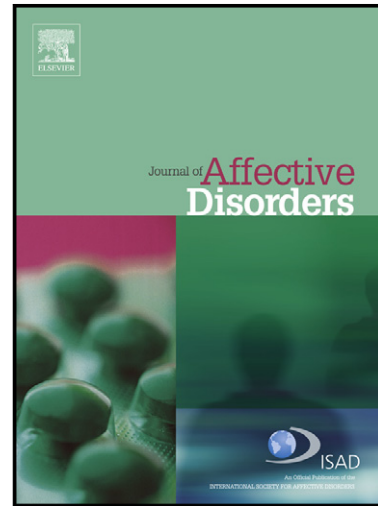


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The impact of insight in a first-episode mania with psychosis population on outcome at 18 months.

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Abstract

Background: To explore whether poor initial insight during a first episode of mania with psychotic features was predictive of poor psychosocial and clinical outcomes at 18 months.

Methods: Secondary analysis was performed on data collected during an 8-week RCT comparing the efficacy of olanzapine versus chlorpromazine as an adjunct to lithium, and at 18-month follow-up. 74 participants were divided into three groups (no insight, partial insight, full insight) according to the insight item from the Young Mania Rating Scale (YMRS). Differences between these three groups were examined at baseline and at 18 months on measures of symptoms (YMRS, HAMD-21, CGI-S), and social and occupational functioning (SOFAS). Baseline differences between the three groups were determined

using general linear models and chi-squared analyses. Group differences from baseline to 18-month follow-up were determined using repeated measures general linear models.

Results: At baseline there were significant differences between the three insight groups in terms of mania and functioning, but at 18 months all groups had improved significantly in terms of psychopathology, mania, depression and social and occupational functioning. There were no significant differences between the three groups at study completion with respect to these domains.

Limitations: The study was limited by the lack of availability of a more detailed rating scale for insight, and it did not account for the duration of untreated psychosis (DUI).

Conclusions: Poor initial insight during a first episode of mania with psychotic features does not predict poor clinical and psychosocial outcome at 18 months.

Key words: Insight; First-episode; Mania; Prognosis; Bipolar Disorder.

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1.0 Introduction

In Homer's *Odyssey*, the sorceress Circe warns Odysseus about the perils he will face sailing into the Sirens' domain; how men have been lured to their deaths on the rocks below through the enchantment of their song. Yet, Odysseus is curious. Knowing that the song will overcome his reason, he orders his men to strap him to the mast and not let him go, no matter how much he protests, whilst the crew plug their ears with beeswax. As they sail through, the song is beautiful, intoxicating, urging Odysseus to sail closer. But as Odysseus thrashes and rails, the deafened crew row on. As the spell fades, Odysseus regains his faculties and is released. They are safe (Homer, 1997).

Homer's classic story richly illustrates the complexity of insight as a psychological concept, demonstrating that in Odysseus's case at least, it is 'state-dependent': madness ensues, insight diminishes; symptoms ameliorate and insight returns. Yet theories of insight delve deeper, and the aetiology of poor insight remains only partially understood. There is broad agreement that insight is a multi-dimensional, as opposed to a binary phenomenon, in that a person is not simply 'insightful' or 'insightless' but exhibits degrees of understanding and awareness in various domains, depending on the clinical stage of illness or remission (Yen et al., 2007). David (1990, pp. 798-809) illustrates this in his definition of insight, that it is an "awareness that one is suffering, in a general way, from a mental (as opposed to a physical) disturbance which could be an illness; more specific awareness that certain experiences including beliefs and perceptions may not be veridical, and further that they too could be part of an illness; acknowledgement of the medical implications of the above, a concrete token of which is informed acceptance of treatment" (cited in Surguladze and David, 1999, p. 163).

De Hart et al. (2009, pp.507-512) and Bressi et al. (2012, pp. 619-624) described three models to explain the aetiology of poor insight. The *clinical model* recognises poor insight as a symptom of mental illness (Amador et al., 1994), whilst the *psychological model* frames poor insight as a coping strategy because greater degrees of insight are associated with worse depressive symptoms (Amador et al., 1994; Pyne et al., 2001). Finally, the *neuropsychological model* describes how executive function and memory play a part in framing current aberrant phenomena in the light of past experience, and if there are deficiencies in these cognitive functions, poor insight may result (Yen et al., 2008,b).

Lack of insight into illness is common across many psychiatric disorders. Individuals with schizophrenia often suffer a lack of insight (Amador and Gorman, 1998) and poor insight has been found to predict adverse clinical and psychosocial outcomes in this population (Amador et al., 1994; Yen et al., 2002). In a study of first-episode schizophrenia patients by Mutsatsa et al. (2006, pp. 356-363) there was a positive correlation between greater levels of global insight and depressive symptoms. The authors describe this association in the context of 'depressive realism' (a term originally coined by Alloy and Abramson (1998, pp. 223-265)) – i.e. "depressed individuals will view themselves more realistically and accurately", whilst "non-depressed individuals have an optimistic cognitive bias that produces an exaggerated belief in their own abilities" (Mutsatsa et al., 2006, p.360). Mood symptoms aside, in the schizophrenia population the link between insight and recovery is less likely to be as synchronous *over time* (McGorry and McConville, 1999). There is some suggestion that as schizophrenic patients journey through remission their level of insight increases independently to their (objective) improvement in symptoms such as delusions and hallucinations (Jørgensen, 1995), or even remains impaired. In other words, in schizophrenia, insight appears to be a trait-like condition (Ghaemi and Rosenquist, 2004).

On the other hand, insight in *bipolar disorder* appears to be state-dependent; it waxes and wanes depending on illness severity, or more specifically with proximity to the manic-end of the spectrum (Ghaemi and Rosenquist, 2004). Interestingly insight is largely intact during episodes of non-psychotic depression (mirroring 'depressive realism' seen in schizophrenia) (Ghaemi et al., 1997), whilst it is usually impaired during manic episodes (Ghaemi et al., 1995). This may lead to over-reporting of depressive symptoms and under-reporting of manic symptoms, thereby affecting diagnostic accuracy (Ghaemi and Rosenquist, 2004).

The concept of the 'manic defence' suggests that mania may be a psychologically protective mechanism (Klein, 1974), with recognition that a "...gross failure in self-evaluation..." can be common (Cassidy et al., 2001, p.399). Some researchers have described a more neuropsychological perspective suggesting that cognitive deficits in insight occur outside a person's awareness (McGorry and McConville, 1999). However, it is notable that while improving insight has traditionally been viewed as a goal, if not a pre-requisite of treatment for mania, such improvements can have both positive and negative consequences for this patient group (Macneil et al., 2009).

The question of whether there is a *predictive* value to impaired insight in bipolar disorder, in relation to clinical and psychosocial outcomes, remains unanswered. Yen et al. (2008a, pp. 121-127) followed a cohort of bipolar I patients over 2 years, and found that insight in terms of acknowledgement of the illness and relabeling of psychotic phenomenon at baseline did not have any significant effect on adverse clinical outcomes. However, they also found that initial impaired insight into the *validity of treatment*, as well as an increased numbers of prior hospital admissions were independent predictors of symptom severity at follow-up (Yen et al., 2008a). This may reflect lack of confidence in pharmacotherapy, subsequent lack of compliance and a fatalistic approach to the chronicity of the condition (Bressi et al., 2012).

It is important then to understand insight in a first-episode psychotic mania population, a sample that has not been influenced by prior experience of the mental health system, because if poor initial insight during the *first* episode predicts worse outcomes over time, this could be a useful intervention point. To the best of our knowledge, research into the relationship between initial insight (assessed at first presentation to psychiatric services) and longitudinal psychosocial/clinical outcomes, specifically within the first-episode psychotic mania group, is scant. Many of the previous studies in the literature have been cross-sectional in nature, with patients not necessarily recruited at the same phase of illness. This subjects them to confounders, including exposure to prior treatment.

Thus, the aim of this study was two-fold: (i) to examine difference between three insight groups (insight, partial insight, and full insight) on demographics and clinical variables; and (ii) to delineate whether insight during the first episode of psychotic mania predicted 18-month symptomatic and functional outcomes. It was expected that poor insight would be prevalent in individuals experiencing the acute symptoms of first episode mania. It was further predicted, that those with lower levels of insight during first episode mania will have more severe psychopathology, higher levels of mania, lower depression, and lower levels of social and occupational functioning at 18-month follow-up.

2.0 Method

2.1 Design

This study involved secondary analysis of data collected for a randomised controlled trial (RCT) which involved comparison of olanzapine versus chlorpromazine as an adjunct to lithium in the treatment of a first-episode manic episode with psychotic features (Conus et al., in submission). The treatment phase ran over 8 weeks, with follow-up occurring up to 18-months post treatment (Macneil et al., 2012).

A detailed description of the demographics and method for the RCT has been described elsewhere (Conus et al., in submission), but some elements are worth emphasising in relation to the present study:

2.2 Patient Population

Participants were males and females aged between 15 and 28 who were admitted to the Early Psychosis Prevention and Intervention Centre (EPPIC), Melbourne, Australia for the treatment of a first episode of psychotic mania. All patients admitted between October 2001 and February 2006, with the first episode of psychotic mania, were assessed against inclusion/exclusion criteria. All participants were diagnosed with a first manic or mixed episode with psychotic features within bipolar I or schizoaffective disorder, as per DSM-IV criteria (American Psychiatric Association, 1994). A minimum baseline Young Mania Rating Scale score of 20 or more was also required, as was informed consent. However, to avoid selection bias, and in accordance with local Ethics Committee guidelines, those involuntary participants who lacked capacity were consented by the authorised treating psychiatrist on their behalf, until such time as they clinically improved. At this juncture, they were given the opportunity to provide informed consent to participate in the trial, and those that refused had their data destroyed.

Exclusion criteria included: organic mental disease including mental retardation; the use of neuroleptics or mood-stabilizers in the two months preceding admission to EPPIC; a prior significant history of mental illness; pregnancy or lactation; history of epilepsy; history of severe allergy or hypersensitivity to medications; and clinically relevant biochemical or haematological abnormalities. Patients who were non-fluent in English, and those who posed an immediate risk to themselves or to others were also excluded (Conus et al., in submission).

2.3 Assessment

2.3.1 Insight

Insight into illness was assessed at baseline using the single insight item from the Young Mania Rating Scale (YMRS). Insight on this item is measured on a five-point scale. For the purpose of this study, this item was recoded into the following three categories: (i) Insight (0: “Present; admits illness; agrees with need for treatment” and 1: “Possibly ill”); (ii) Partial insight (2: “Admits behaviour change, but denies illness” and 3: “Admits possible change in behaviour, but denies illness”); and (iii) No insight (4: “Denies any behaviour change”).

The design of this current study, i.e. employing secondary analysis of data previously collected, precluded use of more insight-specific rating scales, because they were not utilised in the original RCT and its follow-up (Conus et al., in submission; Macneil et al., 2012). The Scale to assess Unawareness of Mental Disorder (SUMD) and the Schedule for the Assessment of Insight – Expanded Version (SAI-E) have been developed to assess the multiple domains of insight and use of these tools now afford researchers a better empirical understanding of how insight changes over time, and indeed how insight differs between disease processes (Amador et al., 1993; Kemp and David, 1996). The present study, however, was limited to being more binary in its assessment of insight.

2.3.2 Diagnosis

With psychiatric diagnoses during the early stages of a psychotic disorder being inherently fragile, further assessment at 12 months was felt necessary. The Structured Clinical Interview for DSM-IV Axis I Disorders – Patient Edition (SCID-I/P) (First et al., 2002) was used to confirm a diagnosis of either bipolar I or schizoaffective disorder at this point, adding robustness to the study.

2.3.3 Other measures

At baseline all participants in the RCT had faced a battery of assessment tools evaluating illness severity, depressive symptoms, positive psychotic symptoms, negative symptoms, substance abuse co-morbidity and functional level (Conus et al., in submission). Of particular relevance to the present study were the Young Mania Rating Scale (YMRS), the Clinical Global Impression Scale (CGI-S) (Guy, 1976) and the 21-item Hamilton Depression Rating Scale (HAMD-21) (Hamilton, 1967). Social and occupational functioning was measured using the Social and Occupational Functioning Assessment Scale (SOFAS) (Goldman et al., 1992). These measures were re-administered at 18 months.

2.4 Procedure

During the original RCT, research assistants, who were blind to treatment status, used diagnostic, symptomatic and functional assessments to prospectively evaluate participants. All participants were case-managed, and received regular medical reviews with pharmacological treatment randomised to either ‘lithium + olanzapine’ or ‘lithium + chlorpromazine’ (Conus et al., in submission; Macneil et al., 2012).

2.5 Data Analysis

All analyses were conducted using IBM®SPSS® Version 21. Baseline differences between the three groups were determined using general linear models and chi-square analyses. For the general linear

models, trend analysis was also conducted to determine whether a linear or quadratic trend could fit the data. Post hoc analyses were conducted when required using the Tukey Honestly Significant Difference (HSD) test. Group differences from baseline to 18-month follow-up were determined using repeated measures general linear models; group was the between subjects variable and time (baseline and 18 months) was the within subjects variable. From these models, the main effects for group (overall was there a difference between the three insight groups regardless of time) and time (overall was there change from baseline to 18 months regardless of group) were tested along with the interaction between group and time (do the three insight groups differ significantly across time). When the main effect for group or the interaction term was significant, simple main effects analyses and post hoc analyses using Tukey HSD test were conducted.

3.0 Results

There were 98 individuals assessed for eligibility and 83 were randomised. Of those who were randomised, nine refused access to data after stabilisation of symptoms, leaving 74 cases at baseline (refer to Conus et al. (in submission) for further details). Of 83 patients initially recruited into the original RCT, follow-up data was available for 46 at 18-months follow-up. There were no differences between those who did not complete 18 months follow-up in terms of demographic and clinical variables at baseline. The mean age was 21.5 (SD=2.9), with 67.6% of participants being male. Just over 80% (82.4%, $n=64$) of the cohort had a diagnosis of bipolar I. The remaining 17.6% had a diagnosis of schizoaffective disorder (Table 1).

Out of the sample of 74 patients, 21.6% ($n=16$) had insight into their mental state at baseline, 44.6% ($n=33$) had partial insight and 33.8% ($n=25$) had no insight.

There were no significant differences between the three insight groups in terms of age, gender ratio or diagnoses (refer to Table 1). At study entry, all three groups differed significantly with respect to overall symptom severity on the CGI-S, $F(2,71)=26.30$, $p<.001$, with a linear relationship between level of insight and symptom severity noted, $F(1,71)=33.58$, $p<.001$. Post hoc analyses indicated that those with insight had significantly lower symptom severity scores compared to the two remaining groups, $p<.05$.

At study entry, all three groups differed significantly in terms of manic symptoms, $F(2,71)=26.30$, $p<.001$. There was a linear relationship between level of insight and severity of manic symptoms, $F(1, 71)=52.56$, $p<.001$. Post hoc analyses indicated that all three groups differed significantly from one another at the $p<.05$ level, with those having no insight having the most severe manic symptoms. There was also a significant difference between the three groups with respect to functioning at baseline, $F(2,71)=14.17$, $p<.001$, with a linear trend being noted, $F(1,71)=27.36$, $p<.001$. Those with insight had significantly better social and occupational functioning than those with partial or no insight (at the $p<.05$ level).

There was a significant interaction between insight group and time for YMRS, $F(2, 43)=3.29$, $p=.047$. This finding was largely driven by significant differences between the insight groups for baseline YMRS scores; there were no significant group differences at 18-month follow-up. The interactions between group and time were not significant for the CGI-S, $F(2, 50)=0.38$, $p=.684$, HAMD, $F(2, 40)=0.91$, $p=.412$, and the SOFAS, $F(2, 50)=2.26$, $p=.115$. The main effects for time were significant for all variables, indicating that all three patient groups had improved significantly in terms of YMRS, CGI-S, and HAMD-21 scores, reflecting global remission of manic and depressive symptoms as well as reduction in the

severity of psychopathology. SOFAS scores across all three groups also significantly improved, reflecting improvements in social and occupational functioning (see Figures 1 to 4).

There were no significant differences *between* the three groups at 18-month follow-up on any measure (all $p > .05$).

Discussion

The present study was a secondary analysis of data collected during a RCT and the follow-up at 18 months (Conus et al., in submission; Macneil et al., 2012). The RCT allowed mining of a rich data seam, which to the best of our knowledge is unique. We were able to longitudinally investigate a cohort of patients, with a de-novo diagnosis of mania with psychotic features, over months rather than weeks. By virtue of the RCT design, a key strength of the data set is that both pharmacological and psychological interventions have been controlled for, at least during the initial 8 weeks of the trial.

Our hypothesis was that poor baseline insight during first presentation of mania would predict poor clinical and psychosocial outcomes at 18 months. The hypothesis in itself is reasonable as the first episode of any psychotic disorder is a turbulent and kinetic time. It is a time of maximal confusion and denial, when the mind first begins to reframe current aberrant phenomena in the light of past experience and 'reality' implodes. Lacking insight at this juncture, whilst understandable, would presumably be unhelpful in terms of future compliance to treatment.

However, this study refutes the hypothesis – initial insight was not associated with symptomatic or functional outcome at 18 months. In an acutely unwell population of individuals with a first-episode of psychotic mania insight appears to be a global casualty, with only 21.6% retaining full insight. This may support the theory that loss of insight is symptomatic of mania with psychotic features (Amador et al., 1994). Indeed, those with poorer insight had more severe psychopathology and manic symptoms, as well as poorer functioning at baseline. In addition, poorer insight in first-episode mania appears to be unrelated to depressive symptoms. This may reflect the paucity of depressive symptoms in our population, i.e. the number of patients presenting with mixed-mania, or could add credence to the belief that poor insight is not a feature of depressive illness (MacQueen et al., 2001).

Over the 18-month study period all three groups ('no insight', 'partial insight', 'full insight' at baseline) significantly improved in terms of severity of psychopathology, mania, depression and social/occupational functioning. There were no significant differences between these three groups at 18 months, which suggests that poor insight is not a clear predictor of longitudinal outcome. Why would this be the case if lack of insight has been shown to be a proxy marker for severity of initial symptoms? Certainly all patients received high quality psychosocial interventions in a specialist early psychosis service. All patients were robustly medicated with a mood-stabiliser and antipsychotic, at least for the 8 weeks of the RCT until such time that treating doctors were free to adjust medications as clinically appropriate. All participants received regular case management throughout the entire 18 months, whilst some were also seen by a psychologist and received a manualised psychological treatment for young people with first episode mania (Macneil et al., 2012). The latter intervention included a module specifically addressing psycho-education, insight and adaption. However it must be added that psycho-education is implicit within case management, and that these differing psychosocial interventions were randomised across the three insight groups. It would seem that no matter how severe the initial insult, early intervention has positive outcomes.

This view compliments the work of Yen et al. (2008a, pp. 121-127) during their 2-year prospective study. They found that poor initial awareness of illness was not an independent predictor of outcome in bipolar I patients, which is in keeping with our findings. However, they did find that the number of

previous hospitalisations and impaired baseline insight into the *validity of treatment*, were independent predictors of clinical severity at 2 years. But these were the only elements of insight (as measured by the SUMD) that had positive predictive value for clinical outcome. Our cohort of patients had no previous hospitalisations and no prior experience of the mental health system. They were therefore less likely to feel hopeless about future disease chronicity and the efficacy of treatment. As the recovery model was consistently espoused during case management, poor compliance was less of an issue. McQueen et al. (2001, pp. 163-170) found that between 30-60% of bipolar patients fail to regain full social and occupational functioning, and it seems that older patients have more insight throughout the course of their illness into the negative impact of psychopathology on social outcome (Bressi et al., 2012). But ours was a youth cohort which was still responsive to early intervention, and it did achieve a return to high social and occupational functioning, as evidenced by high SOFAS scores across all insight groups.

The question of whether insight at baseline might predict insight at follow-up naturally follows on from our original hypothesis. We were able to answer this, to some degree, with our study population. At 18 months, insight data was available for 46 out of the 83 patients initially recruited. Only one patient had no insight at follow-up, and this patient had no insight at baseline. Of those that had no insight at baseline, 9 had full insight at 18 months and 3 had partial insight. No further analysis could therefore be conducted because of the lack of variability in the 18-month insight domain of the YMRS ($X^2(1)=.596, p=.440$). It seems that insight, or lack thereof, at baseline is unrelated to the level of insight at 18-month follow-up, at least in our sample population. To put this another way, if insight was a global casualty during first-episode psychotic mania, insight was a global spoil during recovery and remission.

This present study has some limitations, not least the simplicity and binary nature of the insight item within the YMRS. The Scale of Unawareness in Mental Disorder (SUMD) is a far superior scale as it measures multiple aspects of insight into illness, and is valid and reliable for large groups of patients with psychotic mood disorders at various stages of their illness (Dell'Osso et al., 2002). However, the SUMD wasn't available to this present study by virtue of it being a secondary analysis of existing data. Future studies into lack of insight as a clinical/ psychosocial outcome predictor in the first-episode population may seek to use the SUMD tool instead. A further limitation is that we did not account for the duration of untreated illness (DUI), defined as the time between the first mood episode and the first adequate pharmacological intervention, which has been shown to be a positive predictor for adverse clinical outcome (Bressi et al., 2012). Altamura et al. (2010, pp. 385-391) for example, have found that those bipolar patients with longer DUI have a greater propensity to suicide. Future research should therefore consider the correlates between DUI and impaired insight as predictors of psychosocial and clinical outcome. Finally, we only controlled for pharmacological and psychological interventions during the initial 8-week RCT. Thereafter clinicians were free to treat in whatever way they felt clinically appropriate at the time. Ours was a secondary analysis of existing data, limited to the catchment area of southwest Melbourne. Further studies may wish to expand the sample size to include other geographical areas, as well as utilising a prospective study design. This would improve the generalisability of findings.

Conclusion

Our hypothesis that poor initial insight would be predictive of poor clinical and psychosocial outcome at 18-month follow-up was not supported by this study. However the data is important because it infers the validity of early psychosis intervention regardless of initial severity of illness and degree of insight. Returning to Odysseus and the Sirens, some might view the story as a classical paradigm of insight in first-episode mania, with insight being state-dependent. If we can support patients through their first episodes with robust psychological and pharmacological treatments, bound with assertive case

management just as Odysseus was bound to the mast, it appears that patients can come out well the other side.

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Contributors.

Leo Smith – First author, Psychiatry Registrar. Responsible for crafting the paper from an original poster by Shelton, Berk, Hasty, Cotton, Henry, Daglas, Gentle, McGorry, Macneil and Conus. Responsible for the Introduction (including literature review), Discussion and Conclusion.

Clare Shelton – Lead author on the original poster presented at the International Early Psychosis Association's 7th International Conference, Amsterdam, 2010. Developed the method for this study with Berk, Cotton and Macneil. Clare is also a clinical psychologist and case manager and delivered manualised psychological treatments utilised during the 18-month follow-up period.

Michael Berk – Professor. Head of the 'Mania Group' at Orygen Youth Health Research Centre. Overall responsibility for methodology of studies coming from the group. Approved the final manuscript.

Melissa Hasty – Melissa is a clinical psychologist and case manager and delivered manualised psychological treatments utilised during the 18-month follow-up period.

Sue Cotton – Psychologist and Senior Biostatistician. Responsible for Results and Data Analysis. Developed the method for this study with Berk, Shelton and Macneil.

Lisa Henry – Senior Research Fellow. Lisa takes on the senior administrative role in the 'Mania Group', and was involved in the logistics of the original RCT.

Rothanthi Daglas – Research Assistant. Involved in the administration of assessment tools.

Ellen Gentle – Research Assistant. Involved in the administration of assessment tools.

Patrick McGorry – Professor. Founder and Head of Orygen Youth Health Research Centre. Approved the final manuscript.

Craig Macneil – Lead author of a paper examining data at 18-month follow-up to the original RCT. Also developed the method for this study with Berk, Shelton and Cotton. Craig is a senior clinical psychologist and case manager and delivered manualised psychological treatments utilised during the 18-month follow-up period.

Philippe Conus - Lead author and designer of the original 'First episode mania RCT of olanzapine vs. chlorpromazine in addition to lithium.'

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Table 1

Comparison between three insight groups with respect to demographics and baseline clinical characteristics

		Full n=16	Insight Partial n=33	None n=25	Statistic	df	p value	
Demographics								
Age	M(SD)	20.3 (2.7)	22.0 (3.0)	21.6 (2.7)	F	2.05	2,71	.137
Gender %Male	% (n)	56.3 (9)	60.6 (20)	84.0 (21)	χ^2	4.75	2	.093
Diagnosis %Bipolar	% (n)	93.8 (15)	78.8 (26)	80.0 (20)	χ^2	1.82	2	.403
Baseline characteristics								
YMRS	M(SD)	28.0 (5.2)	35.6 (4.9)	40.9 (6.6)	F	26.30	2,71	<.001
CGI-S	M(SD)	4.7 (0.7)	5.7 (0.7)	6.0 (0.8)	χ^2	17.20	2,71	<.001
HDRS	M(SD)	6.9 (5.0)	8.7 (7.5)	8.5 (5.0)	F	0.49	2,71	.614
SOFAS	M(SD)	47.3 (10.0)	34.2 (10.7)	29.8 (10.3)	F	14.17	2, 71	<.001

* YMRS, Young Mania Rating Scale; CGI-S, Clinical Global Impressions Scale - Severity; HDRS, Hamilton Depression Rating Scale; SOFAS, Social and Occupational Functioning Scale

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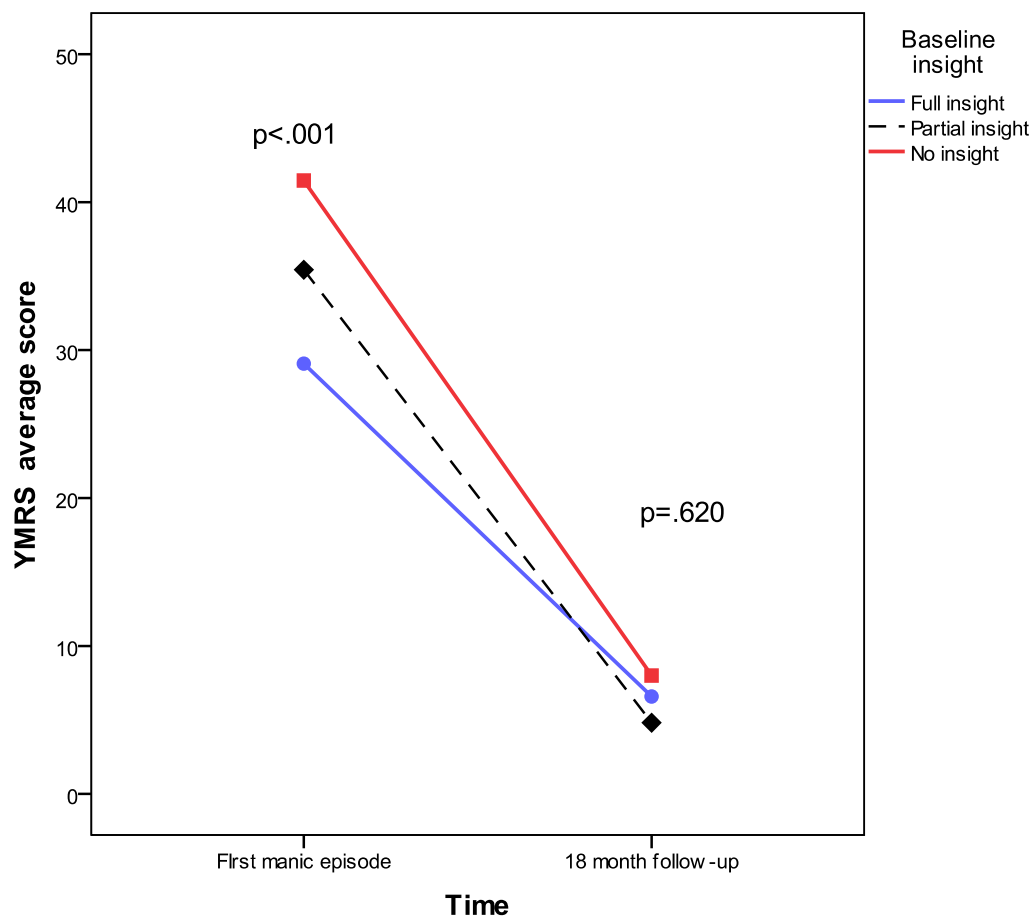


Figure 1. Change in YMRS scores over 18 months

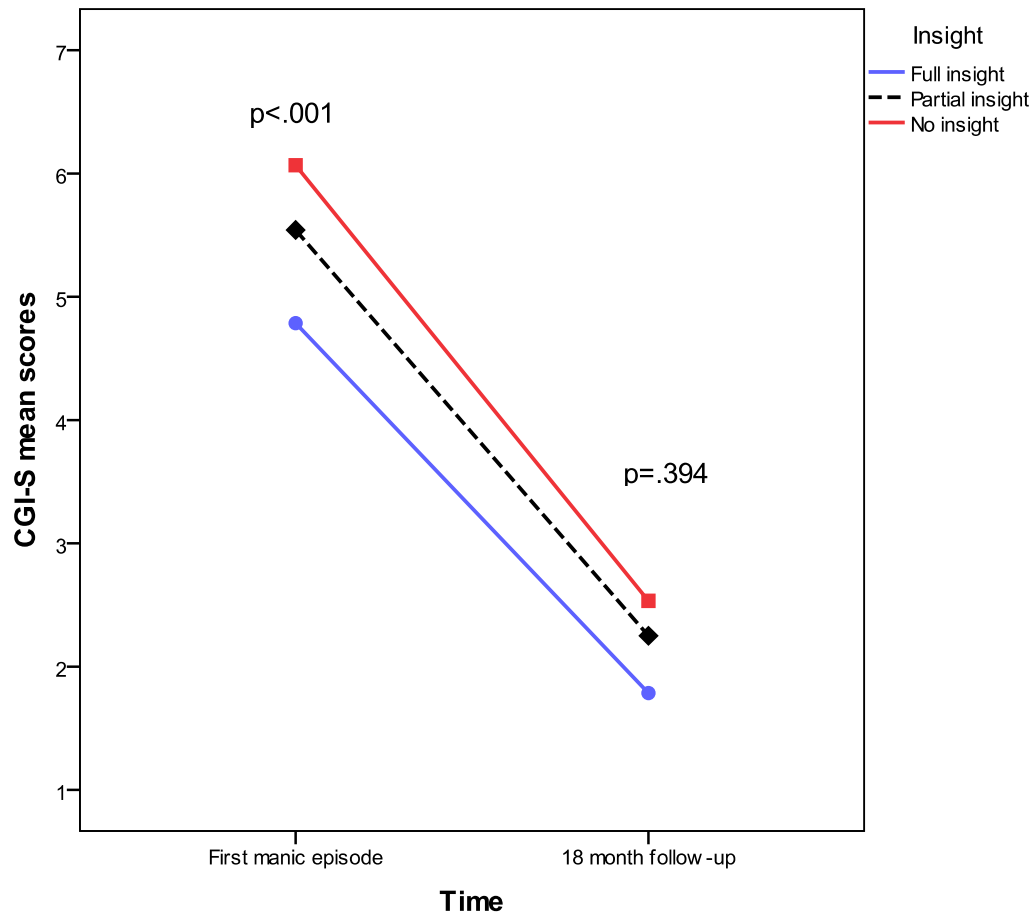


Figure 2. Change in CGI-S scores over 18 months

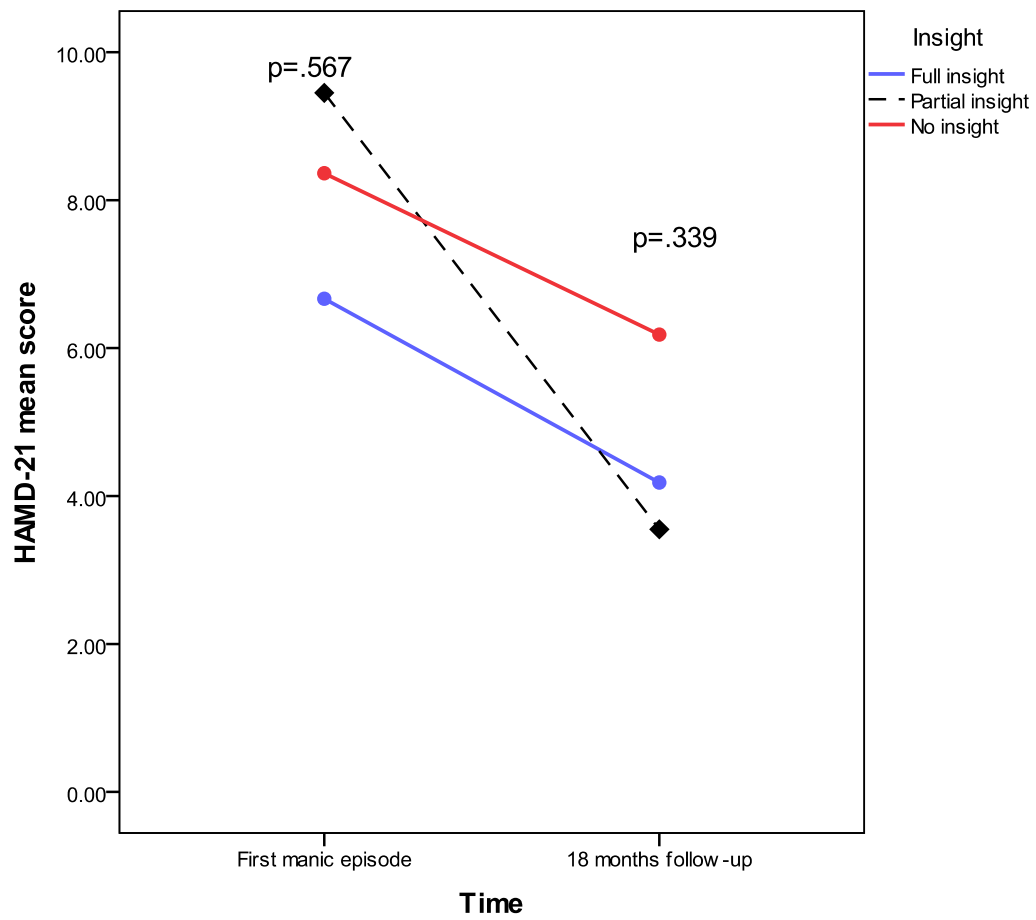


Figure 3. Change in HAMD-21 scores over 18 months

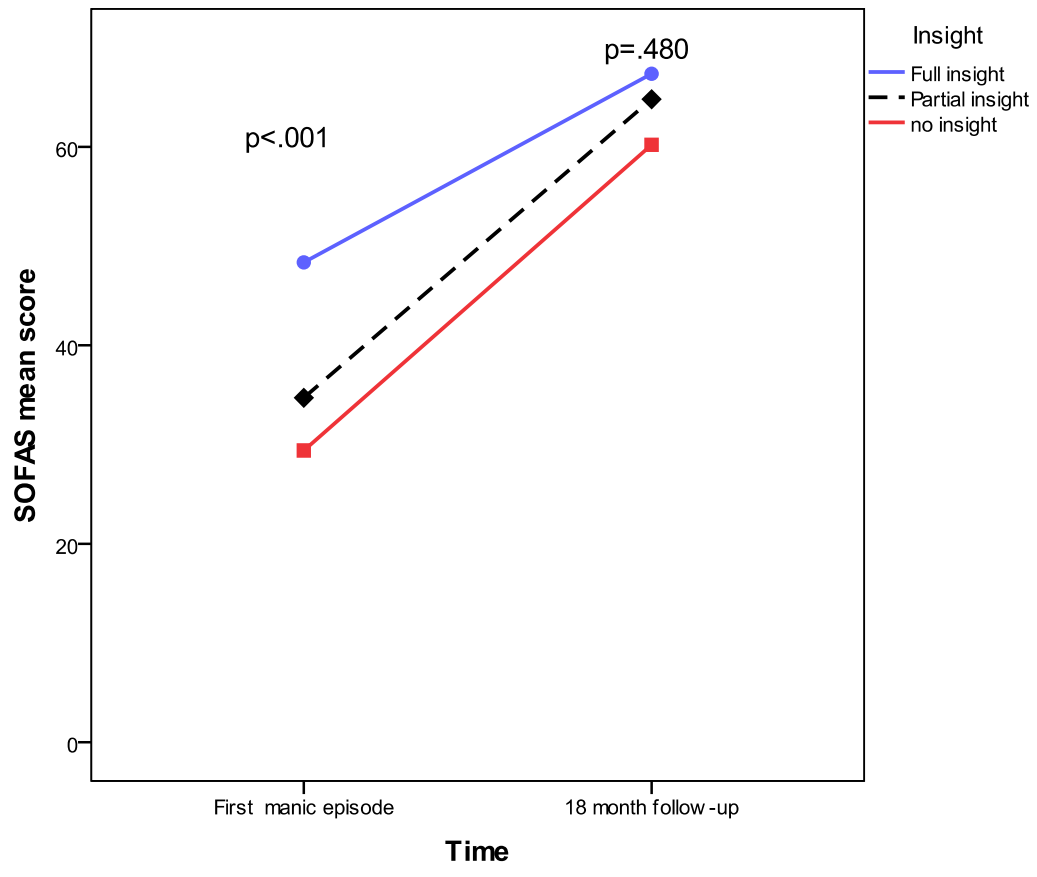


Figure 4. Change in SOFAS scores over 18 months