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The Cumulative Impact of Nonsevere Life Events Predicts Depression Recurrence During Maintenance Treatment with Interpersonal Psychotherapy (IPT-M)

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Abstract

While much research has focused on the role of severe life events as risk factors for depression onset, less is known about the relationship between nonsevere life events and depression recurrence. The current study examined the cumulative effects of nonsevere and positive life events on depression recurrence in an outpatient sample of recurrently depressed women treated to remission with interpersonal psychotherapy (IPT). A Cox proportional hazards model was used to test this relationship in 124 adult women who entered into the maintenance phase of IPT treatment (IPT-M) and completed at least one Life Events and Difficulties Schedule (LEDS) interview. The cumulative experience of nonsevere life events that were subject- or joint-focused and non-independent was significantly related to depression recurrence during the maintenance treatment phase. None of the other event categories were significantly related to depression recurrence. These findings may help to clarify the mechanisms by which life events contribute to depression recurrence and to guide the development of more efficacious maintenance treatments.

Keywords

Major Depressive Disorder; Life Events and Difficulties Schedule; Interpersonal Psychotherapy; stress sensitization; stress generation

It is now widely recognized that, for a majority of patients, unipolar depression represents a recurrent disorder (Frank & Kupfer, 2003; Keller, 2003) that is associated with high levels of lifetime morbidity (Donohue & Pincus, 2007; Wells et al., 1989). Because the risk of depression recurrence increases with each subsequent lifetime episode (Angst, 1992; Thase, 1990), a better understanding of the factors that predict depression recurrence holds tremendous clinical

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significance. Research conducted over the past 15 years has underscored the importance of severe life stress in predicting initial lifetime depression onset (for example: Brown, 1993; Brown & Harris 1978; Kendler, Kessler, Neale, Heath, & Eaves, 1993). Yet, much less is known regarding the potentially complex role that life stress may play in predicting subsequent depression recurrence over the lifetime course of this disorder. Moreover, relatively little is known about the precise role that nonsevere life stress may play in predicting risk for depression recurrence (for e.g., see Monroe and Harkness, 2005).

Few studies have examined directly the role of nonsevere life stress on depression recurrence. In one study, Ormel and colleagues (2001) found that nonsevere life events predicted depression recurrence but not first episode onset in a community sample of subsyndromal and depressed elderly. Similarly, Monroe and colleagues (1996, 2006) found a relationship between nonsevere life events and increased risk of depressive episode recurrence in a clinical sample of depressed patients receiving maintenance pharmacologic depression treatment.

While these studies suggest that nonsevere life events may be important in predicting depression recurrence, much work remains to be done to understand this relationship. For example, Monroe and colleagues found that nonsevere events that were “fateful” (outside of the person's control) were associated with depression recurrence. This finding is in line with previous work showing that life stress that is beyond the control of the individual is particularly salient for depression onset (Stueve, Dohrenwend, & Skodol, 1998). However, other studies have suggested that individuals with depressive disorders increase their likelihood of relapse or recurrence by creating interpersonal contexts that are stressful (Hammen, 1991; Hammen, 2006). This level of interpersonal dysfunction may be particularly salient for individuals with a lifetime history of recurrent depressive episodes (Harkness, Monroe, Simons, & Thase, 1999).

Finally, relatively little is known about how depression treatment impacts the relationship between life stress and depression recurrence. In a recent study examining life event data collected in the Treatment of Depression Collaborative Research Program, patients in the medication conditions were significantly more reactive (defined by changes in depressive symptoms) to stressful life events following termination of treatment than the patients in the psychotherapy conditions (Hawley, Ho, Zuroff, & Blatt, 2007). Monroe and colleagues (1996, 2006) examined the relationship between life events and depression recurrence in a sample of recurrently depressed patients. In this study, nonsevere life events were associated with a greater risk of depression recurrence during maintenance treatment, but only in those patients assigned to continue antidepressant medications during the maintenance treatment phase (and not among patients assigned to discontinue antidepressant medications, a group that ultimately showed extremely high rates of recurrence).

In another prospective maintenance treatment study of recurrently depressed women, Harkness and colleagues (2002) showed that severe life events were not predictive of episode recurrence in the context of treatment with maintenance interpersonal psychotherapy (IPT-M). However, the authors did find a significant association between severe life events and time to index depressive episode onset, a period of time in which the women were not receiving treatment. The authors suggested that IPT-M may be protective of episode recurrence by decreasing the potency of severe life stress to precipitate further depressive episodes. This study used a sophisticated analytic strategy that tested the additive effects of events over time. Although the authors also tested a model that included all life events regardless of severity, they did not specifically examine the effects of nonsevere life events on time to recurrence. Taken together, all four studies (Harkness et al., 2002; Hawley, Ho Zuroff, & Blatt, 2007; Monroe, Roberts, Kupfer, & Frank, 1996; Monroe et al., 2006) suggest that there may be differential effects of

treatment on the experience of life stress and how life stress may be related to depression recurrence.

Methodological challenges of accurately measuring and analyzing nonsevere life events present other complicating factors to examining the life event-depression relationship. First, a review of previous studies highlights the need for choosing measurement strategies that are sensitive enough to capture both severe and nonsevere life stress. Second, one must consider various study designs used to capture the experience and impact of life events. A majority of published studies divide the length of the interview period into segments and compare the rates of events in each segment to determine a “risk period.” Other studies only examine events that occur during a pre-defined time period (e.g., six weeks prior to recurrence). While this may be an important way to look at the effects of single, high-impact events that occur prior to episode onset, these models do not address the possible additive nature that life events may have over time or the broader temporal aspects of the association between life events and depression.

Assessing the cumulative impact of multiple life events that occur over time may be particularly important when evaluating the impact of nonsevere events, which occur with relatively greater frequency than severe life events. The accumulation of multiple, nonsevere life stressors may have a “wearing down” effect on an individual's reserves (Frank et al., 1996; Surtees & Ingham, 1980). Consequently, the impact of any single nonsevere event may, in part, depend upon the broader context of previously-experienced life stress. Thus, statistical approaches that test the cumulative impact of life events, rather than evaluating single events in isolation, may allow for a more global picture of frequent yet nonsevere life event stress burden.

Most studies examining life events and depression have focused on the role of negative life events. In contrast, little is known about the effect of positive life events in relationship to depression recurrence. There is some evidence that positive life events may be associated with depression remission (Brown, 1993; Leenstra, Ormel, & Giel, 1995). However, it is unclear whether positive life events may be protective from depression relapse or recurrence. Just as the experience of negative life events may increase the risk of relapse or recurrence, the cumulative effects of positive life events may also be important. In particular, active treatment with IPT may facilitate the generation of positive life events because of the treatment's focus on improving interpersonal functioning and developing more effective coping strategies. Therefore, we also wanted to examine the possible protective effects of positive life events.

In the current study, we sought to examine the cumulative effects of nonsevere and positive life events on depression recurrence in an outpatient sample of recurrently depressed women treated to remission with IPT. Women were evaluated over a two-year period of maintenance interpersonal psychotherapy (IPT-M), with the experience and timing of life events assessed via annual Life Events and Difficulties (LEDS) interviews (Brown & Harris, 1978). We utilized Cox regression analyses to model the timing of events as well as the cumulative effects of multiple events over the entire maintenance period. We classified events into three mutually exclusive categories that accounted for both the severity of the event as well as any positive meaning of the event. We then used these categories to test the relationship between the cumulative experience of these types of events and recurrence during the maintenance phase of treatment with IPT-M.

The current study was developed to test two primary hypotheses: 1) the cumulative experience of nonsevere events during the maintenance treatment phase will be associated with decreased time to episode recurrence (increased risk of recurrence), and 2) the cumulative experience of positive events during maintenance treatment will be associated with an increased time to episode recurrence (protective effect/decreased risk of recurrence). In order to evaluate the independent effects of nonsevere and positive life events, we tested these hypotheses within

models that simultaneously accounted for the cumulative impact of severe, nonsevere, and positive life events as well as patient characteristics relevant to recurrence risk. A secondary aim of the study was to explore the nature of those events most associated with episode recurrence. Drawing from the extant literature (for example, Monroe et al., 2006), we evaluated two additional event-related dimensions: Focus (or the extent to which the event is focused on the subject or on others) and Independence (or the extent to which event occurrence was likely to be independent of the subject's influence). We then tested this classification of events in a *post hoc* analysis of the above cumulative model.

Method

The data used in the current study were drawn from the Maintenance Psychotherapy in Recurrent Depression study (MPRD; MH 49115, E. Frank, PI). The MPRD study was developed to examine the effectiveness of varying “doses” of Interpersonal Psychotherapy in the prevention of relapse in recurrent MDD. The University of Pittsburgh Institutional Review Board approved the study protocol. All patients provided written informed consent prior to their participation in any research procedures.

Study sample and design

The study population consisted of 124 adult women with a history of recurrent unipolar depression who were treated to remission and entered the maintenance treatment phase of the MPRD protocol. Inclusion criteria for the parent study were: 1) females aged 20 to 60; 2) currently in an episode of depression; 3) at least one prior episode of major depression within the last two and a half years; 4) a remission period of at least 10 but not more than 130 weeks between the index and previous episodes; 5) and Hamilton Rating Scale for Depression (17-item) score of 15 or above. Exclusion criteria were 1) meeting criteria for another Axis I disorder, except comorbid anxiety or eating disorders NOS; 2) drug or alcohol abuse within the past two years; 3) history of manic episodes; 4) meeting full criteria for borderline or anti-social personality disorders; 5) suicidal or psychotic symptoms requiring inpatient hospitalization; 6) early onset dysthymia; 7) presence of significant medical illness.

Procedures and design of the MPRD study are described in detail elsewhere (Frank et al, 2000; Frank et al., 2007). Briefly, patients entered the first phase of the protocol in an acute major depressive episode and began treatment with interpersonal psychotherapy (IPT). Following remission of the index episode (defined as three consecutive weeks of Hamilton Rating Scale for Depression (HRSD) scores of ≤ 7), patients were entered into an 8-week continuation phase. Patients who did not remit with psychotherapy alone were given combination treatment of IPT and pharmacotherapy. This treatment continued until remission at which point they entered into the continuation phase of 20 weeks. If they remained in remission during the 20 weeks, they were then tapered off of the medication and received IPT alone for 4 to 6 weeks prior to entering the two-year maintenance treatment phase. Patients were discontinued from the study if they failed to remit after 24 weeks of treatment or if they experienced a relapse of depressive symptoms during the continuation (or medication taper) phase. Patients who remained in remission during the continuation phase entered the maintenance phase of preventive psychotherapy (IPT-M) for a period of two years or until recurrence (defined as two consecutive HRSD scores of ≥ 15 and meeting DSM-IV criteria for a depressive episode as determined by a psychiatrist not affiliated with the study). Once entered into the maintenance treatment phase, all patients were randomly assigned to receive weekly, bi-weekly, or monthly IPT-M.

Measures

Schedule for Affective Disorders and Schizophrenia (SADS; Endicott & Spitzer, 1978)—The SADS is a semi-structured diagnostic interview developed for use in research studies of affective and schizophrenic disorders. This instrument was used prior to 1994, at which time it was replaced by the Structured Clinical Interview for DSM-IV.

Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1994)—The SCID is a structured diagnostic interview that was designed to correspond to DSM-IV diagnoses. The SCID has shown to be both reliable and valid in diagnosing Axis I disorders (Williams et al., 1992). Diagnostic evaluators were Masters or PhD level social workers, psychologists, or psychiatric nurses who underwent extensive training, certification and clinic reliability checks. All SADS and SCID diagnostic data were posted to the study coordinator and one study investigator within two days of patient interview to verify the clinical diagnosis.

Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960)—The HRSD is a symptom assessment tool for use with persons diagnosed with depressive disorders. Patients were assessed at each clinic visit. The HRSD was used to define treatment remission and recurrence. Inter-rater reliability levels for the MPRD study exceeded .90.

Life Event and Difficulties Schedule (LEDS; Brown & Harris, 1978)—The LEDS instrument is a semi-structured interview that measures both the occurrence and the likely contextual meaning of life events and difficulties. Ratings are based on “how a typical person would be expected to think/feel about an event” based on the situational context. The ratings do not take the subject’s feelings, reactions, or biases into account. All LEDS interviews were conducted while the participant was in remission of the depressive episode in order to prevent bias in recall of events (Bebbington, 1986). LEDS interviews were conducted once prior to entrance into maintenance phase and once yearly during maintenance treatment.

Trained raters used the Bedford College criteria to rate the severity of identified life events on a four-point scale (marked, moderate, some, little/none). Each event was rated in terms of long-term threat (peak threat/unpleasantness 10 to 14 days after start of an event). Potential positive aspects of each event were also rated on a four-point long-term contextual positivity scale (marked, moderate, some, little/none). All ratings were verified at consensus meetings that consisted of the LEDS research team director (BA) and bachelor and master's level interviewers that had received extensive training from George Brown and Tirril Harris, either at Bedford College, London or at WPIC in Pittsburgh. Consensus panel raters were blind to onset and offset dates of depressive episodes. All discrepancies among raters were resolved through consensus, guided by the LEDS “dictionary” that contains over 5,000 case vignettes to provide anchoring examples and standardization. Previous work with the LEDS has indicated sufficient interrater reliabilities for threat ratings ($k = .86$; Harkness et al., 2002) and positivity ratings ($k = .73$ Brown, 1993; $k > .60$ Leenstra et al., 1995).

In order to simultaneously account for both long-term contextual positivity ratings and long-term threat ratings of each event, ratings were divided into three distinct categories based on Tu and colleagues (2000): Severe events, nonsevere events, and positive events. Severe level events are those events that are rated as marked or moderate on long-term threat, and some or none on long-term positivity. The second category, nonsevere events, constitutes events that are rated as some or none on long-term threat and some or none on long-term positivity. The final category consists of positive events. Positive events are rated as some or none on long-term threat and marked or moderate on long-term positivity. A category consisting of events rated marked or moderate on long-term threat and marked or moderate on long-term positivity

was also created; only three events fell into this category however, and were thus excluded from the analyses. See Table 1 for examples of each category of events.

One advantage of using the LEDS is that it classifies events on a number of different dimensions, allowing investigators to more precisely categorize types of events. Two additional dimensions, focus and independence, are included as part of the LEDS ratings. Focus refers to the extent to which the event is focused on the subject or on others. An event was considered subject-focused if the event occurred to the subject or jointly to the subject and someone else. The event was considered other-focused if it was focused on a possession or pet or focused on another person. Independence identifies the extent to which the event occurrence was likely to be independent of the subject's influence. An event was rated as 'independent' if the event was judged to be totally independent or there was unlikely to be influence from the subject. An event was rated as 'possibly independent' (alternatively referred to as 'non-independent' for conceptual clarity) if the event seemed to reflect compliance with an external situation, an intentional act, negligence or carelessness, ending contact with another, or if the event fell in the love/sex domain.

Data analytic plan

All data were analyzed using SAS[®] for Windows version 8 (SAS Institute Inc, Carey, NC). To test the primary hypotheses we utilized the Cox proportional hazards model (Kalbfleisch & Prentice, 2002, pp.33) with each of the three categories of life events (severe, nonsevere, positive) included in the model as time-dependent covariates. The Cox model was used to test the effect of life events on time to recurrence during maintenance IPT treatment (hypotheses 1 and 2). The date at which the patient entered the maintenance phase of treatment was the starting point of the latency process and the end point was the date of recurrence or the end of the study. In this Cox model, a negative value for the regression parameter denotes that the event increases time to *recurrence*, or prolongs time in the maintenance phase, while a positive value for the parameter indicates that the event is increasing the risk for recurrence. Age at time of study, duration of index episode, age of first depression onset, pre-maintenance HRSD score, the use of adjunctive antidepressant medication during the acute phase of treatment, and the average number of treatment sessions per week during maintenance treatment were also included in the model as covariates to control for potential confounding effects. If a patient did not experience a recurrence, the response was treated as censored.

Results

Sample characteristics

Of the 233 women enrolled in the MPRD study, 135 achieved remission and entered into the maintenance phase of treatment. Seven of these women had a Bipolar II diagnosis and were excluded from the analyses. One hundred twenty-four of the women participated in at least one LEDS interview and were therefore included in the current analyses. Demographic and clinical characteristics are shown in Table 2.

Of the 124 women entered in the maintenance phase who had LEDS data, 67 women completed the study without a recurrence, 29 experienced a recurrence, and 28 terminated treatment prior to the end of the study. On average, those who terminated during the maintenance phase were younger than either those who completed or those who recurred $F(2,121) = 5.58, p < .005$. Patients who had a recurrence during the maintenance phase had higher HRSD scores at entry into the maintenance phase of treatment than those who completed the two years without a recurrence $F(2,121) = 3.00, p = .05$. The patients who recurred averaged roughly two weeks longer in the acute phase of treatment than those who did not recur and were more likely to

have required adjunctive antidepressant medication during the acute phase $\chi^2(2, n=124) = 8.83$, $p=.01$.

Life event occurrence during maintenance phase

Table 3 shows the total number of events experienced in each category during the maintenance phase of treatment. As can be seen in the table, severe and positive events were relatively uncommon while nonsevere events were the most frequently occurring, with a median of five nonsevere events reported over the course of maintenance treatment.

Primary analyses

As seen in Table 4, neither severe nor positive events were associated with depression recurrence. In contrast, after controlling for the other model covariates, nonsevere events significantly predicted episode recurrence. For each additional nonsevere event experienced the risk of recurrence increased by 37%. Depression score at entry into maintenance treatment was also associated with recurrence, women with greater depressive symptoms displayed a shorter time to depression recurrence.

Secondary analyses

To further explore the types of nonsevere events most associated with episode recurrence, we divided those events into four categories based on LEDS Focus and Independence event ratings: subject-focused/independent (134 events), subject-focused/possibly independent (285 events), other-focused/independent (107 events), and other-focused/possibly independent events (12 events). These event categories were then included in the Cox model described in the primary hypotheses sections above. As there were only 12 events of 538 that could be classified as other-focused/possibly independent, these events were not included in the model. As shown in Table 5, subject-focused/possibly independent events were significantly associated with risk of recurrence: as the number of these types of events increased, the risk of recurrence increased by almost 39%. The other nonsevere event categories, subject-focused/independent and other-focused/independent, were not significantly associated with time to recurrence.

Discussion

The relationship between life stress and MDD has been widely studied, though the majority of studies have examined the role of severe events. The current study examined the cumulative effects of nonsevere life events on recurrence in an outpatient sample of recurrently depressed women treated to remission with IPT. Using the “gold standard” of life event measurement, the LEDS, we were able to characterize life events throughout an entire two-year phase of maintenance treatment with IPT-M. This allowed us to examine severe, nonsevere, and positive life events in a clinical sample during a controlled treatment trial while the women were engaged in prophylactic IPT-M, a treatment specifically designed to prevent depressive episode recurrence by enhancing interpersonal functioning.

In this study, we accounted for event severity as well as both positive and negative dimensions of life events by classifying LEDS events into one of three mutually exclusive categories: Severe (marked/moderate threat, little/no positivity), nonsevere (little/no threat, little/no positivity), and positive (little/no threat, marked/moderate positivity). Consistent with our first hypothesis, we found a significant relationship between the cumulative experience of nonsevere life events and depression recurrence during maintenance IPT treatment. This relationship was striking; the risk of recurrence increased by approximately 37% for each additional nonsevere event experienced. These findings extend the previous report, in which Harkness and colleagues (2002) used a similar cumulative proportional hazards model to

examine the relationship between severe events and risk of recurrence within an initial subset of the MPRD sample. This early report did not find a significant relationship between severe events and recurrence; however, there was a trend association between events of any severity and risk of recurrence during the maintenance treatment phase. In addition to the expanded sample size examined in the current study, we captured simultaneously positive and negative dimensions of threat, multiple levels of threat severity, and additional prognostic factors such as age of onset and HRSD scores.

The associated finding that the cumulative experience of *severe* life events was not associated with episode recurrence should be interpreted with caution and within the context of the broader study findings. It is important to consider that nonsevere events occurred at a significantly higher frequency than severe events, with patients reporting a median of *five* nonsevere events but only *one* severe event (and even fewer positive events) during the maintenance treatment phase. Therefore, it is not surprising that in our sample, the cumulative burden of these nonsevere events was the strongest predictor of recurrence.

In some respects, the current findings are consistent with the “kindling” (Post, 1992) or “stress sensitization” model of depression recurrence. The stress sensitization hypothesis asserts that while severe stress is necessary to trigger initial depressive episodes, over time, even minor perturbations become enough to initiate a recurrence (see Monroe & Harkness, 2005 for a theoretical review). Because nonsevere events are generally more common than severe events, a recurrence may be initiated before the rarer severe event occurs. It is also possible that people who become reactive to stress may over-anticipate or over-react to increasingly minor stressors as a conditioned response to stress (Monroe & Harkness, 2005).

It is important to note, however, that the current study was not developed as a direct test of the kindling or stress sensitization hypotheses. Previous tests of these models have generally evaluated the potency of individual life events in isolation, rather than evaluating the cumulative impact that such events may have over extended periods of time. Thus, alternate interpretations of results obtained in the current study should be acknowledged. First, given the low frequency of severe life events observed, the current study may have been underpowered to evaluate the cumulative potency of severe life events. Alternatively, it is possible that the cumulative threat of multiple nonsevere events is equal to the threat engendered by a single severe life event. Clearly, future research will be needed to further clarify these life event relationships.

The cumulative experience of positive events was not associated with risk of recurrence, contrary to our hypotheses. One potential reason for the lack of predictive findings of positive events in our sample could be the low occurrence of positive events. It is uncertain whether the low frequency of positive event reports was actual or artifactual. On the one hand, these women (who had experienced an average of over four previous MDD episodes, with many having a first episode beginning during adolescence or earlier) may not yet have the resources, environments, or interpersonal skills to experience positive events or change their environments to make positive event occurrence more likely. Alternately, recurrently depressed women may be less likely to recognize or report positive events, consistent with the trait-negative bias that is well documented in depression (Gotlib, Krasnoperova, Neubauer, & Joormann, 2004; Leppanen, 2006; Segal et al., 2006). It should also be noted that the primary goal of using the LEDS in this study was to examine factors related to onset of depression recurrence; thus, the interviewers and raters may have been biased towards identifying events with more negative connotations and may have been less likely to elicit positive events during the LEDS interview. However, as the raters were highly trained and the ratings were reviewed during consensus meetings, this possibility seems unlikely. Finally, it is possible that the recurrently depressed women may not be as sensitive to the potentially positive mood effects

of positive events, and are more sensitive to the negative mood effects associated with negative events (e.g. Segal et al., 2006).

The finding that the cumulative impact of nonsevere events is associated with risk of recurrence is consistent with previous findings reported by Monroe and colleagues (1996; 2006). However, in contrast to Monroe and colleagues, who found an association between nonsevere events and episode recurrence only in patients treated with antidepressant medication during maintenance treatment, in our sample we found an association between nonsevere events and recurrence in patients who were being treated with psychotherapy alone. It is important to consider differences in the design and analyses of these studies when evaluating this seemingly discrepant result. Specifically, Monroe et al used logistic regression models to evaluate the likelihood of recurrence based on event occurrence within a specified 6-week period (i.e., in the 6 weeks prior to recurrence versus a “matched” 6-week period for patients who did not recur). In contrast, the current study evaluated the cumulative impact of all nonsevere life events that occurred over the 2-year course of maintenance treatment. It is possible that the robustness of the statistical methods used in the current study, including the examination of the cumulative effects of nonsevere events, may have increased our ability to find an effect in non-medicated patients.

Alternately, it is important to note that the acute treatment approaches differed between the current trial and that examined by Monroe et al (1996, 2006). The Monroe et al. data were drawn from a trial in which patients were treated to acute remission with a combination of medication and IPT, and were subsequently assigned to one of five maintenance treatment conditions, three of which included medication discontinuation. In this trial, patients who were discontinued from medications displayed a significantly higher recurrence rate than those who continued medications throughout maintenance treatment (with recurrence rates of 67% versus 23%, respectively, in the sample included in Monroe et al. 2006). In the current trial, patients were treated sequentially, i.e., all patients received acute phase IPT and only those who failed to remit with IPT alone received adjunctive medication treatment. While full study results (see Frank et al., 2007) indicate that those patients who required adjunctive medications to achieve acute depression remission were more likely to recur in the maintenance treatment phase (in which medications were discontinued), on the whole the maintenance treatment outcomes in this study were quite favorable. Specifically, only 23% of the patients included in the current study sample recurred during maintenance treatment.

Monroe et al. (2006) hypothesized that maintenance treatment medication use may have served to reverse the process of stress sensitization in his sample, lowering patients' recurrence liability such that relatively more impactful life events (including those assessed by typical stress measures) are required to bring about recurrence. Alternately, he postulated that other nonstress factors, such as a strong biological diathesis, may have played a role in the high recurrence rates observed in those patients who discontinued medications, thereby diluting the effect of psychosocial stress (Monroe et al., 1996). To these potential explanations we would add one other: that the process of discontinuing effective antidepressant medication treatment may itself be associated with a biologically-based vulnerability to depression recurrence that may or may not be associated with psychosocial life stress.

Additional *post hoc* analyses were completed to explore the nature of the relationship between nonsevere events and recurrence in more detail. We categorized the nonsevere events according to the focus (subject/joint or other) and independence of the event (degree to which the subject may have contributed to the event). Using these event categories in our cumulative survival model, we found that nonsevere events that were subject or joint-focused and non-independent significantly predicted time to episode recurrence, with each additional event in this category

increasing risk by about 39%. None of the other nonsevere event categories were associated with episode recurrence.

This finding is in contrast to findings by Monroe and colleagues (2006), who found that the “fateful” nonsevere life events were associated with depression recurrence. Events that are outside the control of the individual have been found to be particularly salient in initiating depressive episodes (see Shrout et al., 1989; Stueve, Dohrenwend, & Skodol, 1998). However, many studies have also found an association between non-fateful severe life events and depression onset, suggesting that the severity of the event may be equally as important as the degree of individual responsibility (Stueve et al., 1998).

Our finding that the accumulation of subject-focused, non-independent events predict depression recurrence is, moreover, consistent with the stress generation hypothesis as described by Hammen (for a review, see Hammen, 2006). Hammen (1991) observed that depressed individuals actively contribute to their own stressful environments. Hammen also argued that this stress generation phenomenon is not solely the consequence of acute depressive symptoms, but rather is associated with an enduring pattern of interpersonal dysfunction that continues even when individuals are no longer depressed (Hammen, 1991; Hammen & Brennan, 2002; Hammen, 2006). The current study was not designed as a direct test of Hammen's stress generation model. However, it is possible that for a subset of women, enduring patterns of interpersonal dysfunction contributed to the generation of frequent non-independent, nonsevere life events that, over time, contribute to depression recurrence. Clearly, more research is needed to examine this hypothesis.

This kind of stress reactivity, or vulnerability to become depressed in the face of frequent, nonsevere life events, also highlights other areas of related research. For example, models examining negative affect regulation suggest that individuals who are vulnerable to depression have increased difficulty regulating daily affect compared to nonvulnerable individuals (Ingram, Miranda, & Segal, 1998). Daily process designs have been used to measure shifts in daily mood in response to stress (Gunthert, Cohen, Butler, & Beck, 2005; O'Neill, Cohen, Tolpin, & Gunthert, 2004). This type of stress assessment may, moreover, help to overcome common limitations of retrospective questionnaires, such as recall bias and distorted information processing (Cohen, Gunthert, Butler, O'Neill, & Tolpin, 2005). The use of a daily process design models in which an individual's reactivity to daily life events is measured may be a more sensitive way to help further elucidate the relationship between nonsevere life events and episode recurrence.

Several limitations to this study must be addressed. First, the collection of life event data was retrospective. Although every effort was made to minimize the effects of recall bias, this concern remains. Second, the results of our study may not be generalizable to other patient populations. Our sample consisted of primarily white, relatively well-educated women who sought treatment at an academic medical center. Male depressed patients may have different risk factors for remission and relapse, particularly in relation to life events. Moreover, depressed patients meeting full criteria for a diagnosis of borderline personality disorder (BPD) were excluded from participation; BPD patients may be at particular risk for life event occurrence and/or reactivity. Additionally, our analyses of the effects of life events on maintenance treatment outcomes could only be carried out on those patients who were able to reach the maintenance phase of treatment. Those patients who did not remit with acute treatment, or who terminated or relapsed prior to reaching the maintenance treatment phase may show different patterns of life event effects than what we found. Third, the current trial did not include a non-depressed control group. Thus, we do not know if the rate of life events or the ratio of nonsevere to severe life events reported by our patients is different from what would be expected in a non-depressed sample.

Finally, it is important to consider that the current trial did not include a no-treatment control group. Thus, we are not able to test whether the influence of nonsevere life events on recurrence is specific to recurrence while receiving IPT treatment or may be associated with recurrence more broadly. We are also not able to test whether IPT-M treatment had a positive impact on either patients' experience of, or sensitivity to, life event stress. Despite this caveat, the current findings have important implications for IPT.

The primary results of the MPRD study (Frank et al., 2007) indicate that those women who initially respond to IPT treatment alone during the acute treatment phase were generally likely to continue to benefit from IPT as a maintenance treatment. On the other hand, the subset of women who recurred appeared to be more stress reactive, generated more interpersonal stress, and may have had more difficulty maintaining an interpersonal focus during IPT-M treatment sessions. Previous work has suggested that IPT is most effective when the therapist is able to maintain the focus of therapy on interpersonal themes (Frank, Kupfer, Wagner, McEachran, & Cornes, 1991; Frank et al., 2007). Nonsevere life events may divert the therapy focus, requiring the therapist to continually "put out small fires" rather than focus therapeutic attention on making progress within the interpersonal problem area identified as the focus of treatment. Alternatively, since nonsevere life events are not typically a focus of IPT, it is possible that the therapist discounted more minor stressors that ultimately have an impact on recurrence over time. Identifying vulnerability patterns early in treatment may help to more effectively focus therapy or to address chronic interpersonal dysfunction more aggressively. This is an important area for future investigation with the potential for developing more efficacious maintenance therapies.

In summary, we found a significant association between the cumulative experience of nonsevere life events and depression recurrence in an outpatient sample of recurrently depressed women receiving maintenance IPT. *Post hoc* analyses in our sample suggest that the cumulative experience of nonsevere events that are subject- or joint-focused and non-independent may be particularly important in predicting depression recurrence, suggesting a possible role of stress generation in this process. It remains unclear whether the patients who recurred are more sensitive to life events or have low social support, poor coping styles, or an inability to utilize psychotherapy effectively. This remains an important issue for future research. Our findings support the hypothesis that the cumulative experience of nonsevere life events is associated depression recurrence over the course of maintenance IPT treatment. Future research is needed to further elucidate the mechanism by which this may occur. Such research may help to facilitate improvements in therapy techniques used to treat these vulnerable patients and provide guidance as to which patients are more likely to require adjunctive or combination maintenance treatments.

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Table 1**Examples of life events in each rating category**

Event category	Description	
Severe	1	S's daughter, age 15, died in a car accident.
	2	S's husband of 8 years initiates a separation. S moves in with her mother who is age 86 and suffers from dementia.
Nonsevere	1	S takes the medical school entrance examination (MCAT).
	2	S's son falls off his bike a breaks his arm. He is given a cast in the ER. There are no further complications.
Positive	1	S is notified that she has been chosen to receive a national award that will provide money towards her graduate education.
	2	S is offered and accepts a full-time job with benefits. S has been unemployed for the past six weeks.

Table 2
Demographic and clinical characteristics for all LEDS participants (n=124)

Variable	Mean (SD)	
Age at study entry	38.14 (10.07)	
Education (years)	15.08 (1.87)	
Age at 1 st episode	25.43 (8.95)	
# Previous episodes	4.73 (3.00)	
Duration of episode (wks)	27.44 (21.38)	
Baseline HRSD25	21.93 (3.63)	
Pre-Maintenance HRSD25	4.40 (3.55)	
Race	N	%
White	109	88
Black	8	6
Hispanic/Other	7	6
Employment Status		
Full-time	72	58
Part-time	28	23
Homemaker	11	9
Laid-off/Unemployed	1	8
Student	3	2
Marital Status		
Married	52	42
Divorced/Separated	31	25
Never Married	38	31
Widowed	3	2

Table 3
Number of events occurring during maintenance treatment (n=124)

Event category	Total # events	Mean # per patient (SD)	Median # (range)
Severe	190	2.21 (3.16)	1 (0-23)
Nonsevere	538	6.23 (4.53)	5 (0-22)
Positive	69	0.80 (1.05)	0 (0-5)

Table 4
Cox regression results with event classifications as time-dependent covariates (n=124)

	Parameter estimate	Standard error	χ^2	Pr> χ^2	Hazard ratio
Severe	-.22	.16	1.82	.18	.81
Nonsevere	.31	.10	10.09	.002	1.37
Positive	.34	.25	1.88	.17	1.41
Meds	.73	.41	3.18	.07	2.07
Age at study entry	.04	.02	3.52	.06	1.04
Duration of episode	.02	.01	2.26	.13	1.01
Age at 1 st episode	-.05	.03	3.66	.06	.95
Pre-Maint HRSD25	.16	.05	11.04	.0009	1.17
Sessions/week	.87	.54	2.65	.10	2.40

Note. Meds refers to antidepressant medication required during Acute phase coded 0 for no and 1 for yes. Duration refers to the duration of the index episode; Sessions/week refers to the average number of sessions per week each patient received during Maintenance.

Table 5
Post hoc analyses showing Cox regression with nonsevere events classified according to focus and independence (n=124)

Covariate	Parameter estimate	Standard error	X ²	Pr>X ²	Hazard ratio
Severe	-.14	.16	.79	.37	.87
Positive	.26	.27	.93	.33	1.29
Sub-Foc/Ind	.15	.17	.78	.38	1.16
Sub-Foc/Poss	.33	.13	5.97	.01	1.39
Oth-Foc/Ind	.33	.21	2.53	.11	1.40
Meds	.85	.42	4.13	.04	2.34
Age at study entry	.03	.02	2.00	.16	1.03
Duration of episode	.01	.01	1.59	.21	1.01
Age at 1 st episode	-.05	.03	3.31	.07	.95
Pre-Maint HRSD25	.18	.05	11.81	.0006	1.20
Sessions/week	.72	.56	1.66	.20	2.16

Note. Sub-Foc/Ind refers to subject-focused/independent nonsevere events; Sub-Foc/Poss refers to subject-focused, possibly independent nonsevere events; Oth-Foc/Ind refers to other-focused/independent nonsevere events; Meds refers to antidepressant medication required during Acute phase coded 0 for no and 1 for yes. Duration refers to the duration of the index episode; Sessions/week refers to the average number of sessions per week each patient received during Maintenance.