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Role of stressful life events and kindling in bipolar disorder: Converging evidence from a mania-predominant illness course

Karthick Subramanian^{a,*}, Siddharth Sarkar^b, Shivanand Kattimani^a, Ravi Philip Rajkumar^a, Venkatalakshmi Penchilaiya^c

^a Department of Psychiatry, Jawaharlal Institute of Post Graduate Medical Education and Research, Puducherry, India

^b Department of Psychiatry and NDDTC, All India Institute of Medical Sciences, New Delhi, India

^c Department of Psychiatry, Vinayaka Mission's Kirupananda Variyar Medical College & Hospitals, Salem, India

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ABSTRACT

Stressful life events can precipitate relapses and recurrences in bipolar disorder. Kindling in bipolar disorder has been linked to maladaptive psychological reactivity to minor stressful life events. Systematic studies on life events and kindling are rare in bipolar disorder with a manic predominant polarity. One hundred and forty-nine remitted patients with bipolar I disorder were recruited. The National Institute of Mental Health-Life Chart Methodology was used to depict the illness course retrospectively, and the Presumptive Stressful Life Events Scale-Lifetime version was used to record the stressful life events. The role of stressful life events and the probability of kindling were assessed using appropriate statistics. There was a mania-predominant course of bipolar disorder in the sample with 55.7% ($n = 83$) having only recurrent mania. Family conflict and altered sleep patterns were the commonly reported stressful life events. When controlled for the severity of the stressor, the stressful life events were often associated with the initial episodes rather than the latter ones. Kindling may occur in bipolar disorder with mania as the predominant polarity. However, retrospective recall bias and hospital-based sampling limit generalizability of such observations.

1. Introduction

Bipolar disorder is a severe mental illness characterised by recurrent mood episodes with a global prevalence of around 2.4% (Merikangas et al., 2011). Multiple factors determine the precipitation and progression of the illness. Apart from studying the biological basis underlying bipolar disorder, environmental and psychosocial antecedents have become the cynosure of recent research (El Kissi et al., 2013; Gershon et al., 2013; Simhandl et al., 2015). By imparting unhealthy affective fluctuations, stressful life events have played key roles in inducing relapses and recurrences in bipolar disorder (Johnson et al., 2016; Koenders et al., 2014). Common to the episodic patterns of bipolar disorder and epilepsy is the increased reactivity of the disease to minor stress encountered during the illness course. An outgrowth of such observations is the “kindling hypothesis” of mood disorders (Post et al., 1982). The hypothesis further prompted clinicians to contemplate a common pathophysiology for bipolar illness and epilepsy (Wiglusz et al., 2015). Contemporary research divulges that the psychological adaptability of patients with bipolar disorder can become less tenacious over the course of illness rendering them vulnerable for relapses even

with minor stressful events providing support to the hypothesis (Kemner et al., 2015a, 2015b). There seems to be a differential effect of stressful life events in precipitating various polarities of mood episodes – with positive life events leading to mania and negative life events to depression or mixed states (Aldinger and Schulze, 2017). Notwithstanding, studies have found contradicting results regarding kindling and argue that kindling may not impart any significant clinical or therapeutic differences in patients with bipolar disorder (Anderson et al., 2016; Hlastala et al., 2000). One needs to cautiously draw conclusions as substantial methodological differences can obscure the reliability of the observations from various studies.

Compared to the wealth of published literature in the West, systematic assessment of stressful life events in mood disorders, is rare in developing countries like India. We attempted to find the types of life events associated with precipitating mood episodes and whether life events had any role in kindling mood episodes in bipolar disorder. We hypothesized that over the course of illness, mood episodes would recur even with minimal or the absence of stressful life events.

* Correspondence to: Department of Psychiatry, Jawaharlal Institute of Post Graduate Medical Education and Research (JIPMER), Dhanvanthri Nagar, Puducherry 605006, India.
E-mail address: karthick.jipmer@gmail.com (K. Subramanian).

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2. Methods

2.1. Setting, participants, and procedure

The study was conducted in a general hospital psychiatric unit in southern India, which caters subsidized treatment to patients hailing from a rural background. The psychiatric facility provides inpatient care for severe mood episodes and conducts regular monthly follow-up clinic for stable patients with bipolar disorder. The patients were recruited from both the out-patient and in-patient services who had reliable informants.

Patients aged 18–60 years, of either gender, diagnosed with bipolar I disorder, confirmed using Structured Clinical Interview for DSM-IV (SCID-I) research version (First et al., 2007), with duration of illness at least three years were enrolled into the study after getting informed consent. A total 194 subjects satisfied the inclusion criteria. We excluded patients with acute behaviour disturbances ($n = 30$) and intellectual disability ($n = 14$). The Institute Ethical Committee cleared the study protocol.

The participant's demographic characteristics were recorded in a semi-structured proforma. The illness course was charted using the National Institute of Mental Health-Life Chart Methodology Clinician Retrospective Chart (NIMH-LCM-CRC) (Roy-Byrne et al., 1985). The chart aids in the computation of episode characteristics such as the number, polarity, duration and association with life events. The nature of the stressful life event was coded using the Presumptive Stressful Life Events Scale (PSLES) lifetime version (Singh et al., 1984). The patient was asked about the presence or absence of such events by the interviewer (KS). A verbal translation of the items in PSLES was provided wherever necessary. The data was entered as stressful life event present (if present, the type of event), absent or not recalled. The patients or their family members were asked to recall any stressful life event, which had submitted itself before the onset of the mood episode. The time duration prior to the episode was kept as “anytime less than one month” (an average number based on previous retrospectively-designed studies) (Boland et al., 2012; Yan-Meier et al., 2011). The severity of the stressful life events was measured using the PSLES stress severity score which in turn are similar to those provided by Holmes and Rahe (Holmes and Rahe, 1967). The current mood symptom severity was recorded using Young's Mania Rating Scale (YMRS) (Young et al., 1978) and Hamilton Depression Rating Scale-17 item version (HDRS) (Hamilton, 1960). Study recruitment occurred from September 2012 to July 2014, through convenience sampling.

2.2. Assessments

The NIMH-LCM-CRC is a clinician-rated instrument used for depicting the life course of bipolar disorder. The chart helps in a systematic inquiry of the illness course by encompassing parameters like polarity of the illness, duration of the illness in years, the number of episodes and the proportion of time spent in illness. The information was collected from the patient, the caregivers, and the relevant medical records. When discrepancy arose, the information marked in medical records were given preference after arriving at a consensus between the principal investigators (KS and SK). The episodes, which were associated with stressful life events, were marked in the chart.

The PSLES is a 51-item self-report scale for listing out the common stressful life events. It has excellent reliability and an extensive application in the Indian research. The PSLES provides the list of possible stressful life events relevant to the region's socio-cultural context. The participants were asked to recall the type of stressful life event and tick the appropriate item on the scale. The mean stress scores for each life event was computed from the scores provided by Singh et al. (1984). The PSLES includes “change in sleep habits” as one of the stressors. For the purpose of the study, we asked the patient and the key informant about “events which caused sleep disturbance”. If the sleep dysfunction

is caused by an event (say, participating in events where the person missed hours of sleep due to his/her physical exertion, travel, exam preparation, marriage preparation, etc.) only then we coded it as a stressor. Sleep dysfunction as such is not coded under stressful life event.

YMRS and HDRS are widely used interviewer-rated instruments for assessing symptoms of mania and depression respectively. The YMRS has 11 items, while the HDRS comprises of 17 items, with higher scores reflecting greater mood symptoms. The present study included patients in remission, i.e. with scores of YMRS < 7 and HDRS < 8 to minimize the recall bias.

2.3. Statistical analysis

Demographic and clinical details were represented using mean, standard deviation, frequency, and percentages. The proportion of episodes, which was preceded with a stressor, was computed. For ascertaining the relationship of the number of an episode with the presence of a stressor, Somers' d was calculated. This metric was also used to determine the relationship of the number of an episode with the severity of the episode gauged by the mean stress score on the PSLES. Since the number of episodes and the presence of stressors as per PSLES had a non-normal distribution, an ordinal analysis was used to assess a relationship between the episode number and the presence of a stressor. The Somers' d uses one dependent variable (number of an episode) and one independent variable (presence/ severity of stressor). The advantage of Somers' d lies in it being a measure of directional assessment, i.e. one of the variables can be designated as dependent and another independent. The values of Somers' d, as in correlational analysis, range between -1 and 1 . Values more than ‘0’ imply a positive relationship while values less than ‘0’ imply a negative relationship. Sensitivity analysis was carried out using subgroups of different genders, patients with only unipolar mania/hypomania and those with more than six episodes. We wanted to assess whether the incidence of a stressor increased or decreased in frequency among patients with a greater number of episodes as well. The cut-off was set at six episodes because the mean number of episodes in the sample was 5.3. A p -value < 0.05 was considered significant. Statistical analysis was carried out using SPSS version 19 (IBM Corp, 2010).

3. Results

The present analysis included 149 patients with bipolar I disorder (One patient with 60 episodes was excluded to remove the outlier). The mean age of the sample was 37.7 (± 9.7) years. Seventy-one (47.7%) of these patients were males, 103 (69.1%) were educated up to high school, 79 (53.0%) were employed, and 133 (89.3%) belonged to Hindu religion. The average duration of illness was 13.2 (± 8.0) years, and the mean number of episodes was 5.3 (± 3.1). Eighty-three patients (55.7%) had only recurrent manic/ hypomanic episodes.

Summating the episodes in all the patients, a total of 791 mood episodes occurred during the course of illness (Mania = 630, Depression = 140, Hypomania = 12, Mixed = 9). Stressful life events as a precipitating factor were noted in 298 episodes (37.7% of all episodes). The type of stressor according to PSLES is summarized in Table 1. Family conflict was the most common type of stressor reported. The presence of a stressor did not significantly differ across the type of episodes ($\chi^2 = 6.663$, $p = 0.083$).

The Somers' d metric for the number of episodes as a dependent variable and presence of a life stressor as an independent variable was -0.299 ($p < 0.001$). This suggested that life stressors were more likely to occur in the initial episodes than the latter episodes. When the relation of the number of episodes with the severity of the life stressor (based upon scores available from Singh et al.) was assessed, the Somers' d value was found to be -0.241 ($p < 0.001$). This reiterates that upon controlling for the severity of stressor, the life events were

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