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Age at onset, course of illness and response to psychotherapy in bipolar disorder: results from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)


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Background. The course of bipolar disorder progressively worsens in some patients. Although responses to pharmacotherapy appear to diminish with greater chronicity, less is known about whether patients' prior courses of illness are related to responses to psychotherapy.

Method. Embedded in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) was a randomized controlled trial of psychotherapy for bipolar depression comparing the efficacy of intensive psychotherapy with collaborative care (a three-session psycho-educational intervention). We assessed whether the number of previous mood episodes, age of illness onset, and illness duration predicted or modified the likelihood of recovery and time until recovery from a depressive episode in patients in the two treatments.

Results. Independently of treatment condition, participants with one to nine prior depressive episodes were more likely to recover and had faster time to recovery than those with 20 or more prior depressive episodes. Participants with fewer than 20 prior manic episodes had faster time to recovery than those with 20 or more episodes. Longer illness duration predicted a longer time to recovery. Participants were more likely to recover in intensive psychotherapy than collaborative care if they had 10–20 prior episodes of depression (NNT=1.9), but equally likely to respond to psychotherapy and collaborative care if they had one to nine (NNT=32.0) or >20 (NNT=9.0) depressive episodes.

Conclusions. Number of previous mood episodes and illness duration are associated with the likelihood and speed of recovery among bipolar patients receiving psychosocial treatments for depression.

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Key words: Bipolar disorder, mood episodes, psychotherapy, staging.

Introduction

Bipolar disorder is a chronic and debilitating illness, characterized by episodes of mania and/or depression. Kraepelin first noted that the course of bipolar disorder tends to worsen over time, a finding that has been replicated (Zis et al. 1980; Roy-Byrne et al. 1965; Kessing et al. 1998; Rosa et al. 2012). Bipolar patients with earlier onset and/or more mood episodes often experience a more chronic and continuous course of illness (Leboyer et al. 2005), diminishing response to pharmacological treatment (Franchini et al. 1999; Leboyer et al. 2005; Ketter et al. 2006), significant psychiatric co-morbidity (Leboyer et al. 2005), more frequent hospitalizations (Goldberg & Erret, 2002, Leboyer et al. 2005), higher rates of disability (Magalhães et al. 2012a), medical morbidity (Angst et al. 2002; Magalhães et al. 2012b), lower cognitive functioning (Lewandowski et al.
elevated rates of suicide attempts and completions (Angst et al. 2002; Leboyer et al. 2005), and impaired interpersonal relationships and quality of life (Magalhães et al. 2012a).

Several psychosocial treatments, adjunctive to pharmacotherapy, have been designed to treat acute mood symptoms, prevent relapse and mitigate functional impairments in patients with bipolar disorder. These include family-focused therapy (FFT), psychoeducation, cognitive–behavioral therapy (CBT), as well as interpersonal and social rhythm therapy (IPSRT) and there are emerging data for mindfulness, dialectical behavior therapy and Internet-based approaches (Lauder et al. 2013; Perich et al. 2013; Van Dijk et al. 2013). When combined with pharmacotherapy, these treatments have been shown to hasten recovery from episodes, delay mood episode recurrences, reduce residual mood symptoms, and improve psychosocial functioning (Miklowitz, 2008). Similar to treatment with pharmacotherapy (Franchini et al. 1999, Ketter et al. 2006; Berk et al. 2011), failure to intervene early in the course of illness may affect outcomes with psychotherapy. For example, Scott et al. (2006) compared 20 sessions of CBT with treatment as usual among patients with recurrent bipolar disorders (two or more prior episodes of mania or of hypomania). A post-hoc analysis demonstrated that patients with fewer than 12 episodes were less likely to relapse with adjunctive CBT, whereas patients with more than 12 episodes were less likely to relapse with treatment as usual (Scott et al. 2006). Similar findings were reported by Colom et al. (2010) in a trial of psycho-education for euthymic bipolar patients, who found that psycho-education did not delay time to recurrence in patients with a history of more than seven past episodes. Patients with more than 14 past episodes did not experience a reduction in time spent ill, whereas individuals with between nine and 14 episodes experienced fewer days ill in mood episodes when treated with psycho-education (Colom et al. 2010). However, a meta-analysis of 10 psychotherapy trials did not find a predictive or moderating effect of the number of episodes on relapse (Lam et al. 2009).

The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) was a multisite study of naturalistic course and randomized treatments. Embedded in the STEP-BD was a randomized controlled trial of intensive psychotherapy (either CBT, IPSRT or FFT) plus pharmacotherapy versus collaborative care (a three-session psycho-education intervention) plus pharmacotherapy for the treatment of acute bipolar depression. Results showed that patients in intensive therapy recovered from depressive episodes more rapidly than patients in collaborative care (Miklowitz et al. 2007a,b), and were more likely to recover if they had co-morbid anxiety disorders (Deckensbach et al. 2014). In the present study we examined data from the STEP-BD trial of psychotherapy to explore the role of prior illness course and age at onset in treatment outcome. Specifically we investigated whether prior illness course and age at onset (a) predict the likelihood of recovery or time until recovery from depression, and (b) moderate the response to treatment (i.e. intensive psychotherapy versus collaborative care). We hypothesized that (1) individuals with fewer mood episodes, shorter illness duration and later age at onset would have higher recovery rates and take less time to recover; and (2) intensive psychotherapy would be more effective than collaborative care among chronic patients with more mood episodes.

Method

Study design

The STEP-BD was a National Institute of Mental Health (NIMH)-funded multisite study designed to investigate the naturalistic course and effectiveness of treatments for bipolar disorder. The detailed methods of the research program have previously been described elsewhere (Sachs et al. 2003). Embedded in the STEP-BD was a randomized controlled treatment arm of psychotherapy for acute bipolar depression (Miklowitz et al. 2007b). Participants in the psychotherapy treatment trial were randomly assigned to 9 months of manualized weekly treatment with intensive psychotherapy (up to 30 sessions) of FFT, CBT or IPSRT, or to 6 weeks of treatment (up to three sessions) with collaborative care (Miklowitz & Otto, 2007). All four psychotherapies shared the common ingredients of psycho-education, relapse prevention planning and illness management. Collaborative care was a brief intervention that drew on a variety of the most common evidence-based psychosocial strategies for bipolar disorder with a focus on psycho-education (Miklowitz & Otto, 2007). The three intensive psychotherapies were designed as enhanced versions of fundamental psycho-education interventions with specific theoretical foundations and treatment strategies. FFT involved educating the family about bipolar disorder and the impact of the family system on its course of illness, as well as enhancing communication and problem solving between family members and patients (Miklowitz et al. 2000). CBT included re-structuring cognition distortions, challenging negative thoughts, problem solving and activity planning (Lam et al. 2003). IPSRT emphasized stabilizing social rhythms that are common antecedents of mood episodes and addressing interpersonal problems.
including grief, role disputes and relationship difficulties (Frank et al. 2000, 2005). A detailed description of the nature, scope, study design and participants in the psychosocial pathway of the STEP-BD can be found in Miklowitz & Otto (2007).

Participants

Eligible participants (n=293) met the Diagnostic and Statistical Manual, 4th revision (DSM-IV) criteria for bipolar I or II disorder and an acute episode of depression, as confirmed by the Mini-International Neuropsychiatric Interview (Sheehan et al. 1998), and were enrolled in the randomized trial of psychotherapy. To be eligible for the trial, participants had to be taking or willing to initiate treatment with a mood-stabilizing or atypical antipsychotic medication. Participants with rapid cycling bipolar disorder were excluded from the larger STEP-BD pharmacotherapy trial with which this study was affiliated, because of the possible association between rapid cycling and antidepressant use. Of the 293 participants, 205 provided information at their baseline visit regarding the number of previous lifetime episodes of mania and depression, age of illness onset and illness duration. Patients who did not provide this information did not differ from those who did on any patient characteristics (all p’s>0.126), with the exception of level of education ($\chi^2(1, n=271)=5.14, p=0.023$), which was higher among individuals not included in this subsample.

Measures

Course of illness and onset were assessed using the Affective Disorders Evaluation (ADE) (Sachs et al. 2003). In the ADE, episodes of depression and mania were reported separately in categorical fashion (e.g. 10–20 depressive episodes), and thus did not allow for the analysis of continuous data. Also, due to the separate categorization of manic and depressive episode frequency, the effects of these two clinical states were investigated separately. For this study, subcategories of number of episodes were defined a priori as one to nine, 10–20, or >20 lifetime episodes each for depression and mania. The distribution of our subsample, as well that of the full STEP-BD study enrollment according to mood episode history, are presented in Table 1.

Age at onset was assessed by inquiry into DSM-IV defined episodes of mania, hypomania, depression and mixed states. Subjects were then asked to identify the age at which they first experienced such episodes. Age at onset for bipolar disorder was defined as the earliest age at onset of a manic, hypomanic or mixed episode. Illness duration was computed by subtracting the ADE age of bipolar disorder onset from age at time of study enrollment, reflecting the length of time with a bipolar diagnosis at study entry.

At each treatment visit, mood symptoms were assessed using the Clinical Monitoring Form (CMF) (Sachs et al. 2002). Inter-rater reliability coefficients (referred to ‘gold standard’ ratings for CMF depression and mania items) of the blinded physician ratings ranged from 0.83 to 0.99 (intraclass $r’s$). Participants were considered ‘recovered’ if they experienced 4 or 2 moderate mood symptoms for 5 or 8 consecutive weeks. Participants were considered ‘not recovered’ if they failed to meet these criteria for either number or duration of mood symptoms (Sachs et al. 2003).

Data analyses

Predictor analyses

To evaluate whether previous mood episodes, age at onset and illness duration predicted likelihood of recovery and time until recovery, we conducted logistic regression and Cox proportional hazard (survival) models. All analyses were by intention to treat. Patients were included until their final assessment point, with a maximum of 365 days in the study.

Table 1. Distribution of mood episode history in the study sample (n=205) and full STEP-BD sample (n=4361)

<table>
<thead>
<tr>
<th></th>
<th>Depressive episodes</th>
<th>Manic episodes</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>1–9</td>
<td>10–20</td>
</tr>
<tr>
<td>n</td>
<td>%*</td>
<td>n</td>
</tr>
<tr>
<td>Study sample (n=205)</td>
<td>68</td>
<td>33</td>
</tr>
<tr>
<td>Full STEP-BD sample (n=4361)</td>
<td>1369</td>
<td>39</td>
</tr>
</tbody>
</table>

STEP-BD, Systematic Treatment Enhancement Program for Bipolar Disorder.

*Percentages for the full STEP-BD sample are calculated based on percentage of valid cases.
(mean = 166.48, s.d. = 102.58) (Sachs et al. 2003). The proportionality of risk assumption was met for all survival analyses. Mood episodes, age at onset and illness duration were evaluated independently in separate regression models. To evaluate the ability of these variables to predict recovery status after adjusting for the effects of treatment, treatment condition (psychotherapy or collaborative care) was included as an independent variable. Patients with 1–9 or 10–20 manic or depressive episode variables were compared with those who had more than 20 episodes to evaluate recovery status relative to the most chronic patients. In a previous study, we found that the presence of a lifetime co-morbid anxiety disorder moderated the effects of psychotherapy in the STEP-BD (Deckersbach et al. 2014). Therefore, we included anxiety and other co-morbidities as covariates. Specifically, effect size estimates [odds ratios (ORs) and R²] for each course of illness variable (i.e. number of depressive/manic episodes, illness duration, age at onset) are presented before and after adjusting for these covariates. Covariates were added individually to examine the effect of each covariate, and then added as a group of covariates to test their combined effect. Because of missing data, the sample was reduced with the addition of each control variable.

**Moderator analyses**

To evaluate whether mood episodes, age at onset or illness duration moderated the likelihood of or time until recovery, we added an interaction term with treatment condition to the models. Our moderator analysis follows the methods outlined by Kraemer & Kupfer (2006), who recommend that effect sizes define exploratory moderators of treatment because of the potential for the statistical significance of the moderator to change with sample size. Consistent with previous studies (Fisher, 1970; Nickerson, 2000; Kraemer, 2008; Pincus et al. 2011; Vitiello et al. 2012), our exploratory analyses of the moderating effects of prior illness course used a less stringent α threshold of 0.10. Moderators meeting this threshold were then explored in respect of the magnitude of the treatment effects at each level of the proposed moderators (Kraemer & Kupfer, 2006).

The measure of treatment effects that may best reflect clinical significance is the number needed to treat (NNT) (Cook & Sackett, 1995; Altman & Andersen, 1999). Computational procedures for NNT have been previously described. The value can be interpreted as the number of patients one would expect to treat with the investigation treatment (intensive psychotherapy) to have one more responder (or one fewer non-responder) that if the same number were treated with the control condition (collaborative care). NNT is presented with 95% confidence intervals (CIs) for sensitivity and specificity using the Newcombe–Wilson score method without continuity correction (Newcombe, 1998). An NNT of 2 is considered large, an NNT of 3.5 is considered medium, and an NNT >9 is considered small (Kraemer & Kupfer, 2006).

**Results**

**Study sample**

Demographic and clinical characteristics for the total sample (n = 205), stratified by number of episodes for both depressive and (hypo)manic episodes, are presented in Table 2. Associations between mood episodes and age at onset and illness duration are also displayed in Table 2.

**Psychosocial treatment outcome**

The overall superiority of psychotherapy relative to collaborative care in the full sample (n = 293) has been previously reported (Miklowitz et al. 2007b). Consistent with these results, in this subsample (n = 205), intensive psychotherapy yielded significantly faster time until recovery (b = 0.42, p = 0.021, OR = 1.53, 95% CI 1.07–2.19) and greater likelihood of recovery (b = 0.66, p = 0.024, OR = 1.94, 95% CI 1.09–3.45) relative to collaborative care.

**Course of illness**

Frequencies, means and standard deviations for previous depressive and (hypo)manic episode groups are reported in Table 2.

Patients with 1–9, 10–20, and 20+ previous depressive episodes differed with respect to their age at onset (F_{2,202} = 14.84, p < 0.001), illness duration (F_{2,202} = 13.44, p < 0.001), number of lifetime anxiety disorders (F_{2,194} = 5.07, p = 0.007), number of lifetime co-morbidities (F_{2,202} = 4.34, p = 0.014) and proportion of individuals with at least one lifetime diagnosis of an anxiety disorder [χ²(2, n = 197) = 6.31, p = 0.043]. All other comparisons were non-significant (all p’s > 0.146; see Table 2).

Patients with 1–9, 10–20, and 20+ prior (hypo)manic episodes differed with respect to their age at onset (F_{2,202} = 16.80, p < 0.001), illness duration (F_{2,202} = 20.53, p < 0.001), and at the trend level, the number of lifetime anxiety disorders (F_{2,194} = 2.94, p = 0.055), co-morbid conditions (F_{2,202} = 2.74, p = 0.067), any lifetime anxiety disorder [χ²(2, n = 202) = 5.49, p = 0.064]. All other comparisons were non-significant (all p’s > 0.184; see Table 2).