Journal of Affective Disorders 135 (2011) 298–304

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Preliminary communication

Prospective predictors of mood episodes in bipolar disorder

Julia W.Y. Kam [a,*], Amanda R. Bolbecker [b], Brian F. O'Donnell [b], William P. Hetrick [b], Colleen A. Brenner [a]

[a] Department of Psychology, University of British Columbia, Canada
[b] Department of Psychological & Brain Sciences, Indiana University-Bloomington, United States

ARTICLE INFO

Article history:
Received 9 June 2011
Accepted 29 June 2011
Available online 23 July 2011

Keywords:
Bipolar disorder
Mood episode
Prospective predictors
Cognition
Auditory evoked potentials
MADRS

ABSTRACT

Background: Bipolar disorder (BD) is associated with alterations in mood, personality, cognition and event-related potential (ERP) measures. The relationship between these multidimensional measures of state and subsequent course of the illness is not well understood. Therefore, this study aimed to prospectively identify factors that predicted the course of mood episodes.

Methods: Sixty-five participants with BD were administered the auditory P300 oddball task, clinical assessment instruments and cognitive tests at baseline, and were subsequently administered the SCID interview once a month by telephone for 12 months.

Results: Hierarchical regression analyses indicated that the Montgomery–Asberg Depression Rating Scale (MADRS) predicted the number of months spent in a depressed state ($p<.001$) and in a mixed state ($p=.001$), while both the MADRS ($p<.001$) and time to complete Trails A ($p=.033$) predicted total number of months in a mood episode (across all mood states). Among euthymic patients at entry, Cox regression analyses indicated that higher ratings on both the MADRS ($p=.017$) and Hypomanic Personality Scale (HPS; $p<.001$) were associated with both increased likelihood of a mood episode and less time until the onset of a mood episode.

Limitations: The sample size is relatively small, not all participants completed 12 months, and follow-up assessments were conducted via telephone.

Conclusions: Our results suggest that affective and cognitive measures, and personality factors, especially the MADRS and HPS, serve as important predictors of the course of mood episodes or relapse in BD patients. These prospective markers of acute mood states may be used to guide treatment decisions.

Bipolar disorder (BD) is a chronic illness characterized by recurring mood episodes of depression, mania, or mixed states, which often lead to debilitating clinical and functional outcomes. 30–60% of patients experience occupational impairment and social dysfunction even during inter-episode euthymic states (MacQueen et al., 2001). This functional impairment during euthymia may be a result of the progressive nature of the disorder, as the number of mood episodes has been linked to cognitive decline (Clark et al., 2002) and structural abnormalities in the prefrontal cortex and cerebellar vermis (see Strakowski et al., 2005 for a review). A recent study also documented progressive decreases in cerebellar and temporal lobe gray matter that were correlated with number of mood episodes and with declines in cognitive function (Moorhead et al., 2007). Given the repercussions associated with recurrent mood episodes, it is important to accurately predict the onset of acute mood episodes in BD so that prophylactic measures may be employed. As such, this study

* Corresponding author at: Department of Psychology, University of British Columbia, 2136 West Mall, Vancouver, B.C., Canada V6T 1Z4. Tel.: +1 604 822 3120; fax: +1 604 822 6923.
E-mail address: julia@psych.ubc.ca (J.W.Y. Kam).

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doi:10.1016/j.jad.2011.06.060

aimed at identifying those variables that predict the general course of illness and the onset of a mood episode.

Much of the current literature regarding prognosis in BD has focused on symptom and psychosocial markers to predict functional outcome and either symptomatic or syndromal recovery. Symptomatic recovery generally refers to substantial improvement in symptoms of the illness as indexed by symptom ratings scales, whereas syndromal recovery is typically defined as not meeting criteria for a DSM illness episode. Thus far, research indicates that female gender, shorter initial hospitalization and lower initial depression ratings predicted shorter time to syndromal recovery, while lower socioeconomic status and medication noncompliance were associated with poorer syndromal recovery (Delbello et al., 2007; Keck et al., 1998; Treuer and Tohen, 2010). Alternatively, older age of onset, higher socioeconomic status and shorter initial hospitalizations were associated with greater functional recovery (Keck et al., 1998; Post and Miklowitz, 2010; Treuer and Tohen, 2010). Further, there seems to be a robust reciprocal relationship between depressive symptoms and functional impairment. For example, studies have shown that functional impairment at baseline was predictive of subsequent depressive symptoms during follow-up; as well, relatively minor changes in depressive (but not manic) symptoms had a significant impact on functional impairment. This suggests that more severe or persistent depressive symptoms are associated with a more severe course and functional impairment. Supporting this, the presence of depressive symptoms during a euthymic state has been associated with a shorter time to the onset of a mood episode (Simon et al., 2007; Treuer and Tohen, 2010; Weinstock and Miller, 2008). These findings, along with reports that patients with BD spend the majority of time in a depressive episode relative to other mood episodes (Judd et al., 2002), highlight that full depressive episodes and subsyndromal depressive symptoms are associated with a worse general course of illness in BD.

Personality traits and temperament have also been implicated in predicting the course of illness. For example, harm avoidance was a significant predictor of depressed mood episodes (Farmer and Seeley, 2009), as were trait depression and neuroticism (Christensen and Kessing, 2006; Wilhelm et al., 1999). Further, Bipolar I patients who experienced mixed episodes were more likely to meet criteria for personality disorders and endorsed greater levels of depressive, cyclothymic, irritable and anxious temperament compared to those without mixed episodes (Röttig et al., 2007; although see Di Florio et al., 2010). Those with BD and co-morbid personality disorders were also less likely to reach syndromal recovery after hospitalization for a manic episode (Dunayevich et al., 2000). Likewise, individuals with a hypomanic personality, as indexed by high scores on the Hypomanic Personality Scale (HPS), were more likely to experience mood episodes (Eckblad and Chapman, 1986; Klein et al., 1996), specifically manic or hypomanic episodes (Meyer and Hautzinger, 2003). As one of the only self-report mania scales, the HPS predicted BD at a 13-year follow-up of high-scoring college students (Kwapil et al., 2000). Taken together, these findings suggest that personality traits and temperament factors both influence the quality of acute mood states in those with BD. However, for the most part these results speak to the general course of illness and do not predict the onset of an individual, impending mood episode prior to its initiation.

Although bipolar disorder has been reliably associated with enduring cognitive deficits and neurophysiological abnormalities, these characteristics are not commonly used to predict the onset of a mood episode. For instance, cross-sectional studies using electrophysiological measures have reported increased latencies and reduced amplitudes of the P300 event-related potential (ERP) component in bipolar patients (Degabriele and Lagopoulos, 2009; Muir et al., 1991; O'Donnell et al., 2004; Souza et al., 1995). This indicates that they have disrupted context updating, a neural process indexed by P300 in which the current mental representation in working memory is updated upon detection of a new stimulus (Polich, 2007). In addition, bipolar patients display impaired neurocognitive performance compared to healthy controls, especially with regard to verbal memory and executive functions (Andersson et al., 2008; El-Badri et al., 2001; Ferrier et al., 1999; Malhi et al., 2005; Martinez-Aran et al., 2004; Treuer and Tohen, 2010). For example, Jabben et al. (2010) found that depressive, but not hypomanic, symptoms in euthymic patients were associated with worse verbal list learning. Importantly, some neuropsychological deficits such as working memory persist over time when assessed in a euthymic or symptomatic state (Hill et al., 2008; Mur et al., 2008), and cannot be attributed to medication status, substance abuse or residual symptoms (Torres et al., 2010b). This has been taken as evidence that impaired cognitive abilities are stable characteristics and do not vary as a function of mood state.

As a result of these enduring neuropsychological deficits in BD, several studies have investigated whether neuropsychological measures predict functional outcome. For example, Jaeger et al. (2007) found that attention and ideational fluency significantly predicted functional recovery after 12 months. Likewise, verbal learning and memory were predictive of functional outcome at 6 months (Torres et al., 2010a) and at 12 months (Martino et al., 2009). A composite neurocognitive score, including working memory, vigilance and visual-motor processing measurements, also predicted changes in functioning over a 1-year period (Tabares-Seisdedos et al., 2008). The majority of these prospective studies found that poorer performance on at least one cognitive domain predicts worse functioning in BD. Nonetheless, no studies to our knowledge have considered cognitive or electrophysiological measures as prospective predictors of individual mood episodes.

As reviewed above, many observational studies have used demographic, symptom and personality measures to help characterize the overall course of illness in those with BD. These studies have primarily focused on correlations between index variables and functional outcomes. Few have used a prospective design to predict the onset of an individual mood episode, although cognitive styles rather than neurocognitive measures were previously used as potential predictors in these studies (Alloy et al., 2008; 2009). Despite the consistent findings of cognitive and electrophysiological deficits in cross-sectional studies of BD, no studies have used these variables as prospective predictors in a longitudinal design. Therefore the aims of the current study are to prospectively identify factors that predict not only the general course of illness (i.e. number of months spent ill) but also the onset of a