Efficacy of Mirtazapine for Prevention of Depressive Relapse: A Placebo-Controlled Double-Blind Trial of Recently Remitted High-Risk Patients

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Background: The necessity of antidepressant continuation-phase therapy following acute-phase response has resulted in the need to characterize the longer-term efficacy and safety of all new medications. Previous studies using "extension" protocols suggest that mirtazapine has sustained antidepressant effects. The current study was performed to evaluate the efficacy and safety of up to 1 year of mirtazapine therapy, using a more rigorous, randomized, placebo-controlled discontinuation design.

Method: An intent-to-treat sample of 410 patients meeting DSM-IV criteria for moderate-to-severe recurrent or chronic major depressive episodes began 8 to 12 weeks of open-label therapy with mirtazapine (flexibly titrated, 15–45 mg/day). Thereafter, 156 fully remitted patients (according to Hamilton Rating Scale for Depression and Clinical Global Impressions-Improvement scores) were randomly assigned to receive 40 weeks of double-blind continuation-phase therapy with either mirtazapine or placebo.

Results: Mirtazapine therapy reduced the rate of depressive relapse by more than half, with 43.8% of patients relapsing on treatment with placebo as compared with 19.7% of the mirtazapine-treated patients. The discontinuation rate due to adverse events was 11.8% for active mirtazapine therapy versus 2.5% for placebo. Although weight gain was significantly greater in the group receiving active medication during the double-blind phase ($p = .001$), patients taking mirtazapine gained only 1.4 kg (3.1 lb) across the 40 weeks of continuation therapy, and there was no difference in the rates of weight gain as a new-onset adverse event.

Conclusion: Continuation-phase therapy with mirtazapine is effective and well tolerated.

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Placebo-controlled studies consistently indicate that the risk of relapse within 6 months of discontinuation of acute-phase antidepressant pharmacotherapy ranges between 40% and 60%.[1–4] As a result, at least 4 to 6 months of continuation-phase therapy is almost always recommended for patients who respond to antidepressant medications.[5–7] It is therefore necessary to confirm both the efficacy and safety of continuation-phase therapy with all new antidepressant medications.

Mirtazapine, a piperazinoazepine compound with virtually no effect on monoamine reuptake, is one of the more recently introduced antidepressants.[8] The antidepressant effects of mirtazapine are thought to be mediated by blockade of α_2-noradrenergic autoreceptors, which increases norepinephrine release, and through the effects of norepinephrine, which stimulates α_1 heteroreceptors on serotonergic cell bodies, indirectly increasing the release of serotonin.[5] Mirtazapine also blocks histamine and serotonin 5-HT_2 and 5-HT_3 receptors. These latter effects also may contribute to antidepressant and anxiolytic effects, as well as cause adverse events such as weight gain and sedation.[8]

Although the acute-phase efficacy of mirtazapine is now well documented,[9,10] the only data available pertaining to longer-term use were collected in "extension" protocols, in which patients responding during short-term double-blind trials continued into longer-term treatment.[11] These data suggested that mirtazapine has sustained antidepressant effects,[11] but are not adequate to establish longer-term safety or efficacy.[3] We now report the results

of a randomized, placebo-controlled study utilizing discontinuation design to test the efficacy and safety of up to 1 year of mirtazapine therapy. We hypothesized that mirtazapine therapy would result in significantly fewer relapses during double-blind continuation therapy than placebo, without significant differences in tolerability.

METHOD

This study was conducted at 12 clinical research centers across the United States (see acknowledgments at end of article). Patients (aged 18 years and older) were potentially eligible for participation if they met criteria for a principal DSM-IV diagnosis of major depressive disorder and had at least 1 of 2 risk indicators: (1) recurrent subtype, with at least 1 prior episode within the past 5 years, or (2) chronic subtype, with a current episode duration of ≥ 2 years. Diagnoses were based on a clinical interview conducted by a study psychiatrist and recorded using a checklist of DSM-IV criteria. In most cases, structured diagnostic interviews (e.g., the Schedule for Affective Disorders and Schizophrenia or the Structured Clinical Interview for DSM-IV) were not utilized to confirm eligibility. Current episode duration and lifetime history of prior depressive episodes also were determined during this interview. Potentially eligible patients had to be in reasonably good health, not have abused drugs or alcohol for at least 3 months before enrollment, and provide explicit written informed consent. Patients had to agree not to begin psychotherapy during the study, although they were permitted to remain in ongoing psychotherapy (minimum duration = 3 months). Female patients also had to agree not to become pregnant during the study (i.e., for up to 1 year) and, if sexually active and capable of becoming pregnant, to use a proven form of contraception (e.g., oral contraceptives or double-barrier methods).

Patients could not enter the study if they had received monoamine oxidase inhibitors within the previous 14 days, selective serotonin reuptake inhibitors other than fluoxetine within 7 days, fluoxetine or any investigational drug within 30 days, or any other psychotropic drugs within 7 days. Patients were not eligible for study participation if they had ever taken mirtazapine or if they had failed an adequate trial (at least 4 weeks of therapy at minimally effective doses) of any approved antidepressant in the current episode. The following concomitant conditions led to patient exclusion: anorexia or bulimia nervosa, obsessive-compulsive disorder, schizophrenia, dementia, or bipolar disorder. Additionally, patients judged to have severe borderline, antisocial, or schizoid personality disorders were excluded. Other psychiatric comorbidities (e.g., panic disorder, generalized anxiety disorder, or avoidant personality disorder) were not exclusion criteria as long as the depressive disorder was considered to be the principal (i.e., clinically predominant) diagnosis.

Consenting and potentially eligible patients first began a 7- to 10-day single-blind placebo lead-in. During this time, patients received a complete medical history and physical examination, as well as an electrocardiogram (ECG) and screening laboratory studies. A reduction of no more than 20% in Hamilton Rating Scale for Depression (HAM-D)[12] scores was permitted during the 7- to 10-day single-blind placebo lead-in period. Chloral hydrate, 500 to 1000 mg q.h.s., was permitted during the lead-in if needed for symptomatic treatment of insomnia. Severity of depression at intake was determined using the first 17 items of the HAM-D[12]; a minimum score of 18 was required to enter the study. The structured interview guide for the HAM-D[13] was used, and raters were evaluated at the beginning of the study and periodically thereafter to ensure reliability.

Acute-phase therapy with mirtazapine was initiated at 15 mg/day, with titration to 30 mg/day permitted after at least 1 week. A maximum dose of 45 mg/day was allowed after at least 2 weeks of therapy. Patients were seen for follow-up visits after 1, 2, 3, 4, 6, 8, and (if necessary) 10 and 12 weeks of therapy. The flexible length of the acute phase was chosen to maximize the number of fully remitted patients available to participate in the double-blind study. Outcome was evaluated at each visit with the HAM-D and the Clinical Global Impressions scale (CGI).[14] Adverse events were recorded by the treating psychiatrist according to standard conventions. The query "Have you experienced any adverse events or side effects since your last visit?" was used to elicit the patient's spontaneous reports. Both new-onset adverse events and those that persisted from visit to visit were recorded.

The goal of acute-phase treatment was complete remission, as defined by HAM-D scores of ≤ 7 and CGI scores of 1 or 2 (i.e., much or very much improved), which had to be sustained for at least 2 weeks. No fewer than 8 and no more than 12 weeks of treatment were permitted in which to meet these criteria. Patients not remitting were withdrawn from the protocol at week 12. Patients who met remission criteria were eligible to enter the 40-week double-blind continuation-phase protocol.

The double-blind continuation-phase treatment was randomly assigned, with approximately 50% of the patients switched immediately from active mirtazapine to identically appearing placebo tablets. The dosage of study medication was required to be stable during the continuation phase; no further increases or decreases in the number of tablets were permitted. Continuation-phase visits were required at monthly intervals, although interim visits were permitted if clinically indicated (i.e., if an increase in depressive symptoms occurred). When patients scored ≥ 15 on the HAM-D, interim visits were scheduled within 1 week. The physical examination, ECG, and laboratory studies were repeated at the endpoint of double-blind therapy.

Table 1. Demographics and Select Clinical Characteristics for Patients in the Open-Label and Double-Blind Treatment Phases[a]

Characteristic	Open-Label Phase	Double-Blind Phase	
	Mirtazapine (N = 410)	Mirtazapine (N = 76)	Placebo (N = 80)
Age, mean (SD), y	39.5 (12.2)	40.1 (12.0)	40.7 (11.3)
Female subjects, N (%)	230 (56.1)	40 (52.6)	39 (48.8)
Race			
Asian, N (%)	5 (1.2)	0 (0.0)	1 (1.3)
African American, N (%)	22 (5.4)	2 (2.6)	6 (7.5)
White, N (%)	364 (88.8)	71 (93.4)	69 (86.3)
Other, N (%)	19 (4.6)	3 (3.9)	4 (5.0)
Weight, mean (SD), kg	81.6 (20.0)	80.4 (19.5)	83.8 (19.9)
Height, mean (SD), cm	170.7 (10.7)	171.5 (10.0)	171.9 (12.1)
Primary diagnosis			
Chronic MDD, N (%)	199 (48.5)	35 (46.1)	37 (46.3)
Recurrent MDD, N (%)	211 (51.5)	41 (53.9)	43 (53.8)
HAM-D score			
Beginning of phase, mean (SD)	22.7 (3.6)	5.0 (4.0)	7.7 (6.7)
End of phase, mean (SD)	10.4 (7.5)	6.1 (7.2)	10.7 (8.8)
CGI score at end of phase, mean (SD)	2.3 (1.3)	1.6 (1.1)	2.3 (1.3)

[a]Abbreviations: CGI = Clinical Global Impressions scale, HAM-D = Hamilton Rating Scale for Depression, MDD = major depressive disorder.

The a priori definition of relapse for use in the primary analysis was the site principal investigator's determination that the patient was clinically depressed and required an immediate change in treatment. Previously, Montgomery and Dunbar[15] had found this to be a sensitive indicator of syndromal relapse. This definition was chosen (instead of a multistage procedure including an independent evaluator) because it is directly generalizable to clinical practice and it lessens ethical concerns about the length of exposure to placebo among a group of higher-risk patients who may have been withdrawn from active antidepressant medication.[16] Our decision regarding the definition of relapse was also partly based on difficulties implementing an operationalized, multistage definition of recurrence in an earlier double-blind study.[17] For the secondary analysis, relapse was defined a priori by any one of the following criteria: (1) HAM-D score ≥ 18, (2) HAM-D scores of ≥ 15 at 2 consecutive weekly visits, or (3) any suicide attempt or suicide. The secondary criteria for relapse were chosen to safeguard against site-to-site or idiosyncratic differences in the investigators' determinations.

Statistical Analyses

The sample size was chosen so that the study's analyses would have at least 80% power ($p = .05$) to test the hypothesis that relapse rates would be at least 25% lower in the mirtazapine group compared with the placebo group (i.e., 25% vs. 50%). We projected a 30% intent-to-treat (ITT) remission rate by the end of the acute phase.[2] Thus, we planned to enroll up to 500 patients in the acute phase in order to randomly assign 150 patients (75 per treatment group) in the continuation-phase trial.

The overall relapse rates for the placebo and mirtazapine groups were compared using Cochran-Mantel-Haenszel chi-square tests, controlling for treatment center. Heterogeneity among centers was assessed with the Breslow-Day test[18] for binary data. Other comparisons of categorical variables, including sustained remission rates, attrition rates, and side effects, were made with either Cochran-Mantel-Haenszel chi-square tests or, in the case of small numbers, Fisher exact tests. A survival analysis was conducted on time to relapse, with the curves plotted using Kaplan-Meier methods.[18] Significance of between-group differences was tested with the log-rank test.[19] Finally, HAM-D and CGI scores during double-blind therapy were compared using an analysis of covariance model that included treatment group and center, as well as their interaction. The final score from the acute phase served as the covariate. It was predicted that the group receiving active mirtazapine therapy would have significantly lower HAM-D and CGI-Improvement scale (CGI-I) scores than the group switched to double-blind placebo.

RESULTS

Acute-Phase Mirtazapine Therapy

Clinical response. A total of 421 patients enrolled in the acute-phase trial, of which 418 began open-label mirtazapine therapy and were included in the safety analyses. Of those beginning therapy, 410 (98%) completed at least one postbaseline assessment and were included in the acute-phase efficacy analyses. Patient characteristics of the ITT study group are described in Table 1. Overall, the study group was predominantly white (88.8%) and at midlife (mean age = 39.5 years); 56.1% were women. The study group was relatively evenly split between patients with chronic (48.5%) and recurrent (51.5%) subtypes. The average patient was moderately depressed (mean HAM-D score = 22.7).

The mean ± SD daily dose of mirtazapine among the ITT group was 30.6 ± 8.8 mg. The mean final HAM-D score of the ITT sample was 10.4 ± 7.5. During the acute phase, 231 patients (56.3%) achieved at least 50% reduction in HAM-D scores. An acute-phase therapy remission rate of 43% (178/410) was observed. Fifty-three responders did not achieve full remission and were not eligible to enter the continuation phase.

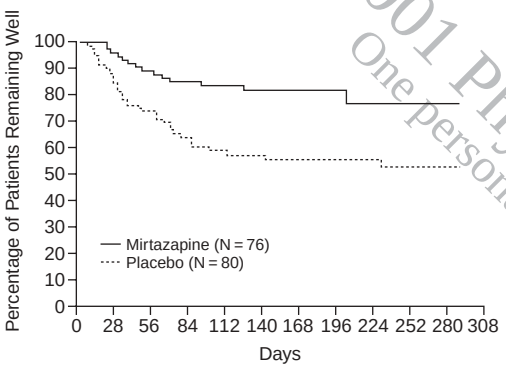
Tolerability and safety. Adverse events most frequently reported during acute-phase therapy are summarized in Table 2. During open-label mirtazapine treatment, the most frequently reported adverse events were somnolence (48%), increased appetite (23.7%), dry mouth (22.7%), and weight gain (20.7%). By the final visit of open-label

Table 2. Incidence and Persistence of Adverse Events During Open-Label and Double-Blind Therapy, With Mirtazapine or Placebo

	Acute-Phase Mirtazapine Therapy (N = 410)		Double-Blind Continuation Phase			
			Mirtazapine (N = 76)		Placebo (N = 80)	
Adverse Event	Incidence (%)	Prevalence[a] (%)	Persistent Adverse Events[b] (%)	New Adverse Events (%)	Persistent Adverse Events[b] (%)	New Adverse Events (%)
Somnolence	48	15	7	5	9	5
Increased appetite	24	18	9	4	15	3
Dry mouth	23	9	7	5	9	5
Weight increase	21	23	25	8	23	7
Headache	18	1	1	12	0	16
Dizziness	16	5	1	3	0	4
Upper respiratory tract infection	13	7	1	21	1	23
Nervousness	12	2	0	3	1	1
Fatigue	11	7	3	4	5	1

[a]Observed rate at week 12 or endpoint.
[b]Observed rate of adverse events persisting throughout the continuation phase.

Figure 1. Kaplan-Meier Survival Curves for Time to Depressive Relapse as Determined by Investigator During Double-Blind Treatment With Mirtazapine or Placebo



therapy (i.e., weeks 8 to 12 or endpoint), the prevalence of most adverse events had decreased considerably (see Table 2). The mean increase in weight during the open-label phase was 2.5 ± 3.2 kg (5.6 ± 7.1 lb).

One hundred ninety-four patients (46%) did not complete the acute-phase protocol. Sixty-nine patients (16.5%) withdrew due to adverse events. The most common adverse events leading to premature discontinuation were somnolence (26/418; 6%), weight gain (6/418; 1%), increased appetite (5/418; 1%), fatigue (4/418; 1%), and dizziness (3/418; 1%). Forty-seven patients (11%) were lost to follow-up. Thirty-eight patients (9%) terminated early because of nonresponse, including 2 patients who attempted suicide. Lastly, 40 patients (10%) withdrew for other reasons (e.g., schedule conflict, moved away).

Double-Blind Continuation Therapy

Clinical response. A total of 161 (90%) of the 178 fully remitted patients were randomly assigned to begin double-blind therapy. Of the 17 patients not randomly assigned, 15 were not enrolled in the double-blind study because the enrollment goal was met, and 2 declined further participation. Five additional patients dropped out before the first follow-up visit on double-blind therapy. The ITT sample for the double-blind continuation phase thus consisted of 156 patients.

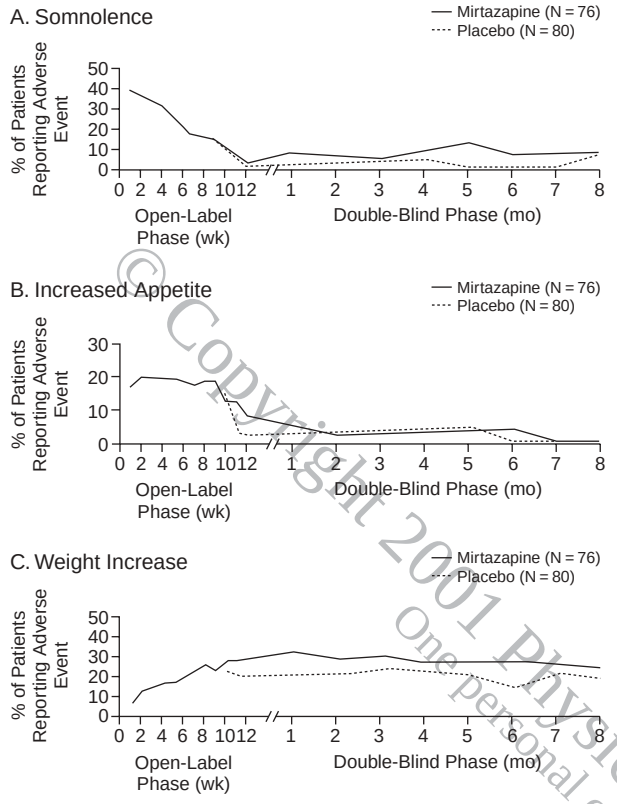
Sociodemographic and clinical characteristics did not differ significantly between the patients randomly assigned to double-blind therapy with mirtazapine (N = 76) and placebo (N = 80) (see Table 1). The mean daily dose of the active mirtazapine group was 38.6 ± 9.0 mg.

Investigator-determined relapse rates during the 40-week double-blind continuation phase were 19.7% (15/76) in the mirtazapine group and 43.8% (35/80) in the placebo group. This difference was highly significant (Cochran-Mantel-Haenszel $\chi^2 = 10.48$, df = 1, p =. 001). The secondary analysis using symptom criteria for relapse yielded virtually identical results (mirtazapine, 19.7% [15/76]; placebo, 42.5% [34/80]; Cochran-Mantel-Haenszel $\chi^2 = 9.72$, df = 1, p = .002). There was 99% agreement between the primary and secondary criteria for relapse. Of note, there were no suicides nor any suicide attempts during double-blind therapy.

The survival curves of the mirtazapine and placebo groups during double-blind therapy are illustrated by Figure 1. The between-group difference in the distribution of relapse risk over time was highly significant (primary analysis: log-rank $\chi^2 = 10.82$, df = 1, p =. 001). Among those who relapsed, relapse occurred more rapidly in the placebo group (median = 36 days) than in the mirtazapine group (median = 48 days). The results of the survival analysis using the secondary relapse criteria were virtually superimposable (log-rank $\chi^2 = 9.85$, df = 1, p = .001).

The mean HAM-D scores of the mirtazapine and placebo groups at week 40 or the endpoint of double-blind treatment were 6.1 ± 7.2 and 10.7 ± 8.8, respectively (F = 6.88; df = 1,134; p = .01). A similar advantage was apparent on mean CGI-I scores, with the mirtazapine group scoring 1.6 ± 1.1 and the placebo group scoring 2.3 ± 1.3 (F = 8.44; df = 1,134; p = .004). Seventy-two percent (55/76) of the patients who received active mirtazapine were fully recovered at the end of the continuation phase (i.e., sustained HAM-D score ≤ 7), as compared with only 47.5% (38/80) of placebo-treated patients (p = .002, Fisher exact test).

Figure 2. Prevalence of Common Adverse Experiences Over Time With Mirtazapine Compared With Placebo: Observed Case Analysis



Tolerability and safety. A similar number of subjects in each group reported new-onset adverse events during the 40-week double-blind protocol (mirtazapine, 36%; placebo, 30%) (see Table 2). Only upper respiratory tract infection (mirtazapine, 21.1%; placebo, 22.5%) and headache (mirtazapine, 11.8%; placebo, 16.3%) were reported at rates > 10% during double-blind therapy.

Figure 2 summarizes the prevalence of the 3 most common persistent adverse events (somnolence, increased appetite, and weight gain) across open-label and double-blind study participation. Complaints of somnolence decreased quickly during the open-label phase and did not differ significantly between the active mirtazapine and placebo groups during the double-blind continuation phase. Complaints of increased appetite began to diminish after the eighth week of active therapy. By the end of 1 month of double-blind therapy, there was no significant difference in reports of increased appetite between the 2 treatment groups. Complaints of weight gain leveled off but persisted in the 20% to 30% range during the continuation phase. The group receiving active mirtazapine reported somewhat higher, albeit not statistically significant, rates of weight gain than the placebo group during double-blind treatment (e.g., 5%–10% differences; see Figure 2).

A total of 11.8% of patients (9/76) withdrew from double-blind mirtazapine therapy due to adverse events, as compared with 2.5% of patients (2/80) in the placebo group (p = .029, Fisher exact test). No single adverse event was associated with significantly greater attrition from the group receiving active mirtazapine, however. The 9 patients who withdrew from mirtazapine therapy because of adverse events gave the following reasons: weight increase (N = 5), hyperglycemia (N = 1), respiratory disorder (N = 2), and granulocytopenia (N = 1). The 2 patients who withdrew from placebo reported weight increase and menorrhagia.

There were no significant differences between the mirtazapine and placebo groups on hematologic measures, electrolyte levels, liver function studies, urinalysis, or other laboratory parameters. Likewise, mirtazapine treatment had no effects (relative to placebo) on heart rate or ECG variables. The only significant difference in vital signs during double-blind treatment was weight change (mirtazapine, mean increase = 1.42 ± 4.62 kg [3.16 ± 10.27 lb]; placebo, mean decrease = –1.67 ± 3.01 kg [–3.71 ± 6.69 lb]; F = 23.24, df = 1,148; p < .001).

DISCUSSION

The results of this study demonstrate that continuation-phase therapy with mirtazapine provides clinically and statistically significant protective effects against depressive relapse. As in most studies of other effective antidepressants,[3,5–7] continuation-phase therapy with mirtazapine cut the rate of relapse in half, and only about 20% of the mirtazapine-treated patients relapsed during the 40-week double-blind study. Moreover, patients receiving active mirtazapine during the continuation phase had superior outcomes with respect to HAM-D measurement of symptoms, global improvement, and the probability of sustained remission. Overall, the study results confirm the earlier findings of Montgomery et al.,[11] who evaluated longer-term therapy with mirtazapine using an extension design of double-blind, acute-phase therapy protocols.

Mirtazapine therapy was generally well tolerated and was not associated with significant changes in laboratory parameters, pulse, blood pressure, or ECG profiles. The principal tolerability problems reported during acute-phase mirtazapine treatment were increased appetite, weight gain, and sedation. The observed incidence of these side effects is consistent with that of earlier controlled studies of short-term mirtazapine therapy.[9,10] There was relatively rapid adaptation to sedation, and, during double-blind therapy, complaints of sedation were no more common in the mirtazapine group than in the placebo group. Reports of increased appetite also diminished over the first 8 to 12 weeks of treatment and did not differ between the active and placebo groups following 1 month of double-blind therapy.

The incidence of self-reported weight gain was 21% by the end of open-label mirtazapine therapy, rose to 30% among patients who continued to take active medication during the continuation phase, and was relatively stable after the third month of therapy. The prevalence of weight gain among the patients switched to placebo at no point differed significantly from that of the active mirtazapine group. There was also no difference between groups in the incidence of new-onset weight gain during the continuation phase (mirtazapine, 7.9%; placebo, 7.3%). The significant difference in weight change during continuation-phase therapy was as much a function of weight loss in the placebo group (–1.67 kg [–3.71 lb]) as of weight gain in the mirtazapine group (+1.42 kg [+ 3.16 lb]). Moreover, the weight gain during up to 40 weeks of mirtazapine continuation therapy had only about half the magnitude of the weight gain observed during the first 8 to 12 weeks of therapy (+ 2.5 kg [+ 5.56 lb]). When taken together, these findings suggest that if weight gain is not problematic during acute-phase mirtazapine therapy, it is unlikely to become a problem during longer-term therapy. Nevertheless, effective strategies are needed to help those patients who gain an unacceptable amount of weight during mirtazapine therapy.

This study has several limitations that may influence interpretation of the results. First, we did not employ interim assessments during the initial weeks following the double-blind switch of mirtazapine to placebo. Consequently, although we observed no evidence of discontinuation symptoms following the abrupt withdrawal of mirtazapine, our design was not sensitive enough to detect subtler, transient symptoms.

Second, our study did not require the use of structured diagnostic interviews to confirm eligibility or systematically identify comorbidities. Moreover, our primary definition of relapse was based on the investigators' impressions, not on an independent assessment according to standardized criteria. Although these methodological limitations did not compromise testing of the study's hypotheses, the use of standardized evaluations would have helped to ensure internal validity.

Third, the external validity or generalizability of this randomized clinical trial is limited by the exclusion of patients with more severe comorbidities or prior treatment resistance, as well as by the loss of an unknown number of patients who were unwilling to consent to participate in a study in which placebo may be substituted for active medication. Ultimately, the results of randomized clinical trial studies must be placed beside the findings of less highly controlled investigations. In the case of longer-term pharmacotherapy, for example, the naturalistic study by Dawson et al.[20] provides complementary "real world" information on the effectiveness of continuation-phase pharmacotherapy. The continuation phase of the Sequenced Treatment Alternatives to Relieve Depression study (STAR*D)[21] will provide prospective data on the longer-term tolerability and effectiveness of a number of different antidepressant strategies for patients with a history of recent antidepressant nonresponse.

Fourth, the rather consistent demonstration of significant drug-placebo differences in studies of diversely different antidepressants underscores the relative fragility or vulnerability of patients who have just responded to pharmacotherapy. Beyond longer-term pharmacotherapy, which is by far the best-established approach to relapse prevention, results of several recent studies[22–24] indicate that a brief, sequential course of focused cognitive-behavioral therapy can attenuate the risk of relapse. Thus, an indefinite course of antidepressant medication may not be the only viable alternative for patients at a high risk for depressive relapse.

In summary, this study demonstrated both the efficacy and safety of up to 1 year of mirtazapine therapy for patients with recurrent or chronic forms of major depressive disorder. Our study does not, however, address the utility of mirtazapine for maintenance-phase therapy, which may extend for years or even decades. To date, there are only a handful of published multiyear studies of any of the newer antidepressants. The public health significance of recurrent depression[4,6,7] should make it a priority to correct this deficiency with additional longer-term studies. The relative merits of the different classes of antidepressants for maintenance therapy, both in terms of efficacy and tolerability, also deserve head-to-head study.

Drug names: fluoxetine (Prozac), mirtazapine (Remeron).

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