Efficacy and Safety of Mirtazapine in Major Depressive Disorder Patients After SSRI Treatment Failure: An Open-Label Trial

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Objective: To evaluate the efficacy and safety of mirtazapine in depressed outpatients who have shown nonresponse or intolerance to selective serotonin reuptake inhibitor (SSRI) therapy.

Method: In this open-label, 8-week study, the efficacy and safety of mirtazapine among 103 outpatients with DSM-IV major depressive disorder who had failed previous therapy with an SSRI (fluoxetine, paroxetine, or sertraline) were evaluated. The primary efficacy measure was the 17-item Hamilton Rating Scale for Depression (HAM-D-17), and safety assessments included reported adverse events, routine laboratory assessments, physical examinations, and assessments of vital signs. A 4-day washout period followed by mirtazapine treatment was compared with an immediate switch from the SSRI to mirtazapine.

Results: Based on mean HAM-D-17 scores at endpoint and response rates of 48% based on the criterion of ≥ 50% reduction in HAM-D-17 score, mirtazapine was found to be an effective treatment for a substantial proportion of patients for whom an SSRI was ineffective and/or poorly tolerated. Mirtazapine was well tolerated, with sedation and appetite increase/weight gain the most commonly reported adverse events. In addition, no difference in efficacy, safety, or tolerability was observed for patients undergoing an immediate switch from an SSRI (after having been tapered to the minimal effective dose) to mirtazapine, compared with those undergoing the imposition of a 4-day drug-free washout.

Conclusion: These results suggest that an immediate switch to mirtazapine may be a valid therapeutic option among patients who cannot tolerate or do not respond to SSRIs.

(J Clin Psychiatry 2001;62:413–420)

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Supported by Organon Inc., West Orange, N.J.

Financial disclosure: Dr. Fava has received research support and honoraria from Eli Lilly and Company, SmithKline Beecham Pharmaceuticals, Pfizer Inc, Wyeth-Ayerst Laboratories, Organon Inc., Bristol-Myers Squibb Co., GlaxoWellcome, and Solvay Pharmaceuticals; honoraria from Forest Pharmaceuticals, Janssen Pharmaceuticals, Lundbeck, Knoll Pharmaceuticals, Parke-Davis, and Somerset Pharmaceuticals; and research support from Abbott Laboratories, Roche Pharmaceuticals, Novartis, Pharmavite, Lorex Pharmaceuticals, Sanofi/Synthelabo Pharmaceuticals, and Litchwer Pharmaceuticals GmbH.

Presented as a poster at the 152nd annual meeting of the American Psychiatric Association; May 15–20, 1999; Washington, D.C.

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Approximately 29% to 46% of depressed patients show only partial or no response to an initial course of treatment with antidepressants.[1] Lack of efficacy and intolerance are frequent causes of treatment failure or discontinuation. Clinicians frequently switch patients who have failed to respond to antidepressant treatment to other pharmacologic agents, often substituting another antidepressant of the same or a different drug class.

Recently, we surveyed 423 U.S. and Canadian psychiatrists to find out what they would do if a patient failed to respond to 8 weeks or more of an adequate dose of a selective serotonin reuptake inhibitor (SSRI). Switching to a non-SSRI agent was the most popular choice among survey respondents, with 44% indicating this preference.[2] Among respondents whose first choice was to switch to a non-SSRI, dual-acting agents and bupropion were the most frequently designated agents.[2]

Depressed patients are switched from one antidepressant to another of a different class mostly to obtain a different neurochemical effect (e.g., switching from a relatively selective agent to a dual-action agent). In addition, patients who cannot tolerate one agent may show greater

tolerance to an alternate drug with a different side effect profile.

A significant issue that has arisen in studies on the efficacy of switching strategies is the occurrence of discontinuation-emergent adverse events (particularly with short-acting serotonergic agents such as paroxetine and venlafaxine), which may be attributed to the drug to which patients have been switched. The significant psychological and somatic symptoms that have been reported in more than 50% of patients discontinuing antidepressants such as paroxetine and venlafaxine[3,4] may contribute to the lack of tolerance of the switch itself.

Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA) that directly blocks central presynaptic α_2 autoreceptors and heteroreceptors and is also a direct inhibitor of serotonin-2 (5-HT_2) and 5-HT_3 receptors. As a result, mirtazapine enhances central noradrenergic and 5-HT_1–mediated serotonergic neurotransmission. A previous study by Catterson and Preskorn[5] found that 59% of 49 amitriptyline nonresponders exhibited good response on switching to mirtazapine in a crossover phase. Mirtazapine has also shown strong efficacy compared with fluoxetine,[6] and some studies suggest an early onset of action for mirtazapine compared with paroxetine and citalopram.[7,8] Thus, mirtazapine may prove a viable pharmacotherapeutic option for patients who have not responded to SSRI treatment.

This study evaluates the efficacy and safety of mirtazapine among depressed outpatients who have not responded to and/or not tolerated treatment with SSRIs. In addition, the effects of an immediate switch from an SSRI to mirtazapine were compared with those of a nonimmediate switch to mirtazapine, i.e., a switch following SSRI discontinuation and a washout period of 4 days.

METHOD

Subjects

Eligible subjects were adult (≥ 18 years of age) outpatients with a current diagnosis of DSM-IV major depressive disorder who had failed either to respond to an adequate trial with an SSRI (i.e., fluoxetine, paroxetine, or sertraline) or to tolerate SSRI treatment. For patients discontinuing the SSRI due to lack of response, an "adequate trial" was defined as treatment for at least 4 weeks and no more than 6 months, within the dose range for the SSRI specified in the package insert.[9] For patients discontinuing due to intolerance, the SSRI trial was defined as lasting at least 4 days and less than 4 weeks within the dose range for the SSRI specified in the package insert.[9] All eligible patients were assessed while still on SSRI treatment to eliminate the possibility of bias related to the patient's subjective, retrospective recall of events. Patients enrolled in the study as SSRI treatment failures expressed a desire to stop taking the SSRI due to inefficacy and/or intolerance, showed < 50% improvement on treatment with the SSRI, and scored ≥ 16 on the 17-item Hamilton Rating Scale for Depression (HAM-D-17)[10] while still taking the SSRI. The degree of improvement on treatment with the SSRI was determined with a modified version of the Massachusetts General Hospital (MGH) Antidepressant History Questionnaire.[1] The study was approved by the institutional review boards at each site, and written consent was obtained from all subjects prior to study participation.

Patients who were not simply nonresponders, but in fact were refractory to treatment for the current episode of depression were excluded from the trial. Treatment-refractory subjects were defined as those who had received an adequate trial of treatment with 3 different classes of antidepressants (i.e., tricyclic antidepressants, monoamine oxidase inhibitors, and SSRIs) and had not responded to treatment and those who had received an adequate trial of treatment with 2 different classes of antidepressants as well as electroconvulsive therapy (ECT), and had not responded. For purposes of describing treatment-refractory patients, an adequate trial of drug treatment was defined as at least 4 weeks but not longer than 18 weeks in the current episode of depression.

Other exclusion criteria included a history of seizures; ECT within 3 months of study enrollment; clinically significant abnormal laboratory parameter results suggesting the presence of a previously undiagnosed illness; aspartate aminotransferase or alanine aminotransferase values > 2 times the upper limit of normal; clinically significant abnormal physical examination findings; a primary DSM-IV diagnosis of schizophrenia, anxiety disorders (except for specific phobias), eating disorders, bipolar disorder, or personality disorder; untreated/uncompensated endocrine disorders; serious risk for suicide; a history of alcohol or drug abuse within 6 months of enrollment; and the need for concomitant treatment with psychotropic medication for a sleep disorder. Potential subjects were evaluated through pretreatment (screening) assessments, including physical examination and medical and psychiatric history and the use of the Adult Personal Data Inventory, the MGH Antidepressant History Questionnaire, a DSM-IV diagnosis checklist, and the HAM-D-17.

Study Design

This study was an 8-week open-label trial conducted at 7 academic sites in the United States. In addition, the study included a double-blind pretreatment period, to enable comparison of the effect of an immediate switch from SSRI treatment to mirtazapine with a switch to mirtazapine preceded by a 4-day washout. The study tested the hypothesis that there would be no difference in the efficacy of mirtazapine related to washout condition or SSRI group, as assessed by the degree of improvement in the primary efficacy measure of depression (HAM-D-17)

over the double-blind study period and the 8-week open-label period. With this study, we also wanted to evaluate possible differences in SSRI discontinuation–emergent somatic symptoms (as assessed by the Symptom Questionnaire somatic symptoms subscale[11]) in relationship to washout condition or SSRI group (intermediate- to long-acting SSRIs [sertraline and fluoxetine] vs. a short-acting SSRI [paroxetine]).

The pretreatment period of the study included up to 2 patient visits. Subjects were first evaluated to determine if they were taking SSRI doses higher than the minimum doses (fluoxetine, > 20 mg/day; paroxetine, > 20 mg/day; or sertraline, > 50 mg/day). Those who were taking a higher dose were tapered to the minimum dose between the first and second pretreatment visits. Subjects who were already taking the minimum dose were assigned immediately to the second pretreatment visit.

All subjects were then randomly assigned to a washout or immediate-switch group and treated under double-blind conditions for 1 week. Subjects in the washout group continued SSRI treatment for 3 days, then took placebo for 4 days. Those in the immediate-switch group continued to take their SSRI at the minimum dose for 7 days. Thus, on starting mirtazapine in the open-label phase of the study, patients in the immediate-switch group underwent an immediate switch, whereas patients in the washout group underwent a switch to mirtazapine preceded by a 4-day washout.

Following the double-blind pretreatment week, open-label treatment with mirtazapine was started at 15 mg/day at visit 0 (baseline). Subjects received an 8-week course of mirtazapine treatment with the dose adjusted as needed in 15-mg increments at each visit, up to a maximum of 45 mg/day. The efficacy and safety of mirtazapine were assessed at weeks 1, 2, 4, 6, and 8 following the initiation of mirtazapine therapy.

Evaluation of Efficacy

The primary efficacy measure for this study was the HAM-D-17. This instrument was administered at each visit by the clinical study investigators. Secondary efficacy measures included the Clinical Global Impressions-Severity of Illness scale (CGI-S),[12] the Clinical Global Impressions-Improvement scale (CGI-I),[12] the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q),[13] and the Symptom Questionnaire. The CGI-S and CGI-I consist of clinician-rated assessments of illness severity and degree of improvement.[12] The Q-LES-Q is a self-reporting questionnaire aimed at assessing the degree of enjoyment and satisfaction experienced by patients.[13] Sexual functioning is one of the domains assessed by the Q-LES-Q. The Symptom Questionnaire is a 92-item self-reporting instrument consisting of 4 symptom subscales (anxiety, depression, somatic symptoms, and anger/hostility) and 4 well-being subscales, with somatic well-being as one of them.[11]

Evaluation of Safety

Safety analysis was performed for all patients who took at least 1 dose of mirtazapine (all-subjects-treated group). Measures of safety included reported adverse events, routine laboratory assessments (performed at the first pretreatment visit and at week 8), physical examinations (performed at the first pretreatment visit and at week 8), and the patient's vital signs, including blood pressure, heart rate, body temperature, respiration rate, and body weight (assessed at both pretreatment visits and at all study weeks that included a clinic visit).

Statistical Analyses

Statistical analyses were performed by SSRI group and washout condition for the primary efficacy parameter, change from baseline HAM-D-17 score. In addition, the proportion of responders, defined as subjects demonstrating at least a 50% reduction in HAM-D-17 scores from baseline, was analyzed as a secondary efficacy parameter. Other secondary efficacy parameters included the CGI-I, CGI-S, Q-LES-Q, and Symptom Questionnaire, based on change from baseline scores. Analyses were done for scheduled assessments at baseline and weeks 1, 2, 4, 6, and 8, using the last-observation-carried-forward (LOCF) approach, for all continuous variables at all timepoints post-baseline. All statistical tests were 2-sided, and statistical significance was set at $p \leq .05$.

For change in the HAM-D-17 scores, a 2-way analysis of variance on rank transformed data with washout condition and SSRI group as factors (including interaction) was performed. In the case of a significant interaction ($p \leq .05$), the interaction was further analyzed by comparing washout and immediate-switch conditions within an SSRI group. The ranking was done with all observations to be compared in the washout conditions and in the SSRI groups, as appropriate. Analysis of the 50% reduction in HAM-D-17 score was performed using the Cochran-Mantel-Haenszel test, adjusting for SSRI group. The Breslow-Day test was used to test for a statistically significant interaction between washout condition and SSRI group, and washout and immediate-switch conditions were compared within SSRI groups using the Fisher exact test.

Postbaseline safety analyses were based on the all-subjects-treated open-label group, defined as all subjects who completed the double-blind pretreatment period and who received at least 1 dose of mirtazapine during the open-label phase after undergoing baseline evaluation. In addition, safety analyses to test for washout effects were performed for all subjects treated with double-blind medication.

Additional post hoc analyses, including descriptive statistics on baseline and clinical characteristics and efficacy analyses, were performed on the all-subjects-treated open-label group. For this purpose, study subjects were classified into 3 groups: nonresponders, SSRI-intolerant

Table 1. Disposition of Study Subjects at Baseline by SSRI Pretreatment and Washout/Immediate-Switch Condition, N[a]

	Washout			Immediate Switch			
Population	Fluoxetine	Paroxetine	Sertraline	Fluoxetine	Paroxetine	Sertraline	Total
All subjects who were dispensed open-label mirtazapine	20	11	19	22	13	18	103
All-subjects-treated group[b]	19	11	18	22	13	18	101
Intent-to-treat group[c]	17	11	17	20	12	17	94
Subjects who completed the study	11	6	10	12	9	10	58
Subjects who prematurely discontinued (total)	8	5	8	10	4	8	43
Due to adverse events	7	1	6	5	2	5	26
Due to other reasons	1	4	2	5	2	3	17

[a]Abbreviation: SSRI = selective serotonin reuptake inhibitor.
[b]All subjects who took at least 1 dose of the study medication (mirtazapine).
[c]All subjects who took mirtazapine for at least 1 week and had at least 1 postbaseline efficacy assessment.

Table 2. Demographic Data and SSRI Treatment Parameters by Washout/Immediate-Switch Condition at Baseline[a]

	Washout			Immediate Switch			
Variable	Fluoxetine (N = 19)	Paroxetine (N = 11)	Sertraline (N = 18)	Fluoxetine (N = 22)	Paroxetine (N = 13)	Sertraline (N = 18)	Total (N = 101)
Age, y, mean (SD)	40.8 (11.3)	47.9 (14.7)	44.6 (13.4)	42.5 (12.3)	46.3 (12.7)	44.9 (13.9)	44.1 (12.8)
Female subjects, N	11	7	12	16	7	9	62
Patients tapered from SSRI, N	3	1	8	2	3	6	23
Final SSRI dose, mg, mean (SD)	24.2 (10.7)	21.0 (3.2)	83.3 (48.5)	21.8 (5.9)	21.5 (6.9)	72.2 (35.2)	NA
Duration of SSRI treatment, d, mean (SD)	65.3 (51.2)	60.6 (55.8)	46.9 (36.4)	36.6 (30.4)	60.2 (49.2)	47.5 (53.8)	51.4 (45.7)

[a]Includes subjects who took at least 1 dose of the study medication (mirtazapine). Abbreviations: NA = not applicable, SSRI = selective serotonin reuptake inhibitor.

subjects, and relapsers (or protocol violations). Nonresponders were defined as those patients who were on SSRI treatment for more than 4 weeks prior to initiation of the study, but were not effectively treated by the SSRI (i.e., < 50% improvement on treatment with the SSRI, according to the MGH Antidepressant History Questionnaire). Intolerant subjects were those on SSRI treatment for less than 4 weeks who experienced adverse events necessitating discontinuation of the drug. Relapsers were defined as those who had ≥ 50% improvement while on treatment with the SSRI prior to study initiation for ≥ 4 weeks, according to the MGH Antidepressant History Questionnaire, but who subsequently failed treatment due to inadequate drug efficacy (thereby not meeting the criteria of the study and representing protocol violations).

RESULTS

Of the 129 subjects screened and deemed eligible, 116 were randomly assigned to the initial 1-week double-blind pretreatment phase of the study. Thirteen patients discontinued during this phase, with 103 completing double-blind pretreatment. We then enrolled all 103 patients into the subsequent 8-week open-label treatment phase of the study (63 women and 40 men, mean ± SD age = 44.0 ± 12.9 years; mean HAM-D-17 score at baseline = 20.4 ± 4.1). Open-label mirtazapine was dispensed to all 103 patients. Subsequently, 101 took at least 1 dose of mirtazapine (all-subjects-treated group). The intent-to-treat (ITT) group consisted of 94 patients who took mirtazapine for at least 1 week during the open-label phase and had at least 1 postbaseline efficacy assessment.

Washout Versus Immediate-Switch Subjects

Of the 94 ITT subjects, 49 underwent an immediate switch instead of washout, while 45 underwent a washout period prior to entering the open-label phase. The disposition of study subjects is shown in Table 1. Of the 103 patients remaining after the double-blind pretreatment phase of the study, 58 completed the 8-week, open-label course of treatment with mirtazapine, and 43 prematurely discontinued from the study due to adverse events (N = 26) or for other reasons (N = 17). Demographic data and SSRI treatment parameters are summarized for each of the 6 study groups, as classified by pretreatment (fluoxetine, paroxetine, or sertraline) and washout conditions (immediate switch or washout) in Table 2, and response to pretrial SSRI treatment is summarized by pretreatment in Table 3. The mean daily dose of mirtazapine for these 6 groups ranged from 24.3 to 27.5 mg/day.

At baseline, immediately after the end of the double-blind, randomized pretreatment period (washout vs. immediate switch), mean HAM-D-17 scores were 20.3 and 20.4, respectively. No statistically significant differences in the mean HAM-D-17 change scores were found for subjects undergoing washout versus immediate switch after

Table 3. Response to Pretrial SSRI Treatment (all subjects dispensed open-label mirtazapine), N[a]

Population	Fluoxetine (N = 42)	Paroxetine (N = 24)	Sertraline (N = 37)	Total (N = 103)
SSRI nonresponders	34	18	24	76
SSRI-intolerant subjects	6	4	8	18
SSRI relapsers	2	2	5	9

[a]Patients classified as relapsers on pretrial SSRI treatment represent protocol violations. Abbreviation: SSRI = selective serotonin reuptake inhibitor.

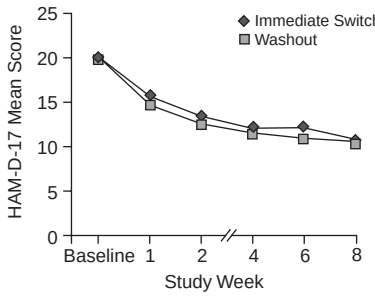
the first week of open-label mirtazapine treatment. The mean reduction from baseline in HAM-D-17 scores at endpoint was 9.5 for the washout and 9.3 for the immediate-switch conditions (Figure 1). There were no statistically significant differences in the proportions of subjects with a 50% or greater improvement in their HAM-D-17 scores within the washout or immediate-switch conditions for any of the SSRI treatment groups. When the SSRI groups were combined, 48% of subjects under both the washout and immediate-switch conditions had ≥ 50% improvement at endpoint.

SSRI Discontinuation–Emergent Somatic Symptoms

We evaluated changes from screening to baseline in the Symptom Questionnaire somatic symptoms subscale scores as a possible measure of discontinuation-emergent adverse events and compared them between the group taking longer-acting SSRIs (sertraline- and fluoxetine-treated patients) and the group taking a relatively short-acting SSRI (paroxetine). This comparison revealed a significant difference between the SSRI groups in the washout condition, but not in the immediate-switch condition. Among ITT patients in the washout condition, while the paroxetine-treated patients (N = 11) showed a mean increase of 1.5 ± 3.8, the sertraline- and fluoxetine-treated patients (N = 34) showed a mean decrease of 1.2 ± 3.3. The difference in change score between paroxetine-treated patients and sertraline/fluoxetine-treated patients was statistically significant ($p < .03$). In the immediate-switch condition, while the paroxetine-treated patients (N = 12) showed a mean increase in symptoms of 0.1 ± 2.4, the sertraline- and fluoxetine-treated patients with valid scores on the questionnaire (N = 36) showed a mean decrease of 0.4 ± 2.9 (not significant).

Upon initiation of mirtazapine treatment, there was a reduction in Symptom Questionnaire somatic symptoms subscale scores from the baseline visit to the week-1 visit in the washout condition for both the paroxetine-treated patients (mean decrease = 0.8 ± 2.6) and the sertraline- and fluoxetine-treated patients (mean decrease = 0.5 ± 3.6). For immediate-switch patients, this reduction also occurred for both the paroxetine-treated patients (mean decrease = 0.4 ± 2.8) and for the sertraline- and fluoxetine-treated patients (mean decrease = 1.2 ± 3.7).

Figure 1. HAM-D-17 Mean Score From Baseline to Week 8 (open-label study phase) by Washout Condition for Intent-to-Treat Patient Population, SSRI Groups Pooled[a]



[a]Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, SSRI = selective serotonin reuptake inhibitor.

SSRI Nonresponders and SSRI-Intolerant Subjects

Eight of the 94 ITT patients (open-label phase) failed to meet the criterion of < 50% improvement during pretrial SSRI treatment according to the MGH Antidepressant History Questionnaire and therefore represented protocol violations. These patients were considered to be relapsers and not nonresponders, nor SSRI intolerant. As relapsers, they were excluded from the analyses of SSRI nonresponders versus SSRI-intolerant subjects. Therefore, of the remaining 86 patients, 69 were classified as nonresponders to SSRIs, and 17 were categorized as SSRI intolerant.

Among the 69 SSRI nonresponders (25 women and 44 men, mean age = 44.3 ± 13.1 years), the mean HAM-D-17 score at baseline was 20.7 ± 4.2, and the mean CGI-S score at baseline was 4.1 ± 0.5. The 69 nonresponders consisted of 29 patients who had been on treatment with fluoxetine, 18 with paroxetine, and 22 with sertraline.

For the 17 SSRI-intolerant patients (10 women and 7 men, mean age = 40.2 ± 8.9 years), the mean HAM-D-17 score at baseline was 19.9 ± 4.3, and the mean CGI-S score at baseline was 4.0 ± 0.5. Of these patients, 6 had taken fluoxetine; 3, paroxetine; and 8, sertraline.

SSRI nonresponders. For SSRI nonresponders within the ITT patient group (N = 69), there was a marked decrease in mean HAM-D-17 score from baseline to endpoint, with a mean change of 10.0 ± 6.8. Mean changes in HAM-D-17 score from baseline by SSRI were 8.4 ± 5.6 among fluoxetine nonresponders, 13.1 ± 7.7 among paroxetine nonresponders, and 9.7 ± 6.9 among sertraline nonresponders. The overall response rate (≥ 50% reduction in HAM-D-17 total score from baseline) for the SSRI-nonresponder group was 48% (33/69). HAM-D-17 response rates by SSRI were 38% (11/29) among fluoxetine nonresponders, 67% (12/18) among paroxetine nonresponders, and 46% (10/22) among sertraline nonresponders.

Table 4. Changes in HAM-D-17 Score From Baseline and Response Rates[a]

Variable	SSRI Nonresponders (N = 69)			SSRI-Intolerant Subjects (N = 17)			SSRI Relapsers (N = 8)			Total (N = 94)		
	Fluoxetine (N = 29)	Paroxetine (N = 18)	Sertraline (N = 22)	Fluoxetine (N = 6)	Paroxetine (N = 3)	Sertraline (N = 8)	Fluoxetine (N = 2)	Paroxetine (N = 2)	Sertraline (N = 4)	Fluoxetine (N = 37)	Paroxetine (N = 23)	Sertraline (N = 34)
Baseline HAM-D-17 score												
Mean	19.69	22.50	20.59	20.50	19.00	19.75	19.50	20.00	17.25	19.81	21.83	20.00
SD	(2.93)	(5.08)	(4.67)	(5.32)	(4.00)	(4.10)	(2.12)	(5.66)	(3.59)	(3.29)	(4.96)	(4.44)
Endpoint HAM-D-17 score												
Mean	11.31	9.44	10.86	12.17	7.67	11.00	23.00	14.50	10.00	12.08	9.65	10.79
SD	(5.74)	(6.09)	(6.33)	(7.96)	(5.51)	(6.41)	(5.66)	(10.61)	(1.63)	(6.51)	(6.26)	(5.88)
Change in HAM-D-17 score from baseline to endpoint												
Mean	8.38	13.06	9.73	8.33	11.3	8.75	−3.50	5.50	7.25	7.73	12.17	9.21
SD	(5.56)	(7.73)	(6.94)	(4.80)	(6.51)	(8.78)	7.78	(4.95)	(2.50)	(6.03)	(7.48)	(6.95)
Response rates at endpoint												
N	11	12	10	3	2	4	0	1	0	14	15	14
(%)[b]	(37.9)	(66.7)	(45.5)	(50.0)	(66.7)	(50.0)	(0.0)	(50.0)	(0.0)	(37.8)	(65.2)	(41.2)

[a]Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, SSRI = selective serotonin reuptake inhibitor.
[b]Response is defined as at least 50% reduction in HAM-D-17 total score from baseline.

SSRI-intolerant subjects. With respect to SSRI-intolerant subjects in the ITT study population (N = 17), mean HAM-D-17 score decreased from baseline to endpoint (mean change = 9.1 ± 6.9). Mean changes in HAM-D-17 score from baseline by SSRI were 8.3 ± 4.8 among patients intolerant to fluoxetine, 11.3 ± 6.5 among those intolerant to paroxetine, and 8.8 ± 8.8 among those intolerant to sertraline. The overall response rate (≥ 50% reduction in HAM-D-17 total score from baseline) for the SSRI-intolerant group was 53% (9/17). HAM-D-17 response rates by SSRI for patients intolerant to fluoxetine, paroxetine, and sertraline, respectively, were 50% (3/6), 67% (2/3), and 50% (4/8). Table 4 shows HAM-D-17 changes from baseline and response rates by SSRI and response to SSRI.

Tolerability

Of the 101 all-subjects-treated patients, 58 completed the study and 43 dropped out prematurely. Dropouts consisted of 26 patients (26%) who discontinued due to adverse events and 17 patients (17%) who discontinued for other reasons (e.g., lost to follow-up). Adverse events resulting in premature discontinuation for 16 of the 26 subjects were psychiatric symptoms, i.e., aggravated depression (N = 3), mania (N = 2), insomnia (N = 1), somnolence (N = 6), and nervousness (N = 4). The remaining adverse events resulting in discontinuation were paresthesia (N = 2), hypesthesia (N = 1), dyspepsia (N = 1), constipation (N = 1), weight increase (N = 3), coronary artery disorder (N = 1), and edema (N = 1). For those subjects who withdrew from the study due to adverse events, discontinuation occurred in the majority of subjects during the first (N = 12) and second (N = 9) weeks of treatment with mirtazapine. There was no statistically significant difference in dropout rates between patients who underwent the SSRI washout period and those who were immediately switched to mirtazapine (29% and 23%, respectively). In addition, the premature termination rates by SSRI were comparable for the washout and immediate-switch conditions.

For SSRI nonresponders only, the overall dropout rate was 43% (33/76), with 22% (17/76) discontinuing due to adverse events. For patients intolerant to SSRI treatment, the overall dropout rate was 33% (6/18), with 22% (4/18) withdrawing from the study due to adverse events.

The adverse events most commonly reported by mirtazapine-treated patients were somnolence (50%), increased appetite (30%), headache (29%), weight gain (23%), dizziness (21%), and nervousness (20%). All side effects, including weight gain, were evaluated by patient self-report. Table 5 shows the incidence of commonly reported adverse events by pretreatment group.

Symptom Questionnaire

The results of the self-rated Symptom Questionnaire showed a significant ($p < .05$) reduction in self-rated

Table 5. Most Commonly Occurring Adverse Events (incidence ≥ 10%) by SSRI and Washout/Immediate-Switch Condition, All-Subjects-Treated Patient Population, N (%)[a]

	Fluoxetine		Paroxetine		Sertraline		All SSRI Groups		
Event	Washout (N = 19)	Immediate Switch (N = 22)	Washout (N = 11)	Immediate Switch (N = 13)	Washout (N = 18)	Immediate Switch (N = 18)	Washout (N = 48)	Immediate Switch (N = 53)	All Patients (N = 101)
Somnolence	11 (58)	12 (55)	5 (45)	3 (23)	9 (50)	10 (56)	25 (52)	25 (47)	50 (49.5)
Increased appetite	2 (11)	10 (45)	2 (18)	4 (31)	7 (39)	5 (28)	11 (23)	19 (35)	30 (29.7)
Increased weight	3 (16)	8 (36)	2 (18)	4 (31)	3 (17)	3 (17)	8 (17)	15 (28)	23 (22.8)
Dizziness	4 (21)	6 (27)	2 (18)	3 (23)	3 (17)	3 (17)	9 (19)	12 (23)	21 (20.8)
Nervousness	3 (16)	3 (14)	3 (27)	3 (23)	2 (11)	6 (33)	8 (17)	12 (23)	20 (19.8)
Headache	5 (26)	4 (18)	4 (36)	7 (54)	5 (28)	4 (22)	14 (29)	15 (28)	29 (28.7)
Diarrhea	3 (16)	4 (18)	2 (18)	4 (31)	0 (0)	3 (17)	5 (10)	11 (21)	16 (15.8)
Edema	1 (5)	0 (0)	0 (0)	1 (8)	0 (0)	0 (0)	1 (2)	1 (2)	2 (14.9)
Dyspepsia	3 (16)	1 (5)	1 (9)	0 (0)	3 (17)	4 (22)	7 (15)	5 (9)	12 (11.9)
Fatigue	3 (16)	0 (0)	0 (0)	2 (15)	3 (17)	4 (22)	6 (13)	6 (11)	12 (11.9)
Back pain	1 (5)	2 (9)	2 (18)	4 (31)	0 (0)	2 (11)	3 (6)	8 (15)	11 (10.9)
Constipation	4 (21)	1 (5)	0 (0)	2 (15)	2 (11)	2 (11)	6 (13)	5 (9)	11 (10.9)
Insomnia	0 (0)	3 (14)	1 (9)	1 (8)	2 (11)	4 (22)	3 (6)	8 (15)	11 (10.9)

[a]Abbreviation: SSRI = selective serotonin reuptake inhibitor.

symptoms on all 4 symptom subscales (depression, anxiety, somatic symptoms, and anger/hostility) during the open-label course of treatment with mirtazapine.

Q-LES-Q

On 9 of the 10 subscales of the Q-LES-Q, the mean change scores increased significantly ($p < .05$) from baseline to endpoint, indicating an improvement in quality of life on each of the subscales. The dimensions of life assessed included physical health, sexual drive, work, school performance, and other dimensions of daily life. The only scale that did not reflect improvement was school for the immediate-switch group. Only a small subset of patients (N = 5) were in school, and none of the 5 patients who had baseline school data provided data on this dimension at endpoint. Perhaps because the scale is lengthy and self-rated, many subjects did not fully complete the Q-LES-Q.

Item 9 of the overall satisfaction subscale of the Q-LES-Q consists of the question, "Taking everything into consideration, during the past week how satisfied have you been with your sexual drive, interest, and/or performance?" Of the 74 patients on treatment with SSRIs who rated themselves at screening as having poor or very poor sexual functioning on this item of the Q-LES-Q, 40 (54%) reported an improvement in sexual functioning at endpoint after mirtazapine treatment, and 32 (43%) rated themselves as having fair-to-very-good sexual functioning at endpoint.

CONCLUSION

Our study indicates that an immediate switch from SSRIs to mirtazapine is as well tolerated and effective as a switch following a washout period. Of this patient population consisting of patients for whom SSRI treatment had failed, 57% (58/101) completed the 8-week course of treatment with mirtazapine, and 48% of patients (21/45, immediate-switch group; 23/47, washout) had a 50% or greater improvement on their HAM-D-17 scores at endpoint (analysis based on LOCF approach). No statistically significant differences were observed between washout and immediate-switch patients in mean HAM-D-17 scores, response rates according to criteria involving a 50% or greater reduction in HAM-D-17 scores, or rates of withdrawal due to adverse events. This suggests that there is no apparent need for washout when switching from an SSRI to mirtazapine.

Our results also indicate that switching to mirtazapine is a safe and effective approach for depressed patients who do not respond to or do not tolerate SSRIs. The response rates in our study populations (washout and immediate-switch) approximate 50%. In addition, the 4-day washout condition was associated with significantly higher rates of discontinuation-emergent adverse events (as measured by the change in somatic symptom subscale score of the Symptom Questionnaire) during the washout period in the group of patients treated with the relatively short-acting SSRI paroxetine, but not in the group of patients treated with the relatively longer-acting SSRIs sertraline and fluoxetine. The scores in the somatic symptom subscale of the Symptom Questionnaire actually decreased on initiation of treatment with mirtazapine, suggesting that the immediate switch to mirtazapine may be beneficial even for those patients experiencing discontinuation-emergent adverse events with short-acting SSRIs such as paroxetine.

Furthermore, in line with the overall findings of our study, the response rate involving a 50% or greater reduction in HAM-D-17 scores for the SSRI-nonresponder group was 48% (33/69). This is consistent with the findings of a previous study by Catterson and Preskorn[5] of a 59% response rate among amitriptyline nonresponders who switched to mirtazapine in a crossover phase.

Sedation and appetite increase/weight gain were the most commonly observed adverse events associated with mirtazapine treatment, as would be expected based on the package insert information.[9] The incidences of dizziness, nervousness, headache, diarrhea, and insomnia were higher than would be expected based on previous double-blind, placebo-controlled clinical trials.[9] In these previous studies, adverse events are reported at rates of 7% for dizziness, and ≤ placebo for nervousness, headache, diarrhea, and insomnia.[9] Higher incidences of adverse events in open-label versus double-blind studies of antidepressant agents have been observed before and are a well-known, though poorly understood, phenomenon. On the other hand, it is possible that some of these adverse events may be related to the discontinuation of the SSRIs, as they have been frequently described in studies of discontinuation-emergent adverse events with SSRIs, particularly with short-acting ones.[3,4] With respect to sexual functioning, the majority of patients in this study who had experienced sexual side effects while on treatment with their SSRI reported improvement in sexual functioning on switching to mirtazapine, and, in fact, a substantial proportion of these patients reached a level of sexual functioning that was fair to very good.

The main limitation of the study is the lack of a control arm, meaning that we cannot rule out the possibility of nonspecific, placebo-like effects. However, it is unlikely that such a nonspecific effect would lead to a 50% response among nonresponders to SSRI treatment who were switched to mirtazapine. One of the methodological strengths of this study is related to the fact that the assessment of treatment nonresponse was made while the patients were still taking their SSRI, thereby minimizing the risk of recall biases, and after patients had been exposed to adequate doses and durations of SSRI treatment. Since less than half of the patients required tapering to the minimum dose of the SSRI, it is possible that some of the patients enrolled into our study might have responded to higher doses of their SSRI. On the other hand, the fact that most patients did not require a taper at the time of study enrollment does not necessarily imply that higher doses had not been tried prior to study enrollment, since clinicians referring patients to the study may have tapered the SSRI dose in preparation for study enrollment.

These results suggest that an immediate switch to mirtazapine after patients were tapered to the minimum effective SSRI dose is an effective and well-tolerated treatment among depressed patients who cannot tolerate or do not respond to SSRIs. The efficacy and safety of the immediate mirtazapine switch appeared to be independent of the short- or long-acting properties of the SSRI and warrant further study. A double-blind study comparing the switch to mirtazapine with the switch to another SSRI is currently ongoing.

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin), fluoxetine (Prozac), mirtazapine (Remeron), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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