

Stressful Life Events and Social Rhythm Disruption in the Onset of Manic and Depressive Bipolar Episodes

A Preliminary Investigation

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Background: The association between stressful life events and onset of bipolar episodes is unclear. The association between bipolar episode onset and types of life events that disrupt social routines, and potentially sleep, has not yet been investigated.

Methods: Thirty-nine bipolar patients with primarily manic (n = 20) or depressed (n = 19) index episodes were interviewed with the Bedford College Life Event and Difficulty Schedule to determine the presence of severe events during 8-week pre-onset and control periods. All life events were also rated for degree of social rhythm disruption (SRD).

Results: More bipolar subjects experienced at least 1 SRD event and severe event in the pre-onset vs control peri-

ods. When subjects were divided into those with manic or depressive onsets, the only significant pre-onset vs control difference was for manic patients with SRD events. Additionally, the proportion of subjects with a pre-onset SRD event was greater for manic than for depressed patients.

Conclusions: We found evidence that life events characterized by SRDs routines are associated with the onset of manic, but not depressive, episodes. Severe events seem to be related to onset of bipolar episodes, although it remains unclear whether severe events relate differentially to depressive and manic onsets.

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WHILE GENETIC and biologic factors are known to play a major role in the etiology of bipolar disorder, psychosocial factors are gaining increasing attention in explaining the timing, type, and outcome of bipolar episodes.¹ In particular, many studies have identified an association between stressful life events and bipolar episode onset.²⁻¹⁹ The nature of this association, however, is unclear, as abundant methodologic limitations render overall conclusions tenuous (see Johnson and Roberts²⁰ for review). Yet even among investigations that employed self-report questionnaires and/or semistructured interviews to determine occurrence of severely threatening life events, dated episodes from symptom onset, omitted events that were likely to have been illness-related, and used adequate control groups, results are inconsistent.^{5,7,14,18,21} Further, although it has been well documented that severe life events are provoking agents for the onset of unipolar depression,^{22,23} depressive onsets in addition to manic onsets have been investigated in only 2 of these studies.^{14,21}

In addition to the severity or psychological threat associated with life events, it has been suggested that the degree of disruption in social routines associated with an event, even an event representing little psychological threat, may play an important role in the onset of affective episodes.^{24,25} Interest in such "social rhythm disruption (SRD) events" comes from the hypothesis that disturbances in social rhythms or routines may promote disruptions in circadian rhythms, which in turn promote onset of affective episodes in vulnerable persons.²⁵ This theory derives from the observations that social routines, such as timing of sleeping, eating, and exercise, help to entrain circadian rhythms^{24,26}; and that disruptions in circadian rhythms have been implicated in the pathogenesis of both depression and mania.²⁷⁻³¹

The present study was conducted to examine the role of SRD events and severely threatening events in the onset of depressive and manic bipolar episodes. Several steps were taken to address past methodologic problems. For example, stressful life events were assessed according to the rigorous Bedford College Life Event and Difficulty Schedule (LEDS) methodology³² with additional SRD ratings made in a similar manner. In ad-

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SUBJECTS AND METHODS

SUBJECTS

The study population consisted of 39 bipolar patients who constitute a subpopulation of 102 participants in an ongoing study of maintenance therapies (pharmacotherapy plus psychotherapy and/or medication clinic visits) in bipolar disorder at Western Psychiatric Institute and Clinic, Pittsburgh, Pa. The larger population was composed of men and women aged 21 to 65 years, recruited from medical referrals, self-referrals, and public information campaigns. Initial diagnoses were determined by structured clinical interviews (Schedule for Affective Disorders and Schizophrenia–Lifetime Version³³ or Structured Clinical Interview for Axis I DSM-IV Disorders [SCID]³⁴) conducted by research nurse clinicians or social workers at study enrollment. These interviews also yielded episode onset dates based on the emergence of the first bipolar symptom and onset characterizations that reflected the course of the index episode from onset until study enrollment (mean, 19.3 weeks). Confirmation of these index episode classifications (eg, primarily manic, manic cycling to depressed, mixed, and so on) was made by a consensus panel review of each patient's recent life history of affective symptomatology. We selected for this preliminary investigation the first 39 subjects who (1) had an index episode characterized by a single polarity from the onset of the episode until admission to our protocol (n = 20 manic patients, 19 depressed patients); (2) had achieved remission of their index episode; and (3) had completed the life events interview.

On study enrollment, subjects were required to be currently experiencing a definite major depressive or manic episode per Research Diagnostic Criteria³⁵ or SCID criteria³⁴ and to have a lifetime diagnosis of bipolar I disorder. Subjects were also required to have had at least 2 prior episodes of bipolar disorder, at least 1 within 5 years of index episode, and at least a 12-week remission between index episode onset and the most recent past bipolar episode. Additional inclusion criteria were scores of 7 or higher on the Raskin Severity of Depression Scale^{36,37} and 15 or higher on the 17-item Hamilton Rating Scale for Depression (HRS-D)³⁸; or 7 or higher on the Raskin Severity of Mania Scale^{36,37} and 15 or higher on the Bech-Rafaelsen Mania Scale.^{39,40} Exclusion criteria included: (1) rapid cycling (≥ 4 episodes per year); (2) any recent

psychiatric diagnoses other than mania or depression (except for anxiety disorders and phobias); (3) history of recent *chronic* drug or alcohol abuse; (4) schizophrenia, organic affective syndrome, or unspecified functional psychosis; (5) borderline or antisocial personality disorder; (6) serious medical illness; and (7) in women, pregnancy or refusal to use contraception. Informed consent was given by all subjects.

LIFE EVENTS METHODS

Life events were assessed using the LEDS.³² This semistructured interview was used to assess the period between interview date and 1 year prior to index episode onset, and was conducted after patients had been in treatment for at least 12 weeks and had achieved remission of acute symptoms (scores of ≤ 7 on the HRS-D and Bech-Rafaelsen Mania Scale for 3 consecutive weeks). Accordingly, the LEDS was administered an average of 43 weeks after onset of the index episode. The LEDS interviewers were trained either by the developers of the LEDS at Bedford College, London, England, or by their trainees at Western Psychiatric Institute and Clinic. Interviewers were unaware of which pre-onset and control periods were under study and were not involved in clinical assessment or treatment of study patients.

On completion of the LEDS interview, events were rated for severity by a consensus panel composed of the initial interviewer plus additional LEDS interviewers. Consensus panel members were blind to episode polarity, onset date, and 8-week pre-onset and control periods of interest. A hallmark of LEDS methodology is that ratings are contextual, reflecting what most people would be expected to feel about an event based on the particular biographical circumstances of the subject. Severity ratings are made independently of the patient's reported reactions to an event and of any current psychiatric symptoms. Each rating is anchored to an example in a "dictionary" of precedent examples. Events are rated on a 4-point scale of severity indicating degree of contextual threat or unpleasantness (1, marked; 2, moderate; 3, some; 4, little or none). "Severe events" are those events directly affecting the subject and rated 1 or 2 on long-term threat (the threat of an event 10-14 days after it occurs).

Severe events were also rated on the degree to which they could be considered a manifestation of current

Continued on next page

dition, onset dates and episode types were determined during structured clinical interviews, and a within- and between-subjects design was used. It was hypothesized that the proportion of subjects experiencing at least 1 SRD event or severe event would be significantly greater during an 8-week pre-onset period relative to an 8-week episode-free control period. Whether pre-onset rates of SRD or severe events would differ between manic and depressive onsets was explored in secondary analyses.

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

The total study sample comprised 18 men and 21 women, ranging in age from 19 to 63 years. The only significant

demographic difference between the 2 patient groups was age, as depressed patients were more than 7 years older than manic patients (**Table 1**). As presented in **Table 2**, manic patients scored lower on the Global Assessment Scale⁴³ than depressed patients, indicating that manic episode onsets were associated with greater global impairment. Additionally, index episodes of manic patients were more likely to be characterized by pretreatment hospitalizations than were those of depressed patients, and depressed patients had more past depressive episodes than did manic patients.

LIFE EVENT ANALYSES

SRD Events

Of all SRD events experienced by subjects in this investigation during pre-onset and control periods (N = 30), rat-

bipolar symptoms. Any event that was determined by LEDS criteria and interviewer judgment to be definitely or even possibly related to current bipolar symptoms was excluded from analyses. Events were also rated on the degree to which their occurrence was independent of the subject's influence. Both independent and possibly independent (including intentional) events were included in analyses.

The LEDS has been shown to be a reliable and valid life stress instrument. High interrater agreement of the occurrence, severity, and dating of life events has been repeatedly demonstrated, as has high interrespondent agreement when a subject and close relative have been interviewed independently by different interviewers.^{22,41,42} High interrater reliability has also been demonstrated in our own research group with other mood disorder samples ($\kappa = 0.86$). Finally, numerous studies have pointed to the association between LEDS-defined life events and onset of a wide range of illnesses.²³

SRD METHODS

Each life event of any severity identified by LEDS criteria was subjected to an additional rating of SRD. This rating, developed in our research group, reflects the degree to which a given event is likely to have an acute effect on the sleep-wake cycle. Accordingly, an event would receive a high SRD rating if it contributed to potential acute sleep disruption (eg, going to the hospital emergency room at 1 AM or overseas travel) or to substantial desynchronization in routine that would likely promote sleep disruption or change in sleep/wake routine (eg, being fired from a full-time job without immediately starting another, starting full-time college, or marital separation).

Similar to LEDS ratings, SRD ratings are contextually determined by consensus panel, are guided by clearly delineated criteria and a dictionary of examples, and range from 1 (marked) to 4 (no disruption). The SRD ratings were developed to be conservative, such that for an event to receive an SRD rating other than 4 (ie, no disruption) there had to be significant change in routine and/or potential sleep disruption. The term SRD events refers to any LEDS events rated 1 to 3 on SRD.

Consistent with LEDS methodology, illness-dependent events were excluded from SRD analyses, and events that were independent or possibly independent of the

subject's agency were included in SRD analyses. Ratings of a subset of SRD events were found to show high interrater agreement in our research group ($\kappa = 0.94$).

DESIGN AND ANALYSES

Within-subject (pre-onset vs control period) comparisons of SRD and severe events were conducted for all bipolar subjects. In secondary analyses, these comparisons were repeated separately for patients with manic and depressive onsets, and between-subject (manic vs depressed) comparisons of SRD and severe events in the pre-onset period were conducted. These data were reported in terms of rates of patients experiencing at least 1 SRD event or severe event during pre-onset or control periods of measurement. The pre-onset period in this investigation was the 8-week period prior to onset of the index episode, which is consistent with the 4- to 12-week pre-onset periods highlighted in many comparable investigations.^{3,5,14,21,22}

In addition to 8-week pre-onset periods (weeks 0-8 prior to onset), 8-week control periods were selected for each subject from the remaining 1 year pre-onset data. To control for seasonal effects on mood cycling, we selected a control period for each subject as close as possible to the last 8 weeks of the 52-week pre-onset interview period. This 8-week period (weeks 45-52 prior to onset) was the modal control period, but the average control period was between pre-onset weeks 41 through 48. This reflects the fact that, in some cases, not all of the last 8 weeks of the pre-onset year were covered in the interview ($n = 5$; 2 depressed subjects, 3 manic subjects) or collateral data indicated that subjects had been experiencing clear-cut bipolar symptoms during that period ($n = 6$ manic subjects). In these cases, we selected as a control period the 8-week interval closest to pre-onset weeks 45 to 52 that was at least 4 weeks away from the end of a prior episode and was not part of an 8-week pre-onset period for a subsequent episode.

For within-subject analyses, 1-tailed McNemar tests were used to determine whether a significant proportion of subjects experienced at least 1 SRD or severe event in the pre-onset but not control periods of study. For secondary between-group analyses, proportions of manic and depressed subjects with at least 1 pre-onset SRD or severe event were compared using a 2-tailed Fisher exact tests for contingency tables. Alpha levels were set at .05.

ings of 1, 2, and 3 occurred 7%, 10%, and 83% of the time, respectively. Examples of these events were: returning from work in Africa (SRD = 1), adding part-time work to full-time college (SRD = 2), moving to a new residence, breaking a limb, taking a vacation, losing a roommate, and losing a part-time job resulting in unemployment (SRD = 3 for all).

Overall, twice as many bipolar subjects experienced at least 1 SRD event during pre-onset vs control periods of study (**Figure**). Thirty-three percent of bipolar subjects experienced at least 1 SRD event in the pre-onset but not control period compared with 13% who had at least 1 SRD event in the control but not pre-onset period (McNemar $P = .05$). Percentages of subjects with SRD events in both and neither period of study were 8% and 46%, respectively.

When the subjects were divided into groups with clearly manic and clearly depressive onsets, it was found

that the proportion of subjects with at least 1 SRD event was substantially greater during pre-onset than control periods for manic patients, but not for depressed patients (**Figure**). Fifty-five percent of manic subjects experienced at least 1 SRD event in the pre-onset but not control period, vs 10% who experienced at least 1 SRD event in the control but not pre-onset period (McNemar $P = .01$). In contrast, for depressed patients, 11% had SRD events in the pre-onset but not control period, compared with 16% who had them in the control but not pre-onset period (McNemar $P = .50$). Social rhythm disruption events were observed in both periods of study for 10% of manic and 5% of depressed subjects, and in neither period of study for 25% of manic and 68% of depressed subjects. Finally, between-group comparisons confirmed that the association between SRD and onset

Table 1. Demographic Characteristics of Study Patients*

Characteristic	Total Group (N = 39)	Manic Subjects (n = 20)	Depressed Subjects (n = 19)
Sex			
Male	18	7	11
Female	21	13	8
Mean ± SD age, y†	34.5 ± 10.0	30.9 ± 9.0	38.3 ± 9.7
Race			
African American	2	2	0
White	35	16	19
Other	2	2	0
Marital status			
Married	10	3	7
Divorced/separated	11	5	6
Single	18	12	6
Educational level			
High school	5	2	3
Partial college	14	9	5
College graduate	10	4	6
Graduate/professional School	10	5	5

*Data are expressed as number of subjects unless otherwise indicated.
†P < .05.

Table 2. Clinical Characteristics of Study Patients: Current Episode and Course of Illness*

Characteristic	Total Group (N = 39)	Manic Subjects (n = 20)	Depressed Subjects (n = 19)
GAS score at entry†	...	40.3 ± 7.6	51.1 ± 7.6
HRS-D score at entry (17-item)†	...	6.8 ± 4.8	20.6 ± 4.8
Raskin-D score at entry†	...	3.8 ± 0.8	9.1 ± 1.7
Raskin-M score at entry†	...	11.5 ± 2.4	3.3 ± 0.5
Bech-Rafaelsen score at entry†	...	28.2 ± 7.9	1.6 ± 2.1
Duration of index episode, wk	...	11.4 ± 7.1	18.6 ± 15.5
No. of patients hospitalized between index episode onset and start of study†	...	16	3
Age at onset of first episode, y	20.3 ± 6.3	19.5 ± 3.4	21.0 ± 8.0
No. of previous manic episodes	3.8 ± 4.6	3.6 ± 3.7	4.0 ± 5.5
No. of previous depressive episodes†	5.4 ± 6.5	2.5 ± 2.1	8.9 ± 8.3
No. of previous total episodes‡	9.3 ± 9.8	5.9 ± 5.0	13.4 ± 12.4

*Data are expressed as mean ± SD unless otherwise indicated. GAS indicates Global Assessment Scale⁴³; HRS-D, Hamilton Rating Scale for Depression³⁸; Raskin-D, Raskin Severity of Depression Scale^{36,37}; Raskin-M, Raskin Severity of Mania Scale^{36,37}; Bech-Rafaelsen, Bech-Rafaelsen Mania Scale^{39,40}, and ellipses, not applicable.

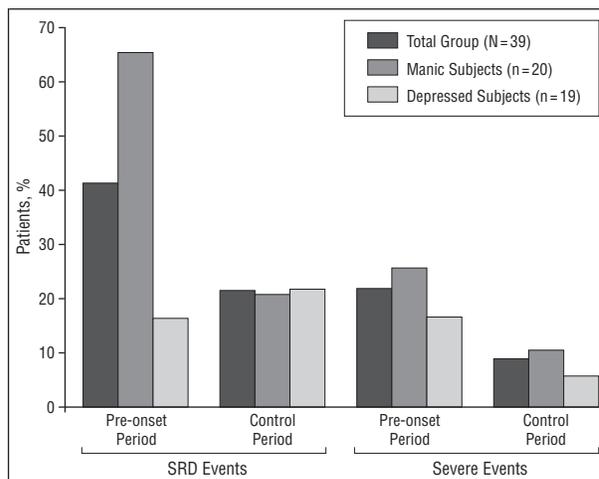
†P < .001.

‡P < .01.

was unique to manic episodes, as the proportion of subjects with at least 1 SRD event during the pre-onset period was found to be significantly greater among manic than among depressed subjects (Fisher = 9.74, exact P = .003) (Figure).

Severe Events

When traditionally defined severe events, as opposed to SRD events, were considered in all bipolar subjects together, it



Percentages of all bipolar patients (total group) and of patients with manic and depressed onsets who experienced at least 1 social rhythm disruption (SRD) event or severe event during the 8-week pre-onset and control periods. Significantly more manic than depressed subjects experienced at least 1 SRD event in the pre-onset period (Fisher exact P = .003).

was found that more than twice as many bipolar subjects experienced at least 1 SRD event during pre-onset vs control periods of study (Figure). Fifteen percent of subjects had at least 1 severe event in the pre-onset but not control period, compared with 3% who had a severe event in the control but not pre-onset period (McNemar P = .06). Percentages of subjects with SRD events in both and neither period of study were 5% and 77%, respectively.

When considered separately, the proportions of subjects with at least 1 severe event during the pre-onset period were found to be similar to corresponding rates in the control period in both the manic and depressed groups (Figure). Twenty percent of manic and 11% of depressed subjects experienced at least 1 severe event in the pre-onset but not control period, whereas 5% of manic and 0% of depressed subjects experienced a severe event in the control but not pre-onset period (McNemar P = .19 and .25 for manic and depressed subjects, respectively). Severe events occurred in both pre-onset and control periods for 5% of both manic and depressed subjects, and occurred in neither period of measurement for 70% of manic and 84% of depressed subjects. Finally, rates of subjects with at least 1 severe event in the 8-week pre-onset period were similar among manic and depressed subjects (Fisher = .52, exact P = .69) (Figure).

COMMENT

The finding that the pre-onset periods for all bipolar episodes were characterized by an excess of severely threatening life events relative to control periods in this investigation is consistent with the findings of some^{5,14} but not all^{7,18,21} similar investigations of manic and depressed episodes. That no significant differences were observed when depressed and manic onsets were considered separately is likely a result of the small sample sizes of the subgroups, because the differences between pre-onset and control rates of subjects with at least 1 severe event were 3-fold for depressed subjects and more than 2-fold for manic subjects. It seems, then, that severe events, which

have been shown to be important in the onset of unipolar depression,^{22,23} may also play an important role in the precipitation of bipolar episodes. Larger sample sizes and comparison with psychiatric and normal control samples would likely elucidate the role of severe events in the onset of both manic and depressive episodes.

THE NOVEL finding in this investigation was that life events characterized by SRD during an 8-week pre-onset period were strongly associated with onset of manic, but not depressed, bipolar episodes. Although it has been hypothesized that SRD that could ultimately affect the sleep/wake cycle could lead to onset of affective episodes in vulnerable persons,^{25,29,44} this is the first time that the measurement of SRD has been attempted in community-dwelling subjects. Future studies should address the treatment implications of these findings and explore the hypothesized association between SRD and onset of depressed episodes.

To the extent that sleep reduction is inherent in the criteria for many SRD events, the findings here may be consistent with the hypothesis posited by Wehr and colleagues⁴⁵ that psychosocial factors that seem to trigger the onset of mania could do so via their capacity to cause sleep deprivation. Actual sleep reduction, however, was not measured in this investigation, and a minority of SRD events may involve increased rather than decreased sleep (eg, becoming unemployed after full-time employment).

It had been expected that life stressors involving SRD would also be related to onset of depressive episodes. The limitations of small sample sizes of the subgroups has already been noted. Yet, perhaps the positive findings for mania but not depression in the present study reflect the acute nature of SRD assessed in this investigation. According to the sleep deprivation hypothesis of manic onsets, mania can be triggered by an acute disruption in the sleep/wake cycle.⁴⁵ In the onset of depressed episodes, however, the disruption may be more gradual. For example, Healy and Williams^{30,31} have hypothesized that stressful life events could precipitate depressive episodes by disruption of routines, which in turn disrupt the environmental cues that entrain circadian rhythms. Similarly, Ehlers and colleagues^{24,25} have proposed that stressful life events may trigger depression by acting as *zeitstorsers* (time disturbers). Such social rhythm disrupters, in turn, are thought to promote dysfunction in circadian rhythms, ultimately leading to somatic changes and then depression. Hence, because SRD may affect depressive onsets more gradually than manic onsets, it is possible that the 8-week pre-onset window studied in this investigation was of sufficient duration to observe an association between SRD events and onset for manic episodes, but was too short for depressive episodes.

The general lack of findings for patients with depressive onsets could also reflect some inherent difficulties with dating the onset of depressive episodes. Onset of initial symptoms of index episode was determined in structured interviews early in the study protocol. Because depressive symptoms tend to develop gradually and may be more difficult to recall relative to the often acute

onset of manic symptoms, it is likely that the onset dates assigned to manic episodes are more precise than those assigned to depressive episodes.

When considering the differences in SRD findings for manic and depressed onsets, the patients with depressive onsets in this investigation were older, had more past episodes, and had been ill longer than patients with manic onsets. That early episodes are more subject to the influence of life events than later episodes has been suggested by Post⁴⁶ and others,^{3,6,10,12,14,18,47} but remains controversial.^{13,48,49} According to this hypothesis, an association between life events and onset would be expected among manic but not among depressed subjects, because manic patients in our study were younger and had fewer past episodes. Indeed, in the present investigation, the proportion of subjects with LEDS-defined events of any severity in the pre-onset period was greater among those with manic onsets (80%) relative to those with depressed onsets (42%). Moreover, this rate was greater in the pre-onset period of manic subjects relative to such rates in their own control periods. To clarify that the finding of an increased pre-onset rate of SRD events among manic subjects was not an artifact of the increased rate of all life events in the pre-onset period among subjects with manic episodes, we examined the ratio of SRD events to total LEDS events. While 81% of manic subjects with any pre-onset LEDS event had at least 1 pre-onset SRD event, only 38% of depressed subjects with a pre-onset LEDS event had at least 1 pre-onset SRD event. This suggests that the SRD results in the present investigation are not a function of the higher pre-onset rates of life events among manic subjects, and therefore seem to be independent of the group differences in course of illness and age. The definitive test would be comparisons of patient groups with similar courses of illness.

A potential limitation of the within-subject SRD findings in our investigation is the possibility that data in the control periods have been affected by recall bias. As noted earlier, the LEDS was administered an average of 43 weeks after the onset of the index episode, and covered the 52 weeks up to and including index episode onset. It could be argued, therefore, that the findings in the present study reflect the relative ease in recalling events in the pre-onset period relative to the control period. Arguing against this potential recall bias are the following: (1) prior research on recall with the LEDS maintains that the fall-off in memory for severe events and/or events salient to the subject is minimal for 1 to 5 years^{50,51}; (2) both pre-onset and control periods may have been similarly subject to recall effects, as both were many months prior to interview; and (3) contrary to expectations if recall bias was operating, the proportion of depressed subjects in this investigation with an SRD event was somewhat greater during the control period than the pre-onset period. Future studies could control for any possible recall bias by collecting data more prospectively.

The key finding of this report, that SRD, perhaps reflecting sleep and/or circadian rhythm disruption, is related to the onset of mania, is important in supporting a biologic etiology for manic episodes. Equally exciting is that this evidence emerges from the application of a life event and stress methodology derived from a psychosocial per-

spective of mood disorders. The interdisciplinary approach reflected in this report argues for the continued exploitation of methods that cut across traditional biological/psychosocial boundaries.

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