Mirtazapine Versus Other Antidepressants in the Acute-Phase Treatment of Adults With Major Depression: Systematic Review and Meta-Analysis

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Objective: To conduct a comprehensive, systematic review and meta-analysis of the efficacy and tolerability of mirtazapine over other antidepressants in the acute-phase treatment of major depression.

Data Sources: Studies were initially identified through electronic searches of the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register up to June 2006. The following search terms were used: *depress**, *dysthymi**, *adjustment disorder**, *mood disorder**, *affective disorder*, *affective symptoms*, and *mirtazapine*. No language restriction was imposed. The reference lists of the included studies, previous relevant systematic reviews, and trial registers were also hand searched. Pharmaceutical companies and experts in the field were contacted for more studies.

Study Selection: Twenty-five randomized controlled trials were included.

Data Extraction: Two independent assessors examined the quality of the trials and extracted data on an intention-to-treat basis.

Data Synthesis: The primary outcome measure was the relative risk (RR) of response (99% CIs) at the conclusion of acute-phase treatment. In relation to the early phase of treatment (at 2 weeks), there were no statistically significant differences between mirtazapine and the tricyclics in terms of the response (RR = 0.90, 99% CI = 0.69 to 1.18, p = .30 [8 trials contributed to this outcome]) or remission (RR = 0.87, 99% CI = 0.52 to 1.47, p = .50 [8 trials]) outcomes, but mirtazapine was superior to the selective serotonin reuptake inhibitors (SSRIs) in terms of both the response (RR = 1.36, 99% CI = 1.13 to 1.64, p < .0001 [12 trials]) and remission (RR = 1.68, 99% CI = 1.20 to 2.36, p < .0001 [12 trials]). In the subgroup analyses, mirtazapine significantly produced more response than paroxetine (RR = 2.02, 99% CI = 1.09 to 3.75, p = .003 [3 trials]) and venlafaxine (RR = 1.77, 99% CI = 1.08 to 2.89, p = .003 [2 trials]). At the end of acute-phase treatment (6–12 weeks, all trials), no significant differences were observed in the efficacy outcomes. No significant differences were observed between mirtazapine and the other antidepressants in terms of either the total number of dropouts due to any reason (21 trials) or the total number of dropouts due to the development of side effect (23 trials) during the trials.

Conclusions: Although mirtazapine is likely to have a faster onset of action than SSRIs, no significant differences were observed at the end of 6 to 12 weeks' treatment. Clinicians should focus on other practically relevant considerations to tailor treatment to best fit the needs of individual patients.

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Mirtazapine is an antidepressant drug with a unique pharmacologic profile: (1) it exerts potent antagonism of central α_2-adrenergic autoreceptors and heteroreceptors, which enhances both norepinephrine and serotonin release, and (2) it exhibits antagonism to both 5-HT_2 and 5-HT_3 receptors, which results in a net increase in 5-HT_1–mediated neurotransmission.[1,2]

The efficacy of mirtazapine in comparison with that of other antidepressants has been investigated in several meta-analyses.[3–7] However, these analyses are already considered to be outdated[3,4] and/or do not report on the outcome related to remission,[3,5,7] even though remission has been shown to be the best predictor of the long-term prognosis.[8]

A group of researchers agreed to join forces under the rubric "Multiple Meta-Analyses of New Generation Antidepressants Study" to systematically review all available evidence for each specific newer antidepressant. To date, we have completed an individual review of fluoxetine.[9] The aim of the present study was to assess the evidence for the efficacy and tolerability of mirtazapine compared with other types of antidepressants prescribed for acute-phase treatment of major depression.

METHOD

Study Inclusion Criteria

All existing randomized controlled trials (RCTs) of mirtazapine for acute-phase treatment of depression were considered. Patients aged 18 years or older who were diagnosed with unipolar major depression based on explicit clinical or research criteria, such as DSM-IV,[10] were identified. We excluded trials including patients with depression with psychotic features and those in which more than 20% of the participants had bipolar depression. A concurrent primary diagnosis of other Axis I or Axis II disorders and the presence of a serious concomitant medical illness were also used as exclusion criteria. No language restriction was imposed.

The control conditions included other antidepressant agents, such as tricyclic antidepressants (TCAs) or heterocyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), a serotonin-norepinephrine reuptake inhibitor (SNRI), monoamine oxidase inhibitors or newer agents, and nonconventional (herbal products, i.e., Hypericum) antidepressant agents. Neither mirtazapine nor these control medications were to be used as an augmentation strategy.

Two independent reviewers checked the eligibility of each study for inclusion in the meta-analysis and also individually assessed the quality of the eligible trials according to the criteria of the Cochrane Collaboration Handbook, which pays particular attention to the adequacy of the random allocation concealment and double blinding.[11] Any disagreements were resolved through discussion.

Data Sources

RCTs were initially identified on June 2, 2006, by conducting a search of the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register (CCDANCTR), which maintains updated searches of the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE, EMBASE, CINAHL, PsycINFO, PSYINDEX, and LILACS, and by hand searches of major psychiatric journals, medical journals, and conference proceedings. Studies are continuously coded in the CCDANCTR based on their research characteristics, e.g., in terms of the kind of interventions used and the concomitant use of interventions, by manual examination of entire articles. The studies already coded are being stored in CCDANCTR-Studies and the others, in CCDANCTR-References. For the purpose of meta-analysis, CCDANCTR-Studies was searched by using the following strategy: in the diagnosis field, the terms *depress**, *dysthymi**, *adjustment disorder**, *mood disorder**, *affective disorder*, and *affective symptoms* were entered; in the intervention field, the term *mirtazapine* was entered. CCDANCTR-References was searched by using the following strategy: in the keyword field, the terms *depress**, *dysthymi**, *adjustment disorder**, *mood disorder**, *affective disorder,* and *affective symptoms* were entered; in the free-text field, the term *mirtazapine* was entered.

Trial databases (e.g., the Medicines and Healthcare products Regulatory Agency in the United Kingdom) and ongoing trial registers (e.g., clinicaltrials.gov in the United States) in the United States, United Kingdom, Netherlands, European Union, Japan, and Australia were also hand searched for published, unpublished, and ongoing RCTs.

Pharmaceutical companies and experts in the field were asked about whether they knew of any study that might meet our inclusion criteria. The literature reference lists of the included trials and of previous systematic reviews were checked for published reports and for citations of unpublished research.

Outcome Measures

We decided, a priori, to subdivide the treatment outcome indices into those in the early phase (at 2 weeks after treatment commencement), after the conclusion of acute-phase treatment (between 6 and 12 weeks), and after the conclusion of continuation treatment (between 4 and 6 months). The primary outcome in our systematic review was defined as a response at the conclusion of acute-phase treatment, represented by a reduction of at least 50% in score on the Hamilton Rating Scale for Depression (HAM-D)[12] or Montgomery-Asberg Depression Rating Scale.[13] We did not employ the original authors' definitions of the primary outcomes per se because investigators or journal editors might selectively withhold some of the measured outcomes because of the poor strength of the result (outcome reporting bias).[14]

We used remission as the secondary outcome, represented by a score of 7 or less on the 17-item HAM-D[14] and of 8 or less on all the other longer versions of HAM-D.

Regarding the acceptability and tolerability of a drug, the total "drop-out rate due to any reason" and total "drop-out rate due to the development of side effect" during the trials were also examined.

Data Extraction

Two reviewers independently extracted the data. Any disagreement was resolved by discussion.

Statistical Analysis

The extracted data were analyzed by using the RevMan 4.2 software,[15] with double data entry to avoid input errors. The relative risks (RRs) were calculated by using a random effects model that was found to have high generalizability in our empirical examination of the summary effect measures for meta-analyses.[16] When dichotomous outcomes were not reported but a baseline mean and a follow-up point mean plus a standard deviation (SD) of scores on a depression severity scale were provided, we imputed the number of patients with response and remission by using a validated statistical method, for example, according to the following formula for the response outcome[17]:

> number of responders at endpoint = number of participants at endpoint × normal standard distribution corresponding to (50% of the baseline score – endpoint score)/SD.

When the SD was not reported, we imputed its value by pooling the SDs reported in the other included trials.[18] When data were reported by the last-observation-carried-forward (LOCF) method, the LOCF data were used for the analysis. In other cases, we applied the intention-to-treat analyses for all outcomes, whereby all dropouts not included in the original analyses in the RCTs were included as nonresponders or nonremitters. If a statistically significant difference was found, the number needed to treat (NNT) was calculated.

Heterogeneity between trials was investigated by the I^2 statistic[19] and the χ^2 test. If significant heterogeneity was identified, potential sources were investigated.

Funnel plot analysis and the Egger regression method[20] were used for detecting publication bias, which occurs when authors of the original trials are more likely to submit, or editors to accept, positive rather than null (negative or inconclusive) results.

It has been reported that subgroup analyses should be performed and interpreted with caution because multiple analyses might lead to false-positive conclusions.[21] We planned, a priori, to perform subgroup analyses for individual comparator drugs and also for the treatment settings (e.g., psychiatric inpatients or outpatients in primary care) because the treatment setting is thought to reflect the severity of depression.

Sensitivity analyses were also planned a priori, excluding trials for which the response rates had to be calculated based on the above imputation method and excluding trials funded by or with at least 1 author affiliated to a pharmaceutical company marketing mirtazapine.

With regard to the response and remission outcomes, a p value < .01 was chosen to test the null hypothesis, and the 99% confidence interval (CI) was calculated to highlight statistically significant differences with a high degree of confidence. We set the level of significance at .01 because multiple comparisons were to be conducted, and we reasoned that only robust differences between treatments should inform clinical practice.[9] In other words, we accorded priority to avoiding type I over type II errors with regard to the efficacy outcomes. By contrast, we set the α level at .05 and calculated the 95% CI for the outcomes of total number of dropouts and number of dropouts due to the development of side effect during the trials because it was considered that a type II error should be avoided in the evaluation of the tolerability outcomes.

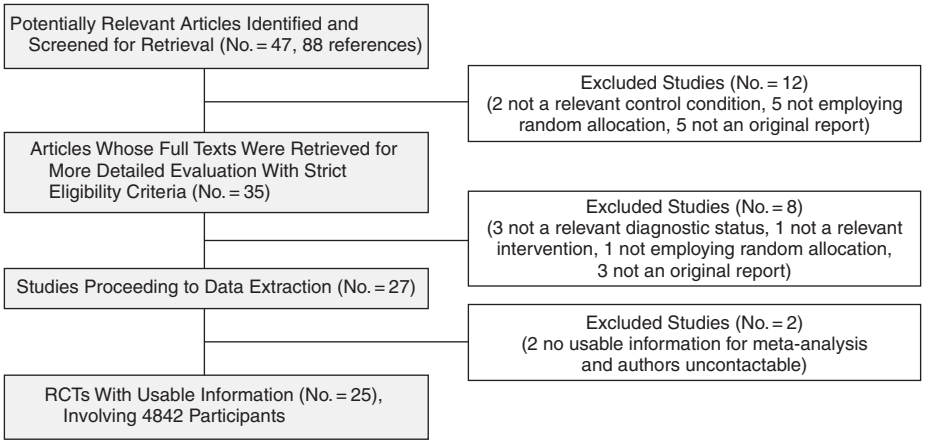
In the assessment of the clinical significance of the efficacy outcome, we considered a difference in the RR of at least 0.1 to be clinically significant.[9] Adopting this cut-off value, we classified estimates into the following 5 groups: Group A—mirtazapine is clinically better than the comparator drug (both the RR and the lower limit of the 99% CI are over 1.10), Group B—mirtazapine is certainly clinically not worse and probably better than the comparator drug (RR > 1.1 and the lower limit of the 99% CI is in the range of 0.90 to 1.10), Group C—uncertain whether there is a clinically significant difference between mirtazapine and the comparator drug (RR > 1 and the lower limit of the 99% CI < 0.90, or RR < 1 and the upper limit of the 99% CI > 1.10), Group D—mirtazapine is certainly clinically not better and probably worse than the comparator drug (RR < 0.9 and the upper limit of the 99% CI is in the range of 0.90 to 1.10), and Group E—mirtazapine is clinically worse than the comparator drug (both RR and 99% CI < 0.90).

RESULTS

Description of Studies

Our initial search strategy yielded 47 trials including 88 references (Figure 1). After examining their titles and abstracts, we chose 35 trials, and their full texts were obtained. Through a reference search and contact with experts in the area and the manufacturer of mirtazapine (Organon), we also obtained information on unpublished data not available in the published literature,[22,23] and unpublished data from the manufacturer (Organon: trial 85146 on file). Twenty-seven trials were finally identified as satisfying our inclusion criteria. However, we were not able to obtain any additional data in regard to 2 trials[24,25] that lacked adequate information for meta-analysis because we were not able to contact the authors. We therefore included 25 trials with a total enrollment of 4842 patients in our final analyses.

Figure 1. Trial Flowchart for the Included Studies



Abbreviation: RCT = randomized controlled trial.

In 9 trials, a TCA (amitriptyline in 6, clomipramine in 1, doxepin in 1, and nortriptyline in 1) was used as the comparator drug; in 12, an SSRI (citalopram in 1, fluoxetine in 5, fluvoxamine in 1, paroxetine in 3, and sertraline in 2) was used; in 2, an SNRI (venlafaxine) was used; and in 2, another antidepressant (trazodone) was used (Table 1). No trials using any other SNRIs as the comparator, such as duloxetine or milnacipran, were identified. The patients were followed up for 6 weeks (range: 5–24 weeks) in a majority of the trials (15 trials), in all but 1 of which the patients were diagnosed with depression based on the DSM. A large majority of the trials (23 trials) were sponsored by or had at least 1 author affiliated with a pharmaceutical company. Elderly subjects (> 65 years of age) were included in 16 trials. Only psychiatric inpatients were enrolled in 5 trials, focus was placed on patients in primary care in 1 study, and both psychiatric inpatients and outpatients were included in the other trials. Two trials[23,26] focused on refractory or treatment-resistant depression. Outcomes in terms of the response and remission were obtained in 11 trials without using the imputation method. In regard to the tolerability outcomes, 21 trials provided the number of "dropouts due to any reason," and 21 trials reported the number of "dropouts due to the development of side effect" during the trials; these trials did not always overlap. None of the trials reported whether the allocation concealment was adequately performed. All trials but 1[26] were undertaken on a double-blind basis, and the one exception employed blind evaluators for the assessment of the depression severity.

Efficacy (response and remission rates)

At early phase of treatment (at 2 weeks). At 2 weeks, a response had been achieved in 616 (26.6%) of the 2316 patients treated with mirtazapine, and a remission had been achieved in 222 (9.6%) of the 2316 patients.

In comparison with TCAs, mirtazapine showed no superiority or inferiority in terms of either the response (RR = 0.90, 99% CI = 0.69 to 1.18, p = .30) or the remission outcomes (RR = 0.87, 99% CI = 0.52 to 1.47, p = .50) (Table 2). The same results were obtained in the subgroup analyses conducted to compare mirtazapine with the individual TCAs.

When compared to SSRIs, mirtazapine demonstrated statistically significant superiority, in terms of both the response (RR = 1.36, 99% CI = 1.13 to 1.64, p < .0001, NNT = 11) (Figure 2) and the remission outcomes (RR = 1.68, 99% CI = 1.20 to 2.36, p < .0001, NNT = 25) (Table 2). Among the individual SSRIs, mirtazapine was found to be significantly superior to paroxetine (RR = 2.02, 99% CI = 1.09 to 3.75, p = .003, NNT = 8) in terms of the response outcome, but not the remission outcome. Mirtazapine was not superior to sertraline in terms of the response outcome but was found superior in terms of the remission outcome (RR = 1.73, 99% CI = 1.01 to 2.98, p = .009, NNT = 12).

Mirtazapine was significantly superior to the SNRI in terms of the response outcome (RR = 1.77, 99% CI = 1.08 to 2.89, p = .003, NNT = 6) but not the remission outcome (RR = 2.21, 99% CI = 0.93 to 5.26, p = .02). No significant difference, in terms of either the response or remission outcome, was observed between mirtazapine and trazodone (response: RR = 1.11, 99% CI = 0.60 to 2.04, p = .66; remission: RR = 1.00, 99% CI = 0.29 to 3.40, p = 1.00).

Among the subgroups classified by the treatment setting, we found no statistically significant differences, except for a significant difference in the response outcome in 1 trial[49] between mirtazapine and paroxetine in the

Table 1. Characteristics of the Included Studies in the Meta-Analysis

Randomized Controlled Trial[a]	Comparator	Follow-Up (wk)	Inpatient/ Outpatient Setting	Diagnostic Criteria	Mirtazapine, N	Comparator, N	Baseline Score, Mean (SD)			Dose (mg)		Funded By	Needs Imputing	
							Outcome Measure	Mirtazapine	Comparator	Mirtazapine	Comparator		Remission/ Response Rate	SDs for Continuous Data
Hoyberg et al (1996)[34]	Amitriptyline	6	In and out	DSM-III	56	59	HAM-D-21	26.7 (4.8)	25.7 (4.9)	15–45	30–90	Industry	Yes	Yes
Mullin et al (1996)[35]	Amitriptyline	5	In and out	DSM-III	79	77	HAM-D-17	22.5 (3.9)	22.6 (4.0)	20–60	75–225	Industry	Yes	No
Organon 85146	Amitriptyline	6	In	DSM-III	103	104	HAM-D-17	27.3 (4.5)	26.2 (4.7)	20–60	75–225	Industry	No	No
Bremner (1995)[36]	Amitriptyline	6	Out	DSM-III	50	50	HAM-D-17	28.3 (NS)	27.3 (NS)	5–35	40–280	Industry	Yes	Yes
Smith et al (1990)[37]	Amitriptyline	6	Out	DSM-III	50	50	HAM-D-17	23.4 (NS)	23.7 (NS)	35[b]	280[b]	Industry	Yes	Yes
Zivkov and De Jongh (1995)[38]	Amitriptyline	6	In	DSM-III	125	126	HAM-D-21	28.0 (4.9)	27.6 (4.8)	20–60	75–225	Industry	Yes	No
Richou et al (1995)[39]	Clomipramine	6	In	RDC	87	87	HAM-D-21	27.7 (5.7)	26.7 (5.4)	20–80	50–200	Industry	Yes	Yes
Marttila et al (1995)[40]	Doxepin	6	In and out	RDC	83	80	HAM-D-17	22.0 (3.9)	22.4 (3.8)	20–65	75–300	Industry	Yes	Yes
Fava et al (2006)[26]	Nortriptyline	14	Out	DSM-IV	114	121	HAM-D-17	19.8 (7.0)	18.6 (5.9)	15–60	25–150	NIMH	No	Yes
Leinonen et al (1999)[41]	Citalopram	8	In and out	DSM-IV	137	133	MADRS	29.6 (4.9)	29.1 (4.5)	15–60	20–60	Industry	Yes	Yes
Amini et al (2005)[42]	Fluoxetine	6	In and out	DSM-IV	18	18	HAM-D-17	25.8 (4.0)	24.8 (3.6)	30 (fixed)	20 (fixed)	Unclear	No	Yes
Hong et al (2003)[43]	Fluoxetine	6	Out	DSM-IV	66	66	HAM-D-17	23.1 (5.1)	24.3 (5.2)	15–45	20–40	Industry	No	Yes
Versiani et al (2005)[44]	Fluoxetine	8	In and out	DSM-IV	147	152	HAM-D-17	NS	NS	30–60	20–40	Industry	No	Yes
Wheatley et al (1998)[45]	Fluoxetine	6	In and out	DSM-III-R	66	67	HAM-D-17	26.0 (4.4)	26.1 (4.3)	15–60	20–40	Industry	Yes	Yes
Winokur et al (2003)[46]	Fluoxetine	8	Unclear	DSM-IV	9	13	HAM-D-21	25.6 (7.6)	26.7 (5.3)	45 (fixed)	40 (fixed)	Industry	Yes	No
Schoemaker et al (2002)[22]	Fluvoxamine	6	Out	DSM-IV	205	207	HAM-D-17	23.8 (4.0)	24.0 (3.6)	15–45	50–150	Industry	Yes	Yes
Benkert et al (2000)[47]	Paroxetine	6	Out	DSM-IV	139	136	HAM-D-17	22.4 (3.3)	22.4 (3.2)	15–45	20–40	Industry	No	Yes
Schatzberg et al (2002)[48]	Paroxetine	8	Out	DSM-IV	128	126	HAM-D-17	22.2 (3.5)	22.4 (3.5)	30–45	30–40	Industry	No	Yes

(continued)

Table 1. (continued) Characteristics of the Included Studies In the Meta-Analysis

Randomized Controlled Trial[a]	Comparator	Follow-Up (wk)	Inpatient/ Outpatient Setting	Diagnostic Criteria	Mirtazapine, N	Comparator, N	Baseline Score, Mean (SD)			Dose (mg)		Funded By	Needs Imputing	
							Outcome Measure	Mirtazapine	Comparator	Mirtazapine	Comparator		Remission/ Response Rate	SDs for Continuous Data
Wade et al (2003)[49]	Paroxetine	24	Out (GP)	DSM-IV	99	98	HAM-D-17	23.8 (3.76)	24.4 (3.51)	30–45	20–30	Industry	No	Yes
Behnke et al (2003)[50]	Sertraline	8	Unclear	DSM-IV	176	170	HAM-D-17	NS	NS	30–45	50–150	Industry	No	Yes
Thase et al (2000)[23]	Sertraline	8	Out	DSM-IV	124	126	HAM-D-17	21.6 (3.2)	22.0 (3.1)	15–45	50–200	Industry	No	Yes
Guelfi et al (2001)[51]	Venlafaxine	8	In	DSM-IV	78	79	HAM-D-17	29.5 (3.0)	29.2 (2.9)	45–60	75–375	Industry	No	Yes
Benkert et al (2006)[52]	Venlafaxine	6	Out	DSM-IV	130	128	HAM-D-17	24.6 (2.8)	24.9 (2.9)	45 (fixed)	225 (fixed)	Industry	Yes	Yes
van Moffaert et al (1995)[53]	Trazodone	6	In	DSM-III	100	100	HAM-D-17	29.2 (4.9)	27.5 (5.1)	24–72	150–450	Industry	Yes	Yes
Halikas et al (1995)[54]	Trazodone	6	Out	DSM-III	50	50	HAM-D-21	24.6 (NS)	24.6 (NS)	5–35	40–280	Industry	Yes	Yes

[a]Only 1 main article for each of the studies is cited.
[b]The Smith et al[37] trial did not specify the minimum dose.
Abbreviations: GP = general practitioner, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, HAM-D-21 = 21-item Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, NIMH = National Institute of Mental Health, NS = not specified, RDC = Research Diagnostic Criteria.

primary care setting (N = 197, RR = 3.63, 99% CI = 1.17 to 11.22, p = .003, NNT = 6).

For the sensitivity analyses, we limited the trials to those that did not employ the imputation method for the analysis of response or remission and found that, overall, mirtazapine was superior to SSRIs in terms of the response (N = 1789, RR = 1.39, 99% CI = 1.06 to 1.82, p = .002, NNT = 11) and the remission outcomes (N = 1789, RR = 1.78, 99% CI = 1.20 to 2.64, p = .0002, NNT = 17); mirtazapine was significantly better than paroxetine in terms of the response outcome (N = 726, RR = 2.02, 99% CI = 1.09 to 3.75, p = .003, NNT = 8) and better than sertraline in terms of the remission outcome (N = 596, RR = 1.73, 99% CI = 1.01 to 2.98, p = .009, NNT = 13), but other comparisons revealed no significant differences.

Neither significant heterogeneity nor publication bias (Egger regression statistics: p = .84 for all trials; p = .23 for trials comparing mirtazapine with SSRIs only) was encountered in any of the comparisons.

At the end of the acute-phase treatment (most commonly at 6 weeks). At the end of acute-phase treatment, a response had been achieved in 1413 (61.0%) of the 2316 patients treated with mirtazapine, and a remission had been achieved in 847 (36.6%) of the 2316 patients.

Our primary analysis (Table 2) showed no statistically significant differences. In the analysis of subgroups classified by the types of compounds used, mirtazapine was not found to be superior to any other types of antidepressants, except for its superior remission outcome in comparison with paroxetine (RR = 1.34, 99% CI = 1.04 to 1.73, p = .003, NNT = 10).

No significant heterogeneity was observed. However, publication bias was identified in all of the included trials (p = .01) as well as in the trials comparing mirtazapine with SSRIs (p = .0003) (Figure 3).

At the end of the continuation phase treatment (at 24 weeks). Only 1 study[49] comparing mirtazapine with paroxetine contributed to the outcome. A response had been achieved in 59 (59.6%) of the 99 patients treated with mirtazapine, and a remission had been achieved in 35 (35.4%) of the 99 patients.

No statistically significant differences were observed between mirtazapine and paroxetine as the comparator (Table 2).

Tolerability

Overall, 512 (25.2%) of the 2030 patients treated with mirtazapine withdrew from treatment at some time point during the treatment course. There were no statistically significant differences between the patients treated with mirtazapine and the patients treated with TCAs (RR = 0.87, 95% CI = 0.70 to 1.08, p = .20), SSRIs (RR = 1.07, 95% CI = 0.92 to 1.26, p = .38), SNRI (venlafaxine) (RR = 0.82, 95% CI = 0.58 to 1.16, p = .25), or another antidepressant (trazodone) (RR = 0.93, 95% CI = 0.58 to

Table 2. Summary of Efficacy Data of Mirtazapine

Comparator Agent	No. of RCTs	Participants, N	Response		Remission	
			RR[a]	99% CI	RR[a]	99% CI
At early phase of treatment (at 2 weeks)						
TCAs	8	1294	0.90	0.69 to 1.18	0.87	0.52 to 1.47
Amitriptyline	5	722	0.83	0.58 to 1.19	0.70	0.32 to 1.54
Clomipramine	1	174	0.92	0.49 to 1.73	0.90	0.29 to 2.75
Doxepin	1	163	1.07	0.62 to 1.86	1.23	0.47 to 3.19
Nortriptyline	1	235	0.85	0.16 to 4.62	0.71	0.07 to 7.25
SSRIs	12	2626	1.36*	1.13 to 1.64	1.68*	1.20 to 2.36
Citalopram	1	270	1.85	0.75 to 4.59	2.43	0.29 to 20.47
Fluoxetine	5	622	1.18	0.80 to 1.74	1.53	0.66 to 3.58
Paroxetine	3	726	2.02*	1.09 to 3.75	2.16	0.78 to 5.95
Sertraline	2	596	1.26	0.96 to 1.64	1.73*	1.01 to 2.98
Fluvoxamine	1	412	1.26	0.84 to 1.90	1.40	0.66 to 2.98
SNRI						
Venlafaxine	2	415	1.77*	1.08 to 2.89	2.21	0.93 to 5.26
Other antidepressant						
Trazodone	2	300	1.11	0.60 to 2.04	1.00	0.29 to 3.40
At the end of acute-phase treatment (most commonly at 6 weeks)						
TCAs	9	1501	0.96	0.85 to 1.07	0.90	0.73 to 1.11
Amitriptyline	6	929	0.96	0.82 to 1.12	0.90	0.69 to 1.19
Clomipramine	1	174	0.97	0.74 to 1.26	0.84	0.48 to 1.47
Doxepin	1	163	0.95	0.71 to 1.26	0.96	0.61 to 1.53
Nortriptyline	1	235	0.94	0.59 to 1.49	0.88	0.47 to 1.64
SSRIs	12	2626	1.06	0.97 to 1.16	1.09	0.95 to 1.26
Citalopram	1	270	0.96	0.85 to 1.09	0.97	0.77 to 1.22
Fluoxetine	5	622	1.23	0.96 to 1.59	1.07	0.80 to 1.44
Paroxetine	3	726	1.13	0.93 to 1.38	1.34*	1.04 to 1.73
Sertraline	2	596	0.99	0.84 to 1.17	1.10	0.80 to 1.53
Fluvoxamine	1	412	1.05	0.86 to 1.28	0.91	0.69 to 1.20
SNRI						
Venlafaxine	2	415	1.24	0.96 to 1.60	1.38	0.88 to 2.18
Other antidepressant						
Trazodone	2	300	1.11	0.60 to 2.04	1.31	0.68 to 2.50
At the end of continuation treatment (at 24 weeks)						
SSRI						
Paroxetine	1	197	1.24	0.88 to 1.75	1.57	0.87 to 2.86

[a]Relative risk (RR) greater than 1 indicates an advantage to mirtazapine.
*p Value < .01.
Abbreviations: RCT = randomized controlled trial, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

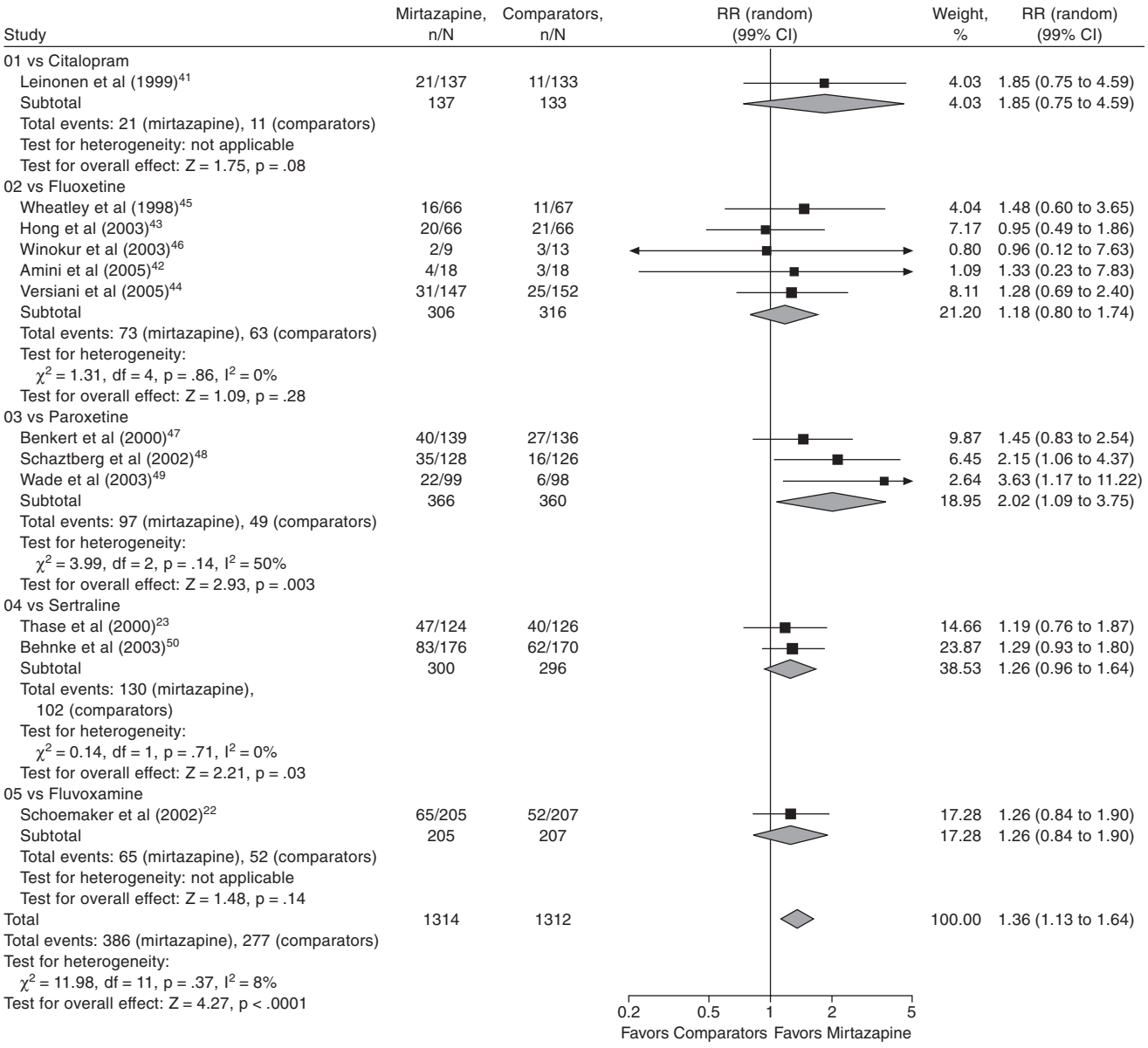
1.50, p = .76) (Table 3). The subgroup analyses for individual compounds showed that the patients treated with mirtazapine were more likely to withdraw due to any reason than were the patients treated with sertraline (RR = 1.33, 95% CI = 1.01 to 1.75, p = .04, number needed to harm [NNH] = 14), but no differences were found in any other comparisons.

Concerning side effects, 224 (10.4%) of the 2146 patients treated with mirtazapine withdrew due to the development of side effect during the trials. Tolerance of mirtazapine was similar to that of other classes of antidepressants, including the SSRIs (RR = 1.22, 95% CI = 0.87 to 1.73, p = .25), SNRI (RR = 0.59, 95% CI = 0.27 to 1.29, p = .19), and another antidepressant (trazodone) (RR = 0.66, 95% CI = 0.30 to 1.46, p = .31), while the tolerability of mirtazapine was marginally superior to that of the TCAs (RR = 0.68, 95% CI = 0.45 to 1.03, p = .07) (Table 3). In the subgroup analyses of the difference between mirtazapine and individual antidepressants, the tolerability of mirtazapine was found to be significantly lower than that of sertraline (RR = 2.58, 95% CI = 1.28 to 5.24, p = .008, NNH = 11), while the drug was marginally better tolerated than amitriptyline (RR = 0.63, 95% CI = 0.39 to 1.03, p = .07).

Clinically Significant Differences in Efficacy

Assuming that a difference in the RR of more than 0.1 is a reasonable estimate of a clinically important difference in efficacy, mirtazapine was certainly clinically not worse and probably better than paroxetine, sertraline, and venlafaxine and was uncertain to be clinically significantly better or worse than other compounds in terms of the efficacy at 2 weeks during the treatment phase (Table 4). In regard to the outcomes after acute-phase treatment, mirtazapine was certainly clinically not worse and probably better than fluoxetine, paroxetine, and venlafaxine;

Figure 2. Response With Mirtazapine in Comparison With SSRIs at 2 Weeks



Abbreviations: RR = relative risk, SSRI = selective serotonin reuptake inhibitor.

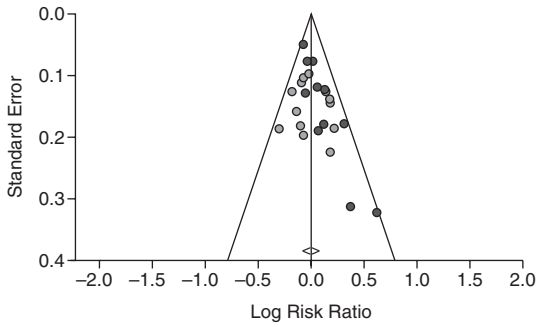
its inferiority or superiority to other compounds was uncertain.

DISCUSSION

This is the first systematic review and meta-analysis using a comprehensive search and a novel methodology that examined the efficacy of mirtazapine in terms of both response and remission for the treatment of depression. The results of this study showed, in a systematic way, the comparable tolerability of mirtazapine to that of other antidepressants.

We concluded from the results that mirtazapine is likely to have a faster onset of therapeutic action than either SSRIs or SNRIs, especially paroxetine and venlafaxine, but that the difference decreases and no longer exists by approximately 6 weeks. These results were confirmed even after an additional sensitivity analysis was conducted after excluding the 2 trials[23,26] that focused on treatment-resistant depression (data available upon request). Although the faster onset of therapeutic action of mirtazapine in comparison with that of the SSRIs has been reported previously from a non–head-to-head review of the results from 3 RCTs,[6] our systematic review

Figure 3. Funnel Plot of Response at the End of Acute-Phase Treatment (most commonly at 6 weeks)[a,b]



[a]Black circles indicate studies comparing mirtazapine with selective serotonin reuptake inhibitors (SSRIs).
[b]Gray circles indicate studies comparing mirtazapine with antidepressants other than SSRIs.

Table 3. Summary of Tolerability Data of Mirtazapine

Comparator Agent	No. of RCTs	Participants, N	RR[a]	95% CI
Withdrawal due to any reason				
TCAs	7	1166	0.87	0.70 to 1.08
Amitriptyline	5	829	0.92	0.71 to 1.19
Clomipramine	1	174	0.86	0.54 to 1.35
Doxepin	1	163	0.57	0.28 to 1.16
SSRIs	11	2327	1.07	0.92 to 0.26
Citalopram	1	270	2.18	0.98 to 4.85
Fluoxetine	4	323	1.09	0.78 to 1.51
Paroxetine	3	726	0.89	0.73 to 1.08
Sertraline	2	596	1.33*	1.01 to 1.75
Fluvoxamine	1	412	1.16	0.80 to 1.68
SNRI				
Venlafaxine	1	258	0.82	0.58 to 1.16
Other antidepressant				
Trazodone	2	300	0.93	0.58 to 1.50
Withdrawal due to the development of side effect				
TCAs	8	1266	0.68	0.45 to 1.03
Amitriptyline	6	929	0.63	0.39 to 1.03
Clomipramine	1	174	1.13	0.46 to 2.78
Doxepin	1	163	0.32	0.07 to 1.55
SSRIs	11	2604	1.22	0.87 to 1.73
Citalopram	1	270	1.94	0.60 to 6.30
Fluoxetine	4	600	1.06	0.66 to 1.68
Paroxetine	3	726	0.77	0.53 to 1.14
Sertraline	2	596	2.58*	1.28 to 5.24
Fluvoxamine	1	412	1.58	0.87 to 2.87
SNRI				
Venlafaxine	2	415	0.59	0.27 to 1.29
Other antidepressant				
Trazodone	2	300	0.66	0.30 to 1.46

[a]Relative risk (RR) less than 1 indicates an advantage to mirtazapine.
*p Value < .05.
Abbreviations: RCT = randomized controlled trial, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

showed that this result on comparative efficacy was not the same for all SSRIs. In terms of tolerability, mirtazapine was not statistically significantly superior or inferior to other antidepressants apart from sertraline, the tolerability of which was found to be superior to that of mirtazapine.

Since mirtazapine was not demonstrated to be significantly superior clinically to other antidepressants, the results of this meta-analysis may suggest that clinicians should take into consideration other clinically vital factors, such as the differences in the side-effect profile, in clinical practice.[27]

Regarding mirtazapine, because of its unique pharmacologic profile, some antihistaminergic effects have been thought to bring about drowsiness, sedation, dry mouth, and increase in the appetite and body weight.[1] These side effects might have brought a significantly higher dropout rate in the patients treated with mirtazapine than that in the patients treated with sertraline, as observed in this study.

Concerning the study design and analytical approach, there were several differences between the present review and previous reviews.

First, we imputed the response and remission outcomes by applying the threshold of the most conventional and prevalent depression severity scales by a validated statistical method and did not use the outcomes defined by the authors of the original trials. Although this methodology may appear arbitrary and to have possibly resulted in less of the important information from the original trials being reported, recent evidence has shown that, in the published RCTs, statistically significant outcomes for efficacy tend to be more fully reported than nonsignificant outcomes do and that, in 62% of trials, at least 1 primary outcome was changed, introduced, or omitted with reference to the protocols.[28] For this reason, we decided to adhere to our criteria defined a priori for the response and remission outcomes and impute them when they were unavailable from the original trials. We think that, as long as the selective reporting of outcomes remains prevalent, our methodology should be used in future systematic reviews.

Second, in addition to the response rate, we took the remission rate into account as 1 of the outcomes. Previously reported meta-analyses have generally taken into account only the response outcome. However, a recent series of RCTs on the effectiveness of the sequential use of antidepressants and cognitive-behavioral therapy for depression named the Sequenced Treatment Alternatives to Relieve Depression (STAR*D), one of which[26] was included in our systematic review, revealed that, in depression, the remission rather than the response rate was more consistently associated with a better prognosis in terms of the long-term outcome.[8] Therefore, we propose that all future studies on this subject should report on the remission outcome in addition to the response outcome.

Limitations of the Study

This systematic review was not without its own methodological problems. First, most of the trials included in

Table 4. Clinical Significance of Efficacy Differences

Time Point	Group A, Mirtazapine Is Clinically Better Than	Group B, Mirtazapine Is Certainly Clinically Not Worse and Probably Better Than	Group C, Uncertain Whether There Is a Clinically Significant Difference Between Mirtazapine and	Group D, Mirtazapine Is Certainly Clinically Not Better and Probably Worse Than	Group E, Mirtazapine Is Clinically Worse Than
At 2 weeks	NA	Paroxetine, sertraline, venlafaxine	Amitriptyline, clomipramine, doxepin, nortriptyline, citalopram, fluoxetine, fluvoxamine, trazodone	NA	NA
At the end of acute-phase treatment (most commonly at 6 weeks)	NA	Fluoxetine, paroxetine, venlafaxine	Amitriptyline, clomipramine, doxepin, nortriptyline, citalopram, sertraline, fluvoxamine, trazodone	NA	NA

Abbreviation: NA = not applicable.

our meta-analysis were funded or conducted under the advice of a manufacturer of mirtazapine. On the other hand, it has been repeatedly reported that industry sponsorship could influence trial outcomes in favor of a drug manufacturer.[29–31] Moreover, we were unable to rule out the possibility that the dosing of either mirtazapine or of the comparator drug might have been designed in such a way as to induce differences in favor of mirtazapine, because the doses of the comparator drugs seemed lower than the usual dose in clinical practice in some of the included trials, especially in some of the trials comparing mirtazapine with fluoxetine or paroxetine (Table 1). We initially intended to conduct a sensitivity analysis by excluding trials sponsored by pharmaceutical companies but did not because only 2 out of the 25 trials were free of industry sponsorship. Furthermore, apart from the sponsorship bias, the fact that mirtazapine was always compared with older compounds in this analysis may have led to a "wish bias,"[32] which would also have made the more favorable results for mirtazapine and thus have undermined the validity of the results. Additional RCTs funded by nonprofit organizations are needed in order to establish a rigorous evidence base.

The second limitation of the review was the treatment durations in the included RCTs. Sixteen of the 25 included trials followed up the participants for 6 weeks. The STAR*D study revealed that one third of those showing a response to treatment with antidepressants did so only after 6 weeks of therapy (and half of those who showed remission did so after 6 weeks).[8] In addition, the durations of the RCTs included in our analysis were not sufficiently long to address the long-term side effects of mirtazapine. Addressing them may require a systematic review of studies dealing with the long-term effects of the drug, since this review focused only on acute-phase treatment.

We are also concerned about the representativeness of the populations recruited in the included trials. Most of the included trials were carried out to investigate the efficacy of mirtazapine. Generally speaking, efficacy trials tend to include only symptomatic volunteers with no concomitant medical or psychiatric diseases, as opposed to enrolling patients seeking health care in typical clinical treatment settings.[33] Thus, efficacy trials may eventually lead to results with only limited ecological validity and generalizability for clinical practice. Future research on mirtazapine should consist of effectiveness trials, enrolling patients seen in everyday practice.

Clinical Implications

Although mirtazapine is highly likely to have a better efficacy profile than paroxetine or venlafaxine in terms of early response, in view of the similar efficacy of mirtazapine and other antidepressant agents, the results of the study led us to conclude that clinicians should also focus on other practically or clinically relevant considerations, such as differences in the side effect profiles, to tailor the treatment to best fit an individual patient's needs.

Future Research

We hope that researchers who undertake meta-analyses in the field of clinical psychopharmacology in the future use our imputation methods to pool a validated and standard set of outcomes, instead of employing the outcomes defined by the authors of the original trials, in order to minimize outcome reporting bias.

Since the great majority of trials on the efficacy of mirtazapine are funded by its manufacturer and thus might be subject to some sponsorship bias, future RCTs on the effectiveness of mirtazapine should be funded by nonprofit organizations. Furthermore, the effectiveness of mirtazapine should be investigated by conducting RCTs using patients from "real-life" settings of populations seeking treatment in ordinary clinical practice settings.

Drug names: citalopram (Celexa and others), clomipramine (Anafranil and others), doxepin (Sinequan, Zonalon, and others), duloxetine (Cymbalta), fluoxetine (Prozac and others), mirtazapine (Remeron and others), norepinephrine (Levophed and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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