Mirtazapine Compared With Paroxetine in Major Depression

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Background: The aim was to compare the efficacy and tolerability of mirtazapine with those of paroxetine.

Method: 275 outpatients with a diagnosis of major depressive episode (DSM-IV) and a score ≥ 18 on the 17-item Hamilton Rating Scale for Depression (HAM-D-17) were randomly assigned to 6 weeks of treatment with mirtazapine (15–45 mg/day) or paroxetine (20–40 mg/day). Efficacy was assessed by the HAM-D-17, Hamilton Rating Scale for Anxiety (HAM-A), and Clinical Global Impressions scales (Severity and Improvement), and analyses were performed on the intent-to-treat sample (127 mirtazapine-treated patients and 123 paroxetine-treated patients).

Results: Mean daily doses were 32.7 mg of mirtazapine and 22.9 mg of paroxetine. Thirty patients in the mirtazapine group and 33 in the paroxetine group dropped out. Both drugs were equally effective in reducing symptoms of depression. At week 1, the mean HAM-D-17 total score was significantly lower in mirtazapine- than paroxetine-treated patients (16.5 vs. 18.8, p = .0032). Similarly, significantly more mirtazapine-treated patients were HAM-D-17 responders (≥ 50% decrease from baseline) at weeks 1 (23.2% vs. 8.9%, p = .002) and 4 (58.3% vs. 44.5%, p = .04). Both treatments were equally effective in reducing anxiety. However, the reduction in mean HAM-A total score was significantly greater with mirtazapine than with paroxetine at week 1 (–5.1 vs. –3.5, p = .0435). Tolerability of both treatments was good, with more nausea, vomiting, tremor, and sweating in the paroxetine group and more weight increase and influenza-like symptoms in the mirtazapine group.

Conclusion: Mirtazapine and paroxetine were equally effective after 6 weeks of therapy and were both well tolerated. A potentially faster onset of overall therapeutic efficacy of mirtazapine was suggested by significant differences between treatments after 1 week of therapy that were due to slightly larger improvements of several core symptoms of depression as well as distinct prevention of treatment-emergent worsening of anxiety and physical components of depression.

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The antidepressant effect of mirtazapine, the first noradrenergic and specific serotonergic antidepressant (NaSSA), appears to be related to enhancement of central noradrenergic and serotonin-1 (5-HT$_1$)-mediated serotonergic neurotransmission.[1] Direct blockade of presynaptic α_2 receptors by mirtazapine results in increased norepinephrine release that, in turn, enhances 5-HT release via stimulation of α_1 adrenoceptors on the serotonergic cell body. Enhanced 5-HT release is also mediated via direct blockade of the inhibitory α_2 heteroreceptors located on 5-HT terminals. This enhanced 5-HT release is mediated only by the 5-HT$_1$ receptor; mirtazapine directly blocks 5-HT$_2$ and 5-HT$_3$ receptors, an effect that may account for its anxiolytic and sleep-improving properties and its lack of adverse events typically associated with the selective serotonin reuptake inhibitors (SSRIs).[2]

The antidepressant efficacy of mirtazapine has been shown to be significantly superior to that of placebo and trazodone and comparable to that of well-established tricyclic antidepressants such as amitriptyline, clomipramine, and doxepin.[3,4] Recent studies have also demonstrated that mirtazapine is at least as effective as the SSRIs fluoxetine[5] and citalopram[6] and that it has statistically significant benefits during the early weeks of treatment. Mirtazapine is effective in long-term treatment[7] and in patients with severe depression[8,9]; it also has beneficial effects on anxiety and sleep disturbance in depressed patients.[10,11]

The relative lack of anticholinergic and adrenergic side effects with mirtazapine means that its safety and tolerability profile is more favorable than that of the tricyclic antidepressants and trazodone.[12,13] Moreover, it lacks the serotonergic side effects and sexual dysfunction[14] associated with the SSRIs. Slight and transient sedative effects have been reported with mirtazapine, but these are mainly observed at subtherapeutic dosages (< 15 mg/day).[15]

The antidepressant efficacy of the SSRI paroxetine is well established,[16] and, like mirtazapine, it is better toler-

ated than the tricyclic antidepressants. However, based on their pharmacology, evidence suggests that there may be differences in tolerability profile between paroxetine and mirtazapine.[17] This study was designed to demonstrate equivalent antidepressant and anxiolytic efficacy and to compare tolerability of mirtazapine with that of paroxetine in patients with major depressive episode with changes in the 17-item Hamilton Rating Scale for Depression (HAM-D-17) score as the primary efficacy outcome measure.

PATIENTS AND METHOD

This multicenter, randomized, double-blind comparison of mirtazapine and paroxetine was conducted at 50 centers in Germany. The study protocol was approved by the local ethics committee, and the study was conducted in accordance with Good Clinical Practice standards.[18] All patients provided written informed consent after the procedures and any possible side effects had been fully explained.

Patients

Patients were recruited in general practice and in psychiatric outpatient departments. In total, 11 research assistants (psychiatric residents, research fellows, and psychologists) who had been trained in rating patients with the psychiatric scales and in performing structured diagnostic interviews with the Mini-International Neuropsychiatric Interview (MINI)[19,20] were responsible for checking eligibility of selected patients. Training consisted of rating 5 different videotapes from patients with major depressive disorder, with the requirement that the sum scores on the HAM-D and the Hamilton Rating Scale for Anxiety (HAM-A) of any rater did not differ more than ± 2 points from an independent expert rating. The MINI was taught in a 1-day lecture, and volunteers were trained during 3 to 5 supervised exercise administrations. The research assistants were engaged by the clinical research organization and met the patients at the centers to perform all psychiatric investigations and ratings during the study.

Patients (men or women, aged from 18 to 70 years) fulfilling DSM-IV criteria for major depressive episode[21] and with a total score ≥ 18 on the HAM-D-17[22] at the start and end of a placebo washout period were eligible for inclusion in the study. Reasons for exclusion included a current depressive episode of more than 12 months' duration, a lack of response to at least 2 adequate antidepressant therapies during the current episode, more than 3 previous episodes that did not respond to adequate antidepressant therapy, a reduction of ≥ 25% in the HAM-D-17 score during the placebo washout period, suicide risk defined as a score of 4 to 6 on item 10 of the Montgomery-Asberg Depression Rating Scale (MADRS),[23] and current bipolar disorder, depressive disorder not otherwise defined, panic dis-

order (with or without agoraphobia), agoraphobia without a history of panic disorder, schizophrenia, organic mental disorder, eating disorder (anorexia or bulimia nervosa), specific phobia, social phobia, or generalized anxiety disorder. The latter 3 conditions were only considered as exclusion criteria if they caused clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Patients were also excluded if they were pregnant, lactating, or of childbearing potential and not taking adequate contraceptive measures; were suffering from alcohol/substance abuse or epilepsy; had a history of seizure disorder; had ever received treatment with an anticonvulsant for epilepsy or seizures; or had clinically meaningful physical disease or abnormal findings on physical examination or laboratory testing. The following treatments must have been stopped within the indicated intervals before the start of active study medication: electroconvulsive therapy, 3 months; depot neuroleptics, 2 months; fluoxetine, 4 weeks; benzodiazepines, 2 weeks; monoamine oxidase inhibitors, 2 weeks; paroxetine, current episode, and other psychotropic drugs, 1 week. Any supportive psychotherapy must have been stopped at least 4 weeks prior to study entry.

Treatment Schedule

Following a 3- to 7-day placebo washout period, patients were randomly assigned to receive treatment with either mirtazapine or paroxetine for 6 weeks. The dose of mirtazapine was increased from 15 mg/day on days 1 and 2 to 30 mg/day from day 3 onward; an increase to 45 mg/day was permitted after 2 weeks in nonresponders. Nonresponders were defined by Clinical Global Impressions scale (CGI) ratings in the efficacy index of "slight" or "unchanged/worsened" and no "outweighs therapeutic efficacy" ratings in the tolerability index. Paroxetine was started at a dose of 20 mg/day and could be increased to 40 mg/day after 2 weeks in nonresponders. Both drugs were given once daily, mirtazapine in the evening and paroxetine in the morning, using a double-dummy technique.

Concomitant treatment with psychotropic drugs (including benzodiazepines), sedative drugs (including sedative antihistamines), or antihypertensive medication (guanethidine, guanoxan, clonidine, prazosin, or α-methyldopa) was not allowed. The only exception was chloral hydrate (1 g/day for up to 3 successive days/week), which was permitted for sleeping problems.

Assessments

Assessments were performed at screening and baseline (day 0) and at weeks 1, 2, 3, 4, and 6 of active treatment (or on premature withdrawal from the study).

Efficacy was assessed using the HAM-D-17 (including item, factor, and subscale analyses and percentage of responders), the HAM-A,[24] the CGI (Severity and Improvement) scales,[25] the Beck Depression Inventory (BDI),[26,27]

the Welzel-Kohnen Colored Scales (WKFS),[28] and the Short-Form 36 (SF-36; a measure of quality of life).[29]

The question whether the course of treatment effects might be different between 2 treatments that are equivalent at endpoint was investigated by comparisons between mirtazapine and paroxetine at each visit. Differences in assessments soon after start of treatment were of special interest, because they might represent one treatment's faster onset of global therapeutic action as indicated by the HAM-D-17 sum score. To distinguish between antidepressive efficacy and other influences, such as reduction of physical symptoms and/or prevention of increase of severity in particular symptoms due to a drug's side effects, the same analyses were performed with item 1 (depressed mood) and the Bech melancholia factor (calculated from items 1, 2, 7, 8, 10, and 13)[30] of the HAM-D-17, which cover core symptoms of depression.

Safety and tolerability were assessed using adverse event monitoring, the UKU Side Effect Rating Scale,[31] CGI tolerability ratings, physical examination, vital signs, laboratory assessments, and electrocardiogram (ECG). All adverse events were coded using the dictionary terms from the World Health Organization Adverse Reaction Terminology.[32]

Statistical Analyses

A sample size of 120 patients per group who completed at least 4 weeks of treatment was estimated to be sufficient to detect a clinically relevant difference[33] between the 2 groups of δ = 2.9 with a standard deviation of 8.0 in the HAM-D-17 total score.

Efficacy analyses were based on the intent-to-treat patient sample, thus including all randomly assigned patients who received at least one dose of study medication and had at least one postbaseline efficacy assessment. An observed case analysis was performed for each visit, and a last-observation-carried-forward analysis was performed for the endpoint assessment. Quantitative data were analyzed using the Student t test. Qualitative data were analyzed using the chi-square test or the Fisher exact test for binary data or the Mantel-Haenszel chi-square test for ordinal data. For the difference in HAM-D-17 changes from baseline, 95% confidence intervals were calculated with weights for raters to control for center effects.[34] The analysis of equivalence was done according to the confidence interval inclusion rule.

The incidences of spontaneously reported or observed adverse events were presented using summary tables and were based on all randomly assigned patients who took at least one dose of study medication and had at least one postbaseline safety assessment (safety population). Differences between groups were analyzed by the Fisher exact test. Percentages of patients with a clinically relevant change in body weight (≥ 7% increase or decrease from baseline as suggested by the U.S. Food and Drug Admin-

Table 1. Demographic and Disease Characteristics at Baseline (safety sample)[a]

Characteristic	Mirtazapine (N = 135)	Paroxetine (N = 134)
Gender, %		
Male	37	35
Female	63	65
Age, y		
Mean ± SD	47.2 ± 11.1	47.3 ± 10.3
Range	21–68	21–69
Weight, mean ± SD, kg		
Men	81.3 ± 11.4	79.6 ± 11.8
Women	69.5 ± 13.9	69.3 ± 15.6
First episode of major depression, %	41.5	43.3
Previous episodes of major depression, %	56.3	54.5
Single episode	44.3	41.9
Recurrent episode	54.9	55.8
Duration of current episode, mean ± SD, d[b]	98 ± 86	110 ± 104
Mean HAM-D-17 score	22.4 ± 3.3	22.4 ± 3.2
Mean HAM-A score	25.3 ± 7.4	26.4 ± 7.2

[a]Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, HAM-D-17 = 17-item Hamilton Rating Scale for Depression.
[b]N = 133 in the mirtazapine group, N = 131 in the paroxetine group.

istration) were calculated. Differences in mean body weight between the groups were compared using the Student t test.

All tests were 2-sided, and statistical significance was defined as p ≤ .05. All statistical analyses were performed using SAS version 6.11.

RESULTS

A total of 311 patients were screened for participation in the study, 275 of whom were randomly assigned to treatment (139 in the mirtazapine group and 136 in the paroxetine group). No postbaseline values for safety or efficacy were available from 6 patients because of early withdrawal from the study (lost to follow-up). In total, 269 were included in the safety sample (135 in the mirtazapine group and 134 in the paroxetine group), and 250 were included in the intent-to-treat sample (127 in the mirtazapine group and 123 in the paroxetine group).

Both treatment groups were well matched at baseline with respect to demographic and disease characteristics (Table 1). The mean HAM-D-17 score at baseline in the intent-to-treat sample was 22.4 in both groups; the mean HAM-A score at baseline was 25.3 in the mirtazapine group and 26.4 in the paroxetine group. The majority of patients in both groups were rated markedly ill on the CGI-Severity of Illness scale (55% in the mirtazapine group and 59% in the paroxetine group); 13% in each group were rated severely ill.

Dropouts

Seventy-eight percent of the mirtazapine-treated patients and 76% of the paroxetine-treated patients completed the 6-week study period. The reasons for with-

Table 2. Reasons for Dropout in Either Treatment Group (all randomly assigned patients)

Reason	Mirtazapine (N = 139)		Paroxetine (N = 136)	
	N	%	N	%
Lack of efficacy	3	2.2	7	5.1
Adverse event	12	8.6	10	7.4
Patient's decision (no further reason reported)	4	2.9	9	6.6
Other	11	7.9	7	5.1
Total	30	21.6	33	24.2

drawal were similar in both groups, although slightly more paroxetine-treated than mirtazapine-treated patients dropped out owing to lack of efficacy (5.1% vs. 2.2%) (Table 2).

Dosage

The mean daily dosage was 32.7 mg of mirtazapine and 22.9 mg of paroxetine. The majority of patients (98 [77.2%] in the mirtazapine group and 94 [76.4%] in the paroxetine group) did not require dose escalation after 2 weeks. Dose escalation was necessary in 23 patients (18.1%) in the mirtazapine group (to 45 mg/day) and 18 patients (14.6%) in the paroxetine group (to 40 mg/day). The remaining 17 patients withdrew from the study at an early stage.

Efficacy

Both treatments were equally effective in reducing the mean HAM-D-17 total score. However, mirtazapine was associated with a faster onset of action: the mean HAM-D-17 score was significantly lower in the mirtazapine group than in the paroxetine group at week 1 (16.5 vs. 18.8, p = .0032) (Figure 1). At endpoint, the mean HAM-D-17 total score was 10.7 in the mirtazapine group and 11.9 in the paroxetine group. The 95% confidence interval for differences between both treatments was –2.98 to 0.33, which is slightly larger than the predefined equivalence range of 3.0 points and reveals a tendency to a larger improvement in the mirtazapine group.

Analysis of the HAM-D-17 response rate (≥ 50% decrease from baseline in HAM-D-17 total score) also revealed a faster onset of action with mirtazapine. As shown in Figure 2, significantly more patients had responded to mirtazapine than to paroxetine by week 1 (23.2% vs. 8.9%, p = .002). The percentage of responders remained higher in the mirtazapine group throughout the rest of the study, the difference achieving statistical significance again at week 4 (58.3% vs. 44.5%, p = .04). At endpoint, 58.3% of patients in the mirtazapine group and 53.7% in the paroxetine group were considered HAM-D-17 responders.

The percentage of patients achieving a HAM-D-17 score of ≤ 7 (complete remission) was high in both groups (40.9% and 34.1% at endpoint with mirtazapine and paroxetine, respectively) (Figure 3). Consistently, a faster onset

Figure 1. Change in Mean 17-Item Hamilton Rating Scale for Depression (HAM-D-17) Total Score During Treatment (intent-to-treat sample)[a]
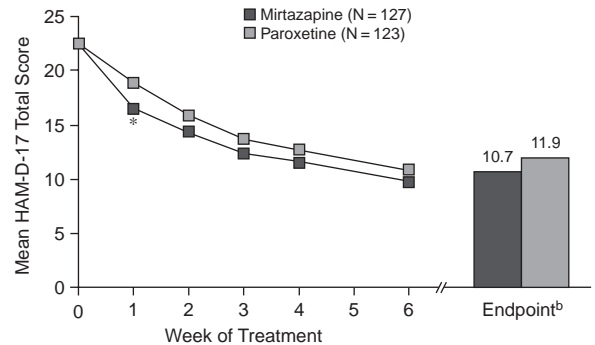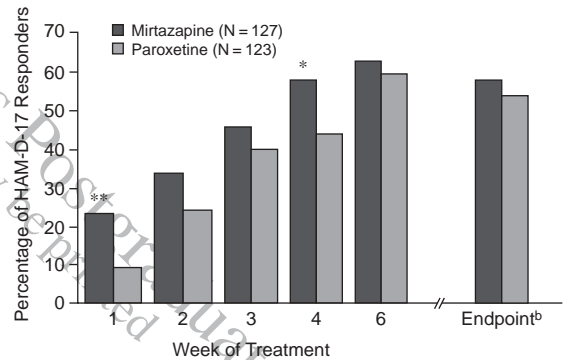

[a]Observed case analysis for weeks 1 to 6 assessments: number of patients (mirtazapine/paroxetine) = 125/123, 121/114, 117/111, 115/110, and 109/104 at weeks 1, 2, 3, 4, and 6, respectively.
[b]Last-observation-carried-forward analysis for endpoint.
*p ≤ .01, mirtazapine vs. paroxetine (2-sided t test).

Figure 2. 17-Item Hamilton Rating Scale for Depression (HAM-D-17) Response Rate (≥ 50% decrease from baseline in HAM-D-17 total score) During Treatment (intent-to-treat sample)[a]

[a]Observed case analysis for weeks 1 to 6 assessments: number of patients (mirtazapine/paroxetine) = 125/123, 121/114, 117/111, 115/110, and 109/104 at weeks 1, 2, 3, 4, and 6, respectively.
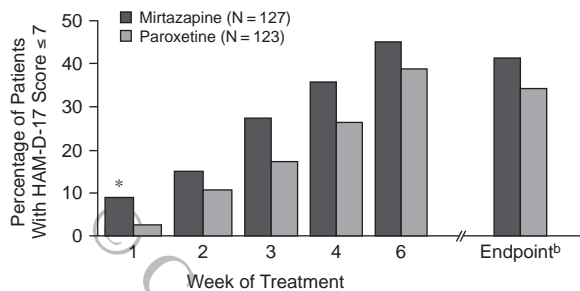[b]Last-observation-carried-forward analysis for endpoint.
*p ≤ .05, mirtazapine vs. paroxetine (2-sided chi-square test).
**p ≤ .01, mirtazapine vs. paroxetine (2-sided chi-square test).

of action was observed with mirtazapine: the percentage of completely remitted patients (HAM-D-17 score of ≤ 7) was significantly higher with mirtazapine than with paroxetine at week 1 (8.8% vs. 2.4%, p = .03).

Analysis of item 1 of the HAM-D-17 (depressive mood) and the Bech melancholia factor of the HAM-D-17 revealed similar improvements with both treatments, although again there was a trend for a faster onset of action with mirtazapine. At endpoint, the mean HAM-D-17 item 1 score was reduced by 1.7 and 1.8 and the Bech melancholia factor by 6.0 and 5.9 in the mirtazapine and parox-

Figure 3. Percentage of Patients With a 17-Item Hamilton Rating Scale for Depression (HAM-D-17) Score ≤ 7 During Treatment (intent-to-treat sample)[a]

[a]Observed case analysis for week 1 to 6 assessments: number of patients (mirtazapine/paroxetine) = 125/123, 121/114, 117/111, 115/110, and 109/104 at weeks 1, 2, 3, 4, and 6, respectively.
[b]Last-observation-carried-forward analysis for endpoint.
*p ≤ .05, mirtazapine vs. paroxetine (2-sided chi-square test).

Figure 4. Change in Mean Hamilton Rating Scale for Anxiety (HAM-A) Total Score During Treatment (intent-to-treat sample)[a]

[a]Observed case analysis for week 1 to 6 assessments: number of patients (mirtazapine/paroxetine) = 125/123, 121/114, 118/111, 116/110, and 109/104 at weeks 1, 2, 3, 4, and 6, respectively.
[b]Last-observation-carried-forward analysis for endpoint.
*p ≤ .05, mirtazapine vs. paroxetine (2-sided t test).

etine groups, respectively. Data on the other HAM-D-17 items, factors, and subscales analyzed in this study will be described in a separate report.

Both treatments significantly reduced anxiety as measured by the HAM-A; at endpoint, the mean HAM-A total score was 14.8 in the mirtazapine group and 16.2 in the paroxetine group (Figure 4). The faster onset of action seen with mirtazapine on measures of depression was also observed on the HAM-A, with the reduction in mean total score significantly greater with mirtazapine than with paroxetine at week 1 (–5.1 vs. –3.5, p = .04).

At endpoint, the percentage of patients classified as responders according to the CGI-Improvement scale (assessed as being "much" or "very much" improved) was 70.1% in the mirtazapine group and 65.6% in the paroxetine group.

Data obtained from the BDI, WKFS, and SF-36 in this study will be described in a separate report.

Safety and Tolerability

Both treatments were well tolerated. Only 8.6% of mirtazapine- and 7.4% of paroxetine-treated patients dropped out of the study prematurely due to adverse events. The percentage of patients reporting at least one adverse event was similar in the mirtazapine and paroxetine groups (68.1% and 63.4%, respectively). Adverse events reported by more than 5% of patients in either group are shown in Table 3. As expected, side effects typical for SSRIs like nausea, vomiting, tremor, and increased sweating were more common with paroxetine, while mirtazapine-treated patients were more likely to report weight increase and influenza-like symptoms. On the UKU Side Effect Rating Scale, more detailed information regarding sexual functioning was detected in favor of mirtazapine. Results based on an analysis of all new or worsened UKU symptoms show increased sexual desire of 5.5% for mirtazapine ver-
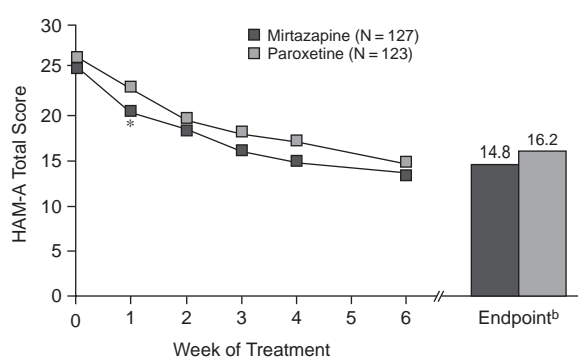
Table 3. Adverse Events Spontaneously Reported in More Than 5% of Patients in Either Treatment Group (%)

Adverse Event[a]	Mirtazapine (N = 135)	Paroxetine (N = 134)
Dry mouth	14.1	8.2
Headache	9.6	10.4
Somnolence	11.1	7.5
Weight increase	14.8[b]	3.7
Dizziness	8.9	8.2
Fatigue	8.9	8.2
Diarrhea	8.1	8.2
Nausea	4.4	11.2[c]
Constipation	7.4	6.7
Influenza-like symptoms	9.6[c]	3.7
Nervousness	3.7	6.7
Increased sweating	2.2	7.5[c]
Pain	3.7	5.2
Dyspepsia	3.0	5.2
Back pain	1.5	6.0
Tremor	0.7	5.2[c]
Vomiting	0.7	5.2[c]

[a]World Health Organization Adverse Reactions Terminology.
[b]p ≤ .05 (Fisher exact test).
[c].05 < p < .10 (Fisher exact test).

sus 2.4% for paroxetine and a statistically significant difference in orgasmic dysfunction (mirtazapine, 3.1% vs. paroxetine, 13.5% [p = .048]). Although differences in sexual functioning might be more pronounced during long-term treatment, these results provide clear evidence for differences in sexual functioning between the 2 treatment groups. All other data obtained from the UKU Side Effect Rating Scale will be described separately.

At endpoint, mean body weight increased by a mean ± SD of 1.1 ± 2.0 kg in the mirtazapine-treated group and was reduced by 0.2 ± 1.7 kg in the paroxetine-treated group. This difference was statistically significant (p < .0001, 2-sided t test). An increase in body weight

≥ 7% compared with baseline was seen in 10 mirtazapine-treated patients, and a decrease ≥ 7% was seen in 3 paroxetine-treated patients.

No clinically relevant changes were found in heart rate, blood pressure, ECG, or laboratory parameters in either group.

DISCUSSION

In this study, both mirtazapine and paroxetine were equally effective in reducing the overall symptoms of depression and anxiety in patients with major depressive episode. A significantly greater effect was consistently seen with mirtazapine in all major efficacy variables at the first week of therapy. There was a tendency for a larger improvement at endpoint analysis in the mirtazapine group compared with the paroxetine group.

Progress in the field of antidepressants has been predominantly defined by the development of drugs with improved tolerability profiles. The SSRIs, for example, avoid the cardiotoxicity and anticholinergic side effects of the tricyclic drugs. However, there has been little progress in the development of drugs with improved clinical efficacy characteristics, such as an increase in the proportion of patients who respond, a reduction in the delay to onset of action, or a reduction in the level of residual symptoms. It is a close-to-universal finding that antidepressants require 4 to 6 weeks of administration to exert their full therapeutic effect.[35]

Although this study was neither designed nor empowered as an onset-of-action study, some indications are worthy of further consideration. At week 1, mean HAM-D-17 total scores were reduced significantly more in the mirtazapine group than in the paroxetine group (by 2.3 points). Although this difference appears small, it was highly statistically significant (p = .0032) and approaches clinical significance.[36] Moreover, the percentage of HAM-D-17 responders and HAM-D-17 complete remissions was significantly greater with mirtazapine than with paroxetine at week 1.

These results confirm parallel findings with mirtazapine from a placebo-controlled trial[37] in which statistically and clinically significant differences in total HAM-D score and mood item 1 score between mirtazapine and placebo were evident as early as week 1. Similar results have also been observed in previous double-blind comparisons with SSRIs. For example, the mean HAM-D-17 total score was reduced significantly more at weeks 3 (treatment difference of 3.4 points) and 4 (treatment difference of 3.8 points) by mirtazapine than by fluoxetine in a recent double-blind comparison.[5] The percentage of HAM-D-17 responders in the present study was also greater at all timepoints, an effect that achieved statistical significance at weeks 1 and 4. Similarly, in a double-blind comparison with citalopram,[6] the MADRS score was reduced significantly more by mirtazapine than by citalopram at week 2, as were HAM-A and CGI-Severity scores. Thus, the current results are in concordance with previous placebo and active-control studies, although the lack of a placebo arm should be taken into account when interpreting these findings.

The definition of the correct methodology for evaluating time of onset for antidepressants is still a subject of debate.[36,38–41] The advantages for mirtazapine over several SSRIs during the first weeks of treatment may be due to the different pharmacologic profiles of the antidepressants. While beneficial effects of SSRIs on depressed mood, anxiety symptoms, and other depression-related complaints usually need several weeks of continuous treatment, the superior effects of mirtazapine on anxiety and a number of depression-related symptoms, but without statistically significant effect on the depressed mood item, seem to occur as early as week 1 of treatment. This conclusion is derived from the significant differences in HAM-A, CGI, and HAM-D scores that favor mirtazapine during the early phase of treatment. A detailed itemwise analysis of rates of patients who improved, worsened, or remained unchanged between baseline and week 1 revealed that more patients improved under mirtazapine than under paroxetine treatment in almost all items of the HAM-D-17.

Regarding the Bech melancholia factor, impairments at work and other activities (42.4% [mirtazapine] vs. 29.3% [paroxetine]), psychic anxiety symptoms (47.2% vs. 35.0%), and depressed mood (54.4% vs. 48.7%) improved in favor of mirtazapine. Also, sleep items were more positively affected by mirtazapine than by paroxetine (sleep disturbances during the night, 42.4% vs. 31.7%, respectively). On the other hand, the rate of patients who worsened during the first week of treatment was higher in the paroxetine group in 12 of 17 items. In this respect, differences were most pronounced in psychic (8.2% [mirtazapine] vs. 17.0% [paroxetine]) and physical (8.8% vs. 21.1%) anxiety symptoms, gastrointestinal symptoms (1.6% vs. 13.8%), and weight loss (0.8% vs. 13.9%). These data show that the observed differences between both treatments at week 1 were due to both a slightly larger rate of patients with decreased severity in specific symptoms of depression under mirtazapine treatment and especially a paroxetine-induced worsening in anxiety and physical components of depression. Because the severity of depressive symptoms is not solely determined by depressed mood but also by anxiety symptoms, sleep, psychomotor disturbances, and somatic complaints, a faster relief of these symptoms is clinically relevant.

The reasons for the delay in onset of therapeutic action have been the subject of speculation for many years; the principal pharmacologic effects of most antidepressants (monoamine uptake blockade, for example) occur very quickly. It has been postulated that the delay in onset of the therapeutic actions of antidepressants may be due to

adaptive changes in monoamine synapses that counteract their acute pharmacologic effects. It is further postulated that the dual mechanism of action of mirtazapine on both norepinephrine and serotonin may decouple these adaptive mechanisms and allow the acute pharmacology of mirtazapine to be more rapidly expressed[42] by increasing the serotonergic firing rate immediately, in contrast to most other antidepressants. Indeed, other dual-acting drugs with a more favorable side effect profile than most tricyclic antidepressants also appear to have a rapid onset of action (e.g., the serotonin-norepinephrine reuptake inhibitors).[43]

Both treatments were well tolerated in the current study. As expected from the different pharmacologic profiles of the drugs, there were some differences in their tolerability profiles. Paroxetine was associated with more nausea, vomiting, tremor, and sweating, while mirtazapine was more frequently associated with increased body weight and influenza-like symptoms. Although body weight increase was significantly more common with mirtazapine, the mean increase in weight was only 1.1 kg, and only 7.4% of patients had an increase of 7% or more from baseline.

In conclusion, mirtazapine and paroxetine were equally effective and well tolerated after 6 weeks of therapy in patients with major depressive episode. However, mirtazapine was significantly more effective than paroxetine after the first week of therapy because of a slightly larger improvement in several core symptoms of depression and especially because of the distinct prevention of an increase in anxiety and gastrointestinal symptoms as well as weight loss. These differences suggest a potentially faster onset of overall therapeutic action for mirtazapine in depressed patients.

Drug names: amitriptyline (Elavil and others), citalopram (Celexa), clomipramine (Anafranil and others), clonidine (Catapres and others), doxepin (Sinequan and others), fluoxetine (Prozac), methyldopa (Aldoclor and others), mirtazapine (Remeron), paroxetine (Paxil), prazosin (Minipress and others), trazodone (Desyrel and others).

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