Mirtazapine: Efficacy and Tolerability in Comparison With Fluoxetine in Patients With Moderate to Severe Major Depressive Disorder

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Objective: To compare the efficacy and tolerability of mirtazapine and fluoxetine in depressed inpatients and outpatients.

Method: Patients with a major depressive episode (DSM-III-R), a baseline score of ≥ 21 on the 17-item Hamilton Rating Scale for Depression (HAM-D), and ≥ 2 on HAM-D Item 1 (depressed mood) were randomly assigned to a 6-week treatment with either mirtazapine (N = 66, 15–60 mg/day) or fluoxetine (N = 67, 20–40 mg/day). The upper limit of the mirtazapine dose range was above the dose range approved in the United States (15–45 mg/day). Efficacy was evaluated by the HAM-D, Clinical Global Impressions, the Visual Analogue Mood Rating Scale (VAMRS), and the Quality of Life Enjoyment and Satisfaction Questionnaire (QLESQ). The efficacy analyses were performed on the intent-to-treat group using the last-observation-carried-forward method.

Results: Mean total 17-item HAM-D scores at baseline were 26.0 for the mirtazapine- and 26.1 for the fluoxetine-treated group. The decrease from baseline on the HAM-D was larger in the mirtazapine than in the fluoxetine group throughout the treatment period, reaching statistical significance at days 21 and 28. At assessments from day 21 and onward, the absolute difference between the 2 study groups favoring mirtazapine ranged from 3.7 to 4.2 points, the magnitude of difference usually seen between an efficacious antidepressant drug and placebo. Mean dosages at weeks 1–4 were 36.5 mg/day for mirtazapine and 19.6 mg/day for fluoxetine; the respective dosages at weeks 5–6 were 56.3 mg and 35.8 mg. Similar numbers of patients dropped out due to adverse events; tolerability profiles were comparable except for changes in body weight from baseline which were statistically significantly more pronounced in the mirtazapine group compared to the fluoxetine group.

Conclusion: We found that mirtazapine was as well tolerated as fluoxetine and significantly more effective after 3 and 4 weeks of therapy.

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Mirtazapine is the first noradrenergic and specific serotonergic antidepressant (NaSSA).[1] Its antidepressant effect appears to be related to enhancement of central noradrenergic and 5-HT_1-mediated serotonergic neurotransmission. Mirtazapine directly and potently blocks α_2 presynaptic autoreceptors, which results in an increase of norepinephrine release and enhancement of noradrenergic neurotransmission.[2] The norepinephrine released in this manner potentiates 5-HT release by increasing serotonergic activity via stimulation of excitatory α_1-adrenoceptors on the serotonergic cell body. This is possible since mirtazapine has a very low affinity for α_1-adrenoceptors.[2] Mirtazapine also directly blocks α_2 heteroreceptors, which are located on serotonergic nerve terminals and have an inhibitory function on serotonin release. Thus, mirtazapine enhances serotonergic 5-HT_1-mediated neurotransmission, as it directly blocks 5-HT_2 and 5-HT_3 receptors.[2] Pharmacologic activity resides predominantly in the parent compound, and the contribution of the only pharmacologically active metabolite, demethyl-mirtazapine, to the total pharmacodynamic profile of mirtazapine is 3% to 6%.[3]

The antidepressant efficacy of mirtazapine was demonstrated in several placebo-controlled studies.[4–6] In com-

parative short-term studies, mirtazapine has proved to be more efficacious than trazodone[7] and equally efficacious as established antidepressants such as amitriptyline,[4,6,8,9] clomipramine,[10] and doxepin.[11]

Mirtazapine appears to be efficacious in inpatients as well as in outpatients,[12] and shows beneficial effects on the symptoms of anxiety and sleep disturbance associated with depression.[13] In a meta-analysis comparing mirtazapine and amitriptyline in patients with 17-item Hamilton Rating Scale for Depression (HAM-D) scores ≥ 25, both drugs showed equivalent efficacy.[14] Mirtazapine has demonstrated superior tolerability to the tricyclic antidepressants and trazodone, primarily on account of its relative absence of anticholinergic, adrenergic, and serotonin-related adverse effects, in particular gastrointestinal adverse effects and sexual dysfunction.[15,16] It appears that sedation may be related to subtherapeutic dosages and that it is reported in substantially fewer patients when the drug is used in appropriate dosages (≥ 15 mg as a single evening dose) from the beginning of the treatment.[17]

The effectiveness of fluoxetine is well established,[18] and it is generally accepted that it is as effective as tricyclic antidepressants (TCAs) in moderately depressed outpatients but with tolerability advantages.[19] The present study is the first to compare the efficacy and tolerability of mirtazapine and fluoxetine in patients with major depression. Based on published reports, it was assumed that both compounds would be equally effective, but tolerability profiles might be different.

METHOD

This study was a multicenter, randomized, double-blind comparison of mirtazapine and fluoxetine, performed in 8 centers in the United Kingdom, 7 centers in Belgium, and 5 centers in The Netherlands in the period between August 1994 and March 1996. The patients satisfying inclusion and exclusion criteria were recruited from the psychiatric population of inpatient and outpatient clinics. The Ethics Committee of each center approved the study. Each participating patient gave written informed consent before starting any study-related activity. The study was conducted in compliance with the Declaration of Helsinki and consecutive amendments, Good Clinical Practice standards, and the national regulations in the country where the study was conducted.

Female and male patients between 18 and 75 years, fulfilling the DSM-III-R criteria for a major depressive episode[20] according to the DSM-III-R checklist, with a total score of ≥ 21 on the 17-item HAM-D (17-HAM-D)[21] and a score of ≥ 2 on the HAM-D item 1 (depressed mood) at the start and end of the placebo-washout period, were eligible for participation in the study. On the day of screening, the duration of the present depressive episode should have been at least 2 weeks while not exceeding 12 months. Others not eligible for the study were patients with a history or presence of a bipolar disorder, depressive disorder (not otherwise specified), anxiety disorder (within the last 2 years), schizophrenia, adjustment disorder, schizotypal or borderline personality disorder, organic mental disorder, eating disorders (within the last 2 years), epilepsy or a history of seizure disorder or treatment with anticonvulsant medication for epilepsy or seizures; alcohol or substance abuse during the last 12 months; postpartum depression within 12 months after delivery; or those assessed by investigator as being at high risk of committing suicide. If the patients had a previous history of any meaningful renal, hepatic, respiratory, cardiovascular, or cerebrovascular disease or other serious, progressive physical disease, there must have been evidence that the condition was currently stable. Nonresponders to antidepressant treatment (i.e., lack of response to 2 or more adequate antidepressant therapies given for at least 6 weeks during the current depressive episode or patients with 3 or more previous episodes of depression that did not respond to adequate antidepressant therapy), patients treated with an adequate dose of an antidepressant (at least 75–150 mg of amitriptyline or equivalent for at least 6 weeks) within 1 week prior to screening or with a monoamine oxidase inhibitor (MAOI) within 2 weeks prior to screening, previously using fluoxetine for the current episode of depression, or treated with electroconvulsive therapy within 3 months prior to screening were also not eligible for participation. In addition, patients could not be under treatment with any medication that affects central and/or peripheral serotonergic and/or noradrenergic neurotransmission, in particular antihypertensive drugs of the guanethidine type, clonidine, β-blockers, and alpha-methyldopa; could not have used benzodiazepines more than 4 days per week during the 3 months preceding the study; and had to be able to discontinue the use of psychotropic drugs. The use of sedating antihistaminics was prohibited. Females of childbearing potential and not practicing a reliable method of birth control were excluded, as well as pregnant or lactating women or women who intended to become pregnant in the course of the study. Patients designated as fast placebo responders (i.e., showing a decrease of ≥ 25% in the total 17-HAM-D score during the placebo washout period) were excluded as well. In case of intolerable anxiety symptoms or sleep problems, the investigators had the option to administer temazepam (20 mg), oxazepam (15 mg), or nitrazepam (5 mg). Concurrent formal psychotherapy for the treatment of depression was not allowed.

After a 3- to 7-day, single-blind, placebo washout period, patients were allocated to treatment with either mirtazapine or fluoxetine, according to the centrally prepared randomization list. Active medication was prepared as indistinguishable looking tablets and packaging was performed using a double-dummy technique. The

Table 1. Dosing Schedule

Study Day	Mirtazapine		Fluoxetine	
	Morning	Evening	Morning	Evening
Washout period	1 × placebo	1 × placebo	1 × placebo	1 × placebo
1–4	1 × placebo	1 × 15 mg	1 × 20 mg	1 × placebo
5–7	1 × placebo	2 × 15 mg	1 × 20 mg	2 × placebo
8–28	1 × placebo	3 × 15 mg	1 × 20 mg	3 × placebo
29–42	1–2 × placebo	3–4 × 15 mg	1–2 × 20 mg	3–4 × placebo

doses of mirtazapine were 15–60 mg/day, and of fluoxetine 20–40 mg/day; the dosing schedule is shown in Table 1. Deviations from the dosing schedule were allowed only in cases of development of intolerable adverse events.

The 17-HAM-D, Clinical Global Impressions-Severity of illness (CGI-S),[22] Visual Analogue Mood Rating Scale (VAMRS)[23,24] restricted to 6 selected items (alert/drowsy, calm/excited, well-coordinated/clumsy, lethargic/energetic, agitated/tranquil, and tense/alert), and Quality of Life Enjoyment and Satisfaction Questionnaire (QLESQ, short version)[25] were assessed and baseline complaints, adverse events, and vital signs were registered at baseline. Further assessments were performed at days 7, 14, 28, and 42. In addition to the above mentioned variables, at all assessments from day 7 onward the Clinical Global Impressions-Global Improvement (CGI-G)[22] ratings were performed as well. All self-rating scales were used in local versions. In this study, no laboratory measurements were performed. Information about adverse events was obtained by questioning of participating patients and/or their examination. Adverse events were defined as any new complaint or symptom emerging during the study period or any complaint/symptom that existed before but increased in severity during the study period. All adverse events were coded using the dictionary terms from the World Health Organization adverse reactions terminology.[26]

Statistical Analysis

Sample size calculations were based on the number of patients needed to detect a difference between the 2 groups that was 0.5 times the standard deviation (SD) of changes from baseline in the individual items of the VAMRS, estimated to be 10% to 20% of the range of the scale. A sample size of 60 patients per group was calculated to be sufficient to detect such a difference between the 2 treatment groups, with a power of 80% and a significance level of 5%.

Efficacy analyses were based on the intent-to-treat (ITT) patient sample, thus including all randomly assigned subjects who received at least 1 dose of study medication and had at least 1 postbaseline efficacy assessment, using the last-observation-carried-forward (LOCF) method. Specific time frames were defined in advance for each visit (± 3 days) to determine acceptability of efficacy data for analysis. Changes from baseline in total 17-HAM-D scores; HAM-D item 1 score; anxiety-somatization, retardation, and sleep disturbance factor scores derived from the 17-HAM-D scale; 6 selected items on the VAMRS; CGI scores; and QLESQ were statistically analyzed by means of an analysis of variance (ANOVA; 2-way; with treatment and center as factors). Assessments at weeks 4 and 6 were defined as the main time points, and the analysis on other time points was performed in an exploratory manner to check the consistency of data. Wilcoxon test adjusting for center was used where applicable.

Percentages of responders (i.e., patients with ≥ 50% decrease from baseline in total 17-HAM-D scores) and remitted patients (i.e., patients with a total 17-HAM-D score of ≤ 7) were also calculated and compared using Cochran-Mantel-Haenszel test[27] adjusting for center. Estimates of treatment effects were calculated and presented with corresponding (2-sided) 95% confidence intervals (95% CI). The incidences of adverse events were presented using frequency tables, and were based on all randomly assigned patients who took at least 1 dose of study medication. Percentages of patients with a clinically relevant change in body weight (≥ 7% increase or decrease from baseline, a criterion suggested by the Food and Drug Administration) were tabulated.

All tests performed were 2-sided and deemed statistically significant if $p \leq .05$. All analyses were performed using SAS 6.11 (SAS Institute, Inc.; Cary, N.C.) under MS Windows on a personal computer.

RESULTS

Patient Population

One hundred fifty-one patients were screened for participation in the study. Of these, 133 were randomly assigned to either treatment group at baseline and received at least 1 dose of study medication (mirtazapine, N = 66; fluoxetine, N = 67). Sixty mirtazapine-treated and 63 fluoxetine-treated patients were included in the ITT group.

Both treatment groups were well matched at baseline with respect to demographic characteristics and mean group scores on 17-HAM-D and HAM-D item 1 (depressed mood) (Table 2). Approximately 70% of patients in either treatment group had a major depressive episode-melancholic type, while 58.3% of patients in the mirtazapine group and 52.4% of patients in the fluoxetine group were severely depressed (17-HAM-D score of ≥ 25). At baseline, the number of patients using benzodiazepines was 17 (28.3%) and 11 (17.5%) in the mirtazapine and fluoxetine group, respectively. These patients continued to use benzodiazepines during the study. In addition, 4 patients in the mirtazapine group (6.7%) and 10 (15.9%) in the fluoxetine group started to use at least 1 of the 3 al-

Table 2. Demographic Characteristics and Group Mean Rating Scale Scores at Baseline (ITT Group)*

Characteristic	Mirtazapine (N = 60)	Fluoxetine (N = 63)
Gender		
Male	45.0%	41.3%
Female	55.0%	58.7%
Age (y)		
Mean ± SD	47.2 ± 15.3	47.5 ± 14.8
Range	18–73	22–75
Height (cm)		
Mean ± SD	167.4 ± 11.1	167.7 ± 11.3
Range	140–193	146–193
Body weight (kg)		
Mean ± SD	70.5 ± 15.9	69.5 ± 14.6
Range	44.0–107.0	40.0–101.5
DSM-III-R diagnosis		
296.2x (single episode)	33.3%	28.6%
296.3 (recurrent episode)	66.7%	71.4%
Patients with suicide attempts in the past	25.0%	20.6%
Duration of the present episode		
< 1 month	15.0%	12.7%
1–6 months	61.7%	66.7%
7–12 months	23.3%	20.6%
Patients with melancholic type of depressive episode	73.3%	71.4%
Patients hospitalized at baseline	15.0%	15.9%
17-HAM-D (Mean ± SD)	26.0 ± 4.4	26.1 ± 4.3
Depressed mood item (Mean ± SD)	3.0 ± 0.6	2.9 ± 0.7
Baseline severity of depression		
17-HAM-D < 25 (moderately depressed)	41.7%	47.6%
17-HAM-D ≥ 25 (severely depressed)	58.3%	52.4%

*Abbreviations: 17-HAM-D = 17-item Hamilton Rating Scale for Depression, ITT = intent to treat.

lowed benzodiazepines temazapam, oxazepam, or nitrazepam. The difference between the number of patients starting the use of benzodiazepines in the 2 treatment groups is not statistically significant (exploratory post hoc analysis, p = .156; Fisher exact test, 2-sided).

Mean Daily Dosages of Study Medication (ITT Group)

The mean daily dosage of study medication was 39.8 mg/day of mirtazapine and 23.8 mg/day of fluoxetine (Table 3). During the first 28 study days, the mean daily dosages used were 36.4 mg of mirtazapine and 19.6 mg of fluoxetine. Between study days 29–42, the respective dosages were 56.3 and 35.8 mg/day.

Dropouts

Seventy-four percent of the mirtazapine-treated patients and 69% of the fluoxetine-treated patients completed the 42-day study period. Slightly more fluoxetine- (13.4%) than mirtazapine-treated patients (10.6%) dropped out due to adverse events, as well as because of lack of efficacy (7.5% vs. 4.5% in the fluoxetine and mirtazapine group, respectively) (Table 4).

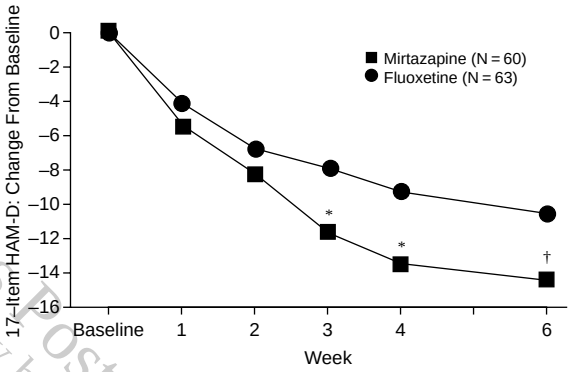
Table 3. Mean ± Daily Dosage of Study Medication (ITT Group)

Day	Mirtazapine (N = 60)	Fluoxetine (N = 63)
Day 1–28	36.4 ± 5.5	19.6 ± 0.9
Day 29–42	56.3 ± 18.1	35.8 ± 10.7
Day 1–42	39.8 ± 10.1	23.8 ± 3.8

Table 4. Percentages of Dropouts in Either Treatment Group (All Randomized Patients)

Reason	Mirtazapine (N = 66)	Fluoxetine (N = 67)
Lack of efficacy	3 (4.5%)	5 (7.5%)
Adverse events	7 (10.6%)	9 (13.4%)
Other reasons	7 (10.6%)	7 (10.5%)
Total	17 (25.8%)	21 (31.3%)

Figure 1. Mean 17-HAM-D Scores: Changes From Baseline During 6 Weeks of Treatment With Either Mirtazapine (15–60 mg/day) or Fluoxetine (20–40 mg/day)



*p ≤ .05, mirtazapine vs. fluoxetine (ANOVA, 2-sided).
†p = .054, mirtazapine vs. fluoxetine (ANOVA, 2-sided).

Efficacy

Reductions from baseline in group mean 17-HAM-D scores were evident in both treatment groups throughout the study period. The magnitude of change was larger in the mirtazapine-treated group from day 7 onward, reaching a statistically significant difference over the fluoxetine group at days 21 (the estimated treatment difference –3.4 in favor of mirtazapine; 95% CI = –6.1 to –0.76; p = .016; derived from ANOVA model) and 28 (the estimated treatment difference –3.8 in favor of mirtazapine; 95% CI = –6.61 to –1.02, p = .009; derived from ANOVA model) (Figure 1). At endpoint, the magnitude of change was –14.2 points in the mirtazapine group and –10.3 in the fluoxetine group (the estimated treatment difference of –3.2 in favor of mirtazapine; 95% CI = –6.4 to 0.02; p = .054, derived from ANOVA model) (Table 5).

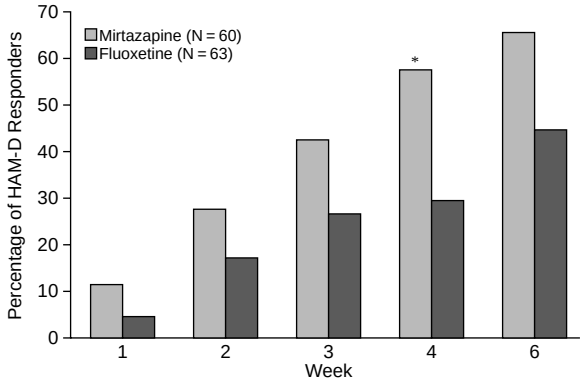
Decreases from baseline in depressed mood item scores were also evident in both groups. The reductions were larger in the mirtazapine group, reaching a statisti-

Table 5. Efficacy Variables at Endpoint: Estimated Treatment Differences, Corresponding 95% CIs, and p Values (ITT Group, LOCF Analysis)*

Efficacy Variable	Estimated Treatment Difference (Mirtazapine Minus Fluoxetine)	95% CI	p Value
17-HAM-D	–3.17	–6.36 to 0.02	.054
Depressed mood item	–0.23	–0.67 to 0.22	.322
Anxiety/somatization factor	–0.88	–2.20 to 0.44	.196
Retardation factor	–0.75	–1.89 to 0.40	.203
Sleep disturbance	–0.29	–0.95 to 0.37	.390
CGI-Severity of Illness	–0.50	–1.05 to 0.04	.075
VAMRS			
Alert/drowsy	–2.61	–14.49 to 9.27	.668
Calm/excited	–5.98	–17.55 to 5.60	.314
Well coordinated/clumsy	–1.36	–12.63 to 9.91	.814
Lethargic/energetic	4.00	–8.15 to 16.15	.520
Agitated/tranquil	5.61	–5.25 to 16.48	.314
Tense/relaxed	3.57	–6.51 to 13.64	.490
QLESQ	2.14	–2.30 to 6.58	.348

*Abbreviations: CGI = Clinical Global Impressions, CI = confidence interval, 17-HAM-D = 17 item Hamilton Rating Scale for Depression, ITT = intent to treat, LOCF = last observation carried forward, QLESQ = Quality of Life Enjoyment and Satisfaction Questionnaire, VAMRS = Visual Analogue Mood Rating Scale.

Figure 2. Percentages of HAM-D Responders (≥ 50% Decrease From Baseline in 17-HAM-D Scores)



*p ≤ .05, mirtazapine vs. fluoxetine (Cochran-Mantel-Haenszel test, 2-sided).

Table 6. Adverse Events Reported in More Than 5% of Patients in Either Treatment Group

Adverse Event (WHO Dictionary Term)	Mirtazapine (N = 66)	Fluoxetine (N = 67)
Fatigue	6.1%	4.5%
Drowsiness	10.6%	7.5%
Dizziness	7.6%	9.0%
Headache	9.1%	17.9%
Dry mouth	18.2%	4.5%
Nausea	3.0%	10.4%
Somnolence	18.2%	13.4%
Blurred vision	7.6%	1.5%

cally significant difference at day 28 (the estimated treatment difference of –0.39 in favor of mirtazapine; 95% CI = –0.76 to –0.03; p = .04, derived from ANOVA model). At all assessment points more mirtazapine-treated subjects were classified as HAM-D responders (≥ 50% decrease from baseline in 17-HAM-D score), and the difference with the fluoxetine group was statistically significant at day 28 (p = .006) (Figure 2). At endpoint, 23.3% and 25.4% of patients in the mirtazapine and the fluoxetine group respectively had 17-HAM-D scores ≤ 7 (Cochran-Mantel-Haenszel test adjusting for center, 2-sided, p = .39). The magnitude of change in 3 HAM-D factors (anxiety/somatization, retardation, and sleep disturbance factor) was larger in the mirtazapine group, although the difference with the fluoxetine group did not reach the level of statistical significance.

Percentages of patients classified as responders according to the CGI criterion (assessed as being "much" or "very much" improved) were also higher in the mirtazapine group. Although at endpoint more of mirtazapine-treated patients (63.3%) than fluoxetine-treated patients (54.0%) were classified as CGI responders, the difference was not statistically significant (p = .677; Cochran-Mantel-Haenszel test adjusting for center, 2-sided).

With regard to the 6 different items of the VAMRS, the results showed that subjects from both treatment groups became more alert, calm, energetic, tranquil, and relaxed. A statistical difference favoring mirtazapine was found at day 7 for the items "calm/excited," "lethargic/energetic," and "agitated/tranquil." Both treatment groups showed an improvement in quality of life as assessed by QLESQ, with no statistically significant differences between the groups.

Tolerability

The incidences of adverse events were low in both treatment groups, and usually were reported by ≤ 10% of patients. The adverse events reported by more than 5% of patients in either treatment group are presented in Table 6. More fluoxetine-treated patients complained of headache and nausea, whereas more mirtazapine-treated patients complained of dry mouth and blurred vision. Adverse events typical of sexual dysfunction were not reported in either treatment group. Reported adverse events were further categorized as "activating" (insomnia, anxiety, agitation, nervousness, tremor, and palpitations) or "sedating" (somnolence, asthenia). The incidence of activating adverse events was 18.2% in the mirtazapine group and 25.4% in the fluoxetine group; while the respective incidences of sedating adverse events were 18.2% in the mirtazapine group and 13.4% in the fluoxetine group. Furthermore, "typical" serotonin selective reuptake inhibitor (SSRI) adverse events occurred in 24.2% of the mirtazapine-treated patients and 38.8% of the fluoxetine-treated patients. None of the differences in reported adverse events was statistically significant. Blood pressure and

heart rate measurements remained within safety limits for both treatment groups.

An increase in body weight of ≥ 7% compared with baseline was registered in 8 mirtazapine-treated patients, and a decrease of ≥ 7% in 2 mirtazapine- and 2 fluoxetine-treated patients. In addition, an exploratory analysis was performed to compare changes in mean body weight. At endpoint, mean body weight of the mirtazapine-treated group was increased by 1.84 ± 2.52 kg, and of the fluoxetine-treated group decreased by 0.54 ± 2.32 kg. This difference was statistically significant (p = .0001, Wilcoxon test, 2-sided).

DISCUSSION

In this study, mirtazapine demonstrated antidepressant efficacy superior to the SSRI fluoxetine. This was shown consistently by a larger magnitude of changes from baseline present on all efficacy variables. Statistically significantly larger magnitudes of change were present in the group mean 17-HAM-D scores at days 21 and 28. An absolute difference of 3.7–4.2 points in favor of mirtazapine on the 17-HAM-D was observed at days 21, 28, and 42. This is the magnitude of difference usually seen between an efficacious antidepressant drug and placebo and indicates a clinically relevant effect of active medication.[28] Also, the statistically significant differences favoring mirtazapine were seen in the depressed mood score (day 28) and percentage of responders according to the HAM-D criterion (day 28). However, the fact that the present study was lacking a placebo-arm should be taken into account when interpreting results. There is also a possibility that results reflect that mirtazapine is more rapidly effective than fluoxetine and that a longer duration of a study (e.g., 8 weeks) with a design specifically addressing onset of response would resolve this issue.

The mean daily dosages of mirtazapine are in line with dosages used in previously reported comparisons with other active compounds[7–11] and recommendations in Europe.[12] However, this is higher than the dosages recommended in the United States (15–45 mg/day). The mean daily dosage of fluoxetine was consistent with the mean dosage used in other trials contrasting fluoxetine and other agents.[29,30] The difference between the groups was not statistically significant with respect to use of benzodiazepines during the study period according to the protocol.

In general, both drugs were well tolerated. Fewer mirtazapine-treated patients (10.6%) prematurely discontinued the study due to adverse events, while the treatment with fluoxetine in a standard dosing schedule resulted in 13.4% of premature discontinuations due to adverse events. Some expected differences in tolerability profiles did emerge in this study: treatment with fluoxetine was related to more reports of activating adverse events, while mirtazapine was related to more reports of sedating adverse events. However, the differences between the 2 compounds were low and statistically nonsignificant. It is also important to recognize that the methodology for evaluating activation/agitation in antidepressant trials is still evolving and is not well validated, and it is suggested that further studies are needed to clarify this methodological issue.[29] In addition to methodological problems related to evaluation of activation/agitation, the sample size of 133 patients may lack the power of detecting subtle differences in tolerability profiles. The only difference in tolerability between the 2 treatments was observed in body weight changes, with the mirtazapine-treated group showing a statistically significant increase from baseline compared with the fluoxetine group.

The most important result of this study was the superior antidepressant efficacy of mirtazapine. One of the possible explanations could be the high percentage of melancholic and/or severely depressed patients in both treatment groups. The efficacy of mirtazapine was found to be equivalent to that of a standard TCA such as amitriptyline[14] or clomipramine[10] in the treatment of severely depressed patients. By contrast, there are reports that fluoxetine is significantly less effective than the TCA nortriptyline[31] or venlafaxine[32] in the treatment of melancholic or severely depressed patients. Although the exclusion criteria applied in this study aimed to exclude nonresponders to previous treatment with antidepressants, there is a possibility that some of the patients had failed 1 adequate SSRI trial, which could have biased sampling in favor of mirtazapine.

In conclusion, the results of this study, the first to compare mirtazapine with an SSRI, show that mirtazapine was as well tolerated as fluoxetine and significantly more effective after 3 and 4 weeks of therapy.

Drug names: amitriptyline (Elavil and others), clomipramine (Anafranil), clonidine (Catapres), doxepin (Sinequan and others), fluoxetine (Prozac), guanethidine (Ismelin), mirtazapine (Remeron), nitrazepam (Mogadon), nortriptyline (Pamelor and others), oxazepam (Serax and others), temazepam (Restoril and others), trazodone (Desyrel and others), venlafaxine (Effexor).

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