Olanzapine/Fluoxetine Combination in Patients With Treatment-Resistant Depression: Rapid Onset of Therapeutic Response and Its Predictive Value for Subsequent Overall Response in a Pooled Analysis of 5 Studies

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Objective: To characterize response profiles of olanzapine/fluoxetine combination therapy in treatment-resistant depression (TRD) and to investigate predictive relationships of early improvement with olanzapine/fluoxetine combination for subsequent response/remission during the acute phase of treatment.

Method: Results were pooled from 5 outpatient studies comparing oral olanzapine/fluoxetine combination, fluoxetine, or olanzapine for a maximum of 8 weeks in patients with TRD who had at least 1 historical antidepressant treatment failure during the current episode and who failed a prospective antidepressant therapy during the study lead-in period. Mean Montgomery-Asberg Depression Rating Scale (MADRS) total and core mood items scores from the 8-week evaluation period were compared across treatment groups. Positive and negative predictive values (PPVs, NPVs) were computed from olanzapine/fluoxetine combination–treated patients demonstrating response and remission based on whether they demonstrated early improvement.

Results: Mean olanzapine/fluoxetine combination MADRS score reductions were significantly greater than fluoxetine by week 0.5 and olanzapine by week 1. Significantly more olanzapine/fluoxetine combination patients demonstrated MADRS onset of response compared with fluoxetine and olanzapine patients ($P < .001$ for both MADRS total and core mood items). In olanzapine/fluoxetine combination patients, 38.1% exhibited MADRS total score response versus 26.9% of fluoxetine patients ($P < .001$) and 22.2% of olanzapine patients ($P < .001$). NPVs for MADRS total and core mood items response and remission ranged from 85.7% to 92.1%; PPVs ranged from 29.9% to 45.1%.

Conclusions: Olanzapine/fluoxetine combination is superior to fluoxetine and olanzapine in producing early improvement in patients with TRD. The absence of early improvement is highly predictive for overall response failure.

Trial Registration: clinicaltrials.gov Identifier: NCT00035321

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Treatment-resistant depression (TRD) is broadly defined as major depressive disorder (MDD) that has failed to adequately respond to antidepressant therapy.[1–3] Reports of the prevalence of TRD within the community of patients with depression range anywhere from 10% to 60%.[1,4–8]

In recent years, a new strategy has shown promise in the treatment of patients with TRD: combination therapy of a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) with an atypical antipsychotic agent. In 2 randomized, double-blind, placebo-controlled studies of aripiprazole administration in combination with standard antidepressant therapy in patients with depression, response and remission rates for aripiprazole adjunctive therapy were significantly higher than those observed for placebo.[9,10] In November 2007, the US Food and Drug Administration (FDA) approved the use of aripiprazole as adjunctive treatment in unipolar depression.[11]

The combination of fluoxetine with the atypical antipsychotic olanzapine was approved by the FDA in March 2009 for the treatment of patients with TRD. To date, 5 randomized, double-blind studies investigating the efficacy and safety of olanzapine/fluoxetine combination therapy versus fluoxetine or other antidepressant treatments in patients with TRD have been completed. In 2 parallel, 8-week studies of olanzapine/fluoxetine combination, fluoxetine, or olanzapine therapy in outpatients with TRD, pooled results showed that olanzapine/fluoxetine combination demonstrated evidence of benefit over either monotherapy, as well as a significantly greater incidence of rapid onset of response (defined as a ≥ 25% improvement from baseline indicators of depression within 2 weeks from baseline) than fluoxetine or olanzapine. However, 1 of the 2 parallel studies failed to

demonstrate statistical superiority of olanzapine/fluoxetine combination over monotherapy after 8 weeks of treatment.[12] In a small, 8-week, double-blind study of olanzapine/fluoxetine combination, fluoxetine, or olanzapine therapy in 28 outpatients with TRD, olanzapine/fluoxetine combination demonstrated superior improvement and rapid onset of response over monotherapy.[13,14] In a larger follow-up study, olanzapine/fluoxetine combination therapy demonstrated significantly greater improvement in depressive symptoms over monotherapy by week 2 of treatment; however, statistical superiority of olanzapine/fluoxetine combination therapy over monotherapy was not achieved at endpoint.[15] Finally, olanzapine/fluoxetine combination therapy failed to demonstrate statistical superiority over monotherapy in a 12-week, double-blind study of 483 patients with TRD, but it demonstrated significant improvement in depressive symptoms over monotherapies by week 1 of treatment.[16]

In summary, the superiority of olanzapine/fluoxetine combination over fluoxetine and olanzapine was observed in 2 of the 5 studies, and a consistent pattern of early therapeutic improvement was observed for olanzapine/fluoxetine combination. An integrated summary of the efficacy and safety of olanzapine/fluoxetine combination in patients with TRD was recently submitted to the FDA, and a pooled efficacy and safety analysis of these 5 studies was recently published.[17]

We determined that this pattern noted above merited additional investigation; furthermore, given the variation in design among the 5 studies, we determined that the pattern of early therapeutic improvement should be investigated in a large population utilizing unified criteria for analysis. Therefore, in order to further understand the predictive value of the therapeutic response that is observed with olanzapine/fluoxetine combination in patients with TRD, a pooled analysis of rapid response results from these 5 studies was performed. Specifically, the results were pooled from patients who had at least 1 documented historical antidepressant treatment failure during the current depressive episode.

In all 5 studies, early symptomatic improvement was observed with significantly greater frequency in patients treated with olanzapine/fluoxetine combination. The primary outcome of interest in this pooled analysis was to determine if the early improvement of symptoms is predictive of subsequent, clinically meaningful, overall remission with olanzapine/fluoxetine combination therapy. This determination would be of valuable clinical relevance for 3 reasons: (1) rapid symptomatic improvement provides an enhanced benefit to patients with MDD and TRD; (2) a predictive relationship between rapid improvement and subsequent, overall clinically meaningful improvement benefits both patients and physicians, as an early determination of a therapy's potential overall benefits may be able to be made without an extended period of treatment; and (3) the patient's motivation to continue therapy, as well as the therapeutic alliance that exists between the patient and the physician, will be improved if the patient experiences early symptomatic improvement.

METHOD

Montgomery-Asberg Depression Rating Scale

The Montgomery-Asberg Depression Rating Scale (MADRS)[18] was selected as the efficacy measure for this meta-analysis, as it was utilized in all 5 studies. This meta-analysis includes evaluation of MADRS total scores, evaluation of each of the 10 individual items comprising MADRS, and evaluation of the MADRS core mood items score, which is a composite score of 6 items in MADRS that represent key symptoms of MDD: apparent sadness, reported sadness, concentration difficulties, inability to feel, pessimistic thoughts, and suicidal thoughts. Although the core mood items score is a relatively new concept, several recent publications note that these 6 MADRS items represent core symptoms of depression.[19–21]

Studies Selected for Meta-Analysis

The analyses presented here utilize data from 5 clinical studies (1 study protocol included 2 independent, multicenter, randomized, double-blind studies that were run in parallel) in patients diagnosed with MDD (either single episode or recurrent) without psychotic features according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*).[22] The results have previously been published in the scientific literature[12,13,15,16] and as clinical trial registry summaries.[14,23–25] All protocols were reviewed and approved by the appropriate institutional review boards at each study site before initiation of the studies. The studies were conducted in accordance with the Declaration of Helsinki and in conformity with the FDA Code of Federal Regulations (21 CFR, part 50). All participants provided written informed consent before enrollment. A brief summary of methods for each study follows.

Studies HDAO-1 and HDAO-2.[12] These identical, concurrent studies enrolled male and female patients, 18 to 65 years of age, with a Hamilton Depression Rating Scale, 17-item version (HDRS-17)[26] score ≥ 22. Patients also had at least 1 documented historical failure to a ≥ 6-week course of antidepressant therapy (other than fluoxetine) during the current depressive episode. Patients underwent a 3- to 14-day screening period during which they were tapered off excluded medications while undergoing various physical and psychological examinations to determine study eligibility. Following eligibility verification, patients entered an 8-week, open-label, fluoxetine lead-in period. Patients who tolerated fluoxetine 50 mg/d through the end of the lead-in period without demonstrating response to therapy (that is, patients demonstrating fluoxetine treatment resistance) were randomly assigned to receive olanzapine/fluoxetine combination, fluoxetine, or olanzapine during the 8-week, double-blind, acute treatment period. During this period, patients were assessed at week 0.5 (3 to 5 days after initiation of acute treatment), week 1, and weekly assessments thereafter through week 8. Efficacy measures included MADRS,

the Clinical Global Impressions-Severity of Depression (CGI-SD) Scale,[27] the Hamilton Anxiety Rating Scale (HARS),[28] and the Brief Psychiatric Rating Scale (BPRS).[29] *Onset of response* to therapy was defined as a ≥ 25% reduction in MADRS total score from baseline, *response* was defined as a ≥ 50% reduction in MADRS total score from baseline, and *remission* was defined as a MADRS total score ≤ 10 at any time during the acute treatment period.

Study HGFR.[13] This study enrolled male and female outpatients who met *DSM-IV* criteria for depression, had a Hamilton Depression Rating Scale, 21-item version (HDRS-21) score ≥ 20, and had a documented historical failure to at least 1 acceptable course of antidepressant therapy that was not an SSRI during the current depressive episode. Following eligibility verification, patients entered a 6-week, open-label, screening period in which they received fluoxetine ≤ 60 mg/d. Patients who failed to exhibit ≥ 30% improvement in HDRS-21 scores with fluoxetine therapy during the open-label, screening period entered an 8-week, double-blind, acute therapy period in which they were randomly assigned to receive olanzapine/fluoxetine combination, fluoxetine, or olanzapine.[14] Efficacy measures (assessed at weekly intervals; week 0.5 was *not* assessed) included MADRS, HDRS-21, and CGI-SD. *Response* to therapy was defined as a ≥ 50% reduction in MADRS total score from baseline, and *remission* was defined as a MADRS total score ≤ 8 during 2 consecutive visits at any time during the acute treatment period.

Study HGHZ.[15] This study enrolled male and female patients who met *DSM-IV* criteria for unipolar, nonpsychotic MDD. Patients also had at least 1 documented historical failure to a ≥ 4-week course of SSRI therapy. Patients underwent a 2- to 7-day screening and washout period during which they were tapered off excluded medications while they were screened to determine study eligibility. Following eligibility verification, patients entered a 7-week, open-label, nortriptyline dose-escalation period. Patients who failed to exhibit ≥ 30% improvement (decrease) in MADRS total score from baseline with nortriptyline therapy during the dose-escalation period were randomly assigned to receive olanzapine/fluoxetine combination, fluoxetine, olanzapine, or nortriptyline during the 8-week, double-blind, acute treatment period. During this period, patients were assessed at week 0.5 (2 to 5 days after initiation of acute treatment), week 1, and weekly assessments thereafter through week 8. Efficacy measures included MADRS, CGI-SD, and HARS. *Response* to therapy was defined as a ≥ 50% reduction in MADRS total score from baseline, and *remission* was defined as a MADRS total score ≤ 8 during 2 consecutive visits at any time during the acute treatment period.

Study HGIE.[16] This study enrolled male and female patients ≥ 18 years of age who met *DSM-IV* criteria for unipolar, nonpsychotic MDD. Patients also had at least 1 documented historical failure to a ≥ 6-week course of SSRI therapy. Patients underwent a 2- to 7-day screening period; following verification of study eligibility, patients entered a 7-week, open-label, lead-in period in which they received venlafaxine 75 to 375 mg/d. Patients who failed to exhibit ≥ 30% improvement (decrease) in MADRS total score with venlafaxine therapy during the lead-in period were randomly assigned to receive olanzapine/fluoxetine combination (several different dose groups), fluoxetine, olanzapine, or venlafaxine during the 12-week, double-blind, acute treatment period. During this period, patients were assessed at week 0.5 (2 to 5 days after initiation of acute treatment), week 1, and weekly assessments thereafter through week 12. Patients who were assigned to olanzapine/fluoxetine combination, olanzapine, or fluoxetine were tapered off venlafaxine over a 5- to 9-day taper period; patients randomly assigned to venlafaxine therapy remained on the same dosage throughout the taper period. Efficacy measures included MADRS, CGI-SD, HARS, and BPRS. *Response* to therapy was defined as a ≥ 50% reduction in MADRS total score from baseline, and *remission* was defined as a MADRS total score ≤ 8 during 2 consecutive visits at any time during the acute treatment period.

Patient Pooling Criteria for Meta-Analysis

This meta-analysis includes results from patients who had at least 1 historical antidepressant therapy failure during the current depressive episode prior to beginning 1 of the 5 selected studies. Entry criteria for studies HGIE and HGHZ both required at least 1 historical failure to an SSRI but did not specify when that historical failure needed to occur. Therefore, patients with a historical failure that occurred during a previous episode of depression (in some cases, many years prior to study entry) *and* patients with a historical failure that occurred during the current episode of depression were enrolled. The integrated analysis presented in the current article evaluated only those patients with whom the historical failure occurred during the current episode of depression. Therefore, usable results from study HGHZ and study HGIE included only a subset of those studies' overall populations. Further, results were obtained from patients who provided a baseline and at least 1 postbaseline MADRS assessment. Additional analyses (described under Statistical Analyses) required ≥ 1 postbaseline MADRS assessment taken after patients had completed at least 2 weeks of double-blind therapy. Finally, this meta-analysis includes MADRS assessments through 8 weeks of double-blind therapy with olanzapine/fluoxetine combination, fluoxetine, or olanzapine from the 5 selected studies. Results from patients that met these criteria were pooled into 3 analysis groups (olanzapine/fluoxetine combination, fluoxetine, or olanzapine) according to the treatment regimen assigned to patients during the studies' double-blind periods.

Statistical Analyses

Changes in MADRS scores over time. MADRS assessments (total score, core mood items score [composite score

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of MADRS items 1, 2, 6, 8, 9, and 10], and individual scores for each of the 10 MADRS items) at baseline, week 0.5, and weeks 1 through 8 were pooled into 3 analysis groups as previously described. Means and standard errors (SEs) were calculated for baseline scores, and mean changes from baseline (with SEs) were calculated for composite and individual item scores for each of the study timepoints noted previously. Overall and pairwise comparisons (olanzapine/fluoxetine combination versus fluoxetine or olanzapine/fluoxetine combination versus olanzapine) of mean changes from baseline were computed for each study timepoint using an analysis of variance (ANOVA) model.

Kaplan-Meier time-to-efficacy analyses. Treatment efficacy thresholds were categorized as follows: (1) onset of response (defined as a ≥ 25% reduction in MADRS score from baseline); (2) response at endpoint (defined as a ≥ 50% reduction in MADRS score from baseline); and (3) remission at endpoint (defined as MADRS total score ≤ 10 and/or MADRS core mood items score ≤ 6). MADRS total scores, core mood items scores, and changes in scores from baseline were reviewed for each patient to determine both the number of patients who reached these thresholds and the length of time on treatment required to reach these thresholds. The number of patients in each analysis group who exhibited onset of response, response, or remission for MADRS total score or core mood items score was tabulated, and Kaplan-Meier time-to-efficacy analyses and log-rank tests were performed to compare the effectiveness of olanzapine/fluoxetine combination, fluoxetine, and olanzapine treatments as a function of overall time on therapy.

Pattern analyses. To better characterize the persistence of onset of response, response, and remission and to mitigate the effects of false-positive improvements in patients, pattern analyses were applied to MADRS total and core mood items scores across the length of the studies as originally described by Quitkin and colleagues.[30] The categories for pattern analyses included the following:

- Early persistent—an event (onset of response, response, or remission) that was observed within the first 2 weeks of treatment and at all subsequent assessments.
- Delayed persistent—an event that was observed between 3 to 8 weeks of treatment initiation and at all subsequent assessments.
- Nonpersistent—an event that was observed at least once during the 8 weeks of treatment but was not maintained through the final assessment.
- No efficacy—the event (onset of response, response, or remission) was not observed at any time during the 8 weeks of treatment.

Categorical endpoint improvement. Individual patient MADRS total and core mood items scores at endpoint were compared with their respective scores at baseline to determine which of the following 4 levels of categorical improvement they exhibited by their final study visit: (1) worsening to ≤ 25% improvement; (2) 25% to ≤ 50% improvement; (3) 50% to ≤ 75% improvement; or (4) 75% to 100% improvement. The numbers of patients in each category were tabulated, and comparisons between olanzapine/fluoxetine combination versus fluoxetine and olanzapine/fluoxetine combination versus olanzapine were performed using Fisher exact test.

Predictive values. The cumulative incidences of response and remission (defined previously in Kaplan-Meier time-to-efficacy analyses) were tabulated for MADRS total and core mood items scores. These values, along with the incidences of early onset of response (onset of response observed within 2 weeks from baseline), were used to compute conditional probabilities, which were reviewed to assess whether the presence of early onset of response was predictive for subsequent overall response and remission. Conditional probability computations included the following:

- Sensitivity—the probability that a patient who demonstrated response or remission at endpoint was correctly classified as demonstrating early onset of response.
- Specificity—the probability that a patient who did not demonstrate response or remission at endpoint was correctly classified as not demonstrating early onset of response.
- Positive predictive value (PPV)—the proportion of patients who demonstrated response or remission at endpoint who were also among those who demonstrated early onset of response.
- Negative predictive value (NPV)—the proportion of patients who did not demonstrate response or remission at endpoint who were also among those who did not demonstrate early onset of response.
- Total accuracy—the proportion of patients whose 2-week early-onset status accurately predicted their response/remission status at endpoint.

Week 0.5 analyses. The week 0.5 results for the meta-analyses contained herein include only results for patients from studies that had a week 0.5 assessment. As study HGFR study did not include a week 0.5 assessment, HGFR patients were not included in week 0.5 analyses.

Statistical significance. All tests of significance were 2-tailed and performed at the $\alpha = .05$ level.

RESULTS

Patients

A total of 1,146 patients met the a priori selection criteria for the analyses presented here; refer to Trivedi et al[17] for a detailed breakdown of demographics and baseline

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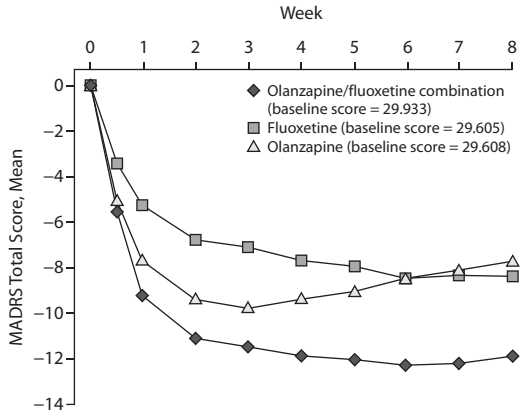
Figure 1. Mean Changes From Baseline in Montgomery-Asberg Depression Rating Scale (MADRS) Total Scores Over Time[a,b,c]



[a]Each comparison of olanzapine/fluoxetine combination versus fluoxetine from week 0.5 through week 8, $P < .001$.
[b]Olanzapine/fluoxetine combination versus olanzapine at week 0.5, $P = .249$.
[c]Each comparison of olanzapine/fluoxetine combination versus olanzapine from week 1 through week 8, $P \leq .011$.

characteristics for these. Of these, 462 patients were administered olanzapine/fluoxetine combination therapy, 342 patients received fluoxetine during the double-blind periods of the 5 studies, and 342 patients were treated with olanzapine monotherapy. Refer to the original study publications for details on the administration of other antidepressants in this meta-analysis population.[12–16]

Changes in MADRS Scores Over Time

Figure 1 depicts mean changes in MADRS total scores from baseline for all 3 analysis groups through 8 weeks of double-blind treatment administration. At week 0.5, the mean reduction in MADRS total score for the olanzapine/fluoxetine combination group was -5.64 ± 0.30 (Table 1), while that observed for the fluoxetine group was -3.38 ± 0.32 ($P < .001$; Table 1). Meanwhile, the difference in mean changes between olanzapine/fluoxetine combination and olanzapine attained statistical significance a few days later at week 1 (-9.24 ± 0.36 for olanzapine/fluoxetine combination versus -7.74 ± 0.41 for olanzapine; $P = .008$). Patients on olanzapine/fluoxetine combination therapy continued to demonstrate superior improvement in MADRS total scores throughout the 8-week evaluation period: *P* values for olanzapine/fluoxetine combination versus fluoxetine comparisons were $P < .001$ from week 0.5 through week 8, while *P* values for olanzapine/fluoxetine combination versus olanzapine comparisons were $P \leq .011$ from week 1 through week 8 (Table 1).

Patients taking olanzapine/fluoxetine combination therapy also demonstrated significant improvement in MADRS core mood items scores over fluoxetine and olanzapine, as shown in Figure 2. As with MADRS total scores, the difference in week 0.5 mean changes from baseline in MADRS core mood items score for the olanzapine/fluoxetine combination group (-2.77 ± 0.19; Table 2) and the fluoxetine group (-2.32 ± 0.22) attained statistical significance ($P = .023$). The olanzapine/fluoxetine combination group demonstrated significant improvement in MADRS core mood items scores over the olanzapine group by week 1 (-5.12 ± 0.23 for olanzapine/fluoxetine combination versus -4.12 ± 0.27 for olanzapine; $P = .005$). As with MADRS total scores, the significant improvements observed with olanzapine/fluoxetine combination therapy on core mood items scores persisted throughout the 8-week evaluation period ($P \leq .023$ for olanzapine/fluoxetine combination versus fluoxetine from week 0.5 through week 8; $P \leq .025$ for olanzapine/fluoxetine combination versus olanzapine from week 1 through week 8; Table 2).

Similar patterns of improvement were observed in several individual MADRS items, as significant improvements ($P \leq .038$; data not shown) were observed for olanzapine/fluoxetine combination over fluoxetine from week 0.5 through week 7 in apparent sadness, reported sadness, inner tension, and suicidal thoughts. Pairwise comparisons of olanzapine/fluoxetine combination versus olanzapine for these items failed to produce differences as dramatic as those seen for olanzapine/fluoxetine combination versus fluoxetine; nevertheless, the patterns observed with these items resembled those observed for olanzapine/fluoxetine combination versus olanzapine in MADRS total and core mood items scores, with significant improvement observed with olanzapine/fluoxetine combination therapy as early as week 1 and significant improvement over olanzapine therapy persisting, for the most part, through week 8.

Kaplan-Meier Time-to-Efficacy Analyses

Table 3 summarizes the incidence of onset of response, response, and remission for patients in each treatment group for both MADRS total and core mood items scores. For MADRS total scores, 66.9% of olanzapine/fluoxetine combination–treated patients demonstrated onset of response versus 49.4% of fluoxetine-treated patients ($P < .001$) and 50.9% of olanzapine-treated patients ($P < .001$). Similar results were observed for MADRS core mood items scores, as 58.7% of olanzapine/fluoxetine combination–treated patients demonstrated onset of response versus 51.8% of fluoxetine-treated patients ($P = .002$) and 42.1% of olanzapine-treated patients ($P < .001$). A significantly larger group of olanzapine/fluoxetine combination–treated patients demonstrated response and remission versus those treated with fluoxetine or olanzapine; however, these differences were not as dramatic for the comparison between MADRS core mood items results for olanzapine/fluoxetine combination versus fluoxetine.

Figure 3 provides Kaplan-Meier time-to-efficacy curves for all 3 treatment groups for MADRS total score onset of response

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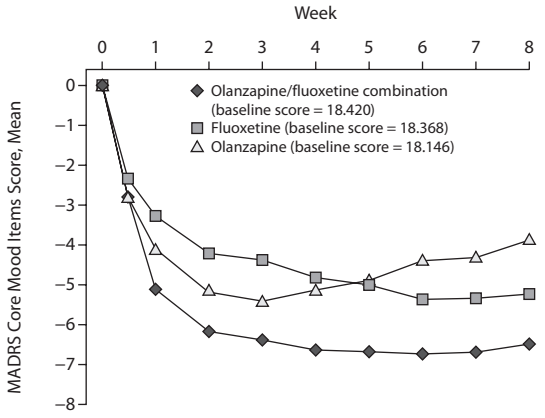
Table 1. MADRS Total Score—Changes From Baseline to Endpoint (LOCF) for Each Visit

Therapy/Comparison	Baseline	Wk 0.5	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8
Olanzapine/fluoxetine combination (N = 462)										
n	462	450	462	462	462	462	462	462	462	462
Mean	29.93	−5.64	−9.24	−11.15	−11.50	−11.88	−12.04	−12.28	−12.31	−12.00
SE	0.32	0.30	0.36	0.39	0.42	0.42	0.45	0.45	0.45	0.46
Fluoxetine (N = 342)										
n	342	331	342	342	342	342	342	342	342	342
Mean	29.61	−3.38	−5.24	−6.79	−7.10	−7.78	−8.02	−8.48	−8.50	−8.32
SE	0.36	0.32	0.38	0.42	0.46	0.48	0.50	0.50	0.51	0.52
Olanzapine (N = 342)										
n	342	333	342	342	342	342	342	342	342	342
Mean	29.61	−5.37	−7.74	−9.47	−9.84	−9.46	−9.06	−8.52	−8.28	−7.90
SE	0.37	0.36	0.41	0.45	0.47	0.48	0.50	0.49	0.51	0.49
Pairwise comparison *P* values[a]										
Olanzapine/fluoxetine vs fluoxetine	.821	< .001	< .001	< .001	< .001	< .001	< .001	< .001	< .001	< .001
Olanzapine/fluoxetine vs olanzapine	.773	.249	.008	.009	.011	.003	.003	< .001	< .001	< .001

[a]Pairwise *P* values are from ANOVA model: change = study therapy.
Abbreviations: ANOVA = analysis of variance, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, N = number of patients in study group, n = number of patients having both baseline and postbaseline measurements, SE = standard error.

Figure 2. Mean Changes From Baseline in Montgomery-Asberg Depression Rating Scale (MADRS) Core Mood Items Scores Over Time[a,b,c]



[a]Each comparison of olanzapine/fluoxetine combination versus fluoxetine from week 0.5 through week 8, $P \leq .023$.
[b]Olanzapine/fluoxetine combination versus olanzapine at week 0.5, $P = .751$.
[c]Each comparison of olanzapine/fluoxetine combination versus olanzapine from week 1 through week 8, $P \leq .025$.

(Figure 3A), response (Figure 3B), and remission (Figure 3C). The results for log-rank tests revealed that olanzapine/fluoxetine combination was statistically superior to fluoxetine and olanzapine for all 3 events ($P < .001$ for all).

Figure 4 provides Kaplan-Meier time-to-efficacy curves for all 3 treatment groups for MADRS core mood items score onset of response (Figure 4A), response (Figure 4B), and remission (Figure 4C). While the results for log-rank tests were not as dramatic as those observed for MADRS total scores, olanzapine/fluoxetine combination was statistically superior to fluoxetine and olanzapine for all 3 events ($P \leq .040$ for all).

Pattern Analyses

Figure 5 presents pattern analyses of patients who demonstrated MADRS total score (Figure 5A) and MADRS core mood items score (Figure 5B) onset of response during the 8-week, double-blind analysis period. For MADRS total scores, 20.0% of olanzapine/fluoxetine combination-treated patients demonstrated early persistent onset of response versus 6.7% of fluoxetine-treated patients ($P < .001$) and 15.9% of olanzapine-treated patients ($P = .175$). A significantly greater number of olanzapine/fluoxetine combination–treated patients demonstrated delayed persistent onset of response (48.9%) compared with olanzapine-treated patients (38.2%; $P = .004$). Patients taking olanzapine/fluoxetine combination therapy were significantly more likely to demonstrate onset of response than patients treated with fluoxetine or olanzapine alone. Specifically, no efficacy was demonstrated by 7.8% of olanzapine/fluoxetine combination–treated patients versus 22.0% of fluoxetine-treated patients ($P < .001$) and 15.2% of olanzapine-treated patients ($P = .003$).

Similar trends were observed with the pattern analysis of MADRS core mood items onset of response, with the notable exception of 2 items: (1) the percentage of olanzapine-treated patients demonstrating early persistent onset of response (8.1%) for MADRS core mood items was noticeably lower than that observed for MADRS total (15.9%) and (2) the percentage of olanzapine-treated patients demonstrating nonpersistent onset of response for MADRS core mood items (37.2%) was markedly higher than that observed for MADRS total (30.7%).

Categorical Endpoint Improvement

Table 4 and Figure 6 present quartile levels of categorical endpoint improvement for patients in each treatment group based on reductions in either MADRS total scores (Figure 6A) or core mood items scores (Figure 6B). Overall, olanzapine/fluoxetine combination provided significant improvement at endpoint over olanzapine, as demonstrated

Table 2. MADRS Core Mood Items Score—Changes From Baseline to Endpoint (LOCF) for Each Visit

Therapy/Comparison	Baseline	Wk 0.5	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8
Olanzapine/fluoxetine combination (N = 462)										
n	462	450	462	462	462	462	462	462	462	462
Mean	18.42	−2.77	−5.12	−6.17	−6.39	−6.63	−6.68	−6.73	−6.69	−6.48
SE	0.20	0.19	0.23	0.26	0.28	0.28	0.29	0.30	0.30	0.31
Fluoxetine (N = 342)										
n	342	331	342	342	342	342	342	342	342	342
Mean	18.37	−2.32	−3.26	−4.21	−4.37	−4.81	−5.01	−5.36	−5.33	−5.23
SE	0.25	0.22	0.25	0.29	0.31	0.32	0.34	0.34	0.35	0.35
Olanzapine (N = 342)										
n	342	333	342	342	342	342	342	342	342	342
Mean	18.15	−2.81	−4.12	−5.15	−5.42	−5.15	−4.89	−4.39	−4.31	−3.86
SE	0.23	0.23	0.27	0.29	0.31	0.32	0.34	0.33	0.35	0.34
Pairwise comparison *P* values[a]										
Olanzapine/fluoxetine combination vs fluoxetine	.811	.023	<.001	<.001	<.001	<.001	<.001	.002	.003	.013
Olanzapine/fluoxetine combination vs olanzapine	.594	.751	.005	.008	.025	.002	<.001	<.001	<.001	<.001

[a]Pairwise *P* values are from ANOVA model: change = study therapy.
Abbreviations: ANOVA = analysis of variance, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, N = number of patients in study group, n = number of patients having both baseline and postbaseline measurements, SE = standard error.

Table 3. Incidence of Onset of Response, Response, and Remission for MADRS Total and Core Mood Items Scores

	Olanzapine/ Fluoxetine Combination		Fluoxetine		Olanzapine		*P* Value[b]	
Analysis[a]	N	n (%)	N	n (%)	N	n (%)	Olanzapine/Fluoxetine Combination vs Fluoxetine	Olanzapine/Fluoxetine Combination vs Olanzapine
MADRS Total Score								
Onset of response	462	309 (66.9)	342	169 (49.4)	342	174 (50.9)	<.001	<.001
Response	462	176 (38.1)	342	92 (26.9)	342	76 (22.2)	<.001	<.001
Remission	462	118 (25.5)	342	58 (17.0)	342	45 (13.2)	<.001	<.001
MADRS Core Mood Items Score								
Onset of response	462	271 (58.7)	342	177 (51.8)	342	144 (42.1)	.002	<.001
Response	462	156 (33.8)	342	98 (28.7)	342	69 (20.2)	.040	<.001
Remission	462	123 (26.6)	342	67 (19.6)	342	50 (14.6)	.010	<.001

[a]Terms of analysis are defined as follows: (1) Onset of response defined as ≥ 25% reduction in MADRS score from baseline; (2) Response defined as a ≥ 50% reduction in MADRS score from baseline; (3) Remission defined as a MADRS Total score ≤ 10 or MADRS Core Mood Items score ≤ 6.
[b]*P* Values are from a log-rank test.
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, N = number of patients in study group, n = number of patients exhibiting the event.

by the increased incidence of higher levels of improvement observed in the olanzapine/fluoxetine combination group compared to the olanzapine group for both MADRS total and core mood items scores ($P < .001$ for both). However, while a comparison of categorical improvement frequencies for olanzapine/fluoxetine combination versus fluoxetine for MADRS total scores revealed that olanzapine/fluoxetine combination demonstrated a superior response profile ($P < .001$), a similar comparison for MADRS core mood items scores failed to demonstrate statistical significance ($P = .249$). A closer look at the olanzapine/fluoxetine combination and fluoxetine columns in Table 4 reveals why, as the percentages of olanzapine/fluoxetine combination–treated and fluoxetine-treated patients observed within each category are similar.

Early Onset of Response and Predictive Value

Table 5 presents the results for calculations of PPV and NPV for response and remission with olanzapine/fluoxetine combination therapy in patients with TRD (based on MADRS total and core mood items scores), using the presence or absence of early improvement (defined as a ≥ 25% reduction in MADRS scores [total or core mood items] from baseline within 2 weeks from olanzapine/fluoxetine combination treatment initiation) as the predictor. The results demonstrate that the absence of early improvement in these patients is highly predictive for the ultimate absence of overall olanzapine/fluoxetine combination treatment efficacy, as NPVs ranged from 85.7% to 92.1% for both response and remission. The PPVs ranged from 29.9% to 45.1%, indicating that the presence of early improvement is not reliably predictive for overall olanzapine/fluoxetine combination treatment efficacy.

DISCUSSION

In this meta-analysis, we examined the therapeutic efficacy of olanzapine/fluoxetine combination in patients with TRD who had at least 1 documented historical antidepressant treatment failure during the current depressive episode prior to entering 1 of the 5 studies evaluated. We conducted post hoc analyses to determine whether a predictive

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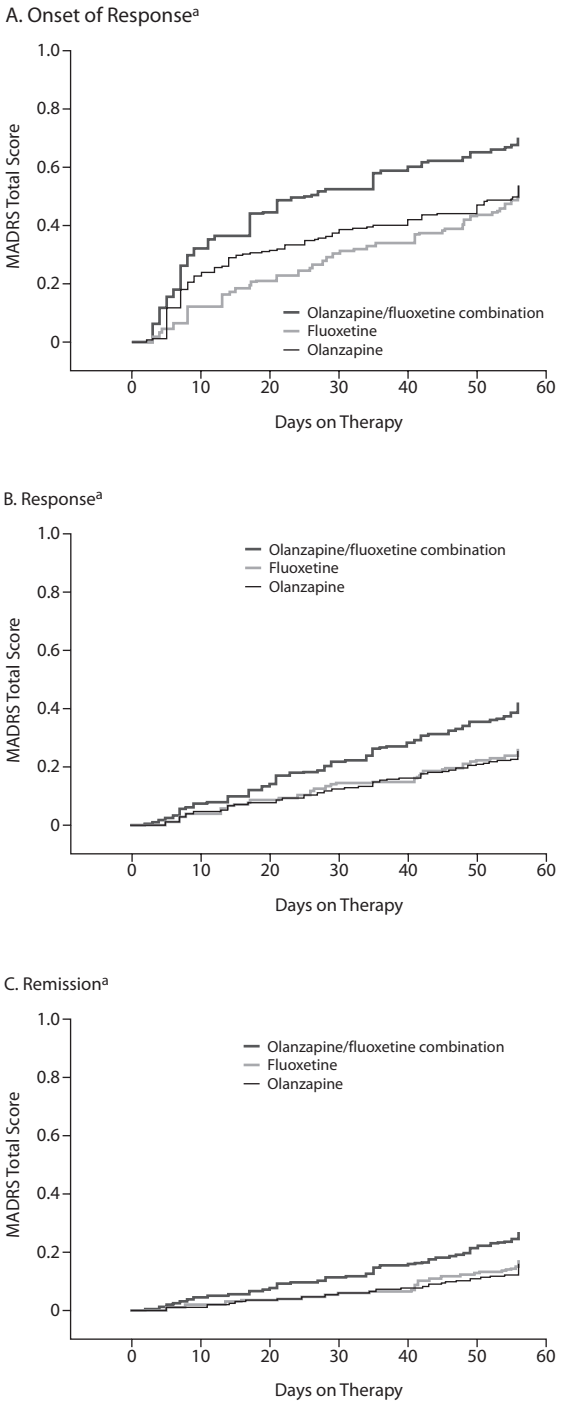
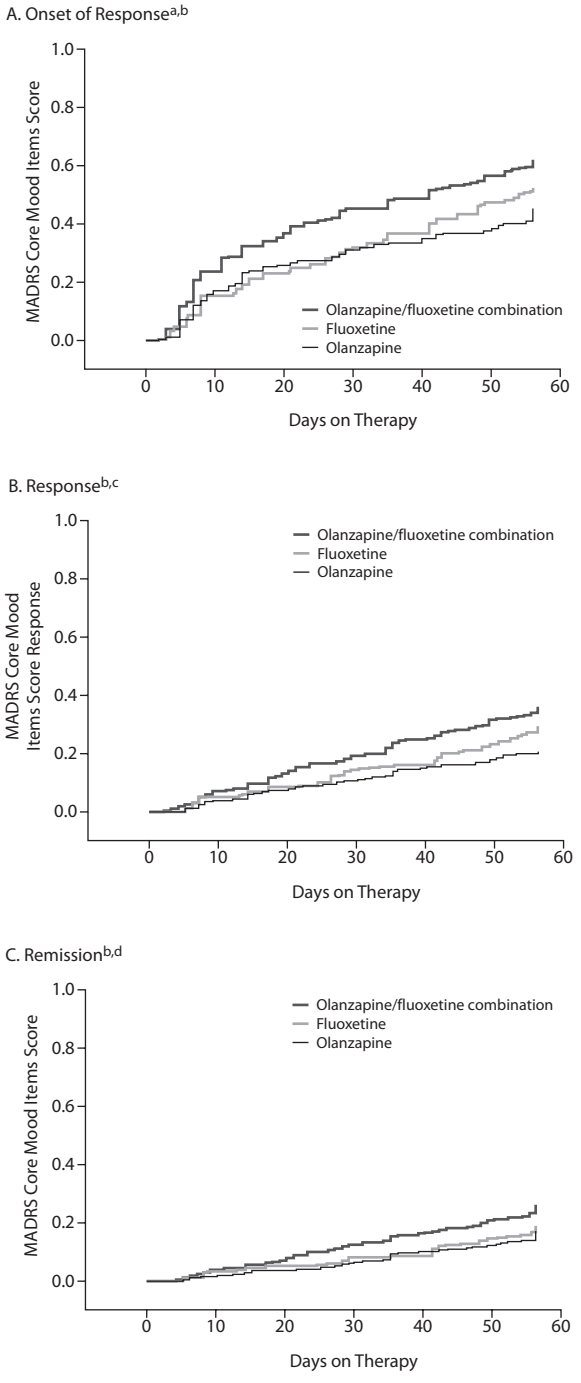
Figure 3. Kaplan-Meier Time-to-Efficacy Curves for Montgomery-Asberg Depression Rating Scale (MADRS) Total Scores



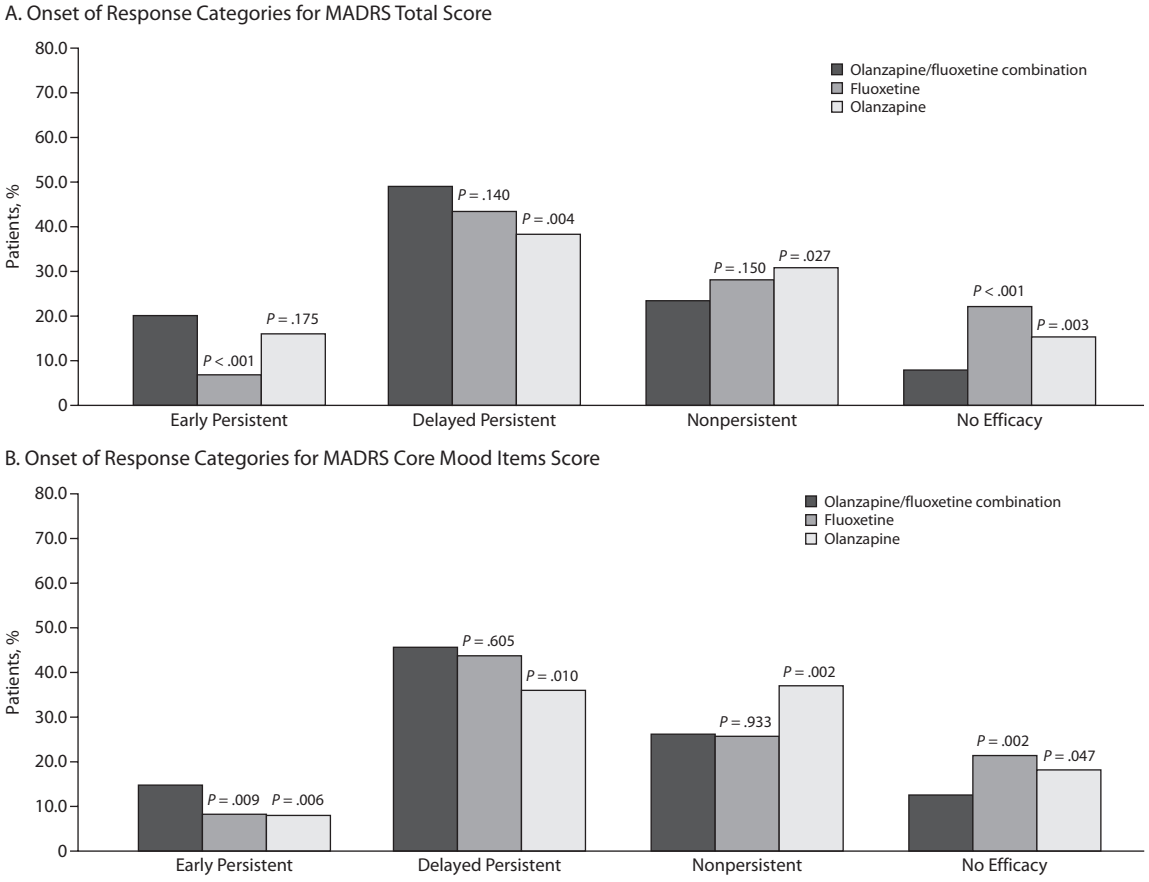
[a]Olanzapine/fluoxetine combination versus fluoxetine and versus olanzapine, log-rank $P < .001$.

Figure 4. Kaplan-Meier Time-to-Efficacy Curves for Montgomery-Asberg Depression Rating Scale (MADRS) Core Mood Items Scores



[a]Olanzapine/fluoxetine combination versus fluoxetine, log-rank $P = .002$.
[b]Olanzapine/fluoxetine combination versus olanzapine, log-rank $P < .001$.
[c]Olanzapine/fluoxetine combination versus fluoxetine, log-rank $P = .040$.
[d]Olanzapine/fluoxetine combination versus fluoxetine, log-rank $P = .010$.

Figure 5. Pattern Analyses for Patients Demonstrating Montgomery-Asberg Depression Rating Scale (MADRS) Total and Core Mood Items Scores for Onset of Response



[a]*P* Values represent comparison between monotherapy and olanzapine/fluoxetine combination therapy.

Table 4. Categorical Endpoint Improvement for MADRS Total and Core Mood Items Scores

	Olanzapine/ Fluoxetine Combination		Fluoxetine		Olanzapine		*P* Value[a]	
Improvement Category	N	n (%)	N	n (%)	N	n (%)	Olanzapine/Fluoxetine Combination vs Fluoxetine	Olanzapine/Fluoxetine Combination vs Olanzapine
MADRS total score								
Worsening to ≤25% improvement	462	153 (33.1)	342	173 (50.6)	342	168 (49.1)	<.001	<.001
25% to ≤50% improvement	462	133 (28.8)	342	77 (22.5)	342	98 (28.7)		
50% to ≤75% improvement	462	105 (22.7)	342	56 (16.4)	342	57 (16.7)		
75%–100% improvement	462	71 (15.4)	342	36 (10.5)	342	19 (5.6)		
MADRS core mood items scores								
Worsening to ≤25% improvement	462	191 (41.3)	342	165 (48.2)	342	198 (57.9)	.249	<.001
25% to ≤50% improvement	462	115 (24.9)	342	79 (23.1)	342	75 (21.9)		
50% to ≤75% improvement	462	82 (17.7)	342	54 (15.8)	342	42 (12.3)		
75%–100% improvement	462	74 (16.0)	342	44 (12.9)	342	27 (7.9)		

[a]*P* Values are from Fisher exact test.
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, N = number of patients in study group, n = number of patients exhibiting the event.

relationship exists between early symptomatic improvement and ultimate overall response or remission.

The results for changes in MADRS scores over time revealed rapid, symptomatic improvement with olanzapine/fluoxetine combination therapy, with dramatic, significant results evident as early as week 0.5. These results are similar to those observed from a placebo-controlled study of olanzapine/fluoxetine combination in patients with MDD with psychotic features—reported by Rothschild et al[31] in 2004—where statistically significant (compared with placebo) improvements in HDRS-24 scores were observed with olanzapine/fluoxetine combination at week 1.

The results for pattern analyses revealed that olanzapine/fluoxetine combination therapy led to significantly greater

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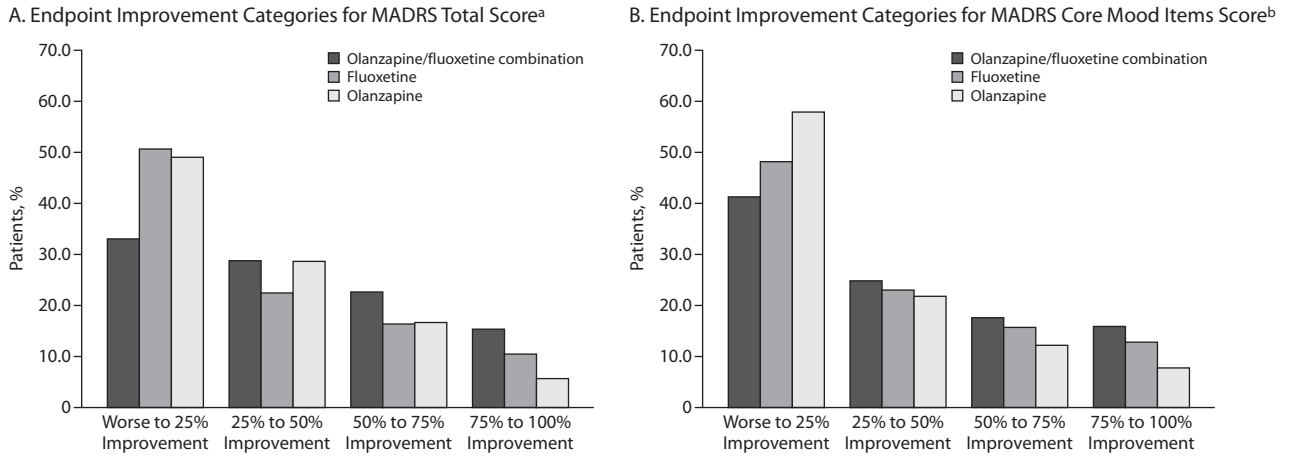
Figure 6. Categorical Endpoint Improvement for Montgomery-Asberg Depression Rating Scale (MADRS) Total and Core Mood Items Scores



[a]Olanzapine/fluoxetine combination versus fluoxetine, $P < .001$; olanzapine/fluoxetine combination versus olanzapine, $P < .001$ (Fisher exact test for both).
[b]Olanzapine/fluoxetine combination versus fluoxetine, $P = .249$; olanzapine/fluoxetine combination versus olanzapine, $P < .001$ (Fisher exact test for both).

Table 5. Does Early Onset of Response[a] Predict Ultimate Response/Remission[b]?

	MADRS Total, %		MADRS Core Mood Item, %	
Analysis	Response	Remission	Response	Remission
Positive predictive value	45.1	29.9	43.9	32.8
Negative predictive value	85.7	92.1	86.8	90.3
Sensitivity	80.8	83.4	79.7	80.0
Specificity	53.9	49.6	56.6	53.1
Total accuracy	62.5	56.5	63.5	59.1

[a]Early onset of response is defined as ≥25% reduction in MADRS score from baseline within 2 weeks from baseline.
[b]Response is defined as a ≥50% reduction in MADRS score from baseline. Remission is defined as a MADRS total score ≤10 or a MADRS core mood items score ≤6.
Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

percentages of patients displaying early persistent and delayed persistent onset of response compared with placebo. A cursory review of the interpretation of such findings, according to Quitkin et al,[30] may lead one to surmise that these results are due to an enhanced placebo response. However, 1 of the assumptions presented by Quitkin et al[30] is that the benefit observed due to placebo effect is shared equally by all therapies within the analysis. Additionally, Thase[32] noted the following in 2001: "An active antidepressant with a more rapid onset of action would shift the proportion of 'true' drug responders into the early persistent category."[(p20)] This is exactly what was observed in the current meta-analysis; moreover, similar patterns of response have been previously reported with other antidepressant therapies, such as venlafaxine.[33]

The results for PPV and NPV calculations indicate that the absence of early improvement with olanzapine/fluoxetine combination therapy (≥25% improvement in MADRS scores within 2 weeks of treatment initiation) is predictive of subsequent nonresponse/nonremission in patients with TRD, as NPVs for all 4 categories were high. In contrast, the results for PPVs were less powerful, as a substantial number of patients who experienced early symptomatic improvement did not ultimately respond to therapy. It is possible that positive expectancy effects may have contributed to low PPVs, as the expectation of improvement following the initiation of treatment with an active drug may have led to perceived improvement (in addition to or in place of actual improvement) during the early stages of the studies under evaluation. Positive expectancy effects can be mitigated or eliminated with the introduction of a placebo group in studies such as these; however, ethical concerns for the safety and well-being of difficult-to-treat patients typically preclude the consideration of placebo administration.

Other limitations of this meta-analysis should be noted. For one, a symptom rating scale that compares active treatment versus placebo (such as the MADRS) may exhibit results that demonstrate statistically significant improvement; nevertheless, those improvements may not be clinically meaningful. To mitigate this limitation and to better understand the effects of olanzapine/fluoxetine combination therapy on the core symptoms of depression, we included the MADRS core mood items score in our battery of efficacy measures. Another limitation is evident from the longitudinal olanzapine results for MADRS total score, MADRS core mood items score, and many of the MADRS individual items scores, as they demonstrated a peculiar pattern. In each case, substantial, dramatic improvement was observed early in the evaluation period, followed by lack of improvement or even regression with continued treatment. These results could be partially

attributed to possible lingering effects of fluoxetine: in 3 of the 5 studies pooled for this meta-analysis, double-blind administration of olanzapine/fluoxetine combination or monotherapy was preceded by a lead-in period in which all patients were administered fluoxetine. Indeed, fluoxetine has a long half-life: the elimination half-life of fluoxetine after chronic administration is 4 to 6 days, while the mean terminal half-life for its active metabolite, norfluoxetine, is 9.3 days.[34] Therefore, it is possible that patients who were randomly assigned to olanzapine therapy in those 3 studies were also deriving benefit from residual fluoxetine as it was slowly metabolized and excreted from their systems.

Another limitation of this meta-analysis lies in the pooling of 5 studies with some differences in the study designs. We alluded to the fact that 2 of these studies did not require patients to have an antidepressant therapy failure during the current depressive episode. By restricting the criteria of this meta-analysis to patients who demonstrated at least 1 such episode (that is, restricting the analyses to patients with TRD who resemble those seen in the clinical setting), we could not include results from a subset of patients who were enrolled in these studies. Also, 2 studies defined historical antidepressant treatment failure as failure to respond after a relatively brief period of therapy: ≥ 4 to 6 weeks.[13–15] Therefore, these studies may have included patients with various levels of resistance to treatment. Finally, 1 of these studies included a 7-week nortriptyline lead-in period; it is possible that a 7-week course of nortriptyline therapy was of inadequate duration to firmly establish response or resistance to treatment.[15]

In conclusion, the results from this meta-analysis suggest that the absence of rapid onset of response was highly predictive for overall response failure, while the presence of rapid onset of response was not predictive for overall outcome. These findings are of clinical relevance for caregivers who are making decisions about the treatment of patients with TRD.

Drug names: aripiprazole (Abilify), fluoxetine (Prozac, Sarafem, and others), nortriptyline (Pamelor and others), olanzapine (Zyprexa), olanzapine/fluoxetine (Symbyax), venlafaxine (Effexor and others).

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