ORIGINAL RESEARCH

Key Words: predictor; response; remission; bipolar disorder; bipolar depression

Predictive Value of Early Improvement in Bipolar Depression Trials: A *Post-hoc* Pooled Analysis of Two 8-week Aripiprazole Studies

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ABSTRACT ~ Objective: *To evaluate the value of early improvement to predict treatment outcome in patients with bipolar depression.* ***Methods:*** *Data were pooled from two aripiprazole, 8-week, randomized, double-blind, placebo-controlled trials in patients with bipolar depression without psychotic features to determine whether early improvement (≥20% reduction in Montgomery–Åsberg Depression Rating Scale (MADRS) Total score at Week 2 or 3) predicts later response (≥50% MADRS Total score reduction at Week 8) or remission (MADRS Total ≤10 at Week 8). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated (LOCF). Univariate and multivariate logistic regression models were used to evaluate early improvement and baseline demographic/clinical characteristics as predictors of response/remission.* ***Results:*** *In total, 311 patients were randomized to placebo and 306 to aripiprazole. Predictive values of early improvement (≥20% MADRS Total score reduction) for remission with aripiprazole at Week 2/3, respectively, were: sensitivity 83%/94%; specificity 41%/33%; PPV 44%/45%; NPV 81%/91%. The corresponding values with placebo were as follows: sensitivity 70%/84%; specificity 60%/51%; PPV 50%/51%; NPV 77%/84%. Univariate linear regression showed that early improvement (≥15%, ≥20%, ≥25%, ≥30% at Week 3) was a significant potential predictor of remission.* ***Conclusion:*** *Absence of early improvement after 3 weeks of treatment reliably predicted non-response/non-remission at study endpoint with high sensitivity and NPV. In patients with <20% improvement after 21 days of aripiprazole monotherapy, treatment should be modified, as continued use is unlikely to result in response/remission. Clinical decision-making to optimize treatment course in bipolar I depression may be*

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appropriate after as little as 2 weeks and certainly within the first 3 weeks of treatment. Psychopharmacology Bulletin. *2010;43(2):1–23.*

INTRODUCTION

It is of particular importance to treat the depressive phase of bipolar disorder effectively, as this pole of the illness predominates in many cases, with depression symptoms occurring 3–4 times more frequently than manic symptoms.[1,2] Furthermore, depression precipitates much of the morbidity and mortality associated with bipolar disorder.[3] Evidence of antidepressant efficacy in bipolar disorder has been observed as early as Day 7 in clinical trials of at least two different atypical antipsychotics.[4,5] However, the onset of efficacy with unimodal antidepressant treatments to date has not been as fast as that seen with treatments for bipolar depression or mania. Traditionally, separation from placebo with unimodal antidepressants takes approximately 4–6 weeks,[6] although more recent evidence suggests that true onset of efficacy may in fact be earlier, within the first 2 weeks of treatment.[7] Given that separation from placebo occurs early in bipolar depression and that early improvement has been shown with high sensitivity to predict stable response and remission in unipolar major depression,[8] the predictive accuracy of early improvement in bipolar depression deserves exploration. Furthermore, given that clinicians cannot rely upon any clear factors to determine a patient's individual response pattern, it would be clinically valuable to determine which patients are likely to respond to a particular medication as early as possible in the course of treatment.

Several studies have identified the utility of early improvement to predict later response or remission with traditional antidepressant agents in patients with major depressive disorder. Empirically derived data from these short-term, randomized, controlled trials suggest that patients who respond or remit to treatment consistently demonstrate improvement within the first 2 weeks of antidepressant administration.[8–10] Furthermore, very few patients who fail to improve early in the course of treatment with traditional antidepressant therapy will show a prolonged, stable response later in treatment.[11–13] Thus, it appears that clinicians may be able to make rational treatment decisions in such patients quite early in the course of treatment. Given this evidence with traditional antidepressant agents and the increasing interest in atypical antipsychotics as treatments for unipolar and bipolar depression, it would be of interest to explore the temporal pattern of improvements in bipolar depression with an atypical antipsychotic.

Aripiprazole is a partial agonist at D_2, D_3 and $5HT_{1A}$ receptors and an antagonist at $5HT_{2A}$ receptors that is pharmacologically distinct

from other atypical antipsychotics[14–17] and has been shown to be superior to placebo in the acute treatment of manic or mixed states associated with bipolar disorder as monotherapy[18,19] or combination therapy.[20] In addition, aripiprazole monotherapy has been shown to prevent relapse in patients with bipolar I disorder experiencing a recent manic or mixed episode.[21] Although the results of two identically designed double-blind, placebo-controlled studies failed to show the efficacy at trial endpoint of aripiprazole monotherapy in the treatment of patients with bipolar I disorder with a major depressive episode,[22] these two studies do provide a large database of patients with bipolar I disorder with a major depressive episode without psychotic features, and a number of patients did show a response or remission to aripiprazole treatment. It was hypothesized that early improvement with aripiprazole treatment would predict later response and remission with high sensitivity and that a high percentage of patients without early improvement would fail to meet response or remission criteria at study endpoint.

METHODS

Study Design

A *post-hoc* pooled analysis was conducted using data from two studies of identical design. Both studies were included in a single publication, which describes the methodology in detail.[22] In brief, both were 8-week, multicenter, randomized, double-blind, placebo-controlled studies of aripiprazole in patients with bipolar depression without psychotic features. Aripiprazole was initiated at 10 mg/day (5 mg twice-daily), then flexibly dosed between 5–30 mg/day based on clinical effect/tolerability. Patients who could not tolerate aripiprazole 10 mg could have the dose reduced to 5 mg; if that was not tolerated, they were discontinued. Dose adjustments could be made in 5 mg increments weekly up to a maximum of 30 mg/day by Week 4.

Patients

The two studies enrolled male and female outpatients, aged 18–65 years, with a diagnosis of bipolar I disorder experiencing a major depressive episode (≥2 weeks and ≤2 years in duration) without psychotic features (Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (Text Revision [DSM-IV-TR]), confirmed by MINI International Neuropsychiatric Interview. Clinically significant depressive symptoms were defined by a Hamilton Depression

Scale (HAM-D; 17-Item) Total score ≥18 with a score ≥2 on Item 1 (depressed mood) at both the screening and baseline visits, and a ≤25% increase or decrease in the Total score between those visits. Patients had to have a Young Mania Rating Scale (YMRS) score ≤12 at both the screening and baseline visits, with a <4-point increase in YMRS Total score between those visits. The full inclusion and exclusion criteria are available in the original publication.[22]

Analyses

In the original studies, the primary efficacy endpoint was the mean change from baseline to Week 8 (last observation carried forward [LOCF]) in the Montgomery–Åsberg Depression Rating Scale (MADRS) Total score and the results are already published.[22] Although the primary endpoint did not separate from placebo, a number of patients either showed a clinically relevant response or remission when treated with aripiprazole. The primary aim of these *post-hoc* analyses was to determine whether early improvement—as defined by ≥20% reduction from baseline in the MADRS Total score at Week 2 or Week 3—can predict later response (≥50% reduction in MADRS Total score at endpoint, Week 8) or remission (MADRS Total score ≤10 at endpoint).

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. The method of calculation of sensitivity and specificity are shown in Table 1. In summary, early improvement would be a highly sensitive test if it correctly identified those individuals who ultimately showed response at study endpoint. Sensitivity is calculated by dividing the number of endpoint responders who demonstrated early improvement by the total number of endpoint responders. More technically, sensitivity is calculated as the number of true positives divided by the total number of positives—comprising true positives and positives wrongly classified as negatives, i.e. false negatives. Early improvement would be a highly specific test if it correctly identi-

TABLE 1

SENSITIVITY/SPECIFICITY CALCULATIONS

	WEEK 8 RESPONDERS (ENDPOINT)	WEEK 8 NON-RESPONDERS (ENDPOINT)	
Week 2 Improver	A: True positive	B: False positive	PPV = A/A+B
Week 2 Non-improvers	C: False negative	D: True negative	NPV = D/C+D
	Sensitivity = A/A+C	Specificity = D/B+D	

PPV, positive predictive value; NPV, negative predictive value.

fied those individuals who did not experience improvement at study endpoint. Specificity is calculated by dividing the number of endpoint non-responders who failed to demonstrate early improvement by the total number of endpoint non-responders. More technically, specificity is calculated as the number of true negatives divided by the total number of negatives—true negatives and false positives who were really negatives. Sensitivity and specificity are inversely proportional, meaning that as the sensitivity increases, the specificity decreases and *vice versa*. PPV is the probability that a patient will achieve a response if they show early improvement. It may be thought of as a measure of confidence in "knowing that the drug is going to work". It is calculated by dividing the number of endpoint responders who showed early improvement by the total population of subjects with early improvement. NPV may be thought of as a measure of confidence in "knowing that the drug is not going to work". NPV represents the probability that a patient will not achieve a response if they do not show early improvement; thus, it is calculated by dividing the number of endpoint non-responders who failed to show early improvement by the total population of subjects without early improvement. The area under the curves of the receiver operating characteristic (ROC) curves for predicting response or remission at endpoint were also generated. The area under the ROC curve represents the percentage of randomly drawn pairs from the endpoint (Week 8) response and non-response groups (or remission/non-remission groups, as appropriate) for which the test correctly classifies the two patients in the random pair at the early improvement timepoint of Week 2 (or 3). For example, an area under the ROC curve for early improvement at Week 2 predicting response at Week 8 of 0.5 means that a randomly chosen individual from the Week 8 responder group has a higher percentage improvement in MADRS Total score at Week 2 than a randomly chosen individual from the Week 8 non-responder group 50% of the time, no greater than by chance. Thus, an area of >0.5 indicates that the predictor has predictive value and predicts response/remission more than just by chance. Comparison of the area under the curve for predictors at Week 2 or Week 3 were also carried out; p-values <0.05 indicate that the areas under the curves for the predictors of early improvement at Week 2 and Week 3 are significantly different.

The analysis investigated the predictive value of a range of criteria for early improvement, using four different timepoints: ≥20% reduction in MADRS total score at Weeks 1, 2, 3, and 4, and using four different MADRS cut-off points at Week 2 and Week 3—≥15%; ≥20%; ≥25% or ≥30%. An additional analysis assessed the predictive value of early improvement for sustained response—defined as ≥50% decrease in the

MADRS total score at Weeks 6, 7, and 8 or sustained remission—MADRS ≤10 at Weeks 6, 7, and 8. Univariate logistic regressions were performed to determine if any demographic or clinical characteristics at baseline are predictive of response or remission. The regressions assessed the predictive value of the following characteristics: treatment, rapid cycling status, protocol, sex, baseline MADRS score, baseline body weight, number of mood episodes within the past 12 months and early improvement (using criteria of ≥15%, ≥20%, ≥25% or ≥30% improvement in MADRS Total score at Week 3). Multivariate logistic regressions were also performed to control for any interactions between the potential confounding baseline characteristics of MADRS Total score, body weight and number of mood episodes in the past 12 months. An additional analysis of the predictive value of early improvement by endpoint dose was conducted. This analysis assumed that patients were receiving the optimum study drug dose at endpoint.

RESULTS

Baseline Demographics and Characteristics

Across the two studies, 373 patients were randomized to aripiprazole, and 376 were randomized to placebo. Baseline demographics were similar between groups and studies, as previously published. More patients discontinued from aripiprazole versus placebo in both Study 1 (46.8% vs. 35.1%) and Study 2 (41.2% vs. 29.8%). The most common reasons for discontinuation in the aripiprazole group versus placebo were adverse events (Study 1: 16.7% vs. 7.4%; Study 2: 10.2% vs. 5.3%) and loss to follow-up (Study 1: 14.0% vs. 8.5%; Study 2: 12.8% vs. 7.4%). Table 2 shows the baseline demographic characteristics, psychiatric history and disease severity of patients who were early improvers and those who were early non-improvers. The two sub-groups were well matched in terms of their baseline characteristics. In addition, both groups had a similar number of prior manic or depressive episodes, and a similar age of onset for the current episode. The mean MADRS Total score at baseline was similar in both groups: early improvers overall 29.2 (placebo 29.0; aripiprazole 29.4); early non-improvers overall 28.8 (placebo 28.5; aripiprazole 29.3). There were no major differences between characteristics of those patients treated with aripiprazole versus placebo in either the early improver or early non-improver groups.

Improvement in Depression Symptoms

The timeframe for improvement of depression symptoms was early and continued throughout the study. Improvement (≥20% reduction in

TABLE 2

BASELINE CHARACTERISTICS OF PATIENTS RANDOMIZED TO ARIPIPRAZOLE OR PLACEBO WHO WERE EARLY IMPROVERS* AND THOSE WHO WERE EARLY NON-IMPROVERS

	EARLY IMPROVER		EARLY NON-IMPROVER	
	ARIPIPRAZOLE (N = 220)	PLACEBO (N = 184)	ARIPIPRAZOLE (N = 65)	PLACEBO (N = 111)
Age, years: mean (SD)	39.9 (11.3)	39.3 (12.8)	40.8 (11.3)	40.9 (11.6)
Sex: n(%) male	81 (36.8)	83 (45.1)	27 (41.5)	38 (34.2)
Ethnicity: n(%)				
White	185 (84.1)	153 (83.2)	51 (78.5)	97 (87.4)
Black	26 (11.8)	27 (14.7)	13 (20.0)	10 (9.0)
American Indian/Alaskan	4 (1.8)	2 (1.1)	0 (0)	0 (0)
Asian	2 (0.9)	1 (0.5)	0 (0)	2 (1.8)
Hawaiian/PI	0 (0)	1 (0.5)	0 (0)	0 (0)
Other	3 (1.4)	0 (0)	1 (1.5)	2 (1.8)
Weight, kg: mean (SD)	86.6 (21.9)[a]	90.2 (21.7)[b]	87.7 (23.5)[c]	89.0 (24.0)
Number of prior episodes, mean (SD):				
manic	14.1 (18.1)[d]	12.7 (15.5)[e]	12.0 (14.2)[f]	12.3 (14.9)[g]
depressive	18.0 (15.9)[h]	17.7 (17.1)[e]	21.6 (19.2)[f]	15.4 (13.5)[i]
Age of onset current episode, years: mean (SD)	39.6 (11.3)	39.0 (12.8)	40.4 (11.3)	40.6 (11.6)
MADRS Total score: mean (SD)	29.4 (5.5)	29.0 (5.9)	29.3 (5.4)	28.5 (5.7)

*Early improver was defined as ≥20% decrease in MADRS Total score from baseline to Week 3
SD, standard deviation; PI, Pacific Islander; MADRS, Montgomery–Åsberg Depression Rating Scale; HAM-D, Hamilton Depression Scale.
[a]n = 218; [b]n = 183; [c]n = 63; [d]n = 214; [e]n = 177; [f]n = 61; [g]n = 105; [h]n = 210; [i]n = 105.

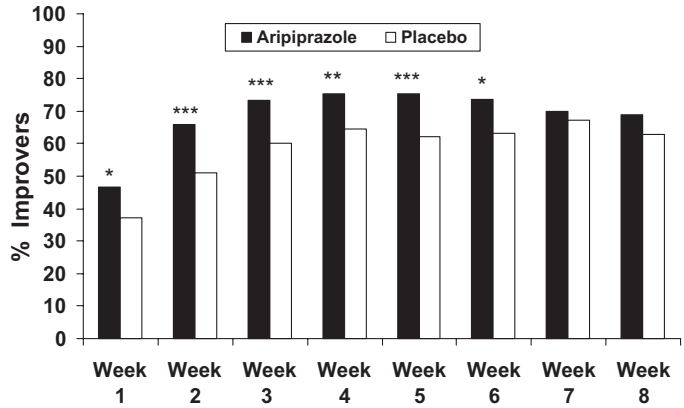
MADRS Total score) was seen in significantly more patients in the adjunctive aripiprazole- than placebo-treated group from as early as Week 1 (46.7% vs. 37.3%) and up to Week 6 (73.6% vs. 63.2%) (Figure 1). By Week 3, the majority of patients had achieved improvement with aripiprazole or placebo (73.3% vs. 60.3%), although it should be noted that there was no significant difference between aripiprazole and placebo beyond Week 6.

Prediction of Later Response/Remission

Evaluation of the predictive value of the early improvement MADRS criterion of ≥20% reduction in MADRS Total score across a range of

FIGURE 1

PERCENTAGE OF IMPROVERS (≥20% DECREASE IN MADRS TOTAL SCORE) AT EACH WEEK OF TREATMENT



*p < 0.05 aripiprazole vs. placebo, **p < 0.01 aripiprazole vs. placebo, ***p < 0.001 aripiprazole vs. placebo

MADRS, Montgomery–Åsberg Depression Rating Scale.

timepoints (Week 1, 2, 3, and 4) showed that the predictive value of this criterion increased over time during the first 3 weeks of treatment (Table 3). At Week 1, the predictive value of a ≥20% reduction in MADRS Total score showed a low sensitivity for both response and remission in either the placebo or aripiprazole arms. At Week 2, using the criterion for early improvement of ≥20% reduction in MADRS Total score in the aripiprazole arm, early improvement predicted later response or remission with high sensitivity (81.3% and 82.9%, respectively) and a high NPV (73.5% and 80.6%, respectively). A slightly higher sensitivity for response (93.9%) and remission (94.2%) and NPV for response (87.7%) and remission (90.8%) were observed with early improvement with aripiprazole at Week 3 than Week 2. Rates of false positives for predicting response and remission were high for both treatment arms at Week 2 (aripiprazole 56.9%/59.5%; placebo 35.1%/40.3%) and Week 3 (aripiprazole 62.8%/67.4%; placebo 45.3%/49.5%). Sensitivity and NPV were higher for aripiprazole than placebo at Week 2 and more robust at Week 3 (Table 3). Rates of false negatives for predicting response and remission were low for both treatment arms at Week 2 (aripiprazole 18.7%/17.1%; placebo 29.3%/30.4%) and Week 3 (aripiprazole 6.1%/5.8%; placebo 17.2%/16.2%).

The receiver operating characteristics (ROC) curves for early improvement at Week 2 and Week 3 predicting later remission are shown in Figure 2. The area under the ROC curves for early improvement at Week 2 or Week 3 predicting later response or remission ranged from

TABLE 3

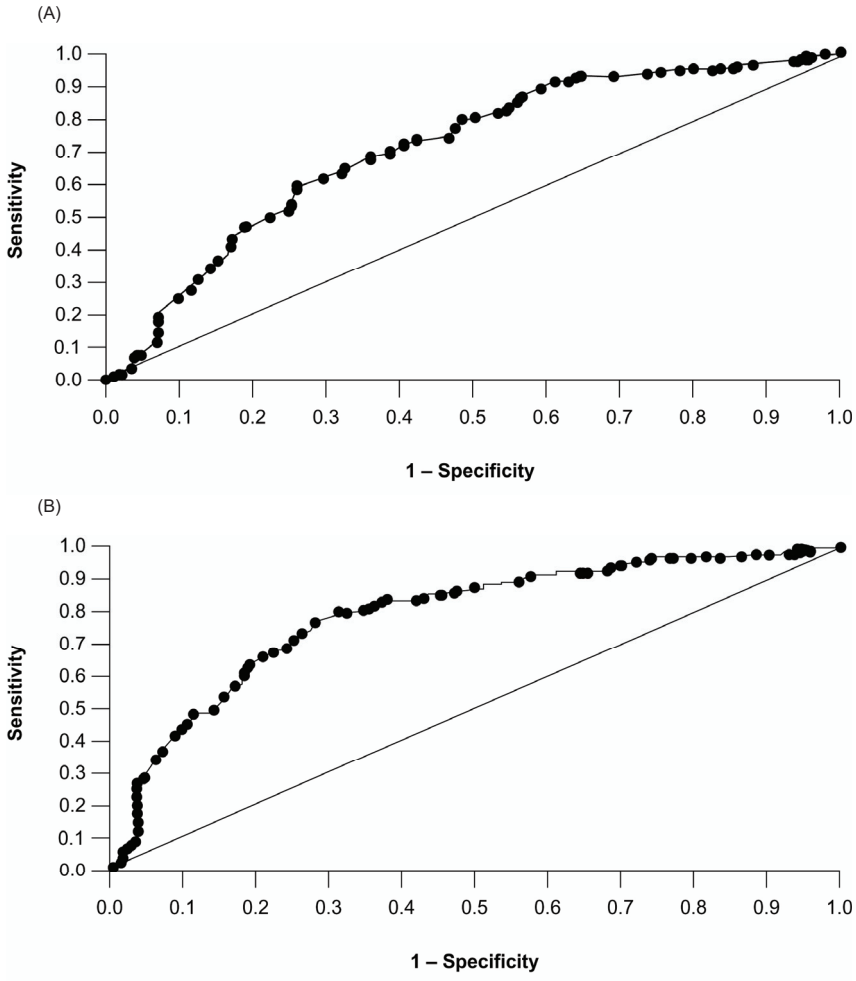
PREDICTIVE VALUE OF EARLY IMPROVEMENT FOR ENDPOINT (WEEK 8) RESPONSE OR REMISSION USING DIFFERING TIME POINTS—WEEK 1, 2, 3, AND 4—TO DEFINE 'EARLY' IMPROVEMENT

CRITERIA FOR IMPROVEMENT ON MADRS TOTAL SCORE	EARLY IMPROVERS	SENSITIVITY (%)		SPECIFICITY (%)		PPV (%)		NPV (%)	
		RESPONSE	REMISSION	RESPONSE	REMISSION	RESPONSE	REMISSION	RESPONSE	REMISSION
≥20% reduction at Week 1									
Placebo (n = 346)	N = 129	54.5	52.5	75.1	70.6	61.2	48.1	69.6	74.2
Aripiprazole (n = 330)	N = 154	59.6	61.4	63.6	61.1	56.5	45.5	66.5	75.0
≥20% reduction at Week 2									
Placebo (n = 311)	N = 159	70.7	69.6	64.9	59.7	62.3	50.3	73.0	77.0
Aripiprazole (n = 306)	N = 208	81.3	82.9	43.1	40.5	54.3	44.2	73.5	80.6
≥20% reduction at Week 3									
Placebo (n = 295)	N = 184	82.8	83.8	54.7	50.5	60.3	50.5	79.3	83.8
Aripiprazole (n = 285)	N = 220	93.9	94.2	37.3	32.6	56.4	44.6	87.7	90.8
≥20% Reduction at Week 4									
Placebo (n = 273)	N = 189	93.7	92.5	51.7	45.5	62.4	51.9	90.5	90.5
Aripiprazole (n = 255)	N = 202	93.3	94.5	33.3	29.3	55.5	42.6	84.9	90.6

Response = ≥50% reduction in MADRS Total score.
Remission = MADRS Total score ≤10 at Week 8.
MADRS, Montgomery–Åsberg Depression Rating Scale.

FIGURE 2

RECEIVER OPERATING CHARACTERISTICS (ROC) CURVES FOR EARLY IMPROVEMENT AT WEEK 2 (A) AND WEEK 3 (B) PREDICTING LATER REMISSION



0.70 to 0.79 with aripiprazole or placebo. With aripiprazole, Week 2 predictive value for response or remission were both 0.71, whereas Week 3 predictive value for response and remission were both 0.79. Thus, there is an estimated 0.71 probability that a Week 8 responder would have had a higher percentage improvement in MADRS Total score at Week 2 than a Week 8 non-responder, and an estimated 0.79 probability that a Week 8 responder would have had a higher percentage improvement in MADRS Total score at Week 3 than a Week 8 non-responder. Early improvement at Week 3 was a stronger predictor of later response ($p < 0.001$) or remission ($p = 0.002$) than Week 2.

MADRS Criteria for Definition of Early Improvement

Using a range of MADRS criteria to define improvement—≥15%, 20%, 25% or 30% reduction in MADRS Total score—showed that the sensitivity decreased and the specificity increased as a function of increasing the percentage change on the MADRS Total score, which defined early improvement at the Week 2 timepoint. The less stringent criterion for early improvement of ≥15% reduction in MADRS Total score at Week 2 (Table 4) or Week 3 (Table 5) showed a high sensitivity for response and remission in both the placebo and aripiprazole arms. When the more stringent criteria for early improvements were applied (either ≥25% or ≥30% reduction in MADRS Total score) at Week 2 (Table 4), the sensitivity of the placebo arm for both response and remission was <70%, but for the aripiprazole arm was still >70% for both response and remission. When the more stringent criteria for early improvements were applied at Week 3 (Table 5), the sensitivity again is lower than with less stringent criteria but does not drop below the cut-off of 70.

Sustained Response/Remission

Early improvement (≥20% reduction in MADRS Total score at Week 2 or Week 3) as a predictor for sustained response (≥50% reduction in MADRS Total score at Week 6, 7, and 8) or sustained remission (MADRS Total score ≤10 at Week 6, 7, and 8) was also assessed (Table 6). Using the same criterion for early improvement of a ≥20% reduction in MADRS Total score at Week 2 or Week 3, almost half of the patients in either the placebo (Week 2: PPV = 48.4%; Week 3: PPV = 45.1%) or aripiprazole (Week 2: PPV = 46.2%; Week 3: PPV = 46.4%) groups who were early improvers showed a sustained response. There was a high level of sensitivity using this criterion for early improvement to predict later response in both the placebo (Week 2: 77.0%; Week 3: 89.3%) and aripiprazole arms (Week 2: 83.5%; Week 3: 96.2%). Sustained remission also showed a high sensitivity for prediction with early improvement by Week 2 (placebo: 76.1%; aripiprazole: 84.4%) or by Week 3 (placebo: 92.3%; aripiprazole: 95.7%). Also, the NPV for sustained remission was high at Week 2 (placebo: 89.5%; aripiprazole: 87.8%) and Week 3 (placebo: 95.5%; aripiprazole: 95.4%) (Table 6).

Logistic Regression Analysis

Results of the logistic regression analysis are shown in Table 7. Univariate linear regression showed that early—Week 3—improvement

TABLE 4

Predictive Value of Early—Week 2—Improvement for Response or Remission and Assessment of Differing MADRS Criteria to Define Early Improvement

Criteria for Improvement on MADRS Total Score	Early Improvers	Sensitivity (%)		Specificity (%)		PPV (%)		NPV (%)	
		Response	Remission	Response	Remission	Response	Remission	Response	Remission
≥15% reduction in MADRS Total score at Week 2									
Placebo (n = 311)	N = 182	79.3	77.4	58.5	52.6	61.0	48.9	77.5	79.8
Aripiprazole (n = 306)	N = 226	84.9	85.6	35.3	32.8	52.2	42.0	73.8	80.0
≥20% reduction in MADRS Total score at Week 2									
Placebo (n = 311)	N = 159	70.7	69.6	64.9	59.7	62.3	50.3	73.0	77.0
Aripiprazole (n = 306)	N = 208	81.3	82.9	43.1	40.5	54.3	44.2	73.5	80.6
≥25% reduction in MADRS Total score at Week 2									
Placebo (n = 311)	N = 147	67.1	67.8	69.0	64.8	64.0	53.1	72.0	77.4
Aripiprazole (n = 306)	N = 184	74.8	77.5	52.1	49.7	56.5	46.7	71.3	79.5
≥30% reduction in MADRS Total score at Week 2									
Placebo (n = 311)	N = 126	60.0	61.7	75.4	71.9	66.7	56.4	69.7	76.2
Aripiprazole (n = 306)	N = 184	70.5	73.9	61.7	59.0	60.5	50.6	71.5	79.9

Response = ≥50% reduction in MADRS Total score at Week 8.
Remission = MADRS Total score ≤10 at Week 8.
MADRS, Montgomery–Åsberg Depression Rating.

TABLE 5

PREDICTIVE VALUE OF EARLY—WEEK 3—IMPROVEMENT FOR RESPONSE OR REMISSION AND ASSESSMENT OF DIFFERING MADRS CRITERIA TO DEFINE EARLY IMPROVEMENT

CRITERIA FOR IMPROVEMENT ON MADRS TOTAL SCORE	EARLY IMPROVERS	SENSITIVITY (%)		SPECIFICITY (%)		PPV (%)		NPV (%)	
		RESPONSE	REMISSION	RESPONSE	REMISSION	RESPONSE	REMISSION	RESPONSE	REMISSION
≥15% reduction in MADRS Total score at Week 3									
Placebo (n = 295)	N = 197	85.8	85.6	49.1	44.6	58.4	48.2	80.6	83.7
Aripiprazole (n = 285)	N = 234	96.2	96.2	30.1	26.0	54.3	42.7	90.2	92.2
≥20% reduction in MADRS Total score at Week 3									
Placebo (n = 295)	N = 184	82.8	83.8	54.7	50.5	60.3	50.5	79.3	83.8
Aripiprazole (n = 285)	N = 220	93.9	94.2	37.3	32.6	56.4	44.6	87.7	90.8
≥25% reduction in MADRS Total score at Week 3									
Placebo (n = 295)	N = 170	77.6	80.2	59.0	56.0	61.2	52.4	76.0	82.4
Aripiprazole (n = 285)	N = 198	90.2	90.4	48.4	42.5	60.1	47.5	85.1	88.5
≥30% reduction in MADRS Total score at Week 3									
Placebo (n = 295)	N = 154	71.6	74.8	64.0	61.4	62.3	53.9	73.1	80.1
Aripiprazole (n = 285)	N = 185	86.4	87.5	53.6	48.1	61.6	49.2	82.0	87.0

Remission = MADRS Total score ≤10 at Week 8.
MADRS, Montgomery–Åsberg Depression Rating.

TABLE 6

PREDICTIVE VALUE OF EARLY IMPROVEMENT FOR SUSTAINED (WEEK 6, 7, AND 8) RESPONSE OR REMISSION

CRITERIA FOR IMPROVEMENT ON MADRS TOTAL SCORE	EARLY IMPROVERS	SENSITIVITY (%)		SPECIFICITY (%)		PPV (%)		NPV (%)	
		SUSTAINED RESPONSE	SUSTAINED REMISSION	SUSTAINED RESPONSE	SUSTAINED REMISSION	SUSTAINED RESPONSE	SUSTAINED REMISSION	SUSTAINED RESPONSE	SUSTAINED REMISSION
≥20% reduction in MADRS Total score at Week 2									
Placebo (n = 311)	N = 159	77.0	76.1	61.1	55.7	48.4	32.1	84.9	89.5
Aripiprazole (n = 306)	N = 208	83.5	84.4	41.4	37.6	46.2	31.3	80.6	87.8
≥20% reduction in MADRS Total score at Week 3									
Placebo (n = 295)	N = 184	89.3	92.3	50.0	46.1	45.1	32.6	91.0	95.5
Aripiprazole (n = 285)	N = 220	96.2	95.7	34.1	28.7	46.4	30.0	93.9	95.4

Sustained Response = ≥50% reduction in MADRS Total score at Week 6, 7, and 8.
Sustained Remission = MADRS Total score ≤10 at Week 6, 7, and 8.
MADRS, Montgomery–Åsberg Depression Rating.

TABLE 7

DEMOGRAPHIC AND CLINICAL FACTORS AND THEIR PREDICTIVE VALUE FOR RESPONSE/REMISSION ACCORDING TO A UNIVARIATE LOGISTIC REGRESSION MODEL

	RESPONSE LIKELIHOOD OR (95% CI)		REMISSION LIKELIHOOD OR (95% CI)	
CHARACTERISTIC	ARIPIPRAZOLE	PLACEBO	ARIPIPRAZOLE	PLACEBO
Treatment (ARI/PBO)	1.10 (0.81–1.48)		1.02 (0.74–1.40)	
Rapid cycling (no. vs. yes)	1.18 (0.41–3.40)	1.44 (0.26–7.94)	1.05 (0.35–3.15)	1.03 (0.19–5.71)
Protocol (Study 1 vs. Study 2)	0.95 (0.62–1.46)	0.80 (0.53–1.23)	1.13 (0.72–1.76)	0.90 (0.58–1.39)
Sex (Female vs. Male)	1.48 (0.95–2.32)	0.93 (0.60–1.43)	1.21 (0.76–1.93)	0.90 (0.57–1.40)
Baseline MADRS score (≤Median vs. >Median)	0.92 (0.60–1.42)	1.13 (0.73–1.73)	1.54 (0.97–2.43)†	1.69 (1.07–2.67)*
Baseline body weight (≤Median vs. >Median)	0.86 (0.55–1.32)	0.99 (0.65–1.51)	0.68 (0.43–1.07)	0.75 (0.48–1.17)
Number of mood episodes within the past 12 months	0.95 (0.77–1.17)	1.08 (0.87–1.33)	1.01 (0.81–1.25)	1.06 (0.85–1.31)
Early improvement				
≥15% improvement in MADRS Total score at Week 3	10.92 (4.19–28.46)***	5.83 (3.28–10.37)***	8.77 (3.06–25.14)***	4.77 (2.61–8.73)***
≥20% improvement in MADRS Total score at Week 3	9.20 (4.19–20.21)***	5.82 (3.37–10.04)***	7.90 (3.27–19.06)***	5.28 (2.95–9.45)***
≥25% improvement in MADRS Total score at Week 3	8.57 (4.46–16.49)***	4.99 (2.99–8.34)***	6.96 (3.40–14.23)***	5.14 (2.97–8.92)***
≥30% improvement in MADRS Total score at Week 3	7.31 (4.06–13.19)***	4.49 (2.74–7.36)***	6.48 (3.38–12.41)***	4.72 (2.80–7.94)***

*$p < 0.05$; ***$p < 0.001$; †$p = 0.07$.

(at all cut-offs, i.e. ≥15%, ≥20%, ≥25%, ≥30%) was a significant potential predictor of remission, in both the aripiprazole and placebo groups. There was also a significant potential predictive value of MADRS baseline severity predicting remission in the placebo group ($p = 0.02$) and a trend in the aripiprazole group ($p = 0.07$). Multivariate regression did not identify any potential interactions between baseline weight, baseline MADRS or number of previous mood episodes.

Predictive Value by Endpoint Dose

The mean aripiprazole dose at endpoint across the two studies was 17.8 mg/day. The mean (SD) dose at Week 2 was 13.1 (3.9) mg/day and at Week 3 was 15.4 (4.8) mg/day. The PPV of early—Week 2—improvement was seen consistently with the 5, 10, and 15 mg/day endpoint doses. Higher doses (20, 25, and 30 mg/day) showed a lower PPV than lower doses (5, 10, or 15 mg/day). Among early improvers, as defined at Week 2, the mean (SD) dose of aripiprazole was 12.7 (4.2) mg/day at Week 2 and 16.3 (7.8) mg/day at Week 8. Among Week 2 non-improvers, the mean (SD) dose of aripiprazole was 13.8 (3.2) mg/day at Week 2 and 22.5 (7.3) mg/day at Week 8. Among Week 3 early improvers, the mean (SD) dose of aripiprazole was 15.0 (4.8) mg/day at Week 3 and 16.6 (7.6) mg/day at Week 8. The non-improvers at Week 3 had a mean (SD) aripiprazole dose of 16.4 (4.1) mg/day at Week 3 and 23.6 (7.2) mg/day at Week 8.

DISCUSSION

In this *post-hoc*, pooled analysis of two 8-week aripiprazole bipolar I depression studies, we have evaluated, for the first time, the clinical utility associated with the observation of early improvement (as defined by a 20% decrease in symptom severity) as a predictor of later response and remission during the short-term treatment of bipolar I depression. The findings of these analyses showed that high rates of early improvement in depressive symptoms occurred in a majority of patients as early as Week 2 in both treatment arms (aripiprazole 66%; placebo 51%). In addition, early improvement at Week 3 was also a highly sensitive predictor of response and remission, not only for aripiprazole (94%/94%), but also for placebo (83%/84%). However, rates of false positives for predicting response and remission were unacceptably high for both treatment arms, even at Week 3 (aripiprazole 63%/67%; placebo 45%/50%). Accordingly, PPVs were only slightly increased above the likelihood of chance (aripiprazole 60%/51%;

placebo 56%/45%), suggesting a low level of confidence in knowing that early improvement was going to be a predictor of later response or remission. On the other hand, NPVs were high (aripiprazole 88%/91%, placebo 79%/84%), suggesting a fairly high degree of confidence in knowing that the absence of early improvement was going to predict reliably the absence of later response and remission. Consistent with high NPVs, rates of false negatives of later response and remission were correspondingly low for both aripiprazole (6%/6%) and placebo (17%/16%).

The high sensitivity of early improvement indicates that later response and remission is almost always preceded by improvement at Week 3. Thus, early improvement may be thought of as a prerequisite for experiencing a successful outcome. For the first time, these findings also suggest that the absence of improvement at 3 weeks may represent a very useful clinical predictor of later outcome. For both aripiprazole and placebo, non-improvement at 3 weeks reliably predicts a low likelihood of later response and remission. If replicated by other studies that extend these findings beyond 8 weeks, the data suggest that clinicians should discontinue or modify treatment with aripiprazole (e.g. target a lower dose of aripiprazole) after 21 days and not needlessly continue use of what will likely be an ineffective treatment.

Evaluation of a range of criteria for the definition of early improvement showed that Week 3, and possibly even Week 2, is an adequate time point to identify early improvers/non-improvers, using a cut-off for the reduction in MADRS Total score of ≥20%. Assessment across a range of timepoints suggests that Week 1 may be too early to make a decision about future response/remission. Evaluation of a range of cut-offs for defining early improvement on the MADRS showed that a ≥20% reduction in MADRS Total score seems to provide the best balance of sensitivity and specificity while optimizing the NPV for later response/remission. Pragmatically, the predictive value of early improvement at Week 3 using the ≥20% reduction in MADRS Total score seems to provide a clinically valuable tool for identifying those patients who are significantly more likely or less likely to benefit from continued treatment. Other authors have also reported a minimum cut-off of ≥20% improvement in depression severity to be a useful threshold because it represents a clinically meaningful change in the patient's symptom status, can be reliably assessed, and exceeds the magnitude of change attributed to inter-rater variability.[9]

Higher doses of aripiprazole showed less congruity with the overall population in the predictors of sensitivity and PPV, whereas lower doses showed less congruity in the predictors of specificity and NPV. Unsurprisingly, there was a notable increase in aripiprazole dosing

among patients who were non-improvers at Week 2 or 3, as the clinician likely sought to raise the dose of blinded medication in order to elicit a positive treatment response. Early improvers at Week 2 or 3 did not show this increase in dosing later in the study. It should be noted that *post-hoc* analyses from this dataset intended to elucidate appropriate dosing in this population have suggested that lower doses (5–10 mg/day) of aripiprazole among patients with higher depressive symptom severity can provide efficacy separation from placebo.[23] Likewise, aripiprazole administration in the lower dose range of 2–15 mg/day was found to be efficacious for the adjunctive treatment of unipolar major depressive episodes among patients incompletely responsive to a standard antidepressant.[24–26]

Several distinctions have emerged in the predictability profiles of early improvement across psychiatric disorders and phases of bipolar illness. First, Szegedi et al. have identified that, in unipolar major depression, the optimal time course for detecting improvement appears to be after the first 2 weeks of treatment.[8,9] In contrast, a better balance of predictability in bipolar depression is obtained when assessing early improvement with aripiprazole after 3 weeks. Second, the clinical value of early improvement was primarily limited to the domains of sensitivity and NPV, similar to findings in major depression and schizophrenia.[27,28] Thus far, only in the disease state of bipolar mania has early improvement (≥25% reduction in the Young Mania Rating Scale at Week 1) been associated with a clinically useful PPV in conjunction with a high sensitivity and NPV.[29] In that study involving treatment with olanzapine or risperidone, more than 70% of patients experiencing early improvement went on to achieve response (≥50% reduction in YMRS Total score) after 3 weeks of atypical antipsychotic therapy. In the present analysis, the PPV had limited clinical utility, correctly predicting response and remission only 56% and 45% of the time, respectively. In addition to assessing early improvement in overall manic symptoms according to the YMRS, Ketter et al. have recently identified that rapid improvement in psychotic symptoms at Day 4 can also serve as a sensitive predictor of subsequent remission from an acute manic/mixed episode.[30]

Apart from early improvement, several other clinical variables were analyzed as predictors of response/remission; however, there was insufficient evidence that any of these potential predictors appeared to be associated with endpoint outcome. Antidepressant medication efficacy often differs as a function of baseline depression severity, although findings are mixed, with some studies showing a higher burden of depressive symptoms to predict improved response to drug treatment.[31,32]

As a *post-hoc* analysis, there are limitations associated with these findings. One criticism of the data may be the lack of separation between aripiprazole and placebo seen on the primary endpoint (change in MADRS Total score) in the original studies.[22] However, a sufficient proportion of patients in the aripiprazole versus placebo arm of each study had shown response (Study 1, 43.2% vs. 39.0%; Study 2, 44.6% vs. 44.3%) or remission (Study 1, 30.2% vs. 27.8%; Study 2, 25.7% vs. 29.0%) at endpoint. The timecourse (Figure 1) of improvement (≥20% reduction in MADRS Total score), as shown in the analyses presented herein, shows that aripiprazole provided symptom improvement in a significantly higher proportion of patients at every timepoint through Week 6 compared with placebo. As a majority of patients in the aripiprazole treatment arm had shown improvement by Week 2, it was deemed clinically appropriate to explore the predictive value of this improvement for later response/remission. Other limitations include the lack of outcomes among patients with bipolar II disorder, comorbid anxiety disorders, or psychotic features. The relatively short period of assessment (i.e. 8 weeks) also limits any inferences that can be drawn regarding long-term outcomes. Evaluating the value of early improvement to predict sustained remission or recovery over several months appears warranted.

The results of these analyses using an atypical antipsychotic are consistent with previous findings for traditional antidepressant agents evaluated in both randomized controlled trials and naturalistic samples.[8–13,33] Similar to antidepressant studies, the results indicate that if patients are not showing improvement after 2 or 3 weeks, there is little chance of response or remission by study endpoint. Similar findings of high sensitivity and NPV as characteristics of early improvement have also been reported for lamotrigine, olanzapine–fluoxetine combination, and quetiapine when prescribed for bipolar depression.[34] It is not known whether switching those patients who do not experience early improvement to a different therapeutic agent would improve outcomes in bipolar disorder. In patients with schizophrenia, a prospective, double-blind study recently showed that switching risperidone early non-improvers to olanzapine after 2 weeks of treatment was associated with greater symptom improvement than remaining on risperidone for an additional 10 weeks.[35] If switching pharmacologic agents early in the course of treatment was also found to be beneficial for early non-improvers with bipolar depression, a substantial shift in clinical practice may ensue, as expert consensus guidelines for bipolar depression typically recommend optimizing the initial treatment over several weeks prior to determining that a patient is not responding adequately.[36,37] Interestingly, the tendency for non-responders to plateau in

their degree of symptom improvement within the first 2–3 weeks has also been used in support of shortening clinical trials of new antidepressants from 6–8 weeks to 3 weeks.[38]

CONCLUSIONS

These data, in patients treated with aripiprazole, suggest that clinical decision-making to optimize the treatment course in bipolar I depression may be appropriate after as little as 2 weeks and certainly within the first 3 weeks of treatment. The presence of early improvement does not appear to be a reliable predictor of clinical outcome. Conversely, the absence of early improvement reliably predicts the lack of response and remission after 8 weeks of treatment. In patients without >20% improvement after 21 days of aripiprazole monotherapy, the findings suggest that treatment should be modified as continued use is unlikely to result in response or remission. ✤

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Previous Presentation

Part of these data have been presented previously in poster format at American Psychiatric Association, 3–8 May 2008, Washington, DC, and the 48th Annual Meeting of the New Clinical Drug Evaluation Unit, 27–30 May 2008, Phoenix, AZ.

Conflict of Interest Disclosure

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