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A prospective study of the trajectories of clinical insight, affective symptoms, and cognitive ability in bipolar disorder

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Abstract

Background—Clinical insight in bipolar disorder is associated with treatment adherence and psychosocial outcome. The short-term dynamics of clinical insight in relationship to symptoms and cognitive abilities are unknown.

Methods—In a prospective observational study, a total of 106 outpatients with bipolar disorder I or II were assessed at baseline, 6 weeks, 12 weeks, and 26 weeks. Participants were administered a comprehensive neuropsychological battery, clinical ratings of manic and depressive symptom severity, and self-reported clinical insight. Lagged correlations and linear mixed-effects models were used to determine the temporal associations between symptoms and insight, as well as the moderating influence of global cognitive abilities.

Results—At baseline, insight was modestly correlated with severity of manic symptoms, but not with depressive symptoms or cognitive abilities. Insight and depressive symptoms fluctuated to approximately the same extent over time. Both lagged correlations and mixed effects models with lagged effects indicated that the severity of manic symptoms predicted worse insight at later

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Contributors

CD: Led the concept formation, analysis, and interpretation of results as well as manuscript preparation

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GS: Contributed to the interpretation of results and manuscript preparation

BM: Contributed to the statistical analytic strategy and interpretation of results

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assessments, whereas the converse was not significant. There were no direct or moderating influences of global cognitive abilities.

Limitations—Our sample size was modest, and included relatively psychiatrically stable outpatients, followed for a six month period. Our results may not generalize to acutely symptomatic patients followed over a longer period.

Conclusions—Clinical insight varies substantially over time within patients with bipolar disorder. Impaired insight in bipolar disorder is more likely to follow than to precede manic symptoms.

Keywords

Bipolar disorder; insight; neuropsychology; depression

INTRODUCTION

Clinical insight is broadly defined as the awareness of one's illness and the ability to recognize the symptoms of that illness and that they warrant treatment (Amador and Kronengold, 1998). There is far less research on insight in bipolar disorder as compared to that in schizophrenia or depression, but a number of studies have indicated that individuals with bipolar disorder frequently experience impairments in insight (Trevisi et al., 2012, Latalova, 2012, van der Werf-Eldering et al., 2011, Pini et al., 2001). Insight impairments are associated with generally static risk factors, including greater neurocognitive impairment as well as time-varying factors, such as manic symptoms (Michalakeas et al., 1994, Dias et al., 2008a). Greater insight, on the other hand, has been associated with better medication adherence (Sajatovic et al., 2009) and higher self-reported quality of life (Dias et al., 2008a). Studies have also found that improvement in insight is associated with better psychosocial functioning (Ghaemi et al., 2000, Yen et al., 2007a). Accordingly, many psychoeducational interventions for bipolar disorder are predicated on the theory that improving insight will result in improved outcomes (e.g., greater perceived need for treatment leading to greater treatment adherence and reduced symptoms)(Simpson et al., 2009, Miklowitz and Scott, 2009). Despite the clinical relevance of insight as a potential risk modifier and psychosocial treatment target in bipolar disorder, there is little prior longitudinal research on the putative pathways among insight, symptoms, and neurocognitive ability. As such, it is unknown whether degradations in insight precede or follow illness fluctuations among patients with and without cognitive impairments.

Although generally viewed as more of a stable trait in schizophrenia(Wiffen et al., 2010), insight has been conceptualized as more of a state-dependent construct in bipolar disorder, with alterations dependent on illness phases(Cassidy, 2010). Several studies have examined change in insight following hospitalization associated with an acute manic episode. Prior review of four such studies identified an approximately 20% improvement in insight after a manic episode(Ghaemi and Rosenquist, 2004). Additional cross-sectional studies have compared self-reported insight between patients in manic, mixed, depressed or euthymic mood states(Cassidy, 2010, Dell'Osso et al., 2002). Subgroup comparisons have suggested that the greatest impairments in insight have been observed among patients experiencing

acute mania, versus those experiencing mixed or euthymic episodes at the time of assessment. Depressive episodes have been associated with unimpaired, even enhanced, insight compared to euthymic episodes.

However, in regard to the direction of the temporal associations between insight and affective symptoms, few studies have employed a prospective design to examine the within-person stability and short-term course of insight in the context of mood fluctuations. Yen et al. (Yen et al., 2007b) followed 54 patients over the course of two years, reporting that insight was stable over time among patients who were free of acute mood episodes or who experienced depressive episodes during the study period. However, insight was diminished during manic episodes and for the majority of manic patients, returned to pre-episode levels; yet, a subset of recurrent patients did not experience restoration of insight post-episode.

In regard to cognitive ability, prior work indicates that insight is positively associated with working memory and executive functioning in bipolar disorder (Dias et al., 2008a) (Dias et al., 2008b, Varga et al., 2006, Yen et al., 2008). However, there are no published reports of the association of neurocognitive ability on trajectories of insight over time in bipolar disorder. Given that insight appears to be more state-dependent in bipolar disorder, it is possible that the interactive effect of neurocognitive ability and insight on mood symptom exacerbations is greater than the effect of each of these risk factors in isolation (Boyer et al., 2012).

Understanding the temporal interdependencies among insight, cognitive ability, and symptoms may help in determining which patients are more at risk for a relapsing course of illness, as well as when and for whom potentially modifiable factors, such as insight, can be targeted to reduce symptom burden experienced over time. In the current study, we examined the temporal course of insight, affective symptoms and states, and neurocognitive ability in a longitudinal observational study of 106 outpatients with bipolar disorder. Participants were assessed at baseline, 6 weeks, 12 weeks, and 26 week follow up. In addition to assessing the stability of insight, we conducted mixed effects concurrently with lagged analyses to examine the temporal direction of associations between insight and subsequent mood symptoms and discrete episode states (as well as the converse). We also examined the potential moderating influence of global cognitive ability. Given that the prevalent conceptualization in models of psychoeducation for bipolar disorder is that lower insight places one at risk for symptom exacerbations (Miklowitz and Scott, 2009), we hypothesized that worse insight at prior time points would predict significantly more severe manic symptoms at later assessments, and that the converse association (mania or depression predicting insight) would not be significant. We further predicted that cognitive ability, measured at baseline, would be associated with diminished insight across subsequent assessments and would be associated with interactive effects with insight in prediction of later symptoms. We explored these same cross-temporal analyses as above with depressive symptoms.

METHOD

Sample Characteristics

The study sample derives from an ongoing study of cognitive and other determinants of the short-term course of capacity to consent to research among patients with bipolar disorder. We examined data from 106 outpatients with a DSM-IV diagnosis of either bipolar I or bipolar II disorder (BD), established by the Structured Clinical Interview for the DSM-IV-TR (SCID(First et al., 1997)). The SCID was conducted by trained research associates and confirmed in consensus meetings in which the SCID responses and other available information were presented to a board certified psychiatrist. Patients were assessed when in various mood states, as no restrictions were placed on symptom status at study entry.

Besides diagnosis, inclusion criteria were fluency in English and ability to provide written consent to participate in the study. Potential participants were excluded if they met DSM-IV criteria for substance dependence within two months preceding enrollment, had been diagnosed with dementia or other neurological/medical conditions known to affect cognitive functioning, or had medical problems that hindered their ability to complete the assessments.

Participants were recruited from a variety of sources, including outpatient psychiatry clinics at the University of California, San Diego (UCSD), the Veterans Affairs San Diego Healthcare System, support groups for bipolar disorder, and community-based assisted living facilities. The parent study was approved by the UCSD Human Research Protections Program as well as the Institutional Review Board of the San Diego Veterans Administration Healthcare System. All participants enrolled in the study provided written informed consent for participation. Prior publications resulting from this study have not included an examination of insight data (Depp et al., 2012).

Study Design

Participants' symptoms, levels of insight, and neurocognitive functioning were assessed at baseline, and then at six weeks, twelve weeks, and 26 weeks after baseline. Because we used mixed-effects models that incorporated data from all subjects regardless of missing data, we included all participants with at least a baseline visit. Participants completed an average of 3.3 assessments (SD = 0.95) with 57% completing all four assessments.

Assessments

Demographic information, clinical history, and measures described below were collected from all participants at the baseline visit. Symptom severity, level of insight, and cognitive functioning were assessed at baseline and at each subsequent visit with the scales describe below.

Clinical Insight

Insight was assessed with the 8-item interviewer-administered Mood Disorders Insight Scale (Sturman and Sproule, 2003), which is adapted from the Birchwood Insight Scale (Birchwood et al., 1994) to reflect insight relevant to mood disorders. The MDIS queries three components of insight: 1) awareness of symptoms, 2) attribution of symptoms

to illness, and 3) belief in the need for treatment. Respondents are asked to respond to questions about their current mental state or, if not in a current episode, to reflect on prior symptoms and treatment. In its prior validation study, MDIS was positively associated with higher clinician-based ratings of insight, better attitudes toward medication, and less severe symptoms (Sturman and Sproule, 2003). Total scores range from 0 to 12 and 0 to 4 for each of three subscales (Awareness of illness, Attribution of symptoms to illness, and Need for treatment).

Affective Symptoms/States

The presence and severity of manic and depressive symptoms was measured with the Young Mania Rating Scale (YMRS (Young et al., 1978)) and the clinician-rated Montgomery-Asberg Depression Rating Scale (MADRS (Montgomery and Asberg, 1979)), respectively. Using data from the SCID, we also classified participants' current episode type within the month preceding each assessment (i.e., euthymic, hypomanic, manic, mixed, or major depressive episode).

Cognitive Ability

The neuropsychological battery comprised the following 10 measures: Digit Symbol—Coding and Letter-Number Sequencing subtests from the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III (Heaton et al., 2001) raw scores), Trail Making (Number-Letter Switching total time), Verbal Fluency (Letter Fluency total correct, Category Fluency total correct, Category Switching total correct) and Color-Word Interference (Inhibition and Inhibition/Switching subtests total correct) from the Delis-Kaplan Executive Function System (D-KEFS) (Delis et al., 2001b), Hopkins Verbal Learning Test – Revised (HVLT-R (Shapiro et al., 1999); total correct across three learning trails); and the Continuous Performance Test – Identical Pairs Version (CPT-IP; d'prime mean 2-, 3-, and 4-digit trials) (Cornblatt et al., 1988). For our analyses, we converted the raw scores into z-scores (with all scores expressed so that higher z-scores reflected better cognitive performance) to calculate a Global Cognitive Composite. The Composite was only calculated when scores from at 7 of the 10 tests were available. None of the composite scores were excluded as a result of having fewer than 7 of the tests available. The internal consistency of the composite score was high at baseline (Cronbach's Alpha = 0.861). For descriptive purposes, we also converted each of the raw scores to an age-corrected scaled score (normative mean 10, SD = 3) based on standard published norms for each test (Wechsler, 1997, Delis et al., 2001a, Nuechterlein and Green, 2006) coded such that higher values represent better performance.

Statistical Analyses

All variables were assessed for normality and non-parametric tests were conducted when necessary. We first determined associations at baseline between MDIS (insight) and demographic/clinical variables using Pearson or Spearman correlations and chi-square tests. Using the longitudinal data, we then calculated the Intra-Class Correlation Coefficient for the MDIS in an intercept-only model with subjects entered as a random effect. We also examined test-retest correlations among subsequent MDIS scores. We then examined the lagged (+/-1,2,3 time points) correlations between insight and symptoms, modeling our analyses on the prior work of Stiglmayr et al. (2008) (Stiglmayr et al., 2008) and described

in Hayes et al.(1998) (Hayes, 1998). P-values from predictor and outcome correlations within each lag are converted to a z-score and are pooled, with significance testing adjusted based on lagged interdependence within predictor and outcome variables. Z-tests were used to determine significance. We also employed linear mixed effects models to assess for linear trajectories in insight and symptoms over time; we assessed both simultaneous and lagged models (1 lag). As a complement to the lagged correlation approach, mixed models incorporate all lags (-1 lag, -2 lags, -3 lags) into the estimate. We assessed two separate sets of lagged models. In the first, we entered lagged insight (MDIS Total Scores) predicting symptom severity (MADRS and YMRS scores). In the second, we reversed the predictors and outcome and examined the lagged association of symptoms with insight. In all models, subjects were entered as a random effect with a first-order autoregressive covariance structure. Each person therefore has unique regression parameters, representing their own relationship between depression and cognitive performance. Finally, we repeated each of the models with Global Cognitive Composite as a main effect and an interaction term with either symptom severity or insight. We set the study alpha at 0.05.

RESULTS

Sample Characteristics (Table 1)

On average, participants were 45.4 years of age ($SD = 11.7$) and had approximately two years of post-secondary education. The majority were male (59.4%) and Caucasian (66%). A total of 78.8% of patients met criteria for Bipolar I disorder and 21.2% for Bipolar II disorder, and the majority (62%) were euthymic per SCID diagnosis at baseline (with 25% experiencing a major depressive episode, and 13% experiencing a hypomanic, manic, or mixed episode within the four weeks preceding the baseline evaluation). Baseline depressive and manic symptoms were, on average, in the mild severity range. A total of 38% of the participants had a prior history of substance use disorders (none had current substance dependence disorders per exclusion criteria). On the MDIS, scores were skewed toward positive insight, with 44% of participants scoring at ceiling (MDIS score of 12) at baseline. The baseline mean Neurocognitive Composite Scaled Score was 9.5 ($SD = 2.3$) which is close to the normative mean scaled score of 10, suggesting minimal overall cognitive impairment in the sample. However, there was also substantial heterogeneity in cognitive function in the sample, as the observed range for the Neurocognitive Composite Scaled Score ranged from 4.7 to 14.8. Due to the non-normal distribution, non-parametric tests or transformations were employed for subsequent analyses.

In terms of current medication status, 71.7% of patients were taking a mood stabilizer, 37.7% an anti-depressant, and 42.7 % were taking an anti-psychotic. Some participants were taking a combination of more than one of these drug classes including 2.8% of patients on both antipsychotics and anti-depressants, 14.2% on both anti-depressants and mood stabilizers, 16.4% on both mood stabilizers and anti-psychotics, and 16% on all three.

Baseline Associations with Insight

Insight (MDIS Total score) was not associated with age ($\rho = 0.012$, $p = 0.905$), education ($\rho = 0.149$, $p = 0.131$), sex ($F(1,102) = 0.5$, $p = 0.707$), or ethnicity ($F(1,102) = 0.1$, $p = 0.919$).

Insight was significantly lower among married patients (married: $m=9.2$, $sd=2.9$ vs. not married $m=10.8$, $sd=1.4$, $F(1,102)=12.5$, $p=0.001$). Insight was negatively associated with YMRS scores ($\rho=-0.239$, $p=0.015$), but not with MADRS ($\rho=-0.020$, $p=0.844$), substance abuse history ($F(1,102)=1.5$, $p=0.212$) nor age of onset of illness ($\rho=0.062$, $p=0.571$). Notably, there was no difference in MDIS scores between patients who were manic/mixed/hypomanic vs. depressed vs. euthymic at baseline ($F(2,94)=0.2$, $p=0.813$). In regard to MDIS subscales, YRMS scores negatively correlated with Awareness of Illness ($\rho=-0.237$, $p=0.016$) but not with the Attribution or the Need for Treatment subscales. MADRS scores did not correlate with any of the MDIS subscales. Global cognitive ability also did not correlate with MDIS Total score. However, Global cognitive ability was negatively associated with the Need for Treatment subscale ($\rho = -0.195$, $p=0.050$).

Longitudinal Analyses

Reliability—The intra-class correlation coefficient (ICC) of MDIS scores with subjects as a random effect was 0.518; stable constructs are typically associated with ICCs that are greater than 0.75, which indicates that insight varies within-patients over time. Test-retest correlations on subsequent testing occasions were moderate to high (baseline to 6 weeks: $\rho=0.707$, $p<0.001$, 6 weeks to 12 weeks: $\rho=0.550$, $p<0.001$, 12 weeks to 24 weeks: $\rho=0.456$, $p<0.001$).

Univariate Lagged Correlation Analyses—As seen in Figure 1, severity of manic symptoms at T-2 and T-3 was significantly and negatively associated in pooled dependent correlation with MDIS score, at roughly the equivalent strength of association as in simultaneous correlation (T-1 was not significant). In contrast, insight preceding manic symptoms was not significant for T-1, T-2, and T-3. There were no lagged associations between depressive symptoms (MADRS) and MDIS scores, or vice versa (Figure not shown).

In addition to dimensional symptom measures, we examined the influence of mood state within 2 months of baseline (hypomanic/mixed/manic episode or major depressive episode vs. euthymic state) on subsequent MDIS Total Scores at 6, 12, and 26 weeks. There were no pairwise differences between manic/hypomanic/mixed ($n=13$), depressed ($n=24$), or euthymic ($n=60$) on MDIS Total Scores at 6, 12, or 26 weeks. We also examined baseline MDIS Total Scores and the likelihood of later depressive or manic episodes. We found that *higher* Baseline MDIS Score was significantly associated with being in more than one major depressive episode at subsequent assessments compared to none ($F(2,86)=3.2$, $p=0.049$). There was no association between baseline MDIS Score and subsequent presence of manic episodes in subsequent assessments.

Mixed Effects Models—We focused on manic symptoms and insight in mixed-effects models given the lack of significant correlations in lagged analyses with depressive symptoms. In the first model, with MDIS score as a predictor lagged (t-1) and time (with subjects as a random effect), the association between lagged MDIS score and YMRS scores was not significant (estimate=-0.47, standard error=0.25, $t=1.8$, $p=0.070$). In the second model, with lagged (t-1) YMRS score as predictor, the associated between lagged YMRS

score an MDIS score was significant (estimate=-0.037, standard error=0.016, $t=2.4$, $p=0.020$). In both models, time was not significant indicating a lack of marked linear trends in YMRS score over the course of the study. Finally, we added Global cognitive ability as a main effect and as an interaction term with YMRS scores, repeating the analyses above. The results did not change, and neither Global cognitive ability nor the interaction term were significant.

DISCUSSION

In this prospective 6-month longitudinal study, we found a number of potentially clinically relevant aspects of the relationships among the trajectories in affective symptoms, cognitive ability, and clinical insight. Although a sizable proportion of patients were at ceiling on the MDIS (thus indicating no impairment in insight), scores fluctuated across follow up assessments, which is consistent with the view that insight is a fluid construct rather than a trait in bipolar disorder (Latalova, 2012, Cassidy, 2010). At baseline and as in prior cross-sectional studies, more severe manic symptoms were associated with worse insight, particularly diminished awareness of illness. In contrast to hypotheses, our longitudinal time-lagged findings were that more severe manic symptoms preceded diminutions in insight, rather than poor insight predicting worsening manic symptoms. Moreover, although we found that depressive symptoms were minimally associated with insight at baseline, better insight at baseline was associated with a greater likelihood of presence of a major depressive episode at subsequent assessments. In contrast to prior studies, global cognitive abilities were not associated with baseline values or to trajectories of insight (although were associated with the Need for Treatment). Overall, our findings suggest that insight is a changeable aspect of bipolar disorder over time, is modestly associated with manic symptoms, and that diminished insight may be more likely to follow rather than precede manic exacerbations.

There are a number of limitations of this study that deserve mention. The sample was comprised of outpatients who were participating in treatment, and who were, on average, exhibiting a mild level of affective symptom severity and high levels of insight. As such, the strength of association between symptoms and insight, and its direction of influence, might differ in more acutely ill and/or inpatient samples. Insight was measured by a single interviewer administered self-report instrument (the MDIS). Although found to be externally valid with regard to other clinician-rated insight instruments in prior study (Sturman and Sproule, 2003), future study should examine alternative methods as well as trajectories of related constructs such as cognitive insight. As a sizeable number of patients scored at ceiling on this instrument, it is possible that more subtle degradations of insight were undetected. A larger sample size over a longer follow up period may have enabled greater power to detect potential moderators as well as patterns of illness course.

The mean level of insight on the MDIS was comparable to that found in a prior study of outpatients with bipolar disorder, with most patients evidencing high levels of insight (Sturman and Sproule, 2003). Nonetheless, our study suggests that the short-term course of insight is rather unstable in bipolar disorder. In comparison to other aspects of bipolar disorder, the MDIS Total Score was approximately as variable within-patients as were total

scores on the MADRS measure of depressive symptoms. Few sociodemographic predictors were associated with insight, and cognitive ability was not associated with overall insight. However, Global cognitive ability was associated with the perceived need for treatment subscale. Prior work had suggested an association between specific cognitive abilities and insight (Dias et al., 2008), which was only evident on one of the three insight subscales (Need for Treatment). It is notable that the strongest contributor to insight, manic symptoms, was modest in association and so a substantial proportion of the between and within person variation insight was unexplained. Given that insight has important ramifications for treatment outcome, future study should examine the influence of clinical features outside of the core aspects of bipolar disorder, which may include other symptom clusters, attitudinal and treatment-related factors (e.g., psychotic features, therapeutic alliance, past exposure to psychoeducation).

In contrast to what was expected, insight was a lagging indicator of manic symptoms rather than a precursor. Our study suggested that manic symptoms observed at baseline were associated with worse insight 6 months later, suggesting that resolution of insight after manic episodes may be delayed. This is consistent with the findings of Yen and colleagues (2007) (Yen et al., 2007b) who found that a subgroup of recurrent patients did not experience resolution of insight after remission from manic episodes. Previous work in schizophrenia using structural equation modeling has also indicated that anxiety/depressive symptoms predict insight rather than the other way around in schizophrenia (Hwang et al., 2009)[g484] These findings demonstrate the potential utility of longitudinal causal modeling in bipolar disorder to evaluate assumptions of psychosocial intervention empirically. The clinical implication of this finding is that even though insight may typically improve after a manic episode (Ghaemi and Rosenquist, 2004), manic symptoms represent a risk factor for residual poor insight. Thus, psychosocial interventions may be particularly useful *after* manic episodes. Additionally, it may be inferred that continued efforts to improve insight, particularly for patients experiencing recurrent manic episodes, is an important component to incorporate into future interventions. Groups receiving psychoeducation focusing on illness awareness, treatment adherence, early detection of prodromal symptoms, and lifestyle regularity have been shown to experience a significant decrease in the number of relapses and number/length of hospitalizations as well as a significant increase in time to recurrences relative to control groups not receiving psychoeducation in these areas (Colom et al., 2003).

Despite the fact that better insight is reported to have some protective benefits and even though depressive symptoms were not strongly associated with insight in lagged or simultaneous analyses, higher insight at baseline in our study was associated with increased probability of a depressive episode observed at later assessments. A positive relationship between insight and subsequent depressive episodes is consistent with some prior work in schizophrenia (Drake et al., 2004) although less often is it seen in bipolar disorder, at least cross-sectionally. It is unclear why greater insight may be associated with risk for depressive episodes, although in prior studies insight is positively associated with hopelessness (Kim et al., 2003). It may be that experiential strategies, such as those used in acceptance and commitment therapy, may be useful in increasing the emotional “tolerance” of accepting and perceiving a need for treatment, while orienting patients toward valued life directions. In any

case, it is evident that a substantial amount of within-and between-person variation in insight is unexplained, and finer-grained longitudinal research could help to identify what role insight has in chronic disability experienced by people with bipolar disorder over time.

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Figure 1.
Time Lagged and Simultaneous Correlations between YMRS Scores and Insight

Table 1

Sample Characteristics at Baseline (n=106)

Variable	Range	Mean (SD) or %
DEMOGRAPHIC		
Age (Years)	21-71	45.4 (11.7)
Sex (% Female)	---	40.6%
Ethnicity (% Caucasian)	---	66.0%
Education (Years)	7-20	14.6 (2.3)
Marital Status (% Married)	---	16%
CLINICAL HISTORY		
Age of Onset of Symptoms	5-49	20.0 (9.1)
Substance abuse history (% with lifetime diagnosis)	---	61%
CLINICAL STATE		
MDIS Total Score	2-12	10.6 (1.9)
MDIS Awareness of Illness	0-4	3.5 (0.9)
MDIS Attribution	0-4	3.6 (0.9)
MDIS Need for Treatment	0-4	3.5 (0.9)
YMRS Total Score	0-34	8.0 (7.7)
MADRS Total Score	0-43	14.0 (9.9)
Neurocognitive Composite Scaled Score	4.7-14.8	9.5 (2.3)

MDIS: Mood Disorders Insight Scale; YMRS: Young Mania Rating Scale; MADRS: Montgomery Asberg Depression Rating Scale