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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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Declaration of Interest

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Abstract

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 moderated 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 [number needed to treat (NNT)=2.0], 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.

Keywords

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*. 1985; 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 & Ernst, 2002, Leboyer *et al*. 2005), higher rates of disability (Magalhães *et al*. 2012a), more medical morbidity (Angst *et al*. 2002; Magalhães *et al*. 2012b), lower cognitive functioning (Lewandowski *et al*. 2011), 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 ar 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 psychoeducation 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*. 2007*a*, b), and were more likely to recover if they had co-morbid anxiety disorders (Deckersbach *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 restructuring cognition distortions, challenging negative thoughts, problem solving and activity planning (Lam *et al*. 2005). 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 as 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 (referenced 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 ≤2 moderate mood symptoms for ≥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 (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 R^2] 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 comorbidities ($F_{2,202}$=4.34, p=0.014) and proportion of individuals with at least one lifetime diagnosis of an anxiety disorder [χ^2(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 [χ^2(2, n=197)=5.21, p=0.074] and education [χ^2(2, n=202)=5.49, p=0.064]. All other comparisons were non-significant (all p's > 0.184; see Table 2). In general, pairwise contrasts indicated that more lifetime mood episodes were associated with earlier onset, longer illness duration, the likelihood of having one or more co-morbid anxiety disorders, and other co-morbidities (see Table 2). Logistic and Cox regression models for recovery and time until recovery, respectively, indicated that having a lifetime anxiety disorder, number of anxiety disorders, number of co-morbidities, and education were unrelated to recovery rates or time to recovery (all p's > 0.10).

Predictor analyses

Results of the modeling sequence, including regression coefficients, ORs, p values, effect sizes and CIs are presented in Table 3.

Mood episodes—Individuals with one to nine previous depressive episodes were more likely to recover (OR=2.12, p=0.030) and had faster time to recovery (OR=1.53, p=0.024) than those with more than 20 previous episodes of depression. The likelihood of recovery and time until recovery for individuals with 10–20 previous episodes of depression was intermediate between those with one to nine and 20+ episodes (Table 3). Previous depressive episodes remained a significant predictor of recovery likelihood after adjusting for illness duration (p=0.041), age at onset (p=0.034), number of manic episodes (p=0.045), lifetime anxiety (p=0.046) or number of co-morbidities (p=0.027), but was reduced to a statistical trend after adjusting for number of anxiety disorders (see Table 4). Although p values were slightly reduced following the inclusion of all covariates, the effect size estimates (OR and R^2) remained almost identical despite reductions in sample size.

Previous depressive episodes remained a significant predictor of time to recovery after adjusting for age at onset (p=0.042) and number of co-morbidities (p=0.029), but the significance was reduced after controlling for illness duration (p=0.099), lifetime anxiety (p=0.062), number of anxiety disorders (p=0.097) or number of manic episodes (p=0.256). Illness duration and previous depressive episodes were positively correlated (r=0.35, p<0.001). When all predictors were entered in one model, number of previous depressive episodes was no longer a significant predictor (Table 4).

Previous (hypo)manic episodes did not predict the likelihood of recovery (p's>0.078; see Table 3). However, individuals with one to nine previous manic episodes (OR=1.53,

p=0.033) and with 10–20 previous manic episodes (OR=1.73, *p*=0.025) recovered faster than those with 20+ manic episodes. Manic episodes remained a significant predictor of time to recovery after adjusting for number of co-morbidities (one to nine episodes, *p*=0.038; 10–20 episodes, *p*=0.025). Having 10–20 previous manic episodes was associated with time until recovery after adjusting for illness duration (*p*=0.037) and age at onset (*p*=0.026). The significance of both one to nine and 10–20 previous manic episodes was reduced when controlling for lifetime anxiety (one to nine episodes, *p*=0.051; 10–20 episodes, *p*=0.053), number of anxiety disorders (*p*=0.065) and previous depressive episodes (*p*=0.387). When all covariates were entered in one model, the significance of previous manic episodes was reduced (see Table 4).

Illness duration—Illness duration did not predict the likelihood of recovery (OR=0.99, *p*=0.494; see Table 3), but increases in illness duration were associated with longer time until recovery (OR=0.98, *p*=0.012), even after adjusting for previous depressive episodes (*p*=0.044), previous manic episodes (*p*=0.043), age at onset (*p*=0.021), lifetime anxiety (*p*=0.008), number of anxiety disorders (*p*=0.010), number of co-morbidities (*p*=0.012) and all predictors in one model (see Table 4).

Age at onset—Finally, age at illness onset neither predicted likelihood of recovery (OR=1.01, *p*=0.575) nor time until recovery (OR=1.01, *p*=0.301) (Table 3).

Moderator analyses

To investigate whether number of previous episodes, illness duration or age at onset moderated treatment outcome, we added an interaction term with treatment condition to the models predicting likelihood of and time to recovery. Number of previous episodes demonstrated a treatment interaction term predicting likelihood of recovery (*p*=0.10). The treatment interaction terms for number of previous manic episodes, age at onset and illness duration did not exceed the set α threshold of 0.10 for further investigation of NNT (all *p*'s > 0.282). The differential NNTs of psychotherapy *versus* collaborative care for patients with one to nine, 10–20, and > 20 lifetime depressive episodes (and for comparison purposes, also manic episodes) are shown in Table 5.

For patients with 10–20 lifetime depressive episodes, 79% (*n*=11) recovered with intensive psychotherapy, whereas only 27% (*n*=4) recovered with collaborative care. These recovery rates corresponded to a large NNT (2.00). That is, one would need to treat two patients with intensive psychotherapy compared with collaborative care to see one additional patient recover with psychotherapy. By contrast, there was no difference in recovery rates to psychotherapy *versus* collaborative care for patients with one to nine lifetime episodes of depression, or for patients with >20 lifetime episodes of depression. For patients with one to nine lifetime depressive episodes, 76% (*n*=32) recovered with psychotherapy and 73% (*n*=19) recovered with collaborative care (NNT=32.00). For patients with >20 lifetime episodes of depression, 63% (*n*=39) recovered with psychotherapy and 52% (*n*=24) recovered with collaborative care (NNT=9.00). This moderator effect was not affected by having a lifetime anxiety disorder, number of anxiety disorders or number of comorbidities,

as these variables were not associated with increased or decreased likelihood of recovery within any subcategory of depressive or manic episodes (χ^2, all p's > 0.10).

Discussion

To our knowledge, this is the first study investigating the role of course of illness and age at onset in the outcomes of adult depressed patients with bipolar disorder undergoing different forms of psychotherapy. The number of previous depressive episodes and illness duration emerged as the strongest predictors of recovery rates and/or time to recovery from depression. Collectively, our findings suggest that depressed bipolar patients with a longer duration of illness and more episodes are less likely to recover from depression and, if they do, take longer to recover compared with patients with fewer episodes and shorter illness duration. This was true independently of which type of therapy (intensive psychotherapy or collaborative care) that patients received or when controlling for other factors that tend to accompany a chronic illness course.

The findings from the predictor analysis are consistent with the results of pharmacotherapy studies that show better response earlier in the course of illness (Berk *et al*. 2013). However, it is unclear whether patients with fewer episodes and a favorable response are (1) in an earlier stage of illness, where they have not yet experienced as many mood episodes, or (2) less prone to experiencing recurrences of mood episodes over the duration of their illness. In this study, patients with the most episodes had both the earliest age at onset and longest illness duration. However, we could not investigate recurrence rates of mood episodes in relation to a patient's illness duration because mood episodes in the STEP-BD were assessed in distinct subcategories, grouping the number of mood episodes (e.g. 10–20). Future studies are needed to investigate whether our findings reflect stage of illness or proneness to recurrence. Of note, patients with the rapid cycling bipolar subtype were excluded from this STEP-BD study, so that our results do not reflect effects of this particular subgroup with a high frequency of episodes.

In contrast to mood episodes and illness duration, age at onset was unrelated to recovery from an acute depressive episode. This is somewhat surprising, given that previous studies in first-episode patient cohorts have reported effects of age at onset in psychosocial treatment outcomes (McMurrich *et al*. 2012). However, in these studies, psychotherapy was largely uncontrolled, and the effects of age at onset pertained to relapse prevention and functional recovery rather than acute recovery of symptoms. Therefore, it is possible that age at onset is relevant to psychotherapy outcome with regard to mood episode recurrence and day-to-day functioning, but may not play a role in the acute stabilization and syndromic recovery of depressive symptoms.

We also investigated course of illness as a moderator of treatment response. As per Kraemer's recommendations, the analysis focused on the magnitude of treatment differences, rather than significance (Kraemer & Kupfer, 2006). Patients with 10–20 prior episodes of depression were more likely to recover with psychotherapy than collaborative care. Patients with less than 10 lifetime depressive episodes responded at equally high rates to both treatments, whereas patients with more than 20 episodes experienced the lowest

recovery rates with both treatments. These findings suggest that intensive psychotherapy for acute depression may be more successful for adult patients with 10–20 episodes, supporting the utility of a personalized medicine approach for tailoring treatment selection and delivery. However, a degree of caution is advised when interpreting the results of this moderator analysis. First, the interaction between number of mood episodes and type of psychotherapy (intensive psychotherapy *versus* collaborative care) did not reach conventional statistical thresholds (p=0.05). Second, as shown in Table 2, the subgroup of patients with 10–20 depressive episodes was smaller than those with one to nine or 10–20 previous depressive episodes. Therefore, these results provide initial support for an advantage of intensive psychotherapy among patients with 10–20 prior depressive episodes, but replication of the findings in larger samples is recommended before drawing firm conclusions about the difference in response rates between the two treatment conditions.

Findings in several studies suggest that repeated mood episodes are associated with increasing treatment resistance (Franchini *et al*. 1999; Leboyer *et al*. 2005; Ketter *et al*. 2006; Scott *et al*. 2006; Colom *et al*. 2010). It is possible that individuals with 10–20 previous depression episodes have reached a level of chronicity where the collaborative care intervention is too brief to provide benefit, but the ‘extra dose’ (i.e. more sessions) and additional treatment ingredients unique to intensive psychotherapies [e.g. enhancing family communication, activity planning, challenging negative thoughts, addressing interpersonal difficulties (Miklowitz *et al*. 2000; Frank *et al*. 2000, 2005; Lam *et al*. 2005)] are enough of a boost to achieve recovery. The relative advantage of intensive psychotherapy, however, was diminished among the most chronic patients with more than 20 episodes. This finding diverges from findings in relapse prevention studies (Scott *et al*. 2006; Colom *et al*. 2010). These found that CBT is more effective than treatment as usual in preventing relapse for patients with less than 12 episodes (Scott *et al*. 2006) and that beneficial effects of psycho-education (*versus* no psycho-education) for relapse prevention can be observed in patients with up to 14 lifetime mood episodes. Although there are methodological differences in these studies to consider when interpreting the results, it is possible that the windows of time where therapies work best are different for acute depression and relapse prevention.

There are several limitations of this study. First, we could only assess the effects of prior illness course on recovery from depression. Although we examined how prior manic episodes were related to recovery from depression, it remains to be investigated how prior illness course may relate to recovery from acute mania. Second, data on the number of prior lifetime episodes of mania or depression were collected retrospectively at study entry, were coded in categories, and may have been subject to recall bias. Third, by virtue of recruiting an adult sample, the majority of participants had several prior mood episodes, whereas first-episode individuals may have been under-represented. Additionally, the sample size of the group of participants with 10–20 prior episodes was comparatively small. Future designs would benefit from stratifying assignment to treatments as a function of mood episode history. Fourth, average age at onset in this subsample was older than that reported in the full psychosocial trial (Miklowitz *et al*. 2007a,b), which may have introduced a bias. Finally, the primary outcome of the study was durable recovery (at least 8 weeks) within a 1-year window after the start of treatment; we do not have longer-term follow-up data beyond this

primary outcome. Therefore, we cannot attest to the long-term effects of intensive psychotherapy *versus* collaborative care on longer-term outcomes, such as recurrences, quality of employment or life satisfaction.

These limitations notwithstanding, our findings suggest that prior illness course in bipolar disorder is a factor contributing to the likelihood and speed of recovery from acute depression with a psychosocial intervention adjunctive to medication. Results from this study, as well as two previous relapse prevention studies (Scott *et al*. 2006; Colom *et al*. 2010), suggest that the needs of the most chronically ill patients may differ from those with a remitting prior illness course. Patients with multiple recurrences and long illness duration may need a tailored, personalized approach, as this may be the most treatment-resistant group. Traditional forms of intensive psychotherapy may not be able to address prevailing cognitive and functioning issues. According to Berk *et al*. (2012), such patients may benefit from tailored 'palliative' programs that focus on setting attainable goals, reducing side-effects, rebalancing the risks and benefits of intervention, and attaining the best quality of life within the patients' limitations (Berk *et al*. 2012). Equally, given the unique psychosocial needs of people who have had a first episode of illness or are early in their illness course, their particular profile may merit specific and tailored approaches (Macneil *et al*. 2012).

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Table 1

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

	Depressive episodes						Manic episodes					
	1–9		10–20		20+		1–9		10–20		20+	
	n	%[a]	*n*	%[a]	*n*	%[a]	*n*	%[a]	*n*	%[a]	*n*	%[a]
Study sample (*n*=205)	68	33	29	14	108	53	75	37	33	16	97	47
Full STEP-BD sample (*n*=4361)	1369	39	642	18	1480	42	1572	45	604	17	1312	37

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

[a]Percentages for the full STEP-BD sample are calculated based on percentage of valid cases.

Table 2

Demographic and clinical characteristics according to number of lifetime depressive and (hypo)manic episodes

		Depressive episodes			(Hypo)manic episodes		
	Overall (*n*=205)	**1–9**	**10–20**	**20+**	**1–9**	**10–20**	**20+**
Mean age, years (S.D.)	39.96 (11.81)	39.38 (11.98)	37.28 (11.69)	41.07 (11.71)	38.04 (12.07)	40.27 (10.34)	41.37 (11.99)
Mean age at onset, years (S.D.)[b,d,e,f]	20.85 (9.56)	25.56 (10.03)	20.37 (8.56)	18.01 (8.34)	25.37 (9.98)	20.55 (9.41)	17.45 (7.75)
Mean duration of illness, years (S.D.)[c,d,e,f]	19.13 (12.48)	13.82 (11.05)	16.90 (13.13)	23.06 (11.85)	12.67 (11.25)	19.73 (11.69)	23.91 (11.49)
Mean depressive severity (S.D.)	7.19 (2.38)	6.94 (2.49)	7.27 (1.64)	7.33 (2.51)	6.88 (2.45)	7.37 (2.11)	7.37 (2.41)
Mean manic severity (S.D.)	1.15 (1.07)	1.18 (1.20)	0.79 (1.10)	1.22 (0.97)	1.15 (1.25)	0.95 (2.11)	1.21 (0.95)
Mean number of sessions (S.D.)	9.46 (10.59)	11.04 (11.50)	8.31 (9.82)	8.78 (10.16)	10.31 (11.19)	10.94 (10.60)	8.31 (10.07)
Mean global functioning (S.D.)	56.75 (9.69)	58.15 (10.73)	56.97 (8.66)	55.80 (9.21)	57.11 (9.93)	56.78 (8.53)	56.54 (9.95)
Mean no. of co-morbidities (S.D.)[d]	1.76 (1.14)	1.46 (1.11)	1.69 (1.26)	1.96 (1.08)	1.53 (1.09)	1.73 (1.21)	1.94 (1.13)
Mean no. of anxiety disorders (S.D.)[d]	1.36 (1.36)	0.98 (1.26)	1.18 (1.09)	1.64 (1.43)	1.07 (1.34)	1.34 (1.12)	1.58 (1.42)
Female gender, *n* (%)	122 (60)	41 (60)	19 (66)	62 (57)	44 (59)	20 (61)	58 (60)
Education >1 year of college, *n* (%)[a]	156 (78)	54 (82)	21 (72)	81 (76)	58 (80)	30 (91)	68 (72)
Married, *n* (%)[a]	68 (33)	21 (31)	11 (38)	36 (33)	51 (68)	13 (39)	31 (32)
Diagnosis, *n* (%)[a]							
Bipolar I	128 (65)	41 (63)	17 (61)	70 (67)	47 (65)	21 (66)	60 (64)
Bipolar II	70 (35)	24 (37)	11 (39)	35 (33)	25 (35)	11 (34)	34 (36)
Lifetime anxiety disorder[c,d]	132 (67)	36 (55)	19 (68)	77 (74)	41 (57)	23 (72)	68 (73)
Normal sleep status, *n* (%)[a,g]	92 (51)	28 (48)	15 (58)	49 (52)	35 (55)	16 (53)	41 (48)
Baseline medications, *n* (%)[a]							
Mood stabilizers	60 (29)	18 (27)	9 (31)	33 (31)	23 (31)	10 (30)	27 (28)
Antidepressants	94 (46)	29 (43)	16 (55)	49 (45)	32 (43)	14 (42)	48 (50)
Atypical antipsychotics	54 (26)	15 (22)	9 (31)	30 (28)	18 (24)	11 (33)	25 (26)
Anxiolytics	53 (26)	16 (24)	6 (21)	31 (29)	16 (21)	9 (27)	28 (29)
Anticonvulsants	114 (56)	20 (59)	18 (62)	56 (52)	43 (57)	17 (52)	54 (56)

S.D., Standard deviation.

[a] Where data points were missing, percentages were calculated out of total number of available cases.

[b] Difference between one to nine and 10–20 depressive episodes ($p<0.05$).

[c] Difference between 10–20 and 20+ depressive episodes ($p<0.05$).

[d] Difference between one to nine and 20+ depressive episodes ($p<0.05$).

[e] Difference between one to nine and 10–20 manic episodes ($p<0.05$).

[f] Difference between one to nine and 20+ manic episodes ($p<0.05$).

[g] Sleep status refers to being a short (<6 h/night), normal (6–8 h/night) or long (>8 h/night) sleeper in the week prior to the baseline visit.

Table 3

Logistic regression and Cox regression analyses evaluating previous mood episodes, illness duration and age at onset as predictors of likelihood of recovery and time until recovery

Predictor	*b*	Wald	OR	(95% CI)	*p*	ΔR^{2} [a]
Previous depressive episode models						
Logistic regression: predicting recovery						0.07
Treatment group[b]	0.63	4.43	1.88	(1.04–3.37)	0.035	
1–9 Depressive episodes[c]	0.75	4.74	2.12	(1.08–4.16)	0.030	
10–20 Depressive episodes[c]	−0.22	0.26	0.35	(0.35–1.86)	0.612	
Cox regression: predicting time until recovery						0.05
Treatment group[b]	0.40	4.72	1.49	(1.04–2.14)	0.030	
1–9 Depressive episodes[c]	0.43	5.06	1.53	(1.06–2.22)	0.024	
10–20 Depressive episodes[c]	0.21	0.53	1.23	(0.70–2.17)	0.468	
Previous manic episode models						
Logistic regression: predicting recovery						0.06
Treatment group[b]	0.62	4.33	1.86	(1.04–3.32)	0.038	
1–9 Manic episodes[c]	0.30	0.88	1.35	(0.72–2.54)	0.349	
10–20 Manic episodes[c]	0.81	0.31	2.25	(0.91–5.54)	0.078	
Cox regression: predicting time until recovery						0.06
Treatment group[b]	0.36	3.74	1.43	(0.99–2.06)	0.053	
1–9 Manic episodes[c]	0.43	4.57	1.53	(1.04–2.27)	0.033	
10–20 Manic episodes[c]	0.55	5.06	1.73	(1.07–2.78)	0.025	
Illness duration models						
Logistic regression: predicting recovery						0.04
Treatment group[b]	0.66	5.06	1.94	(1.09–3.45)	0.025	
Illness duration	−0.01	0.47	0.99	(0.97–1.02)	0.494	
Cox regression: predicting time until recovery						0.06
Treatment group[b]	0.40	4.76	1.50	(1.04–2.15)	0.029	
Illness duration	−0.02	6.29	0.98	(0.97–0.99)	0.012	
Age at onset models						
Logistic regression: predicting recovery						0.04
Treatment group[b]	0.65	4.86	1.91	(1.07–3.41)	0.028	
Age at onset	0.01	0.31	1.01	(0.98–1.04)	0.575	
Cox regression: predicting time until recovery						
Treatment group[b]	0.40	4.64	1.49	(1.04–2.15)	0.031	0.03
Age at onset	0.01	1.07	1.01	(0.99–1.03)	0.301	

OR, Odds ratio; CI, confidence interval.

[a] R^2 for logistic regressions represents Nagelkerke R^2, an estimate of the increment in variance in the probability of recovery accounted for by the predictors tested. R^2 for Cox regressions represents Cox–Snell R^2, an estimate of the relative association between survival and the predictors tested.

[b] Treatment group=intensive psychotherapy (1) versus collaborative care (0).

[c] Depressive and manic episodes: dummy coded with the group with 20+ episodes coded as the reference group; therefore only coefficients relative to the reference group are presented.

Table 4

Effect of previous mood episodes and illness duration as predictors of likelihood of recovery and time until recovery after adjusting for clinical covariates

Covariates	*b*	Wald	OR	(95% CI)	*p*	ΔR^{2} [a]
Previous depressive episode models						
Logistic regression: predicting recovery						
Depressive episodes	0.75	4.74	2.12	(1.08–4.16)	0.030	0.07
Control variables						
Illness duration	0.75	4.17	2.11	(1.03–4.33)	0.041	0.05
Age at onset	0.78	4.51	2.18	(1.06–4.49)	0.034	0.06
Number of manic episodes	0.89	4.03	2.46	(1.02–5.91)	0.045	0.07
Lifetime anxiety disorder	0.72	3.98	2.05	(0.31–1.68)	0.046	0.05
Number of anxiety disorders	0.66	3.36	1.94	(0.96–3.94)	0.067	0.06
Number of co-morbid conditions	0.78	4.86	2.17	(1.09–4.33)	0.027	0.06
All covariates together[b]	0.72	3.27	2.05	(0.94–4.47)	0.071	0.06
Cox regression: predicting time until recovery						
Depressive episodes	0.43	5.06	1.53	(1.06–2.22)	0.024	0.05
Control variables						
Illness duration	0.32	2.72	1.38	(0.94–2.03)	0.099	0.07
Age at onset	0.40	4.14	1.50	(1.02–2.20)	0.042	0.05
Number of manic episodes	0.29	1.29	1.33	(0.81–2.19)	0.256	0.07
Lifetime anxiety disorder	0.37	3.47	1.44	(0.98–2.12)	0.062	0.05
Number of anxiety disorders	0.33	2.76	1.39	(0.94–2.06)	0.097	0.05
Number of co-morbid conditions	0.43	4.78	1.53	(1.05–2.24)	0.029	0.05
All covariates together[b]	0.10	0.15	1.11	(0.65–1.88)	0.704	0.09
Previous manic episode models						
Cox regression: predicting time until recovery						
Manic episodes	0.55	5.06	1.73	(1.07–2.78)	0.025	0.06
Control variables						
Illness duration	0.51	4.37	1.67	(1.03–2.69)	0.037	0.08
Age at onset	0.54	4.93	1.72	(1.07–2.77)	0.026	0.06
Number of depressive episodes	0.47	3.49	1.61	(0.98–2.64)	0.062	0.07
Lifetime anxiety disorder	0.48	3.74	1.62	(0.99–2.63)	0.053	0.06
Number of anxiety disorders	0.47	3.57	1.60	(0.98–2.60)	0.059	0.06
Number of co-morbid conditions	0.55	5.00	1.73	(1.07–2.78)	0.025	0.06
All covariates together[b]	0.42	2.54	1.52	(0.91–2.54)	0.111	0.09
Illness duration models						
Cox regression: predicting time until recovery						
Illness duration	−0.02	6.29	0.98	(0.97–0.99)	0.012	0.06
Control variables						
Age at onset	−0.02	5.35	0.98	(0.97–1.00)	0.021	0.06

Covariates	*b*	Wald	OR	(95% CI)	*p*	ΔR^{2} [a]
Number of manic episodes	−0.02	4.08	0.99	(0.97–1.00)	0.043	0.08
Number of depressive episodes	−0.02	4.05	0.99	(0.97–1.00)	0.044	0.07
Lifetime anxiety disorder	−0.02	6.95	0.98	(0.97–1.00)	0.008	0.07
Number of anxiety disorders	−0.02	6.68	0.98	(0.97–1.00)	0.010	0.07
Number of co-morbid conditions	−0.02	6.35	0.98	(0.97–1.00)	0.012	0.06
All covariates together[b]	−0.02	4.88	0.98	(0.97–1.00)	0.027	0.09

OR, Odds ratio; CI, confidence interval.

[a] R^2 for logistic regressions represents Nagelkerke R^2, an estimate of the increment in variance in the probability of recovery accounted for by the predictors tested. R^2 for Cox regressions represents Cox–Snell R^2, an estimate of the relative association between survival and the predictors tested.

[b] All covariates denote a model where all covariates listed above for a given model were entered as a set of variables into the model. Covariates were added first individually to examine the effect of each covariate, and then added as a group of covariates to test their combined effect.

Table 5

Moderator effects of number of lifetime mood episodes on recovery rates with collaborative care and psychotherapy for bipolar depression

	Psychotherapy			Collaborative care				
	n	Number recovered	% Recovered	*n*	Number recovered	% Recovered	NNT	(95% CI)
Depressive episodes								
1–9	42	32	76	26	19	73	32.00	(−6 to 4)
10–20	14	11	79	15	4	27	2.00	(1 to 6)
>20	62	39	63	46	24	52	9.00	(−13 to 4)
Manic episodes								
1–9	47	33	70	28	16	57	7.65	(−11 to 2)
10–20	21	18	86	12	7	58	3.65	(−24 to 2)
>20	50	31	62	47	24	51	9.14	(−12 to 3)

NNT, Number needed to treat; CI, confidence interval.