Stress Reactivity in Bipolar Patients and Its Relation to Prior History of Disorder

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Objective: Two questions were posed: Does stress precipitate episodes of bipolar I disorder, and does sensitivity to stress differ in episodes later in the course of illness compared to early ones? Method: Fifty-two patients with bipolar I disorder were followed longitudinally for up to 2 years; clinical course was monitored, and interview assessments of life events were made every 3 months. Results: The patients who had episodes of illness during follow-up had experienced significantly more severe stressors and more total stress in the preceding 6 months, and more total stress in the preceding 3 months, than those without episodes. Inconsistent with Post's stress "sensitization" hypothesis, patients with more prior episodes were more likely to have episodes following major stressors, and they relapsed more rapidly. Conclusions: Stressors may precipitate episodes of bipolar illness, especially for patients with more prior episodes. Different versions of the stress sensitization model remain to be tested.
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Given the pernicious course of bipolar disorder (1, 2), the study of stressful life events might prove useful in understanding the timing of episodes. Stress research in subjects with bipolar disorders is relatively sparse, and prospective studies have yielded somewhat inconsistent results (3–6), which may be due, however, to different time frames, methods, and designs. Accordingly, one goal of this study was to examine the role of stressors in bipolar patients' relapse by using a version of a state-of-the-art life event interview (7), a prospective design, and examination of the 1- , 3- , and 6-month life event antecedents of episode onset. In addition, both between-group analyses (subjects with and without recurrences) and within-subject analyses (before and after an episode) were conducted.

A second major goal was to test the often-cited hypothesis that stressors play an important role in the initial stages of bipolar disorder but are less related to later episodes. Post (8), for instance, presented a model of increasing sensitization to stressors in which episodes eventually appear to be autonomous because they occur in the absence of stress or with only minimal stress. Despite the appeal of this model, its empirical basis with respect to bipolar I patients is weak. The small number of relevant studies include methodological problems such as retrospective and unreliable methods of life stress assessment. Moreover, the results themselves are ambiguous, largely failing to demonstrate statistically significant differences between comparison groups (9–12). Therefore, this study tested the effect of stressors on relapse among patients at different stages of illness.

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METHOD

Fifty-two outpatients with bipolar disorder (23 male and 29 female), whose mean age was 41.8 years (SD=10.9), were studied. All gave written informed consent. Eighty-two percent of the group was Caucasian, 12% African American, and 6% "other." The patients were followed for up to 2 years (mean length of follow-up was 22 months, SD=6.2); 90% (N=47) were followed for 2 years. They had had a mean of 3.3 prior psychiatric hospitalizations (SD=2.7), 7.4 depressive episodes (SD=7.8), and 7.6 manic episodes (SD=5.4). Diagnostic information was obtained from periodic clinic visits, and independent life stress interviews were conducted at 3-month intervals with the use of methods based on the Brown and Harris life event interview (7) to evaluate the objective stressfulness of events. Events clearly related to patients' disorders were not included. Detailed information on recruitment, diagnosis, assessments, and their reliabilities was reported in an earlier article (3).

Inspection of symptom time lines indicated that 36 patients experienced a relapse (worsening of symptoms before 8 full weeks of recovery) (N=6) or recurrence (onset of a diagnosable condition following a minimum of 8 weeks of recovery) (N=30). Episodes included hypomania of at least 1 week's duration (N=12), mania (N=15), or a major depressive episode (N=9). Ratings of the aggressiveness of treatment with medication for the 6 months before relapse/recurrence were based on methods reported earlier (2, 3).

Once a relapse/recurrence was identified, two life event scores were determined for 1 month, 3 months, and 6 months before the onset of symptoms: the total objective severity rating for all events and the presence of major-impact events rated above "moderate" (i.e., above 3.5) on the 5-point scale of severity. For individuals who did not experience a relapse, the midpoint of their time lines was used to date the comparison life event periods.

RESULTS

The relapse/recurrence group, compared to the group without episodes, was significantly more likely to have had a severe stressor within the preceding 6 months (χ^2=2.85, df=1, p<0.05, one-tailed, with Yates's correction), and it had had significantly more total stress in the preceding 6 months and 3 months (t=1.85, and t=1.73, respectively, df=50, p<0.05, one-tailed). Results of comparisons for other time periods were not significant. Within-patient comparisons of periods before and after episodes for the patients with sufficient follow-up time also indicated that those who relapsed had significantly more total stress (t=4.02, df=18, p<0.001) and a greater likelihood of a major event before onset of an episode than afterward (McNemar's test for paired data, χ^2=6.13, df=1, p<0.01, one-tailed, with Yates's correction). Relapse was not attributable to differences in aggressiveness of treatment with medication (t=1.44, df=43, n.s.).

Comparison groups were formed on the basis of the median number of prior manic and depressive episodes (zero to eight total episodes versus nine or more) because of the low frequency of patients with one or two prior episodes. Forty percent of the 15 patients in the group with fewer episodes experienced a major-impact event in the preceding 6 months, compared with 76% of the 21 patients with more episodes (χ^2=3.42, df=1, p=0.05, one-tailed, with Yates's correction).

Duplicating "backward" survival analysis procedures reported by Frank et al. (13), we used the Kaplan-Meier estimate of survival functions to determine whether the two episode history groups differed in the time elapsed (counted backward) between the onset of an episode and the occurrence of a major-impact event. There was a significant difference between the two groups (Mantel-Cox log rank test value=3.84, p=0.05): the patients with higher numbers of prior episodes relapsed more rapidly following a major event.

DISCUSSION

Episodes in bipolar I patients were significantly associated with the occurrence of major negative life events in the preceding 6 months, and with higher levels of total stress in both the preceding 3 months and 6 months in comparison with the patients who did not relapse. These findings confirm the importance of stressful life events as contributors to relapse into bipolar disorder. The results were based on longitudinal follow-ups with careful dating of events and independent evaluation of their stressfulness, as well as both between-group and within-patient analyses. Thus, results may vary somewhat depending on the time frame and whether the stress variable is severe events or total stress.

The second question we investigated concerned the role of prior history of episodes in stress reactivity. Relapsed patients who had *greater* numbers of prior episodes were more likely to have had a severe stressor in the preceding 6 months, and they relapsed more rapidly following the major negative event, than those who had fewer prior episodes. This finding contrasts with clinical lore and earlier, albeit methodologically flawed, studies which suggested that stress is an important precipitant only at the beginning of the course of illness.

The present results are not consistent with the "sensitization" hypothesis of Post. However, it must be acknowledged that there may be other versions of sensitization to be tested. The most precise test of the question of whether later episodes are more independent of stress is a longitudinal within-patient analysis, comparing the individual's stress before early episodes and before later episodes. The 2-year time frame of this study was not adequate for such a test.

Further limitations of the study include the relatively small size of the study group, precluding analyses of the specific effects of stress (and episode history) on mania and depression. The study did not include first-episode patients and included very few patients with only one or two prior episodes, and it is possible, although not necessarily likely, that it is the very first few episodes which most distinguish among patterns of stress reactivity. Finally, no account of reactivity to stress is complete without some consideration of psychological factors that affect reactions to stressors, such as interpretations of the meaning of events and coping resources—processes deserving further study in bipolar subjects.

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