Olanzapine/Fluoxetine Combination for Treatment-Resistant Depression: A Controlled Study of SSRI and Nortriptyline Resistance

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Background: This 8-week, double-blind, multicenter study was undertaken to replicate, in a larger sample of patients with treatment-resistant major depressive disorder (MDD; DSM-IV criteria), the results of a pilot study of the olanzapine/fluoxetine combination.

Method: The study was begun in August 1999. The primary entry criterion was a history of failure to respond to a selective serotonin reuptake inhibitor (SSRI). Patients (N = 500) who subsequently failed to respond to nortriptyline during an open-label lead-in phase were randomly assigned to 1 of 4 treatment groups: olanzapine (6–12 mg/day) plus fluoxetine (25–50 mg/day) combination, olanzapine (6–12 mg/day), fluoxetine (25–50 mg/day), or nortriptyline (25–175 mg/day). The primary outcome measure was baseline-to-endpoint mean change in score on the Montgomery-Asberg Depression Rating Scale (MADRS).

Results: At the 8-week study endpoint, MADRS total scores decreased by a mean 8.7 points from baseline (28.5) with the olanzapine/fluoxetine combination, 7.0 points from baseline (28.4) with olanzapine ($p = .08$), 8.5 points from baseline (28.4) with fluoxetine ($p = .84$), and 7.5 points from baseline (28.8) with nortriptyline ($p = .30$), with no significant differences among the therapies. The olanzapine/fluoxetine combination was associated with significantly ($p \leq .05$) greater improvement (decrease) in MADRS scores than olanzapine at weeks 2, 4, 6, and 7; than fluoxetine at weeks 2 through 5; and than nortriptyline at weeks 1 through 4. A post hoc analysis of a subgroup of patients who had an SSRI treatment failure during their current MDD episode (N = 314) revealed that the olanzapine/fluoxetine combination group had a significantly ($p = .005$) greater decrease in MADRS scores than the olanzapine group at endpoint. Safety data for the olanzapine/fluoxetine combination were similar to those for its component monotherapies.

Conclusions: The olanzapine/fluoxetine combination did not differ significantly from the other therapies at endpoint, although it demonstrated a more rapid response that was sustained until the end of treatment. The results raised several methodological questions, and recommendations are made regarding the criteria for study entry and randomization.

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Despite significant psychopharmacologic advances, roughly one third of patients with major depressive disorder (MDD) do not respond to conventional treatments,[1–4] and as many as 50% have only partial response.[1,4] This subset of partially responding and nonresponding patients may be characterized as having treatment-resistant depression (TRD). Given the significant public health concern that TRD represents, not only in terms of morbidity and mortality, but also in terms of lost productivity, economic burden, and diminished quality of life, it is important to understand and develop appropriate treatments for patients with this form of depression.

Clinically, TRD presents along a spectrum, from patients failing monotherapy trials to others failing multiple augmented and/or combined therapies including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), antipsychotics, and electroconvulsive therapy (ECT).[5] Researchers have suggested numerous working definitions and proposed staging of TRD. For instance, Thase et al.[6] described 5 stages of treatment resistance ranging from failure of 1 trial of adequate dose and duration of an antidepressant (Stage I) to failure of 3 to 4 different classes of antidepressants plus ECT (Stage V).

However, TRD is often operationally defined as failure to respond to 2 different trials of antidepressants of adequate dose and duration.[3,4,7]

The symptoms that characterize major depressive disorder are presumed to be associated with brain monoaminergic neuronal dysfunction. The role of serotonin and norepinephrine in the actions of antidepressants is well documented. Yet, because many depressed patients do not respond to SSRIs, norepinephrine reuptake blockers, or combined agents, it is likely that other biochemical factors are involved. Recently, deficits in dopaminergic activity have been found in patients with TRD,[8] suggesting that the pathogenesis of this variant of depression may reflect disturbances in all 3 neurotransmitter systems.[9]

In a preclinical study, Zhang et al.[10] found that coadministration of olanzapine and fluoxetine produced robust, sustained increases in extracellular levels of serotonin, norepinephrine, and dopamine in rat prefrontal cortex. Moreover, while the olanzapine/fluoxetine combination was associated with significant increases from baseline levels of all 3 monoamines, there were synergistic increases in the levels of norepinephrine and dopamine exceeding those associated with individual administration of either olanzapine or fluoxetine.

In a double-blind pilot study,[11] 28 TRD patients treated with the olanzapine/fluoxetine combination had significantly greater improvement on the Montgomery-Asberg Depression Rating Scale (MADRS)[12] than those treated with either olanzapine or fluoxetine alone. Improvement with the combination treatment occurred more quickly (within the first week of treatment) and was superior to improvement with both monotherapies throughout the 8-week trial. In a comparable study,[13] 8 subjects with a history of SSRI failure showed significant improvement on the Hamilton Rating Scale for Depression when risperidone was added to fluoxetine or paroxetine.

On the basis of these studies, a large, double-blind, randomized clinical trial was undertaken to evaluate the efficacy and safety of the olanzapine/fluoxetine combination for treatment of TRD. In order to prospectively confirm treatment resistance, subjects with a history of SSRI failure were given a 7-week open-label trial of the TCA nortriptyline at therapeutic plasma concentrations. Subjects who failed to respond during this lead-in phase were subsequently randomly assigned to the double-blind phase. Thus, all randomized subjects met Thase and Rush's criteria for Stage II or higher treatment resistance.[5] Given the olanzapine/fluoxetine combination's rapid, robust antidepressant effects in the pilot study, it was hypothesized that the olanzapine/fluoxetine combination group would experience greater reductions in depressive symptoms than the other 3 treatment groups. The present study aims to replicate, in a larger patient sample, the findings of the pilot study.

METHOD

Study Design

This 8-week, double-blind clinical trial was conducted at 71 sites in the United States and Canada starting in August 1999. In accordance with the Declaration of Helsinki, each site's ethics committee approved the protocol. Subjects were required to meet diagnostic criteria for unipolar, nonpsychotic MDD according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), and also were required to have had at least 1 past treatment failure to an SSRI after at least 4 weeks of therapy at a therapeutic dose (i.e., citalopram 40 mg/day, fluoxetine 40 mg/day, paroxetine 40 mg/day, or sertraline 150 mg/day). Qualified subjects who completed a 2- to 7-day screening and washout period entered a 7-week nortriptyline dose-escalation period to demonstrate prospective treatment failure to a TCA and to confirm treatment resistance. Treatment failure was defined as less than 30% improvement (decrease) in MADRS total score from baseline. Those subjects who met the nortriptyline treatment failure criterion at the end of the 7 weeks were eligible to enter the 8-week double-blind trial. This prospectively defined cohort of TRD subjects was randomly assigned under double-blind conditions on a 2:2:2:1 assignment schedule to 1 of 4 treatment groups: olanzapine/fluoxetine combination therapy, olanzapine monotherapy, fluoxetine monotherapy, or nortriptyline monotherapy.

All medication was administered orally once per day in the evening. During the lead-in phase, subjects received an initial nortriptyline dose of 25 mg/day, which was increased to 50 mg/day on day 2 and 75 mg/day by day 4 if tolerated. On the basis of investigator assessment, the dose could be titrated by 25 mg up to a maximum of 175 mg/day. Blood nortriptyline levels were to remain within the therapeutic range, defined as 75 to 150 ng/mL, and patients who failed to maintain an adequate blood level were discontinued prior to randomization.

In order to maintain blinding at the completion of the lead-in phase, all subjects appeared to taper off nortriptyline, but only those subjects randomly assigned to the olanzapine/fluoxetine combination, olanzapine, or fluoxetine actually had nortriptyline tapered. Subjects randomly assigned to nortriptyline maintained the dose established during the lead-in. All subjects receiving olanzapine monotherapy or olanzapine/fluoxetine combination therapy began with an initial olanzapine dose of 6 mg/day. All subjects receiving fluoxetine or olanzapine/fluoxetine combination therapy began with an initial fluoxetine dose of 25 mg/day. Both monotherapies could be titrated at the investigator's discretion on a daily basis. All monotherapy groups also took a second placebo pill to preserve the blind. Olanzapine monotherapy dosing could range from 6 to 12 mg/day, and fluoxetine monotherapy dosing could range from 25 to 50 mg/day. Olanzapine/

fluoxetine combination subjects could receive either olanzapine 6 mg/day plus fluoxetine 25 mg/day or olanzapine 12 mg/day plus fluoxetine 50 mg/day.

Concomitant medications with primary central nervous system activity were not allowed with the exception of lorazepam, which was permitted on an as-needed basis for anxiety (≤ 2 mg/day) but could not be administered within 8 hours of a psychiatric evaluation. No other benzodiazepines were permitted. Subjects entering the study while receiving concomitant psychotherapy maintained it throughout the study. Subjects entering the study who were not receiving concomitant psychotherapy were not permitted to begin such therapy until completion of the 8-week trial. ECT was not permitted at any time.

Subjects

Prior to study enrollment, all subjects gave written informed consent to participate. Subjects who met diagnostic criteria for recurrent MDD without psychotic features entered the screening period. Diagnosis was confirmed with the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I)[14] and the MDD Specifiers in the SCID-I-Research Version.[15] Subjects were required to have a MADRS total score ≥ 20 at both the beginning and the end of the screening period as well as a previous (but not necessarily current) failure to achieve satisfactory antidepressant response to a trial of an SSRI. Subjects who developed psychotic symptoms (Brief Psychiatric Rating Scale [BPRS][16] positive item score ≥ 3) during the nortriptyline lead-in phase were not eligible for randomization. All subjects were 18 to 65 years of age. Pregnant or lactating women were excluded as well as subjects who had received ECT within 1 month of the study or who were likely in the opinion of the investigator to require ECT during the course of the study.

Assessments

A screening clinical assessment, which included a standard history, physical and psychiatric examination, vital signs, laboratory profile, and electrocardiography, was performed at the first visit. At subsequent visits, efficacy measures and safety assessments were repeated at scheduled intervals or as clinically indicated.

During the nortriptyline lead-in phase, subjects were seen weekly for the first 3 weeks and every 2 weeks thereafter to evaluate blood nortriptyline levels and to obtain efficacy and safety measures. Nortriptyline was required to be titrated to a therapeutic plasma level no later than 2 weeks after starting medication. If after this 2-week visit nortriptyline levels were within the therapeutic range, then no further assessment of nortriptyline levels was required unless there was a change in dose or if clinically indicated. After randomization to treatment groups, subjects were seen every 2 to 5 days for the first 2 visits and weekly thereafter. Blood nortriptyline levels were not evaluated during the double-blind treatment phase.

The primary efficacy measure was mean change on the MADRS from baseline (i.e., at the time of acute-phase randomization) at endpoint. Secondary efficacy measures included the Clinical Global Impressions–Severity of Illness scale (CGI-S)[17] and the Hamilton Rating Scale for Anxiety (HAM-A).[18] Spontaneously reported treatment-emergent adverse events were recorded at each visit using the Coding Symbols and Thesaurus for Adverse Reaction Terms (COSTART).[19] Emergence of psychosis was monitored using the BPRS. Extrapyramidal symptoms were assessed with the Simpson-Angus Scale,[20] the Barnes Akathisia Scale,[21] and the Abnormal Involuntary Movement Scale (AIMS).[22]

Statistical Methods

Analyses of MADRS total scores employed a mixed-effects model repeated-measures regression (MMRM) methodology on changes from baseline. Although the original protocol specified analysis of variance (ANOVA) with a last-observation-carried-forward (LOCF) methodology, MMRM was selected because it has been shown to provide highly accurate modeling of treatment outcome while accounting for subject dropout.[23] LOCF results for the subjects described in the present study have been disclosed previously.[24] ANOVA with LOCF was used for the HAM-A total score and CGI-S score owing to the infrequent nature of these assessments. Only subjects with a baseline and at least 1 postbaseline visit were included in endpoint analyses. If an individual item score was missing for any subject, then that subject's total score was treated as missing. All analyses were performed on an intent-to-treat basis.

All hypotheses were evaluated for significance with 2-tailed tests at an α level of .05. Least-squares means were used to calculate between-group differences. Pairwise comparisons were considered only when the overall therapy difference was statistically significant. Linear model fixed-effects terms included baseline, treatment, investigator, visit, treatment-by-investigator interaction, and treatment-by-visit interaction. The method of restricted maximum likelihood was used to estimate the parameters of the covariance matrix for within-subject error.

Response and remission rates were compared among the treatment groups. Treatment response was defined as ≥ 50% decrease from baseline to endpoint in MADRS total score during the 8-week acute treatment phase. Remission was defined as 2 consecutive MADRS total scores ≤ 8. Relapse was defined as 2 subsequent MADRS scores ≥ 16 following a remission. The occurrence of treatment-emergent extrapyramidal symptoms was defined as a Simpson-Angus Scale total score ≤ 3 at baseline and > 3 at any postbaseline visit. Treatment-emergent akathisia was defined as a Barnes Akathisia Scale global score < 2 at

Table 1. Reason for Study Discontinuation Recorded on Discharge Summary

	Lead-In Period		Double-Blind Period							
	NRT (N = 946)		OFC (N = 146)		OLZ (N = 144)		FLX (N = 142)		NRT (N = 68)	
Variable	N	%	N	%	N	%	N	%	N	%
Adverse event	95	10.0	10	6.8	14	9.7	4	2.8	2	2.9
Lack of efficacy	33	3.5	5	3.4	6	4.2	9	6.3	2	2.9
Interim criteria not met[a]	191	20.2	1	0.7	2	1.4	2	1.4	0	0.0
Protocol violation	11	1.2	2	1.4	2	1.4	2	1.4	0	0.0
Lost to follow-up	40	4.2	7	4.8	3	2.1	4	2.8	3	4.4
Personal conflict/patient decision	53	5.6	3	2.1	4	2.8	6	4.2	1	1.5
Other	36	3.8	2	1.4	1	0.7	1	0.7	0	0.0

[a]Interim criteria were as follows: < 30% improvement from baseline in MADRS total score, plasma nortriptyline levels within the therapeutic range, and all BPRS positive scale item scores < 3.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, FLX = fluoxetine, MADRS = Montgomery-Asberg Depression Rating Scale, NRT = nortriptyline, OFC = olanzapine/fluoxetine combination, OLZ = olanzapine.

Table 2. Baseline Demographic and Illness Characteristics

	Lead-In Period	Double-Blind Period			
Variable	NRT (N = 946)	OFC (N = 146)	OLZ (N = 144)	FLX (N = 142)	NRT (N = 68)
Age, mean (SD), y	42.5 (10.8)	42.5 (10.7)	43.4 (11.0)	41.7 (11.0)	41.5 (10.1)
Female, %	67.3	67.1	64.6	72.5	67.6
White, %	87.8	90.4	82.6	90.8	88.2
Body mass index, mean (SD), kg/m^2	30.3 (7.8)	30.5 (8.2)	30.3 (7.6)	31.6 (8.8)	32.1 (9.3)
Median length of current episode, d	330	374	302	338	448
≥ 3 MDD episodes over lifetime, %	66.9	66.4	65.3	70.4	66.2
≥ 3 MDD episodes in last 2 y, %	17.0	11.0	16.0	21.1	13.2

Abbreviations: FLX = fluoxetine, MDD = major depressive disorder, NRT = nortriptyline, OFC = olanzapine/fluoxetine combination, OLZ = olanzapine.

baseline and ≥ 2 at any postbaseline visit. Treatment-associated dyskinetic movement was defined as a score ≥ 3 on any of the AIMS items 1 through 7 or a score of ≥ 2 on any 2 of those items at any postbaseline visit if neither of these criteria had been met at baseline. Treatment-emergent laboratory analyte abnormalities were examined for subjects with values within physiologically normal ranges at baseline that were outside normal ranges at any time during the study, and for subjects with baseline values outside normal ranges that worsened over the course of the study. The Fisher exact test was used to evaluate treatment group differences for categorical data.

RESULTS

Subject Characteristics and Disposition

A total of 946 subjects entered the study. Of these, 446 subjects (47.1%) were discontinued during the lead-in phase (mostly owing to not meeting entry criteria for the acute phase). Response (≥ 30% reduction in MADRS total score) rate during the lead-in was 17.7%. A total of 500 subjects were randomly assigned to double-blind therapy (olanzapine/fluoxetine combination N = 146, olanzapine N = 144, fluoxetine N = 142, nortriptyline N = 68). Of those randomized, the proportion of subjects discontinuing the double-blind treatment phase owing to an adverse event did not differ significantly among treatment groups (Table 1). Baseline (i.e., at time of acute phase randomization) demographics and illness characteristics did not differ among the treatment groups (see Table 2 for sample demographics and illness characteristics). Baseline mean (SD) MADRS scores were also similar for the 4 therapy groups (olanzapine/fluoxetine combination: 28.5 [7.5]; olanzapine: 28.4 [7.3]; fluoxetine: 28.4 [7.3]; nortriptyline: 28.8 [6.5]).

Medication Use and Compliance

During the lead-in phase, the mean modal dose (mg/day) for subjects who did not meet the treatment-resistance criterion (i.e., those who had achieved at least a 30% improvement in MADRS score at the end of the phase) was 81.2 (SD = 43.1). For patients who did meet the treatment resistance criterion and were subsequently randomized, the mean (SD) modal nortriptyline dose was 104.6 (29.5) mg/day. During the double-blind treatment phase, mean modal doses (mg/day) were as follows: olanzapine, 8.5 (3.1), plus fluoxetine, 35.6 (12.7); olanzapine, 8.3 (3.1); fluoxetine, 35.8 (12.8); and nortriptyline, 103.5

(33.9). Mean (SD) plasma nortriptyline levels (ng/L) for each visit of the lead-in phase for the randomized patients were as follows: visit 1, 87.9 (37.5); visit 2, 111.1 (33.7); visit 3, 114.5 (31.2); visit 4, 111.3 (36.5); and visit 5, 103.7 (25.5).

Subject compliance was defined as the number of days study drug was taken as prescribed (per subject report) divided by the total number of days in the acute phase, multiplied by 100. Compliance was not significantly different among the therapy groups (olanzapine/fluoxetine combination: 97.0%; olanzapine: 96.6%; fluoxetine: 96.5%; nortriptyline: 96.5%; $p > .50$).

Efficacy

Visitwise MADRS least squares mean change scores are shown in Table 3. There were significant main effects for treatment ($F = 3.77$, $df = 3,602$; $p = .01$) and for visit ($F = 18.89$, $df = 8,3084$; $p < .001$), and there was a significant treatment-by-visit interaction ($F = 1.72$, $df = 24,3090$; $p = .02$). At week 1, the olanzapine/fluoxetine combination group showed significantly greater MADRS improvement than the nortriptyline group ($p = .007$), and at week 2, the olanzapine/fluoxetine combination group separated statistically from all 3 monotherapy groups (olanzapine $p = .029$, fluoxetine $p < .001$, nortriptyline $p < .001$). Additionally, the olanzapine/fluoxetine combination group continued to demonstrate significantly greater MADRS improvement than the olanzapine group at weeks 4, 6, and 7; than the fluoxetine group at weeks 3 through 5; and than the nortriptyline group at weeks 3 and 4. However, at the 8-week study endpoint, the groups were no longer statistically different.

Endpoint response rates did not differ significantly among the therapy groups (olanzapine/fluoxetine combination: 27.5%; olanzapine: 19.3%; fluoxetine: 28.9%; and nortriptyline: 30.3%; $p = .18$). Remission rates also did not differ significantly among the therapy groups (olanzapine/fluoxetine combination: 16.9%; olanzapine: 12.9%; fluoxetine: 13.3%; and nortriptyline: 18.2%; $p = .62$). Of the 72 subjects who remitted, 7 relapsed (9.7%), also with no significant differences among groups ($p = .21$).

For the secondary efficacy measures, the olanzapine/fluoxetine combination treatment group demonstrated a statistically significantly greater decrease in CGI-S score at endpoint compared with the olanzapine group only. There was no evidence of significant between-group differences in HAM-A or BPRS scores (Table 4).

Post hoc analyses of MADRS scores for a subgroup of patients with an SSRI treatment failure during the current MDD episode ($N = 314$) revealed significant main effects for treatment ($F = 4.49$, $df = 3,387$; $p = .004$) and for visit ($F = 12.25$, $df = 8,1994$; $p < .001$), as well as a significant treatment-by-visit interaction ($F = 1.54$, $df = 24,1995$; $p = .04$). Within this subgroup, olanzapine/fluoxetine combination subjects showed significantly greater improvement in MADRS scores at the 8-week study endpoint (–9.1) than olanzapine (–5.6, $p = .005$) subjects, but not nortriptyline (–7.1, $p = .18$) or fluoxetine (–7.9, $p = .33$) subjects.

Table 3. Visitwise Least Squares Mean Change in MADRS Scores From Baseline[a]

Week	Therapy	Least Squares Mean ± SE Change in MADRS Score	vs OFC t	df	p
0.5	OFC	–3.63 ± 0.65	…	…	…
	Olanzapine	–3.78 ± 0.65	0.17	1404	.868
	Fluoxetine	–2.52 ± 0.66	1.20	1403	.230
	Nortriptyline	–2.95 ± 0.94	0.59	1435	.555
1	OFC	–6.90 ± 0.65	…	…	…
	Olanzapine	–5.20 ± 0.65	–1.86	1427	.063
	Fluoxetine	–5.17 ± 0.66	1.88	1427	.061
	Nortriptyline	–3.78 ± 0.95	2.72	1368	.007
2	OFC	–8.99 ± 0.65	…	…	…
	Olanzapine	–6.98 ± 0.65	–2.18	1380	.029
	Fluoxetine	–5.68 ± 0.66	3.56	1367	< .001
	Nortriptyline	–4.70 ± 0.95	3.73	1400	< .001
3	OFC	–9.22 ± 0.65	…	…	…
	Olanzapine	–7.55 ± 0.66	–1.81	1349	.071
	Fluoxetine	–6.10 ± 0.67	3.34	1345	< .001
	Nortriptyline	–5.33 ± 0.95	3.37	1411	< .001
4	OFC	–9.94 ± 0.66	…	…	…
	Olanzapine	–7.86 ± 0.66	–2.23	1313	.026
	Fluoxetine	–6.84 ± 0.68	3.28	1281	.001
	Nortriptyline	–5.96 ± 0.95	3.44	1404	< .001
5	OFC	–9.00 ± 0.67	…	…	…
	Olanzapine	–7.22 ± 0.67	–1.88	1248	.061
	Fluoxetine	–7.13 ± 0.68	1.96	1285	.050
	Nortriptyline	–7.47 ± 0.95	1.31	1353	.190
6	OFC	–9.36 ± 0.68	…	…	…
	Olanzapine	–7.40 ± 0.69	–2.03	1220	.043
	Fluoxetine	–8.09 ± 0.69	1.31	1280	.191
	Nortriptyline	–8.55 ± 0.96	0.69	1322	.491
7	OFC	–8.91 ± 0.69	…	…	…
	Olanzapine	–6.86 ± 0.70	–2.09	1229	.036
	Fluoxetine	–7.91 ± 0.70	1.03	1275	.305
	Nortriptyline	–8.62 ± 0.97	0.25	1286	.805
8	OFC	–8.71 ± 0.70	…	…	…
	Olanzapine	–6.95 ± 0.71	–1.77	1279	.077
	Fluoxetine	–8.51 ± 0.70	0.20	1287	.841
	Nortriptyline	–7.46 ± 0.98	1.04	1329	.298

[a]Mean ± SE baseline MADRS scores: OFC = 28.5 ± 0.6, olanzapine = 28.4 ± 0.6, fluoxetine = 28.4 ± 0.6, nortriptyline = 28.8 ± 0.8.
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, OFC = olanzapine/fluoxetine combination.

Safety

Adverse events. The percentage of subjects reporting any treatment-emergent adverse event was comparable among treatment groups (olanzapine/fluoxetine combination: 88%; olanzapine: 86%; fluoxetine: 84%; nortriptyline: 85%; $p = .83$). The most commonly reported treatment-emergent adverse events (incidence ≥ 10%) in the olanzapine/fluoxetine combination treatment group were asthenia, somnolence, weight gain, increased appetite, headache, anxiety, tremor, nervousness, insomnia,

Table 4. Baseline-to-Endpoint Mean Change on Secondary Efficacy Measures for the Double-Blind Period (last observation carried forward)

	Baseline Score, Mean (SE)				Endpoint Change From Baseline, Mean (SE)				p Value			
Measure	OFC	OLZ	FLX	NRT	OFC	OLZ	FLX	NRT	Overall	OFC vs OLZ	OFC vs FLX	OFC vs NRT
CGI-S	4.4 (0.1)	4.3 (0.1)	4.3 (0.1)	4.4 (0.1)	–1.0 (0.1)	–0.6 (0.1)	–0.7 (0.1)	–0.7 (0.1)	.048	.006	.088	.131
HAM-A	15.7 (0.5)	15.1 (0.5)	14.9 (0.5)	16.1 (0.7)	–5.3 (0.5)	–3.9 (0.5)	–3.9 (0.6)	–3.9 (0.8)	.194	.075	.055	.199
BPRS	15.9 (0.6)	15.2 (0.6)	15.5 (0.6)	16.5 (0.9)	–4.0 (0.6)	–2.9 (0.6)	–3.5 (0.7)	–3.5 (0.9)	.498	.129	.417	.686

Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions–Severity of Illness scale, FLX = fluoxetine, HAM-A = Hamilton Rating Scale for Anxiety, NRT = nortriptyline, OFC = olanzapine/fluoxetine combination, OLZ = olanzapine.

and nausea. Tremor occurred with a greater frequency among subjects in the olanzapine/fluoxetine combination group (11.6%) than in the fluoxetine (2.1%, $p < .001$) or olanzapine (4.9%, $p = .053$) group.

Weight change. Analysis of baseline-to-endpoint mean weight change revealed a significant therapy effect ($p < .001$). Subjects treated with the olanzapine/fluoxetine combination had a significantly greater baseline-to-endpoint mean (SD) weight change (+3.28 [3.5] kg) than fluoxetine-treated subjects (–1.42 [2.61] kg) and nortriptyline-treated subjects (+0.80 [3.06] kg). There was no significant difference in mean weight change between the olanzapine/fluoxetine combination group and the olanzapine group (+2.94 [2.98] kg). The proportion of subjects with weight gain greater than 10% from baseline also revealed an overall therapy effect ($p = .001$). Pairwise comparisons revealed that the olanzapine/fluoxetine combination group had a significantly greater incidence (7.8%) of this type of weight gain than the fluoxetine (0%, $p = .001$) and nortriptyline (0%, $p = .02$) groups but was not significantly different from the olanzapine (4.3%, $p = .32$) group.

Vital signs. Analysis of baseline-to-endpoint mean (SD) changes in blood pressure revealed statistically significant differences between the olanzapine/fluoxetine combination and nortriptyline groups in diastolic standing (–2.8 [9.5] mm Hg and +1.0 [8.3] mm Hg, respectively; $p = .008$), diastolic supine (–3.3 [7.9] mm Hg and +1.1 [8.9] mm Hg, respectively; $p = .003$), systolic standing (–0.4 [13.4] mm Hg and +3.8 [14.2] mm Hg, respectively; $p = .004$), and systolic supine (–2.8 [13.4] mm Hg and +3.0 [13.4] mm Hg, respectively; $p = .002$) blood pressure. Overall, blood pressure with olanzapine/fluoxetine combination subjects showed mean decreases and with nortriptyline subjects showed mean increases in pressure. Baseline-to-endpoint mean (SD) standing pulse rates decreased significantly more with the olanzapine/fluoxetine combination than with olanzapine (–8.9 [12.6] bpm and –3.3 [12.4] bpm, respectively; $p = .004$) or nortriptyline (–2.0 [12.7] bpm; $p = .003$), as did baseline-to-endpoint mean (SD) changes in supine pulse rates (olanzapine/fluoxetine combination: –9.0 [11.0] bpm; olanzapine: –3.2 [11.1] bpm; $p < .001$; nortriptyline: –0.8 [11.2] bpm; $p < .001$).

Laboratory analytes. There were small and clinically insignificant changes in some laboratory analytes consistent with changes seen with olanzapine and fluoxetine monotherapy. The olanzapine/fluoxetine combination group had a small but significantly greater mean increase in total nonfasting cholesterol (+0.36 mmol/L) than fluoxetine (+0.06 mmol/L; $p < .001$), olanzapine (+0.12 mmol/L; $p = .007$), or nortriptyline (+0.03 mmol/L; $p = .004$). Percentage of subjects with nonfasting total cholesterol < 200 mg/dL at baseline and ≥ 240 mg/dL at any time was not significantly different among the therapy groups ($p = .14$). Triglycerides were not measured. The olanzapine/fluoxetine combination was associated with a statistically significant mean increase in prolactin level (+0.36 nmol/L) compared to fluoxetine (+0.05 nmol/L; $p < .001$), olanzapine (+0.26 nmol/L; $p = .017$), and nortriptyline (–0.01 nmol/L; $p < .001$). There were no significant therapy group differences in baseline-to-endpoint mean change in nonfasting glucose level ($p = .34$). Percentage of subjects with nonfasting blood glucose < 200 mg/dL at baseline and ≥ 200 mg/dL at any time was not significantly different among the therapy groups ($p = .22$). There were no significant therapy group differences in categorical analyses of the emergence of abnormally high or low analytes at any time.

There were overall therapy effects across groups in baseline-to-endpoint mean change in hematocrit ($p < .001$), hemoglobin ($p < .001$), and erythrocyte count ($p < .001$), with significantly greater decreases associated with the olanzapine/fluoxetine combination than with fluoxetine or nortriptyline but not olanzapine. There was a statistically significant difference in baseline-to-endpoint mean change in leukocyte count ($p = .040$) between the olanzapine/fluoxetine combination ($+0.11 \times 10^9$/L) and nortriptyline ($+0.72 \times 10^9$/L; $p = .026$). There were no significant differences among treatment groups in the incidence of abnormally high or low hematology values at any time.

Cardiac function. Mean change from baseline to endpoint in corrected QT (QTc) intervals (Fredericia corrected) revealed a statistically significant therapy effect ($p = .045$). There was a mean (SD) increase in QTc for the olanzapine/fluoxetine combination (11.3 [15.9] msec) similar to that for fluoxetine (11.1 [13.9] msec; $p = .48$)

and nortriptyline (6.3 [20.3]; p = .289) but greater than that for olanzapine (2.9 [11.5]; p = .008).

Treatment-emergent extrapyramidal symptoms. There were no overall statistically significant differences among treatment groups in mean change from baseline to endpoint in treatment-emergent parkinsonian symptoms as measured by the Simpson-Angus Scale, akathisia as measured by the Barnes global score, or dyskinesia as measured by the AIMS.

DISCUSSION

The olanzapine/fluoxetine combination group experienced significantly greater improvement in depressive symptoms than all 3 monotherapy groups by week 2 of treatment and maintained symptom improvement throughout the 8-week study. The monotherapy groups showed steady symptom improvement over the course of the trial and ultimately had improvement similar to that of the olanzapine/fluoxetine combination group at the 8-week endpoint. Although the olanzapine/fluoxetine combination did not achieve statistical significance versus the other therapies at the endpoint of the trial, the early and significant improvement with the olanzapine/fluoxetine combination is likely to have clinical relevance. The speed of antidepressant response can be a critical variable, especially when patients are experiencing suicidal ideation.[25] Considering this, it is worth noting that the MADRS improvement experienced by the nortriptyline group remained statistically inferior to that of the olanzapine/fluoxetine combination group until week 5, and the improvement experienced by the fluoxetine group remained statistically inferior to that of the olanzapine/fluoxetine combination group until week 6. However, because the study was not originally designed to assess onset of antidepressant effect, these results must be considered a secondary finding.

There are several possible reasons that the olanzapine/fluoxetine combination group did not maintain statistical separation from the monotherapy groups. First, full response to an antidepressant can take 12 weeks or more,[26] which could account for the later response in the fluoxetine and nortriptyline groups. In addition, by week 5 of treatment, patients in the nortriptyline group had been taking the drug for 12 total weeks (including the lead-in phase). Thus, these subjects had a much longer exposure to (and time to respond to) nortriptyline than the olanzapine/fluoxetine combination group had to the olanzapine/fluoxetine combination. Also, patients and investigators were aware that there was no placebo group, so there may have been an enhanced expectation for improvement for all 4 therapy groups. A final possibility, given the robust effect by endpoint in all 3 monotherapy conditions, is that the population randomized in the double-blind phase was not actually treatment resistant. This would account for the observed response in the fluoxetine and nortriptyline arms. Several aspects of the methodology, discussed below, suggest that this may have been the case.

Although the protocol required a history of an SSRI failure, the failure could have occurred during any episode of depression, including a previous episode. Requiring an SSRI failure during the current episode as a criterion of entry into the study, prior to prospective failure during the nortriptyline lead-in phase, would have been a more conservative approach. This could have resulted in the inclusion of fewer subjects who were not truly treatment resistant. In addition, the stipulated duration of previous failed SSRI treatment (i.e., at least 4 weeks of therapy at an acceptable dose) may have been inadequate, since 4 weeks may not be long enough to distinguish a responder from a nonresponder. Similarly, the 7-week nortriptyline lead-in phase might not have been of sufficient duration to exclude late responders, particularly since the time taken to titrate nortriptyline could have resulted in patients' achieving a therapeutic plasma level relatively late in the phase.

Arguably, the entry criteria for the double-blind acute phase were the major determinants of the degree of treatment resistance in the study population. Importantly, investigators were not blinded to the entry criterion (less than 30% MADRS improvement). This aspect of the study may have led to an unconscious bias toward randomization and continued treatment in the study. Thus, there may have been a tendency toward underrating of subjects at the end of the lead-in phase and an overall less treatment-resistant sample than was intended. The fact that the response rate to nortriptyline during the lead-in was considerably lower than the expected 50% supports this hypothesis. However, the overall low response and remission rates during the double-blind phase are consistent with what would be expected in a TRD sample.

A number of aspects of the study design make interpretation of any comparisons with the nortriptyline arm problematic. The acute phase double-blind sample was selected for resistance to nortriptyline during the 7-week lead-in phase, potentially biasing the outcome against nortriptyline. However, other factors may have biased the study in favor of nortriptyline. Nortriptyline subjects in the double-blind phase had experienced an additional 7 weeks of exposure to the drug, for a total of 15 weeks by the end of the study. By the time the response of patients in the nortriptyline group no longer differed significantly from patients in the olanzapine/fluoxetine combination group, total exposure time to nortriptyline had been 12 weeks, compared to only 5 weeks for the olanzapine/fluoxetine combination, producing an unbalanced design. Also, acute phase nortriptyline subjects were a highly selected group who were tolerant to nortriptyline (because patients who experienced intolerable adverse events were discontinued during the lead-in). This nortriptyline-

tolerant sample may not have been representative of the general patient population.

The subgroup of patients who experienced an SSRI failure during their current episode may more closely resemble patients presenting in a clinical setting with TRD. This sample would include persons who have failed 2 antidepressants, in this case an SSRI and a TCA. The fact that the olanzapine/fluoxetine combination group statistically separated from olanzapine at endpoint and from fluoxetine at week 7 in this subgroup suggests the possibility of more marked treatment differences in favor of the combination in more treatment-resistant patients. However, it should be noted that this subgroup was not specified a priori and so results should be interpreted within the limitations of a post hoc analysis.

The safety findings were consistent with those of a previous 76-week open-label study of olanzapine/fluoxetine safety in patients with MDD (with and without TRD).[27] Although the olanzapine/fluoxetine combination had significantly higher prolactin elevations than olanzapine in the present study, these results were not confirmed in the 76-week safety study or in an integrated database of all olanzapine/fluoxetine combination clinical trials.[28] Cholesterol change with the olanzapine/fluoxetine combination (+0.36 mmol/L) was consistent with that observed in 3 other studies: the 76-week open-label safety study (+0.32 mmol/L),[27] a double-blind study of bipolar depression (+0.27 mmol/L),[29] and a double-blind study of psychotic depression (+0.35 mmol/L).[30] QTc prolongations with the olanzapine/fluoxetine combination were consistent with those found with fluoxetine monotherapy. Mean weight gain with the olanzapine/fluoxetine combination (3.28 kg) was statistically significantly greater than that seen with fluoxetine or nortriptyline, but was not statistically different from that seen with olanzapine monotherapy. In patients with or at risk for obesity, the benefits of antidepressant response should be weighed against the risks of weight gain.

In conclusion, the olanzapine/fluoxetine combination showed a rapid, robust, and sustained antidepressant effect in this sample of TRD patients, along with a safety profile comparable to that of its component monotherapies. Although the study's primary hypothesis, that the olanzapine/fluoxetine combination would be statistically superior to olanzapine, fluoxetine, and nortriptyline at endpoint, was not confirmed, the olanzapine/fluoxetine combination was statistically superior to olanzapine in a more clinically relevant subgroup of patients who had a documented SSRI treatment failure during their current mood episode. Findings regarding the effectiveness of the olanzapine/fluoxetine combination relative to nortriptyline are difficult to interpret owing to several methodological issues. Future studies in this area should employ a TRD definition requiring 2 antidepressant treatment failures during the current mood episode, as well as a study design that includes a lead-in phase duration of at least 8 weeks and blinding of the investigators to the criteria for randomizing patients.

Drug names: citalopram (Celexa and others), fluoxetine (Prozac and others), lorazepam (Ativan and others), nortriptyline (Aventyl, Pamelor, and others), olanzapine (Zyprexa), olanzapine/fluoxetine (Symbyax), paroxetine (Paxil, Pexeva, and others), risperidone (Risperdal), sertraline (Zoloft).

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