Life Events and Bipolar Disorder: Implications From Biological Theories

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Although a number of studies suggest that stressful life events play a role in bipolar disorder, methodological flaws impose serious limitations on this literature. Nonetheless, better designed studies indicate that life events influence the course of bipolar disorder. Little is known, however, about the nature of events that are of particular importance to this disorder. Given the strong biological vulnerability and the unique clinical aspects of bipolar disorder, certain forms of stress may have stronger interactions with vulnerability characteristics. Three major biological theories of bipolar disorder are discussed, with particular attention to their implications for investigations of life events. Although tenuous, these models suggest that greater attention needs to be paid to particular dimensions of life events and the course of disorder.

The zeitgeist of research on bipolar disorder has shifted tides throughout the course of this century. Although early clinical reports emphasized the psychosocial context of the disorder (e.g., Cohen, Baker, Cohen, Fromm-Reichmann, & Weigert, 1954), the dramatic improvement in treatment outcome achieved with the clinical use of lithium led to a climate focused on biological agents, such as genetic predisposition. More recently, limitations in the prophylactic effects of lithium have become more widely recognized, and, in keeping with this state of affairs, a recent National Institute of Mental Health workshop report on treatment of bipolar disorder called for the investigation of the impact of psychosocial factors on the course of illness and psychosocial treatments as an adjunct to pharmacotherapy (Prien & Potter, 1990). Whereas it is well established that genetic agents play a large role in the choice of which individuals develop bipolar illness, the social environment probably affects the frequency and timing of episodes (O’Connell, 1986).

For example, Miklowitz and his colleagues (Miklowitz, Goldstein, Nuechterlein, Snyder, & Mintz, 1988) have demonstrated that individuals who experience high levels of negative family interactions or attitudes are 5 times more likely to relapse within 9 months of discharge. The demonstration of the predictive ability of the environment promotes a growing sense of enthusiasm about the role of psychosocial factors in the course of bipolar illness. Further understanding of the environmental context in bipolar disorder will potentially guide the development of increasingly sophisticated interventions.

Life stress has been seen as one domain of importance in the course of bipolar disorder, and a number of studies have documented higher rates of life events preceding bipolar episodes. As can be seen in Table 1, studies using noninterview measures of life stress have found significant effects across a wide range of research designs. For example, Glassner, Haldipur, and Des-saufersmith (1979) found that manic-depressive patients were 5 times more likely to experience significant role losses than a control group matched on class, race, gender, and age. Ambelas (1979) found that 4 times as many manic patients as surgical control patients experienced a threatening event in the 4 weeks before admission. In addition, as many as 50% of patients recall a major life event preceding their initial episode of bipolar disorder (Dunner, Patrick, & Fieve, 1979; Glassner & Haldipur, 1983). Such results across a wide range of methodologies highlight the need for more intensive exploration of the relation between life stress and bipolar disorder.

In the first half of this article, we review methodological issues related to the investigation of life events in bipolar disorder and discuss findings from the relatively more sound studies. Given support for the importance of stressful life events, we next turn to an examination of the unique aspects of bipolar disorder that are likely to have meaning for the nature and impact of life events. To help establish the parameters and dimensions within which life stress might operate in this disorder, we introduce three major biological models of bipolar disorder. Although these biological models are preliminary, we hope that such discussion eventually might lead to truly integrative biopsychosocial investigations and conceptual paradigms. Our goal is to promote the development of theory and research that neither ignores important domains nor blindly includes them in a vague and poorly specified manner. The latter practice merely serves the “political and palliative” purpose of compromise without fostering any real advancement in understanding (Monroe & Roberts, 1991; see also Barnett, 1993).

Methodological Issues

Despite similarities in findings, studies of life stress in bipolar disorder have differed dramatically in design and methodology.
<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Diagnostic measure</th>
<th>Comparison group</th>
<th>Life stress assessment</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Leff et al. (1976)</td>
<td>63 bipolar inpatients</td>
<td>Chart review for PSE criteria</td>
<td>None</td>
<td>Chart review for independent events in the month before onset</td>
<td>35% of bipolar inpatients reported an event</td>
</tr>
<tr>
<td>Davenport &amp; Adland (1982)</td>
<td>40 married bipolar fathers admitted to National Institute of Mental Health</td>
<td>RDC; 39 primary bipolar; 1 schizoaffective</td>
<td>None</td>
<td>Chart review of childbirths</td>
<td>21/40 male patients had an episode during perinatal period or 12 months postpartum</td>
</tr>
<tr>
<td>Ambelas (1979)</td>
<td>67 hypomanic or manic inpatients; excluded rapid cyclers and ≥10 episodes</td>
<td>Chart review for Feighner criteria (Feighner et al., 1982)</td>
<td>60 surgical control patients</td>
<td>Chart review for events in the month before admission</td>
<td>28% bipolar vs. 6% of controls reported an event</td>
</tr>
<tr>
<td>Thomson &amp; Hendrie (1972)</td>
<td>27 bipolar inpatients</td>
<td>Chart review</td>
<td>47 depressed unipolar patients; 48 age- and sex-matched hospital community controls; 22 medical controls</td>
<td>SRA for events in the year before onset</td>
<td>Bipolar vs. unipolar patients had significantly higher mean life change scores than either control group</td>
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<tr>
<td>Bidzinska (1984)</td>
<td>50 Bipolar I or II patients; ≥3 episodes; no organic affective disorder; no recent electroconvulsive therapy</td>
<td>Not reported</td>
<td>47 unipolar patients; 100 age-matched community controls</td>
<td>Interview for independent events for the 3 months before onset</td>
<td>No bipolar vs. unipolar differences in overall stress; bipolar and unipolar patients reported more stress before onset than normal controls</td>
</tr>
<tr>
<td>Swann et al. (1990)</td>
<td>71 bipolar patients (53 depressed and 18 manic)</td>
<td>RDC</td>
<td>84 recurrent unipolar patients</td>
<td>2 SADS items; clinician’s and patient’s global impression of importance of stress</td>
<td>Unipolar, bipolar—depressed, and bipolar—manic patients were not significantly different in stress ratings</td>
</tr>
<tr>
<td>Clancy et al. (1973)</td>
<td>100 bipolar patients</td>
<td>Chart review for Feighner criteria</td>
<td>225 unipolar and 200 schizophrenic patients</td>
<td>Chart review for events in the 3 months before onset</td>
<td>39% of unipolar patients, 27% of bipolar patients, and 11% of schizophrenics had event reported in chart</td>
</tr>
<tr>
<td>Mayo (1970)</td>
<td>28 bipolar, 7 unipolar, and 5 schizoaffective patients attending lithium clinic</td>
<td>Structured psychiatric interview</td>
<td>None</td>
<td>Interview for events after age 15 and for the 6 months before and after hospitalization</td>
<td>180 lifetime hospitalizations in 40 patients; no excess of stressful events in the year of hospitalization; no analyses by diagnostic group were conducted</td>
</tr>
<tr>
<td>Aronson &amp; Shukla (1987)</td>
<td>30 bipolar outpatients</td>
<td>Chart review for DSM-III diagnosis</td>
<td>10 relapers vs. 20 age- and sex-matched nonrelapers</td>
<td>Reactions within 2 weeks of major hurricane</td>
<td>Relapers had significantly less symptom stability before stress than nonrelapers</td>
</tr>
<tr>
<td>Hall et al. (1977)</td>
<td>38 bipolar outpatients; at least 1 hospitalization for mania; patients with ≥3 episodes per year excluded</td>
<td>Feighner criteria</td>
<td>17 relapers vs. 21 nonrelapers</td>
<td>Modified RLE interview to assess subjective stress at each appointment, every 1–12 weeks</td>
<td>Relapers and nonrelapers did not differ in frequency of life events</td>
</tr>
<tr>
<td>Glassner et al. (1979)</td>
<td>25 bipolar inpatients and outpatients</td>
<td>Feighner criteria</td>
<td>First episode vs. subsequent episode; 25 demographically matched community controls</td>
<td>Patient and family interview based on SRA for events in the year before onset</td>
<td>75% of first episode patients, 56% of subsequent episode patients and 16% of controls reported an event</td>
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*(table continues)*
<table>
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<tr>
<td>Dunner et al. (1979)</td>
<td>79 bipolar patients (11 rapid cyclers)</td>
<td>Feighner criteria</td>
<td>None</td>
<td>Patients and family interview for events in the 3 months before initial episode; life events before subsequent episodes were noted</td>
<td>50% experienced an event before the first episode; 12/79 experienced an event preceding subsequent episodes</td>
</tr>
<tr>
<td>Ambelas (1987)</td>
<td>90 bipolar manic inpatients</td>
<td>Chart review for Feighner criteria</td>
<td>50 first episode and 40 subsequent episode patients; 50 age-matched surgical controls</td>
<td>Chart review for severe, independent events in the 4 weeks to admission</td>
<td>66% of first episode patients, 8% of controls, and 20% of repeat admission patients reported an event</td>
</tr>
<tr>
<td>Ambelas et al. (1986)</td>
<td>20 bipolar manic inpatients with an independent life event preceding index admission</td>
<td>Feighner criteria</td>
<td>Low stress vs. high stress preceding onset</td>
<td>Chart review</td>
<td>Low stress patients were more vulnerable to future episodes than high stress patients over a 6–9-year period</td>
</tr>
<tr>
<td>Glassner &amp; Haldipur (1983)</td>
<td>46 bipolar inpatients and outpatients</td>
<td>Feighner criteria</td>
<td>13 early onset; 33 late onset</td>
<td>Patient and family member SRA interview for events in the year before onset</td>
<td>64% of late onset patients and 23% of early onset patients reported stress preceding initial episode; 61% of late onset patients and 23% of early onset patients reported stress preceding recent onset</td>
</tr>
<tr>
<td>Joffe et al. (1989)</td>
<td>14 bipolar inpatients and outpatients with manic episode in past 14 months; adequate medication</td>
<td>SADS for RDC criteria</td>
<td>14 age- and sex-matched bipolar patients without a mania in the past 14 months</td>
<td>PERI-M life events interview for events in the year before onset</td>
<td>No differences between manic patients and controls in the number of events; manic patients reported more unanticipated, uncontrollable events than controls</td>
</tr>
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</table>

*Note:* PSE = Present State Examination Schedule (Wing et al., 1974); RDC = research diagnostic criteria; SRA = Holmes-Rahe Social Readjustment Scale; SADS = Schedule for Affective Disorders and Schizophrenia (Endicott & Spitzer, 1978); (DSM-III = Diagnostic and Statistical Manual of Mental Disorders (3rd edition; American Psychiatric Association, 1980); RLE = Interview for Recent Life Events (Paykel, 1983); PERI-M = Psychiatric Epidemiology Research Interview Modified Life Events Scale (B. S. Dohrenwend et al., 1978).
In many of these investigations, methodological flaws are severe enough to limit the interpretability of results. The following section briefly discusses critical issues in the assessment of life stress. Interested readers are referred to comprehensive methodological reviews for more detailed examinations (see Brown, 1974, 1981; Brown & Harris, 1978b, 1989b; B. S. Dohrenwend, Dohrenwend, Dodson, & Shroot, 1984; Monroe & Peterman, 1988; Monroe & Roberts, 1990). Our critique focuses particularly on limitations in the areas of long-term recall of life events, ambiguity in self-report instruments, and confounds among life stress, personality, and symptomatology.

The widespread reliance on long-term recall of life events has been particularly problematic in this area, with many investigators asking participants to report events that occurred as long as 10 years before the interview (Dunner et al., 1979; Glassner & Haldipur, 1983). Empirical studies suggest that memory for minor events decreases within a year (Brown, 1989) and, of particular importance, that memories become more systematically biased over time to fit with patients' personal understanding or schema of the disorder (Brown, 1974). This natural process of "effort after meaning" may cause individuals to shift the timing of events, to selectively attend to certain events, and to elaborate more on certain events to make sense out of their disorder. As a result, patients may recall life events that they perceived as contributing to an initial break but be less likely to recall life events that were not temporally linked with such dramatic changes in psychological state (regardless of the true state of affairs).

Unfortunately, most investigations have relied on self-report measures of stressful life events (Dunner et al., 1979; Glassner & Haldipur, 1983; Joffe, MacDonald, & Kutcher, 1989). Vague and ambiguous items found on many of these instruments, such as "serious illness of a family member," allow considerable room for participants' idiosyncratic interpretations (Brown, 1981). For example, whereas some participants might report an aunt's recent cold as being stressful for them, others report the discovery of a spouse's heart condition as not being stressful. Similarly, each item is likely to sample a range of actual experiences (B. P. Dohrenwend, Link, Kern, Shroot, & Markowitz, 1990; Raphael, Cloitre, & Dohrenwend, 1991). That is, many different types and severities of experience can be lumped under the same category. For example, a bad bout of the flu, ongoing problems with arthritis, and terminal stages of cancer all might be reported under the serious illness category. In light of these problems, it is not surprising that life event checklists have poor interrater reliability (Katschnig, 1986). Similarly, in one recent study, only 39% of events identified by questionnaire were considered significant life stressors after further information was collected by interview (McQuaid et al., 1992). Of most concern, this error is likely to be systematic; patient groups are more prone to use a lower threshold in endorsing ambiguous items as a result of factors such as effort after meaning (see Monroe & Simons, 1991).

Furthermore, researchers increasingly have recognized the complex interrelations among stress, psychopathology, and personality (Monroe & Steiner, 1986). Individuals with psychopathology may actually contribute to their level of stress through poor judgment, coping deficits, or actual symptoms. For example, the onset of mania is typically marked by impulsive behaviors. Hypersexuality, irritability, and grandiosity all may create significant interpersonal difficulties. As a result, many stressful events experienced by bipolar patients could be due to their illness or prodromal symptoms, rather than vice versa. In investigating etiological models, it is critical to exclude such events; failure to attend to this important confound artifically magnifies the life stress–illness relation. We believe that the possibility of such reverse causality is particularly problematic in bipolar disorder given the substantial life turmoil produced by symptoms of this illness.

To separate life events that are secondary to psychopathology, some life stress measures rate events along a dimension of independence, or the degree to which they may have been caused by the individual, psychopathology, or both (B. P. Dohrenwend, 1974). For example, events that are outside of the individual's control, such as natural disasters and deaths, would be considered totally independent, whereas taking a voluntary leave of absence because of fatigue and difficulty concentrating would be considered dependent (Brown & Harris, 1986; Tennant, Bebbington, & Hurry, 1981). Similarly, researchers have discussed the need to carefully attend to the timing of events and to select events that occurred before the onset of an episode, preferably before the first symptom of hypomania or depression (Brown & Harris, 1978b). Unfortunately, such information cannot be obtained reliably through self-report checklists. These requirements demand careful probing and investigator-based clinical judgment, possible only with interview-based assessment (Brown & Harris, 1978b).

In summary, although an initial perusal of the life events literature indicates a pattern of significant findings in regard to bipolar illness, significant methodological issues have clearly affected the ability to interpret this body of literature. Given the limitations of self-report methodologies, we now review in greater detail the studies published that adequately assessed life stress through semistructured interviews with attention to life event independence (see Table 2). Although this standard narrows the field to 10 investigations, we believe that these represent the most conservative, methodologically sound, and interpretable studies available.

Review of the Findings

Like Norman and Malla (1993), we organize our review into three prominent designs consisting of contrasts of life stress between (a) bipolar and nonpatient groups, (b) bipolar and other psychiatric patient groups, and (c) well and episodic periods in bipolar patients. Although research has shown a role of life events in the recovery, treatment response, and severity of symptomatology for other disorders (cf. Brown, Lemyre, & Bifulco, 1992; Johnson, Monroe, Simmons, & Thase, 1994; Monroe, Kupfer, & Frank, 1992; Pilkonis, Imber, & Rubinsky, 1984), the current review is limited to life events in the onset and relapse of episodes of bipolar disorder.

Bipolar Versus Nonpatient Groups

Three studies meeting our methodological criteria compared the rates of life events in bipolar patients preceding relapse with those of nonpatient groups. This design attempts to establish whether the
Table 2

Interview-Based Studies of Life Stress in Bipolar Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnostic measure</th>
<th>Population</th>
<th>Life events measure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chung et al. (1986)</td>
<td>DSM-III</td>
<td>14 hypomanic inpatients; onset within 1 year of hospitalization; no psychosis for 6 months before onset; age- and sex-matched nonpatient controls</td>
<td>LEDS completed during hospitalization for 6 months before onset</td>
<td>2/14 hypomanic patients vs. 1/14 controls experienced a severe, independent event (nonsignificant difference)</td>
</tr>
<tr>
<td>Kennedy et al. (1983)</td>
<td>Renard Diagnostic Interview</td>
<td>20 manic inpatients; no hospitalizations for 6 months before or after index episode; demographically matched orthopedic controls</td>
<td>RLE completed 6 to 21 months after discharge for 4 months before admission and 4 months after discharge</td>
<td>Patients experienced 23 severe, independent events before admission vs. 7 after discharge; more manic patients (65.2%) than controls (32%) experienced an undesirable event</td>
</tr>
<tr>
<td>Bebbington et al. (1993)</td>
<td>DSM-III</td>
<td>31 manic inpatients with psychosis; onset in past year; nonpsychiatric, schizophrenic, and psychotic depression controls</td>
<td>Revised LEDS completed after remission for 6 months before onset of psychosis</td>
<td>Manic patients experienced more severe, independent events before relapse than nonpsychiatric controls; depressed patients reported more severe, independent life events than manic and schizophrenic patients</td>
</tr>
<tr>
<td>Perris (1984)</td>
<td>Umea classification</td>
<td>16 depressed bipolar patients; unipolar, unspecified, and reactive-depressive depressed controls</td>
<td>Interview completed after remission for 1 year before episode</td>
<td>Bipolar patients reported an average of 2.5 independent events; unipolar, 1.9; unspecified, 1.9; and reactive-depressive, 2.9 (p &lt; .001)</td>
</tr>
<tr>
<td>Selare &amp; Creed (1990)</td>
<td>PSE</td>
<td>25 manic inpatients with no organic etiology; well for 9 months before onset</td>
<td>LEDS completed during hospitalization for 6 months before onset and at 6 months after recovery</td>
<td>Manic patients experienced more independent events before onset than after recovery</td>
</tr>
<tr>
<td>Elicott et al. (1990)</td>
<td>DSM-III-R</td>
<td>61 bipolar outpatients; remission for 2 months or stable symptoms for 6 months; at least 4 months at medication clinic</td>
<td>Interview based on RLE and LEDS</td>
<td>Patients with high stress had 4.53 times the risk of relapse as patients with low stress</td>
</tr>
<tr>
<td>Hunt et al. (1992)</td>
<td>43 SADS; 19 chart review</td>
<td>62 bipolar inpatients</td>
<td>RLE completed every 3 months for 2 years</td>
<td>6/52 patients had at least one event in the month before relapse vs. 5/144 during control periods</td>
</tr>
<tr>
<td>McPherson et al. (1993)</td>
<td>SADS</td>
<td>58 bipolar inpatients</td>
<td>RLE completed every 3 months for 2 years</td>
<td>No difference in the number of moderate, independent events in the month preceding relapse vs. control periods</td>
</tr>
<tr>
<td>Hammen, Elicott, Gitlin, &amp; Jamison (1989)</td>
<td>DSM-III-R</td>
<td>16 Bipolar I and 9 Bipolar II patients</td>
<td>Interview based on RLE and LEDS completed at 3 and 6 months</td>
<td>Interpersonal vs. achievement events were not differentially associated with relapse in sociotropic or autonomous subgroups</td>
</tr>
<tr>
<td>Hammen et al. (1992)</td>
<td>DSM-III-R</td>
<td>498 Bipolar I and II patients</td>
<td>Interview based on RLE and LEDS completed every 3 months for 18 months</td>
<td>Congruence of events with sociotropic or autonomous cognitive style was not predictive of onset</td>
</tr>
</tbody>
</table>

Note: DSM-III = Diagnostic and Statistical Manual of Mental Disorders (3rd edition; American Psychiatric Association, 1980); LEDS = Life Events and Difficulties Schedule (Brown & Harris, 1978a); RLE = Interview for Recent Life Events (Paykel, 1983); PSE = Present State Examination Schedule (Wing et al., 1974); DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders (revised 3rd edition; American Psychiatric Association, 1987); SADS = Schedule for Affective Disorders and Schizophrenia (Endicott & Spitzer, 1978).

Period before relapse is associated with greater life stress than that which nonpatients typically experience. Chung, Langeludecke, and Tennant (1986) compared 14 hospitalized hypomanic patients with an age- and sex-matched nonpatient sample using the Life Events and Difficulties Schedule (LEDS), a well-developed interview-based approach (Brown & Harris, 1978a, 1979). Although the number of hypomanic patients experiencing a severe, independent or probably independent event in the 6 months before symptom onset was twice that of the control groups, only 2 of the 14 hypomanic patients reported such an event. In part, the low rate of events in this study may be associated with the use of a hypomanic sample. Nonetheless, the hospitalized status of patients suggests rather severe symptomatology. Unfortunately, little information was available concerning clinical characteristics of the sample. Certainly, given this low rate of events, a larger sample size would be required for adequately exploring hypotheses.
Other studies have more successfully documented higher rates of life events in bipolar patients. Kennedy and his colleagues (Kennedy, Thompson, Stancer, Roy, & Persad, 1983) interviewed bipolar patients 6 to 21 months after hospital discharge using the Interview for Recent Life Events (Paykel & Mangen, 1980). Bipolar patients were compared with a control group consisting of orthopedic outpatients matched on age, sex, marital status, social class, and immigration status. Rates of both total and undesirable events were elevated in the 4 months before psychiatric hospitalization in comparison with rates of events in control patients. Unfortunately, the authors relied on hospital admission as the criterion for relapse. Given an average delay of several weeks from symptom onset until hospitalization (Francis & Gaspary, 1994), many negative events actually might have occurred after the onset of mania but before hospitalization (Scclare & Creed, 1990). Furthermore, these comparisons failed to examine the proportion of participants experiencing at least one negative event. The latter concern involves the issue of whether life events have additive impact. In examining onset and relapse of episodes of unipolar depression, most research to date has suggested that the presence of one severe event is a more meaningful predictor than scores summing multiple events of varying severities (see Brown & Harris, 1989a, for a discussion).

Using a modified version of the LEDS, Bebbington and his colleagues (1993) found that hospitalized manic patients experienced higher rates of severe, independent stressors in the 6 months before onset than members of a normal control group. In one of the few examinations of gender differences, they found that more women than men reported events before onset; whereas 53% (8 of 15) of the women reported a severe, independent event in the 3 months before onset, 38% (6 of 16) of the men reported such an event. Nonetheless, male manic patients were still more likely to experience a severe stressor than male controls.

Overall, then, bipolar patients appear more likely to experience stressful life events before episodes than nonpsychiatric controls. However, caution is required in interpreting findings based on three studies (only two of which obtained positive results).

**Bipolar Versus Other Patient Groups**

Three studies have compared the rates of life events between bipolar and other psychiatric patient groups. This approach is based on the questionable premise that stress plays a lesser role in these other disorders (Brown & Harris, 1989b). Perris (1984) examined life stress preceding onset in patients classified as unipolar, bipolar, or reactive-neurotic. Reactive-neurotic patients included those who “have suffered from a depressive episode (recurrent or not) occurring in closer relation to a psychologically understandable stressful event, or in a person with an unstable personality and a manifest proneness to depressive reactions” (Perris, 1984, p. 28). Given these severe confounds in measurement of diagnostic status and predictor variable, it is not surprising that the reactive-reactive group reported higher rates of life stress than the other two groups (which did not differ from each other). Two studies discussed previously also included psychiatric controls. Bebbington et al. (1993) found that manic patients and schizophrenics reported similar levels of life events, whereas psychotically depressed patients reported a higher number of severe, independent life stressors. Finally, Chung et al. (1986) found that schizophreniform patients were more likely to report severe, independent or probably independent events than were hypomanic patients.

Overall, then, results are very preliminary in this area but do not support the notion that bipolar patients are more likely to experience stressful events than patients suffering from psychotic disorders. Such findings are not particularly surprising, given evidence for the role of life events in the onset of psychosis (Brown & Birley, 1968; Day, 1989). Further theory and research is necessary to examine the specific nature of stressful experiences that are particularly relevant to bipolar patients and to determine whether these types of experiences differ from those that are relevant to other diagnostic groups.

**Relapse in Bipolar Disorder**

The final design examines whether life events predict changes in symptomatic status in bipolar patients over time. It is the only design to assess the direct impact of life events on course of the disorder. That is, even if comparisons with community or psychiatric samples yield positive results, it remains unknown how strongly life events change the course of bipolar disorder. In addition, a recent review of life events in schizophrenia suggests that this is perhaps the most sensitive design (Norman & Malla, 1993). To the extent that biological vulnerability remains constant over time, this source of variability is controlled.

In a previously mentioned study, Kennedy and his colleagues (1983) found that rates of independent events with severe, marked, or moderate objective negative impact were elevated in the 4 months before hospital admission when compared with postdischarge rates. In a study using actual symptom onset as a criterion, Scclare and Creed (1990) compared rates of life events in bipolar patients 6 months before relapse and 6 months after recovery using the LEDS. They found that 44% (11 of 24) of their participants experienced an independent severe event in the 26 weeks before onset, in comparison with 21% (5 of 24) who experienced an independent severe event in the 26 weeks after recovery. However, because of the small sample size and consequent limitations in power, this relation was not significant. Furthermore, both of these studies are limited by reliance on long-term recall of stressors, with reporting up to 2.5 years before the interview (Kennedy et al., 1983).

Other studies have avoided reliance on long-term memory by using shorter intervals for recall. In fact, three studies to date have prospectively followed bipolar patients across a 2-year period, with life stress interviews conducted every 3 months (Ellicott, Hammen, Gitlin, Brown, & Jamison, 1990; Hunt, Bruce-Jones, & Silverstone, 1992; McPherson, Herbison, & Romans, 1993). Ellicott and her colleagues (1990) found that patients who received the highest total life event scores had 4.53 times the risk of relapse as patients who did not experience stress. Similarly, Hunt and his colleagues found that the rate of severe, independent events, as defined through the Interview for Recent Life Events (Paykel & Mangen, 1980), was significantly higher in the 3 months before relapse than in other control periods not preceding relapse. Severe events clustered in the
month before relapse; the number of patients experiencing at least one severe, independent event was 3.8 times higher in the month before relapse than during other months.

In contrast, McPherson and colleagues (1993) used the same measures as Hunt and colleagues (1992), yet failed to replicate their findings; bipolar patients did not display an increased rate of life events preceding relapse as compared with other control periods. However, the McPherson et al. sample was differentiated from the Hunt et al. (1992) sample along a number of important dimensions, including increased severity of illness, higher rates of dropout, and less financial stress, rendering cross-study comparisons difficult.

In addition, the Hunt et al. (1992) and McPherson et al. (1993) studies differ from other longitudinal studies in failing to require a well period before study entrance. All studies that have required participants to demonstrate a well period, or to achieve full recovery before study entrance, have documented positive results. Given the greater magnitude of life event effects in populations achieving full recovery, distinctions between relapse and recurrence may be important to explore (cf. Frank et al., 1991). It is possible that life events are more potent in explaining recurrence, whereas individuals who are still short of full recovery are more influenced by ongoing biological dysregulation. However, other cross-study differences preclude conclusions regarding moderators of life event vulnerability.

Interestingly, Hammen, Ellicott, and their colleagues also examined whether stressful life events interacted with cognitive vulnerability in predicting relapse and symptom severity (Hammen, Ellicott, & Gitlin, 1992; Hammen, Ellicott, Gitlin, & Jamison, 1989). Specifically, theory and research in unipolar depression suggest that negative life events that are congruent with a particular area of sensitivity are particularly depressogenic (e.g., Beck, 1983; Hammen, Marks, Mayol, & de Mayo, 1983; Robins & Block, 1983; see Nietzel & Harris, 1990, for a review). For example, someone who derives a sense of self-worth primarily from social relationships may be more vulnerable to depression after interpersonal loss than someone who obtains self-esteem from other domains (Roberts & Hartlage, in press; Roberts & Monroe, 1994). The notion that particular bipolar patients exhibit greater vulnerability to particular types of negative life experiences is conceptually appealing but not well supported, at least as of yet. Nonetheless, this line of research marks an important step in attempting to investigate whether vulnerability matching generalizes to bipolar disorder.

Unfortunately, like most investigations of bipolar disorder, the Hammen and Ellicott studies investigated depressive and manic symptoms pooled together. Although there is a fundamental need to examine relations between episode polarity and life events in the field as a whole, attention to episode polarity may be even more important for models of cognitive vulnerability. If self-worth is a central construct in cognitive vulnerability, matching events might be expected to relate more directly to depressed than manic episodes. If congruent life events have different implications for different phases of bipolar disorder, perhaps being more important in the depressive phase, pooling symptoms would have muddied the waters and made it difficult to find support for this hypothesis.

In summary, life events appear to be more prevalent before relapse in bipolar patients, as opposed to other time periods in their lives. This is reflected in four of the five studies within this area, despite limitations in the statistical power to detect clinically important differences. Of the many findings of different research designs used to investigate the role of life events in bipolar disorder, these longitudinal investigations of relapse appear most meaningful.

Summary of Findings

Despite a variety of methodological issues in the broader literature, studies that have used more careful methodological techniques document an association between life events and bipolar disorder. Although the relation between life events and bipolar disorder has been supported across a number of designs, it has been particularly evident in longitudinal studies of well and episodic periods in bipolar patients. Thus, investigations that attempt to understand the impact of life events on the course of bipolar disorder appear to be the most positive.

Despite the promise of these findings, it is possible that the effects of stressful life events are dependent on medication compliance. For example, major disruptions in lifestyle resulting from severe events may lead to failure to take medications. In this way, compliance could mediate the impact of the psychosocial environment on outcome. To date, preliminary findings have been inconsistent with this possibility (Ellicott et al., 1990; Hunt et al., 1992; Kennedy et al., 1983).

Beyond effects of compliance, it is important for investigators to attend to whether life events effects are buffered by appropriate treatment. To date, effects for life events have emerged in samples varying widely in outpatients (Hunt et al., 1992; Kennedy et al., 1983; Sclare & Creed, 1990), as well as samples receiving careful outpatient follow-up (Ellicott et al., 1990). These preliminary findings suggest that psychosocial factors operate across a range of treatment levels. Nonetheless, researchers need to be cognizant of potential interactions with medication levels and compliance as they design future investigations.

Unfortunately, even among studies using life stress interviews and attending to medication levels, many have significant methodological difficulties, such as a failure to incorporate a standardized structured diagnostic interview (Chung et al., 1986; Ellicott et al., 1990; Hammen, Ellicott, Gitlin, & Jamison, 1989), reliance on hospitalization rather than symptom levels as an index of onset (Kennedy et al., 1983), failure to consider participants with substance abuse separately (Hammen, Ellicott, Gitlin, & Jamison, 1989; Hunt et al., 1992), and insufficient power to detect meaningful group differences (Chung et al., 1986; Hammen, Ellicott, Gitlin, & Jamison, 1989; Kennedy et al., 1983; Sclare & Creed, 1990). Despite these flaws, the literature has been consistent in indicating a relation between life events and relapse in bipolar disorder. In fact, these findings hold across a variety of samples, including Bipolar I and Bipolar II patients (Ellicott et al., 1990), those with depressed and manic episodes (Hunt et al., 1992), and outpatient as well as inpatient samples (Ellicott et al., 1990). These findings have been consistent enough to suggest that life stress is an important factor for further, intensive consideration in the development of bipolar episodes.

Given that the relation between life stress and bipolar disor-
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Order appears to receive moderate empirical support, consideration of the form of life stress that has the most impact is necessary. Whereas some researchers have included events of all severities in their analyses, most have focused on only severe events. Although research on anxiety and unipolar depression suggests that minor events are not associated with onset (Brown & Birley, 1968; Brown & Harris, 1978b), risk for relapse in schizophrenia increases after events of all severities (including minor events). In addition, whereas schizophrenic relapse tends to occur within 3 weeks of life events, individuals appear to be at increased risk for depression for 6 months after a major negative event (Brown & Harris, 1978b). In bipolar disorder, the importance of threat severity, timing of events, and additivity of events remains unknown.

In addition to the need to clarify the role of stressor severity, timing, and additivity, little is known about the type of event that is most likely to contribute to onset. In most research on bipolar disorder, events are treated nonspecifically, with little attention paid to particular dimensions (e.g., loss, danger, and change). However, different types of major life events have demonstrated stronger associations with different types of psychopathology (Monroe & Johnson, 1991). For example, Finlay-Jones and Brown (1981) found that whereas events that contained elements of severe loss were predictive of depression, events that contained elements of severe danger (risk of future crisis) were predictive of anxiety. Similarly, recent research has indicated that recovery from anxiety is facilitated by events that reduce uncertainty about the future, whereas recovery from depression is facilitated by events that lessen an ongoing difficulty or deprivation (Brown, Lemyre, & Bifulco, 1992). For patients with organic gastrointestinal disorders, events that contain elements of goal frustration seem particularly tied to disorder (Craig & Brown, 1984; Ellard, Bearepaire, Jones, Piper, & Tennant, 1990; Harris, 1991). Overall, more precise definitions of stress have enhanced prediction of onset and recovery within a number of disorders.

In addition, researchers have increasingly demonstrated that life stress may operate on specific physiological channels, with different forms of stress resulting in relatively specific endocrine response patterns (Mason, 1971). Unique aspects of stress have been tied to hormonal variations (Baum, Grunberg, & Singer, 1982) and to adrenergic pathways regulated by the sympathetic nervous system (Felten & Felten, 1991). These developments provide further support for the contention that certain aspects of stress may have important links with specific diseases.

Despite success with other disorders, specific models of stress have not been developed with bipolar disorder. This is surprising, given that bipolar disorder is differentiated from other disorders along a number of underlying biological and clinical dimensions. Models of life stress are likely to be more predictive if they are able to accommodate these distinguishing features of bipolar disorder. For example, there is strong evidence of genetic liability for this disorder, with approximately 80% of monozygotic twins raised together (Bertelsen, 1979; Bertelsen, Harvald, & Hauge, 1977) and approximately 67% of monozygotic twins raised apart concordant for bipolar disorder (Price, 1968; see McGuffin & Katz, 1989, for a review). Given the strong biological vulnerability for bipolar disorder, events of lesser severity may be more important in this disorder than in others (Monroe & Simons, 1991).

Beyond the strong biological diathesis, unique clinical features of bipolar disorder are likely to have relevance to the investigation of life events. Perhaps the most striking of these features is the frequency of abrupt changes in course. Manic episodes often achieve full onset from a euthymic state to a full-blown psychosis within a few days or even hours (Winokur, 1976). Likewise, bipolar depressed episodes appear to develop more quickly than unipolar depressed episodes (Winokur, 1976). The speed of episode onset suggests that the timing of life events within this disorder may contrast with that of other disorders.

To date, psychosocial research on bipolar disorder has frequently applied models that have been successful in understanding other psychopathologies, particularly unipolar depression. Nonetheless, within the biological sphere, several theories have attempted to grapple with the unique biological and clinical characteristics of bipolar disorder and to develop integrative models of etiology. Although the field remains in the process of hypothesis generation, these theories provide tentative models of biopsychosocial pathways leading to disorder.

Biological Models of Bipolar Disorder

In hopes of providing more specific direction to life stress endeavors, we discuss three biological models of bipolar illness that have particular implications for life stress. Ideally, such models would inform psychosocial researchers as to the general nature of life experiences that might make a difference in this disorder, as behavioral genetics has done with other psychological characteristics and conditions (e.g., Plomin & Daniels, 1987; Reiss, Plomin, & Hetherington, 1991). Although other biological models are available, we chose these models because of their particularly strong potential for linking biological vulnerability and the social environment. For each model, we provide an overview of the theory, discuss ramifications for life stress, and review current life stress research addressing these tenets. A thorough review of biological research on these models is beyond the scope of this article. We present these models as preliminary examples in the spirit of encouraging the development of greater consideration of potential mechanisms by which life events might affect bipolar disorder. We also hope that increased empirical knowledge of life events may shed new light on these biological theories.

Circadian Rhythms and Life Stress

Within the past several years, theoreticians have attempted to explain the impact of life stress on affective disorders through the destabilizing effects of these life events on critical biological rhythms (Ehlers, Frank, & Kupfer, 1988; Healy & Williams, 1988). These models posit that stressful life events, such as social losses, operate through disruption of daily rhythms and that disruption of these daily rhythms leads to disturbances in sleep and other physiological rhythms that are fundamental in the genesis of affective episodes.

Increasingly, researchers have suggested that circadian rhythms are regulated by two or more internal oscillators
In affective disorders, the oscillator that regulates sleep and certain neuroendocrine rhythms becomes desynchronized from other internal circadian rhythms, so that phase relationships are disrupted. As a result, the sleep–wake cycle and certain neuroendocrine systems become disturbed in most of these individuals (Goodwin & Jamison, 1990). Such disturbances in physiological processes are hypothesized to be central to the etiology of depressive and manic episodes (Wehr, 1991). Hence, one fundamental goal has been the identification of which factors could contribute to dysregulation of these systems.

It is well recognized that environmental cues, or zeitgebers, help synchronize these oscillators with the light–dark cycle as well as with each other. Although light is one potent zeitgeber, social cues are also quite powerful in their ability to regulate these rhythms. For example, social schedules guide the timing of meals and sleeping.

The social zeitgebers theory suggests that major life events disrupt these social cues, or zeitgebers, that help synchronize daily rhythms. Disruptions in social rhythms produce instability in biological circadian rhythms, and this biological instability produces somatic symptoms of depression. For example, marital partners are likely to be a very strong source of social routines, because married couples are likely to dine together, engage in joint activities, and influence each other’s sleep cycles. The loss of a spouse is one of the most potent environmental factors in the onset of depression. Certainly, such a loss would obliterate many social routines and greatly disrupt the regularity of daily rhythms. Individuals who are not vulnerable to depression, because of family history, lack of biological predisposition, or previous experience, will have greater ease in restoring stability to these disturbed biological rhythms and so will not be as likely to become depressed. In short, biological rhythm disturbances operate as a final common pathway for a variety of etiological agents, including biological vulnerability and the psychosocial environment (Ehlers et al., 1988; Healy & Williams, 1988).

Whereas Ehlers and her colleagues (1988) have focused to a large extent on the implications of this model for unipolar depression, Healy and Williams (1989) have provided an extensive set of assumptions relating social zeitgebers to mania. They have suggested that circadian rhythm disturbance can provoke overactivity. This overactivity, because it triggers decreased fatigue and increased streams of associations, may lead to misattributions of increased personal effectiveness and self-esteem. These cognitive distortions are hypothesized to lead to the cardinal features of mania, such as grandiosity and euphoria.

Clearly, this model is impressive in its integration of a broad range of empirical findings concerning the etiology of depression. It provides a framework for developing a final common pathway that would explain a very distinct epigenesis of affective shifts, ranging from the ability of sleep disruptions to provoke mania (Wehr, Sack, & Rosenthal, 1987) to the ability of severe loss to provoke depressive episodes (Brown & Harris, 1978b).

**Empirical support.** A specific measure to assess daily routine shifts, the Social Rhythm Metric, has been developed and validated as correlating with higher levels of depressive symptomatology (Monk, Flaherty, Frank, Hoskinson, & Kupfer, 1990; Monk, Kupfer, Frank, & Ritenour, 1991; Szuba, Yager, Guze, Allen, & Baxter, 1992). As an initial test of the social zeitgebers theory, Flaherty and his colleagues (Flaherty, Frank, Hoskinson, Richman, & Kupfer, 1987) assessed 87 individuals after the loss of a spouse to determine the degree of social disruption as well as depressive symptomatology. Disruption in social routines was highly related to depressive symptomatology. However, the study’s cross-sectional design renders statements of causality impossible.

Only one published study has examined whether schedule disruptions prospectively predict depressive shifts. In a study of spousally bereaved elderly people, Prigerson and her colleagues (1994) found that, contrary to expectations, bereavement was not associated with schedule disruption at a 3-month follow-up. In addition, schedule disruptions did not predict follow-up depression levels. Although results were not supportive of the model, the design was limited by the inability to assess schedule disruption until 3 months after bereavement; by this time, some of the most severe schedule disruption may have been remedied. Further prospective research is necessary to assess this model.

**Implications for life events models.** This model suggests that the pathogenic effects of life events stem from dimensions quite different from those that are typically the focus of psychosocial researchers. Whereas previous research has emphasized the degree of emotional threat and loss as the most predictive elements of life events (particularly for unipolar depression), the circadian model emphasizes schedule disruption as a more important feature and suggests the need to carefully assess the extent to which events disrupt daily routines.

To date, few researchers have attempted to directly explore schedule disruptions and their ability to predict manic episodes. However, certain life stress findings are particularly relevant to this theory within bipolar disorder, although control over confounding variables has been limited. Interestingly, Davenport and Adland (1982) reported that the birth of a child was highly predictive of an affective episode for men. A chart review of all married bipolar fathers admitted to a National Institute of Mental Health research unit who met research diagnostic criteria for bipolar primary affective disorder revealed that 21 of 39 participants experienced an affective episode within the 9 months before or 1 year after fatherhood; 9 participants experienced a postpartum affective episode. Although the authors emphasized the psychological significance of the event, births are uniquely potent schedule disruptions. Similarly, Dunner et al. (1979) found trends for affective episodes to follow both births and increased responsibilities at work. Healy and Williams (1989) discussed similar examples, such as occasional increased vitality after jet travel (Jauhar & Weller, 1962). Although merely suggestive, such findings are interesting and highlight the importance of studying events that may reflect schedule shifts, in addition to those that convey threat.

If the importance of schedule disruptions is supported, a certain paradox emerges in the life stress literature. If one reviews the history of life stress, it is apparent that early measures were much more oriented toward readjustment, or life changes of any valence, than toward emotional threat (cf. the Holmes-Rahe Readjustment Scale; Holmes & Rahe, 1967). Over time, researchers documented that negative events, particularly severe negative events, are much more powerful in predicting on-
set of depression, whereas positive events are much more potent in explaining recovery (Brown, 1989). These findings led to a shift away from measures that merely assessed readjustment to attempts to fully explore the degree of threat inherent in each event. These attempts have been much more successful than more general investigations of readjustment.

However, it is not clear whether the social zeitgebers theory allows a role for the degree of threat beyond schedule disruption. For example, teachers who finish the school year experience an extreme loss of social zeitgebers, perhaps as influential as the loss of a spouse in terms of schedule disruption; however, one would hardly expect affective episodes to be a typical response to the end of the school year, even among bipolar patients. In other words, schedule disruptions do not appear to fully explain the impact of life stressors, and it may be necessary to account for both threat and schedule disruption. Further research that jointly assesses threat and schedule disruption would allow comparisons of these dimensions. It is unclear whether an additive or interactive model for the two dimensions would be more appropriate.

Finally, if the underlying mechanism linking life events and affective disturbance is the loss of entrainment of certain circadian rhythms, then the length of time required for desynchronization of these rhythms would be critical in determining the time period in which life events could have an impact. Thus, rather than examining the occurrence of life events over an arbitrary period of time (e.g., 6 months before relapse), investigators would focus on the time period before relapse that would be required for various rhythms to decouple and run freely. For example, events that occurred a year or more before relapse would be theoretically irrelevant. Further understanding of this biological mechanism potentially could inform investigation of environmental factors by suggesting the temporal window of life event impact.

Biobehavioral Dysregulation

Depue and his colleagues have proposed that there is a continuum of vulnerability to affective disorder reflected in intra-individual variability in biological regulatory control. People with higher levels of biological, affective, and behavioral variability are seen as having greater deficits in homeostatic mechanisms and are therefore thought to be more vulnerable to serious mood episodes. Correspondingly, individuals who exhibit higher levels of variability at baseline will be more vulnerable to the impact of life events, because they have poorer mechanisms for recovery (Depue & Iacono, 1989; Depue, Krauss, & Spoons, 1987).

More specifically, bipolar patients, as well as subsyndromal cyclothymic individuals, are posited as showing dysregulation in the biobehavioral engagement system. This superordinate biobehavioral system is involved in engaging the person in goal-directed behavior. The biobehavioral engagement system also regulates narrower systems such as mood, incentive-reward motivation, sociability-social potency, desire for excitement, and motor activity- arousal (Depue et al., 1987) and is broadly related to the construct of positive affect (Watson & Tellegen, 1985). Of particular relevance, Gray (1982) posited that the biobehavioral engagement system is sensitive to environmental ex-
periences. Essentially, it is turned on by signals of rewarding goal objects and turned off by signals of frustrating nonreward.

Depue and his colleagues have suggested that people vary both in their average level of behavioral engagement and in their variability around their mean level. Presumably, bipolar patients (and cyclothymics) are prone to dysregulation in this system and hence show greater variability. They experience not only periods in which this system is highly activated but periods in which it is highly inhibited. Theoretically, such individuals are more sensitive to environmental signals of reward, which promote goal-directed activity (and, in its extreme, mania), and to signals of frustrating nonreward, which promote disengagement (and, in its extreme, depression). Deficits in the cortisol inhibitory system are considered one biological variable that reflects dysregulation in behavioral engagement. Bipolar patients are expected to exhibit normative initial cortisol responses to life events. However, they are thought to have much more difficulty with recovery after a life stressor and to take longer to return to a stable baseline (Depue, Kleinman, Davis, Hutchison, & Krauss, 1985).

Empirical support. Depue and his colleagues obtained preliminary support for this model in a group of cyclothymic individuals. Cyclothymic participants, relative to control participants, demonstrated chronic hypersecretion of cortisol across stress and nonstress conditions and exhibited higher variability in cortisol levels over time. These findings were interpreted as an overall weakness in cortisol regulation. More relevant to life event models, cyclothymic participants took significantly longer than control participants to return to baseline cortisol levels after a laboratory stressor (math-challenge task; Depue et al., 1985).

In addition to this well-controlled laboratory paradigm, Depue and his colleagues have assessed these relations in a more naturalistic context (Goplerud & Depue, 1985). They followed cyclothymic and noncyclothymic participants across a 28-day period, assessing exposure to stressful events and mood variability. Symptoms were measured with the Inventory of Behavioral Variation (IBV; Depue et al., 1981), a self-report instrument that taps mood and behavioral variability. Cyclothymic participants did not rate life events as more severe than control participants and reported comparable numbers of severe events, as rated by independent judges on the basis of brief descriptions of the events. Interestingly, groups did not differ on the IBV for 7 days preceding a severe event or the day after a severe event. However, whereas normal participants reported returning to prevent mood and behavioral levels in an average of 2.3 days, cyclothymic participants reported an average recovery duration of 7.7 days. Cognitive bias in appraisal was not the driving factor; cyclothymic participants rated the events in a manner comparable to that of control participants. The authors proposed that the source of vulnerability to stress lies in poorly regulated biological recovery processes.

Interestingly, other psychosocial research examining depressive symptomatology in nonclinical samples is consistent with the notion of dysregulation as an important risk factor in affective conditions. In particular, a number of studies have found that temporally unstable self-esteem (Roberts & Gotlib, 1994; Roberts & Kassel, 1994; Roberts & Monroe, 1992), as well as self-esteem that is highly reactive to daily events (Butler, Ho-
kanson, & Flynn, 1994), prospectively predicts increases in depressive symptoms in interaction with stressful life events. Likewise, daily hassles impose a greater toll on people with affective instability (DeLongis, Folkman, & Lazarus, 1988). Furthermore, people who are vulnerable to depression (by virtue of having a positive life-time history) exhibit greater reactivity in their self-esteem to daily events (Butler et al., 1994), as well as greater instability from day to day in their mood (Roberts & Gotlib, 1994).

In short, the model has received preliminary support and merits further empirical attention to its several premises. One of the most important domains for further empirical investigation remains the application of this model to Bipolar I populations.

Implications for life events research. This model suggests that individuals who exhibit the greatest baseline variability in mood will be the most vulnerable to the effects of life events. Support for this premise is found in the work of Aronson and Shukla (1987), who found that, of a sample of bipolar patients, the individuals most likely to relapse after an earthquake were those who were less stable beforehand. Instability incorporated a number of types of patterns, including chronic subsyndromal symptoms, rapid cycling, and chronic dysphoria concerning environmental circumstances.

Given this theory and preliminary evidence that unstable patients may be the most vulnerable to life events, selection of individuals who exhibit an asymptomatic period before onset would be expected to lead to a less vulnerable sample. In contrast to Depue's model, the only longitudinal study that failed to document a life event effect did not require a well period before onset (McPherson et al., 1993). However, longitudinal studies conducted to date differ on a range of sample characteristics, precluding definitive conclusions. Clearly, there is a need for further empirical attention to differences in life stress vulnerability between initially asymptomatic and subsyndromal groups.

Furthermore, this model suggests that the two poles of the disorder (manic and depressed) are triggered by different types of environmental events. Presumably, positive, rewarding events would activate the behavioral engagement system, which would become hyperactive in mania, whereas negative, goal-frustrating events would lead to a shutdown of this system in depression. In contrast, the studies reviewed earlier all examined negative events of various kinds and found that these events could trigger both depression and mania (e.g., Hunt et al., 1992; Swann et al., 1990).

Behavioral Sensitization and Kindling

Post has drawn on data concerning the longitudinal course of the affective disorders, particularly the impact of biological and environmental factors at various phases of the disorder, in developing a model of how environmental events might be translated into biological processes (Post, 1992; Post, Rubinow, & Ballenger, 1984, 1986). He has highlighted two principles of sensitization taken from neurophysiological research as having potentially important implications for the course of bipolar illness: electrophysiological kindling (a model of induced vulnerability to seizures) and behavioral sensitization (a model of how responses to psychomotor stimulants change over time). These principles are viewed as analogous, but not necessarily homologous, to mechanisms associated with bipolar disorder.

Kindling refers to a process by which seizure disorder can be experimentally induced in animals. Experimental research has demonstrated that repeated, intermittent electrophysiological stimulation to certain brain regions, such as the amygdala, at levels initially unable to produce convulsions eventually results in the development of seizures. After a sufficient number of inductions, seizures can become spontaneous, and, in about a third of the cases, the seizures cycle spontaneously. In these cases, there is an evolution from exogenous triggering of seizures to autonomous occurrence without such external stimulation (Post, 1992; Post et al., 1984, 1986).

Interestingly, Post has integrated two empirical bodies of literature in arguing for a similar disease process in bipolar disorder. First, bipolar illness frequently originates with depressive episodes and progresses to manic episodes, episodes become more severe and frequent over time, and rapid cycling often develops later in the course. Second, Post has suggested that the empirical literature demonstrates that initial episodes of recurrent affective disturbance are more likely to be precipitated by life stress than are later episodes. Like kindling-induced seizures, initial episodes of bipolar disorder may require external triggering, yet, over time, repeated episodes might induce an increased vulnerability to further episodes. As the "scars" of previous episodes accumulate, the risk of spontaneous generation increases. Post hypothesized that episodes eventually occur in the absence of life stress or external agents and become autonomously driven (Post et al., 1984, 1986).

Behavioral sensitization refers to a process by which the effects of psychomotor stimulants become magnified as a consequence of repeated exposure. There is a large body of evidence suggesting that repeated, intermittent exposure to psychomotor stimulants increases vulnerability to their effects, even at progressively smaller levels of ingestion (reverse tolerance). The timing of administration, intermittency, and dosage all influence the degree to which animals develop these sensitization effects. In a similar manner, environmental agents could become conditioned at a physiological level, such that individuals develop more intensive reactions to similar stimuli over time. In particular, behavioral sensitization might be applied to life stress, with the effects of life events being amplified with repeated exposure to similar experiences (e.g., repeated interpersonal losses; Post et al., 1984, 1986).

Furthermore, this model suggests sensitization to both environmental events and affective episodes. Theoretically, not only are the effects of stressors amplified with repetition, but the severity and likelihood of further recurrence are increased with each subsequent episode. As such, "episodes beget episodes" (Post, 1992). Post has suggested that conditioning is involved in these processes. Affective episodes become conditioned to cognitions associated with life stressors or to glucocorticoids associated with depression, and these eventually trigger episodes independently of external agents (Post et al., 1984, 1986).

Empirical support. Although intriguing, it is important to note that this theory has drawn on clinical models of course that do not appear universally applicable. Whereas a substantial number of individuals demonstrate deteriorations in course
over time (Goodwin & Jamison, 1990), this developmental pattern is not always present. For example, approximately one third of bipolar individuals begin their illness with a manic episode rather than a depressive episode (Angst, 1978). Similarly, empirical evidence suggests that the vast majority of rapid cycling individuals return to episode patterns resembling those of nonrapid cycling individuals within a 3-year period (Coryell, Endicott, & Keller, 1992).

Implications for life events research. Both the kindling and sensitization models suggest that life stress will be more important in initial episodes than in later episodes. Post (1992) cited 12 studies as documenting a greater effect for stress in the first episode than in later episodes. However, most of these studies have been based on unipolar samples (e.g., Brown, Harris, & Heptworth, 1994); only 4 studies have specifically assessed bipolar patients (Ambelas, 1979, 1987; Glassner et al., 1979; Okuma & Shimoyama, 1972), and these have tended to be of poor design. Nonetheless, this phenomenon has been theoretically popular and has received other empirical attention (Dunner et al., 1979; Glassner et al., 1979).

Almost all of the studies assessing this temporal pattern, however, have been retrospective and, as such, are vulnerable to the possibility that effort after meaning for external causes is more likely for initial episodes. When a first break occurs, both the patient and his or her family are likely to be highly motivated to favor explanations that imply less risk for recurrence, and hence they will search for an environmental culprit. However, as episodes continue to occur, such attributions may no longer be as reassuring. Furthermore, repeated episodes may become less and less distinct in the memory; individuals may be particularly likely to remember the events concerning the initial onset of an illness, because memory is stronger for the initial and latest elements in a sequence (Loftus & Loftus, 1976). For these reasons, retrospective designs are inadequate in testing this hypothesis.

Two cross-sectional studies to date have compared rates of life events among bipolar patients with one episode versus bipolar patients with repeated episodes (Ambelas, 1979, 1987). These findings have generally been supportive of Post’s model. For example, Ambelas (1987) found that 66% of individuals in their first admission for mania appeared to have experienced an event in the 4 weeks preceding onset, whereas only 20% of individuals in repeat admissions appeared to have experienced an event. However, both studies relied on case notes for documentation of life events. These case notes may reflect both patients’ and doctors’ biases in searching for explanations of a first episode. Further studies using life events interviews are necessary to understand the relationship between recurrence and life events.

As discussed previously, this model also suggests that life events become increasingly potent triggers for affective episodes based on their repetition and subsequent conditioning. Interestingly, recent research has found that major life events that thematically match an ongoing life difficulty have particularly severe consequences in terms of the onset of unipolar depression (Brown, Bifulco, & Harris, 1987). By their very nature, ongoing difficulties involve frequent repetition of aversive experiences (e.g., daily recurrent hassles). Cognitive vulnerabilities might be conceptualized similarly. Particular domains of cognitive sensitivity (e.g., sociotropy) probably represent areas of frequent disappointment and difficulty. Research within nonbipolar samples suggests that negative events that match these vulnerabilities might be particularly toxic (Nietzel & Harris, 1990).

In summary, Post has ascribed critical importance to physiological changes that presumably take place after repeated episodes of disorder and repeated encounters with similar types of stressful life events. Accordingly, it becomes important to carefully attend to the course of disorder, as well as to life event type, magnitude, and frequency of repetition, in investigating etiological links between life stress and bipolar disorder. Interestingly, this line of thinking dovetails with recent work suggesting that some people have developed particular cognitive (e.g., Beck, 1983; Hammen et al., 1985) as well as social–environmental (Brown et al., 1987; Brown, Bifulco, Veiel, & Andrews, 1990) sensitivities. However, there is only preliminary evidence that the impact of life stress varies for individuals at different points in their illness and that events that match particular cognitive or environmental sensitivities have greater impact in bipolar patients. Clearly, further research is necessary to evaluate this model.

Discussion

Although there is little evidence that life events are more prevalent in bipolar patients than in other psychiatric groups, life stress appears to exert an important effect on the course of bipolar illness. That is, elevated rates of life events are found in periods preceding onset of episodes relative to other periods in these individuals’ lives. This effect has been demonstrated repeatedly and, more important, has held up when examined with more careful methodologies. However, several theoretical issues remain unexplored within this literature, and there is a general need to develop more refined models of the types of life stress that are likely to be most influential.

A review of preliminary biological models of bipolar disorder suggests a number of theoretical and methodological considerations for future life stress research. Several types of life stress may be more influential, such as events that disrupt schedules, activate or inhibit behavioral engagement, or might be highly sensitized through a history of repetition. We believe that a more refined approach to life events is required and that these dimensions might serve as a useful first step. An essential priority for this field will be the development and assessment of new and theoretically relevant scales. Established interview approaches (e.g., LEDS; Brown & Harris, 1978a) should be used for rating these dimensions.

In addition, the literature reveals several clues as to which individuals will be most vulnerable to the effects of stress. On the basis of Depue’s research, baseline variability in mood and behavioral engagement will be an important predictor. However, paradoxically, Post’s research indicates that patients with the longest and most severe history of mood shifts may experience more autonomous episodes. However, the difference between these models may reflect the populations in which they were developed. Depue has worked largely with nonclinical samples, in which the more severely disturbed individuals are
cyclothymic and may not require clinical attention. In contrast, Post has worked with clinical populations, often including individuals who have particularly severe forms of the disorder. Therefore, there appears to be a middle group of participants who are relatively severely disturbed within a nonclinical context but who are less severely disturbed within a clinical context; such individuals are likely to be most susceptible to the effects of stress. These lines of research indicate that, more so than many other disease processes, there is a particular need for attention to course and severity in bipolar disorder.

Although psychosocial moderators of life stress, such as self-esteem, social support, and family functioning (Brown, Bifulco, & Andrews, 1990; Miller et al., 1992; Roberts & Monroe, 1994), appear useful in studies of unipolar depression, researchers need to be thoughtful in whether and how such factors might be integrated into the emerging understanding of bipolar disorder. Vulnerability factors and pathogenic processes found in unipolar depression will not necessarily operate in the same manner in bipolar disorder, even for depressive phases. Ideally, there should be an ongoing conceptual dialogue involving the growing knowledge bases concerning biological, clinical, and psychosocial processes in bipolar disorder. For example, researchers have found that certain types of cognitive sensitivities increase the risk of unipolar depression when linked with thematically congruent stressors (Hammen, Ellicott, & Gitlin, 1989; Hammen et al., 1992, 1985; Segal, Shaw, Vella, & Katz, 1992). Does such moderation operate in bipolar disorder? Although thematically related events would not seem to have special impact on zeitgeber disruption, they could be conceptualized as being more highly conditioned with depressive experiences (Post, 1992) or as serving as a stronger signal of frustrating nonreward (Depue et al., 1987). If so, they would probably affect depressive, but not manic, phases of the disorder. Given the strong biological underpinnings of bipolar disorder, we believe that it is incumbent on researchers to attempt such conceptual linkages between psychosocial and biological processes and to use them in guiding their research.

Beyond theoretical development, several considerations are recommended to facilitate cross-study comparisons. Future research must take care to fully report the types of life stress correlated with relapse, the sample severity and course, and the timing of life stress. Because different types of events might be important in depressive versus manic phases of the disorder, separate analyses should be conducted for each pole and pooled only if similar relations are established. Furthermore, life event assessment needs to be based on established interview methods (e.g., LEDS; Brown & Harris, 1978a), with careful attention paid to the independence of events from psychopathology. Finally, it is unclear whether an additive model of life events is applicable to bipolar disorder and what severity of events has an impact. These issues need to be explored empirically, as was done in Brown’s remarkably thorough and systematic research on unipolar depression (Brown & Harris, 1978b, 1989a). We hope that this review will help facilitate such research.

References


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