Early Improvement of Specific Symptoms Predicts Subsequent Recovery in Bipolar Depression: Reanalysis of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) Data

Jin Mizushima, MD[a,b]; Hiroyuki Uchida, MD, PhD[a,c]; Mitsuhiro Tada, MD, PhD[a,d]; Takefumi Suzuki, MD, PhD[a,e]; Masaru Mimura, MD, PhD[a]; and Shintaro Nio, MD, PhD[a,d,*]

ABSTRACT

Objective: The aim of this post hoc analysis was to evaluate which specific depressive items could predict subsequent durable recovery in patients with bipolar depression.

Methods: The study population was at least 18 years old and met *DSM-IV* criteria for a major depressive episode associated with either bipolar I or II disorder. The data were derived from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), in which patients with bipolar depression were randomly assigned to treatment for acute depression with a mood stabilizer plus an adjunctive antidepressant drug or placebo. The primary and secondary outcomes were durable recovery (ie, 8 consecutive weeks of euthymia) and treatment-emergent affective switch (ie, transition to mania or hypomania), respectively. Binary logistic regression analysis was performed to identify specific symptoms whose improvement during the first 2 weeks predicted those outcomes; the score change of each individual symptom in the continuous symptom subscales for depression (SUM-D) from week 0 to week 2 was used as an independent variable.

Results: In the evaluable 188 participants who took placebo and active drugs, the improvement in loss of self-esteem ($P = .037$) or loss of energy ($P = .040$) at week 2 was significantly associated with higher chances of subsequent durable recovery. For participants taking active drugs (n = 91), solely the improvement in loss of energy at week 2 was significantly associated with subsequent durable recovery ($P = .027$). There was a significant association between the improvement of psychomotor retardation at week 2 and subsequent affective switch ($P = .008$).

Conclusions: These findings imply that focusing on individual symptoms is important in bipolar depression, rather than relying solely on a summed score in rating scales.

Trial Registration: The original STEP-BD dataset is registered on ClinicalTrials.gov (identifier: NCT00012558).

J Clin Psychiatry 2017;78(2):e146–e151
https://doi.org/10.4088/JCP.15m10573

[a]Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan
[b]Department of Psychiatry, Tachikawa Hospital, Tokyo, Japan
[c]Geriatric Psychiatry Division, Centre for Addiction and Mental Health, Toronto, Ontario, Canada
[d]Department of Psychiatry, Saiseikai Central Hospital, Tokyo, Japan
[e]Department of Psychiatry, Inokashira Hospital, Tokyo, Japan
**Corresponding author:* Shintaro Nio, MD, PhD, Department of Psychiatry, Saiseikai Central Hospital, 1-4-17 Mita, Minato-ku, Tokyo 108-0073 Japan (shin@dd.catv.ne.jp).

Bipolar disorder is a chronic, recurrent condition with negative impact on quality of life. Its lifetime prevalence is reported to be just under 4%,[1] yet it is the sixth-leading cause of disability and its annual cost exceeds those of diabetes and recurrent major depressive disorder.[2] Moreover, patients with bipolar depression exhibit lower quality of life and higher probability of being suicidal compared with those in manic or hypomanic episodes.[3,4] Although some effective treatments for acute mania are available (for example, lithium, anticonvulsant or antipsychotic monotherapy, or their combination[5–7]), the treatment for bipolar depression still remains a significant challenge. In fact, bipolar depression is considered to be more refractory than unipolar depression, with a less favorable treatment response, and represents a significant risk factor for treatment-emergent affective switch.[8–10]

Predicting the prognosis in an early phase of a certain treatment is also crucial for people with bipolar depression since depressive symptoms are found to occur 3 times more frequently than manic episodes[11–14] and more negatively affect the quality of life compared to manic or hypomanic episodes.[4] Total score reductions in assessment scales such as the Hamilton Depression Rating Scale (HDRS) in early weeks predict subsequent treatment outcomes for unipolar depression.[15,16] Furthermore, as for unipolar depression, some certain core depressive symptoms have been identified to serve as predictors of subsequent remission.[17] On the other hand, it remains unclear regarding the contribution of each individual symptom to the subsequent outcome in bipolar depression.

To our knowledge, no report has investigated whether improvements in certain depressive symptoms can predict subsequent durable recovery in bipolar depression. The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) is the largest trial for bipolar disorder, with a sample size of over 5,000, which provides an ideal dataset to address such a clinical question (see Additional Information footnote in the article endmatter section). The objective of this reanalysis was to identify specific symptoms whose improvement at week 2 could serve as a marker for subsequent durable recovery or affective switch, using the dataset of the STEP-BD.

METHODS

Study Design

The STEP-BD trial was funded by the National Institute of Mental Health to study treatment effectiveness, phenomenology, course, and outcome of participants with bipolar disorder in

Clinical Points

- Since bipolar depression negatively affects quality of life, early prediction of treatment outcome plays a significant role.
- Early improvement of loss of self-esteem or loss of energy was associated with subsequent durable recovery of bipolar depression.
- Early improvement of psychomotor retardation was associated with subsequent affective switch to mania.

the United States. Briefly, the STEP-BD trial included both naturalistic and randomized treatment; the present study focuses solely on participants in randomized treatment for bipolar depression. The original STEP-BD dataset is registered on ClinicalTrials.gov (identifier: NCT00012558). Participants who were receiving a mood-stabilizing agent (ie, lithium, valproate, lamotrigine, olanzapine, quetiapine, or aripiprazole) were randomly assigned to additional double-blind treatment, either an adjunctive antidepressant (ie, bupropion or paroxetine) or placebo with the use of an equipoise-stratified randomization method for up to 26 weeks.[18,19] This method enabled treating psychiatrists to choose 1 of 3 randomization strata (ie, placebo vs bupropion, placebo vs paroxetine, and placebo vs either antidepressant) based on participants' and psychiatrists' preferences. Following a complete description of the study, the participants provided written informed consent at study enrollment in the original study, and this post hoc analysis used the data that were made completely anonymous.

Study Population

Study participants were at least 18 years old and met the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*)[20] for a major depressive episode associated with either bipolar I or II disorder. The diagnosis of bipolar disorder was confirmed at entry into STEP-BD by using an affective disorder evaluation form adapted from the Structured Clinical Interview for *DSM-IV*[21] and by the independent administration of the Mini-International Neuropsychiatric Interview.[22] Patients were excluded if they showed unresponsiveness, intolerance, or contraindication in the past to both bupropion and paroxetine and met criteria for a mixed episode or hypomania at the study entry.

Assessment Measures

At study entry, participants were assessed with the Clinical Monitoring Form for mood disorders[23] and some formal rating scales, including the Clinical Global Impressions-Severity of Illness scale (CGI-S).[24] The CGI-S scores range from 1 to 7; higher scores represent a greater severity of illness. The Clinical Monitoring Form is a composite assessment tool developed for use in clinical practice; it includes current mood modules of the Structured Clinical Interview for *DSM-IV* that was modified to include continuous symptom subscales for depression (SUM-D) and mood elevation (SUM-ME). The SUM-D and SUM-ME total scores range from 0 to 22 and from 0 to 16, respectively; higher scores indicate a more severe symptomatology. Validity of the SUM-D and SUM-ME was confirmed by comparing them to formal rating scales such as the Montgomery-Asberg Depression Rating Scale[25] and the Young Mania Rating Scale,[26] respectively.[23] The Clinical Monitoring Form was administered at every follow-up visit. Only the data for the participants who achieved the durable recovery were used, and the scores in individual symptoms in the SUM-D at days 0 and 14 were extracted.

Outcomes

Durable recovery, which was defined as euthymia (ie, presence of no more than 2 depressive or 2 manic symptoms listed in the Clinical Monitoring Form for at least 8 consecutive weeks[19]), was adopted as the primary outcome in the present study. In addition, treatment-emergent affective switch (ie, *DSM-IV*–defined hypomania or mania, or clinically significant treatment-emergent mood elevation judged by treating clinicians in the course of treatment[19]) was adopted as the secondary outcome. The outcomes of interest in this analysis were consistent with those of the original randomized study in the STEP-BD.

Statistical Analysis

To evaluate associations between sociodemographic and clinical characteristics and treatment outcomes, a multivariate logistic regression model with forced entry was conducted after adjustment for antidepressant preference (none, bupropion, or paroxetine) and institution sites. This model contained sex, age, race, bipolar type (ie, bipolar I and II disorders), baseline CGI-S scores, and early score changes of SUM-D total scores (ie, the change of total scores in the SUM-D from baseline to week 2) as covariates. Logistic regression analysis was performed to evaluate associations between improvements in individual symptoms in the SUM-D at week 2 and durable recovery at the treatment exit or affective switch during the study period. In this analysis, the change of each individual symptom in the SUM-D from week 0 to week 2 was used as an independent variable. The analysis was performed for participants who took placebo and active drugs together, and a second analysis was performed solely for the participants who took active drugs only. A third analysis was performed solely for the participants who took placebo only. A P value $< .05$ was considered statistically significant (2-tailed). Statistical analyses were carried out with the SPSS Version 22 (SPSS Inc, Chicago).

RESULTS

Early Prediction of Durable Recovery

Sociodemographic and clinical characteristics of the study subjects (n = 188) who received assessments both at baseline and 2 weeks later are summarized in Table 1. Durable recovery was noted in 67 patients (35.6%). The binary logistic regression analysis showed that the lower CGI-S score at baseline ($P < .001$) and female sex ($P = .049$)

Table 1. Association Between Subsequent Durable Recovery and Baseline Characteristics, Including Early Score Changes of SUM-D Total Score

Characteristic	Odds Ratio	95% CI	*P* Value
Early score changes of SUM-D total score	1.007	0.976–1.038	.675
Antidepressant treatment option			.749
Paroxetine	1.109	0.344–3.582	.862
Bupropion	1.426	0.439–4.637	.555
Site			.476
Drug (reference = placebo)	0.581	0.272–1.241	.161
Age (unit = 1)	1.001	0.971–1.031	.963
Sex (reference group = male)	2.110	1.004–4.431	.049
Race (reference group = Caucasian/white)	3.185	0.838–12.108	.089
Bipolar type (reference group = bipolar I disorder)	0.646	0.277–1.506	.312
CGI-S at baseline	0.370	0.234–0.585	<.001

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, SUM-D = Clinical Monitoring Form symptom subscale for depression.

Table 2. Total and Individual Symptom Scores of SUM-D at Baseline, Week 2, and End Point

SUM-D	Baseline (n = 157)[a]	Week 2 (n = 158)[a]	End Point (n = 167)[a]
Total score	6.705 ± 2.88	5.25 ± 3.44	4.81 ± 3.97
Depressed mood	0.611 ± 0.77	0.517 ± 0.70	0.441 ± 0.66
Insomnia	0.757 ± 0.52	0.576 ± 0.56	0.570 ± 0.55
Loss of appetite	0.491 ± 0.49	0.382 ± 0.43	0.349 ± 0.46
Interests	0.862 ± 0.47	0.665 ± 0.52	0.573 ± 0.58
Loss of self-esteem	0.826 ± 0.47	0.628 ± 0.53	0.561 ± 0.55
Loss of energy	0.838 ± 0.46	0.691 ± 0.64	0.540 ± 0.56
Concentration	0.684 ± 0.50	0.551 ± 0.48	0.493 ± 0.54
Distractibility	0.460 ± 0.48	0.400 ± 0.47	0.392 ± 0.49
Feelings of guilt	0.448 ± 0.50	0.301 ± 0.45	0.283 ± 0.45
Psychomotor retardation	0.392 ± 0.46	0.237 ± 0.39	0.222 ± 0.40
Psychomotor agitation	0.243 ± 0.37	0.237 ± 0.41	0.239 ± 0.42
Suicidal ideations	0.193 ± 0.31	0.161 ± 0.30	0.198 ± 0.36

[a]Values are mean ± SD.
Abbreviations: SUM-D = Clinical Monitoring Form symptom subscale for depression.

Table 3. Association Between Subsequent Durable Recovery and Improvements at Week 2 of Individual Symptoms in the SUM-D Scores

	All Patients			Active Drug			Placebo		
Variable	Odds Ratio	95% CI	*P* Value	Odds Ratio	95% CI	*P* Value	Odds Ratio	95% CI	*P* Value
Depressed mood	0.956	0.843–1.085	.489	0.930	0.727–1.190	.566	0.907	0.756–1.089	.295
Insomnia	0.979	0.816–1.173	.815	0.863	0.638–1.167	.339	1.045	0.813–1.344	.730
Loss of appetite	1.066	0.856–1.326	.568	1.013	0.698–1.470	.945	1.072	0.777–1.480	.671
Interests	1.080	0.851–1.371	.525	1.032	0.691–1.540	.878	1.290	0.893–1.864	.174
Loss of self-esteem	1.284	1.016–1.624	.037[a]	1.357	0.918–2.007	.126	1.198	0.875–1.642	.259
Loss of energy	1.250	1.011–1.545	.040[a]	1.541	1.050–2.262	.027	1.128	0.836–1.522	.431
Concentration	0.882	0.691–1.126	.314	1.004	0.650–1.552	.985	0.776	0.543–1.110	.165
Distractibility	1.002	0.770–1.303	.990	0.835	0.539–1.294	.420	1.130	0.754–1.692	.554
Feelings of guilt	1.046	0.830–1.318	.704	1.049	0.694–1.585	.822	1.059	0.756–1.483	.740
Psychomotor retardation	0.889	0.691–1.145	.364	0.833	0.500–1.386	.482	0.914	0.656–1.275	.596
Psychomotor agitation	0.910	0.687–1.206	.513	0.786	0.484–1.275	.329	0.921	0.631–1.345	.670
Suicidal ideations	1.023	0.721–1.453	.897	1.145	0.540–2.427	.724	0.946	0.591–1.386	.820
CGI-S at baseline	0.263	0.148–0.468	.000	0.289	0.117–0.717	.007	0.212	0.085–0.528	.001
Sex	2.335	0.977–5.579	.056	2.629	0.573–12.067	.214	2.336	0.673–8.112	.182

[a]The result was significant after adjustment for baseline CGI-S and sex.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, SUM-D = Clinical Monitoring Form symptom subscale for depression.

were the factors associated with subsequent durable recovery, whereas antidepressant preference, bipolar type, race, age, and institution site failed to show any significant association. On the other hand, when we included actual antidepressant drugs taken instead of antidepressant preference in the model, there were no significant associations between any of these factors and treatment outcomes. In addition, the early score changes in SUM-D total scores at week 2 failed to show any significant association with the subsequent durable recovery.

The actual total and individual symptom scores of SUM-D at baseline, week 2, and end point are summarized in Table 2.

A significant association was confirmed between the improvement in loss of self-esteem or loss of energy at week 2 and greater chances of subsequent durable recovery after adjustment of the baseline CGI-S score and sex ($P = .037$ and $P = .040$, respectively) (Table 3). In the subgroup of participants receiving active drugs (n = 91), the improvement in loss of energy at week 2 was significantly associated with subsequent durable recovery after adjustment of the baseline CGI-S score and sex ($P = .027$) (Table 3). As for the participants taking placebo (n = 97), improvements in any of the individual symptoms at week 2 were not significantly associated with subsequent durable recovery after adjustment of the baseline CGI-S score and sex (Table 3).

Early Prediction of Affective Switch to Mania

Sociodemographic and clinical characteristics of the study subjects (n = 188) who received assessments at baseline and 2 weeks later are shown in Table 4. Affective switch was noted in 14 patients (7.4%). The binary logistic regression analysis found that there were no specific characteristics that were significantly associated with subsequent affective switch to mania.

A significant association between the improvement in psychomotor retardation at week 2 and subsequent affective switch was confirmed after adjustment of the baseline CGI-S score and sex ($P = .008$) (Table 5). In the subgroup of participants receiving active drugs or placebo, although

Table 4. Association Between Subsequent Affective Switch to Mania and Baseline Characteristics, Including Early Score Changes of SUM-D Total Score

Characteristic	Odds Ratio	95% CI	*P* Value
Early score changes of SUM-D total score	0.979	0.931–1.028	.393
Antidepressant treatment option			.368
Paroxetine	0.261	0.033–2.061	.203
Bupropion	0.614	0.090–4.195	.619
Site			.955
Drug (reference = active drug)	0.562	0.159–1.988	.372
Age (unit = 1)	0.966	0.917–1.018	.196
Sex (reference group = male)	1.864	0.516–6.734	.342
Race (reference group = Caucasian/white)	0.401	0.028–5.801	.502
Bipolar type (reference group = bipolar type 1)	0.392	0.083–1.857	.238
CGI-S at baseline	1.781	0.776–4.087	.173

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, SUM-D = Clinical Monitoring Form symptom subscale for depression.

Table 5. Association Between Subsequent Affective Switch to Mania and Improvements at Week 2 of Individual Symptoms in the SUM-D Scores, All Patients

SUM-D	Odds Ratio	95% CI	*P* Value
Depressed mood	1.007	0.817–1.241	.949
Insomnia	0.846	0.624–1.147	.282
Loss of appetite	1.140	0.813–1.601	.447
Interests	0.956	0.632–1.447	.831
Loss of self-esteem	0.986	0.668–1.455	.943
Loss of energy	0.975	0.709–1.341	.878
Concentration	0.960	0.668–1.379	.824
Distractibility	0.976	0.630–1.512	.913
Feelings of guilt	0.674	0.433–1.050	.081
Psychomotor retardation	1.664	1.139–2.430	.008[a]
Psychomotor agitation	1.186	0.832–1.691	.347
Suicidal ideations	0.920	0.531–1.596	.768

[a]The result was significant after adjustment for baseline CGI-S and sex.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, SUM-D = Clinical Monitoring Form symptom subscale for depression.

an affective switch was observed in 6 patients with active drugs (6.6%) and 8 patients with placebo (8.2%), there were no significant associations between any early improvements of individual symptoms and subsequent affective switch to mania in either of the 2 groups.

DISCUSSION

To the best of our knowledge, this study is the first to evaluate whether early improvements in individual symptoms serve as a marker for durable recovery in patients with bipolar depression, a difficult-to-treat condition. We found that the improvement in loss of self-esteem or loss of energy at week 2 was associated with subsequent durable recovery. Moreover, in a subgroup of participants receiving active drugs, the improvement in loss of energy at week 2 was significantly associated with subsequent durable recovery. We also revealed that the early improvement in psychomotor retardation at week 2 was associated with subsequent affective switch to mania.

Early Prediction of Durable Recovery

Sakurai et al[17] demonstrated that individual symptom trajectories over time serve as a marker for clinical response in unipolar depression. The study showed that the improvements at week 2 in negative self-view and low energy, which are the same symptoms found to be markers in our investigation, were associated with subsequent remission for unipolar depression. The predictors at week 2 found in the study also included sad mood, feeling down, and restlessness.

A time lag appears to exist between improvements in self-view such as self-esteem and perceptions of personal efficacy and those in other typical depressive symptoms at the beginning of treatment. A previous study[27] found that higher self-esteem was associated with more rapid response trajectory in the elderly depressed patients. On the other hand, once the classical depressive symptom improves, the patient would be expected to regain more neutral problem-solving abilities and social skills, which can lead to durable recovery. In addition, loss of energy, another relevant symptom, is synonymous with fatigue or tiredness. Fatigue is one of the symptoms that shows a slower response and is strongly associated with impaired work and social functioning.[28] A previous report[29] supported our findings; rapid relief from a fatigue symptom was essential to achieving remission in patients with depression.

Early Prediction of Affective Switch to Mania

Affective switch to mania or hypomania represents a serious challenge; a hesitancy to use antidepressants in bipolar depression may be a reflection of fear of iatrogenic mood change. As such, identification of risk factors for manic switch is of high clinical relevance. Whereas the SUM-D total score reductions during the first 2 weeks were not associated with subsequent affective switch, the early improvement of psychomotor retardation predicted such switch. Psychomotor retardation has been recognized as one of the most fundamental features of major depressive disorder and is reflected in various contemporary classification systems.[20,30] Interestingly, previous studies have shown that psychomotor retardation may provide prognostic information on response to antidepressant treatment. For example, Flament et al[31] found that the patients with major depression who presented with motor retardation responded less favorably to 6-week treatment with fluoxetine or sertraline compared to those who did not (n = 22). Similarly, other reports[32,33] found that retardation status at baseline had an influence on response to milnacipran. Thus, although this association between the presence of retardation at baseline and good response to antidepressant drugs has not always been a consistent observation in the literature,[32] this distinct symptom could be considered to have a unique role in the prediction of subsequent treatment response and treatment-emergent affective switch.

Only depressed mood and loss of interest or pleasure in nearly all activities are considered to be the essential requirement for the diagnosis of major depressive episode in the *DSM-IV*[20] as well as *DSM-5*.[34] Similarly, there are major

scales for the assessment of depressive symptomatology derived from HDRS: Bech-6,[35] Maier subscale,[36] and HDRS-7[37]; 4 common symptoms in those scales are mood, guilt, loss of interest, and psychiatric anxiety.[38] It is interesting that none of these 4 core symptoms, according to our investigation, was a useful predictor for subsequent recovery or treatment-emergent affective switch in bipolar depression. Our results emphasize the relevance of paying more attention to loss of self-esteem, loss of energy, and psychomotor retardation, which frequently receive less attention compared to more conventional symptoms in the real world.

Limitations

There are several limitations to be noted in this study. First, the STEP-BD trial was not originally designed to focus on individual symptom trajectories in bipolar depression; the present analysis is a post hoc exploratory examination. Second, our outcomes of interest in the present study were durable recovery and affective switch; they are clinically relevant end points but represent only a part of longitudinal management of this chronic illness. Moreover, durable recovery was defined as a period of at least 8 consecutive weeks of euthymia (ie, no more than 2 affective symptoms) in the original study. The present reanalysis adopted the same definition. Nonetheless, this never means that minor, less overt symptoms can be ignored in the treatment of bipolar patients. In fact, previous studies[39–41] have shown that residual or subthreshold mood symptoms are still of high clinical relevance and are indeed associated with substantial adverse consequences, namely, relapse or recurrence and hindrance to functional recovery in patients with bipolar disorder. Thus, the complete absence of affective symptoms for 8 consecutive weeks could have been more ideal as an indicator of durable recovery. The findings in this study should be carefully interpreted in such context. Third, given the number of rating scale items, the findings may simply reflect a random noise. We included all those items since this study focused on the trajectories of the 10 individual symptoms in the SUM-D instead of exploratively and arbitrarily selecting some specific symptom clusters. Still, we did not control for multiple comparisons, and a possibility of type I error cannot entirely be rejected. Finally, generalizability of our findings may be limited in light of the limited choice of antidepressant drugs in the STEP-BD trials (ie, paroxetine and bupropion). There is evidence showing that antidepressant drugs may somewhat differ in terms of both efficacy and tolerability in the treatment of unipolar depressive disorder.[42] Given these limitations, further investigations are clearly warranted to confirm those preliminary results we found in this analysis.

CONCLUSION

In conclusion, clinicians can predict subsequent durable recovery in bipolar depressed patients if they focus on early improvements in loss of energy or loss of self-esteem, whereas to predict subsequent affective switch to a manic or hypomanic state in these patients, they may need to pay more attention to the early improvement of psychomotor retardation. Early improvements of those specific depressive symptoms allow the clinician to potentially identify patients who will subsequently achieve durable recovery or to seek other treatment options for patients who are unlikely to show favorable outcomes with ongoing treatment of their bipolar depression. Although further studies are clearly needed, these findings point to the importance of evaluating individual symptoms in bipolar depression rather than blindly relying on a summed score in the representative rating scales.

Submitted: December 5, 2015; accepted June 22, 2016.

Drug names: aripiprazole (Abilify and others), bupropion (Wellbutrin and others), fluoxetine (Prozac and others), lamotrigine (Lamictal and others), milnacipran (Savella and others), olanzapine (Zyprexa and others), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel and others), sertraline (Zoloft and others).

Potential conflicts of interest: **Dr Mizushima** has received speaker's honoraria from Dainippon Sumitomo, Otsuka, Mochida, and Eli Lilly within the past 5 years. Within the past 3 years, **Dr Uchida** has received grants from Astellas, Dainippon-Sumitomo, Eisai, Eli Lilly, GlaxoSmithKline, Meiji-Seika, Mochida, Otsuka, Shionogi, and Yoshitomi Yakuhin; and has received speaker's honoraria from Abbvie, Dainippon-Sumitomo, Eli Lilly, GlaxoSmithKline, Janssen, Meiji-Seika, MSD, Otsuka, Shionogi, and Yoshitomi Yakuhin. **Dr Suzuki** has received manuscript fees or speaker's honoraria from Astellas, Dainippon Sumitomo, Eli Lilly, Elsevier Japan, Janssen, Meiji Seika, Novartis, Otsuka, and Wiley Japan within the past 5 years. **Dr Mimura** has received grants, consultant fees and/or speaker's honoraria from Asahi Kasei, Astellas, Daiichi Sankyo, Dainippon Sumitomo, Eisai, Eli Lilly, GlaxoSmithKline, Janssen, Meiji, Mochida, Novartis, Otsuka, Pfizer, Shionogi, and Yoshitomi Yakuhin within the past 3 years. Within the past 5 years, **Dr Nio** has received manuscript fees from Dainippon Sumitomo, Eli Lilly, and Yoshitomi Yakuhin; and has received speaker's honoraria from Astellas, Dainippon Sumitomo, Eisai, Eli Lilly, GlaxoSmithKline, Janssen, Mochida, Otsuka, Pfizer, Takeda, and Yoshitomi Yakuhin. **Dr Tada** has no conflicts of interest in relation to this article.

Funding/support: None.

Disclaimer: This article reflects the views of the authors and may not reflect the opinions or views of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) Study Investigators or the National Institute of Mental Health (NIMH).

Additional information: Data used in the preparation of this article were obtained from the limited-access datasets distributed from the STEP-BD, which was supported by the NIMH. The STEP-BD focused on nonpsychotic bipolar disorder in adults seen in outpatient settings. One of the primary purposes of this research study was to determine whether adjunctive antidepressant therapy reduces symptoms of bipolar depression without increasing the risk of mania. The study was supported by NIMH contract #N01MH80001.

REFERENCES

1. Kessler RC, Demler O, Frank RG, et al. Prevalence and treatment of mental disorders, 1990 to 2003. *N Engl J Med*. 2005;352(24):2515–2523.
2. Simon GE, Unützer J. Health care utilization and costs among patients treated for bipolar disorder in an insured population. *Psychiatr Serv*. 1999;50(10):1303–1308.
3. Dilsaver SC, Chen Y-W, Swann AC, et al. Suicidality, panic disorder and psychosis in bipolar depression, depressive-mania and pure-mania. *Psychiatry Res*. 1997;73(1–2):47–56.
4. Michalak EE, Murray G, Young AH, et al. Burden of bipolar depression: impact of disorder and medications on quality of life. *CNS Drugs*. 2008;22(5):389–406.
5. Keck PE Jr, Marcus R, Tourkodimitris S, et al; Aripiprazole Study Group. A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania. *Am J Psychiatry*. 2003;160(9):1651–1658.
6. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders:

update 2009 on the treatment of acute mania. *World J Biol Psychiatry*. 2009;10(2):85–116.
7. Yatham LN. A clinical review of aripiprazole in bipolar depression and maintenance therapy of bipolar disorder. *J Affect Disord*. 2011;128(suppl 1):S21–S28.
8. Grunze H, Vieta E, Goodwin GM, et al; WFSBP Task Force On Treatment Guidelines For Bipolar Disorders. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: update 2010 on the treatment of acute bipolar depression. *World J Biol Psychiatry*. 2010;11(2):81–109.
9. Yatham LN, Kennedy SH, O'Donovan C, et al; Canadian Network for Mood and Anxiety Treatments. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: consensus and controversies. *Bipolar Disord*. 2005;7(suppl 3):5–69.
10. Yatham LN, Kennedy SH, O'Donovan C, et al; Guidelines Group, CANMAT. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: update 2007. *Bipolar Disord*. 2006;8(6):721–739.
11. Post RM, Leverich GS, Altshuler LL, et al. An overview of recent findings of the Stanley Foundation Bipolar Network (part I). *Bipolar Disord*. 2003;5(5):310–319.
12. Altshuler LL, Post RM, Black DO, et al. Subsyndromal depressive symptoms are associated with functional impairment in patients with bipolar disorder: results of a large, multisite study. *J Clin Psychiatry*. 2006;67(10):1551–1560.
13. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry*. 2002;59(6):530–537.
14. Kupka RW, Altshuler LL, Nolen WA, et al. Three times more days depressed than manic or hypomanic in both bipolar I and bipolar II disorder. *Bipolar Disord*. 2007;9(5):531–535.
15. Posternak MA, Zimmerman M. Is there a delay in the antidepressant effect? a meta-analysis. *J Clin Psychiatry*. 2005;66(2):148–158.
16. Taylor MJ, Freemantle N, Geddes JR, et al. Early onset of selective serotonin reuptake inhibitor antidepressant action: systematic review and meta-analysis. *Arch Gen Psychiatry*. 2006;63(11):1217–1223.
17. Sakurai H, Uchida H, Abe T, et al. Trajectories of individual symptoms in remitters versus non-remitters with depression. *J Affect Disord*. 2013;151(2):506–513.
18. Lavori PW, Rush AJ, Wisniewski SR, et al. Strengthening clinical effectiveness trials: equipoise-stratified randomization. *Biol Psychiatry*. 2001;50(10):792–801.
19. Sachs GS, Nierenberg AA, Calabrese JR, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. *N Engl J Med*. 2007;356(17):1711–1722.
20. American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders*. Fourth Edition. Washington, DC: American Psychiatric Association; 1994.
21. First MB, Spitzer RL, Gibbon M, et al. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. (SCID-I/P)*. New York: Biometrics Research, New York State Psychiatric Institute; 2002.
22. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for *DSM-IV* and *ICD-10*. *J Clin Psychiatry*. 1998;59(suppl 20):22–33, quiz 34–57.
23. Sachs GS, Guille C, McMurrich SL. A clinical monitoring form for mood disorders. *Bipolar Disord*. 2002;4(5):323–327.
24. Guy W. *ECDEU Assessment for Psychopharmacology*. Revised Edition. Rockville, MD: NIMH Publication; 1976.
25. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382–389.
26. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978;133:429–435.
27. Gildengers AG, Houck PR, Mulsant BH, et al. Trajectories of treatment response in late-life depression: psychosocial and clinical correlates. *J Clin Psychopharmacol*. 2005;25(suppl 1):S8–S13.
28. Opdyke KS, Reynolds CF 3rd, Frank E, et al. Effect of continuation treatment on residual symptoms in late-life depression: how well is "well"? *Depress Anxiety*. 1996-1997;4(6):312–319.
29. Demyttenaere K, De Fruyt J, Stahl SM. The many faces of fatigue in major depressive disorder. *Int J Neuropsychopharmacol*. 2005;8(1):93–105.
30. Sobin C, Sackeim HA. Psychomotor symptoms of depression. *Am J Psychiatry*. 1997;154(1):4–17.
31. Flament MF, Lane RM, Zhu R, et al. Predictors of an acute antidepressant response to fluoxetine and sertraline. *Int Clin Psychopharmacol*. 1999;14(5):259–275.
32. Burns RA, Lock T, Edwards DRL, et al. Predictors of response to amine-specific antidepressants. *J Affect Disord*. 1995;35(3):97–106.
33. Sechter D, Vandel P, Weiller E, et al; study co-coordinators. A comparative study of milnacipran and paroxetine in outpatients with major depression. *J Affect Disord*. 2004;83(2–3):233–236.
34. American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders*. Fifth Edition. Washington, DC: American Psychiatric Association; 2013.
35. Bech P. Rating scales for affective disorders: their validity and consistency. *Acta Psychiatr Scand suppl*. 1981;295:1–101.
36. Maier W, Philipp M. Improving the assessment of severity of depressive states: a reduction of the Hamilton Depression Scale. *Pharmacopsychiatry*. 1985;18(01):114–115.
37. McIntyre R, Kennedy S, Bagby RM, et al. Assessing full remission. *J Psychiatry Neurosci*. 2002;27(4):235–239.
38. Kennedy SH. Core symptoms of major depressive disorder: relevance to diagnosis and treatment. *Dialogues Clin Neurosci*. 2008;10(3):271–277.
39. Perlis RH, Ostacher MJ, Patel JK, 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(2):217–224.
40. Gitlin MJ, Mintz J, Sokolski K, et al. Subsyndromal depressive symptoms after symptomatic recovery from mania are associated with delayed functional recovery. *J Clin Psychiatry*. 2011;72(5):692–697.
41. De Dios C, Ezquiaga E, Agud JL, et al. Subthreshold symptoms and time to relapse/recurrence in a community cohort of bipolar disorder outpatients. *J Affect Disord*. 2012;143(1–3):160–165.
42. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet*. 2009;373(9665):746–758.

Editor's Note: We encourage authors to submit papers for consideration as a part of our Early Career Psychiatrists section. Please contact Erika F. H. Saunders, MD, at esaunders@psychiatrist.com.