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Research paper

# Trajectories of suicidal ideation over 6 months among 482 outpatients with bipolar disorder

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## ABSTRACT

*Introduction:* Suicidal ideation occurs frequently among individuals with bipolar disorder; however, its course and persistence over time remains unclear. We aimed to investigate 6-months trajectories of suicidal ideation among adults with bipolar disorder.

*Methods:* The Bipolar CHOICE study randomized 482 outpatients with bipolar disorder to 6 months of lithium- or quetiapine-based treatment including other psychotropic medications as clinically indicated. Participants were asked at 9 visits about suicidal ideation using the Concise Health Risk Tracking scale. We performed latent Growth Mixture Modelling analysis to empirically identify trajectories of suicidal ideation. Multinomial logistic regression analyses were applied to estimate associations between trajectories and potential predictors.

*Results:* We identified four distinct trajectories. The Moderate-Stable group represented 11.1% and was characterized by constant suicidal ideation. The Moderate-Unstable group included 2.9% with persistent thoughts about suicide with a more fluctuating course. The third (Persistent-low, 20.8%) and fourth group (Persistent-very-low, 65.1%) were characterized by low levels of suicidal ideation. Higher depression scores and previous suicide attempts (non-significant trend) predicted membership of the Moderate-Stable group, whereas randomized treatment did not.

*Limitations:* No specific treatments against suicidal ideation were included and suicidal thoughts may persist for several years.

*Conclusion:* More than one in ten adult outpatients with bipolar disorder had moderately increased suicidal ideation throughout 6 months of pharmacotherapy. The identified predictors may help clinicians to identify those with additional need for treatment against suicidal thoughts and future studies need to investigate whether targeted treatment (pharmacological and non-pharmacological) may improve the course of persistent suicidal ideation.

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## 1. Introduction

Bipolar disorder affects approximately 1–1.5% of the adult population (Pedersen et al., 2014). In addition to a wide range of psychopathological symptoms experienced by these individuals, such as depressive, manic and psychotic symptoms, suicidal thoughts occur frequently among affected individuals and represent a major suffering (Isometsa, 2014; Nierenberg et al., 2001; Tondo and Baldessarini, 2016). Among individuals with bipolar disorder, the estimated lifetime risk of attempted suicide is 25–50%, with an even higher proportion experiencing suicidal ideation (Isometsa, 2014; Nierenberg et al., 2001; Sokero et al., 2003; Tondo and Baldessarini, 2016). Several clinical correlates of suicidal ideation in bipolar patient samples have been identified such as age of onset, duration of illness, history of psychotic symptoms, or severity of depressive symptoms (Isometsa, 2014; Valtonen et al., 2005; Altamura et al., 2017, Cremaschi et al., 2017), and lithium is thought to have suicide-preventive effects in patients with bipolar disorder (Baldessarini et al., 2006; Zalsman et al., 2016). Nevertheless, the course of suicidal ideation in bipolar disorder, potential predictors of improvement or persistence of suicidal ideation and its response to different treatment regimens over time remain to be established (Isometsa, 2014; Thompson et al., 2014; Tondo and Baldessarini, 2016).

There has been increasing interest in the use of latent growth mixture modelling in psychiatric research to model heterogeneity in the course of symptoms over time (Kaplan et al., 2016; Musliner et al., 2016; Yaroslavsky et al., 2013), including suicidal ideation (Kasckow et al., 2016; Madsen et al., 2016a, 2016b). This method can be used to identify subpopulations sharing similar symptom trajectories over time. For instance, among 521 patients with psychotic symptoms, 33% had moderately stable and 7% had moderately increasing thoughts about suicide over a period of 2 years (Madsen et al., 2016a). Among 468 individuals with depression, 6.3% experienced high and persistent suicidal ideation despite 16 weeks of antidepressant treatment (Kasckow et al., 2016). Few studies have investigated the trajectories of overall mood symptoms in bipolar disorder (Birmaher et al., 2014; Depp et al., 2014; Duffy et al., 2014). Although suicidal thoughts are an important risk factor for completed suicide in patients with bipolar disorder, prototypical trajectories of suicidal thoughts have not been explored in this population.

Hence, our primary aim was to investigate the 6-months trajectories of suicidal ideation in a large outpatient population of adults with bipolar disorder. Our secondary aims were to explore potential predictors for different trajectories of suicidal ideation according to core foundational mood stabilizer treatment (lithium- or quetiapine-based treatment) and whether actual suicide attempts differed between the trajectory classes.

## 2. Materials and methods

### 2.1. Setting

The present study represents a secondary analysis of data from the Clinical and Health Outcomes Initiatives in Comparative Effectiveness for Bipolar Disorder (Bipolar CHOICE) study (Nierenberg et al., 2014), a six month multi-site, randomized trial comparing the effectiveness of lithium- and quetiapine-based treatment among patients with bipolar disorder. Participants were randomized to either lithium or quetiapine along with adjunctive personalized treatments (APT) (except lithium and quetiapine). All participants provided written and verbal informed consent and the study-protocol was approved by the Institutional Review Boards at all participating institutions. Further details regarding materials and methods including the CONSORT diagram are described elsewhere (Nierenberg et al., 2014).

### 2.2. Participants

Bipolar CHOICE applied few exclusion and broad inclusion criteria to maximize heterogeneity of the sample and increase the generalizability of findings. The main inclusion criteria were age ≥ 18 years and a diagnosis with DSM-IV-TR bipolar I or II disorder. Furthermore, patients had to be at least mildly symptomatic at baseline with a Clinical Global Impression scale for bipolar disorder (CGI-BP) score ≥ 3 (Spearing et al., 1997). The primary exclusion criteria were any contraindication to lithium or quetiapine, being in a current crisis, or substance dependence needing inpatient detoxication. Of 692 patients screened, 482 met inclusion criteria and were randomized (Nierenberg et al., 2014).

### 2.3. CHRT scale for assessment of suicidal ideation

Participants were rated with the self-report Concise Health Risk Tracking (CHRT) scale to monitor suicidality at baseline and at weeks 2, 4, 6, 8, 12, 16, 20, and 24. This scale was developed to detect changes in suicide-related factors and has excellent psychometric properties for patients with bipolar disorder (Ostacher et al., 2015; Reilly-Harrington et al., 2016). The CHRT scale is divided into three domains: hopelessness, interpersonal attachment/social support, and active suicidal ideation and behavior (Trivedi et al., 2011). Since we were only interested in the development of suicidal thoughts we used Item 10: *I have been having thoughts of killing myself* as the primary variable to determine trajectories of suicidal ideation among Bipolar CHOICE patients over time. The possible item responses were 0: Strongly disagree; 1: Disagree; 2: Neither agree nor disagree; 3: Agree; and 4: Strongly agree (supplementary Table 1).

### 2.4. Covariates

Based on prior studies (Kasckow et al., 2016; Madsen et al., 2016a, 2016b), the following sociodemographic and clinical covariates at baseline were considered: Gender, age (continuous), marital status (dichotomized into living alone/living with a partner), educational level (high school or less/college or more), employment status (employed or student/not employed), race (Caucasian/all others), previous suicide attempts, previous suicide in the family, randomization group (lithium vs. quetiapine), CGI-depressive and CGI-mania score at baseline, previous psychiatric hospitalization, current anxiety disorder, and a current Post-Traumatic Stress Disorder (PTSD) diagnosis (as diagnosed with the electronic version of the MINI International Neuropsychiatric Interview (Sheehan et al., 1998) based on DSM-IV-TR criteria).

### 2.5. Statistical analysis

We used Mplus Editor (version 7.4) to perform Growth Mixture models (GMM) (Jung and Wickrama, 2008). Information on suicidal ideation collected at up to nine assessments was applied in GMM analyses to identify trajectories of suicidal thoughts and to establish whether subgroups existed within the study population. GMM is a novel data driven approach where trajectories are customized and possible subgroups are identified based on prototypical patterns in slope and intercepts. This approach is useful since it allows for a closer examination of symptom development in various subgroups. Strength of a mixture model is that it represents a probabilistic model for the presence of multiple subpopulations within an overall population and therefore is not burdened with the classic assumption of a single normal distribution for the entire cohort.

We estimated one to five classes GMM models with linear, quadratic and cubic terms and kept the within-group variance fixed for the quadratic and cubic terms. We then compared the different class models in terms of fit estimates (Baysian information criterion (BIC), adjusted