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The burden of repeated mood episodes in bipolar I disorder: Results from the National Epidemiological Survey on Alcohol and Related Conditions (NESARC)

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Abstract

The aim of this study was to examine the association between previous mood episodes and clinical course/functioning in a community sample (NESARC).

Subjects (n=909) meet DSM-IV criteria for bipolar I disorder and provided data on number of prior episode recurrences. Number of prior mood episodes was used to predict outcomes at Wave 1 and Wave 2 of the NESARC. Previous mood episodes accounted for small, but unique variance in outcomes. Recurrence was associated with poorer functioning, psychiatric and medical co-morbidity, and increased odds of suicidality, disability, unemployment, and hospitalization at Wave 1. Recurrences were associated with greater risk for new onset suicidality, psychiatric co-morbidity, disability, unemployment, and poor functioning by Wave 2. The course of bipolar disorder does worsen with progressive mood episodes, but is attenuated in community, relative to clinical samples. Interventions to prevent future relapse may be particularly important to implement early in the course of illness.

Keywords

bipolar; depression; functioning

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Introduction

Kraepelin originally differentiated bipolar disorder and schizophrenia, describing bipolar disorder as an illness with remission between mood episodes as opposed to schizophrenia, which he viewed as a chronic and deteriorating condition (Kraepelin, 1921). However, in recent years, it has become increasingly clear that bipolar disorder, like schizophrenia, may be a condition that tends to worsen with prolonged illness (Kessing et al, 1998; Rosa et al, 2012; Roy-Byrne et al, 1985). Accordingly, in the past decade, there has been a surge of interest in identifying the clinical, functional, and pathophysiological features of bipolar disorder associated with the progression of illness course (Berk et al, 2013; Gama et al, 2013; Magalhaes et al, 2012a; Schneider et al, 2012).

One potential measure that may be useful for understanding exacerbation of symptoms and accumulation of functional problems in bipolar disorder is the number of previous mood episodes. The number of previous mood episodes is not only an intuitive and pragmatic measure of cumulative illness severity, but also central to understanding bipolar disorder as a recurrent and progressive illness (Berk et al, 2013). To date, data regarding outcomes associated with cumulative mood episode morbidity come exclusively from a number of clinical studies. These studies suggest that patients with more lifetime mood episodes experience increasingly severe inter-episode residual symptoms of mania and depression (Perlis et al, 2006), as well as a number of adverse psychosocial, functional, and treatment-related consequences. Specifically, patients with more previous episodes experience more frequent hospitalizations (Goldberg et al, 2002), higher rates of disability (Magalhaes et al, 2012a), increased rates of suicide (Angst et al, 2002), impaired cognitive functioning (Lewandowski et al, 2011), high rates of medical conditions (Angst et al, 2002; Magalhaes et al, 2012a), interpersonal and relationship difficulties (Magalhaes et al, 2012a), and overall lower quality of life (Magalhaes et al, 2012a). Furthermore, evidence from pharmacological and psychosocial treatment outcome studies suggest that failure to intervene early in the illness course is associated with a worsening response to treatment and higher likelihood of relapse (Berk et al, 2011; Colom F, 2010; Franchini et al, 1999; Goldberg et al, 2002; Ketter et al, 2006; Scott et al, 2006).

Although the association between mood episode history and illness severity is relatively well documented in clinical studies, these findings have yet to be replicated in epidemiological community samples. According to Berkson's bias, psychological phenomenon observed in clinical samples might not represent the broader spectrum of people affected by a disorder (Berkson, 1946). Specifically, Berkson showed that estimates of disease severity are exaggerated in clinical samples because individuals seeking clinical care represent a patient population with greater burden of disease and overall distress. It is possible that the association between cumulative mood episodes and symptomatic, cognitive, and functional decline in bipolar disorder is exaggerated (or underestimated) in clinical versus epidemiological samples. Therefore, it is warranted to assess the association of mood episode history and illness features in bipolar disorder using epidemiological data, which provides a larger, more representative population to validate the findings from studies in clinical samples.

The National Epidemiological Survey on Alcohol and Related Conditions (NESARC), sponsored by the US Department of Health and Human Services, National Institute of Health (NIH), and National Institute on Alcohol Abuse and Alcoholism (NIAAA) is a major national survey encompassing a nationally representative US sample of 43,093 respondents (Grant BF, 2003). DSM-IV (APA., 1994) diagnosis of bipolar disorder, mood episode history, and other related socio-demographic and clinical variables were rigorously assessed in the NESARC. The purpose of the current study was to examine the association between number of previous mood episodes and clinical and functional status using the NESARC data. More specifically, we investigated the cross-sectional association between previous mood episodes and clinical and functional outcomes, as well as whether number of prior mood episodes at study entry prospectively predicted changes in clinical and functional status.

Method

Study Design

This study utilizes data from the first and second waves of the NESARC (Grant BF, 2007; Grant BF, 2003). Data acquisition methods of the NESARC have been reported elsewhere (Grant et al, 2005b). Briefly, the Wave 1 survey was administered to non-institutionalized individuals in communities across the United States between 2001 and 2002. Data were obtained using a combination of face-to-face and computer-assisted interviews. 43,093 respondents completed the Wave 1 survey with an overall response rate of 81%.

A longitudinal follow-up to the Wave 1 survey was conducted in 2004–2005(Grant BF, 2007). In Wave 2, all Wave 1 participants were re-interviewed in the follow up period, except of those ineligible due to death, emigration, active military duty during follow-up period, or physical/mental incapacity. The Wave 2 survey yielded an 86.7% response rate, with 34,653 individuals completing follow-up interviews.

Participants

All participants were 18 years or older. Of the 43,093 respondents who completed the Wave 1survey, 1,411 individuals surveyed in the NESARC met DSM-IV criteria for bipolar I disorder. This study includes a subsample of individuals with bipolar I disorder (n = 909) who provided information on the number of previous mood episodes at Wave 1.

NESARC Measures

The NESARC included a wide variety of measures, including demographic information (e.g. age, sex, race (white or nonwhite), marital status (married or not), and completion of high school), psychiatric diagnoses, and clinical outcomes. DSM-IV psychiatric diagnoses were determined using the NIAAA Alcohol Use Disorder and Associated Disabilities Interview Schedule (AUDADIS-IV). Consistent with DSM-IV criteria, psychiatric disorders that were substance induced or due to general medical conditions were not included in this study. The following axis I disorders were evaluated in the Wave 1 of the NESARC: panic disorder with/without agoraphobia, agoraphobia without panic disorder, social phobia, specific phobia, generalized anxiety disorder (GAD), bipolar I disorder, bipolar II disorder, alcohol

use disorder (including abuse or dependence), and drug use disorder (including abuse or dependence; evaluated drugs: amphetamines, opioids, sedatives, tranquilizers, cocaine, inhalants/solvents, hallucinogens, cannabis, heroin, and other drugs). In Wave 2, these conditions were reevaluated to assess the incidence of new cases of psychiatric diagnoses (i.e. disorders that onset during the period of follow up). The AUDADIS-IV demonstrated strong reliability and validity for psychiatric diagnoses (BD I, reliability of $k = .59$ with other mood and anxiety disorders; alcohol use disorders, $k = .74$; drug use disorders, $k = .79$; personality disorders, $k = .53$; Grant et al, 2005a; Grant et al, 2004; Grant et al, 2005b).

Mood Episodes

Number of Repeated Mood Episodes—Manic and depressive episode history were assessed and reported separately. To determine the number of lifetime manic episodes, respondents were asked to identify how many *separate* times in their entire life lasting at least 1 week they felt extremely (excited, elated or hyper/irritable or easily annoyed) and experienced other manic symptoms they endorsed during diagnostic assessment. Surveyors specified that *separate* times were defined as periods separated by at least 2 months with return to normal mood and absence of any symptoms endorsed during previous manic episodes. To assess depressive episodes, respondents were asked a similar question regarding periods lasting at least 2 weeks (separated by at least 2 months) where they felt down, depressed, or lacked interest in things they usually enjoyed, most of the day nearly every day. Number of previous manic episodes and depressive episodes were reported as continuous variables. A cumulative mood episodes variable, total mood episodes, was created by summing total manic and depressive episodes for each participant.

Recurrence Rate—In addition to the number of repeated mood episodes, a measure of recurrence rate was created by dividing the total number of mood episodes by illness duration (i.e. length of time in years diagnosed with bipolar disorder).

Measures of Clinical Outcome and Functioning

Clinical and functional measures were selected a-priori based on findings proposed from reviews of the literature and generated from clinical studies (Berk et al, 2011; Kapczinski et al, 2009; Magalhaes et al, 2012a; Perlis et al, 2006). Clinical indices included bipolar disorder age of onset, illness duration, time until first treatment for bipolar disorder, hospitalization for a manic or depressive episode, history of suicide attempts, history of suicidal ideation, current and lifetime axis I psychiatric co-morbidities, and current medical burden. Illness duration was computed by taking the difference of current age and age of first manic episode. Time of until first treatment for bipolar disorder was computed by taking the difference of age at first treatment for bipolar disorder and age of first manic episode. History of suicide attempts was a binary (yes/no) variable, indicating any lifetime suicide attempt. History of suicidal ideation was a binary (yes/no) variable, capturing individuals who have ever had thoughts of how to kill themselves, wanting to die, or thoughts of death, versus those who have never had such thoughts. Lifetime axis I co-morbidities reflected the total number of lifetime psychiatric conditions and current axis I co-morbidities reflected the total number of psychiatric conditions in the past 12 months. Current medical burden was created by summing the number of medical conditions

confirmed by a physician in the past 12 months. Medical conditions assessed included: arteriosclerosis, high blood pressure, cirrhosis of liver, other liver disease, chest pain/angina pectoris, rapid heartbeat/tachycardia, heart attack/myocardial infarction, other heart disease, stomach ulcer, gastritis, or arthritis.

Functional measures of interest included permanent disability (yes/no), employment status (currently employed full or part-time vs. unemployed), role limitations due to emotional problems, role limitations due to physical problems, and social functioning. Role limitations due to physical or emotional problems and social functioning were assessed using the Short Form 12, version 2 (SF-12v2) (Ware et al, 1996). Each SF-12v2 norm-based subscale score is a continuous variable with a mean of 50 in the general population, a standard deviation of ±10, and a range of 0–100. Lower scores indicate poorer functioning.

Data Analytic Approach

All statistical analyses were done using SPSS statistics version 21 complex sampling procedures, which adjusts variance and point estimates for the multi-stage sampling design and differential selection probabilities used to ascertain the NESARC sample. Weighted percentages and means with their standard error using the study's Wave 2 sampling weights are presented; actual sample sizes are reported. To test the hypothesis that mood episode recurrences would be associated with increased clinical severity and impairments in functioning, we used regression analyses to explore the amount of variance in cross sectional (wave 1 only) and prospective clinical and functional outcomes (wave 1 predicting wave 2) that is accounted for by the number of previous mood episodes. Ordinary least squares hierarchical linear regression models were used for continuous outcome variables and logistic regression models were used for binary outcomes.

We investigated the contribution of total prior mood episodes investigate above and beyond control variables, as well as the relative contribution of depressive versus manic episodes to clinical and functional outcomes. In each regression model of the cross-sectional analysis, demographic control variables (age, sex, race, marital status, and education) were entered first, followed by number of mood episodes. If total number of prior mood episodes was a significant predictor, then manic and depressive episodes were entered together in a second step of a new model to determine the relative contribution of manic and depressive episodes.

For the prospective analysis, to evaluate change in continuously measured variables (e.g. number of co-morbid conditions, medical burden, role and social functioning), the score from Wave 1 was entered on the first step of the model, thus partialing Wave 1 variance in clinical and functional status out of Wave 2 and creating a residual score to change from Wave 1 to Wave 2. Baseline (Wave 1) socio-demographic characteristics were entered on the second step of the model, and mood episodes in the final step. For prospectively observed binary outcome variables (e.g. psychiatric hospitalization, suicide attempt/ideation, disability, and unemployment), all outcomes reflected incidence of a new occurrence during the time of follow up, and thus a standard logistic regression model was used to predict newly observed occurrences, entering socio-demographic covariates on the first step and previous mood episodes on the second. Like the cross sectional analysis, we then conducted

a second series of models, where manic and depressive episodes were entered together in the last step of the model to determine the relative burden of each type of mood polarity.

In addition to mood episodes, several clinical features such as psychiatric co-morbidity (Frias et al, 2015), medical co-morbidity (Soreca et al, 2009), and time until first treatment (Malhi et al, 2014) have been shown to affect the course of bipolar disorder. Thus, we conducted an exploratory set of analyses of an alternative model including these characteristics as control variables in the first step of the cross-sectional and prospective regressions. These analyses investigated whether any observed findings with respect to mood episodes were robust after controlling for additional clinical characteristics, as well as whether psychiatric, medical co-morbidity, or time until treatment improved the models.

Finally, we evaluated the role of recurrence rates with current and prospective clinical status and functioning. This set of analyses first examined whether recurrence rates predicted clinical status and functioning beyond demographic control variables.

Results

Sample Composition

Participants were an average age of 38.47 (SD, 14.16) and 65% (n = 587) female. Demographic, clinical, and functional characteristics of the study sample are presented in Table 1. Participants with missing data on mood episodes (n = 502) had fewer lifetime ($p < .001$) and current co-morbidities ($p < .001$), and better ratings of physical ($p = .040$), emotional ($p < .001$), and social functioning ($p < .001$). In addition, participants with missing data were more likely to be male ($p < .001$), of a non-white race ($p < .001$), and less likely to have been hospitalized ($p = .001$) or experienced suicidal ideation ($p < .001$).

Mood Episodes

Participants meeting lifetime criteria for bipolar I disorder reported an average of 20.03 (SD, 34.79) previous mood episodes; 12.14 (SD, 24.66) of these mood episodes were depressed, and 7.90 (SD, 17.37) were manic.

Cross-sectional Correlates of Repeated Mood Episodes

Our first set of analyses examined the association between number of repeated mood episodes and indices of clinical status and functioning, above and beyond variance in clinical status and functioning that could be explained by demographic characteristics. The variance explained by the modeling sequence is shown in Table 2.

Clinical Correlates of Repeated Mood Episodes—In the multivariate models, repeated mood episodes overall accounted for a relatively small, but unique variance in several clinical features, above and beyond what could be explained by demographic characteristics (see Table 2). Specifically, more lifetime mood episodes were associated with an earlier age of onset ($b = -.06$, $SE = .01$, $p < .001$), longer illness duration ($b = .06$, $SE = .01$, $p < .001$), and longer duration until first treatment for bipolar disorder ($b = .05$, $SE = .01$, $p < .001$). Increases in the number of lifetime mood episodes were associated with a higher

likelihood of hospitalization for bipolar disorder (b = .01, SE = .001, p < .001), having made a lifetime suicide attempt (b = .01, SE = .001, p < .001), as well as lifetime suicidal ideation (b = .01, SE = .003, p < .001). The total number of lifetime mood episodes was also associated with the number of current medical (b = .01, SE = .002, p < .001) and psychiatric co-morbidities (b = .001, SE < .001, p = .037), as well as lifetime psychiatric co–morbidities (b = .003, SE = .001, p < .001).

When total mood episodes was broken down into the relative effects of manic versus depressive episodes, increases in manic episodes independently predicted earlier age of onset (b = −.14, SE = .02, p < .001), longer illness duration (b = .14, SE = .02, p < .001), more current (b = .002, SE = .001, p < .001) and lifetime psychiatric co-morbidities (b = .01, SE = .001, p < .001). The number of previous depressive episodes was not a significant predictor of these outcomes (p's > .066). In contrast, increases in depressive episodes independently predicted the likelihood of suicidal ideation (b = .01, SE = .004, p = .007) and current medical co-morbidities (b = .02, SE = .002, p < .001). Number of manic episodes was not a significant predictor of suicidal ideation or medical co-morbidities (p's > .068). Increases in the total number of manic and depressive episodes were both significant predictors of longer duration until first treatment for bipolar disorder (manic: b = .12, SE = .02, p < .001; depressed: b = .02, SE = .004, p = .003), the likelihood of hospitalization for bipolar disorder (manic: b = .01, SE = .003, p = .020; depressed: b = .01, SE = .001, p < .001), and having made a previous suicide attempt (manic: b = .01, SE = .003, p = .044; depressed: b = .01, SE = .002, p < .001).

Functional Correlates of Repeated Mood Episodes—In the multivariate models, repeated mood episodes accounted for small unique variance in several functional characteristics, above and beyond what could be explained by demographic characteristics (see Table 3). Increases in the total number of lifetime mood episodes were associated with higher likelihood of permanent disability (b = .01, SE = .001, p < .001), unemployment (b = .01, SE = .002, p = .003), role impairment due to physical problems (b = −.06, SE = .004, p < .001), role impairment due to emotional problems (b = −.05, SE = .01, p < .001), and impairment in social functioning (b = −.06, SE = .01, p < .001).

Analysis of the relative effects of manic versus depressive episodes revealed that repeated depressive episodes were a consistent predictor of functional impairments. Controlling for the effects of previous manic episodes, increases in number of previous depressive episodes were associated with higher likelihood of disability (b = .02, SE = .002, p < .001) and poor social functioning (b = −.07, SE = .01, p < .001). Manic episodes did not remain a significant predictor of these outcomes (p's > .058). Manic and depressive episodes were both significant predictors of role impairment due to physical functioning (manic: b = −.02, SE = .01, p = .046; depressive: b = −.08, SE = .01, p < .001) and role impairment due to emotional functioning (manic: b = −.04, SE = .02, p = .037; depressive: b = −.07, SE = .01, p < .001). Manic episodes significantly predicted the likelihood of unemployment (b = .02, SE = .01, p = .001); depressive episodes did not (p = .829)

Prospectively Observed Outcomes Associated with Mood Episode History

Our next set of analyses examined whether the number of repeated mood episodes reported at Wave 1 predicted change in indices of clinical status and functioning at Wave 2, above and beyond change in clinical status and functioning that could be explained by demographic characteristics or Wave 1 clinical/functional severity. Table 3 displays the variance explained by the modeling sequence.

Clinical Outcomes—In the multivariate models, higher number of previous mood episodes reported at Wave 1 was associated with a greater likelihood of newly observed psychiatric hospitalization, (b = .01, SE = .001, p < .001), and suicidal ideation, (b = .01, SE = .001, p < .001) during the follow-up period,. When broken down into the relative effects of depressive versus manic episodes, more prior depressive episodes at Wave 1 predicted greater likelihood of newly observed hospitalization (b = .02, SE = .002, p < .001), and new onset suicidal ideation during the follow up period, (b = .01, SE = .001, p < .001). Number of previous manic episodes reported at Wave 1 did not predict new hospitalization or suicidality (p*'s* > .422*).* Higher number of previous mood episodes at Wave 1 also predicted the number of prospectively observed new onset psychiatric co-morbidities, adjusting for number of co-morbid psychiatric conditions at Wave 1, (b = .01, SE = .001, p < .001). Analysis of the relative effects of manic versus depressive episodes indicated that recurrent depressive episodes predicted the development of more new psychiatric co-morbidities, (b = .01, SE = .001, p < .001), whereas manic episodes did not, (p = .123). Number of prior mood episodes was not prospectively associated with medical burden or suicide attempts (p's > .402).

Functional Outcomes—In the multivariate models, more prior mood episodes at Wave 1 prospectively predicted decline in several areas of functioning after adjusting for socio-demographic characteristics and index functional status. Higher number of prior episodes at Wave 1 was prospectively associated with greater likelihood of disability by Wave 2, (b = .01, SE = .002, p = .001), unemployment, (b = .02, SE = .005, p = .006), decline in role functioning due to physical problems, (b = −.04, SE = .01, p = .000), role functioning due to emotional problems (b = −.05, SE = .01, p < .001), and social functioning, (b = −.06, SE = .01, p < .001),

When broken down into manic versus depressive episodes, prior manic episodes was a significant predictor of developing disability by Wave 2 (b = .01, SE = .004, p = .001); depressive episodes was not (p = .527). Both prior manic and depressive episodes remained significant predictors of unemployment, (manic: b = .03, SE = .01, p = .020; depressive: b = .01, SE = .004, p = .003), decline in social functioning, (manic: b = −.05, SE = .01, p < .001; depressed: b = −.06, SE = .01, p < .001), role impairment due to emotional problems, (manic: b = −.06, SE = .02, p < .001; depressed: b = −.05, SE = .01, p < .001), and role impairment due to physical problems, (manic: b = −.04, SE = .01, p = .001; depressed: b = −.04, SE = .01, p <.001).

Alternative Models: Effects of Psychiatric Co-morbidity, Medical Burden, and Time until First Treatment

These exploratory analyses controlled for Wave 1 psychiatric co-morbidity, medical burden and time until first treatment, to examine the robustness of the effects of mood episodes, as well as whether these clinical attributes were also related to clinical course and functioning. Results indicated that in all cases, mood episodes remained a significant predictor after controlling for these factors. There were additional effects of psychiatric co-morbidity, medical burden, and time until first treatment on outcome.

Psychiatric Co-Morbidity—At Wave 1, psychiatric co-morbidity was associated with role interference due to physical functioning ($b = -1.04$, $SE = .19$, $p < .001$), emotional functioning ($b = -1.96$, $SE = .26$, $p < .001$), and social functioning, ($b = -2.53$, $SE = .17$, $p < .001$), hospitalizations ($b = 1.44$, $SE = .03$, $p < .001$), suicide attempts ($b = .14$, $SE = .03$, $p < .001$), suicidal ideation ($b = .24$, $SE = .04$, $p < .001$), disability ($b = .33$, $SE = .07$, $p < .001$), and unemployment ($b = .28$, $SE = .05$, $p < .001$). Prospectively, psychiatric co-morbidity was associated with likelihood of hospitalization ($b = -.46$, $SE = .07$, $p < .001$), suicidal ideation, ($b = -.29$, $SE = .04$, $p < .001$, disability ($b = .13$, $SE = .07$, $p = .014$), and decline in role performance due to physical functioning ($b = -.41$, $SE = .17$, $p = .026$) over the follow up.

Medical Burden—At Wave 1, medical burden was associated with role interference due to physical functioning ($b = -.03$, $SE = .01$, $p = .003$), emotional functioning ($b = -.06$, $SE = .02$, $p = .001$), suicide attempts ($b = -.01$, $SE = .005$, $p = .037$), and unemployment ($b = .39$, $SE = .04$, $p < .001$). Prospectively, medical burden was associated with likelihood of suicidal ideation ($b = .01$, $SE = .004$, $p = .004$), disability ($b = .06$, $SE = .02$, $p = .003$), unemployment ($b = .05$, $SE = .01$, $p = .001$), and decline in role performance due to physical functioning ($b = -.09$, $SE = .01$, $p = .004$) during the follow up.

Time Until First Treatment—At Wave 1, longer time until first treatment was associated with earlier age of onset ($b = -.73$, $SE = .02$, $p < .001$), longer illness duration ($b = .73$, $SE = .02$, $p < .001$), role interference due to physical functioning ($b = -.19$, $SE = .03$ $p < .001$), emotional functioning ($b = -.12$ $SE = .05$, $p = .035$), and social functioning ($b = -.20$, $SE = .05$, $p < .001$), disability ($b = .03$, $SE = .01$, $p = .028$), and unemployment ($b = .05$, $SE = .01$, $p = .002$). Prospectively, time until first treatment was associated with greater likelihood of hospitalization ($b = .03$, $SE = .01$, $p = .001$), suicide attempt ($b = .04$, $SE = .01$, $p = .007$), ideation ($b = .04$, $SE = .01$, $p < .001$), decline in role performance due to physical functioning ($b = -.14$, $SE = .04$, $p = .004$), and emotional functioning ($b = -.12$, $SE = .05$, $p = .027$) over the follow up.

Recurrence Rates

Our last set of analyses examined whether lifetime recurrence rate of episodes reported at Wave 1 was associated with indices of clinical status and functioning and Wave 1, above and beyond variance that could be explained by demographic factors. We also evaluated whether lifetime recurrence rate of episodes reported at Wave 1 predicted change in clinical

status and functioning at Wave 2, above and beyond demographic characteristics and adjusting for clinical/functional status at Wave 1.

Faster rate of recurrence was associated with an earlier age of bipolar onset, (b = .17, SE = .01, p < .001), longer illness duration, (b = −.17, SE = .01, p < .001), shorter duration until first treatment, (b = −.04, SE = .003, p < .001), more current medical conditions, (b = .05, SE = .01, p < .001), and role interference due to physical functioning, (b = −.05, SE = .01, p < .001). Recurrence rate was not associated with hospitalizations, suicide attempts, suicidal ideation, disability, unemployment, role interference due to emotional functioning, or social functioning reported at Wave 1 (p's > .065).

Prospectively, faster recurrence rate was independently associated with increased likelihood of suicide attempt during follow up, (b = .01, SE = .001, p <.001), development of more psychiatric co-morbidities (b = .004, SE = .001, p < .001, disability, (b = .01, SE = .001, p < .001), decline in role performance due to physical (b = −.03, SE = .005, p <.001) and emotional functioning (b = −.09, SE = .01, p < .001), and decline in social functioning (b = −.14, SE = .14, p < .001). Recurrence rate was not associated with prospectively observed hospitalizations, new onset suicidal ideation, new onset medical co-morbidities, or becoming unemployed over the follow up (p's > .159).

Discussion

We set out to explore the clinical and functional consequences of a chronic and recurrent course of bipolar disorder. In this population-based sample, multiple previous relapses were associated with poor functioning, psychiatric co-morbidity, medical co-morbidity and increased likelihood of suicide/suicidality, disability, unemployment, and hospitalizations. Prospectively, individuals with multiple relapses were at higher risk for hospitalization, disability, unemployment, developing new onset suicidality, psychiatric co-morbidity, and decline in functioning. Collectively, these findings suggest that a recurrent course of illness offers a poor prognosis and that the odds of returning to previous functioning diminish with successive mood episode recurrences. This decline is clinical and functional status is also accounted for in part by additional psychiatric problems, medical illnesses, and failure to intervene or access treatment in the early stages of bipolar disorder.

Recurrent episodes of mania and depression did not contribute equally to clinical and functional status. When we parsed apart the unique effects of recurrent depressive and manic episodes, repeated depressive episodes had a more consistent impact on prospective clinical and functional impairments. This is not to discount the deleterious effects of mania, but rather to highlight that depressive episodes were uniquely related to the development of co-morbidity, suicidal ideation, hospitalization, and disability – outcomes that constitute a particularly significant public health impact. Furthermore, depressive episodes remained predictors of prospectively observed unemployment and decline in functioning, in addition to the effects of mania. These findings are consistent with previous studies that have documented myriad negative outcomes associated with bipolar depression (Bauer et al, 2012) and the widely held clinical notion that treating bipolar depression is one of the greatest unresolved challenges of the disorder. Given the negative consequences associated

with recurrent depression, it is critical to augment research efforts on acute treatments for depression with those designed to prevent depressive relapse.

While results of this study suggest that relapse of depression is more common and problematic than mania, we were not fully able to parse the extent to which mixed symptoms during or outside of reported episodes may have influenced outcomes. Unfortunately, ratings of symptom measures in the NESARC are relatively crude (i.e. present or absent), prohibiting more nuanced analyses of potential underlying symptom clusters that could reflect a predominant polarity(Magalhães, 2001; Magalhaes et al, 2012b). It has been suggested that the relatively weaker link between mania and impairment may be explained by poor insight, whereas when more detailed observer ratings are included in assessment of symptom dimensions, this link becomes stronger (Magalhaes et al, 2012b). Thus, it is an important future direction to use more detailed symptom ratings to explore long-term clinical and functional trajectories in bipolar disorder, paired against self-report of episodes, which could be biased in report of their functional impact.

A clinically relevant question is whether the burden of repeated mood episodes is cumulative, or related to the rate of recurrence (i.e. the speed with which they occur over time). Prior studies reporting better functioning and treatment response earlier in the course of illness (Berk et al, 2011; Colom F, 2010; Franchini et al, 1999; Peters, Under Review; Scott et al, 2006) have not sufficiently disentangled whether patients with fewer episodes are (1) in an earlier stage of illness, or (2) less prone to experiencing recurrences over the duration of their illness. Results from this study suggest that in addition to the number of episodes, recurrence rates affect clinical status and functioning. These findings are consistent with several previous studies indicating poorer prognosis and greater disease burden in rapid cycling bipolar disorder (Kupka et al, 2005; Schneck et al, 2004; Schneck et al, 2008). That both cumulative mood episode and frequency of episode insults offers a poorer clinical and functional prognosis is broadly consistent with recent research on staging models which suggest progressive changes in immuno-inflammatory function, oxidative stress, apoptosis, and neuro- anatomical and functional status occur with prolonged illness (Berk et al, 2013).

The results of this study should be interpreted within the context of its design, strengths, and limitations. Strengths of the study include having a large, nationally representative sample, with a longitudinal follow up assessment. A primary limitation of the study the study is that mood episodes were reported retrospectively. Their validity was not compared with informant reports and thus, and may have been subject to recall bias. Further, many individuals with bipolar disorder were missing data on mood episodes; these participants were healthier with regard to several illness characteristics, suggesting that the most mild phenotype of bipolar disorder in the community may have been underrepresented in our analyses. Related, mood episode recurrences were not recorded in real-time during the period of follow-up and did not assess the length of mood episodes. Finally, interviews were administered by lay-people; rather than clinically trained assessors.

Although mood episodes, significantly contributed to illness severity and impairment it is noteworthy that the overall contribution of mood episode recurrences to the chosen

outcomes in this community sample was very small; mood episodes accounted for approximately 1–7% of the variance in clinical status and functioning. This seems to diverge from the majority of literature from clinical studies, where mood episodes more consistently accounted for medium-sized effects in clinical course and treatment outcome (Berk et al, 2011; Colom F, 2010; Magalhaes et al, 2012a; Peters, Under Review; Scott et al, 2006). One possible explanation for this discrepancy is that a highly recurrent course of bipolar disorder among individuals surveyed in a community setting is less common. In the largest prospective clinical study evaluating the role of illness chronicity, more than half of the sample reported more than 10 previous mood episodes (Magalhaes et al, 2012a), whereas only 35% of this community sample reported more than 10 mood episodes. Another possibility is that patients in clinical studies may constitute a more treatment resistant group, with a more severe constellation of symptoms. Consistent with this notion, Perlis et al., (2006) failed to show convincingly that number of previous episodes predicted worse outcomes among a select group of patients who responded to treatment, raising the possibility that patients who achieve recovery constitute a less severe group, that is not as susceptible to the effects of a chronic course (Perlis et al, 2006). Finally, it is difficult to draw firm conclusions regarding the cumulative burden of mood episodes without a measure of time in episode, as prolonged symptoms could cause greater impairment. The role of episode length has not, to our knowledge, been compared in clinical and epidemiological samples, but could help to explain the degree of divergence from clinical studies regarding the magnitude impact of mood episodes in the community.

Nonetheless, understanding the burden of a recurrent illness course in bipolar disorder is of theoretical and practical significance. These findings are concordant with the staging model (Berk et al, 2014), which predicts that treatment response should be greater earlier in the course of illness. They are also broadly concordant with the construct of neuroprogression, which posits that progressive damage to the neuroanatomic substrate of mood regulation by biochemical processes that flare up in acute illness and decrease the probability of treatment response (Berk, 2009; Berk et al, 2010). Pharmacological and psychosocial treatment studies have consistently demonstrated better treatment outcomes when initiated early in the course of illness (Berk et al, 2011; Colom F, 2010; Franchini et al, 1999; Peters, Under Review; Scott et al, 2006). Thus, future treatment studies may benefit greatly from including longer follow up periods to identify those treatments that are most effective at preventing relapse. This treatment approach may be better achieved by implementing pervasive screening for mood episodes in primary care and community settings, with particular emphasis on identifying early course episodes or at risk features. In that regard, development of treatments that target at-risk samples to delay onset in the first place could have an enormous public health impact in terms of reducing the morbidity associated with a recurrent course.

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Table 1

Demographic, clinical, and functional characteristics of study participants (n = 909)*

Demographic Variables	M or N	SE or %
Age	37.94	.28
Sex (female)	587	62
Race (being white)	721	85
Married	382	52
Completed high school	735	82
Clinical Variables		
Number of previous mood episodes	18.69	.57
Manic episodes	7.59	.29
Depressive episodes	11.10	.37
Recurrence Rate	4.05	.14
Age of first manic episode	25.41	.24
Illness duration	12.48	.27
Age of first treatment for bipolar disorder	31.05	.24
Time until first treatment for bipolar disorder	3.78	.13
Any past hospitalization for mania or depression	231	22
Lifetime suicide attempt	231	23
Lifetime suicidal ideation	688	74
Any past medication use for mania or depression	522	57
Number of lifetime axis I co-morbidities	2.23	.03
Any lifetime anxiety disorder	575	64
Any lifetime drug use disorder	338	40
Any lifetime alcohol use disorder	492	57
Number of current axis I co-morbidities	1.12	.03
Any current anxiety disorder	421	47
Any current drug use disorder	88	10
Any current alcohol use disorder	168	19
Number of current medical conditions	1.45	.08
Functional Variables		
Permanent Disability	105	9
Employed	824	90
Role emotional	43.08	.29
Role physical	47.69	.26
Social functioning	44.05	.25

*Means and percentages are weighted, actual N is reported

Table 2

Hierarchical Regression for Association between Repeated Mood Episodes and Indices of Clinical Status and Functioning[a]

Dependent Variables	1. Demographic Controls[b]	2a. Mood Episodes	2b. Manic and Depressive Episodes
Clinical Correlates	R^2	ΔR^2	ΔR^2
Age of Onset	.38**	.03**	.04**
Illness Duration	.39**	.03**	.04**
Time Until 1st Treatment	.07**	.07**	.11**
Psychiatric Hospitalization[c]	.04**	.03**	.03**
Suicide Attempt[c]	.02	.03**	.03**
Suicidal Ideation[c]	.01	.03**	.03**
LT Axis-I Comorbidity[d]	.01*	.01*	.01*
Current Axis-I Comorbidity	.04**	.00	-
Current Medical Burden	.01**	.01*	.01*
Functional Correlates			
Disability[c]	.14**	.05**	.05**
Unemployment[c]	.18**	.01*	.02*
Role Physical	.14**	.02**	.03**
Role Emotional	.06**	.02**	.02**
Social Role	.04**	.02**	.02*

* $p < .05$,

** $p < .01$

[a] Models were conducted hierarchically, with demographic controls entered on the first step: in the first set of models, total mood episodes were entered on the second step (2a.Mood Episodes). In a second set of models, manic and depressive episodes were entered together on the second step (2b. Manic and Depressive Episodes)

[b] Block of demographic & clinical controls includes: age, sex, education, race, marital status

[c] denotes logistic regression, where R^2 represents the Nagelkerke R^2

[d] LT = lifetime

Table 3

Hierarchical Regression for Prospectively Observed Association Between Mood Episode History and Clinical and Functional Outcomes[a]

Dependent Variables	1. Wave 1 Assessment	2. Demographic Controls[b]	3a. Mood Episodes	3b. Manic and Depressive Episodes
Clinical Outcomes	R^2	ΔR^2	ΔR^2	ΔR^2
Psychiatric Hospitalization[c]	-	.02**	.01**	.02**
Suicide Attempt[c]	-	.05**	.00	-
Suicidal Ideation[c]	-	.03**	.01**	.01*
Number of Comorbidities	.15**	.04*	.02*	.02*
Number Medical Conditions	.002	.02*	.00	-
Functional Outcomes				
Disability[c]	-	.04**	.01*	.01*
Unemployment[c]	-	.04**	.02**	.02**
Role Physical	.23**	.02**	.01**	.01*
Role Emotional	.17**	.02**	.01**	.01**
Social Role	.11**	.02**	.02**	.02**

* $p < .05$,

** $p < .01$

[a] Models were conducted hierarchically, with wave 1 assessment entered on the first step and demographic controls on the second step. In the first set of models, total mood episodes were entered on the third step. In a second set of models, manic and depressive episodes were entered together on the third step.

[b] Block of demographic & clinical controls includes: age, sex, education, race, marital status

[c] denotes logistic regression, where R^2 represents the Nagelkerke R^2. In logistic regression models, Wave 1 assessment value was not included in the first step because dependent variables were defined as new onset over the follow up.