A Double-Blind, Randomized, Group-Comparative Study of the Tolerability and Efficacy of 6 Weeks' Treatment With Mirtazapine or Fluoxetine in Depressed Chinese Patients

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Aim: To compare the efficacy and tolerability of mirtazapine and fluoxetine treatment in a sample population consisting of Chinese patients suffering moderate-to-severe depression.

Method: 133 patients with a diagnosis of major depressive episode (DSM-IV) and scoring 15 or more on the 17-item Hamilton Rating Scale for Depression (HAM-D) were randomly assigned to receive 6 weeks of treatment with either mirtazapine (15–45 mg/day) or fluoxetine (20–40 mg/day). Efficacy was assessed using the HAM-D and Clinical Global Impressions scale, with analyses performed on the intent-to-treat sample using the last-observation-carried-forward method. Safety analysis was based on the all-subjects-treated group.

Results: Mean daily doses were 34.1 mg for mirtazapine (N = 66) and 30.7 mg for fluoxetine (N = 66). Thirty patients in the mirtazapine group and 22 in the fluoxetine group dropped out. Both drugs proved equally effective for reduction of the overall symptoms of depression throughout the treatment period. At day 42, the mean reductions in HAM-D total score (compared with baseline) were 11.8 and 10.6 for the mirtazapine and fluoxetine groups, respectively; however, the changes were not statistically significant. Both treatments were well tolerated, with more nausea and influenza-like symptoms observed for the fluoxetine group, and greater weight increase and somnolence for the mirtazapine analog.

Conclusion: Both mirtazapine and fluoxetine were indistinguishable in effectiveness for treatment of depressive symptoms, and both were well tolerated by our population of depressed Chinese patients. In line with analogous Western reports, the safety of mirtazapine and fluoxetine was comparable for our depressed Chinese patients; however, slightly different side effect profiles were noted for the 2 drugs in our study.

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Mirtazapine is a new antidepressant with a unique pharmacologic profile that differs from currently available antidepressants. It is a specific antagonist of α_2-receptors, which has only a marginal effect on α_1-receptors. Blockade of presynaptic α_2-autoreceptors causes increased norepinephrine release, and direct blockade of inhibitory α_2-heteroreceptors, located on serotonin (5-HT) terminals, leads to increased serotonin release. As the 5-HT_2 and 5-HT_3 receptors are blocked by mirtazapine, however, serotonin release is produced exclusively by stimulation of the 5-HT_1 receptors. This dual action, via both neurotransmitter systems, is the reason that mirtazapine has been termed a noradrenergic and specific serotonergic antidepressant (NaSSA).[1] Analysis of the data from various clinical trials has shown that the overall antidepressant efficacy of mirtazapine is superior to that of placebos[2–4] and comparable to that of amitriptyline, a tricyclic antidepressant.[2,3] Further, the relative lack of anticholinergic and adrenergic side effects associated with mirtazapine treatment means that its safety and tolerability profiles are more favorable than that of amitriptyline.[2,3]

The antidepressant efficacy of the selective serotonin reuptake inhibitor (SSRI) family of antidepressants is well established, and like mirtazapine, SSRIs are better tolerated than the tricyclic antidepressants. Recently, 3 double-blind, randomized trials of Western samples have been conducted comparing mirtazapine with fluoxetine,[5] citalopram,[6] and paroxetine.[7] Compared with fluoxetine, mirtazapine demonstrated significantly superior efficacy

after 3 to 4 weeks of therapy,[5] and the results of the citalopam and paroxetine reports also suggested potentially faster therapeutic onset for mirtazapine.[6,7] Tolerability was good for all 4 pharmaceuticals, with more gastrointestinal side effects (e.g., nausea and vomiting) reported for the SSRI-treated patients and greater weight increase for the mirtazapine-treated patients.[5–7]

Ethnic background can significantly influence both the pharmacokinetics and the pharmacodynamics of drugs, and there may also be substantial impact of racial differences on the efficacy and tolerability of antidepressants.[8,9] As the recent mirtazapine studies were all of Western populations, we conducted a 6-week double-blind trial to compare the efficacy and safety of mirtazapine and fluoxetine for a sample of depressed Chinese patients. The primary objective of our study was comparison of the safety and adverse-event profiles for mirtazapine and fluoxetine. The secondary objective was a comparative evaluation of antidepressant efficacy for these 2 agents. Our results were also compared with those of the Western reports.[5–7]

METHOD

This trial was a multicenter, randomized, double-blind comparison of mirtazapine and fluoxetine, performed in 4 centers in Taiwan, Republic of China, between November 1998 and June 2000.

Patients

Patients were recruited from psychiatric outpatient departments. Inclusion criteria were (1) 18–75 years of age, (2) DSM-IV diagnosis of major depressive episode, (3) 17-item Hamilton Rating Scale for Depression (HAM-D)[10] scores of 15 or more at baseline, (4) duration of current depressive episode between 1 week and 1 year, and (5) provision of informed consent.

Exclusion criteria were (1) pregnancy or lactation; (2) actual suicide risk; (3) history or current diagnosis of bipolar disorder, schizophrenia, psychotic symptoms, schizotypal or borderline personality disorder, or organic mental disorder; (4) current diagnosis (DSM-IV) of anxiety or eating disorder, postpartum depression, epilepsy, or history of seizures or alcohol or substance abuse during the preceding 6 months; (5) clinically relevant progressive disease including renal, cardiovascular, respiratory, or cerebrovascular problems or other serious physical ailments; and (6) clinically relevant abnormal findings during screening.

Treatment Schedule

Only subjects who met all the selection criteria and provided written informed consent were enrolled in the trial. The trial started with a washout period of 6 to 14 days; however, if the subject's condition deteriorated to the extent that treatment could no longer be withheld, this period could be reduced to a minimum of 3 days. This washout period also enabled identification of placebo responders (defined as subjects recording a 25% decrease in HAM-D total score between screening and baseline), who were then excluded.

After this washout period, patients were randomly assigned to receive treatment with either mirtazapine or fluoxetine for 6 weeks. Study medication was prepared for oral administration in capsules/tablets and packaged, without distinguishing characteristics, before delivery using the double-dummy technique. The daily doses were 30 mg/day (days 1–14) for mirtazapine and 20 mg/day (days 1–14) for fluoxetine. The investigator was at liberty to increase the dosage to 45 mg/day of mirtazapine or 40 mg/day of fluoxetine based on clinical response after 14 days of treatment and also to subsequently reduce the dose in the event of intolerable adverse events. Both drugs were given once daily, mirtazapine in the evening and fluoxetine in the morning, using the double-dummy method. The dosages of both drugs were in line with current dosing recommendations.

Other psychotropics, including benzodiazepines or sedating antihistamines, were not allowed. Medication was permitted for mild physical illnesses other than those defined by the exclusion criteria, and up to 4 mg/day of lorazepam or estazolam could be administered in the event of sleeping problems or anxiety symptoms. Formal psychotherapy was not permitted during treatment; however, supportive psychotherapy was allowed.

Efficacy and Adverse-Event Assessment

During the treatment period, safety and efficacy assessments were performed on days 7, 14, 28, and 42, with antidepressant efficacy measured using the HAM-D[10] and Clinical Global Impressions (CGI) instruments.[11]

Information with respect to the possible occurrence of adverse events was obtained from interview and/or examination of the subjects during each visit in the treatment period. Adverse events were defined as any new complaint or symptom emerging during this interval, or any preexisting complaint/symptom that had increased in severity during the study period. Vital signs (heart rate and blood pressure) and body weight were recorded during the visits, with laboratory tests (hematology, blood chemistry, and urinalysis) performed at screening and at the end of treatment.

Statistical Analysis

In order to assess the comparability of the treatment groups, relevant baseline data for important characteristics (demographics, medical history, physical examination, psychiatric data inventory, DSM-IV checklist, inclusion/exclusion criteria, selection checklist) and salient clinical measurements (HAM-D total score and item 1 "depressed mood") were analyzed for the all-subjects-

Table 1. Descriptive Statistics for Demographic and Baseline Hamilton Rating Scale for Depression (HAM-D) Data for the All-Subjects-Treated Group[a]

Variable	Mirtazapine (N = 66)	Fluoxetine (N = 66)	Total (N = 132)
Gender (female/male)	41/25	42/24	83/49
Age, mean (SD), y	47.2 (14.7)	47.1 (15.5)	47.2 (15.0)
Body Mass Index, mean (SD), kg/m^2	23.1 (3.6)	24.0 (4.6)	23.5 (4.2)
HAM-D score, mean (SD)	23.1 (5.1)	24.3 (5.2)	23.7 (5.1)
HAM-D item 1, depressed mood, mean (SD)	2.9 (0.7)	3.0 (0.8)	2.9 (0.8)

[a]Randomized subjects who received at least 1 dose of study medication.

Table 2. Main Reasons for Premature Discontinuation for the All-Subjects-Treated Group[a]

Main Reason	Mirtazapine (N = 66)	Fluoxetine (N = 66)	Total (N = 132)
Adverse events	13	8	21
Subject does not fulfill selection criteria	0	1	1
Subject is unwilling or unable to cooperate for reasons unrelated to the trial	14	7	21
Insufficient therapeutic effects	0	2	2
Other reasons	3	4	7
Total	30	22	52

[a]Randomized subjects who received at least 1 dose of treatment study medication.

treated group (AST; all randomized subjects who had received at least 1 dose of study medication) and for the intent-to-treat group (ITT; all randomly assigned patients who had received at least 1 dose of study medication and had undergone at least 1 postbaseline assessment) using the Student t test or the chi-square test.

Efficacy analyses were based on the ITT group. An observed case analysis was performed for each visit, with a last-observation-carried-forward (LOCF) analysis performed for assessment at the endpoint. Changes in the total HAM-D scores relative to baseline were analyzed using analysis of variance (ANOVA). If the necessary assumptions for the ANOVA were not adequately fulfilled, a Wilcoxon test adjusting for study was performed to compare the 2 treatment groups. Responders were defined by a decrease of at least 50% in the HAM-D total score during treatment relative to baseline, with remitters defined by a HAM-D total score of 7 points or below postbaseline. CGI change relative to baseline was analyzed using the Wilcoxon test adjusting for study.

The AST group was used for the safety analysis. All adverse events, as described by the investigator, were coded using the dictionary terms from the World Health Organization adverse reactions terminology.[12] The number and percentage of subjects experiencing adverse events were analyzed using the chi-square test and Fisher exact test, as necessary.

All tests were 2-sided with the result considered statistically significant if $p \leq .05$. No adjustments were made for multiplicity. Data are presented as mean (SD).

RESULTS

Clinical-Trial Population

One hundred thirty-three subjects were randomly assigned according to trial medication. All but 1 subject received at least 1 dose of trial medication, resulting in a total of 132 treated patients (AST group). A summary of their demographic data is provided in Table 1. The mean baseline HAM-D total scores were 23.1 and 24.3 for the mirtazapine and fluoxetine groups, respectively. Overall, 40% of these subjects had a total score of 25 or more (mirtazapine, 36.4%; fluoxetine, 42.4%), indicating severe depression. Approximately 75% of all subjects scored 3/4 for the HAM-D item "depressed mood."[10]

Of the 132 treated subjects, 80 (mirtazapine, N = 36; fluoxetine, N = 44) completed the 6-week treatment. The main reasons for premature discontinuation are presented in Table 2. Statistical significance was not demonstrated for the rates for dropout or dropout due to adverse events comparing the 2 treatment groups ($p = .212$ and .341, respectively).

Dosing Compliance

The mean (median) daily dosages for the 6-week treatment period were 34.1 mg (31.3 mg) and 30.7 mg (25.5 mg) for the mirtazapine and fluoxetine groups, respectively. The median rate of dosing compliance to active trial medication within the 6-week period was 100% for both treatment groups.

Efficacy

The HAM-D total score was considered the primary parameter for assessment of therapeutic efficacy, with the absolute change from baseline (treatment score minus baseline score) used for statistical analysis. The mean baseline HAM-D total score for the ITT group was modestly, but not significantly, higher for the fluoxetine group (24.6 vs. 23.1; $p = .117$). The HAM-D total score decreased over the course of the 6-week study period for both treatment groups (Figure 1) based on the LOCF approach. This reduction was slightly more pronounced for the mirtazapine-treated patients, especially at days 28 and 42, with a mean reduction in HAM-D total score at day 42 of 11.8 and 10.6 for the mirtazapine and fluoxetine groups, respectively, relative to baseline. The estimated treatment difference at the end of the study period (day 42) was 0.96 in favor of mirtazapine, with a corresponding 2-sided 95% confidence interval of –3.65 to 1.74.

HAM-D responders were defined by a minimum 50% reduction in HAM-D total score from baseline. From day

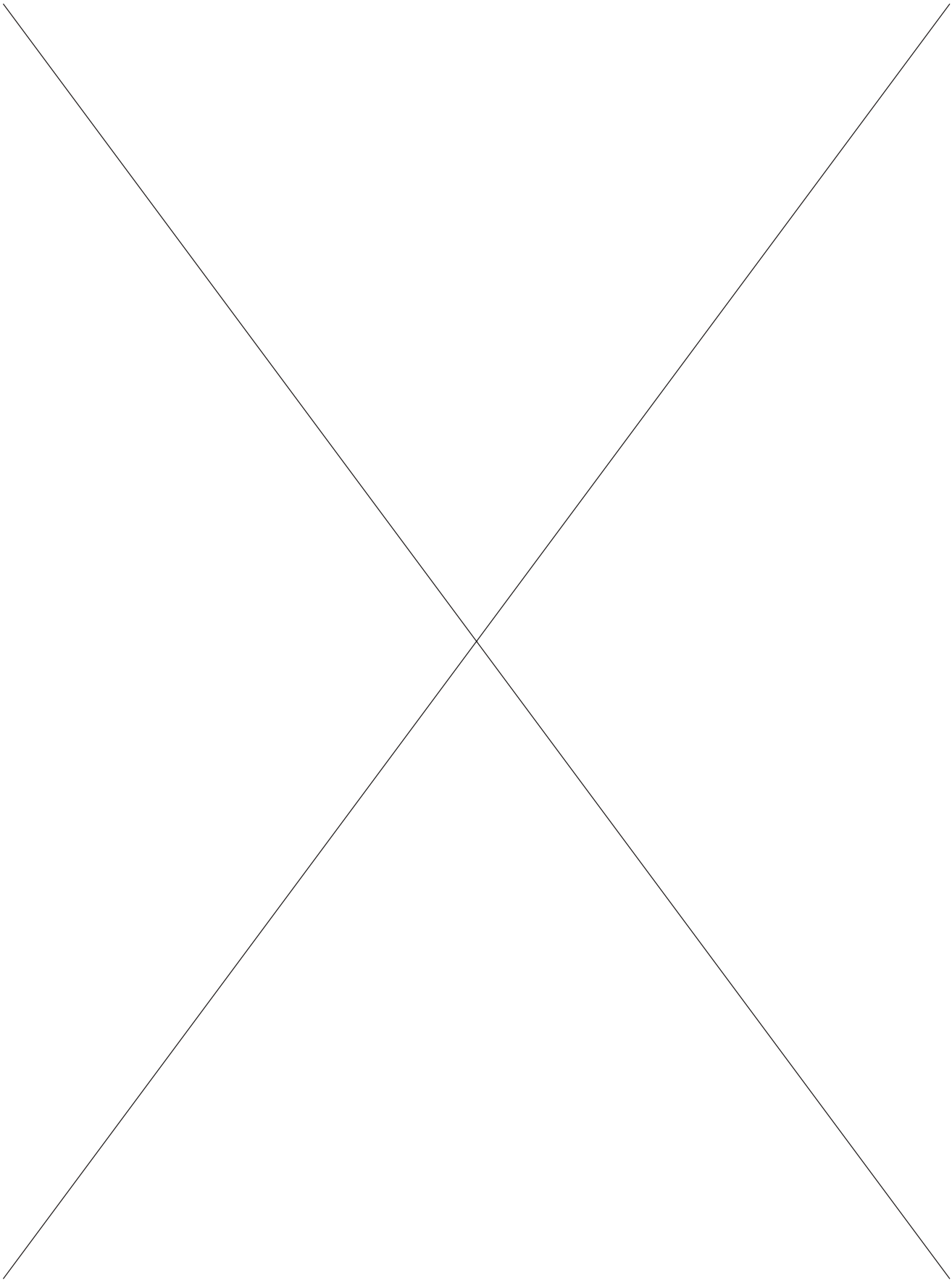
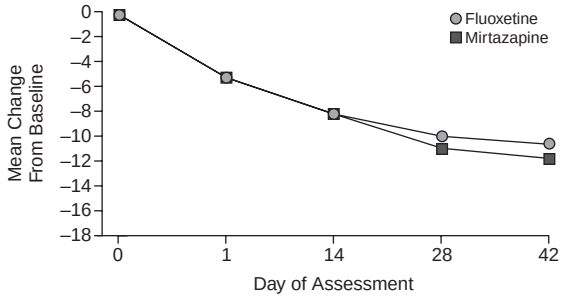
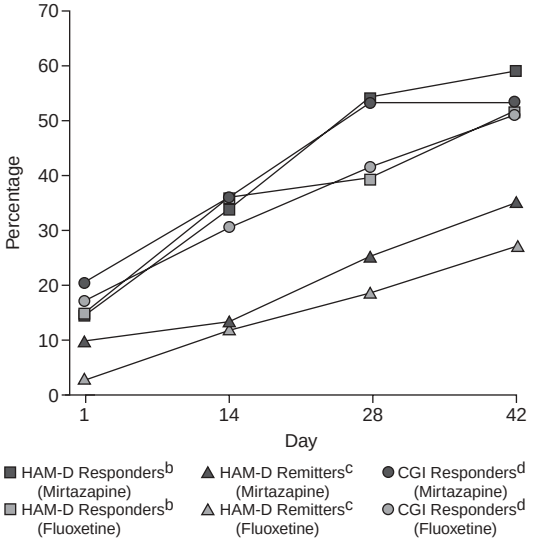


Figure 1. Mean Change From Baseline in Hamilton Rating Scale for Depression Total Score for the Intent-to-Treat Group[a]



[a]Randomly assigned patients who received at least 1 dose of study medication and who underwent at least 1 postbaseline assessment (mirtazapine, N = 60; fluoxetine, N = 59).

Figure 2. Frequency of Hamilton Rating Scale for Depression (HAM-D) Responders, HAM-D Remitters, and Clinical Global Impressions-Global Improvement (CGI) Responders During the Course of the 6-Week Treatment (intent-to-treat group[a])



[a]Randomly assigned patients who received at least 1 dose of study medication and who underwent at least 1 postbaseline assessment (mirtazapine, N = 60; fluoxetine, N = 59).
[b]HAM-D responder defined by a minimum 50% reduction in baseline HAM-D total score.
[c]HAM-D remitter defined by a HAM-D score ≤ 7 during the course of the 6-week treatment.
[d]CGI responder defined by a CGI score of 1 (very much improved) or 2 (much improved).

28 onward, there were more HAM-D responders in the mirtazapine group compared with the fluoxetine group (Figure 2). The largest mirtazapine bias in the HAM-D responder rates was observed on day 28 (53.3% vs. 39.0% for fluoxetine). At day 42, 58% of the mirtazapine-treated subjects and 51% of the fluoxetine-treated subjects were considered HAM-D responders based on the LOCF approach. Further, at all timepoints, more subjects in the mirtazapine group were HAM-D remitters, as defined by a HAM-D score of 7 or below during the 6-week treatment period (Figure 2); however, the differences were not statistically significant. Based on the LOCF approach, 35% of the mirtazapine group and 27% of the fluoxetine analog were in remission by day 42. Figure 2 shows the percentage of subjects who responded to trial medication (as defined by a CGI score change of 1 [very much improved] or 2 [much improved]) during the course of the 6-week treatment. Further, at all assessment points, more subjects in the mirtazapine group were considered responders by the investigator; however, the differences were not statistically significant. Based on the LOCF approach, approximately 50% of the subjects in both treatment groups were judged CGI responders as of day 42.

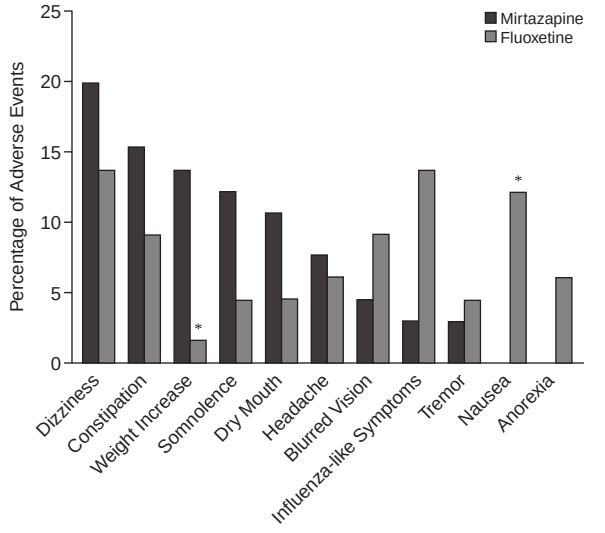
Safety

In total, 85 of the 132 treated subjects reported 1 or more adverse events (mirtazapine, N = 47 [71.2%] vs. fluoxetine, N = 38 [57.6%]). In total, the adverse events for 56 of the 85 subjects (mirtazapine, N = 30 [45.5%] vs. fluoxetine, N = 26 [39.4%]) were judged by the investigator to be possibly, probably, or definitely related to the trial medication. Thirteen (19.7%) of the mirtazapine-treated subjects and 8 (12.1%) of the fluoxetine-treated subjects discontinued therapy prematurely due to adverse events (Table 2).

Based on the WHO preferred terms, the incidence for the most frequently reported adverse events (occurring for more than 5% of the subjects in at least 1 of the treatment groups) is presented in Figure 3. For the mirtazapine group, dizziness (19.7%) was the most frequently reported adverse event, followed by constipation (15.2%), weight increase (13.6%), and somnolence (12.1%). For the fluoxetine group, dizziness (13.6%), influenza-like symptoms (13.6%), and constipation (9.1%) were the most common adverse events. Nausea was determined for 8 of the fluoxetine-treated patients (12.1%) and anorexia for 4 (6.1%), with neither event noted for the mirtazapine group. Further, higher incidence of weight increase ($p = .017$) and lower nausea rate ($p = .006$) were demonstrated for the mirtazapine-treated patients. One patient in the fluoxetine group developed erythema multiforme, which was considered by the investigator as possibly related to the trial medication.

No clinically relevant between-group differences were demonstrated comparing laboratory parameters or vital signs. Two subjects in the mirtazapine group had at least 1 clinically significant, abnormal biochemistry value during the treatment period. An elevated bilirubin total value (day 42, 35.9 μmol/L; baseline, 8.6 μmol/L; normal, 0–34 μmol/L) was noted for 1 patient, while elevated aminotransferase/aspartate aminotransferase was determined

Figure 3. Adverse Events Reported for More Than 5% of the Subjects in the All-Subjects-Treated Group



*p < .05.

for another (day 42, 162.0 μmol/L; baseline 60.0 μmol/L; normal, 0–108 μmol/L).

Clinically significant changes in abnormal body weight (≥ 7% increase from baseline) were noted for 7 subjects in the AST group, including 5 of the mirtazapine-treated patients (7.1%–12.0% increase from baseline) and 2 of the fluoxetine-treated patients (7.2%–16.7% decrease from baseline). Decreases in body weight were recorded for 2 female patients in the fluoxetine group (48.0 kg at baseline to 40.0 kg on day 28 [–16.7%; 105.8 lb–88.2 lb]; 73.3 kg at baseline to 68.0 kg on day 42 [–7.2%; 161.6 lb–149.9 lb]).

DISCUSSION

The study population consisted of patients diagnosed with moderate-to-severe depression. Forty percent of the subjects recorded baseline total HAM-D scores of 25 or more indicating severe depression. Of the ITT group, 52 patients (39.4%) did not complete the study. No significant difference was determined comparing the dropout rates for the mirtazapine and fluoxetine groups ($p = .212$). This dropout rate was higher than rates reported in 3 recent Western studies (22.9%,[7] 28.8%,[5] and 9.6%[6]). Twenty-one (15.9%) of the ITT group dropped out due to adverse effects, with analogous rates in the 3 above studies of 12.0%,[7] 8.0%,[5] and 3.2%.[6] Based on our analysis of the data, the high dropout rate for our Chinese patients may be, in part, due to subjects' lack of sensitivity to the medication. Further study using a different ethnicity for direct comparison may reveal possible racial variations in antidepressant sensitivity.

Recommended starting dosage for mirtazapine therapy is 15–30 mg/day, with the maximum effective dose usually 45 mg/day.[13] Mirtazapine is extensively metabolized in the liver, with the cytochrome P450 (CYP) isoenzymes CYP1A2, CYP2D6, and CYP3A4 mainly responsible for the biotransformation of the agent.[13] Research on cytochrome P450 isoenzymes has demonstrated cross-ethnic differences in genetic polymorphisms of the isoenzymes that may affect drug metabolism.[14] The mean daily mirtazapine dosage for our 6-week treatment (34.1 mg/day) was similar to dosages reported in the 3 Western studies (32.7,[7] 35.9,[6] and 39.8 mg/day[5]). Further, the mean fluoxetine dose in our study was 30.7 mg/day, which is above the 23.8 mg/day reported in one of these comparison studies.[5] This difference could be due to study design (although starting dosage was 20 mg/day of fluoxetine for both studies, the increase to 40 mg was available earlier in our study [day 15 vs. day 29]). Differences in the rate of drug metabolism are another possible explanation for this ethnic variation in fluoxetine response.

In the Western reports, it was found that the HAM-D decrease from baseline was significantly greater for the mirtazapine group in comparison to the fluoxetine group on days 21 and 28, suggesting more rapid onset of efficacy for mirtazapine.[5] In the current study, however, the decrease was similar for the 2 agents over the course of the 6-week treatment (Figure 1). There are several possible explanations for this anomalous finding.[5] First, our result may be a false negative, with the difference in treatment-response rate too small to detect because of our limited sample size. The largest mirtazapine bias in responder rates was observed on day 28 (53.3% vs. 39.0%; Figure 2); however, statistical significance was not achieved. Second, there were slight differences in the fluoxetine dose schedule between the 2 studies as outlined above, with the fluoxetine increase later in the Western study,[5] which may have resulted in delayed therapeutic onset. Third, since it has been reported that mirtazapine offers superior efficacy for treatment of severe depression in comparison to the SSRIs,[15] the difference in therapeutic response may be a reflection of a difference in depression severity between the 2 recruited populations. Finally, the more rapid onset of mirtazapine may be ethnicity-dependent such that the faster onset of mirtazapine is not found in Chinese patients.

More subjects in the mirtazapine group were HAM-D remitters compared with the fluoxetine group at all of the studied timepoints; however, none of the differences were statistically significant (Figure 2). In a previous comparison study of mirtazapine and fluoxetine, the proportion of HAM-D remitters was similar (mirtazapine 23.3%; fluoxetine 25.4%),[5] but lower than in our study (mirtazapine 35.0%; fluoxetine 27.1%); however, the proportion of CGI responders at the end of treatment (day 42) was slightly higher in the Western study (Western study:

mirtazapine 63.3%; fluoxetine 54.0%[5]; our study: mirtazapine 52.5%; fluoxetine 50.8%). In the other 2 Western comparison studies, the proportion of CGI responders to mirtazapine at the endpoint (85.3%[6] and 70.1%[7]) was also higher than in our study. Thus, it appears reasonable to suggest that the issue of ethnicity dependence in mirtazapine response may need further exploration.

Only 13 of the mirtazapine-treated patients (13/66; 19.7%) and 8 of their fluoxetine-treated counterparts (8/66; 12.1%) dropped out of the study prematurely due to adverse events, suggesting both treatments were well tolerated. In total, 85 of the 132 treated subjects reported 1 or more adverse events, with 56 of these events judged possibly, probably, or definitely related to the trial medication by the investigator. Based on the WHO preferred terms, the incidence of the most frequently reported adverse events (those occurring in more than 5% of the subjects in at least 1 of the treatment groups) is presented in Figure 3. The adverse-event profile for our mirtazapine group is very similar to that of previous Western reports in which dizziness, weight increase, somnolence, and dry mouth were the most prevalent side effects[3,5–7]; however, constipation prevalence (15.2%) was the single exception, occurring more frequently than in the analogous Western samples.[3,5–7] As might be expected given the variation in pharmacology, there were some between-group differences in the adverse-event profiles (Figure 3); however, dizziness, constipation, and headache were associated with both antidepressant agents. Nausea, anorexia, and influenza-like symptoms were common among the fluoxetine-treated patients. While nausea and anorexia were not observed in the mirtazapine group, weight increase and somnolence were more common, probably as a consequence of the drug's high affinity for the central histaminergic-1 receptor.[1] Somnolence was reported by a significantly higher percentage of low-dose mirtazapine-treated patients; however, it has been reported that this adverse event occurs less frequently at higher doses and decreases over time.[16] Although weight increase and somnolence were classified as adverse events in this trial, it should be noted that these effects may be beneficial for depressed patients suffering from loss of body weight or experiencing sleep disturbances. Elevated liver function was determined for 2 mirtazapine-treated patients (1 had increased total bilirubin, and elevated alanine aminotransferase/aspartate aminotransferase was determined for another). Very low incidences of clinically relevant changes in the liver enzymes alanine aminotransferase and aspartate aminotransferase have also been reported.[17] It seems reasonable to suggest, therefore, that a follow-up test of liver function may be needed during the initial phase of mirtazapine treatment.

As baseline depression severity may be related to therapeutic antidepressant response, a limitation of the present study is that the mean baseline HAM-D total score was slightly higher for the fluoxetine group.[18] Another limitation is that the final sample size may not have been adequate to provide the statistical power to detect subtle differences between the 2 antidepressants.

In conclusion, mirtazapine and fluoxetine were equally effective for our sample of Chinese patients diagnosed with moderate-to-severe depression. Further, both drugs had different adverse-event profiles, and the adverse events of mirtazapine found in the Chinese patients were similar to Western report. Mirtazapine, with its lower incidence of adverse gastrointestinal effects, may be superior for depressed patients with poor appetite or lowered body weight.

Drug names: amitriptyline (Elavil, Endep, and others), citalopram (Celexa), estazolam (ProSom and others), fluoxetine (Prozac and others), lorazepam (Ativan and others), mirtazapine (Remeron), paroxetine (Paxil).

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