Clinical Utility of Early Improvement to Predict Response or Remission in Acute Mania: Focus on Olanzapine and Risperidone

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ABSTRACT

Objective: To evaluate early improvement associated with atypical antipsychotic treatment as a predictor of later response or remission among patients experiencing an acute manic or mixed episode without psychotic features.

Method: A post hoc analysis was performed on data from a 3-week, randomized, double-blind clinical trial of olanzapine (N = 147) or risperidone (N = 127) to treat inpatients aged 18–70 years meeting *DSM-IV* criteria for bipolar I disorder. Early improvement, measured as percent change (≥ 25% and ≥ 50% cut points) in the Young Mania Rating Scale (YMRS) total score, was assessed after 2 days and 1 week of treatment. Receiver operating characteristic curves, sensitivity and specificity, and positive and negative predictive values were calculated to determine whether early improvement predicted endpoint (week 3) response or remission. The study was conducted from July 2001 through June 2002.

Results: Among 234 patients with ≥ 25% reduction in YMRS total score at week one, 167 (71.4%) responded and 121 (51.7%) remitted at endpoint. Of the 40 patients with < 25% improvement, 25% (n = 10) responded and 5% (n = 2) remitted at endpoint. A total of 157 patients had a ≥ 50% reduction in week 1 YMRS total score, of whom 132 (84.1%) responded and 101 (64.3%) remitted at endpoint. Of the 117 patients with < 50% improvement, 45 (38.5%) responded and 22 (18.8%) remitted at endpoint.

Conclusions: Improvement in manic or mixed symptoms at week 1 appears to be a good predictor of treatment outcome. Patients not having sufficient improvement (< 25% reduction in YMRS score) were less likely to reach response or remission by week 3. Patients who achieved response by week 1 (≥ 50% reduction in YMRS score) were likely to remain responders at endpoint. These data suggest the potential to assess benefit in the treatment of manic or mixed symptoms within 1 week of initiating olanzapine or risperidone.

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In making treatment decisions for patients experiencing an acute manic or mixed episode, it is of clinical importance to identify as early as possible those patients who will ultimately become treatment responders or nonresponders. At present, reliable clinical or pharmacogenomic markers for the prediction of treatment outcomes in acute mania do not exist. A myriad of potential benefits could directly result from the ability to rapidly identify individuals who are not likely to respond to initial drug treatment, including reduced exposure to ineffective medications and decreased costs.[1]

For patients with bipolar I disorder experiencing a manic or mixed episode, combination treatment consisting of a conventional mood stabilizer plus an antipsychotic is generally reserved for more severe episodes or for patients demonstrating a partial response to initial antimanic drug treatment.[2] In clinical trials, a partial response has been operationalized as continued evidence of manic symptoms after a minimum of 2 weeks of treatment (ie, a Young Mania Rating Scale [YMRS] total score ≥ 16 and ≤ 25% improvement from baseline).[3] Clinicians, however, desire to know early on whether or not drug treatment will lead to response or remission. The ability to predict treatment outcomes before 2 weeks would allow for earlier adjustments in pharmacotherapy, such as switching to an alternative medication or adding an adjunctive antimanic drug.

We hypothesized that, in acutely manic patients, the magnitude of symptom improvement within the first few days of drug initiation could be used as a potential predictor of treatment response. At present, it is unclear how long clinicians should wait before altering a first-choice antimanic treatment in the setting of inefficacy or partial nonresponse. Some treatment guidelines[4] recommend that a drug trial for mania extend no longer than 2 weeks if signs of inefficacy are apparent. Limited understanding of early response patterns in bipolar mania may partially account for the ambiguity around what constitutes an adequate duration of initial antimanic treatment.[4] In contrast to other psychotropic medications (eg, antidepressants), the onset of action of oral atypical antipsychotics in the treatment of acute mania may be rapid, with some patients demonstrating antimanic effects in as little as 24–48 hours.[5] Separation from placebo on change in symptom severity on the YMRS, the Brief Psychiatric Rating Scale, and the Clinical Global Impressions scale can be detected as early as 2–6 days after atypical antipsychotic initiation.[6] The ability to detect early differences in manic symptom change between active drug and placebo led us to wonder if a lack of improvement within the first week of treatment is indicative of later nonresponse.

Growing evidence from clinical trials of schizophrenia and major depression already suggests that early response or nonresponse can be predictive of later treatment outcome. Data from 5 randomized, double-blind clinical trials[7] in schizophrenia comparing olanzapine with other atypical antipsychotics showed that ≥ 20% improvement on the Positive and Negative Syndrome Scale (PANSS) total score after 2 weeks of treatment distinguished the likelihood of subsequent response to up to 3 months of antipsychotic therapy with high specificity (80%) and high negative predictive value (84%).[7] In addition, early nonresponders were less likely to demonstrate symptom improvement and were more likely to discontinue treatment.[7]

Similar analyses of the predictive effect of early improvement on later outcomes have also been undertaken in unipolar major depressive disorder. Several studies[1,8–11] suggest that improvement of depressive symptoms within the first 2 weeks of treatment is closely coupled with endpoint treatment response. In a clinical trial of outpatients who eventually responded to fluoxetine, Nierenberg and colleagues[9,12] found that more than one-half of participants began to improve during the first 2 weeks of antidepressant administration. In contrast, early nonresponse to fluoxetine predicted poor 8-week outcomes.

Stassen and colleagues,[10,13–15] in a series of comprehensive analyses, identified that patients experiencing ≥ 20% reduction on the 17-item Hamilton Depression Rating Scale (HDRS-17) total score during the first 2 weeks of antidepressant treatment attained high rates of response (≥ 50% reduction in HDRS-17 score) at study endpoint. In a reciprocal manner, the failure to improve by ≥ 20% on the HDRS-17 during the first 2 weeks of treatment was a robust predictor of the lack of response at study endpoint. Finally, in one of the largest studies[1] conducted to date, involving over 6,500 patients from 41 single-blind or double-blind clinical trials, early improvement predicted stable response and stable remission with a sensitivity ≥ 81% and ≥ 87%, respectively. In this analysis,[1] stable response was defined as a reduction in HDRS-17 score of ≥ 50% from baseline after 4 weeks of treatment that was sustained at all subsequent assessments. Negative predictive values for stable response and remission were also high. The high negative predictive values indicate that patients had little chance of achieving stable response in the absence of improvement within the first 2 weeks of treatment. Even in a naturalistic sample[8] of patients with unipolar major depressive disorder who were not part of a clinical trial, early improvement in depressive symptoms was reliably shown to predict endpoint outcomes.

To our knowledge, only 1 prior publication[16] has addressed the predictive value of early improvement in bipolar mania. In this study of patients receiving ziprasidone monotherapy for acute manic or mixed episodes, rapid improvement in psychotic symptoms after 4 days of treatment predicted acute manic episode remission and mediated overall manic symptom improvement (receiver operating characteristic [ROC] area under the curve [AUC] = 0.71). Given the limited data on early improvement in mania, the present analysis focused on a cohort of patients with bipolar I disorder who were receiving atypical antipsychotic treatment with either olanzapine or risperidone for an acute manic or mixed episode without psychotic features. We hypothesized that early improvement in manic symptoms at week 1, regardless of treatment assignment, would be a sensitive and specific predictor of response and/or remission at week 3. Given that clinicians must also balance expected benefit to the patient with the risk of potential adverse events, the potential relationship between change in metabolic parameters by early improvement status and endpoint treatment outcome was also explored.

METHOD

Study Design

A post hoc analysis was performed on data from a 3-week, randomized, double-blind clinical trial (www.clinicaltrials.gov Identifier: NCT00034580) comparing olanzapine with risperidone in hospitalized patients with bipolar I disorder. The study, which was conducted from July 2001 through June 2002, was approved by the institutional review board at every participating study site before enrolling any patient, and all patients provided written informed consent meeting all regulatory requirements prior to undergoing any study procedure or receiving any study treatment. The study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki.

The study enrolled male and female subjects at 30 US sites who were 18–70 years old and were hospital inpatients at the initial visit. All patients met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) criteria for bipolar I disorder and were experiencing a current manic or mixed episode without psychotic features. The YMRS was used to quantify the severity of manic symptoms, with a total score ≥ 20 required at baseline (visits 1 and 2). Exclusion criteria included serious suicide risk, *DSM-IV* substance dependence within the previous 2 months (except for nicotine and caffeine), a ≥ 3-week duration of hospitalization prior to the initial visit, a ≥ 90-day duration of current manic or mixed episode, or documented history of failure to respond to an adequate period of treatment with olanzapine or risperidone for acute mania.

Olanzapine-treated (N = 147) and risperidone-treated (N = 127) patients with YMRS scores collected at baseline and at week 2 or 3 of the double-blind phase were included in the study population. Results presented are based on last observation carried forward (LOCF) analysis in which week 2 data were used if week 3 data were missing.

Patients randomized to olanzapine received 15 mg/d for the first 2 days, followed by flexible dosing up to a maximum of 20 mg/d (mean modal dose = 14.7 mg/d; N = 165). Patients randomized to risperidone received 2 mg on day 1 and 3 mg on day 2, followed by flexible dosing up to a maximum of 6 mg/d (mean modal dose = 3.9 mg/d; N = 164). Anticholinergic medication (benztropine mesylate, 2 mg/d maximum) was permitted for treatment of, but not as prophylaxis for, extrapyramidal symptoms, and lorazepam was permitted for severe manic agitation (duration not to exceed the initial 7 consecutive days of study drug receipt). A more detailed account of study design and methods has been previously published.[17]

Outcome Measures

For the purposes of this analysis, the following patient groups were defined: (1) early improvers: patients having a reduction in YMRS score ≥ 25% or ≥ 50% at week 1; (2) treatment responders: patients having a reduction from baseline in YMRS score ≥ 50% at the final assessment; and

(3) treatment remitters: patients achieving a YMRS score ≤ 8 at the final assessment.

Statistical Analyses

Analyses of the predictive value of early improvement for later response and remission at 3 weeks were performed on the intent-to-treat population. Early improvement, measured as percent change (≥ 25% and ≥ 50% cut points) in YMRS total score, was assessed after 2 days and 1 week of treatment. Receiver operating characteristic curves were used to identify the early improvement time that best predicted later (week 3) response or remission. The same analyses were carried out using data only from patients who completed the study (completers). The numbers of early improvers, treatment responders, and treatment remitters were analyzed as follows:

- Sensitivity: (early improvers who became later responders or remitters/all patients who became later responders or remitters) × 100.
- Specificity: (early nonimprovers who did not become later responders or remitters/all patients who did not become later responders or remitters) × 100.
- Positive predictive value: (early improvers who became later responders or remitters/all early improvers) × 100.
- Negative predictive value: (early nonimprovers who did not become later responders or remitters/all early nonimprovers) × 100.
- False positives: 100% minus specificity.
- False negatives: 100% minus sensitivity.

The potential relationship of early improvement and response/remission to weight and metabolic changes was measured by comparing least-squares mean changes from baseline in patients who either improved or did not improve at week 1 with patients who either responded or did not respond by week 3.

All statistical analyses were performed using SAS analytic software (SAS Institute, Inc; Cary, North Carolina).

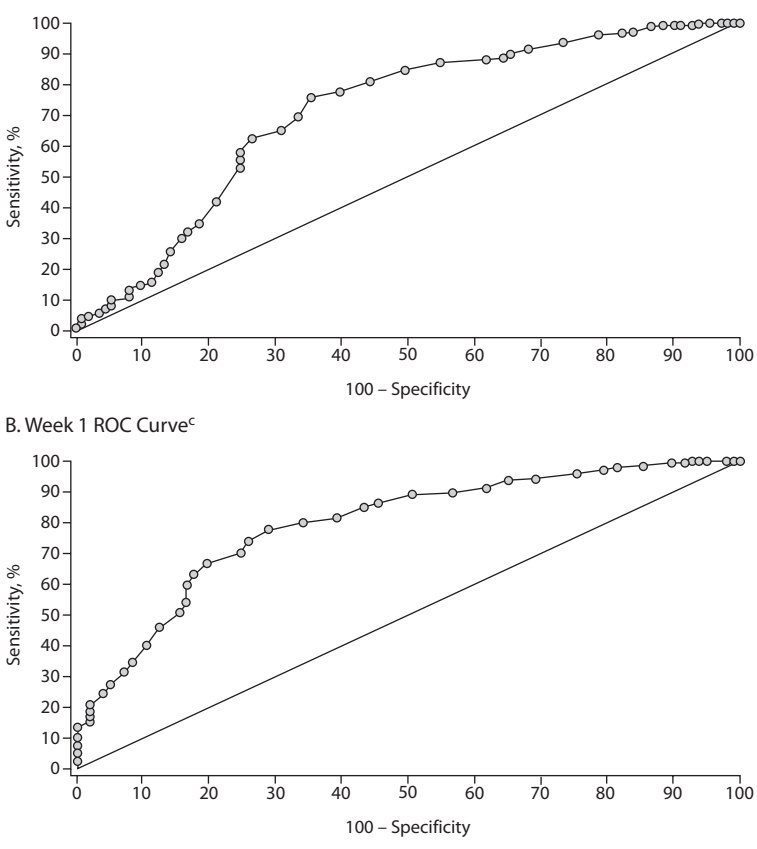
RESULTS

The patient demographic characteristics from which this analysis was derived have been previously published.[17] The original dataset included 329 participants, 73.6% of whom were white and 54.7% of whom were female. A subset of patients (N = 274) had YMRS scores available at the baseline, early, and late time points and were included in the present analysis; 147 patients (53.6%) received olanzapine and 127 (46.3%) received risperidone. Of patients taking olanzapine or risperidone, 94 (63.9%) and 83 (65.3%), respectively, became treatment responders. Remission was observed in 57 olanzapine-treated patients (38.8%) and 66 risperidone-treated patients (52.0%). A large majority of the total sample (234 patients; 85.4%) had at least a 25% reduction in YMRS total score by week 1 of treatment.

In order to determine an optimal time point predictive of later improvement, ROC curves were completed. The ROC area under the curve showed that week 1 values (AUC = 0.80) were more predictive for response than day 2 values (AUC = 0.71) (Figure 1A and 1B). Given this finding, all subsequent analyses were based upon the degree of early improvement at week 1.

Among 234 patients with ≥ 25% reduction in YMRS total score at week one, 167 (71.4%) responded by week 3 and 121 (51.7%) remitted by week 3 (Table 1). When we pooled patients receiving olanzapine or risperidone, the sensitivity values were 94% for responders and 98% for remitters. Positive predictive values for response ranged from 71% to 72%, demonstrating that early improvement is a moderately strong predictor of response. However, the positive predictive values for remission were considerably lower, ranging from 45% to 60%.

Figure 1. Receiver Operating Characteristic (ROC) Curves for (A) Day 2 and (B) Week 1 Young Mania Rating Scale (YMRS) Improvement to Predict Outcome at Week 3[a]



[a]For both curves, predicted outcome is reduction of 50% or more in YMRS total score by week 3.
[b]Area under the curve (AUC) = 0.71.
[c]AUC = 0.80.

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Table 1. Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value of Week 1 Improvement in the Young Mania Rating Scale (YMRS) Score to Predict Week 3 Response or Remission Using Last Observation Carried Forward[a]

	Sensitivity		Specificity		Positive Predictive Value		Negative Predictive Value	
	Response, %	Remission, %	Response, %	Remission, %	Response, %	Remission, %	Response, %	Remission, %
≥ 25% Decrease in YMRS total score at week 1								
All patients	94	98	31	25	71	52	75	95
Olanzapine group	96	100	30	22	71	45	80	100
Risperidone group	93	97	32	30	72	60	70	90
≥ 50% Decrease in YMRS total score at week 1								
All patients	75	82	74	63	84	64	62	81
Olanzapine group	76	88	74	61	84	59	63	89
Risperidone group	73	77	75	66	85	71	60	73

[a]Response was defined as a 50% or greater improvement in the YMRS score by week 3; remission was defined as a YMRS total score of 8 or less at week 3.

Early improvement defined as ≥ 25% reduction in YMRS total score was not highly specific for response (specificity range, 30%–32%) or remission (specificity range, 22%–30%). Of the 234 patients who showed ≥ 25% improvement on the YMRS at week one, 113 (48.3%) were nonremitters at week 3, reflecting a high false-positive rate. In contrast, the negative predictive value for early nonimprovement to predict later nonresponse and nonremission was strong (negative predictive value range, 70%–100%). Of the 40 patients with < 25% improvement, 25% (n = 10) responded and 5% (n = 2) remitted at endpoint. Of 20 olanzapine-treated patients with < 25% YMRS improvement at week 1, none attained remission at week 3. Of 20 risperidone-treated patients with < 25% improvement at week 1, two became remitters at week 3.

When early improvement was defined as ≥ 50% improvement in YMRS total score at week 1, the utility for predicting response and remission became even stronger. Of 157 patients with early improvement, 132 (84.1%) became responders and 101 (64.3%) became remitters at week 3. The sensitivity of early improvement for response and remission was 75% and 82%, respectively. The values for specificity improved to 74% for response and 63% for remission. Among patients with early improvement, only 25 (15.9%) became nonresponders and 56 (35.7%) became nonremitters at week 3, denoting a low rate of false positives. The positive predictive values for early improvement (≥ 50% reduction in YMRS total score at week 1) as a predictor of endpoint response and remission were also robust (positive predictive value ranges, 84%–85% and 59%–71%, respectively). The negative predictive values at this cut point were slightly lower (62% for response and 81% for remission) (Table 1). Of the 117 patients with < 50% improvement at week one, 45 (38.5%) responded and 22 (18.8%) remitted at endpoint.

Completer analyses yielded findings similar to those of the LOCF analyses for the early improvement cut points of ≥ 25% and ≥ 50% reduction in YMRS score to predict endpoint response and remission (data not shown).

Given that clinicians must also balance expected benefit to the patient with the risk of potential adverse events, the potential relationship between changes in body weight, early improvement, and endpoint treatment outcome was also explored. The mean change from baseline in body weight was calculated separately for patients with and without early improvement (≥ 25%) at week 1. The mean increase in body weight among early improvers taking olanzapine (2.7 kg) was similar to those without early improvement (2.5 kg) and had no significant relationship with response or remission status at week 3 ($P = .82$). Likewise, the mean increase in body weight among early improvers taking risperidone (1.6 kg) was similar to those without early improvement (2.7 kg) and had no significant relationship with response or remission status at week 3 ($P = .11$).

DISCUSSION

In an attempt to assess the clinical utility of early improvement as a predictor of outcome in bipolar I mania, we analyzed endpoint rates of response and remission among patients identified as early improvers with olanzapine or risperidone treatment. Two different thresholds of early improvement were tested, including a ≥ 25% or ≥ 50% reduction in YMRS total score after 1 week of treatment. The results show that patients identified as early improvers after 1 week of treatment have higher rates of response and remission than early nonimprovers. Conversely, the lack of early improvement was a strong predictor of nonresponse and nonremission. The results suggest that the majority of improvement with atypical antipsychotics occurs early rather than later[18] and are in agreement with several prior studies conducted with a range of psychotropic medications in other psychiatric disorders, including atypical antipsychotics in schizophrenia,[8,19–21] antidepressants in major depressive disorder,[1,22] and conventional mood stabilizers and atypical antipsychotics in bipolar depression.[23]

Early evaluation of a patient's response to treatment for an acute manic or mixed episode has important implications regarding how soon a clinician should continue or alter initial antimanic drug therapy. Current practice guidelines[2] recommend increasing antimanic therapy as tolerated during the first few days after initiation and then adjusting over several weeks. Although antipsychotic medications are expected to be effective in a matter of days, in the clinical setting it can be difficult to separate spontaneous symptom reduction or immediate placebo effect from the beginning of a true drug response.[22] The present study seeks to provide for the first time an estimate of the sensitivity, specificity, and prognostic value of early improvement for predicting later response or remission in bipolar mania.

From a clinical perspective, the results reveal that patients who ultimately achieve response or remission after 3 weeks are highly likely to have improved within the first week of antimanic drug therapy. On the basis of sensitivity and positive predictive values, early improvement with antipsychotic medications was a moderately strong predictor of subsequent response. The finding of high positive predictive values with olanzapine and risperidone suggests that clinicians should continue the current treatment when a patient achieves ≥ 25% decrease in symptom severity after 1 week of therapy, with the understanding that over 70% of patients exhibiting this level of early improvement went on to meet full response criteria in the present study. If a patient achieves ≥ 50% reduction in symptom severity after 1 week, results of the present study suggest that response will likely be maintained in approximately 84% of cases. Alternatively, the high negative predictive values in this study indicate that 95% of patients with < 25% improvement in mania severity after 1 week of treatment with olanzapine or risperidone will not achieve remission, while 81% of patients with < 50% improvement in mania severity at week 1 will fail to achieve remission. The high negative predictive values imply that patients who do not experience at least 25% improvement in manic symptoms by week 1 are unlikely to respond to or remit with treatment. Accordingly, clinicians should have a high suspicion that the drug is not working and perhaps consider earlier changes in the treatment strategy.

In a related manner, early improvement in the psychotic symptoms associated with acute manic/mixed states has been identified as a subsequent predictor of remission. A reduction in psychosis severity of ≥ 20% at day 4 yielded a sensitivity of 76% and specificity of 58% for predicting remission.[16] The predictive value of early improvement (≥ 20% reduction in Montgomery-Asberg Depression Rating Scale [MADRS] score after 2 weeks of treatment) has also been studied in 10 bipolar depression trials.[23] Some 55% of patients with bipolar depression met criteria for early improvement, much lower than in the present report of bipolar mania in which over 85% of patients had ≥ 25% improvement in manic symptoms by week 1. The positive predictive values for later response in bipolar depression were also relatively low, ranging from 54% to 72%.[23] In comparison, the positive predictive values for response in this study of bipolar mania ranged from 71% to 85%. Thus, early improvement analyses appear to have greater clinical utility for predicting endpoint response in bipolar mania than in bipolar depression.

For the first time in bipolar mania studies, the potential relationship was examined between change in body weight by early improvement status and endpoint response or remission. There was no significant relationship between weight change at week 1 and early improvement status (≥ 25% decrease in YMRS total score) nor between weight change at week 1 and response or remission status at week 3 in either treatment group.

Future Directions

The results of the present trial give rise to interesting questions regarding the utility of switching to an alternative medication once a patient has failed to demonstrate early improvement with initial atypical antipsychotic therapy. In a recent study[24] of 630 patients with schizophrenia or schizoaffective disorder, those patients not showing early improvement with open-label risperidone after 2 weeks of treatment were randomly assigned in a double-blind, flexible-dose fashion to receive either olanzapine or continued treatment with risperidone for another 10 weeks. Switching early risperidone nonresponders to olanzapine resulted in significant symptom improvement according to PANSS total score ($P = .020$) and MADRS total score ($P = .020$) at endpoint. Thus, switching antipsychotic therapy in this trial appeared to enhance improvement in patients who showed lack of early improvement with their initial antipsychotic therapy.[24] To our knowledge, no studies in bipolar depression or mania have evaluated the utility of switching antipsychotics or adding adjunctive treatments in patients demonstrating lack of early improvement. Future studies are needed to determine whether medication changes after as little as 1 week of treatment in early nonimprovers will enhance acute and longer-term outcomes in bipolar disorder.

Limitations

The present study focused on a cohort of patients with bipolar I mania or mixed states who were initially hospitalized, without psychotic features, free of serious suicide risk, and without comorbid substance abuse or dependence within the 2 months prior to enrollment. Thus, the results may not be generalizable to mildly ill or treatment-refractory patients, or to those with unstable medical comorbidities or substance dependence. Although acute efficacy trials for bipolar mania are typically conducted over a 3-week period, this short duration precludes assessment of the value of early improvement for predicting long-term remission from manic or mixed states. The definition of remission employed in this analysis, specifically a YMRS score ≤ 8, did not take into account the severity of any depressive symptoms that may have been present. A more rigorous definition of successful response to a treatment for mania would require the lack of exacerbation of depressive symptoms.[25] It is also unknown whether the predictive power of early improvement would differ if medications other than olanzapine or risperidone were used to treat acute mania or mixed states. Future studies are needed to assess sustained remission over a longer duration.

Whether differences exist in the demographic or illness characteristics of early improvers as compared with early nonimprovers was not assessed. In a related fashion, we do not know whether patients who show initial improvement, but who fail to achieve response or remission, have differences in their illness phenomenology or genetic polymorphisms that are influencing treatment response. Adaptive study designs that randomize early nonimprovers to an alternative antipsychotic or to combination therapy are necessary to evaluate whether an early change in pharmacotherapy improves treatment outcomes for this group of patients.

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CONCLUSION

In summary, efficacy, safety, and tolerability are important when prescribing drug treatments for bipolar mania. However, clinicians also value the predictability of knowing when a drug is going to work and when it is not. In the treatment of bipolar I mania or mixed states, early improvement and early nonimprovement were identified as potential predictors of subsequent response and nonresponse, respectively, to treatment with olanzapine or risperidone. During the treatment of bipolar I mania or mixed states, it may be possible to inform treatment decision-making on the basis of the degree of symptom improvement occurring over the first week of antipsychotic therapy.

Drug names: benztropine (Cogentin and others), fluoxetine (Prozac and others), lorazepam (Ativan and others), olanzapine (Zyprexa), risperidone (Risperdal and others), ziprasidone (Geodon).

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Author contributions: The manuscript was drafted and revised entirely by Drs Kemp and Calabrese and Ms Johnson. Dr Tohen was involved with the conceptualization of the analysis, securing of the information, and interpretation of the data. Ms Wang provided statistical expertise.

Potential conflicts of interest: **Dr Kemp** has been a consultant for Bristol-Myers Squibb; has received grant/research support from NARSAD, the National Institutes of Health, and Takeda; and has been a member of the speakers or advisory boards for AstraZeneca and Pfizer. **Ms Wang** is an employee of Eli Lilly. **Dr Tohen** was an employee of Eli Lilly at the time of the study, and his spouse is an employee and stock shareholder of Eli Lilly. Dr Tohen has been a consultant for Bristol-Myers Squibb, GlaxoSmithKline, Merck, Johnson & Johnson, Otsuka, Sepracor, and Eli Lilly and has received honoraria from AstraZeneca, Forest, and Wyeth. **Dr Calabrese** has received federal funding from the US Department of Defense, the Health Resources Services Administration, and the National Institute of Mental Health; has received grant/research support from Abbott, AstraZeneca, Bristol-Myers Squibb, Cephalon, Cleveland Foundation, Eli Lilly, GlaxoSmithKline, Janssen, NARSAD, Repligen, The Stanley Medical Research Institute, Takeda, and Wyeth; has been an advisory board member for Abbott, AstraZeneca, Bristol-Myers Squibb, Cephalon, Dainippon Sumitomo, EPI-Q, Forest, France Foundation, GlaxoSmithKline, Janssen, Johnson & Johnson, Lundbeck, Merck, NeuroSearch, Ortho-McNeil, Otsuka, Pfizer, Repligen, Schering-Plough, Servier, Solvay, Supernus, Synosia, Takeda, and Wyeth; and has been involved in CME activities supported by AstraZeneca, Bristol-Myers Squibb, France Foundation, GlaxoSmithKline, Janssen, Johnson & Johnson, Merck, Pfizer, Sanofi-Aventis, Schering-Plough, Solvay, and Wyeth. **Ms Johnson** has no financial or other relationships to disclose relative to the article.

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REFERENCES

1. Szegedi A, Jansen WT, van Willigenburg AP, et al. Early improvement in the first 2 weeks as a predictor of treatment outcome in patients with major depressive disorder: a meta-analysis including 6,562 patients. *J Clin Psychiatry*. 2009;70(3):344–353.
2. Yatham LN, Kennedy SH, Schaffer A, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. *Bipolar Disord*. 2009;11(3):225–255.
3. Vieta E, T'joen C, McQuade RD, et al. Efficacy of adjunctive aripiprazole to either valproate or lithium in bipolar mania patients partially nonresponsive to valproate/lithium monotherapy: a placebo-controlled study. *Am J Psychiatry*. 2008;165(10):1316–1325.
4. 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.
5. Kapur S, Arenovich T, Agid O, et al. Evidence for onset of antipsychotic effects within the first 24 hours of treatment. *Am J Psychiatry*. 2005;162(5):939–946.
6. Tohen M, Jacobs TG, Feldman PD. Onset of action of antipsychotics in the treatment of mania. *Bipolar Disord*. 2000;2(3, pt 2):261–268.
7. Kinon BJ, Chen L, Ascher-Svanum H, et al. Predicting response to atypical antipsychotics based on early response in the treatment of schizophrenia. *Schizophr Res*. 2008;102(1–3):230–240.
8. Henkel V, Seemüller F, Obermeier M, et al. Does early improvement triggered by antidepressants predict response/remission? analysis of data from a naturalistic study on a large sample of inpatients with major depression. *J Affect Disord*. 2009;115(3):439–449.
9. Nierenberg AA, Farabaugh AH, Alpert JE, et al. Timing of onset of antidepressant response with fluoxetine treatment. *Am J Psychiatry*. 2000;157(9):1423–1428.
10. Stassen HH, Angst J, Delini-Stula A. Delayed onset of action of antidepressant drugs? survey of results of Zurich meta-analyses. *Pharmacopsychiatry*. 1996;29(3):87–96.
11. Szegedi A, Müller MJ, Anghelescu I, et al. Early improvement under mirtazapine and paroxetine predicts later stable response and remission with high sensitivity in patients with major depression. *J Clin Psychiatry*. 2003;64(4):413–420.
12. Nierenberg AA, McLean NE, Alpert JE, et al. Early nonresponse to fluoxetine as a predictor of poor 8-week outcome. *Am J Psychiatry*. 1995;152(10):1500–1503.
13. Stassen HH, Delini-Stula A, Angst J. Time course of improvement under antidepressant treatment: a survival-analytical approach. *Eur Neuropsychopharmacol*. 1993;3(2):127–135.
14. Stassen HH, Angst J. Delayed onset of action of antidepressants: fact or fiction? *CNS Drugs*. 1998;9(3):177–184.
15. Stassen HH, Angst J, Delini-Stula A. Fluoxetine versus moclobemide: cross-comparison between the time courses of improvement. *Pharmacopsychiatry*. 1999;32(2):56–60.
16. Ketter TA, Agid O, Kapur S, et al. Rapid antipsychotic response with ziprasidone predicts subsequent acute manic/mixed episode remission. *J Psychiatr Res*. 2010;44(1):8–14.
17. Perlis RH, Baker RW, Zarate CA Jr, et al. Olanzapine versus risperidone in the treatment of manic or mixed states in bipolar I disorder: a randomized, double-blind trial. *J Clin Psychiatry*. 2006;67(11):1747–1753.
18. Agid O, Kapur S, Arenovich T, et al. Delayed-onset hypothesis of antipsychotic action: a hypothesis tested and rejected. *Arch Gen Psychiatry*. 2003;60(12):1228–1235.
19. Leucht S, Busch R, Kissling W, et al. Early prediction of antipsychotic nonresponse among patients with schizophrenia. *J Clin Psychiatry*. 2007;68(3):352–360.
20. Leucht S, Shamsi SA, Busch R, et al. Predicting antipsychotic drug response: replication and extension to six weeks in an international olanzapine study. *Schizophr Res*. 2008;101(1–3):312–319.
21. Correll CU, Malhotra AK, Kaushik S, et al. Early prediction of antipsychotic response in schizophrenia. *Am J Psychiatry*. 2003;160(11):2063–2065.
22. Stassen HH, Angst J, Hell D, et al. Is there a common resilience mechanism underlying antidepressant drug response? evidence from 2,848 patients. *J Clin Psychiatry*. 2007;68(8):1195–1205.
23. Kemp DE, Ganocy SJ, Brecher M, et al. Clinical value of early partial symptomatic improvement in the prediction of response and remission during short-term treatment trials in 3369 subjects with bipolar I or II depression. J Affect Disord. In press.
24. Stauffer V, Chen L, Ascher-Svanum H, et al. Switching antipsychotic drugs enhances improvement in patients who show lack of an early response to their initial antipsychotic therapy [abstract]. Presented at the 162nd Annual Meeting of the American Psychiatric Association; May 16–21, 2009; San Francisco, CA. Abstract NR1-090.
25. Tohen M, Frank E, Bowden CL, et al. The International Society for Bipolar Disorders (ISBD) Task Force report on the nomenclature of course and outcome in bipolar disorders. *Bipolar Disord*. 2009;11(5):453–473.