	18	HAM-D
Stuppaeck et al (1994)[100]		Austria and Germany	MD; DSM-III; HAM-D-21 ≥ 18	I	6	PR/20–50, AM/50–250	47.1	30	HAM-D, MADRS, CGI
Szegedi et al (1997)[101]	12	Germany	DD; RDC; HAM-D-17 ≥ 13	O	6	PR/20–40, MP/100–150	44.4	NR	HAM-D, MADRS, CGI, HAM-A, BRMS, RDS, CAS
Szegedi et al (1997)[102]	12	Germany	DD; NR; RDC-8 ≥ 5	O	6	PR/20–40, MP/100–150	NR	28	HAM-D, MADRS, CGI, HAM-A, BRMS, RDS, CAS
Benkert et al (1997)[103]	12	Germany	DD; RDC-8; HAM-D-17 ≥ 13	O	6	PR/20–40, MP/100–150	44.4	28	HAM-D, MADRS, CGI, HAM-A, BRMS, RDS, CAS
Tignol (1993)[104]		France	MD; DSM-III-R; MADRS ≥ 24	I	6	PR/20, FL/20	43.8	27	MADRS-10, CGI, HAM-A-14, VAS
Wade et al (2003)[105]		Scotland	RMD; DSM-IV; HAM-D-17 ≥ 18	O	24	PR/20–30, MI/30–45	40.0	27	HAM-D-17, CGI, PGE
Waintraub et al (2002)[106]		France	MD; DSM-IV; MADRS ≥ 20, HAM-D ≥ 18, MADRS item 10 ≥ 2, HAM-D item 3 ≥ 1	O	12	PR/20–40, TI/12.5–25	41.0	35	HAM-D, MADRS, CGI
Weihs et al (2000)[107]		US	MD; DSM-IV; HAM-D-21 ≥ 18	O	6	PR/10–40, BU/100–300	70.1	43	HAM-D, CGI, HAM-A
Williams et al (2000)[108]	13	US	DYS/minor DD; DSM-III-R; HAM-D-17 ≥ 10	O	11	PR/10–40, PL	71.0	58	HAM-D, HSCL-D-20, SF-36
Schmaling et al (2002)[109]	13	US	DYS/minor DD; DSM-III-R; HAM-D-17 ≥ 10	O	11–25	PR/NR, PL	NR	NR	HSCL-D-20, HAM-D-17, SF-36, RSQ

Abbreviations: AI = amisulpride, AM = amitriptyline, AMDD = atypical major depressive disorder, BDI = Beck Depression Inventory, BRMS = Bech-Rafaelson Melancholia Scale, BU = bupropion, CAS = Covi Anxiety Scale, CGI = Clinical Global Impressions scale, CL = clomipramine, CS = Cornell Scale for Depression, DD = depressive disorder, DO = doxepin, DSM = Diagnostic and Statistical Manual of Mental Disorders, DUAG = Danish University Antidepressant Group, DUAGDS = Danish University Antidepressant Group Depression Scale, DYS = dysthymia, EPI = Eysenck Personality Inventory, FL = fluoxetine, FV = fluvoxamine, GDS = Geriatric Depression Scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, HSCL = Hopkins Symptom Checklist, HSCL-D = Hopkins Symptom Checklist Depression Scale, I = inpatient, ICD = International Classification of Diseases, IM = imipramine, Intl = international, LO = lofepramine, MA = mianserin, MADRS = Montgomery-Asberg Depression Rating Scale, MD = major depression, MDD = major depressive disorder, MI = mirtazapine, MMSE = Mini-Mental State Examination, MO = moclobemide, MP = maprotiline, NE = nefazodone, NO = nortriptyline, NR = not reported, O = outpatient, PGA = Patient Global Assessment scale, PGE = Patient Global Experience, PL = placebo, PR = paroxetine immediate-release, PR CR = paroxetine controlled release, PR IR = paroxetine immediate-release, QOL = quality of life, RDC = Research Diagnostic Criteria, RDS = Raskin Depression Scale, RE = reboxetine, RMD = recurrent major depression, RSQ = Reponse Style Questionnaire, SCAG = Sandoz Clinical Assessment Geriatric scale, SCL = Symptom Checklist, SE = sertraline, SECL = side-effect checklist, SF-36 = 36-item Medical Outcomes Study Short-Form Health Survey, STAI = State-Trait Anxiety Inventory, TI = tianeptine, VAMS = Visual Analogue Mood Scale, VAS = visual analogue scale, VN = venlafaxine.