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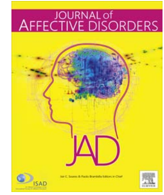

Does stress play a significant role in bipolar disorder? A meta-analysis

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ABSTRACT

Background: There is evidence that stressful life events (LE) play a crucial role in the etiology of bipolar affective disorder (BD). However, primary studies, as well as narrative reviews, have provided mixed results. The present meta-analysis combined and analyzed previous data in order to address these inconsistencies.
Method: Forty-two studies published in 53 records were identified by systematically searching MEDLINE, PsychINFO, and PSYCHINDEX using the terms "bipolar disorder" OR "manic-depressive" OR "bipolar affective disorder" OR "mania" AND "stress" OR "life event" OR "daily hassles" OR "goal attainment". Then, meta-analyses were conducted.
Results: Individuals diagnosed with BD reported more LE before relapse when compared to euthymic phases. They also experienced more LE relative to healthy individuals and to physically ill patients. No significant difference in the number of LE was found when BD was compared to unipolar depression and schizophrenia.
Limitations: When interpreting the present meta-analytic findings one should keep in mind that most included studies were retrospective and often did not specify relevant information, e.g., if the LE were chronic or acute or if the individuals were diagnosed with BD I or II. We could not entirely rule out a publication bias.
Conclusion: The present meta-analyses found that individuals with BD were sensitive to LE, which corroborates recent theoretical models and psychosocial treatment approaches of BD. Childbirth, as a specific LE, affected individuals with BD more than individuals with unipolar depression. Future studies that investigate specific LE are warranted.

1. Introduction

Bipolar disorder (BD) is among the most prevalent psychiatric disorders (Kessler et al., 2005) and is characterized by high rates of recurrences, comorbidities, and functional impairments (Goodwin and Jamison, 2007). Treatment strategies include antidepressant, antipsychotic, and mood stabilizing medications, but many patients nevertheless experience functional impairments and even recurrences of mood episodes (Miklowitz and Johnson, 2012; Rosa et al., 2010). Guidelines such as NICE (2014) or S3 (DGBS and DGPPN, 2013) recommend adding psychological interventions in the treatment of BD. Most psychological treatments focus on stress and relevant coping strategies, and they seem to significantly improve the long term outcome (e.g. Da Costa et al., 2010; Miklowitz, 2008; Mühlig et al., 2012).

While biological and genetic factors play an important role in the etiology of BD (e.g. Frey et al., 2013), Johnson and Roberts (1995) highlight the role of life events (LE) on the course of BD in a first ever published substantial narrative literature review. They concluded that patients with BD reported more LE preceding acute mood episodes relative to euthymic intervals and to healthy control groups. Since Johnson and Roberts' article, more research has focused on the relationship between stress and BD and applied improved methodological approaches in their studies. For example, the type of stressor was more thoroughly assessed by grouping the stressful LE into categories, e.g., if it was related to the achievement of high goals, to losses, or to reward. Prior systematic narrative reviews that summarized these results found that LE relating to goal attainment, social rhythm disruption, seasonal factors (Proudfoot et al., 2011), and high expressed emotions (Altman et al., 2006) influenced the course of BD negatively. Johnson (2005) reviewed, specifically, studies that looked at stress events that could be classified as independent of bipolar psychopathology, i.e., events that are outside of one's control (Hammen, 1991), and found that independent stressors within one year before a mood episode predicted faster relapses and slower recovery. Finally, some questions remain open, e.g., if the vulnerability

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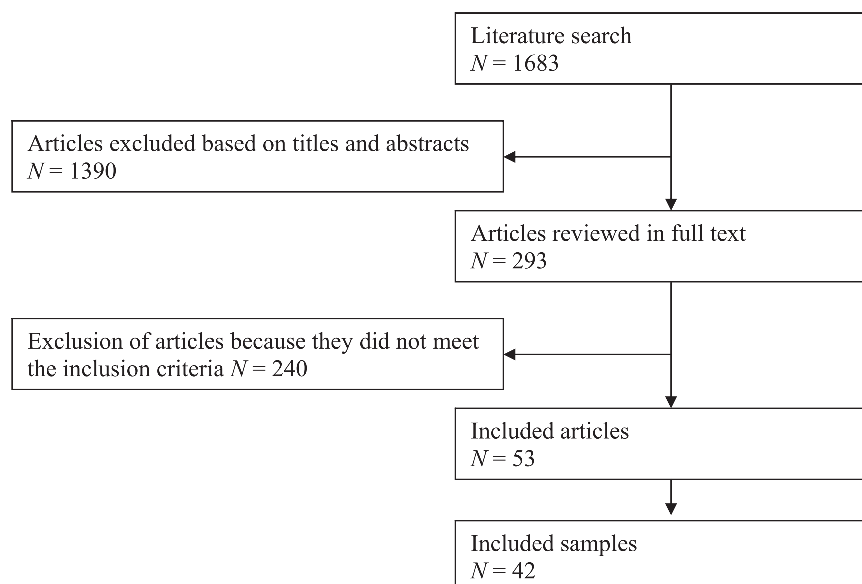

Fig. 1. Study selection procedure.

to stressors is different before onset or before relapse (Bender and Alloy, 2011), or if stressors affect, specifically, individuals with BD or more generally individuals regardless of the psychiatric or physical illness.

The literature reviews, so far, differed in their inclusion and exclusion criteria or in how much inclusion and exclusion criteria were specified. For example, Johnson (2005) only included studies that assessed LE with interviews and excluded studies that relied solely on questionnaires. Others included studies that investigated stress in mood disordered patients more generally (e.g. Bender and Alloy, 2011), while others restricted inclusion to studies recruiting patients only with BD. Statistical properties of the included studies, e.g., sample size and power, are not taken into account, which limits the objectivity and validity of qualitative reviews. Such reviews have their purposes, highlight areas of gaps in the knowledge, and foster theoretical models. However, they make it not easy to test a specific hypothesis or do not allow for statistical testing of such hypotheses (Borenstein et al., 2009).

1.1. Aims of the study

The aim of the present meta-analysis is to evaluate the influence of stress on BD. To our knowledge, this is the first publication that not only reviews but also quantifies the evidence gained, thus far. Based on a systematic literature search we tested the hypotheses (a) that patients with BD would have experienced more LE before mood episodes than before times of stable mood, (b) that patients with BD reported more LE than healthy controls, and (c) that patients with BD reported more LE than patients with physical health problems in order to evaluate the specificity of the stressor for BD. We, additionally, examined whether there were any differences between BD, schizophrenia and unipolar depression with respect to experienced stress levels.

2. Methods

The methodological approach of the present systematic literature review and meta-analyses was a priori planned, documented, and followed the PRISMA guidelines (Moher et al., 2009; Shamseer et al., 2015). Specifically, we addressed the requirements of the PRISMA checklist relating to title, abstract, methods, results, discussion, and findings (Moher et al., 2009). However, we did not publish or register a review protocol.

2.1. Literature search

We conducted a literature search using MEDLINE, PsychINFO, and PSYCHINDEX using the terms “bipolar disorder” OR “manic-depressive” OR “bipolar affective disorder” OR “mania” AND “stress” OR “life event” OR “daily hassles” OR “goal attainment” in “title” and “abstract”. In addition, we scanned the reference lists of reviews, book chapters, and primary studies, and looked at articles citing the included studies. In order to minimize the *file-drawer-problem* (Rosenthal, 1979), we contacted experts in the field and asked them for any unpublished data.

A first search was done in January 2011 and updated and finalized in September 2014. Articles were included if they (1) were published in English or German, (2) focused on an adult sample including patients with BD, (3) adopted a quantitative empirical approach (i.e. qualitative interviews or case studies were not included), (4) provided and analyzed the data separately for patients with BD, (5) defined stress as major LE or as accumulation of minor LE/daily hassles, (6) specified data on the course of the BD (e.g., onset of BD), and (7) the necessary data for a meta-analysis could be extracted from the paper or obtained from the authors. Major LE were defined as events that related to normative transitions in life (e.g., first job), significant life changes (e.g., birth of a child), and major individual experiences (e.g., death of spouse; Kandler et al., 2012). Articles were excluded if they focused on relatives or caregivers of patients, attended to LE in childhood or assessed the stress level via biological indicators (e.g., cortisol level). This led to a final sample of 53 articles that reported data on 42 samples (Fig. 1).

2.2. Quality of the studies

The methodological quality of the 42 studies was quantitatively assessed by a Gold Standard Scale (GSS; Foa and Meadows, 1997) that was adapted for the present meta-analysis. The present GSS assessed the study quality in relation to the study design, the psychiatric diagnosis, the definition of stress, and the description of clinical variables (see Supplementary material A). For example, the GSS took into account if a study was prospective or retrospective, if the diagnosis was established by unstandardized clinical ratings or clinical interviews, if stress was dependent or independent to symptoms of BD, or if the study differentiated between manic and depressive mood episodes. Scores on the GSS range between 0 and 16; the higher the score, the better the methodological quality of the study. The mean GSS score in

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