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Life Events and Relapse in Established Bipolar Affective Disorder

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A New Zealand cohort of 58 patients with bipolar affective disorder was studied prospectively with three-monthly interviews in order to determine the relationship between life events and their relapses. Careful attention was paid to dating life events and the earliest signs of relapse and to assessing the independence of life events from the illness. No statistically significant association was found between life events and the likelihood of relapses, either mania or depression, for the 71% of patients who experienced at least one relapse during the two-year study. This finding is at variance with a companion study, with identical methodology, which found a small increase of life events before relapse. These data add further weight to the previous reports that life events are significant precipitants of bipolar illness only for earlier episodes in the course of this chronic disorder.

Most workers investigating the relationship between life events and unipolar depressive illness have found a clear link (Paykel *et al*, 1969; Paykel, 1978; Brown *et al*, 1973; Lloyd, 1981; Brugha & Conroy, 1985; Cornell *et al*, 1985), although not all (Tennant, 1983). The role of life events in precipitating relapses in bipolar affective disorder has been much less studied. The inconsistent findings from the small literature on life events and bipolar relapse are easily explained by methodological differences. Different diagnostic criteria have been used, different time periods studied, and while some authors cluster all relapses together, others separate manic relapses from depressions or study manic episodes only (Dunner *et al*, 1979; Glassner & Haldipur, 1983; Bidzinska, 1984; Ambelas, 1987; Sclare & Creed, 1990). Some studies have small numbers, raising questions of statistical power (Chung *et al*, 1986 ($n=14$); Lieberman & Strauss, 1984 ($n=3$)).

Dating the onset of illness is difficult in studies with a retrospective design (Paykel, 1983). Illness onset is unlikely to coincide with hospital admission, the point of reference sometimes used (Kennedy *et al*, 1983; Ambelas, 1987). Retrospective studies are often limited by inaccurate recall of events and a tendency for subjects to cluster events or date them close to relapse in order to ascribe some sense of meaning to their illness (Brown & Harris, 1978; Paykel, 1983; Tennant, 1983). These research problems are minimised by prospective designs with accurate dating and classification of relapses and life events. Many studies fail to separate dependent events, that is those likely to have occurred as a consequence of the patient's illness, from independent events (Hall *et al*, 1977; Glassner & Haldipur, 1983; Bidzinska, 1984; Ellicott *et al*, 1990).

Control groups are always considered desirable in epidemiological research and many of the life event studies of bipolar illness have taken the trouble to gather data from various control groups, for example surgical patients (Ambelas, 1979; Kennedy *et al*, 1983; Chung *et al*, 1986), or age- and sex-matched normal controls (Glassner *et al*, 1979; Bidzinska, 1984; Chung *et al*, 1986). However, it is hard to interpret the significance of control data where an illness with a strong genetic loading, like bipolar affective disorder, is compared with normal people or those receiving a cholecystectomy. Such a design is useful to answer the question whether bipolar patients have more or fewer life events than the control group, but not for assessing the role of life events in either onset or relapse of bipolar patients. For that, each patient must serve as their own control.

Goodwin & Jamison (1990) reviewed ten retrospective studies and found an association between life events and relapse in nine of the ten. Since their review, the retrospective study by Sclare & Creed (1990) showed no relationship between life events and the onset of mania. They found no difference in the number of patients experiencing at least one independent event in the six months before onset of manic relapse, from that in the six months after discharge. They noted a trend for patients with a duration of illness of less than five years to experience more severe events.

Three published studies have used a prospective design. Hall *et al* (1977) used a questionnaire-interview method to study life events in a group of previously admitted bipolar-I patients on lithium, excluding the rapid cyclers. There was no difference between the number of life events reported by patients at visits when they had an affective disturbance and those where they were euthymic.

Just under half of the 38 (45%) became unwell over ten months: 16% manic, 21% depressed, and 8% both. Neither did the relapsing patients report more events than those who remained well. This study did not use a structured diagnostic interview to determine relapse. Relapse was defined as a four-week deviation from normal mood on the 7-point global rating scale used routinely in their clinic. This study has been criticised by Ellicott *et al* (1990) for not controlling for medication. No information was provided about the duration of the patient's illness.

Ellicott and colleagues followed 61 bipolar out-patients with three-monthly life event interviews, either in person or by telephone. Relapse was assessed with DSM-III-R criteria by the clinic psychiatrists (American Psychiatric Association, 1987). Patients described more life events before relapse, an effect not explained by differences in medication (Ellicott *et al*, 1990). They used survival analysis with a variant of Cox's proportional hazards model with life events as a time-dependent covariate. Although they do not give duration of illness, the subjects were out-patients followed for at least four months. These authors suggested that there may be subgroups of patients who are vulnerable to life events, perhaps related to the meaning of the event for the individual, a point that has been made anecdotally by others (Ambelas & George, 1988; Brown *et al*, 1987).

Finally, Hunt *et al* (1992) in London followed 62 bipolar patients for two years, with three-monthly interviews to assess mental state and life events. A small increase in life events in the four weeks before relapse, manic and depressive, was found. Only one in five relapses was preceded by a severe life event and only 14% of severe events were followed by a relapse.

This paper presents the results of a two-year prospective New Zealand study of life events and relapse, using an identical design to that of the London study by Hunt *et al* (1992).

Method

The cohort was established through a review of regional hospital case notes and a subsequent diagnostic interview. The case notes of all admissions to psychiatric in-patient units in the Dunedin area of New Zealand from 1 January 1985 to 31 December 1987 were examined. Sixty-five bipolar patients identified as possibly suffering from bipolar affective disorder by this review were interviewed in 1989 using the Schedule for Affective Disorders and Schizophrenia, lifetime version (SADS-L; Endicott & Spitzer, 1978). A Research Diagnostic Criteria (RDC) diagnosis of bipolar affective disorder (Spitzer *et al*, 1978) was confirmed in 58, who were then followed prospectively for two years. Cohort subjects underwent a research interview at three-monthly intervals and at relapse using SADS - Part I (the current version of the Schedule for Affective Disorders and Schizophrenia; Endicott & Spitzer, 1978). The Hamilton Rating Scale for Depression (HRSD, 21-item version; Hamilton, 1960) and the Young Mania Rating Scale (Young *et al*, 1978) were also completed at each interview. The majority of patients, four-fifths, chose to vest their clinical care in the hands of the research team for the duration of the study. Most of these patients were seen more frequently, usually fortnightly or monthly, as determined by clinical need. There was no specified medication regime; the protocol required that they receive the medication deemed optimal by their treating psychiatrist.

All manic, hypomanic, major, and minor depressive relapses meeting RDC were documented and carefully dated. Onset of relapse was taken from the time of the first clear symptom of each illness, confirmed by one of the two research doctors.

Life events were assessed at the three-monthly research interviews with the Interview for Recent Life Events, a semi-structured interview which measures the independence and negative impact of each event (Paykel *et al*, 1971). In the analysis of the life event data, only independent life events were considered. Although dependent events are also important in the evolution of various illnesses (Miller *et al*, 1986), this project was designed to measure the effect of environmental stress in causing relapse, rather than the converse.

An attempt was made to assess the subject's compliance with prescribed medication using clinical assessment and a questionnaire.

A number of statistical comparisons were made. (a) Life event rates for cohort members who relapsed were compared with rates for those who did not relapse at all over the study. (b) Considering only those cohort members who relapsed, data from the pre-relapse periods were contrasted with their own three-month control periods where no relapse occurred. Thus each patient served as their own control. We defined the three-month control periods as commencing when the patient was in a euthymic state, as assessed by SADS-I, the HRSD, and the Young Mania Rating Scale; they ended three months before the onset of relapse. One-month pre-relapse and control periods were defined in a similar fashion. The mean number of life events occurring in the three months before the onset of manic or depressive relapse was compared with the mean number of life events during the control three months. An alternative, more simple method of analysis, using predetermined calendar quarters, was rejected, as relapses and life events could take place during any week of the year. Student's *t*-tests were used to compare the means.

Cox's proportional hazards regression was used to see if there was any relationship between life events and time of relapse. All euthymic periods for subjects were treated as if they were independent. Cumulative life events stress was defined as the sum of the reciprocals of the times before the terminal event (either relapse or completion of the study) at which the life events occurred. This score was entered on its own, after weighting for severity of the event and association with the illness.

Results

At intake, the cohort comprised 58 patients: 28 men and 30 women. All were RDC bipolar I. Their mean age was 37 years (range 18–64 years) and their mean duration of illness was 13 years (range 2–32 years) at the time of first interview; only six patients (10.3%) had an illness of less than five years' duration. Patients had experienced an average of 5.0 previous manic/hypomanic episodes (s.d. 3.7, range 1–16), while the mean number of depressions, major or minor, was 4.1 (s.d. 3.7, range 0–16). The mean number of total episodes was 9.1 (s.d. 6.0, range 1–32). One patient had only one episode, and ten patients three or less.

Forty-nine patients completed the full two-year follow-up: 26 men and 23 women. During the two years, two patients committed suicide, four moved away from the area, and three discontinued follow-up for other reasons. The incomplete data for these nine patients are included up to their exit from the study.

Most patients, 41/58 (71%), relapsed at least once during the two-year follow-up. They suffered a total of 93 relapses (mean 2.3, range 1–8). Thirty-three patients experienced 61 episodes of mania or hypomania, while 21 suffered from 32 depressive relapses, major or minor. Mixed affective episodes were classified with manic episodes.

The mean number of independent life events experienced over the entire two-year follow-up study by those who relapsed did not differ significantly from that of the non-relapsers, 9.31 and 9.92 respectively. There were no differences in the types of events experienced by the two groups. The commonest categories of life events for all participants related to work, health, family, and social life.

For those who relapsed, the mean number of life events of any severity occurring in the three months before any relapse, manic or depressive, did not differ significantly from the three-month control periods (see Table 1). Neither was there a significant difference when only major and negative events were included. The non-significant trend was in the direction of more life events in the control than pre-relapse periods.

Table 1
Life events preceding relapse v. control non-relapse periods of relapsing patients (moderate and severe independent events only)

	One month: mean (s.d.)	Three months: mean (s.d.)	% events over three months which occurred in the one month before relapse
Mania and hypomania	0.28 (0.09)	0.70 (0.16)	40.0
Control	0.22 (0.03)	0.64 (0.09)	34.4
Test statistic	$t=0.71$ (NS)	$t=0.35$ (NS)	
Depression (major and minor)	0.29 (0.10)	0.54 (0.13)	53.7
Control	0.22 (0.03)	0.64 (0.09)	34.4
Test statistic	$t=0.85$ (NS)	$t=0.66$ (NS)	
All relapses (combined)	0.30 (0.07)	0.62 (0.11)	48.4
Control	0.22 (0.03)	0.64 (0.09)	34.4
Test statistic	$t=1.14$ (NS)	$t=0.15$ (NS)	

The mean number of independent events of all degrees of severity occurring in the one month before any relapse did not differ statistically from that occurring during control months. Neither were there differences between the mean number of independent events, moderate to severe, one month before relapse (mania/hypomania and depression) and control one-month periods (see Table 1). However, the consistent (non-significant) pattern was in the direction of more events in the pre-relapse than control periods.

Manic and depressive relapses were examined separately. For neither mania/hypomania nor depression did the mean number of independent moderate to severe events occurring in the three months before a relapse differ from the three-month control period means. The proportions of events which took place in the third of the three months, that is the one month before relapse, are shown in Table 1. For pre-relapse periods, this proportion was numerically more than the one-third expected if events were spread randomly over the whole period, although not statistically greater. For the control data, the proportion of events in the third month was one-third. This suggests a possible clustering of events in the one month before relapse.

The number of relapses preceded by at least one independent event, moderate to severe, in the previous month was examined. For manic/hypomanic relapses, 14/61 (23%) were preceded by an event; for depression 9/32 (28%), and for all relapses, manic and depressive combined, one-quarter (25%) were preceded by at least one life event. The Cox's proportional hazards regression showed that none of the measures of life event stress were significantly related to time of relapse.

One case from the present series illustrates the endurance of appalling adversity without relapse. A 20-year-old man with bipolar disorder lost control of his motorbike, broke his neck, and became tetraplegic. He was not intoxicated. His lithium was continued. He later developed leukaemia and died 18 months into the study. Although he had not been particularly stable before coming into the study, he did not suffer a relapse after his accident. He attributed this to his fundamentalist religion, adopted after his accident. His girlfriend supported him until his death.

Discussion

The design strengths of this study are the prospective time frame, the attention to dating of life events and the earliest symptoms of relapse, and the use of structured interviews for assessing both relapse and life events.

The number of life events occurring one or three months before relapse did not differ statistically from the control non-relapse months from the same patients, although Table 1 shows a non-significant

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pattern of more life events in the third month before relapse than in the control months. This raises the question whether the non-significant result was because the Dunedin cohort was too small and followed for too short a time period. The sample size gave an 80% power to detect a difference of 0.15–0.20 life events per month ($P<0.05$). This is adequate to detect a clinically significant finding.

The London study (Hunt *et al*, 1992) with identical design followed a group of 62 RDC bipolar patients prospectively for two years, defining control periods differently. Significantly more severe events were found in the pre-relapse than control periods, for both manic and depressive relapses, and most of the pre-relapse events were clustered into the one month before relapse. The Dunedin data were reanalysed using the London definition of control periods; this did not alter the non-significance of our findings.

An unsuccessful attempt was made to assess the patients' compliance with recommended treatments, which could confound a link between life events and the course of illness. At one phase the cohort was given a simple compliance questionnaire designed to assess their attitudes towards medication. Less than half completed it, perhaps because most were under the care of the research team and may have felt awkward about revealing their attitudes. The protocol required optimal treatment be given to participants. When poor compliance was suspected, vigorous effort was made to improve the patients' understanding and drug-taking behaviour. It is likely that compliance varies over time in a complex manner not fully understood (Haynes *et al*, 1979).

The question arises of how to explain the discrepancy between the Dunedin study, which found no association between life events and relapse, and that of the London study, which found a small but statistically significant increase in event rate in the four weeks before relapses, both manic and depressive (Hunt *et al*, 1992). As both projects shared identical design and were carried out in close collaboration between all researchers, discrepant results cannot be dismissed on methodological grounds.

The Dunedin cohort appeared to be a more seriously ill group. They had an average of 1.7 relapses over the two-year prospective study, 1.1 episodes of mania, 0.6 of depression, and 71% had at least one relapse; the comparable figures for the London cohort are 0.8, 0.6, 0.2, and 58%. The Dunedin group had a more established illness profile, as shown by the number of episodes experienced at their entry to the cohort study; Dunedin patients had a mean of 9.1 episodes (5.0 manic and 4.1 depressive) while the London cohort had a mean of 7.3 episodes (s.d. 4.9) (5.3 (s.d. 4.1) manic and 2.0 (s.d. 2.4) depressive).

Several previous reports have suggested that life events are more important in early episodes than later in the course of bipolar disorder. An early suggestion of this pattern was made by Stern (1944). Dunner *et al* (1979), in a retrospective approach which would not be acceptable now, asked patients about life events before their onset of illness up to 25 years earlier and found half recalled life events before their first episode but few did for subsequent relapses. Ambelas (1987) compared a group of first-episode manic patients with manic patients in later episodes and surgical controls, and found that the first manic episodes were linked more frequently with life events than later manic relapses and the control surgical conditions. Bidzinska (1984) reported that the three most recent relapses of bipolar disorder were preceded by life events less often than the first three. All these studies suggest that life events may be important precipitants of early episodes of bipolar affective disorder but become less important as the illness progresses. Such an increasingly autonomous course is proposed by the kindling model (Post *et al*, 1984). In addition, the constriction of social networks that tends to occur with a longer duration of bipolar illness may result in reduced exposure to life events in this group (Bidzinska, 1984; Sclare & Creed, 1990; Romans & McPherson, 1992). This points to reduced social activity and progressive withdrawal from usual work and recreational activities as the illness progresses. Many patients describe how their self-confidence is progressively eroded with each relapse. Thus, there is a plausible social explanation for the failure to find a life events link to relapse in well established bipolar disorder, which needs to be considered alongside the proposed neurophysiological explanation given by the kindling model.

There was some difficulty with recruitment at the stage of the diagnostic interview before entry into the study. In Dunedin, 30% of those identified by the chart review were not available for the diagnostic interview: 12 had moved from the area, 13 refused outright, and one died from septicaemia consequent on osteomyelitis after agreeing to participate, but before her assessment. Such a drop-out rate may introduce differential bias between the final study group and a true representative sample.

A theoretically significant difference is the gender composition of the two cohorts: Dunedin 52% women, and London 74% women. There has been no evidence produced to date to suggest that bipolar women are more likely to relapse in the face of an untoward life event than men.

There were socio-economic differences between the two samples. The London cohort was drawn

from the deprived inner-city borough of Hackney, and had a large proportion (34%) of non-white subjects, while Dunedin is a university town with little poverty or social deprivation. The living circumstances of many of the London cohort were substantially more marginal than those of the Dunedin patients. A lower threshold to cause relapse might exist as a consequence of their chronic difficulties. Further research is needed to assess the differential impact of life events on men and women in different socio-economic groups.

Three conclusions can be taken from the pair of studies considered together. Firstly, the time of interest is the one month before relapse, unlike unipolar depressive illnesses where six months is implicated. This finding has the potential for simplifying future research, and brings bipolar disorder more in line with schizophrenia, where three weeks is seen as the relevant time-frame for life event stress precipitating a relapse. Secondly, the number of previous episodes and possibly the patient's socio-economic conditions are relevant to the impact of life events on the course of bipolar illness. Thirdly, the role of life events precipitating relapse in established bipolar disorder is small, of theoretical rather than clinical significance.

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