An Integrated Analysis of Olanzapine/Fluoxetine Combination in Clinical Trials of Treatment-Resistant Depression

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Objective: To evaluate the efficacy of olanzapine/fluoxetine combination (OFC) versus olanzapine or fluoxetine monotherapy across all clinical trials of treatment-resistant depression sponsored by Eli Lilly and Company.

Method: Efficacy and safety data from 1146 patients with a history of nonresponse during the current depressive episode who subsequently exhibited nonresponse during a 6- to 8-week antidepressant open-label lead-in phase and were randomly assigned to OFC (N = 462), fluoxetine (N = 342), or olanzapine (N = 342) for double-blind treatment were analyzed. All patients had a diagnosis of major depressive disorder as defined by DSM-III or DSM-IV criteria. The dates in which the trials were conducted ranged from May 1997 to July 2005.

Results: After 8 weeks, OFC patients demonstrated significantly greater Montgomery-Asberg Depression Rating Scale improvement (mean change = –13.0) than fluoxetine (–8.6, $p < .001$) or olanzapine (–8.2, $p < .001$) patients, via a mixed-effects model repeated-measures analysis. Remission rates were 25.5% for OFC, 17.3% ($p = .006$) for fluoxetine, and 14.0% ($p < .001$) for olanzapine. Adverse events in ≥ 10% of OFC patients were weight gain, increased appetite, dry mouth, somnolence, fatigue, headache, and peripheral edema. Random glucose mean change (mg/dL) was +7.92 for the OFC group, +1.62 for the fluoxetine group ($p = .020$), and +9.91 for the olanzapine group ($p = .485$). Random cholesterol mean change (mg/dL) was +12.4 for OFC, +2.3 for fluoxetine ($p < .001$), and +3.1 for olanzapine ($p < .001$); incidence of treatment-emergent increase from normal to high cholesterol (baseline < 200 mg/dL and ≥ 240 subsequently) was significantly higher for the OFC group (10.2%) than for the fluoxetine group (3.1%, $p = .017$) but not the olanzapine group (8.0%, $p = .569$). Mean weight change (kg) was +4.42 for OFC, –0.15 for fluoxetine ($p < .001$), and +4.63 for olanzapine ($p = .381$), with 40.4% of OFC patients gaining ≥ 7% body weight (vs. olanzapine: 42.9%, $p = .515$; fluoxetine: 2.3%, $p < .001$).

Conclusion: Results of this analysis showed that OFC-treated patients experienced significantly improved depressive symptoms compared with olanzapine- or fluoxetine-treated patients following failure of 2 or more antidepressants within the current depressive episode. Safety results for OFC were generally consistent with those for its component monotherapies. The total cholesterol increase associated with OFC was more pronounced than with olanzapine alone.

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Less than half of patients with major depressive disorder respond to a first-line treatment, and a somewhat larger proportion of patients are unresponsive to a second agent.[1–5] Thus, approximately 20% of patients who seek treatment for major depressive disorder will not respond to 2 sequential treatment trials. Nonresponse (and at times partial response) to antidepressant medication has been termed *treatment-resistant depression* (TRD). Patients with TRD suffer a disproportionate burden of illness, experiencing ongoing significant symptoms that impair their social and occupational functioning, staying at increased risk for suicide while their symptoms go untreated, and having higher long-term rates of recurrence and relapse.[6–9] A clear need exists for more effective antidepressant treatments.

Although most clinicians recognize the problem of TRD, no broadly accepted definition currently exists. TRD is not a unique diagnosis in the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV), and definitions proposed in the clinical literature have changed over time, especially during the past decade. In 1997, Thase and Rush[10] proposed a 5-stage system for TRD, beginning with the first failure to respond to an adequate antidepressant trial (Stage 1). Although few clinicians would consider Stage 1 to represent true TRD, Stage 2 (defined as Stage 1 resistance plus failure of treatment with a second antidepressant from a distinctly different pharmaceutical class) gained wider acceptance and was acknowledged in 2002 by the EU Committee for Proprietary Medicinal Products as indicative of "therapy resistance."[11] This requirement was apparently based on the hypothesis that drugs from different pharmaceutical classes have different mechanisms of action and switching classes should be associated with an increased likelihood of patient response. However, there is now reason to believe that the requirement of failure in 2 different classes may be too restrictive and not a necessary condition for TRD. Evidence is accumulating that switching within class (e.g., from 1 selective serotonin reuptake inhibitor [SSRI] to another) may be nearly as effective as switching between classes[5,12] and that it is appropriate to consider a diagnosis of TRD at the point of the second antidepressant failure, without regard to drug class.

The definition of antidepressant resistance as 2 treatment failures has received clinical validation as well, in that remission rates have been found to drop precipitously after a second antidepressant treatment failure. In the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) trial, the largest prospective study of a sequential series of treatments for depression ever conducted, the Quick Inventory of Depressive Symptomatology–Self-Report remission (exit score ≤ 5) rates[13] were 36.8% and 30.6% for the first[3] and second[4,5] antidepressant treatments, respectively, but dropped to only 13.7% and 13.0% for the third[14,15] and fourth[16] treatments. The relatively small drop in remission rates for the first 2 treatments—followed by a precipitous drop in rates during the third and fourth treatments—clearly called into question the notion of TRD as being on a continuum.

Additionally, discontinuation rates increased after each treatment failure in STAR*D, suggesting that as the number of unsuccessful treatment trials increased, so did patient demoralization and apparent reluctance to undertake and adhere to additional courses of pharmacotherapy. The second antidepressant failure has also been deemed critical in an established TRD staging system[17] and thus appears to be an important clinical milestone. There is clearly an urgent need for a potent, effective treatment after 2 antidepressant failures in order to retain patients in treatment.

Several reports of pharmaceutical treatment of TRD have defined resistance based on 2 or more treatment failures within the current depressive episode.[14,15,18,19] Reports of failure to respond to an antidepressant during previous episodes are very difficult to interpret, as patients' memories of past episodes and outcomes can be unreliable with regard to dose, duration, or type of drug prescribed. Recall for events during the current episode is likely to yield more reliable data, and incorporating the restriction of 2 failures within the *current* episode into clinical trials should aid in excluding less-resistant patients. In addition to being more conservative, this definition of TRD presents a plausible, real-world scenario for encountering TRD in clinical practice, as health care providers will often first consider TRD when a patient has failed 2 consecutive courses of antidepressant treatment while under their care. Incorporating this definition into clinical trials can aid in the generalizability of results to patients seen in clinical practice. Therefore, the definition of TRD as the failure to respond to 2 antidepressants in the current depressive episode can be seen as both clinically relevant and scientifically supported.

It should be noted that vagus nerve stimulation (VNS), currently the only U.S. Food and Drug Administration–approved treatment for resistant depression, is indicated after failure of 4 antidepressant and/or electroconvulsive therapy treatments. VNS is a surgically implanted medical device, and patients can take up to a year to respond.

Olanzapine/fluoxetine combination (OFC), one of the more recent strategies proposed for TRD, has been evaluated in several controlled clinical trials. To date, randomized controlled studies have yielded mixed results. In a small, pilot study[20] of patients with a history of nonresponse to 2 antidepressants during the current depressive episode, patients treated with OFC showed a significantly greater reduction in depressive symptoms than patients treated with olanzapine or fluoxetine. The same results were not seen in 2 larger trials in which the first failure of an antidepressant was not required to be during the current depressive episode.[21,22] The 2 most recent studies of OFC in TRD,[19] which defined treatment resistance as the failure of 2 antidepressants during the current depressive episode, also generated conflicting results: one yielded a significant result on the primary endpoint, whereas the other did not. Although the same pattern of results has been observed for OFC in each study, inconsistencies in TRD definitions, study designs, and measures have hampered the interpretability of results.

The mixed nature of results from these trials could be attributed to several factors. However, when disorders have historically been poorly defined, or case histories are difficult to document, as is the case with TRD, it can be valuable to reexamine evidence from treatment studies that are relatively homogenous. Thus, the purpose of the present article is to evaluate the efficacy of OFC in an

Table 1. Baseline Demographics and Illness Characteristics for Randomly Assigned Patients With Treatment-Resistant Depression[a]: Data From 5 Clinical Trials[19–22]

Variable	OFC (n = 473)	Fluoxetine (n = 352)	Olanzapine (n = 349)
Age, mean (SD), y	44.8 (10.6)	44.2 (10.3)	44.1 (10.8)
Female, n (%)	318 (67.2)	240 (68.2)	226 (64.8)
White, n (%)	419 (88.6)	310 (88.1)	293 (84.0)
BMI, mean (SD), kg/m^2	29.7 (7.4)	30.3 (7.8)	30.1 (7.3)
Length of current episode, median, d	226	191	205
≥ 3 MDD episodes over lifetime, n (%)	315 (66.6)	257 (73.0)	231 (66.2)
Age at onset of first episode, mean (SD), y	28.3 (12.8)	26.3 (12.1)	27.9 (12.1)
MADRS total score, mean (SD)[b]	29.9 (6.9)	29.6 (6.7)	29.6 (6.9)

[a]Defined as failure to respond to 2 trials of antidepressants given at adequate dose and duration in the current episode of depression.
[b]Only patients who had a baseline and at least 1 postbaseline MADRS score are represented here.
Abbreviations: BMI = body mass index, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, OFC = olanzapine/fluoxetine combination.

integrated analysis of the 5 previously reported clinical trials of TRD using a single rating scale, the Montgomery-Asberg Depression Rating Scale (MADRS),[23] and incorporating a uniform and standardized TRD definition (i.e., 2 documented antidepressant failures in the *current* depressive episode, including ≥ 1 prospective antidepressant failure) that reflects current understanding of the disorder. This article also presents the most recent and comprehensive safety data for OFC.

METHOD

Patients

Study participants represented a subset of all randomly assigned patients from all clinical trials of OFC in TRD conducted by Eli Lilly and Company through December 2006. (The dates in which the trials were conducted ranged from May 1997 to July 2005.) Five studies were included: 3 that compared OFC with fluoxetine and olanzapine (HGFR, HDAO 1, and HDAO 2)[19,20]; 1 that compared OFC with fluoxetine, olanzapine, and nortriptyline (HGHZ)[21]; and 1 that compared OFC with fluoxetine, olanzapine, and venlafaxine (HGIE).[22] In view of the documented treatment resistance, these trials did not have placebo arms. All patients met DSM-III or DSM-IV criteria for major depressive disorder and also had 1 or more documented historical antidepressant treatment failures. Patients with psychotic symptoms or Axis I disorders other than major depressive disorder were excluded. Patients were at least 18 years of age and had provided written informed consent after study designs and possible adverse events were described to them. All studies were carried out in accordance with the Declaration of Helsinki. Results of the primary analyses, including those evaluating nortriptyline and venlafaxine, are reported elsewhere.[19–22] In the present analysis, we included only patients who were randomly assigned to OFC, fluoxetine, or olanzapine and who also had a documented historical antidepressant treatment failure during their *current* depressive episode (N = 1146 of 1389 total randomly assigned patients). Selecting only these patients assured that all patients met the same clinically relevant criteria for TRD. Table 1 provides baseline demographic and severity of illness characteristics. The treatment groups did not significantly differ in these pretreatment characteristics.

Measures

The primary efficacy measure for these analyses was the MADRS total score, which was the primary efficacy scale used in 4 of the 5 studies (the primary efficacy scale in the remaining study[20] was the 21-item Hamilton Rating Scale for Depression [HAM-D]). Mean change from baseline to endpoint was analyzed. Other efficacy outcome analyses included baseline-to-endpoint and baseline-to–week 1 mean change on the MADRS, rates of response (defined as ≥ 50% improvement in MADRS total score from baseline to endpoint) and remission (defined as endpoint MADRS score ≤ 10), percentage of days in response and in remission, and Cohen d effect sizes comparing OFC with fluoxetine and OFC with olanzapine. Safety outcome analyses included incidence of unsolicited treatment-emergent adverse events; rate of discontinuation due to adverse event; mean changes and treatment-emergent categorical abnormalities in vital signs, laboratory analyses, and QTc; and treatment-emergent categorical abnormalities on rating scales of extrapyramidal symptoms: Simpson-Angus scale,[24] Abnormal Involuntary Movement Scale (AIMS),[25] and Barnes Akathisia Scale.[26] The QTc correction formula used was $QTc = QT/(RR)^{0.413}$, a nonlinear regression method derived from an analysis of over 13,000 electrocardiogram (ECG) recordings in the Lilly clinical trial database.

Procedure

The study designs for the 5 trials were very similar. Patients were required to have a documented retrospective failure to respond to an antidepressant trial of adequate dose and duration to enter the trials. The first phase of the trials was a 6- to 8-week open-label prospective antidepressant lead-in phase designed to verify resistance. The lead-in antidepressant (given at adequate dose and for adequate duration) was fluoxetine (in 3 studies),[19,20] nortriptyline (in 1 study),[21] or venlafaxine (in 1 study).[22] Patients who did not improve significantly during this lead-in phase (see Table 2 for required criteria) were then randomly assigned to OFC (N = 462),

Table 2. Study Information for the 5 Clinical Trials[19–22] Included in the Analysis

Study Characteristic	HDAO 1 and 2[19,a]	HGFR[20,a]	HGIE[22,a]	HGHZ[21,a]
Retrospective antidepressant failure				
Class	Non-fluoxetine antidepressant	Non-SSRI	SSRI	SSRI
Duration, wk	≥ 6	≥ 4	≥ 6	≥ 4
Timing	Current episode	Current episode	Current or prior[b] episode	Current or prior[b] episode
Prospective antidepressant failure				
Class	SSRI (fluoxetine)	SSRI (fluoxetine)	SNRI (venlafaxine)	TCA (nortriptyline)
Duration, wk	8	6	7	7
Depression severity required for study entry (before lead-in)	HAM-D-17 ≥ 22	HAM-D-21 ≥ 20	CGI-S ≥ 4	MADRS ≥ 20
Depression severity required at randomization	IVR HAM-D-17 total score ≥ 18 *and* no response to fluoxetine where response = decrease in IVR HAM-D-17 of ≥ 25% between beginning and end of lead-in or decrease ≥ 15% between last 2 visits of lead-in	No response to fluoxetine where response = decrease in HAM-D-21 of ≥ 30%	No response to venlafaxine where response = decrease in MADRS of ≥ 30%	No response to nortriptyline where response = decrease in MADRS of ≥ 30%
Duration of double-blind treatment, wk	8	8	12	8
Allowed dosages and ranges, mg/d	OFC: 6/50–18/50 Olanzapine: 6–18 Fluoxetine: 50	OFC: 5–20 olanzapine + 20–60 fluoxetine Olanzapine: 5–20 Fluoxetine: 20–60	OFC: 6/25, 6/50, 12/25, 12/50, or 1/5 (fixed doses) Olanzapine: 6–12 Fluoxetine: 25–50	OFC: 6/25–12/50 Olanzapine: 6–12 Fluoxetine: 25–50
Mean modal dosages, mg/d	OFC: 9/49 Olanzapine: 9 Fluoxetine: 50	OFC: 14/52 Olanzapine: 13 Fluoxetine: 52	OFC: fixed Olanzapine: 8 Fluoxetine: 38	OFC: 9/36 Olanzapine: 8 Fluoxetine: 37

[a]Study codes are merely naming conventions, not abbreviations.
[b]Patients whose retrospective antidepressant failure occurred during a prior episode were not included in the analyses presented in this article.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D-17 = Hamilton Rating Scale for Depression-17 items, IVR = Interactive Voice Response, MADRS = Montgomery-Asberg Depression Rating Scale, OFC = olanzapine/fluoxetine combination, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

fluoxetine (N = 342), or olanzapine (N = 342) for 8 to 12 weeks of double-blind treatment. At the time of randomization, patients included in these analyses had failed to respond to 2 different antidepressants (which were of different drug classes in 72% of patients) in the current depressive episode. Open-label extensions of varying duration followed these double-blind phases; extension data are not presented here. Table 2 provides detailed information on the similarities and differences among the 5 trials.

Statistical Analyses

The first 8 weeks of acute phase treatment data from the patients identified above were pooled (total N = 1146). For MADRS mean change, data were analyzed via a mixed-effects model repeated-measures analysis (MMRM) with therapy, visit, and therapy-by-visit as fixed effects and study as a random effect. For this model, contrasts of least squares means were used to create pairwise comparisons of the OFC treatment group to the other 2 treatment groups. Baseline-to-endpoint results of a last-observation-carried-forward (LOCF) mixed model with change as the dependent variable, therapy as a fixed factor, and study and the study-by-therapy interaction as random effects are also reported. Effect sizes were calculated from least squares mean differences and the sum of the variance components from this LOCF model. Differences in response and remission rates were evaluated via Fisher exact test. Differences in percentage of days in response (defined as the percentage of days that a patient's MADRS total score was ≤ 50% of the patient's baseline score) and remission (defined as the percentage of days that a patient's MADRS total score was ≤ 10) were tested with the Kruskal-Wallis test. Time-to-event estimates were calculated via the Kaplan-Meier method, and events (response or remission) were required to be sustained (i.e., all subsequent MADRS assessments had to meet the respective criteria). Kaplan-Meier curves were compared statistically using the log-rank test.

Differences in safety outcome variables were evaluated with Fisher exact test (for categorical variables) or a 1-way analysis of variance with therapy as the independent variable (for continuous variables).

All tests of hypotheses were done at a 2-sided .05 level of significance; Statistical Analysis System (SAS) version 8 (SAS Institute Inc., Cary, N.C.) was used to perform all analyses.

Table 3. Change From Baseline in MADRS Score by Visit: Randomized Patients in Treatment-Resistant Depression Trials With an SSRI Failure in the Current Episode

Week	Therapy	N	Least Squares Mean Change	Standard Deviation	p vs OFC	p vs Fluoxetine
0.5	OFC	450	–6.08	6.38		
	Fluoxetine	331	–3.34	5.87	< .001	
	Olanzapine	333	–5.37	6.48	.117	< .001
1	OFC	442	–9.75	7.77		
	Fluoxetine	339	–5.20	7.13	< .001	
	Olanzapine	334	–7.83	7.65	< .001	< .001
2	OFC	430	–11.84	8.48		
	Fluoxetine	331	–6.81	7.87	< .001	
	Olanzapine	324	–9.69	8.20	< .001	< .001
3	OFC	418	–12.25	9.22		
	Fluoxetine	328	–7.14	8.42	< .001	
	Olanzapine	308	–10.20	8.52	.002	< .001
4	OFC	408	–12.69	9.09		
	Fluoxetine	312	–7.89	8.75	< .001	
	Olanzapine	294	–9.81	8.72	< .001	.006
5	OFC	393	–12.90	9.62		
	Fluoxetine	300	–8.16	9.11	< .001	
	Olanzapine	277	–9.42	9.22	< .001	.090
6	OFC	381	–13.21	9.70		
	Fluoxetine	294	–8.76	9.06	< .001	
	Olanzapine	255	–8.89	9.21	< .001	.863
7	OFC	370	–13.28	9.61		
	Fluoxetine	288	–8.83	9.25	< .001	
	Olanzapine	244	–8.63	9.60	< .001	.801
8	OFC	365	–12.95	9.96		
	Fluoxetine	283	–8.63	9.55	< .001	
	Olanzapine	241	–8.20	9.19	< .001	.589

Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, OFC = olanzapine/fluoxetine combination, SSRI = selective serotonin reuptake inhibitor.

Table 4. Visitwise Differences Between OFC and Comparators (fluoxetine [FLX] and olanzapine [OLZ]) in MADRS Total Mean Change From Baseline[a]

	HDAO 2[19]		HGFR[20]		HGHZ[21]		HGIE[22]		HDAO 1[19]	
Week	FLX	OLZ	FLX	OLZ	FLX	OLZ	FLX	OLZ	FLX	OLZ
0.5	**5.7**	1.8	NA	NA	1.4	0.8	2.1	1.7	1.4	–0.8
1	**7.6**	2.5	**11.7**	**8.8**	2.4	2.4	2.5	2.1	**3.8**	0.7
2	**6.7**	1.9	**11.3**	**9.6**	**3.9**	2.6	2.7	2.4	**4.2**	1.1
3	**6.3**	2.2	**14.4**	**3.8**	**3.4**	2.3	**3.6**	2.9	**3.5**	0.4
4	**5.4**	**5.4**	**11.9**	**9.4**	**4.2**	**3.3**	**3.4**	2.3	2.8	0.7
5	**4.9**	**3.2**	**10.9**	**10.2**	2.9	**3.2**	**4.5**	**3.1**	2.8	1.3
6	**5.6**	**5.2**	**12.9**	**11.6**	2.7	**3.6**	**3.7**	**3.5**	2.1	1.7
7	**5.1**	**5.7**	**12.3**	**11.4**	**3.0**	**3.8**	**3.9**	**3.1**	2.2	1.9
8	**5.7**	**6.9**	**12.4**	**10.8**	2.0	**3.9**	**4.2**	2.9	1.3	0.6
9							**3.7**	**3.3**		
10							**3.3**	**3.8**		
11							**3.2**	**4.1**		
12							**3.3**	**4.5**		

[a]Positive numbers indicate an advantage for OFC over comparators in MADRS mean change from baseline. A negative number indicates that the comparator had a greater decrease than OFC at that visit. Boldface indicates visits at which the difference between groups may be considered probably or definitely clinically relevant based on the Montgomery et al.[35] criterion (differences of 3 or 4 points, respectively).

Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, NA = not available, OFC = olanzapine/fluoxetine combination.

RESULTS

Efficacy Measures

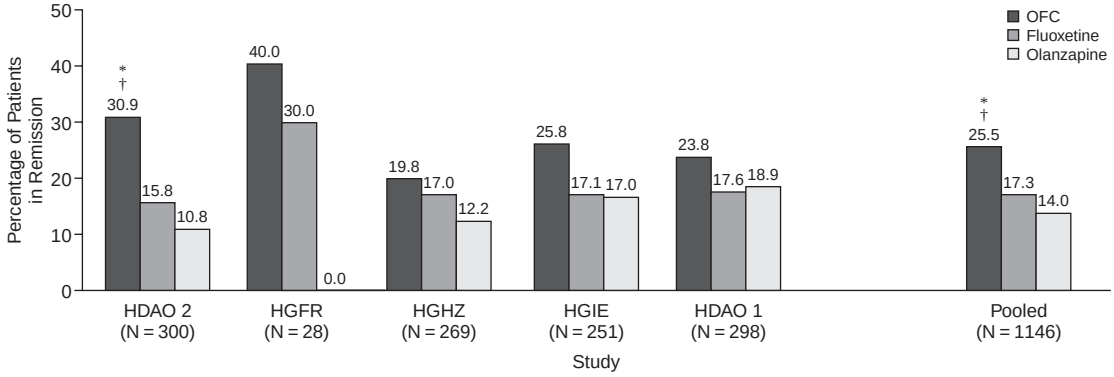
After 8 weeks of double-blind treatment, mean change in the MADRS total score was significantly greater for the OFC group (–13.0, SD = 9.96) than for the fluoxetine (–8.6, SD = 9.55, p < .001) and olanzapine (–8.2, SD = 9.19, p < .001) groups (see Table 3 for results by visit). Results from the LOCF model were similar: endpoint decrease on the MADRS was significantly greater for OFC (–12.2, SD = 10.12) than for fluoxetine (–8.5, SD = 9.72, p = .015) and olanzapine (–7.7, SD = 9.25, p = .007). Similar results were also seen in the LOCF analysis for all randomized patients in the 5 studies (N = 1389): mean change in the MADRS total score was significantly greater for the OFC group (–11.6, SD = 10.16) than for the fluoxetine (–8.7, SD = 9.93, p = .044) and olanzapine (–7.7, SD = 9.46, p = .017) groups. Effect sizes based on Cohen d were 0.371 for OFC versus fluoxetine and 0.441 for OFC versus olanzapine. Table 4 shows the visit-by-visit differences between OFC and comparators in MADRS mean change from baseline at all visits for the 5 studies. Rates of clinical response were significantly higher for the OFC group (40.3%) versus the fluoxetine group (27.8%, p < .001) and the olanzapine group (23.1%, p < .001). Remission rates were also significantly higher for the OFC group (25.5%) versus the fluoxetine group (17.3%, p = .006) and the olanzapine group (14.0%, p < .001). Figure 1 shows remission rates for the integrated analysis and for the same patients grouped by study of origin. Additionally, the mean percentage of days spent in remission was significantly higher for the OFC group (22.5%) than for the fluoxetine group (13.5%, p < .001) and the olanzapine group (13.9% p < .001). Mean percentage of days spent in response was also significantly higher for the OFC group (34.7%) than for the fluoxetine group (21.7%, p < .001) and the olanzapine group (25.3%, p < .001).

Figure 2 shows the Kaplan-Meier curves for time to remission for each of the 3 therapy groups. The time required for 25% of patients to achieve remission was 59 days for the OFC group and 66 days for the fluoxetine group (p < .001). The olanzapine group did not have enough remitters to yield 25th percentile time to remission results. The time required for 25% of patients to achieve response was 40 days for the OFC group, 57 days for the fluoxetine group (p < .001), and 58 days for the olanzapine group (p < .001).

Safety Measures

Table 5 shows treatment-emergent adverse event data for the therapy groups. The rate of discontinuation due to adverse event was significantly higher for the OFC group (11.6%) compared with the fluoxetine (2.6%, p < .001) group, but not significantly different from the rate for the

Figure 1. MADRS Remission[a] Rates for Each Study and for the Integrated Analysis

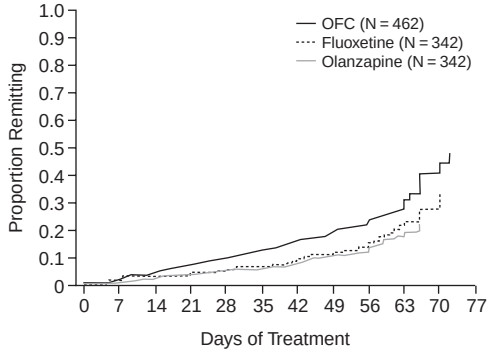


[a]Remission defined as endpoint MADRS ≤10. Placebo not shown because there were no placebo patients in the treatment-resistant depression trials.
*p<.05 vs. fluoxetine.
†p<.05 vs. olanzapine.
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, OFC = olanzapine/fluoxetine combination.

olanzapine group (13.8%, p = .394). Baseline-to-endpoint mean change in weight for the OFC group was +4.42 kg (SD = 3.75), which was significantly different from the weight change for the fluoxetine group (–0.15 kg, SD = 2.64, p < .001), but not the olanzapine group (+4.63 kg, SD = 3.69, p = .381). Potentially clinically significant weight gain (≥ 7% of body weight) was experienced by 40.4% of OFC patients, which was significantly higher than the rate for fluoxetine patients (2.3%, p < .001), but not significantly different from the rate for olanzapine patients (42.9%, p = .515). There were no completed suicides and 1 suicide attempt (in a patient randomly assigned to fluoxetine, study HDAO 2). The groups did not differ in the incidence of suicide-related adverse events termed "suicidal ideation" (OFC: 1.7%, olanzapine: 2.8%, fluoxetine: 1.4%, overall p = .415) or "suicidal depression" (OFC: 0.0%, olanzapine: 0.3%, fluoxetine: 0.0%, overall p = .597).

Baseline-to-endpoint mean change in random (i.e., including both fasting and nonfasting assessments) glucose level (mg/dL) for the OFC group (+7.92, SD = 43.6) was significantly higher than that observed in the fluoxetine group (+1.62, SD = 31.9, p = .020) but not significantly different from that observed in the olanzapine group (+9.91, SD = 29.4, p = .485). Incidence of treatment-emergent normal-to-high (defined as < 140 mg/dL at baseline to ≥ 200 mg/dL at any time using American Diabetes Association criteria[27]) random glucose for the OFC group (2.8%) was not significantly different from that for the fluoxetine (2.3%, p = .812) or olanzapine (3.3%, p = .824) groups. Mean change in random total cholesterol (mg/dL) was significantly higher for the OFC group (+12.4, SD = 32.8) than for the fluoxetine (+2.3, SD = 30.1, p < .001) and olanzapine (+3.1, SD = 32.4, p < .001) groups. The incidence of treatment-emergent

Figure 2. Kaplan-Meier Survival Curves for Time to Remission[a]



[a]MADRS total score ≤ 10 and sustained for all subsequent assessments.
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, OFC = olanzapine/fluoxetine combination.

increase from normal to high random total cholesterol (defined as < 200 mg/dL at baseline and ≥ 240 mg/dL at any time, using the U.S. National Cholesterol Education Program criteria[28]) was significantly higher for the OFC group (10.2%) than for the fluoxetine group (3.1%, p = .017) but not significantly different from the incidence for the olanzapine group (8.0%, p = .569). Mean changes in random triglyceride level (mg/dL) in the OFC group (+39.8) were not significantly different from those in the fluoxetine (+15.9, p = .086) or olanzapine (+51.3, p = .430) groups. The incidence of treatment-emergent increase from normal to high triglycerides (baseline < 150 to ≥ 500 mg/dL) for the OFC group (0.0%) was not significantly different from that for the fluoxetine (0.0%, p ~ 1.0) or olanzapine (0.9%, p = .540) groups. Mean

Table 5. Treatment-Emergent Adverse Events Occurring in ≥ 5.0% of OFC Patients

Event	OFC (%)	Fluoxetine (%)	Olanzapine (%)	p Overall	p OFC vs Fluoxetine	p OFC vs Olanzapine
Weight increased	27.9	7.1	33.5	< .001	< .001	.091
Increased appetite	24.3	6.3	29.2	< .001	< .001	.128
Dry mouth	18.6	6.5	21.2	< .001	< .001	.376
Somnolence	15.6	6.5	13.5	< .001	< .001	.426
Fatigue	14.0	9.4	16.0	.024	.051	.428
Headache	11.8	18.5	11.5	.010	.010	.913
Peripheral edema	11.2	1.1	7.4	< .001	< .001	.074
Tremor	9.7	6.3	5.4	.047	.075	.026
Dizziness	9.5	8.0	8.6	.733	.460	.714
Sedation	8.5	2.8	10.6	< .001	< .001	.333
Hypersomnia	6.1	2.0	8.3	< .001	.005	.270
Diarrhea	5.9	11.6	7.2	.011	.005	.476
Disturbance in attention	5.5	3.4	6.6	.142	.181	.553
Anxiety	5.1	6.5	6.3	.622	.448	.448
Dyspepsia	5.1	2.6	2.3	.062	.074	.045

Abbreviation: OFC = olanzapine/fluoxetine combination.

change in prolactin (μg/L) for the OFC group (+6.1, SD = 12.5) was significantly different from that for the fluoxetine group (+0.9, SD = 6.8, p < .001) but not the olanzapine group (+5.6, SD = 14.7, p = .587).

Mean change in QTc for the OFC group (+4.26 ms, SD = 16.88) was significantly different from that observed in the olanzapine group (–2.36 ms, SD = 16.72, p < .001), but not significantly different from that observed in the fluoxetine group (+1.87 ms, SD = 17.60, p = .086). The treatment groups did not significantly differ in the incidence of QTc increase from baseline to maximum of ≥ 60 ms: 0.3% for OFC, 0.4% for fluoxetine, and 0.0% for olanzapine; p ~ 1.00. There were also no significant group differences in the incidence of absolute QTc ≥ 500 ms: 0% for OFC, 0% for fluoxetine, and 0.4% for olanzapine; p = .416. The records for all OFC patients who had QTc ≥ 450 ms (or 470 ms for women) were manually reviewed; 1 patient was identified, and this patient experienced no cardiovascular-related adverse events or sequelae.

The analyses of treatment-emergent categorical abnormalities on rating scales of extrapyramidal symptoms showed no significant treatment group differences in rate of parkinsonism (defined as Simpson-Angus Scale score ≤ 3 at baseline and > 3 after baseline at any time): 3.3% for OFC, 2.7% for fluoxetine, and 2.1% for olanzapine; p = .578. Regarding akathisia (defined as Barnes Akathisia Scale score < 2 at baseline and ≥ 2 after baseline at any time), the OFC group (10.4%) was not significantly different from either the fluoxetine (7.1%, p = .127) or olanzapine (12.7%, p = .357) group. The treatment groups did not significantly differ in dyskinesia (defined as any score of ≥ 3 on AIMS items 1–7 or ≥ 2 on any 2 AIMS items 1–7 without meeting either criterion at baseline): 0.7% for OFC, 1.5% for fluoxetine, and 1.2% for olanzapine (p = .473).

DISCUSSION

For decades, research in the area of TRD has been limited by inadequate study designs, a lack of standardized definitions and measures, and unreliable treatment histories of TRD. Recent developments in the field, including results from large-scale intervention studies like STAR*D, have brought researchers closer to agreement on these methodological issues. As the field of major depressive disorder treatment moves toward full remission as a treatment goal and the use of more vigorous first-line therapies, the use of atypical antipsychotics as augmentation agents in the treatment of resistant depression is increasing.[29,30] Recent results from the National Institute of Mental Health–funded STAR*D research program have confirmed modest remission rates seen with several treatment steps and have also highlighted the urgency of being aggressive with the management of resistant depression, as is the practice with other chronic medical illnesses such as diabetes, congestive heart failure, and intractable hypertension. The current article evaluated the efficacy of OFC in TRD in 5 clinical trials of TRD, using a definition of TRD that reflects the current state of knowledge regarding the treatment of this disorder. While the primary study results have been previously published individually,[19–22] the current analyses provide the most accurate and comprehensive evaluation of the effectiveness of OFC in a more homogeneously defined group of patients with TRD (defined as failure to respond to 2 trials of antidepressants given at adequate dose and duration in the current episode of depression).

Patients treated with OFC experienced significantly greater improvement in depressive symptoms than those treated with olanzapine or fluoxetine alone, based on baseline-to-endpoint MADRS mean change, response and remission rates, and percentage of days spent in response

and in remission. Although remission rates for the OFC group may seem modest at 25.5%, they were at least as high as those observed for the most effective treatments in the STAR*D trial following 2 antidepressant failures (i.e., 25% for triiodothyronine [T_3] augmentation and 20% for switching to nortriptyline).[14,15] The modest remission rates reported for TRD throughout the clinical literature most likely reflect the severity and chronicity of this disease. The overall effect sizes of OFC in these TRD trials versus fluoxetine (0.371) and versus olanzapine (0.441) were of moderate magnitude and were comparable with effect sizes that have been reported for approved antidepressants relative to placebo in a general major depressive disorder population (ranging from 0.39 to 0.497).[31,32] This point is worth noting, in that the effect sizes for OFC were relative to those for active therapies, rather than placebo, and were observed in a difficult-to-treat patient population.[32]

The advantage of OFC with regard to the onset of depressive symptom improvement was apparent early in treatment, as shown by statistically significant separations between patients treated with OFC and patients treated with fluoxetine or olanzapine at week 1. Although this finding rests on the assumption that both components are superior to placebo, a similar early benefit of OFC has also been reported in a bipolar depressed patient population, in that case with placebo as a comparator.[33] This early effect is also sustained throughout the study period. A similar effect has also been observed with other atypical antipsychotic/SSRI combinations.[30,34] The lack of significant separation between OFC and olanzapine at the one-half week visit may be at least partly explained by the fact that more than half of the olanzapine patients had just experienced a fluoxetine lead-in phase and, due to the long half-life of fluoxetine, were effectively OFC patients. The clinical relevance of the differences in depressive symptom improvement in patients taking OFC relative to fluoxetine and olanzapine is also of interest. In a consensus paper on measuring differences in onset between antidepressants, Montgomery et al.[35] identified a separation of 3 points between treatments on the HAM-D or MADRS as probably clinically relevant and 4 points as definitely clinically relevant. OFC demonstrated an advantage relative to both fluoxetine and olanzapine comparators at 47 of 48 (97.9%) time points (see Table 4) at which the MADRS was assessed across the 5 studies. Although the differences between treatment groups were at times small, the advantage of OFC over comparators was in the range of probably (≥ 3 points) or definitely (≥ 4 points) clinically relevant at most time points.

In the analysis of treatment-emergent adverse events, OFC was generally similar to olanzapine monotherapy. OFC-treated patients did not significantly differ from olanzapine-treated patients in mean weight gain or incidence of potentially clinically significant weight gain (≥ 7%), although OFC did significantly differ from fluoxetine on both of these weight measures. Other treatment-emergent adverse events occurring at a significantly higher rate for OFC patients versus fluoxetine patients were increased appetite, dry mouth, somnolence, peripheral edema, sedation, and hypersomnia (events occurring in ≥ 5% of OFC patients, see Table 5). There were no significant group differences in suicide-related adverse events, but we note that the analyses presented here are not the most thorough way to investigate suicidality. These clinical trials were designed and completed before the importance of using prospective suicide-specific rating scales to assess patient suicidality was widely recognized.[36]

Laboratory findings for OFC were also generally similar to those for olanzapine monotherapy, with the exception of random total cholesterol mean change. Increases in random blood glucose were significantly greater for OFC than for fluoxetine, but there were no differences among the 3 active therapies in the incidence of categorical increase from normal to high. Random total cholesterol mean change for OFC was significantly greater than for fluoxetine and olanzapine, although the incidence of categorical increase in random total cholesterol from normal to high was significantly greater for OFC than for fluoxetine only. The mechanism for the difference in magnitude between OFC and olanzapine in mean increase in random total cholesterol (approximately 12 mg/dL vs. approximately 3 mg/dL) is unclear. There were no significant differences among the therapies regarding mean or categorical changes in random triglycerides. It should be noted that data on triglycerides were collected in only 2 of the studies. Finally, increases in prolactin were significantly greater for OFC than for fluoxetine, but not significantly different from those for olanzapine.

Mean increase in the QTc interval for OFC (4.26 ms) was significantly greater for the OFC group than for olanzapine but not fluoxetine. The 3 active treatment groups did not significantly differ in the incidence of categorical abnormalities in QTc (either absolute QTc ≥ 500 ms or increase to maximum ≥ 60 ms). The clinical significance of a 4- to 5-ms increase in the QTc interval is uncertain. Malik[37] has reported that an increase up to 5 ms can be observed with placebo due to measurement imprecision and natural variability. It should be noted that this was not a thorough QTc investigation, which would ideally be carried out in healthy volunteers (with some patients taking OFC at substantial multiples of maximum therapeutic dose) and would also include a positive control group taking a drug with a known, predictable QTc effect.[38] Also, baseline ECGs were collected before randomization but after any lead-in phase and therefore were subject to the potential effects of the lead-in drug, depending on the study.

No new or clinically significant differences between OFC and comparator groups on assessments of extrapyramidal symptoms were identified, based on mean changes of extrapyramidal symptoms scale scores and percentage of patients with predefined changes in these scale scores.

One limitation of the current analyses is that the analyses were conducted post hoc (although the primary analysis, baseline-to-endpoint MADRS total change for the subset, was an a priori primary or secondary endpoint in 4 of the 5 trials). The definition of TRD used in these analyses also relied partly on patient report in a patient population vulnerable to recall bias.[39] However, the studies did include a prospective treatment failure prior to randomization to OFC. Additionally, results comparing OFC against fluoxetine must be interpreted while considering that more than half the patients in this analysis had shown signs of resistance to fluoxetine upon entering the double-blind treatment phase. Other limitations involve the methodological issues regarding pooling data on a subset of patients from noncontemporaneous trials with different (although very similar) study designs. Finally, only 8 weeks of treatment data were examined. No conclusions can be drawn from these analyses about depressive improvement after 8 weeks of treatment.

In summary, the efficacy and safety of OFC in the treatment of TRD, defined as 2 antidepressant treatment failures in the current depressive episode, were examined across 5 studies in 462 patients. Depressive symptom improvement was robust and significantly greater with OFC than with either olanzapine or fluoxetine alone, and OFC separated from its components by week 1. Results suggest an overall tolerability and safety profile for OFC similar to those of its component monotherapies and more closely resembling the profile of olanzapine. The total cholesterol increase associated with OFC was more pronounced than with olanzapine alone. There is growing support for more aggressive treatment of major depressive disorder in its early stages in order to increase the likelihood of remission and adherence to treatment in this serious, debilitating, and potentially life-threatening illness.[40] Overall, the findings presented here provide supporting evidence for the use of OFC following the second antidepressant treatment failure in a given depressive episode. Studies evaluating long-term effectiveness may also be needed.

Drug names: fluoxetine (Prozac and others), nortriptyline (Pamelor and others), olanzapine (Zyprexa), venlafaxine (Effexor and others).

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