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ORIGINAL RESEARCH

Key Words: aripiprazole, bipolar disorder, antipsychotic agents, psychopharmacology, remission induction

Criteria for Defining Symptomatic and Sustained Remission in Bipolar I Disorder: a *Post-Hoc* Analysis of a 26-Week Aripiprazole Study (Study CN138-010)

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ABSTRACT *~* ***Objective:*** *Remission is a key goal after treating an acute episode of bipolar I disorder, but greater understanding is needed of the correlation between attaining remission at a specific time point and maintaining sustained remission. This post-hoc analysis assessed symptomatic point remission and sustained remission according to either a standard criterion (YMRS ≤ 12) or a set of more rigorous criteria (YMRS ≤ 7, MADRS ≤ 10, and CGI-I = 1) using data from a 26-week, randomized, double-blind, placebo-controlled study with the atypical antipsychotic aripiprazole in patients with bipolar I disorder.* ***Methods:*** *Following ≥ 6 consecutive weeks' stabilization with open-label aripiprazole, 161 patients were randomized (1:1) to aripiprazole or placebo for up to 26 weeks. Symptomatic remission rates were determined at Weeks 8, 16, and 26; sustained remission rates were determined at each visit up until Weeks 8, 16, and 26, including a requirement to maintain remission for ≥ 8 consecutive weeks (frequency counts, LOCF analysis).* ***Results:*** *Compared with the standard criterion (YMRS ≤ 12), symptomatic and sustained remission criteria were fulfilled at a lower rate at all time points when defined with YMRS ≤ 7, and lower still with additional MADRS ≤ 10*

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and CGI-I = 1 criteria. In aripiprazole-treated patients, symptomatic remission rates were consistent at Weeks 8, 16, and 26; sustained remission rates at Week 8 were retained at Weeks 16 and 26. ***Conclusions:*** *When discerning an operational definition of remission in patients with a recent manic or mixed episode, the YMRS ≤ 7 criterion and sustaining this criterion for ≥ 8 weeks can be a useful clinical or research tool for assessing clinical recovery.* Psychopharmacology Bulletin. *2008;41(2):12-23.*

INTRODUCTION

Bipolar I disorder is a lifelong episodic illness that is characterized by manic or depressive episodes followed by symptom-free periods. Remission is a key goal after treating an acute episode of bipolar I disorder; however, there are no established definitions to measure clinical recovery, and recurrence occurs frequently in this patient population.

Further understanding is needed for the correlation between attaining remission at a specific time point and maintaining sustained remission during treatment. The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) examined time to recurrence of mania, hypomania, mixed state, or a depressive episode in subjects who were symptomatic at study entry but subsequently achieved recovery (≤ 2 syndromal features of mania, hypomania, or depression for ≥ 8 weeks, consistent with standard DSM-IV criteria for partial or full remission) and determined that recurrence was frequent and associated with the presence of residual mood symptoms at initial recovery.[1] Of 1,469 participants who were symptomatic at study entry, 858 (58.4%) subsequently achieved recovery.[1] During up to 2 years of follow-up, 416 (48.5%) of these individuals experienced recurrences.[1]

The focus appears to be moving towards increasingly stringent definitions of remission,[2] with some incorporating criteria that require low scores on mood scales for both the total scores and scores for specific items.[3] A study with olanzapine therapy operationally defined symptomatic remission in patients with bipolar I disorder using a combination of rating scales, including the Young Mania Rating Scale (YMRS) (score ≤ 7), the Hamilton-Depression Rating Scale (HAM-D) (score ≤ 7), and the Clinical Global Impression Bipolar Version (CGI-BP) (score ≤ 2).[2] Clinical recovery was defined as meeting the same criteria for ≥ 8 weeks.[2] That open-label study showed that clinically meaningful symptomatic remission was achieved slowly and maintained for ≥ 8 weeks by only a few patients within an average of 7 months of continuous treatment.[2]

The atypical antipsychotic aripiprazole, a dual dopamine/serotonin partial agonist, is indicated for maintenance treatment of patients with bipolar I disorder who have experienced a recent manic or mixed

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episode. The safety and efficacy of aripiprazole have been demonstrated in both short- and longer-term studies in patients with bipolar I mania.[4–6] In a 26-week relapse prevention study, in which patients with bipolar I disorder (manic or mixed) were stabilized for 6 weeks on open-label aripiprazole and then randomized in a double-blind manner to either aripiprazole or placebo, aripiprazole was superior to placebo in delaying the time to relapse.[7]

Here, we present data from a *post-hoc* analysis of that long-term study[7] to assess rates of both symptomatic point remission and sustained remission according to either a standard criterion or a set of more rigorous criteria.

PATIENTS AND METHODS

Study Design

The current analysis to assess symptomatic point remission and sustained remission uses data from a previously reported 26-week, randomized, double-blind, parallel-group, placebo-controlled aripiprazole study in patients with bipolar I disorder (Study CN138-010).[7]

Details of the study methods and inclusion/exclusion criteria have been described previously.[7] Briefly, patients were eligible for entry if they had either recently completed a 3-week, placebo-controlled acute mania study of aripiprazole, if they met eligibility criteria for an acute mania study but had declined participation, or if they had experienced a manic or mixed episode requiring hospitalization and treatment within the previous 3 months. All psychotropic medications, except lorazepam and anticholinergic agents, were discontinued prior to enrollment.

Eligible patients entered a stabilization phase, in which they received open-label aripiprazole, initially 30 mg/day, administered orally, once daily, at approximately the same time each day. Dose decrease to 15 mg/day was permitted at any time, depending on tolerability. Patients were defined as stabilized on open-label aripiprazole if they met the following criteria: YMRS Total score $\leq$ 10 and a Montgomery–Åsberg Depression Rating Scale (MADRS) Total score $\leq$ 13 during four consecutive visits over a minimum of 6 weeks.

Stabilized patients were eligible for double-blind treatment. Those entering the double-blind phase were randomized (1:1) to either continue the dose of aripiprazole they were taking at the end of stabilization or to receive placebo for 26 weeks. On the basis of the investigator's assessment of therapeutic effect and tolerability, the aripiprazole dose could be increased to 30 mg/day or decreased to 15 mg/day at any time.

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The results of the 26-week, double-blind phase have been reported elsewhere.[7]

All study sites received prior institutional review board/institutional ethics committee approval before study initiation and all patients provided written informed consent.

Efficacy Measures and Analyses

The current analysis assessed symptomatic point remission and sustained remission according to either standard criteria (YMRS Total score ≤ 12) or more rigorous criteria (YMRS Total score ≤ 7, MADRS Total score ≤ 10 and CGI-BP – Improvement [CGI-I] score = 1).

Symptomatic point remission rates were determined at Weeks 8, 16, and 26 (frequency counts, last observation carried forward [LOCF] analysis). Sustained remission rates were determined at each visit up until Weeks 8, 16, and 26 based on the same criteria, but included the requirement of maintaining remission for ≥ 8 consecutive weeks (frequency counts, LOCF analysis); patients had a maximum of six visits (four weekly and two bi-weekly) by Week 8, four bi-weekly visits between Week 8 and Week 16, and five bi-weekly visits between Week 16 and Week 26.

Frequency counts of relapse were evaluated for patients achieving symptomatic point remission according to both the standard criterion (YMRS Total score ≤ 12) and a more rigorous criterion (YMRS Total score ≤ 7) at Week 26 (LOCF). Relapse was defined as a discontinuation due to lack of efficacy during the 26-week, double-blind phase. The scope of this definition included all types of relapse (i.e., manic, mixed, depressive, or other).

Analyses were performed using SAS statistical software, version 6.12 or higher (SAS Institute Inc., Cary, NC).

RESULTS

Patient Disposition and Baseline Characteristics

Details of patient disposition and baseline characteristics and demographics have been reported previously.[7] Briefly, of the 567 patients who entered the stabilization phase, 206 completed stabilization, 161 entered the double-blind treatment phase (placebo, $n = 83$; aripiprazole, $n = 78$), and 67 patients completed the 26-week double-blind treatment phase (placebo, $n = 28$ [34%]; aripiprazole, $n = 39$ [50%]).

Overall, at baseline, patients had a mean ± standard deviation (SD) age of 39.6 ± 0.9 years, the majority were female (67%), most were White (65%), 17% were diagnosed as rapid-cycling, 70% of patients

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had a current episode of mania and 30% were experiencing a mixed episode.

Symptomatic Point Remission

The number and percentage of patients at Weeks 8, 16, and 26 (LOCF analysis) who achieved symptomatic point remission according to the standard criterion (YMRS Total ≤ 12) or the elements of the more rigorous criteria (YMRS Total ≤ 7, MADRS Total ≤ 10, and CGI-I = 1) are shown in Table 1.

Compared with the standard criterion, symptomatic remission criteria were fulfilled at a lower rate at all time points when remission was defined as a YMRS Total score ≤ 7, and lower still when the additional criteria of MADRS ≤ 10 and CGI-I = 1 were used (Table 1). Compared with placebo-treated patients, aripiprazole-treated patients tended to fulfill higher rates of symptomatic remission when using YMRS ≤ 7 (Table 1). The majority of patients (~80%) fulfilling the YMRS ≤ 7 criterion also fulfilled the MADRS ≤ 10 criterion (Table 1; Figure 1). Rates of symptomatic remission fulfilled at Week 8 were similar to rates fulfilled at Weeks 16 and 26 (Table 1; Figure 1).

TABLE 1

RATES OF SYMPTOMATIC REMISSION IN PATIENTS TREATED WITH ARIPIPRAZOLE OR PLACEBO FOR 26 WEEKS ACCORDING TO EITHER A STANDARD CRITERION (YMRS ≤ 12) OR MORE RIGOROUS CRITERIA (LAST OBSERVATION CARRIED FORWARD DATA)

CRITERIA FOR SYMPTOMATIC REMISSION	PLACEBO, n/N (%)	ARIPIPRAZOLE, n/N (%)
Week 8		
YMRS ≤ 12	70/81 (86)	66/77 (86)
YMRS ≤ 7	57/81 (70)	61/77 (79)
YMRS ≤ 7 + MADRS ≤ 10	45/81 (56)	48/77 (62)
YMRS ≤ 7 + MADRS ≤ 10 + CGI-I = 1	15/81 (18)	13/77 (17)
Week 16		
YMRS ≤ 12	62/81 (76)	66/77 (86)
YMRS ≤ 7	49/81 (61)	60/77 (78)
YMRS ≤ 7 + MADRS ≤ 10	37/81 (46)	46/77 (60)
YMRS ≤ 7 + MADRS ≤ 10 + CGI-I = 1	10/81 (12)	11/77 (14)
Week 26		
YMRS ≤ 12	57/81 (70)	66/77 (86)
YMRS ≤ 7	48/81 (59)	58/77 (75)
YMRS ≤ 7 + MADRS ≤ 10	36/81 (44)	43/77 (56)
YMRS ≤ 7 + MADRS ≤ 10 + CGI-I = 1	10/81 (12)	9/77 (12)

YMRS, Young Mania Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; CGI-I, Clinical Global Impression Bipolar Version – Improvement.

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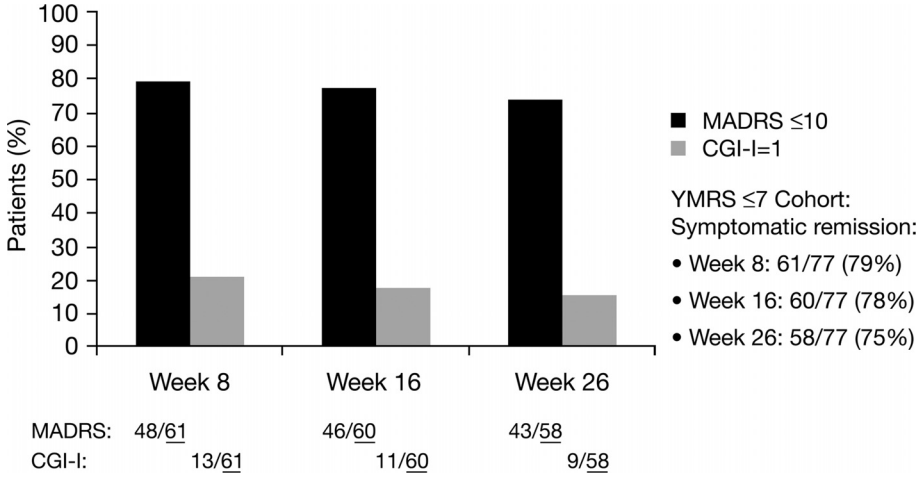
FIGURE 1

RATES OF SYMPTOMATIC REMISSION FOR ARIPIPRAZOLE-TREATED PATIENTS WHO ACHIEVED YMRS TOTAL SCORES ≤ 7 WHO ALSO ACHIEVED MADRS ≤ 10 OR MADRS ≤ 10 PLUS CGI-I = 1 (LAST OBSERVATION CARRIED FORWARD ANALYSIS). YMRS, YOUNG MANIA RATING SCALE; MADRS, MONTGOMERY–ÅSBERG DEPRESSION RATING SCALE; CGI-I, CLINICAL GLOBAL IMPRESSION BIPOLAR VERSION – IMPROVEMENT



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Sustained Remission Rates

The number and percentage of patients at Weeks 8, 16, and 26 (LOCF analysis) who fulfilled sustained remission (≥ 8 weeks; criteria achieved for all visits) according to the standard criterion (YMRS Total ≤ 12) or the elements of the more rigorous criteria (YMRS Total ≤ 7, MADRS Total ≤ 10 and CGI-I = 1) are shown in Table 2.

As with the symptomatic remission rates, when compared with the standard criterion, rates of sustained remission, in general, were lower at all time points when remission was defined as a YMRS Total score ≤ 7 (Table 2). Beyond Week 8, more aripiprazole-treated patients fulfilled sustained remission using the YMRS ≤ 7 criterion than placebo-treated patients. In the subgroup of aripiprazole-treated patients, rates of sustained remission according to the different criteria at Week 8 were retained at Weeks 16 and 26 (Table 2; Figures 2 and 3). Furthermore, the YMRS ≤ 7 criterion identified a large group of patients (~ 50–60%) also fulfilling the MADRS ≤ 10 criterion in the aripiprazole-treated subgroup (Table 2; Figures 2 and 3).

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TABLE 2

RATES OF SUSTAINED REMISSION (≥ 8 WEEKS) IN PATIENTS TREATED WITH ARIPIPRAZOLE OR PLACEBO FOR 26 WEEKS ACCORDING TO EITHER A STANDARD CRITERION (YMRS ≤ 12) OR MORE RIGOROUS CRITERIA (LAST OBSERVATION CARRIED FORWARD DATA)

CRITERIA FOR SUSTAINED REMISSION	PLACEBO, n/N (%)	ARIPIPRAZOLE, n/N (%)
Week 8		
YMRS ≤ 12	59/81 (73)	58/77 (75)
YMRS ≤ 7	47/81 (58)	44/77 (57)
YMRS ≤ 7 + MADRS ≤ 10	36/81 (44)	28/77 (36)
YMRS ≤ 7 + MADRS ≤ 10 + CGI-I = 1	8/81 (10)	5/77 (6)
Week 16		
YMRS ≤ 12	53/81 (65)	56/77 (73)
YMRS ≤ 7	39/81 (48)	42/77 (55)
YMRS ≤ 7 + MADRS ≤ 10	28/81 (35)	22/77 (29)
YMRS ≤ 7 + MADRS ≤ 10 + CGI-I = 1	5/81 (6)	2/77 (3)
Week 26		
YMRS ≤ 12	47/81 (58)	55/77 (71)
YMRS ≤ 7	34/81 (42)	41/77 (53)
YMRS ≤ 7 + MADRS ≤ 10	24/81 (30)	21/77 (27)
YMRS ≤ 7 + MADRS ≤ 10 + CGI-I = 1	4/81 (5)	2/77 (3)

YMRS, Young Mania Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; CGI-I, Clinical Global Impression Bipolar Version – Improvement.

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FIGURE 2

RATES OF SUSTAINED REMISSION FOR ARIPIPRAZOLE-TREATED PATIENTS WHO ACHIEVED YMRS TOTAL SCORES ≤ 7 WHO ALSO ACHIEVED MADRS ≤ 10 OR MADRS ≤ 10 PLUS CGI-I = 1 (LAST OBSERVATION CARRIED FORWARD ANALYSIS). YMRS, YOUNG MANIA RATING SCALE; MADRS, MONTGOMERY–ÅSBERG DEPRESSION RATING SCALE; CGI-I, CLINICAL GLOBAL IMPRESSION BIPOLAR VERSION – IMPROVEMENT

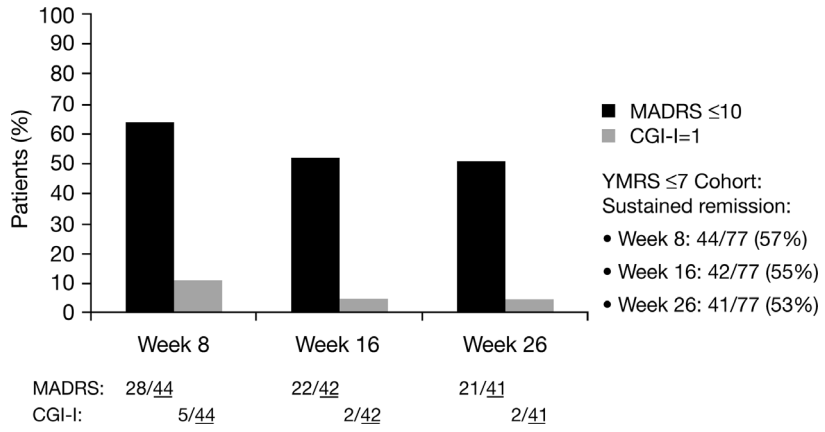

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FIGURE 3

ARIPIPRAZOLE-TREATED PATIENTS WITH SUSTAINED REMISSION AT WEEK 8 WHO MAINTAINED SIMILAR REMISSION CRITERIA AT ALL VISITS UP TO WEEKS 16 AND 26. YMRS, YOUNG MANIA RATING SCALE; MADRS, MONTGOMERY–ÅSBERG DEPRESSION RATING SCALE; CGI-I, CLINICAL GLOBAL IMPRESSION BIPOLAR VERSION – IMPROVEMENT

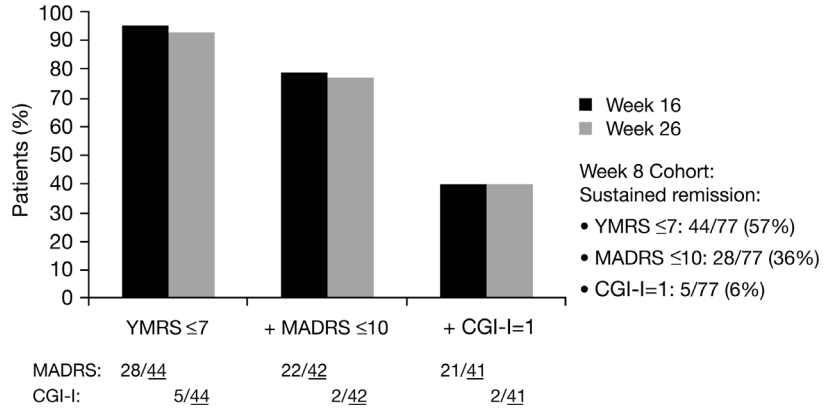

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TABLE 3

NUMBER OF RELAPSES OCCURRING IN PATIENTS TREATED WITH ARIPIPRAZOLE OR PLACEBO FOR 26 WEEKS ACCORDING TO WHETHER PATIENTS ACHIEVED YMRS SCORES ≤ 12 (STANDARD CRITERION) OR ≤ 7 (A MORE RIGOROUS CRITERION) (LAST OBSERVATION CARRIED FORWARD DATA)

	NUMBER OF RELAPSES	
	PLACEBO (*N* = 82)	ARIPIPRAZOLE (*N* = 76)
YMRS ≤ 12	15	9
YMRS > 12	21	10
YMRS ≤ 7	10	6
YMRS > 7	26	13

YMRS, Young Mania Rating Scale.

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Relapse

As shown in Table 3, the more rigorous YMRS criterion (≤ 7) was a more discriminative indicator of relapse than the standard YMRS criterion (≤ 12). Patients achieving YMRS ≤ 7 relapsed less frequently than those with YMRS scores > 7. In contrast, when the standard YMRS criterion was considered, there was little or no difference in either the aripiprazole or placebo groups in the frequency of relapse with patients achieving YMRS ≤ 12 versus those with YMRS scores > 12 (Table 3; LOCF data).

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DISCUSSION

The current analysis of a 26-week, randomized, double-blind, placebo-controlled aripiprazole study assessed rates of fulfillment of criteria for symptomatic point remission and sustained remission according to standard or more rigorous criteria to consider clinically meaningful definitions of remission and recovery in patients with bipolar I disorder.

When more rigorous criteria were used to define either symptomatic or sustained remission, fewer patients with bipolar I disorder met the criteria. In general, using the more rigorous YMRS $\leq$ 7 criterion yielded slightly lower frequency rates than with the YMRS $\leq$ 12 criterion, and additional criteria (MADRS and CGI-I) yielded frequency rates that were lower than using a single rating scale (YMRS). The CGI-I = 1 criterion selected for a very small population in remission, and perhaps a different patient population than those who fulfilled criteria for YMRS $\leq$ 7 plus MADRS $\leq$ 10. The CGI-I criterion does not help to distinguish between active treatment and placebo. As there were, in general, more aripiprazole-treated patients in this population with a recent manic/mixed episode fulfilling the YMRS $\leq$ 7 criterion, comparison of the YMRS $\leq$ 7 and YMRS $\leq$ 12 criteria helped to distinguish between active treatment and placebo early in the course of symptomatic remission, and also later in the course for sustained remission criteria. Sustained remission for $\geq$ 8 weeks appeared to be a good predictor for continued remission, as demonstrated by high retention rates of sustained remission at Weeks 16 and 26 in aripiprazole-treated patients with either standard or more rigorous criteria. The more rigorous YMRS $\leq$ 7 criterion was also a more selective indicator of the risk of relapse, whereby fewer patients with YMRS scores $\leq$ 7 relapsed versus those with YMRS scores $>$ 7 – in comparison there was little difference in the frequency of relapse rates in patients with YMRS $\leq$ 12 versus YMRS $>$12.

In this study, patients treated with both aripiprazole and placebo monotherapy had been stabilized (YMRS $\leq$ 10 and MADRS $\leq$ 13) for at least 6 weeks on open-label aripiprazole prior to entering the double-blind phase of the study, and baseline YMRS scores were 2.6 and 2.1, respectively.[7] Thus, any patient maintaining remission criteria during double-blind treatment with aripiprazole or placebo is reflective of the initial efficacy of aripiprazole during the stabilization phase. The average time needed to achieve stability prior to randomization into the double-blind relapse prevention phase was 13 weeks.[7] Rates of symptomatic point remission were generally higher with aripiprazole versus placebo, with the exception of YMRS $\leq$ 12 at Week 8 and the most rigorous criteria (YMRS $\leq$ 7 + MADRS $\leq$ 10 + CGI-I = 1) at each time point. Rates of sustained remission were generally similar with

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aripiprazole versus placebo, and the sustained efficacy with aripiprazole treatment was demonstrated by the high percentage of patients who maintained similar remission criteria at all visits up to Weeks 16 and 26 as those observed at all visits up to Week 8 (Figure 3).

The use of more rigorous criteria for remission (inclusive of a time component such as ≥ 8 consecutive weeks) identified a selective population of remitters in both the placebo and aripiprazole treatment groups. The more rigorous remission criteria may identify a patient who is truly in remission and not as susceptible to mood lability. Thus, when investigating new treatments for bipolar disorder, these more rigorous criteria may be more useful in operationally defining and assessing remission in clinical trials compared with the standard criterion.

The current data confirm previous findings[2] that sustaining remission is difficult owing to fluctuation in symptomatic stability during the course of treatment. That prior open-label study operationally defined symptomatic remission in patients with bipolar I disorder as YMRS ≤ 7, HAM-D ≤ 7, and CGI-BP ≤ 2, defining clinical recovery as meeting those criteria for ≥ 8 weeks.[2] Clinically meaningful symptomatic remission was achieved slowly and maintained for ≥ 8 weeks by only a few patients within an average of 7 months of continuous treatment.[2] In total, 113 patients participated in an open-label extension phase, receiving olanzapine for 1 year. Of those 113 patients, 79 (70%) achieved symptomatic remission and 40 (35%) sustained remission to achieve clinical recovery, with a median time to clinical recovery of 38 weeks.[2]

With respect to other recent studies to define remission, a pooled analysis of two 12-week, randomized, double-blind studies with quetiapine in patients with acute bipolar mania used five criteria to define remission/euthymia and determine efficacy: (i) YMRS ≤ 12; (ii) YMRS ≤ 12 and MADRS ≤ 10; (iii) YMRS ≤ 12 and MADRS ≤ 8; (iv) YMRS ≤ 8; and (v) YMRS ≤ 8 plus a score ≤ 2 for the YMRS core items of Irritability, Speech, Content, and Disruptive/Aggressive Behavior.[3] In that study, remission rates were higher at Week 3 and Week 12 with quetiapine versus placebo for most criteria (except YMRS ≤ 8 plus ≤ 2 on core items criterion at Week 3), with a slightly lower rate of remission with more stringent criteria compared with the standard YMRS ≤ 12 criterion.[3] The Bipolar Working Group recently developed consensus operational definitions of response, remission, relapse and recurrence based on time points when a treatment decision needed to be made.[8] That Group defined remission as absence or minimal symptoms of both mania and depression for at least 1 week, with sustained remission requiring at least 8 (and perhaps as many as 12) consecutive weeks of remission.[8]

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It should be noted that owing to the aripiprazole stabilization phase prior to randomization in the current study, an enriched population continued into the double-blind monotherapy phase; thus, the results for both placebo and aripiprazole are reflective of those patients who were not acutely manic, but responded and were stabilized on aripiprazole following a recent manic or mixed episode. The study is also limited by the *post-hoc* nature of the analyses and by the use of a depression rating scale (MADRS) in the more rigorous remission criteria in a population of patients with mania as the index episode.

CONCLUSION

In conclusion, the use of more rigorous criteria to define symptomatic or sustained remission selects for fewer patients with bipolar I disorder and may be more useful in assessing remission in clinical trials compared with the standard criterion. These data confirm that sustaining remission is challenging and there is fluctuation in symptomatic stability in the bipolar population. Sustained remission for ≥ 8 weeks appears to be a good predictor for continued remission, as shown by the high retention rate of sustained remission at Weeks 16 and 26 in aripiprazole-treated patients with bipolar I disorder using either standard or more rigorous criteria. The more rigorous YMRS criterion of ≤ 7 also appears to be a more discriminative indicator for the potential to relapse than the standard criterion (YMRS ≤ 12). When discerning an operational definition of remission in patients with a recent manic or mixed episode, the YMRS ≤ 7 criterion and sustaining this criterion for ≥ 8 weeks can be a useful clinical or research tool for assessing clinical recovery. ✤

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CONFLICT OF INTEREST

Prakash S. Masand, Consultant for Bristol-Myers Squibb, Eli Lilly and Company, I3CME, and Janssen Pharmaceutica; Speaker's Bureau for Bristol-Myers Squibb, GlaxoSmithKline, Janssen Pharmaceutica, Pfizer Inc., and Eli Lilly and Company; James Eudicone, Employee of Bristol-Myers Squibb; Andrei Pikalov, Employee of Otsuka America Pharmaceutical, Inc.; Robert D. McQuade, Employee of Otsuka Pharmaceutical Development & Commercialization, Inc.; Ronald N. Marcus, Employee of Bristol-Myers Squibb; Estelle

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REFERENCES

1. Perlis RH, Ostacher MJ, Patel JK, Marangell LB, Zhang H, Wisniewski SR, et al. Predictors of recurrence in bipolar disorder: primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Am J Psychiatry*. 2006;163:217-224.
2. Chengappa KNR, Hennen J, Baldessarini RJ, Kupfer DJ, Yatham LN, Gershon S, et al. Recovery and functional outcomes following olanzapine treatment for bipolar I mania. *Bipolar Disord*. 2005;7:68-76.
3. Ketter TA, Jones M, Paulsson B. Rates of remission/euthymia with quetiapine monotherapy compared with placebo in patients with acute mania. *J Affect Disord*. 2007;100(Supp 1):S45-S53.
4. Keck PE, Jr, Marcus R, Tourkodimitris S, Ali M, Liebeskind A, Saha A, et al. A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania. *Am J Psychiatry*. 2003;160:1651-1658.
5. Sachs G, Sanchez R, Marcus R, Stock E, McQuade R, Carson W, et al. Aripiprazole in the treatment of acute manic or mixed episodes in patients with bipolar I disorder: a 3-week placebo-controlled study. *J Psychopharmacol*. 2006;20:536-546.
6. Vieta E, Bourin M, Sanchez R, Marcus R, Stock E, McQuade RD, et al. Effectiveness of aripiprazole v. haloperidol in acute bipolar mania: Double-blind, randomised, comparative 12-week trial. *Br J Psychiatry*. 2005;187:235-242.
7. Keck PE, Calabrese JR, McQuade RD, Carson WH, Carlson BX, Rollin LM, et al. A Randomized, double-blind, placebo-controlled 26-Week trial of aripiprazole in recently manic patients with bipolar I disorder. *J Clin Psychiatry*. 2006;67:626-637.
8. Hirschfeld R, Calabrese J, Frye M, Lavori P, Sachs G, Thase M, et al. Defining the clinical course of bipolar relapse, recurrence and roughening. *Psychopharmacol Bull*. 2007;40:7-14.