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Research paper

Prediction of near-term increases in suicidal ideation in recently depressed patients with bipolar II disorder using intensive longitudinal data

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ABSTRACT

Background: There are substantial gaps in understanding near-term precursors of suicidal ideation in bipolar II disorder. We evaluated whether repeated patient-reported mood and energy ratings predicted subsequent near-term increases in suicide ideation.

Methods: Secondary data were used from 86 depressed adults with bipolar II disorder enrolled in one of 3 clinical trials evaluating Interpersonal and Social Rhythm Therapy and/or pharmacotherapy as treatments for depression. Twenty weeks of daily mood and energy ratings and weekly Hamilton Depression Rating Scale (HDRS) were obtained. Penalized regression was used to model trajectories of daily mood and energy ratings in the 3 week window prior to HDRS Suicide Item ratings.

Results: Participants completed an average of 68.6 (sd=52) days of mood and energy ratings. Aggregated across the sample, 22% of the 1675 HDRS Suicide Item ratings were non-zero, indicating presence of at least some suicidal thoughts. A cross-validated model with longitudinal ratings of energy and depressed mood within the three weeks prior to HDRS ratings resulted in an AUC of 0.91 for HDRS Suicide item ≥ 2, accounting for twice the variation when compared to baseline HDRS ratings. Energy, both at low and high levels, was an earlier predictor than mood.

Limitations: Data derived from a heterogeneous treated sample may not generalize to naturalistic samples. Identified suicidal behavior was absent from the sample so it could not be predicted.

Conclusions: Prediction models coupled with intensively gathered longitudinal data may shed light on the dynamic course of near-term risk factors for suicidal ideation in bipolar II disorder.

1. Introduction

Bipolar disorder is associated with the highest risk of suicide among psychiatric illnesses (Schaffer et al., 2015b). Rates of suicide are approximately 20 to 30 times that in the general population; 5–10% of people with bipolar disorder die by suicide, and 50–60% of patients attempt suicide in their lifetimes (Pompili et al., 2013; Schaffer et al., 2015b). Bipolar II disorder is associated with similar risk of self-harm as bipolar I disorder (Novick et al., 2010). In addition to their enormous toll on individuals and families, suicidal behaviors produce enormous direct and indirect costs (Stensland et al., 2010). Despite the clear public health need for *indicated* prevention strategies in bipolar disorder (Rihmer, 2007), much of the approach to prediction of suicidal risk in bipolar disorder is based on risk factors that do not change over time (e.g., family history of suicide attempt) and thus have limited prognostic utility in monitoring variation in risk longitudinally or predicting near-term risk (Schaffer et al., 2015a). Indeed, little is known about near term risks for exacerbations in suicidal thoughts despite the potential importance to timely suicide prevention (Glenn and Nock, 2014). Given the heterogeneous, fluctuating course that is characteristic of bipolar disorder, temporally finer-grained assessments obtained during days and weeks of acute illness may enhance near-term risk assessment of suicidal ideation, and may provide greater insight into to the warning signs of suicide-related crises in this high-risk group of patients (Claassen et al., 2014).

A number of prospective and retrospective studies have identified increases in time-varying constructs, such as agitation, dysphoric depression, anxiety, and mixed states, that seem associated with higher risk of suicidal ideation inbipolar disorder I or II (Novick et al., 2010; Schaffer et al., 2015a). These mixed affective states appear to be unique prognostic indicators of suicide risk in bipolar disorder compared to unipolar depression, and do not appear to differ between bipolar I and

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II in terms of frequency or strength of association (Novick et al., 2010; Schaffer et al., 2015a). In contrast, euphoric mania and psychomotor retardation have been associated with comparatively lower risk for suicidal ideation and behavior (Miller et al., 1985). Thus, co-occurring and opposite valence changes in mood and energy that frequently accompany mixed states are potentially prognostic indicators of suicide risk. However, it is unclear (1) when the earliest changes in mood and energy can be detected that predict elevated risk for future suicidal ideation, (2) what kind of change occurs first—i.e., mood or energy, if either, and (3) whether these time-varying changes provide greater predictive accuracy than risk factors that do not change over time. Given that changes in mood and energy occur over days or even hours, intensive longitudinal data (ILD) collection strategies in which high frequency repeated measures are gathered may be of great benefit for delineating the precursors of suicidal exacerbations in bipolar disorder. Although suicidal ideation is an insensitive and imperfect predictor of suicidal behavior, ideation is a major risk factor for suicide attempts (Valtonen et al., 2006) and is associated with other negative events such as hospitalization.

A handful of prior studies have examined ILD-based collection strategies in the context of predicting suicidal ideation and self-injury (Armey et al., 2011; Ben-Zeev et al., 2012; Muehlenkamp et al., 2009; Thompson et al., 2014). In a recent pilot study of 35 clinically euthymic patients with bipolar I or II disorder followed for 8 weeks, we found that changes in daily mood ratings (particularly increase in negative affect) accurately predicted increases in clinician-rated suicidal ideation and behavior in the period 1–3 weeks prior to direct clinical observation (Thompson et al., 2014). We applied functional linear models for this purpose (Ramsay, 2006), a statistical method well suited to ILD because it reduces the potential for over-fitting, which occurs when models are unduly influenced by error or noise. We found this approach more sensitive and specific in predicting suicidal exacerbations than in-person data collected at routine intervals analyzed with ordinary least squares regression. This study provided preliminary evidence that a frequently captured, time-varying predictor (negative affect) could be modeled to accurately predict *future* risk of suicidal ideation at a time point prior to the clinician's first awareness of an exacerbation. This study was limited by inclusion of euthymic patients, a small sample size, and the brief observation period.

Our objective for this study was to extend our prior work on prediction of suicidal ideation in bipolar disorder using ILD, by applying the statistical method to a comparatively larger sample of patients with bipolar II disorder, selected for the presence of a current depressive episode. We used pooled data from participants meeting criteria for bipolar II disorder, currently depressed, and enrolled in one of three clinical trials of Interpersonal and Social Rhythm Therapy (IPSRT) and/or pharmacotherapy. As part of their participation, participants completed the Social Rhythm Metric (SRM) (Monk et al., 1991), a self-report diary that included daily questions about mood and energy for 20 weeks. Since a central aspect of IPSRT is the collection of this daily diary, participants generate a large amount of intra-individual longitudinal data that can be used in prediction models. Moreover, bipolar II disorder is a subtype of the illness that is understudied but associated with high rates of suicide attempts, comparable to those with bipolar I disorder (Novick et al., 2010). We hypothesized that changes (worsening) in daily self-rated mood and energy over a 3-week window would precede a subsequent change (exacerbation) in suicidal ideation as indicated by weekly suicide item ratings on the Hamilton Depression Rating Scale (HDRS-SI). We hypothesized that the combined predictive accuracy of daily self-reported mood and energy ratings would be greater than either item alone and account for a greater variation in suicide ratings than would baseline HDRS total score or baseline HDRS-SI score. We varied estimation across the 3-week window prior to clinician-reported suicide rating to explore the temporal sequence and direction of change in mood and/or energy.

2. Methods

2.1. Study overview

We aggregated data from three trials of IPSRT/quetiapine in bipolar II disorder in which each study included the SRM daily rating. All study procedures were reviewed and approved by the Biomedical Institutional Review Board of the University of Pittsburgh. Potential participants provided informed written consent after receiving a complete description of the study, including a full description of risks associated with study participation. Participants were eligible for inclusion in the current analyses if they were treated in the Depression and Manic Depression Prevention Program at the University of Pittsburgh, were participants in one of the clinical trials for bipolar II disorder described below, and met the following inclusion criteria: Age 18–65 years; lifetime diagnosis of bipolar II disorder and current major depressive episode according to DSM-IV criteria as determined by the SCID-IV (First et al., 1997), currently experiencing at least a moderate level of depressive symptoms as indicated by a 25-item version of the Hamilton Rating Scale for Depression score ≥15. Potential participants were excluded from analyses if they met any of the following criteria: currently receiving treatment with psychoactive medications other than the study medications; diagnosis of substance abuse or dependence within the prior six months; currently pregnant or lactating; diagnosis of borderline or antisocial personality disorder as determined by the SCID for DSM-IV Personality Disorders (SCID-II); or unstable medical condition (such as untreated hypothyroidism) that could produce symptoms that would confound accurate assessment of mood. Suicidal ideation was not an exclusion criteria, although those who required a higher level of care (i.e., hospitalization) were excluded.

All participants received twenty weeks of treatment according to the protocol to which they were assigned. (1) STUDY 1 (previously described) (Swartz et al., 2009) consisted of open treatment with Interpersonal and Social Rhythm Therapy (IPSRT), an evidence based psychotherapy for bipolar disorder (Frank et al., 2005), followed by the addition of lamotrigine at week 12 for IPSRT non-responders (n=11), (2) STUDY 2 (previously described) (Swartz et al., 2012a) was a randomized trial comparing weekly IPSRT to quetiapine,(n=21) or (3) STUDY 3 was a randomized trial of IPSRT plus quetiapine or IPSRT plus placebo (n=54). In all studies, IPSRT was administered weekly. In Study 1 and 2, pharmacotherapy was administered openly and flexibly dosed according to participants' symptoms. In Study 3, quetiapine/pill placebo was administered in a double-blind fashion and flexibly dosed according to participants' symptoms. Participants were assessed weekly by a rater blind to their treatment condition (see Assessments below). We assessed whether there were potentially important differences among the three studies via ANOVA, and we found that there was study-wide variation in age ($F(2, 83)=3.7$, $p=0.029$) and age was included subsequent models. However, there were no significant omnibus differences in regard to sex (Chi-square 0.14, $p=0.928$), baseline depressive symptom severity ($F(2,83)=0.9$, $p=0.415$), or baseline suicidal ideation severity (Chi-square 4.7, $p=0.317$).

2.2. Baseline clinical assessments

Demographic data and psychiatric history were recorded on standardized research forms. Lifetime and current psychiatric diagnoses were assigned using the Structured Clinical Interview for DSM-IV, Clinician Version (SCID). Depressive symptoms were assessed weekly using the expanded 25-item version of the Hamilton Depression Rating Scale (HDRS) (Miller et al., 1985) that includes reverse neurovegetative symptoms. Research assessments were conducted by raters who were blind to participants' treatment assignment. Interrater reliability as measured by intraclass correlations (ICC) were excellent: ICC=0.99 and 0.98 for YMRS and HDRS, respectively.