Long-Term Antidepressant Efficacy and Safety of Olanzapine/Fluoxetine Combination: A 76-Week Open-Label Study

Sara A. Corya, M.D.; Scott W. Andersen, M.S.; Holland C. Detke, Ph.D.; Linda S. Kelly, B.S.N.; Luann E. Van Campen, Ph.D.; Todd M. Sanger, Ph.D.; Douglas J. Williamson, M.B., Ch.B., M.R.C.Psych.; and Sanjay Dubé, M.D.

Background: The olanzapine/fluoxetine combination has demonstrated effectiveness in treatment-resistant depression (TRD). Although this combination is being used by prescribers, this is the first study to examine long-term use. Long-term efficacy and safety were therefore investigated in a group of patients with major depressive disorder (MDD) with and without TRD.

Method: 560 patients who met DSM-IV diagnostic criteria for MDD were enrolled in this 76-week, open-label study (Feb. 2000–July 2002). The Montgomery-Åsberg Depression Rating Scale (MADRS) total score was the primary efficacy measure. Safety was assessed via adverse events, vital signs, laboratory analytes, electrocardiography, and extrapyramidal symptom measures.

Results: MADRS mean total scores decreased 7 points from baseline (31.6 [N = 552]) at 1/2 week of treatment, 11 points at 1 week of treatment, and 18 points at 8 weeks of treatment. This effect was maintained to endpoint with a mean decrease of 22 points at 76 weeks. Response and remission rates for the total sample were high (62% and 56%, respectively), and the relapse rate was low (15%). Response, remission, and relapse rates for TRD patients (N = 145) were 53%, 44%, and 25%, respectively. The most frequently reported adverse events were somnolence, weight gain, dry mouth, increased appetite, and headache. At endpoint, there were no clinically meaningful changes in vital signs, laboratory analytes, or electrocardiography. There were no significant increases on any measure of extrapyramidal symptoms.

Conclusions: The olanzapine/fluoxetine combination showed rapid, robust, and sustained improvement in depressive symptoms in patients with MDD, including patients with TRD. The long-term safety profile of the combination was similar to that of its component monotherapies.

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Corresponding author and reprints: Sara A. Corya, M.D., Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (e-mail: scorya@lilly.com).

Major depressive disorder (MDD) affects approximately 10% of the U.S. population annually[1] and is considered a significant public health concern. Although antidepressant medications may be efficacious in most patients, a large number of patients will experience limited or no benefit from conventional treatment approaches. It is estimated that as many as 10% to 30% of depressed patients fail to respond to treatment with an antidepressant[2–4] and that as many as 46% of patients exhibit only a partial response to antidepressant treatment at best.[5] Although there are varying levels of treatment resistance, treatment-resistant depression (TRD) may be defined as the failure to respond to an adequate dose and duration of at least 2 different antidepressant medications.[4–6]

Given the high prevalence of TRD, there is a clear need for new therapeutic options that will provide both acute and long-term relief from symptoms. A variety of treatment strategies, including combination therapy, have been used to manage this form of depression.[7] Recent evidence suggests that combining the selective serotonin reuptake inhibitor fluoxetine with the mood-stabilizing properties of olanzapine may have enhanced antidepressant effects in patients with TRD. In an 8-week double-blind study of 28 patients with TRD, Shelton et al.[8] found that the olanzapine/fluoxetine combination was not only more effective than either olanzapine or fluoxetine alone, but that the combination therapy also reduced depressive symptoms more rapidly. Furthermore, the olanzapine/fluoxetine combination has shown effectiveness in managing other difficult-to-treat forms of depression such as the depressive phase of bipolar disorder[9] and MDD with psychotic features.[10]

It is estimated that 5% to 9% of all U.S. olanzapine prescriptions are written in combination with fluoxetine.[11] However, the long-term use of the olanzapine/fluoxetine combination has not previously been evaluated. The present 76-week, open-label study was thus undertaken to examine the long-term efficacy, tolerability, and safety of the olanzapine/fluoxetine combination in a population of patients with MDD, which included a subset of patients with TRD.

METHOD

Study Design

This 76-week, open-label trial was conducted at 40 outpatient investigative sites in the United States, Canada, Australia, Italy, Belgium, Poland, and Turkey. Qualified patients who completed a 2- to 7-day screening and washout period entered the 76-week open-label treatment period. Patients were seen twice during the first week, then weekly for the next 3 weeks, biweekly for the next 8 weeks, every 4 weeks for the next 32 weeks, and every 8 weeks for the last 32 weeks. The starting dose was 6 mg of olanzapine and 25 mg of fluoxetine. Thereafter, the dose could be adjusted according to the investigator's clinical judgment within a dose range of olanzapine 6, 12, or 18 mg/day in combination with fluoxetine 25, 50, or 75 mg/day. Dosing was based on the positive findings from the Shelton et al.[8] study of TRD patients. Olanzapine and fluoxetine were administered as separate capsules, taken together once daily in the evening.

In general, concomitant medications with primarily central nervous system activity were not allowed. Chronic benzodiazepine users could maintain their current dose, and non-chronic benzodiazepine users could take lorazepam up to 4 mg/day, or the equivalent, as needed. Patients could initiate or discontinue psychotherapy or phototherapy at any time during the study. Concomitant electroconvulsive therapy was not allowed.

Subjects

A total of 651 patients who met diagnostic criteria for MDD according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) entered the screening period. The diagnosis of MDD was confirmed with the Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV),[12] and the MDD Specifiers in the SCID-I, Research Version.[13] Patients were also required to have a Clinical Global Impressions-Severity of Illness scale (CGI-S)[14] score ≥ 3. At the end of the screening period, 560 patients continued to meet criteria and were enrolled in the study. Treatment resistance was determined by the individual investigators on the basis of patient history of treatment failure to at least 2 different classes of antidepressants administered at adequate dose and duration. Definition of adequate dose and duration was left to individual investigators' discretion, with 4 weeks provided as a suggested minimum standard duration. All patients were ≥ 18 years of age and signed a written informed consent form prior to participating in the study. Pregnant or lactating women were excluded. The protocol was approved by the ethics committee at each site in accordance with the Declaration of Helsinki.

Assessment

Efficacy was measured as mean change from baseline on the Montgomery-Åsberg Depression Rating Scale (MADRS)[15] total score and CGI-S score.[14] Response was defined as a decrease in MADRS total score ≥ 50% from baseline to endpoint. Remission was defined as 2 consecutive MADRS total scores ≤ 8 at any time, and relapse was defined as a MADRS total score ≥ 16 at 2 subsequent visits any time after meeting remission criteria.

The screening assessment, which was conducted at baseline, included a standard history, physical examination, psychiatric examination, laboratory profile, and electrocardiography (ECG). The physical examination was repeated at weeks 52 and 76 or upon early discontinuation. Vital signs were measured at every visit. Laboratory assessments were conducted at baseline and at weeks 12, 24, 36, 52, 68, and 76 or upon early discontinuation. An ECG was conducted at weeks 24, 52, and 76 or upon early discontinuation. Spontaneously reported adverse events were recorded at each visit. Extrapyramidal symptoms were assessed at each visit using the Simpson-Angus Scale,[16] the Barnes Akathisia Scale,[17] and the Abnormal Involuntary Movement Scale (AIMS).[18]

Statistical Methods

All analyses were conducted on an intent-to-treat basis. If an individual test item was missing, then the total score was treated as missing. All hypotheses were tested at a 2-tailed significance level of .05. All significant p values denote a within-group difference from 0 unless otherwise specified. Efficacy analyses used a mixed-effects model repeated-measures (MMRM) methodology, as MMRM has been shown to provide highly accurate modeling of treatment outcome while accounting for nonrandom missing data (i.e., patient dropout).[19,20] This model included the independent factors of investigator and visit, and an unstructured covariance matrix was used to model the within-patient errors. All reported MADRS and CGI-S mean change and percentage change scores are thus least-squares means. Mean change analyses of safety measures used last-observation-carried-forward methodology. Endpoint refers to patient's endpoint (i.e., the time at which the patient discontinued or completed the study). Only patients with both a baseline and at least 1 post-baseline measure

Table 1. Demographics and Baseline Illness Characteristics for Patients Enrolled in Olanzapine/Fluoxetine Combination Study

Variable	All Patients N = 560	Patients With TRD N = 145	Patients Without TRD N = 415
Age at study entry, mean (SD), y	43.0 (12.1)	44.7 (11.8)	42.4 (12.1)
Women, %	67.0	66.2	67.2
White, %	89.3	97.2	86.5
BMI, mean (SD)	28.3 (7.1)	29.9 (6.9)	28.8 (7.1)
MADRS, mean (SD) score	32.3 (6.7)	32.8 (6.9)	32.1 (6.6)
CGI-S, mean (SD) score	4.5 (0.7)	4.8 (0.7)	4.4 (0.7)
Median days of current episode	256	336	235
> 3 MDD episodes lifetime, %	39.1	45.5	36.9
> 2 MDD episodes in last 2 years, %	12.5	13.8	12.0
Patients with psychotic features, %	5.5	2.8	6.5

Abbreviations: BMI = body mass index, CGI-S = Clinical Global Impressions-Severity of Illness scale, MADRS = Montgomery-Åsberg Depression Rating Scale, MDD = major depressive disorder, TRD = treatment-resistant depression.

were included in post-baseline analyses. Percentages for adverse events and reasons for discontinuation use all patients (N = 560) as a denominator.

Time-to-event analyses were conducted using Kaplan-Meier survival analysis. For time to response, the event analyzed was the earliest time at which an endpoint responder experienced a reduction in MADRS total score ≥ 50%. For time to relapse, time was measured from the point at which remission was first achieved. Survival curves were compared using the log-rank test.

Patients' corrected QT interval (QTc) was calculated from the ECG data. To correct for the effect heart rate has on QT interval, QT intervals were corrected using a log-linear-derived regression model formula that was based on 13,039 drug-free ECG recordings from patients in Lilly clinical trials.[21] This formula strikes a balance between Bazett's correction factor, which overcorrects for heart rates > 60 bpm, and Fridericia's correction factor, which overcorrects for heart rates < 60 bpm.[22] All laboratory values and vital signs were evaluated for abnormality using established reference limits.[23]

RESULTS

Patient Characteristics

A total of 560 patients were enrolled in the trial. Of these, 145 (26%) were determined to have TRD, and the remaining 415 (74%) were categorized as non-TRD. Of the 415 non-TRD patients, 8 discontinued after the first visit. Thus, 552 patients (145 TRD and 407 non-TRD) were eligible for mean change analyses. Mean baseline score for all enrolled patients (N = 560) was 32.3 (SD = 6.7) on the MADRS and 4.5 (SD = 0.7) on the CGI-S, indicating moderate to marked illness. Table 1 summarizes demographics and baseline illness characteristics for all patients and for patients with or without TRD at time of enrollment. Mean modal drug dose for the entire sample was 7.5 (SD = 3.5) mg/day for olanzapine and 46.1 (SD = 20.7) mg/day for fluoxetine. Mean modal drug doses for the TRD and non-TRD samples were 7.7 (SD = 3.9) mg/day and 7.4 (SD = 3.3) mg/day, respectively, for olanzapine and 49.5 (SD = 21.5) mg/day and 44.9 (SD = 20.3) mg/day, respectively, for fluoxetine. Thirty-nine percent of all patients took at least 1 dose of a benzodiazepine during the course of the study, with a mean modal lorazepam-equivalent dose of 2.0 (SD = 2.2) mg/day. Significantly more TRD patients (51%) took a concomitant benzodiazepine at some point than did non-TRD patients (35%; p < .001). Mean modal lorazepam-equivalent doses were 2.5 (SD = 3.2) mg/day for TRD patients and 1.8 (SD = 1.6) mg/day for non-TRD patients.

Patient Disposition

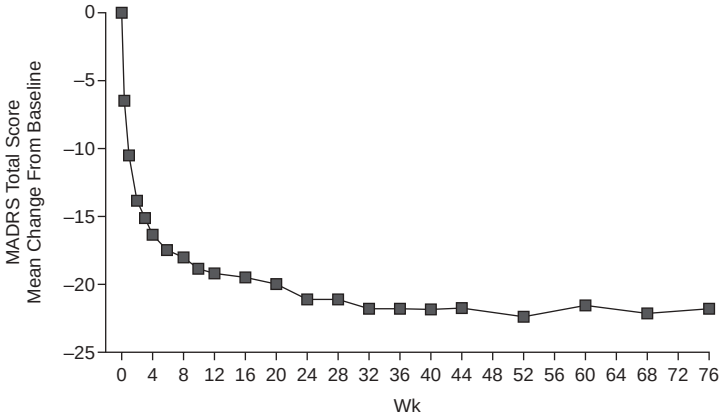
Four hundred thirty-five patients (77.7%) completed 8 weeks of treatment, 348 (62.1%) completed 16 weeks, 254 (45.4%) completed 32 weeks, 177 (31.6%) completed 52 weeks, and 143 (25.5%) completed 76 weeks. The most commonly reported (≥ 5%) reasons for discontinuation from the trial were adverse event (N = 137, 24.5%), lack of efficacy (N = 79, 14.1%), lost to follow-up (N = 61, 10.9%), patient decision (N = 56, 10.0%), and protocol violation (N = 45, 8.0%). Two patients died during the study. One patient was a homicide victim, and 1 patient committed suicide, which was determined to be related to specific situational stressors. Both deaths were deemed by the investigators to be unrelated to the study drug or protocol. The most commonly reported (≥ 1%) adverse events leading to study discontinuation were weight gain (N = 45, 8.0%) and somnolence (N = 27, 4.8%).

Efficacy: All Patients

Mean MADRS total score decreased from baseline (31.6; N = 552) by 6.5 points (18.9%) at 1/2 week of combination treatment, 10.5 points (33.1%) at 1 week, and 18.1 points (56.0%) at 8 weeks. This effect was maintained to the end of the study, with a mean decrease of 21.8 points (67.7%) at 76 weeks (Figure 1). CGI-S mean score decreased from baseline (4.5) by 1.6 points (35.0%) at 8 weeks and by 2.2 points (49.3%) at 76 weeks. MADRS and CGI-S mean change scores were significantly different from baseline (p = .0001) at all time points.

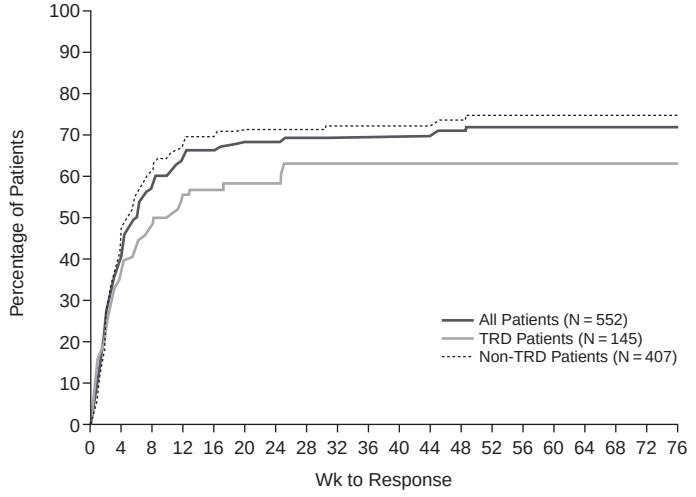
At endpoint, 340 patients (61.6%) met response criteria. Over the course of the study, 311 patients (56.3%) achieved remission. Of those who remitted, 46 (14.8%) relapsed by endpoint. Survival models of times to response, remission, and relapse are presented in Figures 2, 3, and 4, respectively.

Figure 1. Mean Change From Baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) Total Score Over Time for Patients Treated With Olanzapine/Fluoxetine Combination[a]



[a]All post-baseline scores were statistically significantly better than baseline at p = .0001 using a mixed-effects model repeated-measures method. The mean baseline total score was 31.6 for patients with a baseline and post-baseline observation (N = 552).

Figure 2. Time to Response for Patients Treated With Olanzapine/Fluoxetine Combination[a]



[a]Response was defined as a ≥ 50% decrease in MADRS score from baseline to endpoint. Figure depicts the first time endpoint responders achieved ≥ 50% decrease in MADRS. Log-rank p = .026 for TRD vs. non-TRD patients.
Abbreviations: MADRS = Montgomery-Åsberg Depression Rating Scale, TRD = treatment-resistant depression.

Efficacy: Non-TRD and TRD

For patients without TRD (N = 407), mean MADRS total score decreased from baseline (31.3) by 6.0 points (18.3%) at 1/2 week of treatment, 10.3 points (33.2%) at 1 week, and 18.6 points (58.7%) at 8 weeks. This effect was maintained to the end of the study, with a decrease of 22.3 points (70.3%) at 76 weeks (Figure 5). CGI-S mean score decreased from baseline (4.4) by 1.7 points (37.4%) at 8 weeks and by 2.3 points (52.8%) at 76 weeks. MADRS and CGI mean change scores were significantly different from baseline (p = .0001) at all time points. The rate of response in non-TRD patients was 64.6% at endpoint. Over the course of the study, 247 (60.7%) of the non-TRD patients achieved remission. Of the non-TRD patients who remitted, 30 (12.1%) relapsed by endpoint.

For patients with TRD (N = 145), a similar pattern of MADRS mean change results was noted (Figure 3). Mean MADRS total score decreased from baseline (32.6) by 7.2 points (19.5%) at 1/2 week of combination treatment, 10.8 points (31.7%) at 1 week, and 16.2 points (46.8%) at 8 weeks. This effect was maintained to the end of the study, with a mean decrease of 19.2 points (55.9%) at 76 weeks (Figure 3). CGI-S mean score decreased from baseline (4.8) by 1.4 points (27.5%) at 8 weeks and by 2.0 points (39.5%) at 76 weeks. MADRS and CGI-S mean change scores were significantly different from baseline (p = .0001) at all time points. The rate of response for TRD patients was 53.1% at endpoint. Over the course of the study, 64 (44.1%) of the TRD patients achieved remission. Of the TRD patients who remitted, 16 (25.0%) relapsed by endpoint. Survival analysis of times to response, remission, and relapse for patients with and without TRD are presented in Figures 2, 3, and 4, respectively.

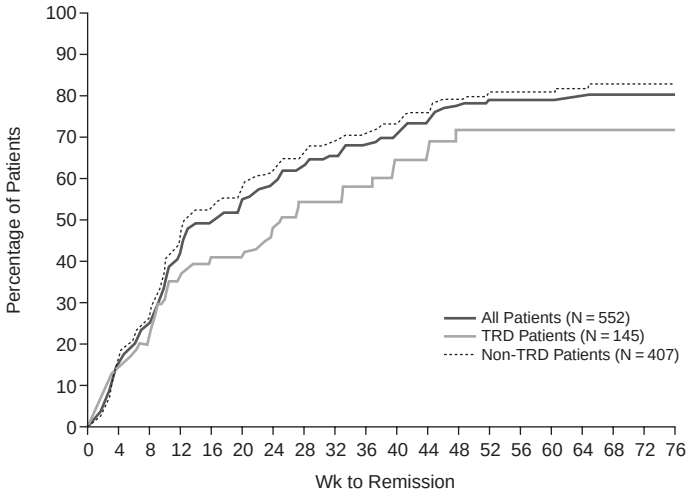
Safety

Adverse events. The 5 most commonly occurring treatment-emergent adverse events were somnolence, weight gain, dry mouth, increased appetite, and headache. Table 2 summarizes the treatment-emergent adverse events reported by ≥ 10% of the patients, in order of frequency. Nineteen percent of patients reported tremor at some point over the course of the study. During the course of the study, 22 patients (3.9%) were hospitalized for depression, and 7 (1.3%) attempted suicide.

Vital signs and weight. There were no clinically significant changes in vital signs at endpoint. However, there was a significant increase in mean body weight from baseline (p < .001). Mean weight gain from baseline to endpoint was 5.6 (SD = 6.6) kg (12.3 [SD = 14.5] lb). At endpoint, 176 patients (31%) had weight gain ≥ 10% from baseline.

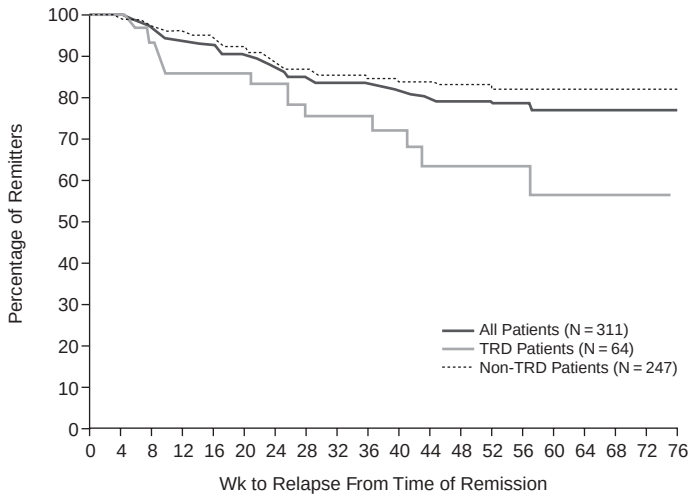
Laboratory analytes. Although there were statistically significant mean changes in a number of laboratory

Figure 3. Time to Remission for Patients Treated With Olanzapine/Fluoxetine Combination[a]



[a]Remission was defined as 2 consecutive MADRS total scores ≤ 8. Log-rank p = .029 for TRD vs. non-TRD patients.
Abbreviations: MADRS = Montgomery-Åsberg Depression Rating Scale, TRD = treatment-resistant depression.

Figure 4. Time to Relapse for Remitted Patients Treated With Olanzapine/Fluoxetine Combination[a]



[a]Relapse was defined as a MADRS total score ≥ 16 at 2 subsequent visits following remission. Log-rank p = .007 for TRD vs. non-TRD patients.
Abbreviations: MADRS = Montgomery-Åsberg Depression Rating Scale, TRD = treatment-resistant depression.

analytes, many of these changes were transient, and none were clinically meaningful. Liver function tests (aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase) showed small but transient mean increases, with treatment-emergent abnormal elevations in 2% to 5% of patients at any time, which then reduced to 0% to 2% of patients at endpoint. Total bilirubin was abnormally low in 17.4% of patients at any time, but by endpoint, this incidence had decreased to 4.2%. Nonfasting glucose showed a small mean increase of 6.2 mg/dL (SD = 32.3) at endpoint. Fourteen patients (2.9%, N = 475) developed abnormally high treatment-emergent glucose levels (≥ 200 mg/dL) at any time, but this reduced to 6 patients (1.3%, N = 475) at endpoint. Six patients (1.1%, N = 560) reported treatment-emergent diabetes mellitus during the course of the 76-week study; 4 of these (0.7%, N = 560) were new cases, and 2 were preexisting cases with treatment-emergent hyperglycemia. No ketoacidosis was reported. Although 4.6% of patients developed abnormally elevated cholesterol at any time during the study, only 1.5% continued to show elevations at endpoint.

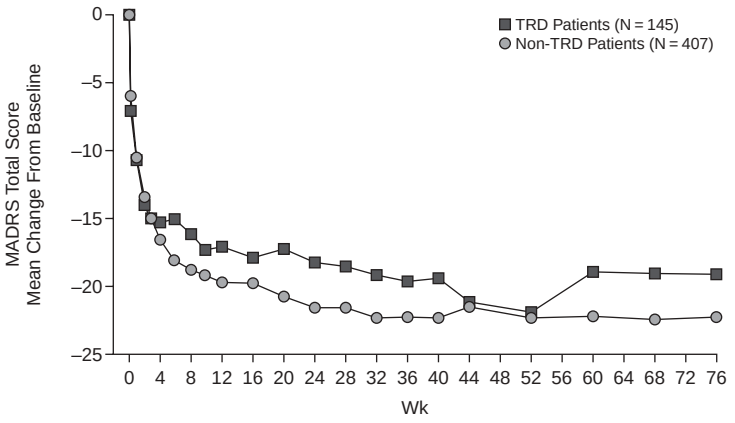
ECG. There was a statistically significant ($p < .001$), but clinically insignificant, increase in QTc. The mean increase for QTc was 6.1 (SD = 17.8) milliseconds. Only 10 patients had baseline-to-endpoint changes ≥ 50 milliseconds. One patient had a QTc ≥ 500 milliseconds. No patients became symptomatic as a result of QTc changes, and no patient discontinued the study due to QT prolongation.

Extrapyramidal symptoms. Baseline means for the Barnes Akathisia Scale, the AIMS, and the Simpson-Angus Scale were all near 0, with 0 indicating the absence of symptoms. Mean change at endpoint on all 3 measures was also near 0, with no statistically significant increases. Mean change scores on the Barnes Akathisia Scale and the AIMS actually showed statistically significant or near-significant decreases ($p = .007$ and $p = .057$, respectively). Treatment-emergent incidence of parkinsonism, akathisia, and dyskinesia was reported by 4.5%, 11.3%, and 1.8% of patients, respectively. A total of 14.5% of patients had increases in any extrapyramidal symptoms. No treatment-emergent tardive dyskinesia was reported.

DISCUSSION

This large, open-label study evaluated the long-term efficacy, tolerability, and safety of the olanzapine/fluoxetine combination in the treatment of patients with MDD, including those with TRD. The current findings indicate not only robust efficacy but also rapid onset and sustained maintenance of effect. The 33% decrease in mean MADRS total score seen at 1 week of treatment not only meets but exceeds criteria for early improvement,[24] and the sustained response from the 56% mean decrease at 8 weeks to the 68% mean decrease in MADRS at 76 weeks is consistent with positive maintenance of effect. Similar findings have also been noted in shorter-term studies of the olanzapine/fluoxetine combi-

Figure 5. Mean Change From Baseline in MADRS Total Score Over Time for TRD Patients and Non-TRD Patients Treated With Olanzapine/Fluoxetine Combination[a]



[a]All post-baseline scores were statistically significantly better than baseline at p = .0001 for both groups using a mixed-effects model repeated-measures method. Among patients with a baseline and at least 1 post-baseline observation, the mean baseline MADRS total score was 32.6 for the TRD group and 31.3 for the non-TRD group.

Abbreviations: MADRS = Montgomery-Åsberg Depression Rating Scale, TRD = treatment-resistant depression.

Table 2. Treatment-Emergent Adverse Events Occurring in ≥ 10% of Depressed Patients Treated With Olanzapine/Fluoxetine Combination (N = 560)

	Incidence	
Event	N	%
Somnolence	267	47.7
Weight gain	223	39.8
Dry mouth	208	37.1
Increased appetite	179	32.0
Headache	125	22.3
Rhinitis	124	22.1
Asthenia	108	19.3
Tremor	105	18.8
Nausea	88	15.7
Anxiety	78	13.9
Pain	71	12.7
Diarrhea	70	12.5
Dizziness	70	12.5
Insomnia	66	11.8
Nervousness	65	11.6
Libido decreased	64	11.4
Pharyngitis	58	10.4

nation treatment in patients with TRD,[8] bipolar depression,[9] and MDD with psychotic features.[10]

In the present study, the TRD patient group showed a similar pattern of response to that of the non-TRD patient group, particularly during the first 4 weeks of treatment. Nevertheless, the numerical differences in MADRS mean change scores as well as the significant differences in times to response, remission, and relapse add validity to the categorization of the patients and indicate that the TRD group was indeed more treatment-resistant. However, despite having failed at least 2 previous trials of different classes of antidepressants, the present TRD sample achieved a mean decrease of 19 points on the MADRS as well as a 53% response rate and a 44% remission rate, with only a 25% relapse rate over a 76-week period.

Another molecule that has been examined as a potential treatment for TRD is the serotonin norepinephrine reuptake inhibitor venlafaxine. Although direct comparison across studies is not possible due to differing study conditions, definitions of TRD, and response criteria, it is useful to place the current olanzapine/fluoxetine findings in the context of other open-label studies. While there are no long-term open-label studies of venlafaxine use, previous acute (8–12 weeks) open-label venlafaxine studies[25] reported response rates of 53% to 62%[25–27] and a 28% remission rate in TRD patient samples that used a single-antidepressant–failure criterion for treatment resistance. When Nierenberg et al.[28] employed a much stricter triple-antidepressant–failure criterion, venlafaxine-treated patients achieved a 30% acute (12 week) response rate.

Overall, the present efficacy results should be interpreted within the inherent limitations of an open-label study. While this type of study closely mirrors typical clinical practice, there is the potential for confounding effects due to rater bias and placebo response. Although the magnitude of placebo effect cannot be precisely determined, the sustained improvement seen in this study is more consistent with a true treatment effect. Placebo response is more typically characterized by a rapid onset of improvement followed by a fluctuating course, rather than the maintenance of effect demonstrated in the current study.[29] Additionally, the robust and sustained pattern of response observed in this open-label study is consistent with the pattern observed in previous double-blind studies of the olanzapine/fluoxetine combination,[8,10] further suggesting that the efficacy results reflect a true drug effect.

It should be noted that spontaneous remission may be an influence in the long-term efficacy results. A number of patients in this study, as in all long-term studies of MDD, may have experienced spontaneous remission of their illness as a result of the natural course of MDD, rather than remission resulting from true drug effect.[30] However, the rapid onset of effect coupled with the sustained improvement in MADRS total scores provide supporting evidence of drug effect. Although the high rate of patient discontinuation has the potential to influence efficacy findings as well, the use of MMRM analysis provides a highly accurate estimate of drug efficacy by modeling the trajectory of each patient's progress up to the point of dropping out.[31]

Rates of patient discontinuation in the present study should be interpreted in the context of a 76-week study. These rates are comparable to those of other long-term

studies.[32,33] In general, results demonstrate a long-term safety profile for the combination that is similar to that of its components. The most frequently reported adverse events have been reported previously with either olanzapine or fluoxetine monotherapy treatment,[34,35] and most of these events were reported at incidence rates similar to those seen with long-term olanzapine treatment[33] or in fluoxetine prescribing information.[35] The only apparent exception to this was the finding of a higher incidence of tremor (19%) in the current study (Table 2) than in previous long-term studies of olanzapine (14%)[33] or fluoxetine treatment (9%–13%).[35] This finding has not been noted in previous studies of the combination[8,10] and is in contrast to the overall low rate of treatment-emergent parkinsonism as assessed by the Simpson-Angus scale. Most of the reported tremors were mild in severity, and only 1 patient discontinued from the study because of tremor. Overall, the incidences of parkinsonism, akathisia, and dyskinesia symptoms were low and similar to those reported previously with long-term olanzapine treatment.[33,36] The 14.5% incidence of any extrapyramidal symptoms was comparable to the 16% rate reported for placebo[34] and the 16% to 20% rate reported in previous studies of olanzapine.[37]

The mean weight gain observed in this study (5.6 kg [12.3 lb]) was similar to that reported for patients receiving long-term olanzapine therapy.[33,37] The changes noted in ECG interval measurements were not clinically significant and were similar to changes noted previously during treatment with fluoxetine.[38] While changes were observed for some laboratory analytes, these changes were not clinically meaningful and were generally similar to those previously reported during treatment with either olanzapine or fluoxetine.[34,35] Of the 4 patients newly diagnosed with diabetes during the course of the study, all were male, and all had multiple pre-existing risk factors for diabetes, including obesity, hypertension, hypercholesteremia, and concomitant use of antihypertensive medications known to induce hyperglycemia. When adjusted for time, the 76-week incidence rate of 0.7% for new cases of diabetes (or 1.1% including the pre-existing cases) in this study was consistent with 1-year incidence rates reported in general adult populations (ranging from 0.3% to 1.3% annually).[39–42] Moreover, the current rate was well below those reported in previous studies of atypical antipsychotics, which had primarily involved schizophrenic patients.[43–46]

In conclusion, evidence from this study supports the long-term antidepressant efficacy and safety of the olanzapine/fluoxetine combination. The findings demonstrate not only a rapid and robust onset of effect but also sustained improvement over 76 weeks of treatment. Although such combination treatment is likely to be unnecessary for most cases of MDD, the olanzapine/fluoxetine combination may represent a possible treatment option for treatment-resistant cases. Further research might also examine whether this combination would be appropriate in the acute treatment of severe cases where need for rapid onset is of particular concern, such as in the case of patients hospitalized for suicidality.

Drug names: fluoxetine (Prozac and others), lorazepam (Ativan and others), olanzapine (Zyprexa), venlafaxine (Effexor).

Note: The olanzapine/fluoxetine combination has not been approved for the indications of major depressive disorder or treatment-resistant depression.

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