A Randomized, Double-Blind Comparison of Olanzapine/Fluoxetine Combination, Olanzapine, and Fluoxetine in Treatment-Resistant Major Depressive Disorder

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Objective: Two parallel, 8-week double-blind studies compared olanzapine/fluoxetine combination, olanzapine, and fluoxetine in outpatients with treatment-resistant depression (TRD).

Method: Treatment-resistant depression was defined as a documented history of current-episode antidepressant failure plus a prospective failure on fluoxetine. Following an 8-week fluoxetine lead-in, 605 nonresponders with DSM-IV major depressive disorder were randomly assigned to olanzapine/fluoxetine combination, olanzapine, or fluoxetine. The primary outcome measure was baseline-to-endpoint mean change on the Montgomery-Asberg Depression Rating Scale (MADRS). The study was conducted from April 2002 to May 2005.

Results: After 8 weeks of double-blind treatment, Study 1 revealed no statistically significant therapy differences in MADRS mean change (olanzapine/fluoxetine combination: –11.0, fluoxetine: –9.4, olanzapine: –10.5). In Study 2, olanzapine/fluoxetine combination demonstrated significantly greater MADRS improvement (–14.5) than fluoxetine (–8.6, $p < .001$) and olanzapine (–7.0, $p < .001$). Pooled study results revealed significant differences for olanzapine/fluoxetine combination (–12.7) versus fluoxetine (–9.0, $p < .001$) and olanzapine (–8.8, $p < .001$). Pooled remission rates were 27% for olanzapine/fluoxetine combination, 17% for fluoxetine, and 15% for olanzapine. Adverse events were consistent with previous studies. Cholesterol mean change (mg/dL) was +15.1 for olanzapine/fluoxetine combination, +0.8 for fluoxetine, and +2.7 for olanzapine. Mean weight change (kg) was +4.9 for olanzapine/fluoxetine combination, +0.4 for fluoxetine, and +5.5 for olanzapine. Nonfasting glucose mean change (mg/dL) was +11.4 for olanzapine/fluoxetine combination, +4.9 for fluoxetine, and +9.9 for olanzapine.

Conclusion: Patients with TRD (defined as treatment failure on 2 antidepressants) taking olanzapine/fluoxetine combination demonstrated significantly greater improvement in depressive symptoms than patients taking olanzapine or fluoxetine in 1 of 2 studies and in the pooled analysis. When considered within the context of all available evidence, olanzapine/fluoxetine combination is an efficacious therapy for patients with TRD.

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Although not a formal diagnosis in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR),[1] treatment-resistant depression (TRD) is one of the greatest clinical challenges that psychiatrists face, and one for which no U.S. Food and Drug Administration–approved pharmacotherapy exists. The broadest definition of TRD is inadequate response to a single course of adequate antidepressant therapy.[2] However, most researchers consider treatment resistance as occurring along a continuum, with degrees of resistance ranging from treatment failure with 1 class of antidepressant to failing several different classes of antidepressants and electroconvulsive therapy. Outcome studies have consistently reported that at least one third of patients do not respond satisfactorily to the first antidepressant trial.[3] Even after multiple interventions, approximately 10% of patients remain depressed,[4]

and the likelihood of response to antidepressants decreases with the number of failed treatment trials.[5] It is likely that patients with TRD remain at high risk of suicide, and there is evidence that they are heavy users of medical services. For example, a retrospective study of medical claims data found that patients with TRD are twice as costly as non-TRD depressed patients, and almost 4 times as costly as insured patients in general.[6]

The lack of agreement on the definition of TRD has led to the development of staging systems for TRD (e.g., the Thase and Rush system[7] and the Massachusetts General staging system[2]) that use standardized terminology to convey degree of resistance. Large-scale intervention studies like STAR*D (Sequenced Treatment Alternatives to Relieve Depression)[8] are utilizing these staging systems in an attempt to identify the most appropriate prescribing strategy at each level of resistance. The first results of the STAR*D study, which ultimately will evaluate different treatment options for nonresponders at 3 levels of resistance, were recently published.[9,10]

Several attempts to apply the principles of evidence-based medicine to the treatment of TRD have yielded disappointing results.[11,12] Of note, the treatments with the best evidence of efficacy, including monoamine oxidase inhibitors, lithium augmentation, and electroconvulsive therapy, are either seldom used or typically deferred until multiple other options have been tried.[11] The lack of firm empirical guidelines for selection among the various pharmacologic treatment options often results in the trial-and-error use of various strategies, and has fostered research on nonpharmacologic alternatives, including more invasive strategies such as vagus nerve stimulation[13] and deep brain stimulation.[14]

It is within this context that the strategy of combining a modern antidepressant (e.g., a selective serotonin reuptake inhibitor [SSRI]) with an atypical antipsychotic has emerged. Blier and Szabo[15] have suggested that the beneficial effects of SSRI/atypical antipsychotic combinations may result from a cascade effect caused by potent 5-HT_{2A} blockade in the presence of 5-HT reuptake inhibition, which disrupts the balance between the serotonin and norepinephrine systems in the brain. To this point, there is preclinical evidence that the combination of olanzapine and fluoxetine acutely increases extracellular levels of serotonin and norepinephrine, as well as dopamine, in the rat brain.[16,17] Clinically, 4 previous studies have provided evidence for the effectiveness and/or safety of olanzapine/fluoxetine combination in major depressive disorder (MDD)[18] and TRD.[19–21] Both of the larger double-blind studies defined TRD as a history of treatment failure (occurring at any time in the past) plus prospective treatment failure, and, although clinically relevant effects favoring olanzapine/fluoxetine combination were observed at some time points, both studies failed to show significant treatment differences at endpoint on their primary efficacy measures versus olanzapine alone and fluoxetine alone. Methodological problems (e.g., lack of blinding of the investigators to the criteria for randomization, inadequate lead-in duration, and insufficient criteria for establishing TRD) made the results of these studies difficult to interpret. The current study was therefore designed to examine the efficacy and tolerability of olanzapine/fluoxetine combination in patients with 2 treatment failures during the current mood episode, including prospective failure to achieve a satisfactory response to fluoxetine monotherapy during an 8-week lead-in phase. It was hypothesized that the olanzapine/fluoxetine combination group would show significantly greater improvement in depressive symptoms than both the olanzapine and fluoxetine monotherapy groups.

METHOD

This randomized, double-blind clinical trial, which was composed of 2 identical concurrent studies, was conducted in the United States and Canada from April 2002 to May 2005. Study sites were randomly assigned to either Study 1 or Study 2. All procedures were conducted in compliance with the Declaration of Helsinki and the standards established by all applicable institutional review boards. Written informed consent was obtained from all patients after complete description of the study. Patients with current or past diagnosis of schizophrenia, schizoaffective disorder, other psychotic disorders, bipolar disorder I or II, posttraumatic stress disorder, or any dissociative disorder (as defined in the DSM-IV) were excluded from the study, as were female patients who were pregnant or nursing. Patients with a current diagnosis of postpartum depression, MDD with atypical features, or MDD with seasonal pattern were excluded. Patients with paranoid, schizoid, schizotypal, antisocial, or severe borderline personality disorder as a comorbid or primary diagnosis were excluded. Significant medical illness was also an exclusion criterion. Concomitant medications with primary central nervous system activity were not allowed, with the exception of lorazepam as permitted at doses up to an equivalent of 4 mg per week.

Patients

Patients ranged in age from 18 to 65 years, and all patients had a 17-item Hamilton Rating Scale for Depression (HAM-D-17)[22] total score of greater than or equal to 22 as measured by Interactive Voice Response System (IVR; Healthcare Technology Systems, Inc., Madison, Wis.), and met DSM-IV criteria for a diagnosis of MDD, recurrent, without psychotic features, confirmed by the Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (SCID-I)[23] plus the MDD specifiers included in the Research Version of the SCID-I.[24] Patients also had documented history of failure to

achieve a satisfactory response to an antidepressant (except fluoxetine) after at least 6 weeks of therapy at a therapeutic dose (e.g., paroxetine 40 mg/day, venlafaxine 150 mg/day, bupropion 300 mg/day, trazodone 450 mg/day), occurring within the current episode of MDD. Whether or not the patient achieved a satisfactory response during this historical antidepressant trial was left to the investigator's clinical judgment. Consenting patients meeting these criteria were eligible to enter the first phase of the study.

Measures

The primary efficacy measure was baseline-to-endpoint last-observation-carried-forward mean change in the Montgomery-Asberg Depression Rating Scale (MADRS) total score.[25] Secondary efficacy measures included MADRS response (≥ 50% decrease in total score at endpoint) and remission (MADRS total score ≤ 10 at endpoint) rates, time to response, time to remission, onset of action as measured by time to achieve partial response (≥ 25% reduction from baseline in MADRS total score), Clinical Global Impressions-Severity of Depression scale,[26] Hamilton Rating Scale for Anxiety,[27] and the Brief Psychiatric Rating Scale.[28] Additional secondary health outcomes measures included the Sheehan Disability Scale[29] and the 36-item Short Form Health Survey (SF-36).[30] The Quick Inventory of Depressive Symptomatology-clinician rating (QIDS-C)[31] was used in the determination of dose titrations (see Study Design).

Safety monitoring included complete physical and psychiatric examinations, medical history, assessment of adverse events, electrocardiography, laboratory analyses, and the following measures of extrapyramidal symptoms: Simpson–Angus Scale,[32] Abnormal Involuntary Movement Scale,[33] and the Barnes Akathisia Scale.[34]

Efficacy and extrapyramidal symptoms scales were administered at baseline and at all acute treatment phase visits, except for the Brief Psychiatric Rating Scale, which was administered only at baseline, randomization, and endpoint. Health outcomes scales were administered only at randomization and endpoint. Adverse events were recorded at each visit.

Study Design

The study consisted of 4 phases: screening, prospective fluoxetine therapy lead-in, randomized double-blind treatment, and open-label treatment. Open-label phase results will be discussed in a separate report. The 3- to 14-day screening phase consisted of screening tests, patient history, and psychiatric and physical examinations. During this phase, patients were tapered off all excluded medications, and all criteria for enrollment were verified. Investigators were blinded to the IVR HAM-D-17 criterion for entry into the study (i.e., IVR HAM-D-17 total score ≥ 22). At the first visit, each patient completed the IVR HAM-D-17, and investigators were immediately informed (by facsimile) as to whether the patient was eligible for the study. Specific safety information, including a suicide score, was also provided at that time.

After screening was complete and eligibility was verified, patients began an 8-week open-label lead-in phase to establish fluoxetine resistance, during which they received fluoxetine at a dose of 25 mg/day for at least the first day, which was titrated up to 50 mg/day by week 2 of the lead-in. Patients who could not tolerate 50 mg/day of fluoxetine were discontinued. Patients who were not deemed ineligible by interim exclusion criteria proceeded to the double-blind acute treatment phase. The interim exclusion criteria were as follows: a patient was discontinued if there was (1) evidence of response to fluoxetine (i.e., a ≥ 25% decrease in the IVR HAM-D-17 score or an IVR HAM-D-17 score of < 18 or a > 15% decrease between week 7 and week 8 of the lead-in phase) or (2) evidence of psychotic features (Brief Psychiatric Rating Scale positive score of ≥ 3). Investigators were blinded to the IVR randomization criteria.

At the beginning of the double-blind treatment phase, patients were assigned in random, equal allocation to 1 of 3 treatment groups: (1) olanzapine 6 mg/day and fluoxetine 50 mg/day; (2) fluoxetine 50 mg/day; or (3) olanzapine 6 mg/day. At 2-week intervals throughout the double-blind treatment phase, each patient was required to be titrated to the next higher dose if (1) no tolerability or safety issues were identified, (2) the QIDS-C score was greater than 11, and (3) the patient had not significantly improved on the QIDS-C relative to baseline (i.e., < 25% improvement for week 2, < 35% for week 4, and < 50% at week 6). All dose titrations were managed through the IVR process, and investigators were not required to calculate patients' QIDS-C improvement or related study drug dose. Possible dose ranges for the 3 treatment groups were as follows: (1) olanzapine 6 and fluoxetine 50 mg/day, olanzapine 12 and fluoxetine 50 mg/day, or olanzapine 18 and fluoxetine 50 mg/day; (2) olanzapine 6, 12, or 18 mg/day, and (3) fluoxetine 50 mg/day. A group receiving only placebo was not included in this design due to ethical concerns regarding the use of placebo in this severely ill, treatment-resistant group of patients and because a placebo-alone group was not necessary to test the hypothesis that olanzapine/fluoxetine combination was superior to fluoxetine and olanzapine monotherapies.

Statistical Analyses

Analyses were done on an intent-to-treat basis. Patients were included in the analysis only if they had a baseline and at least 1 postbaseline measure. Baseline-to-endpoint mean change analyses used last-observation-carried-forward methodology for handling missing data. All reported mean change scores, unless otherwise specified, reflect simple means. Although the original protocol specified analysis of variance with last-observation-

Table 1. Baseline Demographic and Illness Characteristics of Outpatients With Treatment-Resistant Major Depressive Disorder[a]

Variable	Lead-In Period (N = 1313)	Double-Blind Period: Olanzapine/Fluoxetine Combination (N = 200)	Double-Blind Period: Fluoxetine (N = 206)	Double-Blind Period: Olanzapine (N = 199)
Age, mean (SD), y				
Study 1	44.2 (10.5)	43.3 (10.8)	44.8 (10.0)	45.7 (11.1)
Study 2	44.3 (10.3)	45.3 (9.5)	44.5 (9.9)	43.0 (10.4)
Pooled	44.3 (10.4)	44.3 (10.2)	44.6 (10.0)	44.3 (10.8)
Female, N (%)				
Study 1	404 (63.3)	63 (61.8)	61 (58.7)	56 (58.3)
Study 2	459 (68.0)	69 (70.4)	67 (65.7)	67 (65.0)
Pooled	863 (65.7)	132 (66.0)	128 (62.1)	123 (61.8)
White, N (%)				
Study 1	519 (81.3)	87 (85.3)	87 (83.7)	73 (76.0)
Study 2	594 (88.0)	90 (91.8)	90 (88.2)	91 (88.3)
Pooled	1113 (84.8)	177 (88.5)	177 (85.9)	164 (82.4)
BMI, mean (SD), kg/m^2				
Study 1	30.2 (7.3)	31.3 (7.5)	29.9 (6.7)	30.1 (7.1)
Study 2	30.3 (8.0)	29.7 (7.5)	29.0 (7.5)	30.7 (7.2)
Pooled	30.3 (7.7)	30.5 (7.6)	29.4 (7.1)	30.4 (7.1)
Length of current episode, mean (SD), d				
Study 1	…	372.8 (369.4)	391.8 (500.0)	370.3 (583.8)
Study 2	…	502.4 (805.8)	485.0 (741.2)	361.5 (496.9)
Pooled	…	415.4 (550.0)	428.6 (603.3)	366.5 (544.4)
≥ 3 MDD episodes over lifetime, N (%)				
Study 1	…	83 (81.4)	86 (82.7)	77 (80.2)
Study 2	…	74 (75.5)	76 (74.5)	73 (70.9)
Pooled	…	157 (78.5)	162 (78.6)	150 (75.4)
≥ 3 MDD episodes in past 36 months, N (%)				
Study 1	…	35 (34.3)	39 (37.5)	30 (31.3)
Study 2	…	20 (20.4)	26 (25.5)	18 (17.5)
Pooled	…	55 (27.5)	65 (31.6)	48 (24.1)
HAM-D-17 score, mean (SD)				
Randomly assigned patients				
Study 1	26.4 (5.4)	…	…	…
Study 2	26.1 (5.3)	…	…	…
Pooled	26.2 (5.4)	…	…	…
Nonrandomly assigned patients				
Study 1	25.5 (6.1)	…	…	…
Study 2	26.0 (5.6)	…	…	…
Pooled	25.8 (5.8)	…	…	…
MADRS total score, mean (SD)				
Study 1	…	29.6 (7.2)	29.7 (6.9)	29.7 (7.0)
Study 2	…	30.5 (6.2)	30.1 (5.9)	30.1 (6.3)
Pooled	…	30.1 (6.7)	29.9 (6.4)	29.9 (6.7)

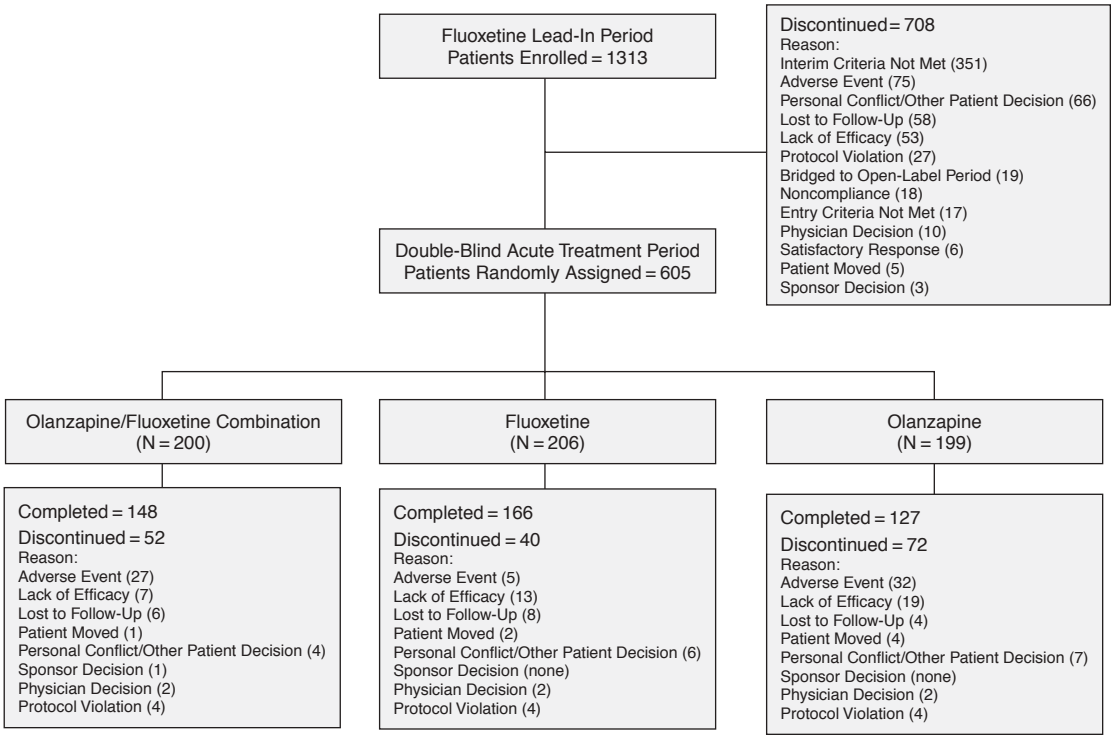
[a]There were no statistically significant between-group differences at baseline.
Abbreviations: BMI = body mass index, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder.
Symbol: … = data not collected.

carried-forward methodology for the primary efficacy analysis, in this article we also present results of a mixed-effects model repeated measures (MMRM) analysis of variance for the MADRS.[35] Contrasts of least-squares means were used to create pairwise comparisons of the olanzapine/fluoxetine combination treatment group to the other 2 treatment groups. Group means were only examined if the omnibus F was significant. Time-to-event estimates were calculated via the Kaplan-Meier method or a proportional hazards cure model,[36] and events (e.g., response or remission) were only counted if they were sustained until the end of the study period. Kaplan-Meier curves were compared statistically using the log-rank test. For the proportional hazards cure model, the latency parameter was used to compare differences among therapies. Categorical variables (e.g., response and remission rates, frequencies of adverse events) were analyzed using Fisher exact test. All analyses were evaluated for significance with 2-tailed tests at an α level of .05 and performed with Statistical Analysis Systems (SAS) software version 8 (SAS Institute, Cary, N.C.).

RESULTS

Table 1 shows baseline demographic and illness characteristics for the lead-in and randomized double-blind treatment phases, for each study individually and for both studies combined. There did not appear to be any consis-

Figure 1. Patient Flow Diagram, Pooled Study Results for Randomized, Double-Blind Comparison of Olanzapine/Fluoxetine Combination, Olanzapine, and Fluoxetine in Treatment-Resistant Major Depressive Disorder



tent treatment-group differences in baseline demographic or illness characteristics, either within or between studies.

Lead-In Phase

A total of 1313 patients entered the 8-week fluoxetine lead-in phase. The mean baseline IVR HAM-D-17 score was 26.2 (SD = 5.4) for subsequently randomly assigned patients, and 25.8 (SD = 5.8) for nonrandomly assigned patients. The mean modal dose of fluoxetine during the lead-in was 47.4 mg/day (SD = 9.3). Patients from the lead-in phase were either randomly assigned to groups in the acute treatment phase (N = 605, 46.1%), discontinued due to interim exclusion criteria (N = 351, 26.7%), discontinued due to some other reason (N = 338, 25.7%), or bridged directly to the open-label phase once the randomization goals of the study were met (N = 19, 1.4%). Figure 1 shows reasons for discontinuation for the lead-in and acute treatment phases. Excluding patients who did not remain in the lead-in phase until at least visit 5 (approximately 4 weeks), a total of 338 (28.9%) of 1169 patients achieved response to fluoxetine in the lead-in (defined as a ≥ 25% decrease in IVR HAM-D-17 score).

Acute Treatment Phase

A total of 605 patients met the criteria for fluoxetine resistance and entered the acute, double-blind treatment phase. The mean baseline MADRS score of 30.0 (SD = 6.6) was in the moderate to severe range. Patient compliance was defined as the ratio of the number of days study drug was taken as prescribed to the total number of days in the acute treatment phase (per patient report). Rates of compliance were as follows: olanzapine/fluoxetine combination, 0.95; fluoxetine, 0.97; olanzapine, 0.94 (p = .079). Mean modal doses by therapy (mg/day) were as follows: olanzapine 8.6 (SD = 4.7) and fluoxetine 48.8 (SD = 7.8); fluoxetine 49.5 (SD = 4.9); and olanzapine 8.7 (SD = 4.8). The percentages of patients taking each possible dose (mg/day) at the end of the study (i.e., the patient's last visit) were as follows: olanzapine/fluoxetine combination 6/50: 54.3%; olanzapine/fluoxetine combination 12/50: 25.4%; olanzapine/fluoxetine combination 18/50: 19.8%; olanzapine/fluoxetine combination 12/100 (patient took 2 doses of 6/50): 0.5%; fluoxetine 50: 100%; olanzapine 6: 55.6%; olanzapine 12: 23.2%; olanzapine 18: 21.2%. An additional 6 patients were randomly assigned but discontinued the study so early (e.g., after the first visit) that no dosing information is available. Rates of benzodiazepine use were not significantly different among the therapies and were as follows: olanzapine/fluoxetine combination, 28.5%; fluoxetine, 33.0%; olanzapine, 31.2%, overall p = .616.

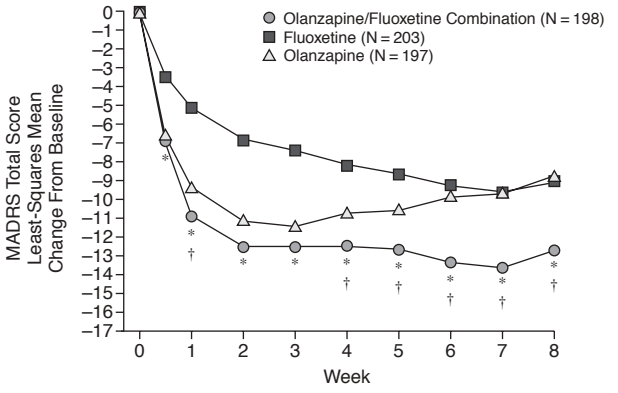
Patient disposition. A total of 441 patients (72.9%) completed the 8-week acute treatment phase, with the following completion rates by group: olanzapine/fluoxetine

Table 2. Baseline-to-Endpoint Mean Change on Efficacy Measures for the Double-Blind Period (last observation carried forward)

Measure	Baseline Score, Mean (SD)			8-Week Change From Baseline, Mean (SD)			p Value		
	Olanzapine/ Fluoxetine Combination	Fluoxetine	Olanzapine	Olanzapine/ Fluoxetine Combination	Fluoxetine	Olanzapine	Overall	Olanzapine/ Fluoxetine Combination vs Fluoxetine	Olanzapine/ Fluoxetine Combination vs Olanzapine
MADRS total									
Study 1	29.5 (7.1)	29.7 (6.9)	29.7 (7.1)	–10.8 (10.0)	–9.4 (9.9)	–10.1 (9.6)	.640	.346	.624
Study 2	30.6 (6.1)	30.1 (5.9)	30.1 (6.3)	–14.6 (10.2)	–9.0 (9.5)	–7.7 (8.2)	< .001	< .001	< .001
Pooled	30.0 (6.7)	29.9 (6.4)	29.9 (6.7)	–12.6 (10.3)	–9.2 (9.7)	–8.9 (9.0)	< .001	< .001	< .001
CGI-Severity of Depression									
Study 1	4.5 (0.7)	4.7 (0.7)	4.6 (0.7)	–1.1 (1.3)	–1.0 (1.2)	–1.1 (1.1)	.681	.384	.722
Study 2	4.7 (0.7)	4.7 (0.7)	4.7 (0.7)	–1.5 (1.3)	–1.1 (1.2)	–0.8 (1.1)	< .001	.004	< .001
Pooled	4.6 (0.7)	4.7 (0.7)	4.7 (0.7)	–1.3 (1.4)	–1.0 (1.2)	–0.9 (1.1)	.003	.008	.001
HAM-A									
Study 1	19.2 (7.2)	19.3 (7.1)	18.0 (5.5)	–6.0 (6.6)	–6.3 (6.3)	–5.1 (7.2)	.427	.656	.399
Study 2	19.7 (5.3)	18.8 (5.2)	19.4 (5.3)	–8.0 (6.8)	–5.1 (6.7)	–4.7 (5.8)	< .001	.001	< .001
Pooled	19.5 (6.4)	19.0 (6.2)	18.7 (5.4)	–6.9 (6.8)	–5.7 (6.6)	–4.9 (6.5)	.008	.051	.002
BPRS									
Study 1	17.1 (7.7)	17.6 (7.7)	16.1 (6.5)	–5.4 (7.5)	–4.8 (7.7)	–4.3 (7.4)	.646	.562	.357
Study 2	15.2 (5.7)	15.3 (5.6)	14.8 (5.5)	–5.9 (6.8)	–4.3 (6.1)	–2.4 (6.2)	.001	.058	< .001
Pooled	16.2 (6.8)	16.5 (6.8)	15.4 (6.0)	–5.6 (7.2)	–4.6 (7.0)	–3.3 (6.8)	.009	.097	.002

Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions, HAM-A = Hamilton Rating Scale for Anxiety, MADRS = Montgomery-Asberg Depression Rating Scale.

Figure 2. Pooled Study Results (mixed-effects model repeated measures) Showing MADRS Visitwise Least-Squares Mean Change From Baseline



*p < .05 vs. fluoxetine.
†p < .05 vs. olanzapine.
Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

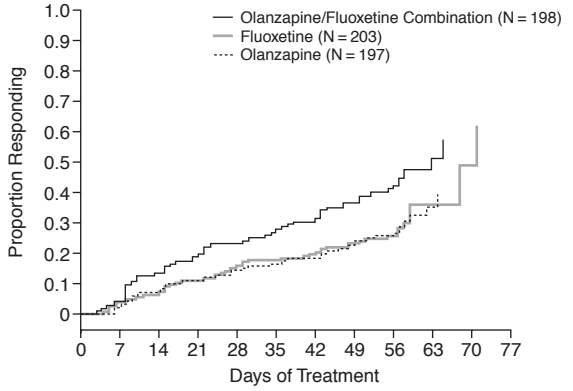
combination, 74.0% (148/200); fluoxetine, 80.6% (166/206); olanzapine, 63.8% (127/199), p < .001. There were significantly fewer olanzapine completers than fluoxetine (p < .001) or olanzapine/fluoxetine combination (p = .031) completers. See Figure 1 for complete patient flow information.

Efficacy. Table 2 provides last-observation-carried-forward mean change from baseline to endpoint for the MADRS total score and other efficacy measures, for each study individually and for both studies combined. Figure 2 displays MMRM pooled study results for MADRS visitwise least-squares mean change from baseline for the 3 therapy groups. Mixed-effects model repeated measures 8-week results were as follows: Study 1 revealed no significant therapy differences in MADRS mean change (MMRM): olanzapine/fluoxetine combination, –11.0 (SD = 10.0); fluoxetine, –9.4 (SD = 10.0, p = .253); olanzapine, –10.5 (SD = 9.5, p = .739). In Study 2, olanzapine/fluoxetine combination demonstrated significantly greater MADRS improvement (–14.5, SD = 10.4) than fluoxetine (–8.6, SD = 9.6, p < .001) and olanzapine (–7.0, SD = 8.5, p < .001). Pooled results revealed significant differences in MADRS mean change for olanzapine/fluoxetine combination (–12.7, SD = 10.3) versus fluoxetine (–9.0, SD = 9.8, p < .001) and olanzapine (–8.8, SD = 9.1, p < .001).

A subgroup analysis based on drug class of historical treatment failure (SSRI-only vs. other) yielded the following results in MADRS mean change: For patients with historical treatment failures on SSRIs only (N = 318), there were significant differences for olanzapine/fluoxetine combination (–14.3, SD = 11.0) versus fluoxetine (–8.5, SD = 8.8, p < .001) and olanzapine (–10.5, SD = 9.3, p = .004). For patients with at least 1 historical treatment failure on a non-SSRI drug class (N = 280), there was a significant difference for olanzapine/fluoxetine combination (–10.7, SD = 9.1) versus olanzapine (–6.9, SD = 8.1, p = .004) but not versus fluoxetine (–9.9, SD = 10.6, p = .445).

Rates of clinical response (≥ 50% improvement in MADRS total score) at endpoint for Study 1 were not different among the therapies and were as follows:

Figure 3. Pooled Study Results Showing Kaplan-Meier Survival Curves for Time to Response (> 50% decrease in MADRS total score)[a]



[a]Overall log-rank χ^2 p value = .002.
Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

olanzapine/fluoxetine combination, 36.6% (37/101); fluoxetine, 29.4% (30/102); olanzapine, 35.8% (34/95); overall p = .496. Study 2 response rates were as follows: olanzapine/fluoxetine combination, 44.3% (43/97); fluoxetine, 29.7% (30/101); olanzapine, 16.7% (17/102); overall p < .001. Pairwise comparisons revealed that the olanzapine/fluoxetine combination response rate was significantly higher than both the fluoxetine response rate (p = .039) and the olanzapine response rate (p < .001). Pooled response rates were as follows: olanzapine/fluoxetine combination, 40.4% (80/198); fluoxetine, 29.6% (60/203); olanzapine, 25.9% (51/197); overall p = .006. Pairwise comparisons revealed that the olanzapine/fluoxetine combination response rate was significantly higher than both the fluoxetine response rate (p = .028) and the olanzapine response rate (p = .003).

Remission rates (MADRS total score ≤ 10 at endpoint) for Study 1 were not different among the therapies and were as follows: olanzapine/fluoxetine combination, 23.8% (24/101); fluoxetine, 17.6% (18/102); olanzapine, 18.9% (18/95); overall p = .522. Study 2 remission rates were as follows: olanzapine/fluoxetine combination, 30.9% (30/97); fluoxetine, 15.8% (16/101); olanzapine, 10.8% (11/102); overall p = .001. Pairwise comparisons revealed that the olanzapine/fluoxetine combination remission rate was significantly higher than both the fluoxetine remission rate (p = .018) and the olanzapine remission rate (p < .001). Pooled study results for remission rates were as follows: olanzapine/fluoxetine combination, 27.3% (54/198); fluoxetine, 16.7% (34/203); olanzapine, 14.7% (29/197); overall p = .004. Pairwise comparisons revealed that the olanzapine/fluoxetine combination remission rate was significantly higher than both the fluoxetine remission rate (p = .012) and the olanzapine remission rate (p = .003).

Figure 3 shows the Kaplan-Meier curves for time to response for each of the 3 therapy groups for both studies combined. The overall test of differences among the 3 survival curves was significant, log-rank χ^2 = 12.5, p = .002. The time required for 25% of patients to achieve response was 30 days for the olanzapine/fluoxetine combination group, 55 days for the fluoxetine group (p = .004), and 53 days for the olanzapine group (p = .002). The time required for 25% of patients to achieve remission was 52 days for the olanzapine/fluoxetine combination group and 71 days for the fluoxetine group (p = .003). The olanzapine group did not have enough remitters to yield 25th-percentile time to remission results. Time for 50% of patients to achieve a partial response (≥ 25% MADRS reduction from baseline), as estimated by a proportional hazards cure model, was significantly shorter for the olanzapine/fluoxetine combination group (6.4 days) than for the fluoxetine group (10.0 days, p < .001) but not significantly different from the olanzapine group (6.8 days, p = .158).

On the Sheehan Disability Scale (both studies combined), olanzapine/fluoxetine combination patients showed significantly greater endpoint improvement (mean = –1.6, SD = 2.8) than the fluoxetine (mean = –1.1, SD = 2.6; p = .027) and olanzapine (mean = –0.9, SD = 2.5; p = .005) groups on the leisure item. Olanzapine/fluoxetine combination patients also showed significantly greater endpoint improvement (mean = –1.7, SD = 2.7) than the fluoxetine (mean = –1.2, SD = 2.6; p = .047) and olanzapine (mean = –0.9, SD = 2.5; p =.001) groups on the family item. There were no significant therapy differences on the work item (p = .457). On the SF-36, the olanzapine/fluoxetine combination group had significantly greater endpoint improvement than the olanzapine group on all subscales except vitality, as well as on the physical component summary but not the mental component summary (see Table 3). The olanzapine/fluoxetine combination group also had significantly greater endpoint improvement than the fluoxetine group on the bodily pain and social functioning subscales, as well as the physical component summary.

Safety. Treatment-emergent adverse events are presented in Table 4. There was an overall statistically significant difference among treatment groups in rates of patient discontinuation due to adverse events. Specifically, fewer patients in the fluoxetine group discontinued due to an adverse event (N = 5, 2.4%) than in the olanzapine/fluoxetine combination (N = 27, 13.5%, p < .001) or olanzapine (N = 32, 16.1%, p < .001) groups. There were no patient deaths in the study. Of all patients randomly assigned to olanzapine/fluoxetine combination, there were 2 with serious adverse events: 1 was reported as bipolar disorder and 1 was reported as pyrexia.

Table 3. Baseline-to-Endpoint Mean Change on SF-36 Summary and Subscale Scores: Pooled Data (last observation carried forward)

		Baseline		Change		p Value		
SF-36 Scale	Therapy	Mean	SD	Mean	SD	Overall	Olanzapine/ Fluoxetine Combination vs Fluoxetine	Olanzapine/ Fluoxetine Combination vs Olanzapine
Summary score–mental	Olanzapine/Fluoxetine combination	21.2	7.1	8.9	12.6	.177	.175	.075
	Fluoxetine	20.2	7.6	7.3	12.3			
	Olanzapine	20.5	7.4	6.7	11.2			
Summary score–physical	Olanzapine/Fluoxetine combination	42.9	11.3	2.1	9.0	.001	.028	< .001
	Fluoxetine	44.0	12.0	0.4	8.7			
	Olanzapine	44.0	11.8	–1.0	9.7			
Physical functioning	Olanzapine/Fluoxetine combination	60.3	27.8	5.9	23.6	.005	.083	.001
	Fluoxetine	63.5	28.7	2.6	22.5			
	Olanzapine	63.2	27.9	–1.2	23.4			
Role-physical	Olanzapine/Fluoxetine combination	27.7	37.0	14.4	43.1	.011	.098	.003
	Fluoxetine	27.2	39.0	8.3	40.0			
	Olanzapine	29.0	40.1	2.4	42.7			
Bodily pain	Olanzapine/Fluoxetine combination	51.8	25.4	10.2	22.9	.008	.012	.004
	Fluoxetine	52.6	25.7	4.8	23.7			
	Olanzapine	52.3	24.5	3.7	23.7			
General health	Olanzapine/Fluoxetine combination	44.2	22.6	8.5	16.8	.004	.096	< .001
	Fluoxetine	45.3	22.9	6.1	18.3			
	Olanzapine	46.0	20.8	3.0	16.6			
Vitality	Olanzapine/Fluoxetine combination	15.8	13.5	13.9	23.1	.141	.080	.095
	Fluoxetine	16.0	15.2	10.3	22.5			
	Olanzapine	14.8	13.1	9.8	21.5			
Social functioning	Olanzapine/Fluoxetine combination	26.4	17.7	18.1	26.7	.002	.027	< .001
	Fluoxetine	25.9	18.2	13.2	23.7			
	Olanzapine	26.6	19.3	9.5	24.3			
Role-emotional	Olanzapine/Fluoxetine combination	6.2	15.1	19.2	37.5	.066	.099	.025
	Fluoxetine	6.8	17.9	13.9	36.0			
	Olanzapine	6.2	15.5	11.9	32.3			
Mental health	Olanzapine/Fluoxetine combination	28.2	14.6	15.5	20.7	.109	.200	.037
	Fluoxetine	26.1	14.8	13.2	20.5			
	Olanzapine	27.6	14.2	11.1	20.2			

Abbreviation: SF-36 = 36-item Short Form Health Survey.

Table 4. Treatment-Emergent Adverse Events Occurring in 10% or More of Olanzapine/Fluoxetine Combination Patients: Pooled Data

				p Value		
Event	Olanzapine/Fluoxetine Combination, %	Fluoxetine, %	Olanzapine, %	Overall	Olanzapine/Fluoxetine Combination vs Fluoxetine	Olanzapine/Fluoxetine Combination vs Olanzapine
Weight increased	35.0	6.8	39.7	< .001	< .001	.353
Increased appetite	32.0	5.8	30.7	< .001	< .001	.829
Dry mouth	28.5	8.7	31.7	< .001	< .001	.514
Somnolence	17.5	5.3	12.1	< .001	< .001	.158
Fatigue	14.0	7.8	14.1	.070	.055	1.00
Headache	12.5	19.4	13.1	.103	.060	.882
Peripheral edema	12.0	1.0	7.5	< .001	< .001	.177
Hypersomnia	10.5	2.4	11.1	< .001	< .001	.873
Tremor	10.5	8.7	8.0	.686	.615	.490

Table 5 provides mean changes on vital sign and laboratory safety measures that had significant therapy differences or were of clinical interest. Mean increase in weight for olanzapine/fluoxetine combination (with baseline BMI as a covariate) was significantly greater than that for fluoxetine alone but not olanzapine alone. Analysis of vital signs revealed significant overall therapy differences in standing pulse mean change and supine pulse. There was a small increase in corrected QT interval for the olanzapine/fluoxetine combination, which was significantly different from that for olanzapine but not significantly different from that for fluoxetine. Patients treated with olanzapine/fluoxetine combination did not experience significant increases in measures of extrapyramidal symptoms.

Analysis of laboratory values revealed no statistically significant therapy differences for mean change in

Table 5. Mean Change on Safety Measures at 8 Weeks: Pooled Data (last observation carried forward)

		Baseline		Change		p Value		
Measure or Test	Therapy	Mean	SD	Mean	SD	Overall	Olanzapine/ Fluoxetine Combination vs Fluoxetine	Olanzapine/ Fluoxetine Combination vs Olanzapine
Weight, kg	Olanzapine/Fluoxetine combination	86.8	23.0	4.9	3.5	< .001	< .001	.058
	Fluoxetine	84.7	23.2	0.4	2.3			
	Olanzapine	85.9	21.6	5.5	3.9			
Standing pulse, bpm	Olanzapine/Fluoxetine combination	76.2	10.9	2.8	11.5	< .001	.002	.065
	Fluoxetine	77.5	11.6	–0.5	10.4			
	Olanzapine	76.0	10.7	5.0	11.8			
Supine pulse, bpm	Olanzapine/Fluoxetine combination	71.0	9.7	3.8	10.1	< .001	< .001	.040
	Fluoxetine	72.4	10.6	0.2	9.9			
	Olanzapine	70.8	10.3	6.0	10.4			
Corrected QT interval,[a] msec	Olanzapine/Fluoxetine combination	418.5	19.4	3.4	17.9	.006	.097	.001
	Fluoxetine	418.6	20.3	0.5	18.0			
	Olanzapine	418.0	16.9	–2.4	17.5			
Nonfasting blood glucose, mg/dL	Olanzapine/Fluoxetine combination	102.9	32.8	11.4	43.6	.237	.120	.843
	Fluoxetine	97.8	30.3	4.9	36.9			
	Olanzapine	94.2	19.6	9.9	29.7			
Fasting blood glucose, mg/dL	Olanzapine/Fluoxetine combination	96.0	10.3	14.1	49.4	.352	.190	.871
	Fluoxetine	99.1	25.4	–3.1	21.3			
	Olanzapine	99.8	26.7	8.3	29.5			
Prolactin, µg/L	Olanzapine/Fluoxetine combination	15.5	13.0	3.4	11.1	.004	.039	.224
	Fluoxetine	13.7	9.2	0.9	7.3			
	Olanzapine	13.4	8.4	5.0	17.0			
Alanine aminotransferase, units/L	Olanzapine/Fluoxetine combination	24.5	14.6	9.2	23.2	< .001	.002	.297
	Fluoxetine	24.3	12.5	0.9	15.8			
	Olanzapine	24.0	15.7	11.8	37.7			
Aspartate aminotransferase, units/L	Olanzapine/Fluoxetine combination	22.1	8.6	5.1	12.1	< .001	.001	.637
	Fluoxetine	23.3	9.7	0.5	10.4			
	Olanzapine	22.6	13.6	5.5	18.1			
Triglycerides, mg/dL	Olanzapine/Fluoxetine combination	194.7	127.4	39.8	122.1	.040	.083	.466
	Fluoxetine	177.9	109.7	15.9	96.5			
	Olanzapine	185.8	161.9	51.3	184.1			
Total cholesterol, mg/dL	Olanzapine/Fluoxetine combination	206.6	40.5	15.1	32.0	< .001	< .001	< .001
	Fluoxetine	215.8	45.6	0.8	31.7			
	Olanzapine	214.7	42.9	2.7	34.0			

[a]QT interval correction was $QTc = QT/RR^{0.413}$.

nonfasting blood glucose or fasting glucose (although the number of patients with fasting glucose values was small). Patients with nonfasting glucose values in ranges of clinical interest[37] were as follows: The percentages of patients with an increase in nonfasting glucose from less than 140 mg/dL at baseline to greater than or equal to 200 mg/dL at endpoint were not significantly different among groups: olanzapine/fluoxetine combination, 1.9% (3/156); fluoxetine, 1.8% (3/167); olanzapine, 4.2% (7/165); p = .385. Also, the percentages of patients with nonfasting glucose ranging from 140 to < 200 mg/dL at baseline and increasing to ≥ 200 mg/dL at endpoint were not significantly different among groups: olanzapine/fluoxetine combination, 50.0% (5/10); fluoxetine, 20.0% (1/5); olanzapine, 75.0% (3/4); p = .341. (It should be noted that very few patients were included in this analysis due to most not meeting the baseline criterion.) Mean change in prolactin for olanzapine/fluoxetine combination was significantly different from that of fluoxetine but not olanzapine. Mean changes in alanine aminotransferase and aspartate aminotransferase for the olanzapine/fluoxetine combination group were significantly different from those of the fluoxetine group but not the olanzapine group.

Mean change in triglycerides for patients treated with olanzapine/fluoxetine combination was not significantly different from that for fluoxetine or olanzapine patients. The percentages of patients with an increase in triglycerides from less than 150 mg/dL at baseline to greater than or equal to 500 mg/dL at endpoint[38] were not significantly different among groups: olanzapine/fluoxetine combination, 0.0% (0/85); fluoxetine, 0.0% (0/103); olanzapine, 0.9% (1/107); p = 1.00. (It should be noted that less than half the sample had triglycerides less than 150 mg/dL at baseline, thus most patients were not included in this analysis.) Mean change in total cholesterol for the olanzapine/fluoxetine combination group was significantly different from that of both the fluoxetine and olanzapine groups. The percentages of patients with increases in total cholesterol from less than 200 mg/dL at baseline to greater than or equal to 240 mg/dL at endpoint[38] were not significantly different among groups: olanzapine/fluoxetine

combination, 8.2% (7/85); fluoxetine, 3.9% (3/77); olanzapine, 7.1% (5/70); p = .531. (It should be noted that less than half the sample had total cholesterol less than 200 mg/dL at baseline, thus most patients were not included in this analysis.)

DISCUSSION

The results of Study 2 and the pooled analysis of both studies provide further evidence that olanzapine/fluoxetine combination is efficacious in treatment-resistant depression (defined as treatment failure on 2 antidepressants). As in each of the previous TRD studies,[19–21] there was an onset of antidepressant effect within 1 week that peaked around week 3 and was maintained for the duration of the study. Overall response and remission rates for olanzapine/fluoxetine combination (40% and 27%, respectively) were similar to those for the Corya et al. study[21] (43% and 30%) but somewhat higher than those for the large Shelton et al. study[20] (28% and 17%). The MADRS total score mean decrease of 13 points for the olanzapine/fluoxetine combination group was similar to findings in the Corya et al. study[21] and the Shelton et al. pilot study[19] but again, somewhat greater than that observed in the large Shelton et al. study.[20]

Recently published results of the STAR*D trial provide additional contextual data on augmentation and switching after not responding to or not tolerating an SSRI. Although the STAR*D trial was open label (not double blind) and the sample was likely less treatment resistant than in the current trial (i.e., having failed only 1 antidepressant), comparisons between the trials may be of interest. Trivedi et al.[10] reported remission rates for augmentation with sustained-release bupropion (29.7%) or buspirone (30.1%) that were comparable to that observed for olanzapine/fluoxetine combination in the current trial (27.3%). Also, the olanzapine/fluoxetine combination remission rate was numerically higher than the remission rates for patients who were switched from citalopram to sustained-release bupropion (21.3%), sertraline (17.6%), or extended-release venlafaxine (24.8%) in the STAR*D trial.[9] Although different efficacy measures were used (HAM-D-17 vs. MADRS), comparison of these results across studies suggests that the olanzapine/fluoxetine combination yielded remission rates that are at least comparable to those observed in the STAR*D trial, despite being studied in a potentially more treatment-resistant sample with a greater baseline severity of depression. (It should be noted, however, that the STAR*D sample, which was largely recruited from community clinical settings, very likely had more medical and psychiatric comorbidities than the current sample.)

Because factors of past treatment response or nonresponse could influence the current results, we conducted a subgroup analysis based on drug class of historical treatment failures. We separated pooled study patients into 2 groups: 1 group had historical treatment failures on SSRIs only and another group had at least 1 failure in another drug class. In general, olanzapine/fluoxetine combination appeared to be more effective in those patients with SSRI-only treatment failures (MADRS mean change of –14.3 vs. –10.7). This should not be surprising, given that patients who have not responded to multiple drug classes can be considered more treatment resistant than those who have not responded to a single drug class. (However, it should be noted that the rate of response after an SSRI within-class switch has been reported as high and similar to that for switching to another class.[9,39,40]) Fluoxetine appeared to be somewhat less effective in those patients with SSRI-only treatment failures compared with those with treatment failures in another drug class. This finding may reflect some degree of class-specific resistance to SSRIs in this subgroup.

In addition to greater overall efficacy than olanzapine or fluoxetine alone, olanzapine/fluoxetine combination was more rapidly efficacious. Time-to-event analyses supported a rapid onset of antidepressant effect for olanzapine/fluoxetine combination. Time to response and remission were significantly shorter for olanzapine/fluoxetine combination than for fluoxetine and olanzapine. In addition, onset of effect, which was defined a priori as time to partial response, was significantly shorter for olanzapine/fluoxetine combination patients (6 days) than for fluoxetine patients (10 days). Time to partial response was not significantly different between olanzapine/fluoxetine combination and olanzapine patients. This may not be surprising, given that partial response was achieved by most patients very early in the acute treatment phase while many olanzapine patients were most likely still affected by residual fluoxetine from the lead-in phase. Olanzapine alone has also been observed to have modest antidepressant effects in bipolar depression.[41]

The clinical relevance of changes and differences in depression scores are always of interest in clinical trials, where large sample sizes can sometimes cause small differences to be statistically significant. In the pooled MMRM analysis, the MADRS 8-week mean change of –12.7 points for olanzapine/fluoxetine combination group brought the group mean down from a baseline of 30.0 to a score of 17.3. Patients with a MADRS total score of 17 are still considered mildly depressed, but are clinically much improved relative to a score of 30, which is in the moderate to severely depressed range.[42,43] Differences between the therapies at 8 weeks were 3.7 points between olanzapine/fluoxetine combination and fluoxetine and 4.0 points between olanzapine/fluoxetine combination and olanzapine. Montgomery et al.[44] proposed that a separation of 3 points between treatments on the MADRS indicates probable clinical relevance and a separation of 4 points indicates definite clinical relevance. Using these

criteria, olanzapine/fluoxetine combination's separations from fluoxetine and olanzapine were in the probably to definitely clinically relevant range. Differences in onset of effect are also important when considering clinical relevance, especially for patients who have already failed several treatments. There were statistically significant differences among the time to response curves for olanzapine/fluoxetine combination versus the 2 monotherapies, and the median time to response results indicated that patients in the olanzapine/fluoxetine combination group took approximately 4 weeks to achieve response, compared with 7 weeks for patients taking the other therapies. A definitely clinically relevant change in MADRS score occurred in olanzapine/fluoxetine combination patients by the 0.5-week visit (see Figure 2); however, it should be noted that probably to definitely clinically relevant changes in the MADRS occurred for the other 2 therapies by this visit as well.

Quality of life was measured by the Sheehan Disability Scale and the SF-36. The Sheehan results revealed advantages for olanzapine/fluoxetine combination over both component monotherapies in leisure and family areas although not work. It is possible that 8 weeks is too short a time period for any therapy to show an impact on a patient's work status. Long-term data from the open-label extension may be more informative in this area. It should also be noted that over one quarter of patients answered "not applicable" to the work question. The 36-item Short Form Health Survey results revealed that olanzapine/fluoxetine combination patients reported significantly greater improvement in functioning than olanzapine patients on all but 1 subscale, and significantly greater improvement in functioning than fluoxetine patients on 2 subscales (bodily pain and social functioning). The greatest improvements for the olanzapine/fluoxetine combination group occurred on the social functioning, role-emotional, and mental health subscales. Improvements on these subscales reflect not only that feelings of depression are decreased but also that depressive symptoms are interfering less with daily occupational and social activities.

There did not appear to be a straightforward explanation for why the 2 studies yielded different results. Approximately one half of contemporary studies of established antidepressants fail to detect significant drug-placebo differences, so a failed study of TRD is not unexpected.[45] Nonetheless, every effort should be made to detect between-trial differences that might explain the discrepant study results. There was a significant study-by-therapy interaction, suggesting possible patient and/or investigator heterogeneity between the 2 studies. However, no single explanation for the different results was identified. One factor considered was different degrees of treatment resistance between the samples. Sackeim[46] concluded that the majority of antidepressant treatment failures are explained by 3 factors: inadequate treatment, treatment nonadherence, and unrecognized comorbidities. If we assume that the first 2 factors can be ruled out in our study, comorbidities might explain at least part of the discrepant results. For example, if patients in Study 1 had more comorbid diagnoses (e.g., personality disorders, anxiety disorders, or unrecognized bipolar II disorder), then those patients as a group may have been less likely to respond to pharmacologic treatment alone. Anxiety disorders and personality disorders (other than paranoid, schizoid, schizotypal, antisocial, and severe borderline personality disorder) were not excluded from the studies. Unfortunately, further information on Axis II disorders for patients who remained in the study was not collected.

Investigator randomization was considered as a factor in the discrepant study results. Investigators were randomly assigned to Study 1 or Study 2 before patients were enrolled. The resulting randomization scenario was one of thousands of possibilities. To investigate the effect of randomization on the outcome of our 2 studies, we performed a simulation of study results for 5000 randomization scenarios. For each iteration, the primary efficacy analysis was conducted. Of the 5000 investigator randomizations examined, 48.4% resulted in 2 successful studies, 51.4% resulted in 1 successful and 1 failed study, and 0.2% resulted in 2 studies that failed to reject the null hypothesis. These results indicate that the probability of obtaining 2 studies with positive results versus 1 positive and 1 negative study was close to 50/50. Indeed, it is not uncommon to have both positive and negative results from identical trials in depression treatment studies.[45]

Safety findings were consistent with previous literature on olanzapine/fluoxetine combination. As in previous studies,[18,20,21] measures of corrected QT interval for olanzapine/fluoxetine combination were similar to those for fluoxetine, whereas hepatic-based safety parameters, extrapyramidal symptoms measures, glucose and lipid values, and weight gain were all similar to those for olanzapine. In the present study, mean total cholesterol change was significantly greater for olanzapine/fluoxetine combination than for olanzapine, and a similar finding was reported in one previous study of olanzapine/fluoxetine combination in TRD. Categorical cholesterol results were not different among the 3 groups. Health care professionals should consider patient factors (e.g., severity of illness, quality of response to alternative medications, and urgency for rapid response based on inpatient/outpatient status and/or active suicidality) as well as the adverse event profile of olanzapine/fluoxetine combination and other treatment choices when making prescribing decisions for TRD patients.

Strengths of the current design include large sample size, blinding of investigators to the criteria for randomly assigning patients, and the use of relatively conservative criteria for establishing TRD. Limitations include the fact that the trial was not placebo-controlled, which prevented

us from ruling out nonpharmacologic explanations for patient improvement (e.g., expectation effects or spontaneous changes in disease course). It is also possible that a trial duration of longer than 8 weeks could have provided additional data on response and remission in this treatment-resistant population.

In conclusion, these studies provide further evidence that the olanzapine/fluoxetine combination is an efficacious treatment for patients with treatment-resistant depression. Although Study 1 failed to confirm statistically significant differences versus the 2 monotherapies, both Study 2 and the pooled analysis showed clear evidence of benefit for olanzapine/fluoxetine combination, with significantly more rapid onset of therapeutic benefit. For many patients, the rapid symptom reduction associated with olanzapine/fluoxetine combination treatment will outweigh any potential risk or discomfort due to adverse events. This is particularly true given the seriousness of the disease state, such that remission of depressive symptoms must be a primary goal. Whether olanzapine/fluoxetine combination is right for any given individual must be determined on a patient-by-patient basis. Although combined therapy with olanzapine and fluoxetine is associated with a broader array of adverse events and greater weight gain than continued treatment with fluoxetine alone, the profound illness burden associated with TRD suggests that the potential clinically significant benefit may well justify the risks in some patients.

Drug names: bupropion (Wellbutrin and others), buspirone (BuSpar and others), citalopram (Celexa and others), fluoxetine (Prozac and others), fluoxetine/olanzapine combination (Symbyax), lorazepam (Ativan and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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