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Research report

Stressful life events in bipolar I and II disorder: Cause or consequence of mood symptoms?

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ABSTRACT

Background: Life events are assumed to be triggers for new mood episodes in bipolar disorder (BD). However whether life events may also be a result of previous mood episodes is rather unclear.
Method: 173 bipolar outpatients (BD I and II) were assessed every three months for two years. Life events were assessed by Paykel's self-report questionnaire. Both monthly functional impairment due to manic or depressive symptomatology and mood symptoms were assessed.
Results: Negative life events were significantly associated with both subsequent severity of mania and depressive symptoms and functional impairment, whereas positive life events only preceded functional impairment due to manic symptoms and mania severity. These associations were significantly stronger in BD I patients compared to BD II patients. For the opposite temporal direction (life events as a result of mood/functional impairment), we found that mania symptoms preceded the occurrence of positive life events and depressive symptoms preceded negative life events.
Limitations: The use of a self-report questionnaire for the assessment of life events makes it difficult to determine whether life events are cause or consequence of mood symptoms. Second, the results can only be generalized to relatively stable bipolar outpatients, as the number of severely depressed as well as severely manic patients was low.
Conclusions: Life events appear to precede the occurrence of mood symptoms and functional impairment, and this association is stronger in BD I patients. Mood symptoms also precede the occurrence of life event, but no differences were found between BD I and II patients.

1. Introduction

The course of bipolar disorder (BD) is assumed to be the result of a complex interaction between genetic and biological vulnerability and environmental factors (Alloy et al., 2005; Johnson and Roberts, 1995; Post, 1992). The severity and frequency of the occurrence of (hypo-) manic and depressed episodes is highly variable and unpredictable among BD patients. In order to improve treatment effect and disease outcome, more insight is needed in factors predicting and contributing to relapse into mood episodes. Stressful life events play an important role in the course of BD. The occurrence of major events in the life of BD patients has been associated with an increased risk of relapse into mood episodes (Ellicott et al., 1990; Hammen and Gitlin, 1997) and increased time until recovery (Johnson and Miller, 1997). Especially negative life events seem to be more common in the months prior to both depressive (Christensen et al., 2003; Cohen et al., 2004; Hosang et al., 2012b; Hunt et al., 1992; Johnson et al., 2008b; Malkoff-Schwartz et al., 1998) and manic episodes (Hall et al., 1977; Hosang et al., 2012a; Joffe et al., 1989; Kim et al., 2007; Mathew et al., 1994; Pardoen et al., 1996). One of the more recent studies, and the largest follow up study on life events in BD to date, shows that negative life events especially precede depressive symptoms and life events involving goal attainment precede manic symptoms (Johnson et al., 2008a). However both for depression (Mcpherson et al., 1993; Pardoen et al., 1996) and mania (Christensen et al., 2003; Cohen et al., 2004; Johnson et al., 2008b; Mcpherson et al., 1993) findings are inconsistent, and the exact nature, strength and direction of the associations are still unclear.

Further, it has been suggested that life events may also occur as a consequence of the disorder. The so-called 'stress generation theory' in unipolar depression (Hammen, 1991) states that individuals with depressive symptomatology may generate stressful events, (for example, marital problems, or loss of a job) due to their depressive symptoms. There is a substantial amount of evidence that supports this relationship in unipolar depression (Liu and Alloy, 2010), and hence, whether this also holds for BD

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patients remains unclear, since only one prospective study (Bender et al., 2010) to date examined this association and found that hypomanic symptoms predicted increases in both negative and positive life events and depressive symptoms appeared to be less stronger predictors of subsequent life events.

There are several factors that complicate examining the association between life events and mood, which may have contributed to inconsistent results. One of the factors that may explain part of the inconsistencies may relate to the BD subtypes that have been studied, as previous studies strongly differ in terms of the specific BD diagnosis. Some studies examined samples including all BD subtypes (Christensen et al., 2003), others only included cyclothymic and BD II patients (Nusslock et al., 2007) or only BD I patients (e.g. Johnson et al., 2008b). This might contribute to inconsistent findings, since growing evidence indicate that BD I and II differ on both clinical (Baek et al., 2011), genetic (Heun and Maier, 1993; Vieta et al., 1997) and neurocognitive characteristics (Liu et al., 2010; Simonsen et al., 2008). For instance, compared to BD I, BD II is associated with more comorbidity of psychiatric illnesses Baek et al., 2011 (Vieta et al., 2000). Further, BD II is associated with a more chronic course with more frequent episodes (Judd et al., 2003; Mantere et al., 2008; Vieta et al., 1997) which may lead to the process of 'kindling' (Post, 1992), meaning that in time mood episodes may appear more easily without being triggered by any environmental stressor. It is however unclear to what extend kindling is involved in BD in general and in patients with BD II in particular.

A second factor that may have contributed to inconsistent findings is the fact that most prospective studies rely on rather small sample sizes, ranging from $N=41$ to $N=56$ (Christensen et al., 2003; Cohen et al., 2004; Johnson et al., 2000; Mcpherson et al., 1993) and short follow-up periods. They therefore may have lacked statistical power to detect a consistent association between life events and mood symptoms. To date, only Johnson et al. (2008b) studied the effect of life events on bipolar mood in a prospective study with both a large sample size ($N=125$) and a relatively long follow-up period (27 months).

Third, it remains difficult to determine whether life events are a cause or a consequence of bipolar mood episodes. Several studies tried to control for this by excluding those life events that were rated by the researchers as dependent of mood symptoms (e.g. losing a job due to a current depression), and only including life events rated as independent of mood symptoms (e.g. illness or death of a relative) (e.g. Christensen et al., 2003; Hammen and Gitlin, 1997; Hunt et al., 1992; Johnson et al., 2008b). However, even though dependent life events may strictly speaking be consequences of the disorder, this does not mean that these events cannot have an adverse effect on the course of the disease as well, illustrating the difficulty in determining the temporal direction of the association.

In the current two-year prospective follow-up study among 173 BD patients we aimed to examine both temporal directions of the association between negative and positive life events and depressive and mania symptomatology and functional impact of mood disturbances. Additionally, to control for possible differences between BD I and II, we examined BD subtype as a possible moderator of the association between life events and mood symptoms and functional impact.

2. Materials and methods

2.1. Method

2.1.1. Participants

This is a 2-year prospective follow-up study among 173 bipolar outpatients with a diagnosis of BD I ($N=121$) or BD II ($N=52$) (also including BD not otherwise specified ($N=2$) and cyclothymia ($N=1$)) according DSM-IV-TR diagnostic criteria. All patients treated for BD by the Outpatient Clinic for Mood Disorders in The Hague (The Netherlands) were invited to participate in the study, either by letter or directly by their treating physician. After written informed consent was obtained, 173 patients were willing to participate and enrolled into the follow-up study. Participants were older than 18 years. Exclusion criteria in this study were schizo-affective disorder, neurological disease and substance abuse disorders.

Diagnoses of BD and psychiatric Axis I co-morbidities were based on DSM-IV criteria and were assessed with a standardized diagnostic interview developed by Sheehan et al. (1998) using the Dutch version of the MINI International Neuropsychiatric Interview Plus (version 5.00-R; MINI-PLUS), with good interrater (kappa $>.75$) and retest reliability (kappa $>.75$) (Sheehan et al., 1998; van Vliet and de Beurs, 2007) DSM-IV axis II comorbidity was not assessed. The Questionnaire for Bipolar Illness, Dutch translation (Leverich et al., 2001; Suppes et al., 2001) was used to specify subtypes of BD, its course over time and detailed information about age of onset of first symptoms regarding hypomanic, manic, and depressive episodes.

Of the total sample, 90.2% of the patients ($N=156$) completed at least 1 year follow-up, eventually a cumulative number of 44 (25.4%) patients dropped out before the end of the study. The most common reasons for patients to quit prematurely were being too unstable, being hospitalized, deeming the research too burdensome, discontinuing treatment at our outpatient clinic, and not showing up at an appointment more than 2 times. Fig. 1 shows the flow-chart with the number of patients who dropped out at the different time points.

2.1.2. Procedure

All patients signed informed consent before entering the study. After completing the baseline measurement with a psychiatric interview, assessment of current and past mood, and patient and disease characteristics, patients had face-to-face contacts with the research assistant at 3-, 6-, 9-, 12-, 15-, 18-, 21-, and 24-months follow-up. During these contacts manic and/or depressed mood, medication use and stressful life events during the past three months were assessed (see Fig. 1). In order to increase accuracy of recall of mood severity in the past three months and the occurrence of life events, information from diaries, calendars, patient files or other anchor points were used.

2.2. Materials

2.2.1. Life events

The occurrence of life events was assessed every 3 months by Paykel's (Paykel et al., 1971) self-report questionnaire consisting of 61 life events, which was independently completed by the patients. This instrument categorizes possible life events into 10 groups (i.e., employment, education, financial status, somatic health, loss, living place, relationship, criminality, family and social problems, and other events). Patients rated whether the events on the list occurred within the preceding 3 months, and if so they rated on a 5-point scale how upsetting the event has been to them.

The 61 single life event items were summarized into 2 main categories: the number of negative life events, and the number of positive life events. This led to a total of 39 negative life events, such as increasing arguments with the spouse, the end of a romantic relationship, business failure, serious illness of a family member, failure to an important exam, demotion at work, and unemployment for one month. A total of 11 positive life events consisted of events such as promotion at work, engagement, marriage, and a wanted pregnancy. A total of 11 life events, that