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Life Stress and Treatment Course of Recurrent Depression: II. Postrecovery Associations With Attrition, Symptom Course, and Recurrence Over 3 Years

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Life stress was studied in relation to postrecovery attrition, symptom course, and recurrence of depression over 3 years. Participants were 67 individuals with recurrent depression who had responded to treatment. Life stress was assessed for the prior 12 weeks at acute treatment entry (T1), initial recovery (T2), and after 17 weeks of sustained recovery (T3). Severe life events at T1 predicted greater attrition, a more favorable postrecovery symptom course, and a lower likelihood of recurrence over 3 years. Life stress at T2 was not predictive of outcomes. Finally, undesirable life events at T3 tended to predict a worse symptom course and a higher likelihood of recurrence, particularly for individuals on medication. The findings are discussed in terms of (a) different processes influenced by life stress over time and (b) limitations of existing longitudinal research for studying the effects of life stress over prolonged intervals.

It is well-known that a depressed person who responds to treatment is vulnerable to a subsequent re-emergence of depressive symptoms (Keller et al., 1984). In a review of the literature, Belsher and Costello (1988) concluded that approximately 50% of individuals who recover from an episode of depression experience a relapse or recurrence within 2 years. Recent research suggests that life stress might help to explain such variability in treatment outcome and posttreatment clinical course (e.g., Lewinsohn, Hoberman, & Rosenbaum, 1988; Monroe, Bellack, Hersen, & Himmelhoch, 1983; Monroe & Depue, 1991; Reno & Halaris, 1990; Segal, Shaw, Vella, & Katz, 1992). Although the results of these studies incorporating life stress appear promising for understanding the conditions that lead to recurrence of depression, lack of common methodologies and of consistent participant selection procedures preclude firm conclusions at the present time (e.g., definition of treatment response; measurement of life stress; duration and frequency of patient follow-up; subtypes of depression; see Monroe & McQuaid, 1994).

From a different vantage point, there are other compelling reasons for studying life stress and the recurrence of depression. An enduring problem in the study of mood disorders has been the suspected heterogeneity of this broad nosological grouping with respect to etiology. The call has been frequent and fervid to develop finer subgroup distinctions to better delineate causal processes (e.g., Abramson, Metalsky, & Alloy, 1989; Depue & Monroe, 1978). Thus, recurrent depression may be characterized by different etiologic factors compared to nonrecurrent depression. Compatible with this notion, but somewhat different in emphasis, is the idea that for individuals with recurrent depression later episodes arise because of different combinations of causal factors relative to earlier episodes. For example, Kraepelin (1921) noted that one of his patients became depressed "after the death first of her husband, next of her dog, and then of her dove" (p. 179). Post (1992) has suggested that the contribution of stress changes with the progression of episodes for individuals with recurrent depression. More specifically and in line with Kraepelin's comments, Post hypothesized that individuals with recurrent depression become sensitized to stressors over time, so that progressively less severe stressors can trigger subsequent episodes (with a concomitant shift toward more biological processes dominating the causal picture). Overall, research on recurrent depression is important for understanding the processes that lead to onset for a subgroup of the depressed population with a particularly pernicious lifetime course, as well as for possibly shedding light on more universal processes involved with the initiation of depressive episodes in general.

In addition to the theoretical importance of studying stress in the etiology of recurrence, other consequences of stress may have more general implications for longitudinal research on psychopathology. For example, much of the recent information

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about the treatment course and outcome of depression derives from large-scale longitudinal investigations (Klerman, 1990). Such studies typically compare (a) the short-term treatment course as a function of the type of acute treatment initially received (e.g., Elkin et al., 1989; Murphy, Simons, Wetzel, & Lustman, 1984); or (b) the long-term maintenance of recovery as a function of initial treatment or of particular follow-up treatments (e.g., Frank et al., 1990; Prien et al., 1984; Simons, Murphy, Levine, & Wetzel, 1986). Because these designs are longitudinal, a number of participants inevitably leave the protocol over time. Little is known about what factors contribute to this progressive attrition or the manner in which such attrition might influence substantive interpretations of the research. For instance, Hollon, Shelton, and Loosen (1991) noted that longitudinal designs could create a "differential sieve": Particular types of people might be systematically excluded over time, thereby limiting generalizability of the findings on the basis of the final treatment sample. Life stress could be one factor that influences sample composition over time.

The purpose of the present article is to report prospective data for life stress in relation to attrition, symptom course, and recurrence of depression over 3 years for recovered individuals receiving continued treatment. The sample is a subset of a larger sample described in a previous article on life stress and acute treatment response in recurrent depression (Monroe, Kupfer, & Frank, 1992), composed now of patients who responded to acute treatment. It is important to emphasize that the research was designed specifically to select individuals with recurrent depression who had clearly recovered from an index episode in order to study factors related to the postrecovery treatment course and recurrence of depression.

The overall design of the research encompasses three distinct phases. The first phase is the acute phase, during which patients received a combined treatment of imipramine (150–300 mg) and interpersonal psychotherapy (IPT; Klerman, Weissman, Rounsaville, & Chevron, 1984). The second phase is the continuation phase, a 17-week period immediately following a favorable clinical response to the acute phase treatment, during which patients continued to receive the same combined treatment. To remain in the protocol during this continuation phase, patients were required to sustain symptom improvement over the 17-week duration (see *Definition of Clinical Responses and Recurrence*). The final phase is the maintenance phase, a 3-year period following successful completion of the continuation phase. In this latter phase patients were randomized into a maintenance therapies treatment protocol (see *Definition of Clinical Responses and Recurrence*). Life stress was assessed for the previous 12 weeks at three separate times corresponding with entry into these phases: the acute phase (T1), the continuation phase (T2), and the maintenance phase (T3).

On the basis of our prior research with individuals with recurrent depression and other studies of severe forms of depression in relation to life stress, the general hypothesis was that life stress would predict poorer outcomes (Monroe, Kupfer, & Frank, 1992; Zimmerman, Pfohl, Coryell, & Stangl, 1987). More specifically, the major hypotheses were that life stress would predict (a) greater attrition over the continuation and maintenance phases; (b) relatively poor symptomatic functioning for patients who remained in the protocol during the continuation and maintenance phases; and (c) recurrence of depression for patients during the maintenance phase of the study.

Method

Participants

Participants for the present study were a subsample of patients participating in the Maintenance Therapies for Recurrent Depression treatment protocol (Frank et al., 1990). Patients were recruited through self-referral, medical referral, and a public information campaign for treatment of recurrent depression. All participants were required (a) to be in at least their third episode of definite major depression (M = 6.29 episodes in the present sample) as determined by Research Diagnostic Criteria (RDC; Spitzer, Endicott, & Robins, 1978); (b) to be between the ages of 21 and 65; (c) to have had no more than 2½ years between the onset of the index episode and the most recent previous episode; and (d) to have had at least a 10-week period of remission separating the previous episode from the index episode. Patients were also required to score 7 or above on the Raskin Severity of Depression Scale (Raskin, Schulterbrandt, Reatig, & McKeon, 1969) and 15 or above on the Hamilton Rating Scale for Depression (HRSD; 17 item version; Hamilton, 1960) on two evaluations separated by 2 weeks. Exclusion criteria included medical conditions (e.g., pregnancy; major cardiovascular, renal, liver, or endocrine disease; organic brain syndrome; mental retardation; or a medical history precluding treatment with tricyclic antidepressants) and other psychiatric conditions (e.g., schizophrenia, schizoaffective disorder, unspecified functional psychosis, alcohol–drug dependence and abuse).

One hundred and nine consecutive patients who were admitted to the larger treatment study of recurrent depression were selected for participation in the present study (see Frank et al., 1990).[1] Of this initial sample, 91 patients (67 women, 24 men) had full life stress and symptom data; 67 of these (46 women, 21 men) attained criteria for initial treatment response and therefore constituted the present sample (see *Definition of Clinical Responses and Recurrence*). Mean duration of the index episode prior to treatment entry for the 67 responders was approximately 24 weeks, and mean age at the protocol entry was 41.05 years (SD = 10.23). Ninety-seven percent of the patients were White; 61% were currently married and not separated.

Materials

Patients meeting criteria for entry into the treatment protocol were administered a comprehensive battery of measures. For the present article, the major indices are the assessment of life stress, assessment of depression, definition of treatment response, and definition of recurrence.

Life Stress Assessment

After acceptance into the acute phase of the treatment protocol, patients received a modified version of the Psychiatric Epidemiology Life Events Research Interview (PERI) Life Events Scale (Dohrenwend, Krasnoff, Askenasy, & Dohrenwend, 1978) and were requested to re-

[1] Most patients who did not complete the requirements for the initial study (Monroe, Kupfer, & Frank, 1991) terminated treatment prior to 12 weeks for a variety of reasons (e.g., noncompliance with treatment procedures, scheduling conflicts, medication side effects). Owing to scheduling conflicts, a further subset of 5 patients did not receive initial life stress assessments.

port all events occurring 12 weeks prior to the day of the interview. The PERI Life Events Scale is a self-report checklist of life events that was developed in response to criticisms of the first-generation life events scales (e.g., the Schedule of Recent Experiences; Holmes & Rahe, 1967); the present modified version contained 110 events (including provisions for writing in events not covered in the listing). Following completion of this measure, each person was administered a semi-structured interview in which the endorsed experiences were probed with specific questions tailored to the particular event, and further information was sought concerning other aspects of the individual's life required to perform the ratings. All interviews were tape recorded. On entry into the continuation phase and maintenance phase of the study, patients again were assessed with these procedures for the period of time covered since the prior assessment. To control for time differences between the three assessment periods and to focus on more recent forms of stress, we limited the interval for all three assessments to the 12 weeks prior to the day of the assessment.

A presenter provided the relevant information from the life stress interview to a panel of raters (typically 2–4 persons; range = 1–4) who were trained in the Bedford College Life Events and Difficulties Schedule (LEDS) procedures for (a) defining life events and difficulties and (b) rating dimensions of these stressors (Brown & Harris, 1978. Raters were trained by Scott M. Monroe, who in turn was trained by T. Harris.) Relevant information pertaining to stressors was presented first, with raters allowed to ask clarifying questions. Raters were blind to information about the person's subjective response to stressors and about clinical status (i.e., depressive symptoms and response to treatment). Subsequently, each rater provided his or her ratings of the major dimensions. All discrepancies were then resolved through raters' discussion and consensus. (For all of these tasks, the LEDS manuals were available to provide anchoring examples and standardization; e.g., there are more than 5,000 case vignettes to assist in defining events and assigning threat ratings.) All events that were direct consequences of depression were excluded from the analyses (e.g., work problems caused by poor concentration, fatigue, irritability, etc.).

Previous work with the LEDS has established two types of life stress as most important for predicting the onset of depression: severe events and severe difficulties (Brown & Harris, 1989a; Bebbington et al., 1988). These are explicitly defined categories based on a high degree of contextual threat and unpleasantness and a high likelihood of prolonged adverse consequences. (See Brown, 1989, or Monroe, Kupfer, & Frank, 1992, for further details about these well-standardized procedures.) Such severe forms of stress are relatively infrequent, and others have suggested that events possessing a lesser degree of contextual threat are of relevance for recurrent depression (Kraepelin, 1921; Post, 1992). Consequently, we also included unpleasant events that met LEDS definitional criteria but did not meet the severity criteria for severe events (see Monroe, Kupfer, & Frank, 1992). The undesirable events are events that are definitely unpleasant but that do not possess the highly aversive quality of the severe events. (Note that we include in the general undesirable category the severe events; i.e., severe events are part of the more broad class of undesirable events.)

Within the LEDS rating system, all events are rated on the basis of extensive information about the circumstances surrounding the event and on the particular individual's biographic circumstances (i.e., "contextual" ratings; see Brown & Harris, 1978, 1989a). There is no universal assignment of scores on the basis of summary descriptions of the events. Nonetheless, examples are useful for understanding the general types of events typically included in the severe and undesirable categories used in the present study. Examples of severe events included several terminations of core relationships, a broken engagement, or a very serious fight with spouse. Examples of undesirable events included appearing for a court case, mother's minor stroke, greatly reduced contact with sister, and termination from a part-time writing job. Examples of severe difficulties include highly negative marital relationships (e.g., constant serious arguing, infidelity, threats of divorce, physical abuse), very impoverished economic circumstances (e.g., cannot pay bills, evicted or possessions repossessed), serious ongoing problems with children, and highly problematic work situations. Overall, the LEDS system has proven to be a very reliable and valid measure of life stress (see Brown & Harris, 1989b; Monroe & Roberts, 1990). In a previous project using the same procedures, pairwise comparisons of four raters on long-term threat ratings (that form the basis for defining severe events; see Footnote 2) ranged from .76 to .81 (M = .78; corrected for chance agreement with Cohen's kappa).

Symptom Measures

The 17-item HRSD, the Raskin Severity of Depression Scale, and the 21-item Beck Depression Inventory (BDI; Beck, Steer, & Garbin, 1988) were used to assess the presence and severity of depressive symptoms at each clinic visit. The HRSD and Raskin were completed by a clinical evaluator, and the BDI was completed by the patient. Clinicians performing the HRSD and Raskin were blind to the patient's stress ratings. The Raskin Severity of Depression Scale is commonly used to assess depressive functioning in patient populations and was used in the present study in concert with the HRSD for patient selection and for defining clinical response (see *Definition of Clinical Responses and Recurrence*). All measures are well-documented in terms of reliability and validity in the study of depression (Monroe et al., 1983; Rabkin & Klein, 1987).

During the continuation and the maintenance phases, scores on the BDI and HRSD were averaged over multiple assessments and tested in relation to prior life stress.[2] Because patients were required to maintain symptoms below specific criteria to remain in the protocol for the continuation phase (see *Definition of Clinical Responses and Recurrence*), there is a ceiling on symptom levels that constricts mean levels of scores and lessens the likelihood of detecting significant effects. It is also likely, however, that vulnerability may be reflected in variation over time, as well as in mean levels (Depue & Monroe, 1986). Consequently, we also examined the relations between prior life stress and the standard deviation of patient symptoms scores during the two postrecovery treatment phases.

Definition of Clinical Responses and Recurrence

Patients were required to attain scores of ≤ 7 on the HRSD and ≤ 5 on the Raskin scale for three consecutive weeks to be considered treatment responders. These criteria take into account both the degree of residual symptomatology and the duration of sustained improvement for defining clinical outcome and are comparable to other response criteria recently used or recommended in the literature (Frank et al., 1991; Kupfer & Frank, 1987). The majority of individuals responded within 16 weeks of treatment (55 of 67); we also included the additional 12 patients who responded with extended treatment (see Monroe, Kupfer, & Frank, 1992).

Individuals who responded to treatment were required to maintain

[2] As indicated below, treatment sessions were scheduled weekly for the first 12 weeks, biweekly for the next 8 weeks, and then monthly. Consequently, the frequency of assessments could vary across patients depending on how quickly they responded. Furthermore, because some patients also left treatment prematurely or suffered an early recurrence, there was additional variability in the number of assessments available per patient. To address this issue, we used the average scores in the analyses.

the response criteria (i.e., ≤ 7 on the HRSD and ≤ 5 on the Raskin scale) for an additional 17 weeks. This continuation phase was designed to ensure recovery from the index episode: Any re-emergence of symptoms during this period meeting formal diagnostic criteria for depression was defined as a relapse (and the patient was discontinued from the study). Patients who did not sustain treatment response, but did not meet formal diagnostic criteria for depression, also were discontinued from the study. Once again, it should be emphasized that this is a useful design feature to clearly define the phenomenon of recurrence and to operationally distinguish it from the related concept of relapse (i.e., relapse being a continuation of the index episode, recurrence being the emergence of a new episode; see Frank et al., 1991).

After successful completion of the continuation phase, patients entered the maintenance phase and were randomly assigned to one of five treatment conditions (see *Treatment Considerations*). During the maintenance phase, patients' symptoms could exceed the symptom limits imposed during the continuation phase but could not meet RDC criteria for major depression and still remain in the protocol (the latter being defined as recurrence of depression). Overall, patients received the assigned maintenance treatment until they (a) left the protocol (e.g., attrition owing to moving, noncompliance, relapse, or not maintaining clinical improvement during the continuation phase); (b) met formal RDC diagnosis of recurrence of depression; or (c) completed the full 3 years in the maintenance treatment protocol without recurrence of depression.

Recurrence of depression was defined formally by a two-step procedure. If a patient presented with substantial symptoms, he or she was observed and evaluated twice within a 7-day period. If an independent evaluator and the patient's clinician judged that the patient met RDC for major depressive disorder, and the independent evaluator rated the patient as having a minimum of HRSD ≥ 15 and Raskin ≥ 7 on both occasions, the patient was seen by an independent senior psychiatrist who was not affiliated with the study and who was blind to the patient's treatment assignment. If the outcome of this latter evaluation indicated an episode of major depression, recurrence was formally declared.

Treatment Considerations

All patients initially received the same treatment for the acute episode, consisting of pharmacotherapy (imipramine, 150–300 mg/day) and IPT. Treatment sessions were scheduled weekly for the first 12 weeks, biweekly for the next 8 weeks, and then monthly. Once the patient had sustained recovery criteria for a total period of 20 weeks, he or she was randomized into a 3-year maintenance treatment protocol comparing five different treatment regimens. These treatments consisted of monthly (a) maintenance IPT (IPT-M) alone, (b) IPT-M with imipramine, (c) IPT-M with placebo, (d) imipramine and medication clinic visits, and (e) placebo and medication clinic visits (see Frank et al., 1990).

Design and Analyses

Life stress was assessed covering the previous 12-week time period at the beginning of acute (T1), continuation (T2), and maintenance phases (T3) of treatment (see Figure 1). As per the methods of Brown and Harris (1989a) and our previous research using similar procedures (Monroe, Kupfer, & Frank, 1992; Monroe, Simons, & Thase, 1991; Monroe, Thase, & Simons, 1992), patients were divided into those with and without a severe event, an undesirable event, and a severe difficulty. However, there were too few patients with a severe event at T3 ($n = 4$) for meaningful statistical analysis. Furthermore, analyses based on severe difficulties did not yield noteworthy findings. Consequently, we report the results for (a) severe and undesirable events at T1, (b) severe and undesirable events at T2, and (c) undesirable events at T3.

The dependent variables were attrition, depressive symptomatology, and recurrence of depression. Yet, it could not be assumed that attrition and symptoms were uniformly associated with life stress across the continuation and maintenance phases of the study (e.g., in the continuation phase patients received the same treatment, whereas in the maintenance phase patients were randomized into five different treatment regimens; in the continuation phase patients were required to maintain specific symptom reductions, whereas in the maintenance phase they were not). Consequently, attrition and depressive symptoms were examined separately for the continuation and maintenance phases. (Recurrence by definition could only be studied in the maintenance phase.)

Although prospective designs are essential for addressing causal relations in psychopathology research, multiple time points of assessment for the independent variables and varying time periods over which dependent variables reveal meaningful variation pose challenges for disentangling causal factors and mediating processes. For example, life stress assessed on entry into the acute phase may predict later attrition, but such effects could be mediated by other factors that are correlated with earlier life stress (e.g., changes in symptoms or increases in later life stress). To address these concerns, we conducted several preliminary and subsequent subsidiary analyses designed to eliminate alternative explanations of the major findings. Such an approach also raises legitimate concerns about Type I errors. We attempted to handle these throughout the Results section by demonstrating consistency of effects across different analytic approaches and, in one instance, replication of effects with an expanded sample (rather than by partitioning alpha). To simplify the presentation, many of the additional analyses appear in the footnotes.

Logistic regression was used to test the relationship between the independent variables and the dichotomous dependent variables (attrition, recurrence; model chi-square values or improvement chi-square values are reported depending on the particular analysis). For continuous dependent measures, t tests were performed to compare groups of patients with and without prior life stress (for comparisons where variance between groups differed significantly, tests based on separate variance estimates were used). When controlling for other predictor variables in the prediction of continuous variables, standard linear regression analyses were performed.

Results

The major demographic variables (i.e., sex, marital status, age) were unrelated to the dependent variables, with the exception of age being inversely related to mean BDI symptoms during the maintenance phase ($r = -.30$, $p < .05$). With respect to relevant clinical variables (i.e., duration of index episode, number of previous episodes, age at onset of first episode) and the dependent variables, only the number of previous depressive episodes was related in the present sample to any of the dependent variables. Individuals with fewer previous episodes were less likely to complete the protocol during the continuation phase ($M = 4.15$ vs. $M = 6.81$), $t(63.83) = 2.27$, $p < .03$. Separate analyses to control for differences in age or prior episodes did not substantively alter the findings reported below.

Descriptive information for life events variables is presented in Table 1. Of the initial 67 individuals who responded to acute treatment, 14 left the protocol during the continuation phase (due to attrition, relapse, or failure to maintain symptom gains), and 13 left during the maintenance phase (due to attrition). Of the remaining 40 patients who entered the maintenance phase, 24 suffered a recurrence and 16 completed the

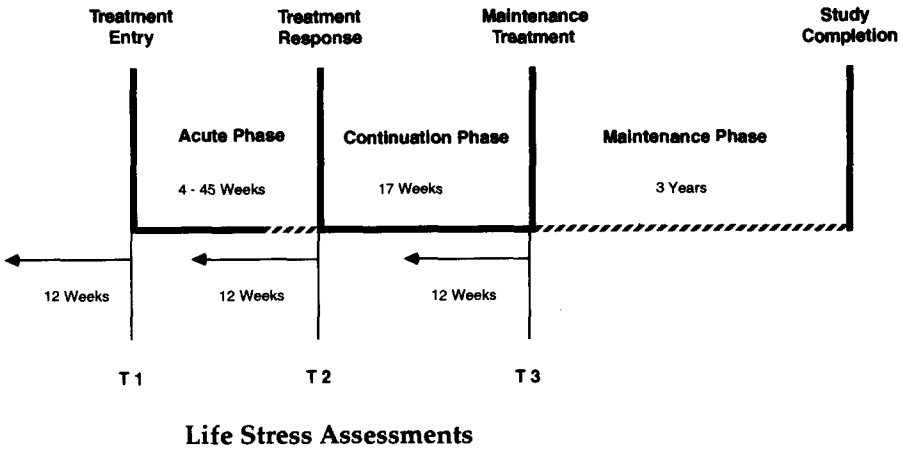

Figure 1. Study design for the assessment of life stress during acute treatment entry (T1), the continuation phase (T2), and the maintenance phase (T3) in the prospective prediction of attrition, symptom course, and recurrence of depression.

full 3 years without a recurrence of depression. (See Figure 2 for a summary of patient flow.)

Preliminary Analyses

Analyses were performed initially to determine general relationships between the dependent variables and other study variables irrespective of life stress. To repeat, these findings provide the basis for the subsidiary analyses for the major hypotheses and thereby permit conservative control over alternative explanations of the life stress findings.

With regard to the stability of major study variables over time, mean depressive symptoms during the continuation phase were significantly predictive of subsequent depressive symptoms during the maintenance phase (BDI, $r = .37$, $p < .01$; HRSD, $r = .32$, $p < .05$). Severe events and undesirable events, in contrast, tended not to be correlated over time (i.e., severe events did not predict subsequent severe events; undesirable events did not predict subsequent undesirable events). For instance, the association between life events occurring during one

Table 1
Descriptive statistics for T1, T2, and T3 Life Stress for Patients Who Responded to Acute Treatment

	Patients with stress		Patients without stress		
Event	*n*	%	*n*	%	Range
T1. Life stress 12 weeks prior to acute phase					
Severe	9	13	58	87	0–3
Undesirable	29	43	38	57	0–4
Severe difficulty	14	21	53	79	0–2
T2. Life events 12 weeks prior to continuation phase					
Severe	13	19	54	81	0–3
Undesirable	35	52	32	48	0–4
T3. Life events 12 weeks prior to maintenance phase					
Severe	4	8	49	92	0–2
Undesirable	13	25	40	75	0–3

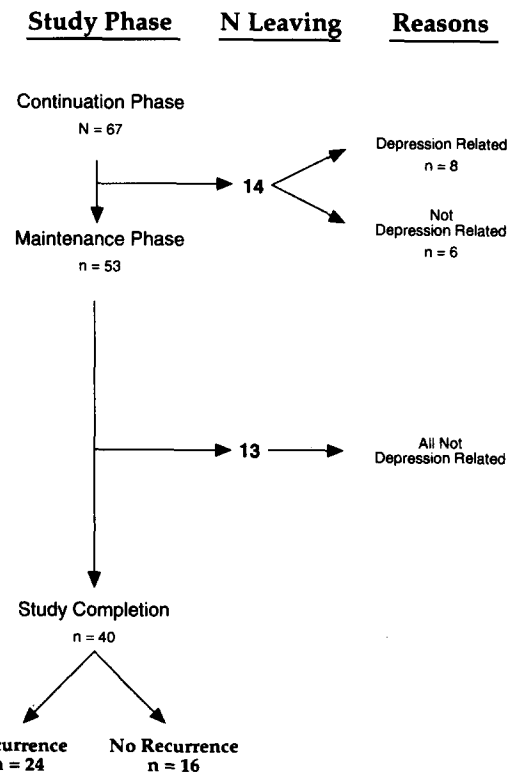

Figure 2. Patient flow through phases of study with regard to attrition and recurrence.

time period with those occurring during one of the other two time periods was only significant for events at T1 with events at T2 (e.g., undesirable events at T1 were associated with undesirable events at T2), $\chi^2(1, N = 67) = 5.84, p < .02$; none of the other associations between events occurring during the three time periods were statistically significant.

In terms of attrition, the 14 patients who left treatment during the continuation phase were more symptomatic during this phase. Mean BDI scores for the assessments were 8.85 for those not completing the continuation phase versus 3.22 for those who remained, $t(14.59) = 3.28, p < .01$. For HRSD scores, the respective means were 8.33 versus 3.64, $t(13.94) = 3.42, p < .01$. There were several different reasons for not completing the continuation phase of the study. The major subgroup was patients who experienced a relapse of symptoms ($n = 6$). Two other people had reasons for leaving the protocol that were also directly related to depression (one had a suicide attempt, another did not sustain the treatment response). The remaining individuals left because of medication side effects ($n = 3$), noncompliance ($n = 2$), or moving ($n = 1$).

In contrast, the 13 individuals who dropped out of the protocol during the maintenance phase had significantly lower mean HRSD ratings for the repeated assessments during the maintenance phase ($M = 4.84$ vs. $M = 7.75$), $t(37.14) = 2.37, p < .03$, as well as less variability in HRSD symptoms over time ($M = 3.01$ vs. $M = 4.85$), $t(32.70) = 3.04, p < .01$. There were no differences between the attrition versus no attrition groups on the BDI during the maintenance phase. Again, there were several reasons for patients not continuing in the protocol during this phase. Nine patients left against medical advice, whereas 4 left because of reasons beyond their control (i.e., liver dysfunction; moved to a foreign country; died in an accident; developed medical problems).

The amount of time patients spent in either the continuation or maintenance phases of the study was related to their symptomatic functioning. With regard to the continuation phase, the number of days was positively related to HRSD mean scores ($r = .29, p < .05$) and HRSD variability ($r = .31, p < .05$). There were no significant associations for the BDI indices during this phase of the study. In contrast, for the maintenance phase the number of days was negatively associated with symptomatology for all BDI and HRSD indices ($rs = -.54$ through $-.62$; all $ps < .01$).

In terms of symptomatic functioning and eventual recurrence, there were no differences for continuation phase symptomatology between those who did or did not suffer an eventual recurrence in terms of mean BDI or HRSD scores. In contrast, persons who later had a recurrence experienced greater variability in their BDI during the continuation phase: $M = 3.11$ versus $M = 1.77$, $t(31.52) = 2.48, p < .02$. As would be expected during the maintenance phase, those who experienced a recurrence had significantly greater mean symptoms and variability for both the BDI and the HRSD during the maintenance phase (all $ps < .001$).

Finally, for hypotheses involving the maintenance phase it is essential to establish whether type of treatment is related to the dependent variables. The primary dimensions of treatment were whether the patient received active medication or received psychotherapy. We collapsed across the five treatment groups and created two dichotomous variables: (a) presence or absence of medication and (b) presence or absence of psychotherapy.[3] In terms of attrition during the maintenance phase, medication status was unrelated to dropping out, but psychotherapy status was significantly related for the present sample (39% without psychotherapy dropped out vs. 13% with psychotherapy), $\chi^2(1, N = 53) = 4.70, p < .04$.[4] In terms of symptoms during the maintenance phase, patients receiving medication had significantly lower BDI mean scores (3.09 vs. 7.29), $t(48.02) = 3.46, p < .001$, and significantly lower variability in BDI (2.88 vs. 4.70), $t(48) = 2.15, p < .04$. Similar results held for mean HRSD scores (4.83 vs. 8.86), $t(48.79) = 3.16, p < .01$, but not for HRSD variability. Psychotherapy was unrelated to symptomatic functioning.

In terms of recurrence for the larger treatment study (see Frank et al., 1990), both medication and psychotherapy demonstrated clinical efficacy (those receiving active medication having a lower likelihood of recurrence and those receiving psychotherapy having longer survival times before recurrence). In the present subsample, medication status was again a strong predictor of a lower probability of recurrence (25% with active medication suffering recurrence versus 62% without medication), $\chi^2(1, N = 53) = 7.51, p < .01$.[5] There was no effect for psychotherapy on likelihood of recurrence for the present analyses.

Attrition

Continuation Phase Attrition

The T1 and T2 life stress assessments preceded entry into the continuation phase (see Figure 1). The results for these two time periods are reported separately below.

T1 life stress. There was no relationship between severe events at T1 and attrition during the continuation phase. However, there was a significant association between undesirable events and attrition: Individuals who dropped out were significantly more likely to have experienced at least one undesirable event prior to treatment entry (10 of 14 dropouts) compared to patients who remained (19 of 53 completers; 71% vs. 36%), $\chi^2(1, N = 67) = 5.75, p < .02$. Because greater concurrent depressive symptoms also predicted attrition during this phase (see *Preliminary Analyses*), additional analyses were run controlling for concurrent mean BDI and HRSD depressive symptoms. It is interesting that both severe events and undesirable events predicted attrition strongly once these symptoms were

[3] Note that these are overlapping designs, for the control placebo condition is included in the treatment absent group for both categorizations.

[4] It should be noted that the effect for psychotherapy status on attrition did not generalize to the full treatment sample (see Frank et al., 1990).

[5] Including only the patients who completed this phase of treatment (i.e., excluding dropouts), the effect remains significant: 38% with medication suffering recurrence versus 75% without; $\chi^2(1, N = 40) = 5.68, p < .02$.

taken into account statistically: severe events, $\chi^2(1, N = 65) = 4.26$, $p < .04$; undesirable events, $\chi^2(1, N = 65) = 5.19$, $p < .03$.

One might wonder whether participant loss during this phase is associated primarily with depression-related departures (as opposed to non-depression-related reasons for leaving). If so, the present findings would be limited in their generalizability to research where similar study-specific continued improvement criteria are imposed by design. Additional analyses performed for the 8 patients with depression-related reasons for dropping out (i.e., relapse, overdose, and no treatment response; excluding patients who dropped out for other reasons) did not yield significant findings with regard to T1 life stress on attrition (although one must be mindful of statistical power considerations with such numbers), $\chi^2(1, N = 61) = 2.02$, $p = .15$. However, additional analyses based on the 6 patients with non-depression-related reasons for dropping out (i.e., excluding from the analysis the depression-related attriters) continued to evidence a significant association with T1 undesirable events, $\chi^2(1, N = 59) = 5.15$, $p < .03$. Consequently, the prediction afforded by life stress cuts across many stated reasons for attrition from the protocol during this phase and, most important, is not confined solely to depression-related attrition.

T2 life stress. Patients with severe or undesirable events did not differ from those without in terms of attrition during the continuation phase.

Maintenance Phase Attrition

Findings are reported separately for T1, T2, and T3 life stress assessments.

T1 life stress. Individuals who dropped out of the protocol during the 3-year maintenance phase were significantly more likely to have experienced a severe event at T1 (4 of 13 dropouts) compared to those who completed the formal protocol (2 of 40 completers; 31% vs. 5%), $\chi^2(1, N = 53) = 5.51$, $p < .02$. As noted previously, lower mean and variability scores for the HRSD during the maintenance phase also significantly predicted greater attrition during this phase. Controlling for these factors reduced the association for T1 severe events ($p = .20$). However, reversing entry order to control for T1 severe events also attenuated the contribution of these symptom indices ($p = .20$). Therefore, maintenance phase attrition is predicted largely by the shared variance between prior T1 severe events and later symptomatic functioning during this study phase. Undesirable events at T1 did not significantly predict attrition during the maintenance phase, $\chi^2(1, N = 53) = 2.36$, $p = .12$.

Finally, as noted before with regard to the preliminary analyses, whether or not the patient received psychotherapy was related to maintenance phase attrition in the present sample. Once psychotherapy status was controlled, T1 severe events continued to significantly predict attrition: $\chi^2(1, N = 53) = 5.61$, $p < .02$.[6]

T2 life stress. There was no difference in the dropout rate of patients with prior life events versus those without during the maintenance phase

T3 life stress. Individuals with and without undesirable events at T3 did not differentially drop out of treatment during this phase of the study.

Summary: Attrition

With regard to attrition over the continuation phase of treatment, T1 undesirable life events and higher concurrent depressive symptoms were significant predictors of patients leaving the protocol. Controlling for concurrent symptoms in the analysis, T1 undesirable events continued to significantly predict those who left during this study phase. (T1 severe events were significantly predictive only when concurrent symptom indices were controlled statistically.) With regard to the maintenance phase of treatment, T1 severe events also significantly forecasted greater attrition, whereas lower mean and variability in depressive symptoms also were associated with greater attrition. Further analyses indicated that T1 severe events and symptom indices during the maintenance phase were predictive because of common variance. Finally, analyses controlling for the effects of psychotherapy on attrition did not alter the basic findings. Overall, there is a consistent relationship wherein life stress prospectively predicts eventual patient loss from the protocol.[7]

Symptom Course

As noted in the *Preliminary Analyses* section, the number of days in the continuation and maintenance phases was significantly related to measures of symptoms during the respective phases. To control for this, we entered the number of days in the relevant study period initially into the respective regression analyses.

Continuation Phase Symptoms

Analyses are reported separately below for T1 and T2 life stress assessments.

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[6] We noted previously that of the 13 patients who left during this phase, 9 left against medical advice and 4 left for other reasons. The latter group included individuals who wished to continue in the protocol but could not owing to a variety of reasons (i.e., liver dysfunction; moved to foreign country; died in an accident; developed medical problems). Because these 4 patients might not be considered "true" dropouts, we ran secondary analyses excluding them. The results remained essentially unchanged: Patients who dropped out of the protocol were significantly more likely to have experienced a severe event (3 of 9 dropouts) at T1 compared to patients who completed the protocol (2 of 40 completers; 33% vs. 5%), $\chi^2(1, N = 47) = 4.96$, $p < .03$. Once again parallel to the findings for the continuation phase, the prediction afforded by T1 life stress cuts across many stated reasons for leaving the protocol.

[7] Although our approach has been to analyze the data separately for the continuation and maintenance phases assuming that the major phenomena of interest—associations between life stress and attrition or depressive symptoms—are likely to differ during these time periods, it is noteworthy that the findings for T1 life stress hold when the two treatment phases are combined. Collapsing across the continuation and maintenance phases, both T1 undesirable events and T1 severe events significantly predict overall attrition (63% of patients who dropped out had experienced an undesirable event vs. 30% who did not drop out, $p < .01$; 26% of patients who left experienced a severe event vs. 5% of those who completed the study, $p < .02$).

T1 life stress. None of the comparisons for mean symptoms or for the stability of symptoms were significant.

T2 life stress. Comparisons for continuation phase depressive symptoms or symptom variability did not reveal differences between individuals with and without T2 severe or undesirable events.

Maintenance Phase Symptoms

Analyses are reported separately below for T1, T2, and T3 life stress assessments.

T1 life stress. Individuals with a severe event at T1 who entered into the maintenance phase had lower mean BDI scores over the available assessments (F change = 4.24, $p < .05$) and greater stability in their BDI scores over time (F change = 6.19, $p < .02$).[8] With respect to the HRSD ratings, patients with a severe event at T1 also had lower mean levels (F change = 7.22, $p < .01$) and greater stability over time (F change = 8.89, $p < .01$). None of the analyses based upon undesirable events were significant. Because preliminary analyses indicated that subsequent medication treatment also was related to symptomatic functioning during this phase, analyses for the significant findings were run again controlling for medication status. T1 severe events continued to significantly predict mean BDI (F change = 4.05, $p < .05$) and variability (F change = 6.47, $p < .02$). With respect to HRSD ratings controlling for medication status, T1 severe events also significantly predicted HRSD mean scores (F change = 7.30, $p < .01$) and HRSD variability (F change = 8.67, $p < .01$).

T2 life stress. None of the comparisons for severe or undesirable events was significant with regard to mean depressive symptoms or variability during the maintenance phase.

T3 life stress. Patients with T3 undesirable events subsequently were more symptomatic during the maintenance phase compared to patients without such experiences. Mean BDI scores were significantly greater given prior T3 undesirable events (F change = 4.98, $p < .04$). BDI variability over this time period, too, was increased as a function of these prior stressors (F change = 7.07, $p < .02$). In terms of mean HRSD ratings, T3 undesirable events were again highly significant predictors (F change = 7.03, $p < .02$). HRSD variability, though, was unrelated to T3 undesirable events.

Subsidiary analyses taking medication status into account indicated that the findings for T3 stress were not due entirely to such treatment factors. T3 undesirable events still evidenced a trend to predict BDI mean scores: F change = 3.33, $p < .08$. BDI variability was predicted significantly by these types of experiences, F change = 6.10, $p < .02$. Mean HRSD scores also continued to be significantly predicted by T3 undesirable life events when controlling for medication status: F change = 4.96, $p < .04$. Because T1 severe events also predicted symptomatic functioning during the maintenance phase, further analyses were run to control for T1 severe events (in addition to medication status). T3 undesirable events no longer predicted BDI mean scores (F change = 2.08, $p = .15$), yet T3 undesirable events tended to predict mean HRSD scores (F change = 3.13, $p < .09$). Reversing entry order and controlling for T3 undesirable events (along with medication status), T1 severe events were still generally predictive of symptomatic functioning during this study phase: BDI mean scores (F change = 2.77, $p = .10$), BDI variability scores (F change = 4.68, $p < .04$), HRSD mean scores (F change = 5.35, $p < .03$), and HRSD variability scores (F change = 6.89, $p < .02$).

Summary: Symptom Course

Severe events from the T1 assessment predicted fewer depressive symptoms and more stable symptom profiles during the maintenance phase. These results were not altered appreciably once medication status was taken into account. In contrast, undesirable events at T3 predicted greater symptomatology during the maintenance phase. Again, the latter association tended to hold once medication status was taken into account statistically. However, these latter associations were attenuated when T1 severe events were controlled, with T1 severe events being the major predictor of symptom course during the maintenance phase. Overall, prior life stress predicts symptom course, but the nature of the prospective associations varies depending on the timing of the particular stressor involved.

Recurrence

Of the 53 persons who entered the maintenance phase in this subsample, 24 (45%) suffered a recurrence during the following 3 years. Below are reported the associations of T1, T2, and T3 life stress with this outcome. (See Figure 1.)

T1 Life Stress

Individuals with a severe event at T1 were less likely to experience a recurrence during the 3 years of maintenance treatment (0 of 6) compared to those without such stress (24 of 47; 0% vs. 51%), $\chi^2(1, N = 53) = 7.86$, $p < .01$. Controlling for medication status indicated that T1 severe events continued to be a highly significant predictor of nonrecurrence, $\chi^2(1, N = 53) = 8.26$, $p < .01$. Finally, because BDI variability during the continuation phase was also found previously to predict recurrence prospectively (see *Preliminary Analyses*), controlling for this predictor in addition to medication status did not alter the basic finding, $\chi^2(1, N = 51) = 7.31$, $p < .01$.

Because patients who dropped out during the maintenance phase tended to do so with fewer depressive symptoms, it seems reasonable to include them in the analyses as nonrecurrences. However, it might be argued that, given the lack of knowledge of their clinical fate for the full 3-year period, a more conservative approach would be to exclude them from these recurrence analyses. Patients with a severe event at T1 still tended to be less prone to recurrence (0 of 2) compared to those patients without a prior severe event when dropouts were excluded from these

[8] Three patients who made it to the maintenance phase had less than 2 BDI and HRSD assessments during this phase (owing to early recurrence). In addition, there were other—albeit relatively few—instances of missing data for these measures. Consequently, the data reported for these analyses during this period vary slightly in terms of the available n.

analyses (24 of 38; 0% vs. 63%), $\chi^2(1, N = 40) = 3.82$, $p = .051$. Similar associations held for severe events when excluding dropouts and controlling for medication status, $\chi^2(1, N = 40) = 3.89$, $p < .05$. Finally, when continuation phase BDI variability is added to medication status as a control variable, a severe event at T1 still tended to predict subsequent nonrecurrence for this sample excluding dropouts, $\chi^2(1, N = 40) = 2.89$, $p < .09$.

T2 Life Stress

Comparisons between patients with and without severe or undesirable life events at T2 were not significant predictors of subsequent recurrence.

T3 Life Stress

Individuals with an undesirable event at T3 were more likely to experience a recurrence (9 of 13) than those without such experiences (15 of 40; 69% vs. 38%), $\chi^2(1, N = 53) = 4.03$, $p < .05$. Controlling for the association between recurrence and medication status, the main effect of T3 undesirable life events is reduced below statistical significance ($p = .15$). However, there was a significant interaction between medication status and T3 undesirable life events predicting recurrence, $\chi^2(1, N = 53) = 7.73$, $p < .01$. The nature of the interaction suggests that the effect of life stress is conditional on the presence or absence of active medication. For patients receiving medication, T3 undesirable events predict a greater likelihood of recurrence compared to those without. For the patients not on medication, there is no association between recurrence and T3 undesirable life events.[9] Controlling additionally for continuation phase BDI variability, the interaction remains significant, $\chi^2(1, N = 51) = 4.79$, $p < .03$.[10]

Because T1 severe events were found previously to predict a lower likelihood of recurrence, further analyses were performed controlling for T1 severe events. The interaction between medication status and T3 undesirable events continued to be significant, $\chi^2(1, N = 53) = 8.74$, $p < .01$. The improvement in the model was also significant when entry order was reversed to test the independent prediction of T1 severe events beyond that afforded by T3 undesirable events and medication status (including their interaction), $\chi^2(1, N = 53) = 8.02$, $p < .01$. Controlling for continuation phase BDI variability in addition to T1 severe events and medication status did not appreciably alter the significant interaction between T3 undesirable events and medication status, $\chi^2(1, N = 51) = 5.91$, $p < .02$. Reversing entry order in this analysis did not influence to any important extent the contribution afforded by T1 severe events beyond T3 undesirable events, medication, and their interaction, $\chi^2(1, N = 51) = 7.28$, $p < .01$. Overall, both types of stress independently predict recurrence, yet in an opposite manner.

Once again addressing the matter in a more conservative manner by omitting maintenance phase dropouts from these analyses, T3 undesirable events continue to evidence a trend predicting recurrence (82% vs. 52%), $\chi^2(1, N = 40) = 3.24$, $p < .08$. Controlling for medication status again reduces the variance accounted for by undesirable events below statistical significance ($p = .12$), whereas the interaction between medication status and undesirable events remains significant, $\chi^2(1, N = 40) = 4.77$, $p < .03$.[11] Controlling additionally for continuation phase BDI variability, the significance level of the interaction is reduced, $\chi^2(1, N = 40) = 2.67$, $p < .11$.[12]

Controlling for T1 severe events in these regression analyses excluding dropouts still indicates the significance of the T3 undesirable events and medication interaction, $\chi^2(1, N = 40) = 5.08$, $p < .03$. Reversing entry order to conservatively test the predictive utility of T1 severe events after controlling for T3 undesirable events, medication status, and their interaction, T1 severe events continued to reveal a trend toward significance, $\chi^2(1, N = 40) = 3.53$, $p < .07$.[13] Once again, the interaction for all analyses suggested that the effect of undesirable events held primarily for the patients who received active medication.

Finally, given concerns about relatively low cell frequencies in particular cells of these analyses (see Footnotes 9 and 11), we added 63 new patients to the sample for the specific purpose of replicating and extending the T3 undesirable life events and medication interaction. (These new patients are identical in characteristics to the core group of patients previously analyzed, except that owing to resource limitations we do not have life stress information for them on treatment entry [T1]. Their

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[9] In terms of the separate cells, 3 of 3 (100%) individuals on medication with an undesirable event suffered a recurrence versus 3 of 21 (14%) individuals on medication without such events; 6 of 10 (60%) individuals not on medication with an undesirable event suffered a recurrence compared to 12 of 19 (63%) individuals not on medication without an undesirable event. This suggests that patients on medication without T3 undesirable events have the lowest likelihood of recurrence. The numbers are small, however, once the interaction is probed, raising concerns about the reliability of the effect—a point we address in more detail. (The interaction was tested as a routine precaution to satisfy the requirements of homogeneity of regression lines in covariate regression analysis, not as a primary prediction.)

[10] Note, too, however, that although patients were randomized to treatment conditions, T3 undesirable events tended to be more common in the nonmedicated treatment groups (11 of 29) compared to the medicated treatment groups (2 of 24; 38% vs. 8%), $\chi^2(1, N = 53) = 3.60$, $p < .06$.

[11] In terms of the separate cells for this interaction, 3 of 3 (100%) individuals on medication with an undesirable event suffered a recurrence versus 3 of 13 (23%) individuals on medication without such events; 6 of 8 (75%) individuals not on medication with an undesirable event suffered a recurrence compared to 12 of 16 (75%) individuals not on medication without an undesirable event. This again suggests that patients on medication without T3 undesirable events have the lowest likelihood of recurrence.

[12] Note, too, that the previous trend for an association between T3 undesirable events and medication status is no longer evident for this more conservative analyses; that is, T3 undesirable events were no more common in the nonmedicated treatment groups (8 of 24) compared to the medicated treatment groups (3 of 16; 33% vs. 19%), $\chi^2(1, N = 53) = 1.06$, $p = .30$.

[13] Controlling for continuation phase BDI variability in addition to T1 severe events and medication status slightly reduced the significant interaction between T3 undesirable events and medication status, $\chi^2(1, N = 40) = 3.09$, $p < .08$. Reversing entry order in this analysis did reduce the contribution afforded by T1 severe events beyond T3 undesirable events, medication, and their interaction for this analysis: $\chi^2(1, N = 51) = 2.77$, $p < .10$.

inclusion therefore is confined to further probing and documenting the specific T3 undesirable events and medication condition interaction.) In terms of the main effects, individuals with an undesirable event at T3 tended to be more likely to experience a recurrence (25 of 43) than those without such experiences (30 of 73; 58% vs. 41%), $\chi^2(1, N = 116) = 3.16$, $p < .08$. Controlling for the association between recurrence and medication status, the main effect of T3 undesirable life events again was reduced below statistical significance ($p = .44$). However, the interaction between medication status and T3 undesirable life events is again highly significant, $\chi^2(1, N = 116) = 11.65$, $p < .001$. The nature of the interaction is identical to the previous one: For patients receiving medication, T3 undesirable events predicted a greater likelihood of recurrence compared to those without; for the patients not on medication, there was no association with T3 undesirable life events.[14] Controlling additionally for continuation phase BDI variability, the interaction remained significant, $\chi^2(1, N = 116) = 9.92$, $p < .01$.[15] Adopting again a more conservative approach and confining the sample to only patients who did not drop out during the maintenance phase, the trend for T3 undesirable events as a main effect is no longer evident ($p = .10$). Most important, however, the interaction between T3 undesirable events and medication status remains highly significant, $\chi^2(1, N = 93) = 10.64$, $p < .01$.[16] Controlling additionally for continuation phase BDI variability, the interaction continues to be significant, $\chi^2(1, N = 116) = 9.46$, $p < .01$.

It is worth noting that the significant interaction between T3 undesirable events and medication status is essentially independently replicated in this new sample of 63 added patients. In all approaches to analyzing the question (i.e., testing only the main effects and subsequent interaction; controlling additionally for BDI variability during the continuation phase; using the full 63 patient sample or only the 53 patients who did not drop out during the maintenance phase), the T3 undesirable events and medication status interaction remained highly significant (all $ps < .01$).

Summary: Recurrence

Both severe events at T1 and undesirable events at T3 predicted recurrence, but with an opposite direction of association. Severe events at T1 foreshadowed a lower likelihood of eventual recurrence, whereas undesirable events at T3 predicted a higher likelihood of recurrence. Subsidiary analyses to determine the robustness of these effects across different treatments indicated that the effects for severe events at T1 was independent of medication treatment, whereas the effect for undesirable events at T3 primarily was conditional on receiving active medication. Both forms of life stress prospectively forecasted recurrence or nonrecurrence independent of one another.

Discussion

In general, life stress was found to predict attrition, symptom course, and recurrence. Yet the effects were more complicated than originally hypothesized, varying with respect to the specific type of stress and the timing of the particular clinical outcome under consideration (see Figure 3 for a summary of the findings). Perhaps most important, these results demonstrate how stress, attrition, and symptom course interrelate over time, which in turn sculpts the empirical picture of recurrence and its correlates. In discussing these findings, we first address separately the major study hypotheses. We then take a more integrative perspective, discussing the collective implications of life stress, attrition, and symptom course for the prediction of recurrence. Finally, we conclude with a discussion of the strengths and weaknesses of the present work, providing suggestions for future research.

Attrition

One of the most remarkable findings is that life events assessed at T1 prospectively predicted attrition over the following 3 years. Patients with an undesirable event occurring during the 12 weeks prior to treatment entry (T1) were more likely to exit the protocol during the continuation phase (71% vs. 36%). Similarly, patients with a severe event at T1 were at greater risk for dropping out during the maintenance phase (67% vs. 33%). Overall attrition (combining both continuation and maintenance attrition) indicates that people with a severe event at T1 were much more likely to not complete the study (78% vs. 34%), as were people with any T1 undesirable event (59% vs. 26%; see Footnote 7). Thus, attrition is more than twice as likely for an individual with recurrent depression, given the presence of stress prior to entry into treatment.

To obtain a more complete picture of the implications of life stress over time, it is useful to combine these findings with those of our previous report on life stress and acute treatment response (Monroe, Kupfer, & Frank, 1992). In terms of not completing the protocol, for the original sample of 91 patients 7 dropped out during acute treatment, 17 did not respond to initial treatment, 14 did not complete the continuation phase, and 13 dropped out during the maintenance phase. Casting these numbers cumulatively in terms T1 life events is especially illuminating. Of the 18 patients with a severe event at T1, only 2 completed the entire longitudinal protocol (11%, vs. a 52% completion rate for patients without such stress). Of the 46 pa-

[14] In terms of the separate cells, 7 of 11 (64%) individuals on medication with an undesirable event suffered a recurrence versus 5 of 38 (13%) individuals on medication without such events; 18 of 32 (56%) individuals not on medication with an undesirable event suffered a recurrence compared to 25 of 35 (71%) individuals not on medication without an undesirable event. This again indicates that patients on medication without T3 undesirable events have the lowest likelihood of recurrence.

[15] It should be noted, though, that again there was an unexpected association between incidence of T3 undesirable events and medication status (i.e., fewer events for patients on medication), $\chi^2(1, N = 116) = 8.03$, $p < .01$.

[16] In terms of the separate cells, 7 of 9 (78%) individuals on medication with an undesirable event suffered a recurrence versus 5 of 26 (19%) individuals on medication without such events; 18 of 27 (67%) individuals not on medication with an undesirable event suffered a recurrence compared to 25 of 31 (81%) individuals not on medication without an undesirable event.

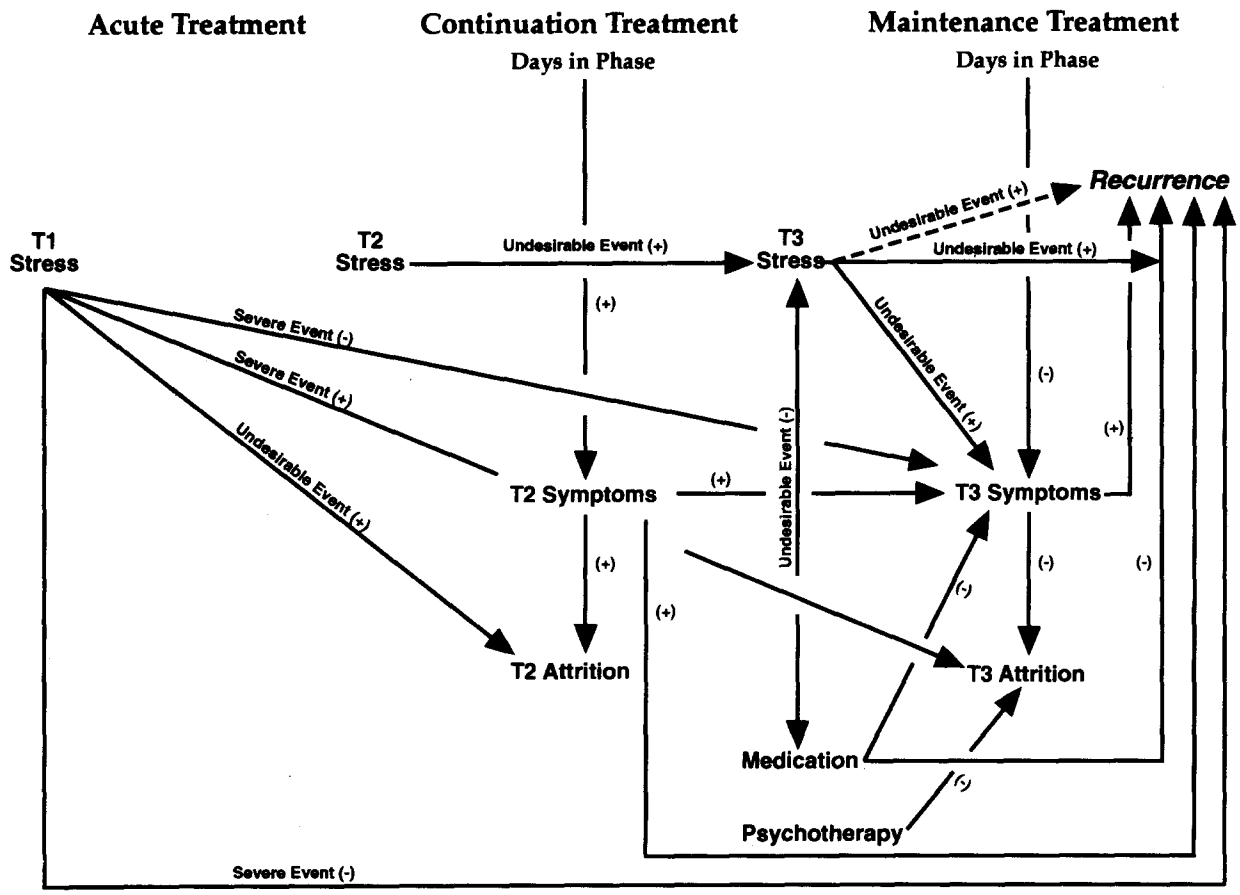

Figure 3. Summary figure of the major study findings. (We thank an anonymous reviewer for providing the basic form for this figure.) T1 = acute treatment entry; T2 = continuation phase; T3 = maintenance phase.

tients with an undesirable event preceding T1, only 12 completed the study (26%, vs. a completion rate of 62% for patients without such stress).[17] Overall, there is a clear and very strong prospective association between life stress occurring prior to treatment entry and patient loss over prolonged periods of time.

The underlying reasons for attrition from the study, however, change over time. As indicated in our previous research, many individuals with recurrent depression who suffer severe life events prior to treatment entry never meet clinical response criteria and thereby by definition are excluded from further study of postrecovery course (Monroe, Kupfer, & Frank, 1992). Once there is a clinical response, however, the mechanisms underlying attrition likely change. For the continuation phase, examining the reasons recorded for withdrawal indicate that the majority of individuals left because of depression-related matters (6 had a relapse, 1 had an overdose, and 1 did not sustain recovery). Other causes for departure included intolerable side effects (n = 3), noncompliance with medication schedule (n = 2), and moving (n = 1). However, it appears that the prediction from prior life stress holds primarily for patients who left because of "other causes" and not because of depression-related reasons. This is an important point, for it indicates that the present findings cannot be attributed to design-imposed symptom restrictions during the continuation phase. In other words, these results place greater confidence in the generalizability of the findings for stress and postrecovery attrition. Overall, there may be two subgroups of people who leave during the continuation phase: those with problematic symptoms who tend not to have prior life stress and those with lower symptoms who tend to have prior life stress.

For the 3-year maintenance phase, the findings are even more apparent with regard to selective attrition, symptomatic course, and prior life stress. Although mean ratings of depressive symptoms and variation over time were significantly reduced for patients with T1 severe events, such events simultaneously predicted an increased likelihood of leaving the protocol. Thus, attrition during this phase of the study is predominantly associ-

[17] Of the 73 patients without severe events, 38 remained in the final sample, and the comparison with dropouts is highly significant statistically, $\chi^2(1, N = 89) = 11.19$, $p < .001$. Of the 45 patients without undesirable events, 28 remained in the final sample, and the comparison with dropouts again is highly significant statistically, $\chi^2(1, N = 89) = 12.35$, $p < .001$.

ated with prior life stress and factors not related to poor clinical status. Once again, the effect of stress on attrition appears to be relatively nonspecific, covering a wide range of possible reasons.

One explanation of such nonspecific effects of stress may be that individuals for whom stress was associated with their symptoms are less likely to view continued treatment as necessary once the episode and symptoms (and perhaps stress) subside. Consequently, they may have less motivation to remain in a time-consuming treatment protocol and possess a lower "threshold" for leaving because of various reasons. The nature of the present sample—individuals with recurrent depression with a minimum of three lifetime episodes of major depression—casts some doubt on this view (for such individuals would be more likely to see their psychiatric problems in a chronic light and deserving of continued treatment). Yet additional comparisons of responders who completed the protocol versus those who did not, and more importantly of patients with severe events prior to treatment entry versus those without, suggest that people with fewer lifetime episodes of depression were less likely to complete the protocol (respectively, $p < .03$; $p < .02$). It is conceivable, then, that prior stress may be associated with a lower threshold for deciding to leave treatment. A somewhat complementary perspective is that lower symptoms may mediate the relationship between early life stress and later attrition. That is, because patients who experienced a severe event at T1 also were found to have fewer symptoms during the maintenance phase, it may be that experiencing fewer symptoms is a means through which there is a lowering of the threshold for leaving treatment.[18]

Alternatively, stress may reflect broader life issues and contexts that have a bearing on clinical response and long-term treatment adherence (Monroe & Depue, 1991). There are several ways to conceptualize this issue, all of which entail viewing stress as a relatively enduring feature of the individual's life. First, stress may be a marker for "stormy lifestyles" (Zimmerman et al., 1987). Second—related yet more benign—stress may be a marker for eventful environments. Finally, there may be a combination of these two alternatives (Hammen, 1991; McGuffin, Katz, & Bebbington, 1988; Monroe & Simons, 1991). This raises the possibility that the measures of stress prior to treatment entry serve as a "marker" for individuals who have more permanent stressful conditions in their lives or perhaps lives that are simply more frequently "in flux." Although life stress tended not to be highly correlated over time in the three assessments for the present study, the time points selected may not be representative of the patient's typical life situation (particularly with regard to the effects of depression and treatment). It remains to be examined in greater detail how such hypothetical eventful environments or characteristics of the person may lead to a diminished likelihood of adhering to long-term treatment and may relate to symptom course. Yet it could be that such early stress reflects an underlying propensity for a variety of life changes, all of which conspire against remaining in treatment (e.g., from moving through being "too busy" to continue in treatment). Overall, the data suggest that many factors must be considered with regard to the reasons why such forms of stress predict future attrition.

Symptom Course

Contrary to our expectations, severe events occurring prior to treatment entry did not predict a worse postrecovery symptom course. It is interesting that severe events assessed at T1 predicted a more favorable postrecovery symptom course during the maintenance phase. (Also of note is that this effect held even when medication status was taken into account.) Yet in light of the strong effects of T1 severe events on recovery as documented previously (Monroe, Kupfer, & Frank, 1992), along with the present consequences of T1 severe events for attrition, these associations must be interpreted cautiously. One cannot easily isolate the operative element between stressors, timing of stressors, and the shifting composition of the sample over time. Yet this does not mean that the present results are not without substantive importance. For example, it is clear that for those who remain in the study by the continuation phase, patients with prior severe stress have a more benign postrecovery clinical course. Furthermore, stressors occurring at a later point in time predict increased symptoms and a greater likelihood of recurrence for patients who remain (i.e., T3 undesirable events).

These results may help to explain some inconsistencies in the literature with regard to life stress and treatment outcome. Several investigations have found prior life stress to predict a better treatment outcome, whereas other studies have reported life stress to predict a relatively poor outcome (see Monroe & McQuaid, 1994). These inconsistencies largely have been attributed to differences in methods or participant samples. For example, we previously suggested that prior life stress may be associated with a more favorable treatment course for patients without a history of prior depression but may be related to a relatively poor treatment course for patients with recurrent depression (Monroe, Kupfer, & Frank, 1992). The present results, however, extend these findings to suggest that the timing of outcome comparisons is another important consideration, which suggests different processes involved with life stress. Thus, people with prior life stress and recurrent depression tend to do poorly during acute treatment and over short time periods. However, people with prior life stress and recurrent depression who recover subsequently exhibit a better follow-up course. In other words, life stress may inhibit the potential for recovery for some individuals, but for those who do recover, life stress may signify a subset of patients who will display a more favorable postrecovery symptom course.

In important contrast to the findings for T1 life stress, though, are the prospective findings for T3 undesirable events presaging a more problematic symptom course during the maintenance phase. As originally hypothesized, stress at this time point was associated prospectively with a more noxious symptom profile. Again, this effect held once relevant treatment variance was accounted for (i.e., medication status). This indicates that despite the progressive loss of many patients over time (many of whom leave in association with prior life stress), stressors occurring at a later date still are prognostic of subsequent symptomatology. Thus, undesirable events occurring well after

[18] We thank an anonymous reviewer for pointing out this interesting possibility.

initial recovery prospectively predict later postrecovery symptoms and even more clinically severe outcomes, as is discussed in the next section.

Recurrence of Depression

The present findings also suggest that life stress over time reflects different processes of relevance for the recurrence of depression. In terms of life stress prior to treatment entry, the selective attrition of patients in relation to antecedent life stress qualifies interpretations. For example, if for some individuals prior stress serves as a marker for a turbulent social milieu or for stress responsivity, and if such stress also is related to both the probability of dropping out and the probability of recurrence, differential loss of these people from the study lessens the likelihood that the contribution of stress to recurrence would be detected. In fact, one would expect the outcome that was actually found: Individuals with prior life stress who remained are from a different subset of individuals with more stable environments, or who are more stress resilient, and therefore less likely to experience a recurrence. Nonetheless, we acknowledge this difference from our original predicted outcome and await further work with larger samples to clarify how life stress over time might and might not forecast eventual recurrence.

Another way to view this matter would be that life stress prior to treatment entry serves as a marker for persons who are relatively unlikely to have a subsequent recurrence. Individuals who do not experience life stress just prior to treatment entry could possess a greater diathesis for recurrent depression; they would be more likely to make it into the sample initially and would be more likely to suffer a recurrence after recovery. In contrast, patients who were depressed initially in association with life stress occurring prior to treatment entry are less likely to succumb again (owing to their lower diathesis). In the present data, prior stress "marks" individuals with lower maintenance phase symptoms, as well as a lower likelihood of recurrence. Lack of such stress "marks" individuals with possibly greater diatheses, which are evident in greater ongoing dysregulation of affective functioning and a higher likelihood of recurrence. In general, then, prior life stress might not be directly related to subsequent nonrecurrence per se, but rather prior life stress might signal persons with different diatheses and consequently different probabilities of recurrence.[19]

However, and quite essential, life stress occurring at a later point in time still predicts clinical recurrence, albeit most potently in interaction with medication treatment. In keeping with the findings for life stress and symptom course during the maintenance phase, T3 undesirable events portended a greater likelihood of recurrence. Thus, despite concerns raised by the effects of T1 stress on attrition as well as the possible implications of T1 stress for a lower likelihood of subsequent recurrence, T3 stress was an important element in predicting subsequent clinical consequences. Yet the average time to recurrence was approximately 28 weeks in the present sample; further research is required to understand how T3 stress impacts over this time frame to increase the probability of later recurrence. Once again, larger patient samples and more detailed information on the lives of the people during the maintenance phase are required to address this important issue.

It is interesting that T3 undesirable events interacted with medication status in predicting recurrence. The effect of life stress appears to be primarily for individuals receiving active medication. Although this may seem counterintuitive (i.e., it would be the unmedicated individuals who would seem to be more vulnerable to the adverse effects of life stress), one must bear in mind the nature of the present sample. Patients were carefully selected to have a high likelihood of recurrence (and indeed the proportion experiencing this outcome in the present sample attests to the success of these procedures). It is likely that the diathesis for depression is unusually strong for these patients and that without effective intervention recurrence is a very frequent outcome because of a variety of factors that may bring about episode onset. Given such a relatively high proportion of people suffering recurrence without effective intervention (68% of unmedicated patients suffered recurrence in the full sample; Frank et al., 1990), there may be relatively little specific predictive capability for life stress. Other nonstress factors, such as biological predisposition, may primarily determine outcome or dilute stress effects. Effective treatment—active medication in this case—may lower the overall liability to depression, so that different factors can come into play with respect to the probability of recurrence. In a sense, medication might help "turn back" a developmental progression of the pathological processes that become established with successive episodes.

Such thinking is in line with such notions as stress sensitization, wherein active medication partially reverses the kindling and sensitization process, and reintroduces the pivotal importance of life stress (Post, 1992). Alternatively, it is conceivable that life stress may affect medication compliance, which in turn affects vulnerability (Frank, Perel, Mallinger, & Thase, 1992). Once again, further work is required to replicate these findings based on relatively small numbers and to test further facets of the issue. Overall, though, the prospective relationship of stress with recurrence in this population points toward potentially important considerations for understanding recurrence and its prevention.

Collective Implications

Most research on life stress and depression has focused on the role of stress in the onset of depression. Yet it is not surprising

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[19] We are grateful for the comments of an anonymous reviewer and Ken Sher that helped to clarify this point. In response to their comments, we ran exploratory analyses comparing patients in the maintenance phase with and without T1 severe events along a variety of clinical and demographic variables. (This was done to help clarify other dimensions along which such patients might differ and thereby to possibly further inform our interpretations of the data.) The only statistically significant comparisons between the two groups was that patients with T1 severe events had fewer prior depressive episodes than patients without such events ($M = 4.33$ vs. $M = 7.13$), $t(41.74) = 2.05$, $p < .05$. Thus, this fits nicely with the interpretation that T1 severe events may serve as a marker for individuals who have a lower diathesis for depression.

that life stress also predicts other aspects of behavior that have a bearing on clinical matters. This issue becomes most apparent when stress effects are examined over more prolonged periods of time, as in the present investigation. These effects, if not understood, can cloud perspectives on the role of stress in the genesis of depressive episodes. For example, the present findings indicate that the notion of a "differential sieve" operating over time in longitudinal studies of psychopathology is quite plausible (Hollon et al., 1991). Individuals with recurrent depression with increased life stress prior to or shortly after treatment entry appear to drop out, or are terminated from, the protocol over time in longitudinal treatment studies at a higher rate than those without prior life stress. Such processes place important caveats on inferences drawn from analyses based on the final sample. The reasons given for leaving or terminating treatment among patients in the present study suggest that it will not be easy to design studies to avoid this selective attrition. However, it is feasible to routinely assess the forms of stress found to be predictive, as well as to periodically monitor the clinical status of those who do not complete a protocol to ascertain their eventual clinical fate.

Other consequences of stress, too, may subtly modify our picture of depression in clinical populations. For instance, in a recent study with a different sample of patients we found that life stress influences the timing of entry into treatment following onset of a depressive episode (Monroe et al., 1991). Life stress may therefore also serve as a selective filter for who enters treatment. Most broadly, life stress may influence who seeks treatment and when, who responds to treatment and when (Monroe, Kupfer, & Frank, 1992), as well as who leaves treatment and when. Thus, although studies of treatment of depression and the factors related to long-term outcome are clearly needed, findings on the basis of such work alone portray only part of the picture of depression over time. These limitations might be particularly relevant for shedding light on relationships with life stress. It is in the dynamic relations between stress, treatment seeking, attrition, and symptom course that longitudinal research can begin to provide a better perspective on the nature of recurrence: its predictors, causes, and possible limitations of current research designs for fully explicating such processes.

Few prospective studies exist on life stress and recurrence, and none to our knowledge has examined the issue over a 3-year period of continued observation incorporating three separate life stress assessments. The procedures used in the present study to assess life stress, the measures of clinical status, and the methods used to define recurrence provide a strong methodological foundation for testing the study hypotheses. Yet possible limitations should be addressed. One might wonder how representative our sample was in terms of treatment participation. For example, if participants in this investigation were more likely to drop out than participants in other treatment studies, then the questions we have raised about the generalizability of other research would be limited. We believe, however, the opposite to be the more probable reality. Patients in the present study were attended to solicitously and continuously, and many found the clinic and its personnel to be the first remedy to their chronic disabilities associated with depression and thereby a stable refuge. Extreme effort and expense was provided to keep people in the protocol and to follow them at periodic intervals if they moved within a reasonable distance. Consequently, attrition was probably minimized. Indeed, the overall attrition rate was among the lowest reported in a clinical trial for depression extended over such a long period of time. Perhaps the most likely generalizability implication would be that our data underestimate the association between life stress and attrition for other longitudinal treatment studies.

Of course, other generalizability issues must be recognized and targeted for future study. For example, our findings apply most readily to patients with a history of highly recurrent depression. Additional work is needed to clarify whether such processes might extend to patients with fewer lifetime episodes or patients with nonrecurrent depression (Monroe & McQuaid, 1994). Furthermore, the findings are predicated on patients who have recovered from a particular combination of treatment (i.e., IPT and imipramine) and who are continued in different permutations of these treatments (plus a placebo condition). Patients recovering with the aid of other forms of intervention, and perhaps more pointedly patients who do not maintain continued treatment postrecovery, may evidence different associations with life stress. Future research should demarcate the boundaries of generalizability for the present findings.

Given the longitudinal nature of the present research, there are several predictors and clinical outcomes of relevance over time. This necessarily results in a rather large number of analyses and consequently raises legitimate concerns about experimentwise error. (Additionally, controlling for other predictors in our subsidiary analyses increases the internal validity of our major findings while simultaneously adding somewhat to concerns about chance effects.) We have tried to be relatively specific in our analyses targeting our primary hypotheses, yet we note that the substantive strengths of the research must be weighed against this methodological weakness.

Notable in terms of an absence of effects are the findings for long-term difficulties. Despite a reasonable incidence of difficulties in the sample (see Table 1), they were not strong predictors of any of the major outcomes. It appears that acute forms of stress, rather than chronic ones, are more important for predicting treatment participation, symptom course, and recurrence.[20] In terms of T2 life stress, there were fewer associations overall with the dependent measures than with stress assessed at the other two time points. Although the findings again indicate that postrecovery symptom course can be exacerbated by postrecovery stressors, it appears that stressors at this point in time (T2) are not systematically related to later attrition or to subsequent recurrence. Whereas this could be due simply to a lack of highly stressful events reported during this time period for the

[20] We have noted before that this may be in part due to the manner in which ongoing difficulties were initially assessed in the present study compared to the manner in which the LEDS interview covers such material (Monroe et al., 1991). Despite this difference, however, there was clearly sufficient frequency of ongoing stressors in the present sample, suggesting that such forms of adversity are not strongly associated with the outcomes in the current investigation. Nonetheless, future work using the full LEDS interview should be performed before such possible effects can be ruled out with confidence.

present sample (i.e., severe events), it might also suggest that (a) effective treatment lowers the likelihood of extreme stressors occurring at this time, (b) following a recently sustained response patients are relatively immune to highly adverse consequences of stress (e.g., a type of refractory period with regard to stress effects in treatment), or (c) stressors occurring just after a clinical response simply do not influence the likelihood of leaving treatment prematurely or of later recurrence. Further work on larger samples experiencing more severe forms of stress will help to clarify this issue.

Finally, the data on life stress in the present study covered the 12-week period prior to the acute, continuation, and maintenance phases of treatment. It will be useful in future work to enlarge the temporal scope of stress assessments, both retrospectively and prospectively, for we have been able to cover only a small portion of the time period involved with regard to the assessment of life stress. Retrospectively, it is important to distinguish between stressors occurring prior to onset and those occurring after onset of the depressive episode. For example, because we restricted our assessment of life stress to the 12 weeks prior to treatment entry, and the mean time between onset of the index episode and treatment entry for the present sample was 24 weeks, our stress measures do not directly address etiologic considerations. Assessments must be explicitly geared toward determining onset timing and then probing psychosocial circumstances preceding onset. Prospectively, it will be useful to monitor at regular intervals the life stress of each individual as he or she progresses further through the protocol to determine whether subsequent stressors affect the clinical course of the disorder.

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