

Adjunctive Aripiprazole for Depression: Predictive Value of Early Assessment

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It is estimated that antidepressants are 50% to 70% effective for major depressive disorder (MDD), and their delayed onset of effect has been identified as a treatment challenge.^{1,2} Historically, the delay in onset of efficacy for traditional antidepressants has been thought to be as long as 4 to 6 weeks, although recent work has challenged this hypothesis.³ The latency in the onset of therapeutic effect potentially prolongs the impairments associated with depression and leaves a patient more vulnerable to an increased risk of suicide and likelihood of prematurely discontinuing treatment.^{1,2,4} Indeed, it is estimated that only 25% to 50% of patients continue with their antidepressant regimen for the length of time recommended by guidelines.⁵ This is an important consideration, as the economic cost of depression is significant and inadequately treated depression costs even more,^{6,7} a price further increased by latency in the onset of antidepressant therapy (ADT).^{1,2}

Personalizing patient care and optimizing outcomes are becoming increasingly important; both patients and physicians will benefit economically in terms of cost savings and in terms of wellness and quality of life.⁸ With the need to optimize patient care comes the desire to know early in the course of treatment whether a patient will eventually respond to treatment, and evidence is emerging that early response to antidepressant medication can predict later response/remission with high sensitivity.⁹⁻¹¹ Clinical markers of efficacy can aid in decision making about a patient's treatment program but can also shift the risk-benefit profile of a treatment strategy for MDD. For example, if early onset of efficacy is of prognostic value for later response/remission, this may encourage patients to work through any tolerability issues, and patients who experience early improvement may be more compliant with their medication.¹² Moreover, patients who do not respond to a given therapy over a sufficient period of time will likely require treatment adjustments, including dose increases or medication switches. Early understanding of when to stay the course and when to adjust treatment will assist in clinical practice.

Current practice guidelines recommend that antidepressant efficacy should be assessed after as little as 2 weeks to determine the level of response, and measurement-based tools (such as the Clinical Global Impression scale) should be used to do so.¹³ A recent review of consensus guidelines defines the goals of treating depression as

Objectives: To determine whether early symptom improvement with adjunctive aripiprazole in major depressive disorder (MDD) predicts overall symptom remission.

Study Design: Post hoc pooled analysis of 3 randomized, double-blind studies evaluating efficacy, safety, and tolerability of adjunctive aripiprazole or placebo with standard antidepressant therapy (ADT) in inadequate responders to a prospective 8-week ADT and at least 1 historical ADT.

Methods: A multivariate logistic regression model was developed to determine factors predicting remission most strongly at the end point. Remission was defined as a Montgomery-Åsberg Depression Rating Scale (MADRS) total score of 10 or less at end point.

Results: Early improvement in depression symptoms was the most significant predictor of remission. In adjunctive aripiprazole and placebo groups, improvement of 20% or more in MADRS total score (week 2) was a significant predictor of remission. At week 2, high sensitivity and high negative predictive values (NPVs) were reported for remission in both treatment arms. In the adjunctive aripiprazole arm, early improvement predicted later MADRS remission with high sensitivity (88.0%) and a high NPV (91.5%). Positive predictive value was moderate in both the adjunctive aripiprazole (45.4%) and placebo (37.5%) arms; specificity was 55.0% with adjunctive aripiprazole and 71.5% with placebo.

Conclusions: Week 2 was a clinically meaningful time point to identify early improvers, and lack of improvement early in treatment was a highly significant predictor of lack of later remission. Early assessment of changes in symptoms could prove useful in clinical practice and more appropriately target healthcare costs.

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Take-Away Points

Because the economic cost of caring for patients with major depressive disorder is high, early identification of treatment responders and nonresponders may help clinicians make more timely decisions for treatment adjustment during the course of treatment.

- Adjunctive aripiprazole provides early (week 2) improvement in depression symptoms in a significantly greater proportion of patients than adjunctive placebo.
- Early improvement was shown to be a significant predictor of later remission; lack of improvement was associated with later nonremission.
- Objective rating of depression symptoms using a validated scale, especially within 2 weeks of a treatment change, should become routine in follow-up care.

(1) achievement of symptomatic remission and (2) achievement of full functional recovery.¹³ However, it is known that up to 70% of patients with MDD do not achieve remission after an adequate course of at least 1 ADT.¹⁴⁻¹⁶ Importantly, patients who respond to treatment have lower associated costs per patient and a higher quality of life than nonresponders.¹⁷ Thus, if after 2 to 4 weeks a patient with MDD has not responded to treatment, or achieved only a partial response to treatment, a change in dose, a switch to a new drug, or augmentation therapy may be warranted.

Among the augmentation options, evidence from large, well-controlled clinical trials supports the use of atypical antipsychotics to augment antidepressant monotherapy in patients who have unresolved symptoms. The efficacy and tolerability of aripiprazole as adjunctive therapy to ADT have been demonstrated in 3 large, randomized, double-blind, placebo-controlled trials.¹⁸⁻²⁰ However, the predictive value of early symptom assessment in patients with MDD receiving adjunctive medication to standard ADT has not previously been evaluated. Here, we present a post hoc analysis of pooled data from 3 studies of adjunctive aripiprazole to evaluate the predictive value of early symptom assessment in patients with MDD who had an inadequate response to standard ADT.

METHODS

Study Design

This analysis used pooled data from 3 identically designed, similarly sized, multicenter, randomized, double-blind studies conducted in the United States evaluating the efficacy, safety, and tolerability of aripiprazole versus placebo as adjunctive treatment to standard ADT in patients who had an inadequate response to a prospective 8-week trial of the same antidepressant agent and at least 1 historical ADT.¹⁸⁻²⁰

Study participants eligible for enrollment in any of the 3 studies met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)* criteria for a major depressive episode²¹ that had lasted 8 weeks or more prior to inclusion without an adequate response. The Mini-

International Neuropsychiatric Interview (MINI)²² was conducted during the screening phase to confirm the patient's diagnosis of MDD and to rule out exclusionary comorbid psychiatric diagnoses. An inadequate response to antidepressant treatment was defined as a less than 50% reduction in depressive symptoms severity, as assessed by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire, within the current depressive episode. Patients were characterized by having an inadequate response to at least 1, but no more than 3, adequate antidepressant trials (duration of >6 weeks at an adequate dose as specified in the Antidepressant Treatment Response Questionnaire).

Eligible patients with MDD (17-item Hamilton Depression Scale [HAM-D17] total score ≥ 18) entered an 8-week prospective ADT phase and a 6-week randomized phase. During the prospective treatment phase, patients received 8 weeks of therapy with escitalopram (10 or 20 mg/day), fluoxetine (20 or 40 mg/day), paroxetine controlled release (37.5 or 50 mg/day), sertraline (100 or 150 mg/day), or venlafaxine extended release (150 or 225 mg/day), per investigator choice, and a single-blind, adjunctive placebo. Patients with an inadequate response (<50% reduction in HAM-D17 total score; HAM-D17 ≥ 14 and Clinical Global Impression Improvement score of ≥ 3 at the end of the ADT phase) were randomized 1:1 to continue the same ADT (no dose adjustment was permitted) plus either adjunctive placebo or aripiprazole (2-20 mg/day) for 6 weeks; patients in the third study were also required to have a Clinical Global Impression Improvement score of 3 or more at study week 6. The pooled demographic characteristics of the population across the 3 studies have been published previously²³; patients were, on average, approximately 45 years of age, and mostly female and white.

Assessments and Analyses

The primary efficacy end point used in these studies was the mean change from end of the prospective treatment phase (baseline) to the end of the randomized, double-blind phase in the clinician-rated Montgomery-Åsberg Depression Rating Scale (MADRS) total score.²⁴ The subject-rated Inventory of Depressive Symptomatology (IDS) was included as a secondary efficacy outcome.²⁵

This post hoc analysis used pooled data from these 3 studies to evaluate the predictive value of early improvement with adjunctive aripiprazole to predict overall symptom remission. Early MADRS improvement was defined as a 20% or more reduction from baseline in MADRS total score at week 2 (ob-

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■ **Table 1.** Calculation of Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value

	Week 6 Response or Remission ^a	Week 6 No Response or Remission	
Early improvement (week 2) ^b	A: True positive	B: False positive	PPV = A/(A + B)
No early improvement (week 2)	C: False negative	D: True negative	NPV = D/(C + D)
	Sensitivity = A/(A + C)	Specificity = D/(B + D)	

MADRS indicates Montgomery-Åsberg Depression Rating Scale; NPV, negative predictive value; PPV, positive predictive value.
^aWeek 6 response: ≥50% decrease in MADRS total score from baseline at end point. Week 6 remission: MADRS total score ≤10 at end point.
^bEarly improvement: ≥20% decrease in MADRS total score from baseline at week 2.

served case data) of the randomized, double-blind adjunctive treatment phase. Data at week 3 were also analyzed. Early IDS improvement was defined as a 20% or more reduction from baseline in IDS total score at week 2 of the randomized, double-blind, adjunctive treatment phase. Remission was defined as an MADRS total score of 10 or less at the end point.

Both univariate and multivariate logistic regression models were developed to determine which factors predicted remission most strongly at the study end point. The following variables were included in both models: sex, baseline MADRS score (median split), body weight (median split), duration of current episode (median split), antidepressant (serotonin-norepinephrine reuptake inhibitors vs selective serotonin reuptake inhibitors), number of prior ADT failures, and time and early improvement group for MADRS and IDS (univariate only). Separate multivariate models were developed for early improvement at week 2 and week 3; the univariate analysis also included treatment (adjunctive aripiprazole/placebo) and study as additional variables. The variables were selected based on prior knowledge of previous studies that explored predictors of response in patients with depression.

Table 1 shows how sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. Analyses were conducted using the last-observation-carried-forward method on the efficacy sample, which comprised all patients randomized to treatment who received at least 1 dose of double-blind study medication and had at least 1 post-randomization efficacy evaluation. Receiver operating characteristic (ROC) curves with area under the curve (AUC) values were also calculated for response and remission at end point using early improvement at weeks 2 and 3 as predictors.

RESULTS

Subject Disposition and Baseline Demographics

In total, 1092 patients had an inadequate response following completion of the 8-week prospective treatment of ADT and were randomized to double-blind treatment with adjunctive aripiprazole (n = 550) or adjunctive placebo (n

= 538) (4 randomly assigned patients did not receive double-blind study medication).¹⁸ The completion rate was high in both treatment groups (adjunctive aripiprazole, 85.3%; adjunctive placebo, 87.2%) and discontinuation due to adverse events was low in both groups (adjunctive aripiprazole, 4.4%; adjunctive placebo, 1.7%). **Table 2** shows the baseline demographic characteristics, psychiatric history, and disease severity of patients who were early MADRS improvers and those who were early MADRS nonimprovers.

Treatment

The mean adjunctive aripiprazole dose across all ADTs on the last day of treatment was 11.0 (2-20) mg/day, and was similar between ADT groups, although no formal statistical analysis was performed (escitalopram 11.2 mg/day; fluoxetine 9.9 mg/day; paroxetine 9.8 mg/day; sertraline 12.2 mg/day; venlafaxine extended release 10.8 mg/day). Among early improvers, as defined at week 2, the mean (standard deviation [SD]) dose of aripiprazole was 7.6 (2.8) mg/day at week 2 and 9.6 (4.9) mg/day at week 6. Among week 2 nonimprovers, the mean (SD) dose of aripiprazole was 8.2 (2.5) mg/day at week 2 and 11.7 (6.2) mg/day at week 6.

Improvement in Depression Symptoms

At the end point, the mean reduction in MADRS total score was significantly greater in patients receiving adjunctive aripiprazole than in patients receiving placebo (−9.7 vs −6.6; $P < .001$). Improvement (≥20% reduction in MADRS total score) was seen in significantly more patients in the adjunctive aripiprazole treatment group than the adjunctive placebo group at all time points (**Figure 1A**). Remission was achieved by significantly more patients receiving adjunctive aripiprazole than by patients receiving placebo from week 2 onward (**Figure 1B**).

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Of the demographic and clinical factors assessed as potential predictors of remission, an early improvement in depression symptoms (≥20% in MADRS total score), using week 2 criteria, was a significant predictor of remission with aripiprazole in the multivariate analysis (**Figure 2**). Furthermore, more

■ **Table 2.** Baseline Characteristics of Patients Randomized to Receive Aripiprazole or Placebo

Characteristic	Early Improver ^a		Early Nonimprover	
	Aripiprazole (n = 291)	Placebo (n = 184)	Aripiprazole (n = 212)	Placebo (n = 302)
Age, mean (SD), y	46.0 (10.7)	46.3 (10.1)	44.9 (10.6)	44.0 (11.2)
Male, n (%)	75 (25.8)	62 (33.7)	79 (37.3)	101 (33.4)
Ethnicity, n (%)				
White	260 (89.4)	162 (88.0)	184 (86.8)	274 (90.7)
Black	25 (8.6)	17 (9.2)	14 (6.6)	21 (7.0)
American Indian/Alaskan	2 (0.7)	1 (0.5)	0 (0)	1 (0.3)
Asian	1 (0.3)	1 (0.5)	7 (3.3)	3 (1.0)
Hawaiian/Pacific Islander	0 (0)	0 (0)	3 (1.4)	0 (0)
Other	3 (1.0)	3 (1.6)	4 (1.9)	3 (1.0)
Weight, mean (SD), kg	84.1 (19.6)	87.4 (20.1) ^b	87.1 (21.8)	88.3 (23.6) ^c
Prior depressive episodes, mean (SD), n	5.9 (11.2) ^d	6.7 (12.0) ^e	4.8 (4.7) ^f	5.2 (9.8)
Duration of current episode, mean (SD), y	42.5 (64.4)	43.6 (76.3)	41.5 (66.7)	41.9 (61.6)
MADRS total score, mean (SD)	25.3 (5.8)	25.8 (5.8)	26.5 (6.3)	27.2 (6.0)
Prior adequate ADTs, n (SD)	1.4 (0.6)	1.4 (0.6)	1.3 (0.6)	1.4 (0.6)
ADT, n (%)				
Escitalopram	91 (62.3)	55 (37.7)	74 (46.8)	84 (53.2)
Fluoxetine	46 (65.7)	24 (34.3)	31 (40.3)	46 (59.7)
Paroxetine CR	24 (51.1)	23 (48.9)	16 (41.0)	23 (59.0)
Sertraline	47 (58.8)	33 (41.3)	39 (39.4)	60 (60.6)
Venlafaxine XR	83 (62.9)	49 (37.1)	52 (36.9)	89 (63.1)

ADT indicates antidepressant therapy during the 8-week prospective treatment phase; CR, controlled release; MADRS, Montgomery-Åsberg Depression Rating Scale; SD, standard deviation; XR, extended release.

^aEarly improvers were patients with a $\geq 20\%$ decrease in MADRS total score from baseline to week 2.

^bn = 182.

^cn = 300.

^dn = 285.

^en = 183.

^fn = 212.

patients who responded at week 2 achieved remission at week 6 in the aripiprazole group (65.7%) compared with the placebo group (34.3%). A lower baseline (ie, less ill patients) MADRS score (less than or equal to the median vs greater than the median) and IDS score were also significant predictors of remission in the week 2 multivariate model (Figure 2). Similar results were observed using the week 3 criteria for early improvement: early improvement in depression symptoms ($\geq 20\%$ in MADRS total score) (odds ratio [OR] 18.9; 95% confidence interval [CI] 8.0-44.7), lower baseline MADRS score (OR 2.4; 95% CI 1.5-3.9), and IDS score (OR 1.7; 95% CI 1.1-2.8) were significant predictors of remission.

The univariate analysis produced similar results; patients with an improvement of 20% or more in MADRS total score at week 2 were 10 times more likely to achieve remission, and patients with a 20% or more improvement in IDS score at

week 2 were approximately 5 times more likely to achieve remission, than those without this improvement.

The predictive value of nonimprovement at week 2 for later MADRS remission is shown in **Table 3**, where NPVs exceed 90%. The PPV was moderate in both the adjunctive aripiprazole (45.4%) and adjunctive placebo (37.5%) arms, and specificity was 55.0% with adjunctive aripiprazole and 71.5% with adjunctive placebo. The predictive value of early improvement at week 3 for MADRS remission was similar to that at week 2, thus making week 2 an early and clinically useful time point for assessment. At week 3, early MADRS improvement predicted later MADRS remission with high sensitivity (96.0%) and a high NPV (96.2%) (data not shown).

Predictive response was also assessed in patients who were deemed to be early improvers or nonimprovers based

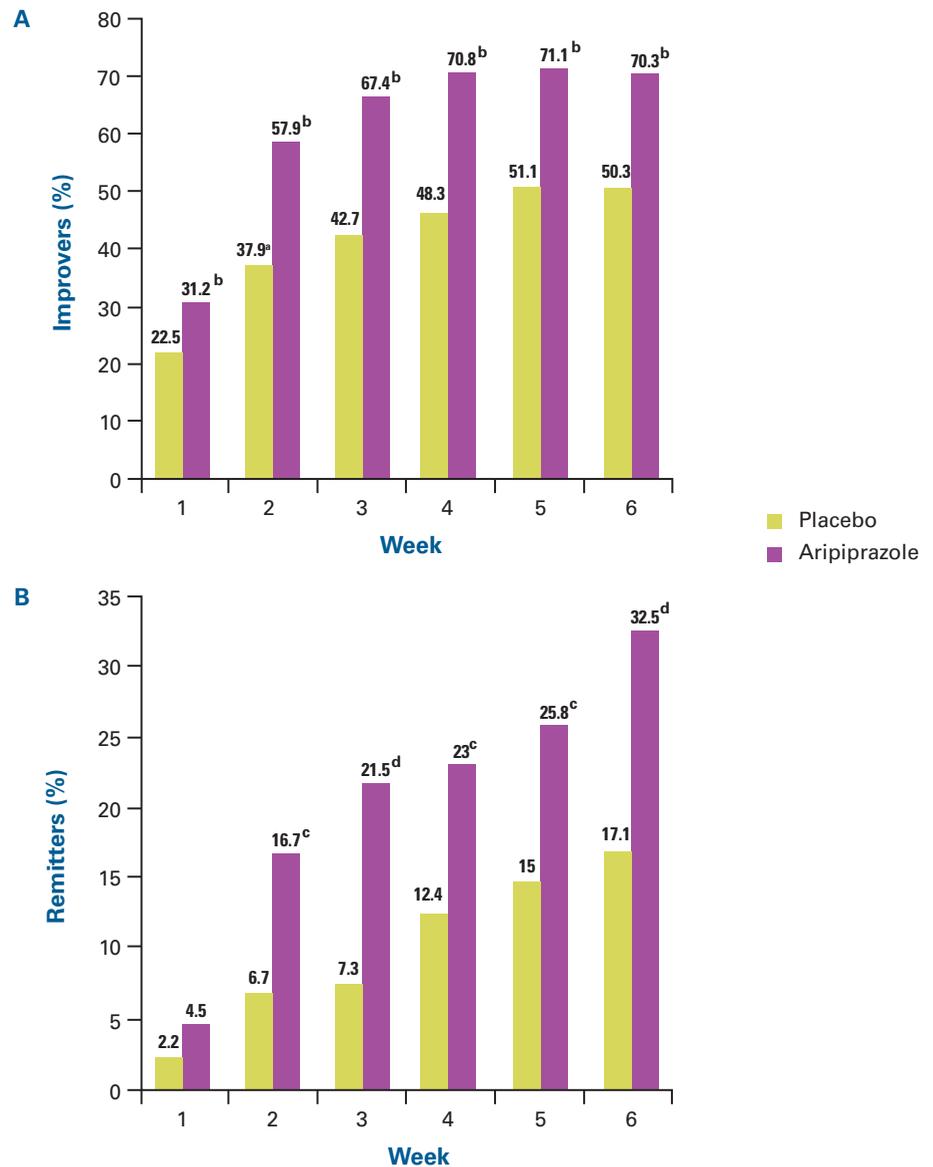
on the patient-rated IDS total score at week 2. In the adjunctive aripiprazole and placebo arms, early IDS improvement predicted later MADRS remission with moderate sensitivity (63.8% and 61.7%, respectively). Slightly higher NPV was reported for remission in the adjunctive placebo arm (91.3%) than in the adjunctive aripiprazole arm (82.7%). The PPV was moderate in both the adjunctive aripiprazole (50.8%) and adjunctive placebo (39.7%) arms, and specificity was 73.7% with adjunctive aripiprazole and 81.1% with adjunctive placebo.

The ROC curves for early improvement at week 2 and the AUC for early improvement at week 2 predicting later remission with adjunctive aripiprazole or placebo were both 0.81. The AUCs for early improvement on the clinician-rated MADRS scale at week 2 predicting later response with adjunctive aripiprazole was 0.81, whereas with adjunctive placebo it was 0.82. The AUC for early improvement at week 3 predicting later response in patients receiving adjunctive aripiprazole was 0.85, whereas with adjunctive placebo it was 0.86. The AUC for early improvement at week 3 predicting later remission in patients receiving adjunctive aripiprazole was 0.83; with adjunctive placebo it was 0.85. A comparison of the area under the ROC curves of weeks 2 and 3 showed a statistically significant difference in favor of week 3; however, the magnitude of the difference in the areas makes this finding of low clinical significance.

DISCUSSION

This study demonstrates that among patients with MDD who receive adjunctive aripiprazole as augmentation to ADT, week

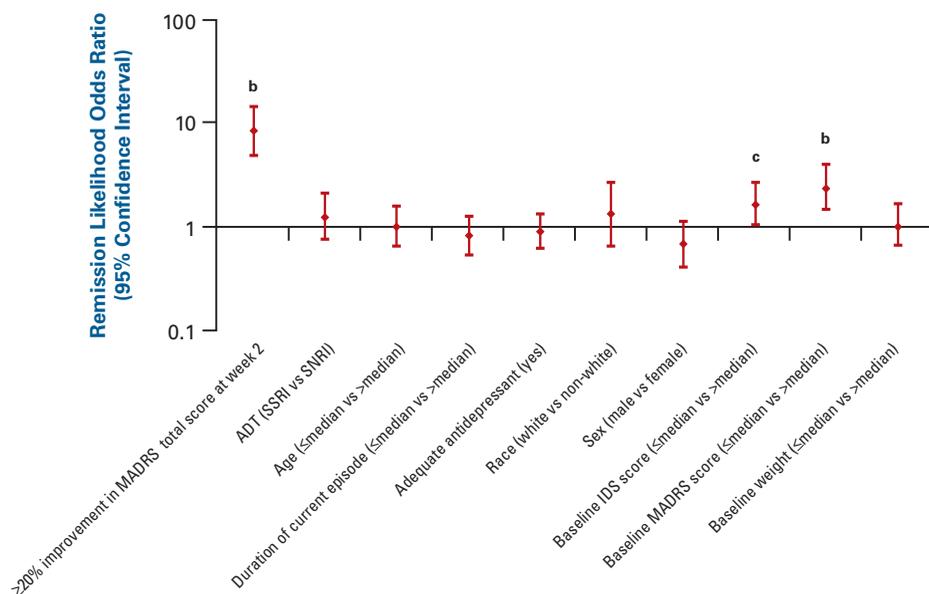
Figure 1. (A) Percentage of Improvers by Double-Blind Treatment Study Week (Observed Cases)^a and (B) Percentage of Remitters by Double-Blind Treatment Study Week



MADRS indicates Montgomery-Åsberg Depression Rating Scale.
^aImprovers were patients who had a $\geq 20\%$ decrease in MADRS total score from baseline.
^b $P < .0001$ versus adjunctive placebo; observed cases.
^c $P < .01$ versus placebo.
^d $P < .001$ versus placebo.

2 is a clinically meaningful time point to identify early improvers ($\geq 20\%$ decrease in MADRS total score from baseline), who were nearly 10 times more likely to achieve remission. Based on a high NPV for remission, failure to improve early with adjunctive treatment also was predictive of failure to improve later in treatment. Thus, the data strongly support the value of early assessment to inform clinical decisions in the treatment of MDD. Clinicians should reassess a patient's condition within 2 weeks

■ **Figure 2.** Demographic and Clinical Factors and Their Predictive Value for Remission^a With Aripiprazole According to a Multivariate Logistic Regression Model Using Week 2 Criteria for Early Improvement



ADT indicates antidepressant therapy; IDS, Inventory of Depressive Symptomatology; MADRS, Montgomery-Åsberg Depression Rating Scale; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

^aPatients in remission had an MADRS total score of ≤ 10 at week 6.

^b $P < .001$.

^c $P < .05$.

of starting a new ADT regimen and consider adjusting the overall treatment regimen (eg, further dose titration of ADT and/or augmenting agent) or switching treatment in patients who do not show some improvement. A heightened level of follow-up and vigilance is also warranted. Similar PPVs and NPVs were observed in the adjunctive aripiprazole and adjunctive placebo groups. These data suggest that the NPV can detect patients who do not improve at week 2 and predict later nonresponse if the same treatment is continued to week 6, irrespective of the type of therapy they are receiving.

The findings reported here with adjunctive treatment are similar to those in antidepressant monotherapy studies that used the criterion of a 20% score reduction as an early indicator of improvement rated by the HAM-D17 rather than MADRS scale.⁹⁻¹¹ The 20% or more reduction in symptom score is often chosen, as it can be reliably measured and translates into clinically meaningful change in the severity of depression.¹¹ Monotherapy studies with mirtazapine and paroxetine have shown that early improvement ($\geq 20\%$ reduction in HAM-D17) predicted stable response ($\geq 50\%$ reduction in HAM-D17 at week 4 or 6) and stable remission (HAM-D17 score of ≤ 7 at week 4 or 6) with high sensitivity.¹⁰ Early improvement ($\geq 20\%$ reduction in HAM-D17) during the course of treatment with a range of ADTs with different pharmaco-

logic profiles is also useful in predicting stable response.¹¹ Nonresponse ($< 20\%$ in HAM-D17 score) to fluoxetine as early as week 2 has been shown to predict a poor 8-week outcome.⁹ Additionally, the absence of early improvement ($\geq 25\%$ reduction in MADRS total score) with fluoxetine/olanzapine combination treatment was predictive of subsequent nonresponse or nonremission in patients with treatment-resistant depression.²⁶

Similarly, in a pooled analysis of 10 randomized, double-blind, placebo-controlled trials, the absence of early improvement appeared to be a highly reliable predictor of eventual nonresponse and nonremission (NPV of 74% and 82%, respectively).²⁷

The value of a 2-week assessment is underscored by the fact that patients who achieved an early 20% improvement in their MADRS scores were nearly 10 times more likely to achieve remission. Perhaps more striking, the vast majority of patients ($> 90\%$) who had not experienced an early 20% symptomatic improvement by week 2 did not achieve remission. Taken together, regardless of current treatment, the data support the clinical value of early assessment using either the clinician-rated MADRS or the patient-rated IDS scale.

Interestingly, the early improvement in symptomatology as a predictor of remission was observed as a function of the change in both MADRS and IDS scores, which are clinician- and patient-rated scales, respectively. This observation is in agreement with data from Reimherr and colleagues, who recently reported a cross-correlation analysis that also found that improvements in depressive symptomatology could be reliably identified by clinicians and patients alike.²⁸

Adjunctive aripiprazole was significantly more likely than adjunctive placebo to provide early improvements in depression symptoms. Changes in specific depressive symptoms were not included in the analysis presented here, but previous analyses of pooled data from 2 studies used in the present analysis have established that adjunctive aripiprazole significantly improved the core depressive symptoms (8 of 10 MADRS and

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■ **Table 3.** Predictive Value of Early Improvement^a (Week 2) for End Point (Week 6) Remission, Efficacy Sample

Treatment Arm	Early Improvers, n	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Placebo (n = 486)	184	83.1	71.5	37.5	95.4
Aripiprazole (n = 503)	291	88.0	55.0	45.4	91.5

MADRS indicates Montgomery-Åsberg Depression Rating Scale; NPV, negative predictive value; PPV, positive predictive value.

^aEarly improvers had a $\geq 20\%$ reduction from baseline in MADRS total score at week 2. Patients in remission had an MADRS total score of ≤ 10 at week 6.

12 of 30 IDS items) compared with ADT alone.²⁸ From week 3 to week 6 of adjunctive treatment, the proportion of patients meeting early improvement criteria remained similar to the proportion at week 2—an important point given that improvement within the first 2 weeks was shown to be a highly sensitive predictor of remission.²⁹

The mean dose of adjunctive aripiprazole in the early improver and early nonimprover groups was similar at week 2 (7.6 ± 2.8 and 8.2 ± 2.5 mg/day, respectively); both groups had an increase in their average adjunctive aripiprazole dose during the study, suggesting that the dose of aripiprazole is not dependent on whether a patient responds early to treatment or not. This implies that physicians should consider not increasing the dose of adjunctive aripiprazole too quickly but should rather consider remaining in the dose range of 5 to 10 mg/day during the first 2 to 4 weeks of treatment. Furthermore, guidelines suggest that patients should receive the recommended level of monitoring as per the product label during treatment initiation so that medication can be tailored in patients who respond early and in those who do not. In particular, as nonadherence with medication has been identified as a significant problem in the treatment of depression, physicians should include nonadherence as an important part of their patients' follow-up. It has been found that patients receiving a new course of ADT receive far less monitoring than is recommended.³⁰

On the basis of our findings, we recommend that physicians should consider providing closer follow-up for patients who were deemed early nonimprovers after 2 to 3 weeks of treatment than for patients who were deemed early improvers. Physicians should carefully assess the patient's adherence to both the antidepressant and the adjunctive aripiprazole, and then consider whether the medications are being dosed appropriately for that particular patient. If both drugs are considered to be in the therapeutic dose range, then an increase in the frequency of follow-up should be implemented, followed by a dose increase in 1 or both of the medications with the requisite monitoring for potential side effects. If there is still no meaningful response by 4 to 6 weeks of treatment, then the physician should consider a change in treatment plan.

The findings reported herein are strengthened by the relatively large numbers of patients with MDD included in this

pooled analysis, although appropriate caution in the interpretation is needed because this is a post hoc, exploratory analysis. Other potential limitations of this study are the reliability of the statistical significance of end points that are not the primary outcomes, the short duration of adjunctive treatment, and the exclusion of patients with established medical comorbidities. Notably, however, the results do concur with the findings of many other depression studies, which report the value of examining early treatment response patterns in the pharmacotherapy of MDD.^{10,11,31-33} This study was conducted in patients who showed an incomplete response to at least 1 historical and 1 prospective ADT; as such, it is unclear how the predictive value of early improvement might change in patients who are in a different phase of treatment, who have more severe or refractory depressive episodes, or who initiate treatment with ADT and aripiprazole concurrently.

The value of early identification of treatment response or nonresponse in MDD is not only beneficial to the patient in terms of optimizing clinical outcome, but also allows the physician to assess the benefit of treatment before the development of any long-term adverse reactions, thus limiting long-term exposure to those patients who receive substantial benefit from therapy. Early identification of treatment response should also not be underestimated from an economic perspective. Major depressive disorder is a significant health problem with economic implications for patients, their employers, and the healthcare system.³⁴ It was estimated in 2000 that the economic burden of depression was approximately \$83 billion.³⁵ In patients with MDD, nonstability of treatment is associated with significantly higher treatment costs compared with a stable regimen.³⁶ Costs for unstable patients comprised more urgent care use, higher comorbidity rates, and higher total, depression-related, and non-depression-related direct costs.³⁶ In a recent report, it was estimated that in the United States in 2005, the annual per-patient adjusted costs were \$9948 and \$6215 in unstable versus stable patients.³⁶ Additionally, treatment resistance among patients with depression is associated with a 40% increase in care costs.⁶ Given the high economic burden of MDD, especially for patients who are not receiving a stable treatment regimen or who are treatment resistant, attaining patient remission is an important treatment goal. The ability to identify early improvement in patients with MDD

and use this as a marker of later remission could potentially impact favorably on cost of care of these patients.

CONCLUSIONS

Our findings add to the literature supporting the value of early assessments in optimizing treatment of depression. The likelihood of remission is considerably greater for patients showing some improvement at week 2, while patients who do not show improvement after 2 weeks of adjunctive medication have little chance of achieving remission by 6 weeks. The regular utilization of objective symptom rating scales is encouraged in clinical practice in order to measure the extent and trajectory of clinical response to treatment early and effectively. Adjunctive aripiprazole provides early improvement in depression symptoms in a significantly greater proportion of patients than adjunctive placebo. Week 2 assessments are clinically meaningful to identify not only early improvers, but also early nonimprovers. A 20% improvement at week 2 was associated with a 10-fold greater chance of remission, while lack of early improvement predicted lack of later remission with more than 90% NPV. Our findings support the value of early symptom assessment in MDD for multiple stakeholders, including patients, clinicians, and payers.

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