

Research Article

ACUTE AND CHRONIC STRESS EXPOSURE PREDICTS 1-YEAR RECURRENCE IN ADULT OUTPATIENTS WITH RESIDUAL DEPRESSION SYMPTOMS FOLLOWING RESPONSE TO TREATMENT

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Background: *One of the strongest predictors of depression recurrence in those who respond to treatment is the presence of residual depressive symptoms. Our goal was to examine stressful life event exposure as a mechanism of recurrence in previously depressed patients with residual depression symptoms. That is, we predicted that higher levels of residual symptoms will significantly predict exposure to acute life events that will then heighten prospective recurrence risk.* **Methods:** *Participants included 68 adult outpatients with major depression (42 women; age 18–60) who completed a 12-month naturalistic follow-up after achieving remission in a 20-week randomized, open label trial of interpersonal psychotherapy, cognitive-behavioral therapy, or antidepressant medication. Depression recurrence was defined as the reemergence of an episode of major depression as determined by structured interview. Acute life events and chronic stressors were assessed at the end of follow-up using a contextual interview.* **Results:** *Posttreatment depression scores significantly prospectively predicted an increased risk for recurrence, and acute life events in the follow-up period. Cox regression survival analyses modeling life events as time-dependent covariates showed that life event exposure mediated the relation of residual symptoms to recurrence even controlling for chronic stress.* **Conclusions:** *Our findings implicate residual symptoms in heightening depression recurrence risk through exposure to stressful life events. Depression recurrence adds significantly to the burden of the disorder. Therefore, rigorous follow-up of patients targeting the stressful context has the potential to prevent a lifelong pattern of illness.* *Depression and Anxiety 31:1–8, 2014. © 2013 Wiley Periodicals, Inc.*

Key words: *depression; life events/stress; treatment; stress; empirically supported treatments*

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INTRODUCTION

Major depressive disorder (MDD) is a highly recurrent condition,^[1,2] and even among patients who respond to treatment, recurrence rates remain as high as 50% within 2 years.^[3–6] One of the strongest predictors of recurrence in those who respond to treatment is the presence of residual depression symptoms,^[6–9] with a greater number of residual symptoms significantly predicting recurrence in trials of antidepressant medication

(ADM),^[10] interpersonal psychotherapy (IPT),^[11] and cognitive therapy (CT).^[12,13]

Treatment continuation and maintenance strategies have shown success in decreasing relapse and recurrence rates following acute treatment. For example, continuation-phase CT (C-CT)^[14] reduced recurrence rates compared to supportive control from 74 to 36% over a 2-year follow-up, and was most effective in preventing recurrence in patients with the highest levels of residual symptoms.^[15] Similar decreases in recurrence rates have been reported following maintenance medication^[5] and maintenance IPT.^[16] These results are encouraging. Nevertheless, recurrence rates of over one third of patients are still high, particularly given that they occur despite rigorous time- and cost-intensive continuation and maintenance interventions.^[17] We critically lack an understanding of the mechanisms that link residual symptoms to recurrence. Knowing why residual symptoms are associated with an increased risk of recurrence may ultimately lead to cost-effective refinements to acute treatments that promote the ultimate goal of full and lasting recovery.^[3]

Studies of the prospective course of MDD have shown repeatedly that stressful life events are the strongest proximal predictors of MDD onset,^[17-19] and are crucial contributors to recurrence.^[20-22] For example, evidence from two independent trials of maintenance IPT in women with recurrent MDD^[23,24] has shown that acute life events (e.g., fired from job) experienced during the maintenance phase following treatment response significantly predict MDD recurrence, as well as a shorter time to recurrence.^[25,26] Of specific relevance to the current study, naturalistic prospective studies have demonstrated that subsyndromal depression symptoms are associated with a variety of stressful contexts, including higher levels of chronic stress, as well as the generation of dependent life events (e.g., relationship breakups), and prospective exposure to independent stressors (e.g., friend's suicide attempt).^[27-31] In sum, findings on recurrence following successful treatment suggests three things. First, the presence of residual symptoms following response to acute treatment increases risk for recurrence. Second, subthreshold depression symptoms are associated with elevated levels of stressful life events. Third, stress significantly increases risk for recurrence. In the current study we propose a mechanism that integrates these independent research findings. Specifically, we propose that the presence of residual symptoms following treatment response prospectively heightens risk for exposure to both dependent and independent stressful life events, which subsequently heighten risk for depression recurrence.

We provide a rigorous test of the above model by controlling for the background context of chronic stress (e.g., chronic financial difficulties, ongoing family conflict). This is important because chronic stress also increases the likelihood of exposure to, and generation of, acute stressful life events.^[32,33] Further, as noted above, chronic stress is associated with less symptom

improvement, and higher concurrent rates of recurrence, in studies of depressed outpatients.^[34,35] Despite these documented relations, to our knowledge, there are no prospective studies examining the role of chronic stress in triggering recurrence. Furthermore, very few studies control for chronic stress when examining the association between acute stressful life events and recurrence.^[36]

The current design involved a 16-week randomized trial of Cognitive Behavioral Therapy (CBT), IPT, and ADM with a 12-month naturalistic follow-up. Our hypotheses pertain to patients who met criteria for a sustained response to the acute treatment trial and were entered into the follow-up phase. First, we hypothesize that higher acute treatment end-point depression severity scores (i.e., residual symptoms) will prospectively predict a higher likelihood of recurrence. Second, higher levels of residual symptoms will be associated with higher levels of chronic stress, and will prospectively predict a greater likelihood of acute stressful life events in the follow-up period. Finally, acute stressful life events will mediate the predictive relation of residual symptoms to recurrence controlling for level of chronic stress.

MATERIALS AND METHODS

PARTICIPANTS

Ethical approval for this study was obtained by the Research Ethics Board at the Centre for Addiction and Mental Health, University of Toronto. All patients provided written informed consent. Inclusion criteria were (1) Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)^[1] criteria for MDD; (2) age between 18 and 60; (3) Hamilton Depression Rating Scale (Ham-D) ≥ 16 ^[37]; (4) no ADM or electroconvulsive therapy (ECT) in the past 6 months. Patients were excluded if they met DSM-IV criteria for bipolar disorder, a psychotic disorder, substance disorders, organic brain syndrome, or a concurrent medical illness.

The study flow chart and results of the acute treatment trial have been presented previously.^[38-40] Briefly, of the 466 participants who were recruited from community mental health providers or newspaper advertisements and attended an initial clinical interview, 209 met study criteria and were randomized. Consistent with published attrition rates,^[41,42] 69 patients (33%) did not complete the protocol. Of the 140 completers, 108 (77%) met criteria for a sustained response (see below) and were entered into the 12-month follow-up phase. The 31 patients who failed to respond to treatment were offered further treatment outside of the protocol.

Sixteen patients (15%) did not complete the follow-up phase. This attrition rate is similar to that reported in previous examinations of MDD recurrence following CBT, IPT, or ADM.^[3,5,43] Those who completed the follow-up did not differ from dropouts on any demographic or clinical variable (all P s > .10). Importantly, dropouts were neither differentially distributed across treatment conditions, $\chi^2(2) = 2.44, P = .30$, nor did they differ significantly from completers in level of residual symptoms (M s = 3.00, 4.26; S Ds = 2.66, 3.81; $t[106] = 1.27, P = .21$). Life event data were missing for 24 patients (26%) because they either could not be contacted for the interview or they refused the interview. Therefore, the sample with complete data comprised 68 patients. There were no significant differences between patients who did or did not receive the interview on any demographic or clinical variable (all P s > .21). Importantly, patients who did or did not receive the interview were neither differentially distributed across treatment

conditions, $\chi^2(2) = 4.49, P = .11$, nor did they differ in terms of level of residual symptoms, $M_s = 4.04, 4.34; SD_s = 2.60, 4.16; t(65.26) = .41, P = .69$, or recurrence status, $\chi^2(1) = .38, P = .54$.

MEASURES

Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P). [44] The SCID-I/P was used to diagnose MDD and other Axis I disorders. Clinical psychology doctoral students trained to "gold standard" reliability status and supervised by a licensed clinical psychologist with extensive experience in clinical trials conducted the diagnostic interviews. The SCID I/P has strong reliability and validity.^[45]

Hamilton Depression Rating Scale (Ham-D). The 17-item Ham-D is a semistructured, clinician-rated interview designed to assess severity of depression.^[37] It is the most widely used measure of depression severity in clinical trials.^[46]

Life Events and Difficulties Schedule (LEDS-II). [47] The LEDS is a semistructured contextual interview and rating system that collects detailed information regarding acute life events and chronic stressors in several domains (e.g., health, education, relationships, etc.). Interviews were audiotaped, and a team of two to four coders rated each life event and chronic stressor using the LEDS manual that includes over 5,000 anchored examples and rating rules. Interviewers and raters were unaware of patients' treatment assignment, recurrence status, or subjective reaction to the stressors, and all received extensive training and supervision in the Bedford College LEDS procedures from the first author. Discrepancies among raters were discussed and consensus ratings were used in all analyses.

Acute life events involve a major change in a person's life circumstances (e.g., fired from job, important relationship breakup). Interviewers queried for life events that had occurred at any point following acute treatment termination and prior to recurrence or end of follow-up (i.e., at any point during the up to 12-month follow-up period). The LEDS has documented validity over a retrospective recall period of 12 months.^[32] Life events were rated for their level of contextual threat on a 4-point scale (1, marked; 2, moderate; 3, some; 4, little or none). The interrater agreement on the threat ratings of events was excellent ($\kappa = .94$). We chose to examine "severe" events (rated marked or moderate on threat) because they are the most relevant in provoking MDD episodes.^[32,48] Consistent with LEDS procedure, dichotomous (presence/absence) variables were used due to the relatively low frequency of severe events.

Events were also rated for independence. Independent events are totally or nearly totally independent of the behavior of the individual (e.g., job layoff due to plant closure, father's suicide), and dependent events are at least partly dependent upon the behavior or characteristics of the individual (e.g., fired from job due to repeated absences, loss of a romantic relationship).^[32,47] Raters achieved 100% agreement in rating independence. Accordingly, the acute life event variables examined in the current study included the presence versus absence of a "severe" independent or dependent event.

Chronic stressors are ongoing difficulties in any of the above domains (e.g., persistent health problems, such as migraines, ongoing financial difficulties, etc.). The median duration of chronic stressors was 71.04 weeks ($M = 109.24, SD = 116.07$), all were present in the follow-up period, and the majority had begun prior to follow-up. That is, they formed the chronic context that patients were experiencing at the end of their acute treatment and transition to follow-up. Chronic stressors were rated on a 6-point threat scale (1, high marked; 2, low marked; 3, high moderate; 4, low moderate; 5, mild; 6, very mild)^[47] and for independence. The interrater agreement was once again excellent for both threat ($\kappa = .86$) and independence ($\kappa = 1.00$). Frequencies of severe chronic stressors, defined as high marked, low marked, or high moderate on threat, were too low (fewer than 10 patients) to

permit statistical analyses. Therefore, we examined the total number of dependent or independent chronic stressors of any threat level.

TREATMENT PROTOCOL

Acute Phase. As documented previously, patients randomized to CBT^[49] or IPT^[50] received weekly sessions for 16 weeks and were medication-free throughout the study. Therapists were Ph.D.- or M.S.W.-level, and were all judged adherent to treatment protocols by a Ph.D.-level psychologist who rated patient sessions using the Collaborative Study Psychotherapy Rating Scale (CSPRS).^[51] Patients in the ADM condition were seen by their treating psychiatrist once every 2 weeks for 16 weeks for medication management and supportive care. Patients received an ADM chosen at the discretion of their psychiatrist, with reference to the Canadian Network for Mood and Anxiety Treatment (CANMAT)^[52] guidelines that include a wide range of ADMs, usual effective dosages, and dosage ranges.^[38-40] A trained research assistant blind to patients' treatment assignment administered the Ham-D to all patients weekly. A sustained response was defined as $\geq 50\%$ decrease in Ham-D scores from baseline to treatment end-point and a final Ham-D score < 8 that was maintained for at least 3 weeks.^[53,54]

Follow-Up Phase. The 12-month naturalistic follow-up phase did not involve any further treatment. A research assistant unaware of patients' acute treatment assignment administered the Ham-D to all patients monthly. If the score exceeded 15, patients attended a face-to-face Ham-D interview with a graduate research assistant. If the score was in the same range, a SCID-I/P interview was administered to determine whether patients met criteria for a major depressive episode. New episodes occurring within 4 months of the beginning of follow-up were defined as *relapses*, and those occurring after 4 months were defined as *recurrences*.^[54] The LEDS was administered at the end of follow-up to cover all stressors experienced over follow-up.

DATA ANALYSIS

The steps of our mediation model were as follows: (1) Cox regression survival analysis modeled time to recurrence from residual symptoms; (2) Pearson and biserial correlations modeled the relation of residual symptoms to acute life events and chronic stressors; (3) biserial and point-biserial correlations modeled the relation of acute life events and chronic stressors to recurrence. If steps 1, 2, and 3 are significant, then testing mediation is appropriate. In our fourth step, we used Cox regression survival analysis to model time to recurrence from residual symptoms and acute life events, controlling for chronic stressors. Only the life event and chronic stress variables that were significant in steps 2 and 3 were entered into the model. Life events were entered as time-varying covariates to account for the fact that those who spent more time in follow-up had more opportunity for exposure to events. Inferential statistical tests of indirect effects have not yet been developed for use in Cox regression.^[55] Therefore, we determined that mediation was achieved if the previously significant relation of residual symptoms to recurrence risk was no longer significant in the model containing the stressors.^[56] Further, to provide an indication of the strength of the mediation effect, we calculated the percentage of the effect of residual symptoms on recurrence that was mediated through the stress variables, using the formula $(B_{\text{direct}} - B_{\text{indirect}})/B_{\text{direct}}$, where $B_{\text{direct}} = B$ for the direct effect of residual symptoms on recurrence, and $B_{\text{indirect}} = B$ for residual symptoms in the model including the stress variables.^[57]

RESULTS

DESCRIPTIVE SAMPLE CHARACTERISTICS

Over the 12-month follow-up, 2 (3%) patients suffered a relapse and 13 (19%) suffered a recurrence.

TABLE 1. Demographic and clinical characteristics of the sample by relapse/recurrence status

Variable	No recurrence (<i>n</i> = 53)	Recurrence (<i>n</i> = 15)	<i>t</i> or χ^2
Female sex, <i>n</i> (%)	33 (62)	9 (60)	.025
Age, <i>M</i> (<i>SD</i>)	41.32 (12.86)	47.60 (11.87)	1.70*
Years of education, <i>M</i> (<i>SD</i>)	16.25 (2.33)	16.53 (2.53)	.40
Blishen index, <i>M</i> (<i>SD</i>) ^a	43.61 (22.08)	34.18 (26.81)	1.34
Number previous episodes, <i>M</i> (<i>SD</i>)	2.83 (2.07)	2.80 (2.14)	.04
Age at first MDD onset, <i>M</i> (<i>SD</i>)	28.60 (12.04)	34.33 (16.68)	1.49
Baseline Ham-D score, <i>M</i> (<i>SD</i>)	17.85 (3.27)	19.93 (4.82)	1.58
Comorbid diagnoses, <i>n</i> (%)			3.02
Dysthymia	2 (4)	1 (2)	
Social phobia	2 (4)	1 (2)	
Specific phobia	0 (0)	1 (2)	
Posttraumatic stress disorder	1 (2)	0 (0)	
Generalized anxiety disorder	0 (0)	1 (2)	
Total dependent difficulties, <i>M</i> (<i>SD</i>)	0.89 (1.22)	2.00 (2.07)	2.64**
Total independent difficulties, <i>M</i> (<i>SD</i>)	0.98 (1.20)	1.87 (2.56)	1.91*
Severe dependent events, <i>n</i> (%)	17 (32)	3 (20)	.82
Severe independent events, <i>n</i> (%)	14 (26)	8 (53)	3.87**

^aThe Blishen index contains 514 Canadian professions ranked on a scale with a mean of 42.7 and *SE* of 13.3 [58]. The Blishen index value indicates the current sample to be middle class by Canadian standards. **P* < .10; ***P* < .05.

Recurrences and relapses are hereafter considered together and termed “recurrence.” The mean time to recurrence was 30.47 weeks (*SD* = 14.82). Those who suffered a recurrence were older, at a trend, than those who stayed well, but no other demographic or clinical variable significantly distinguished the groups (see Table 1). Recurrence rates were lower following CBT (*n* = 2/22, 9%) than IPT (*n* = 8/28, 28%) or ADM (*n* = 5/18, 28%), but not significantly so, $\chi^2(2) = 3.18, P = .20$. The relation of residual symptoms to recurrence did not differ across treatments (ORs = 1.07–1.17; *P*s = .16–.49), therefore, we collapsed the treatment conditions.

The percentages of the sample that experienced at least one severe independent or dependent event in follow-up were 32% (*n* = 22) and 29% (*n* = 20), respectively. The mean totals of independent and dependent chronic stressors were 1.18 (*SD* = 1.62) and 1.13 (*SD* = 1.51), respectively. Those with a severe independent event had higher baseline (i.e., start of acute treatment) Ham-D scores than those without (*M*s = 19.73, 17.63; *SD*s = 3.68, 3.60; *t*[66] = 2.23, *P* < .05). Further, higher baseline Ham-D scores were significantly associated with more independent, *r*(66) = .240, *P* < .05, and dependent, *r*(66) = .242, *P* < .05, chronic stressors.

TABLE 2. Partial correlations of residual depression symptoms and recurrence status to acute life events and chronic stressors controlling for baseline Ham-D scores and age

	End-point Ham-D score	Recurrence
Total dependent difficulties	.37**	.27*
Total independent difficulties	.35**	.18
Severe dependent events	.08	-.11
Severe independent events	.23***	.26*

Note: **P* < .05; ***P* < .005; ****P* < .07.

No other demographic or clinical characteristics were related to the stress variables (all *P*s > .10).

STEP 1: RESIDUAL DEPRESSION SYMPTOMS PREDICT RECURRENCE

A Cox regression survival analysis modeling time to recurrence with end-of-treatment Ham-D scores and age entered as predictors was significant, $\chi^2(2) = 7.13, P < .05$. Consistent with hypotheses, higher residual symptoms following acute treatment predicted a shorter time to, and increased risk of, recurrence, OR = 1.14, Wald = 4.51, *P* < .05, CI₉₅: 1.01, 1.28.

STEP 2: RESIDUAL DEPRESSION SYMPTOMS AND STRESS

Consistent with hypotheses, controlling for age and baseline Ham-D scores, patients with higher levels of chronic independent and dependent stress had significantly higher end-of-treatment Ham-D scores (see first column of Table 2). Further, the relation of residual symptoms to the likelihood of a severe independent event in the follow-up period approached significance.

The correlational analyses for acute life events are difficult to interpret because of the varying duration of exposure to life events in the follow-up period. Therefore, to examine the prospective relation of end-of-treatment Ham-D scores to life events, we modeled time to the first life event in follow-up. Patients with higher levels of residual symptoms had a significantly shorter time to their first severe independent event, $\chi^2(1) = 4.89, OR = 1.10, Wald = 5.30, P < .05, CI_{95}: 1.01, 1.20$. The model predicting time to first severe dependent event failed to reach significance, $\chi^2(1) = 2.17, OR = 1.10, Wald = 2.32, P = .14, CI_{95}: .97, 1.24$.

STEP 3: STRESS EXPOSURE PREDICTS RECURRENCE

Consistent with hypotheses, controlling for age and baseline Ham-D scores, a higher total number of dependent difficulties, and a higher likelihood of having a severe, independent event in follow-up were significantly associated with a greater risk of recurrence (see second column of Table 2).

TABLE 3. Coefficients for Cox regression models predicting relapse/recurrence from residual depression symptoms, acute life events, and chronic stressors

	Wald	OR	<i>P</i>	CI ₉₅
End-point Ham-D	.03	1.01	.86	.89, 1.15
Total dependent difficulties	3.94	1.34	<.05	1.004, 1.79
Severe independent events	3.52	1.03	.06	1.00, 1.06

STEP 4: STRESS MEDIATES THE RELATION OF RESIDUAL SYMPTOMS TO RECURRENCE

The previous steps demonstrated that only severe independent events and total number of dependent chronic stressors were significantly associated with residual symptoms and an increased risk of recurrence. Therefore, the presence/absence of a severe independent event, modeled as a time-varying covariate, was included as the mediator in the Cox regression survival analysis predicting recurrence from end-point Ham-D scores, and controlling for dependent chronic stressors. The model was significant, $\chi^2(3) = 12.06$, $P < .01$. Consistent with hypotheses, end-of-treatment Ham-D scores no longer significantly predicted recurrence in the model containing severe independent life events and chronic dependent stress (see Table 3), and 90.8% of the effect of residual symptoms on recurrence was mediated through the stress variables. Chronic stressors, and acute life events as a trend, continued to predict time to recurrence.

THE TIMING OF DIFFICULTIES: DESCRIPTIVE ANALYSES

Determining the temporal order of residual symptoms and chronic stressors was not the focus of the current investigation. Nevertheless, we sought to provide an exploratory examination of this issue by categorizing dependent chronic stressors based on whether they began prior to the start of the follow-up period or whether they began at some point during the follow-up period. Twenty-four patients (34%) reported a chronic stressor that started before follow-up (and persisted into follow-up), and 20 (28%) patients reported a chronic stressor that started in the follow-up period. Given the low numbers after stratification by time period, the analyses below should be interpreted as preliminary and descriptive in nature.

Residual Ham-D scores were significantly associated with the total number of chronic stressors that had their onset at some point *during* the follow-up period, partial $r(64) = .39$, $P < .005$. Further, the association between chronic stressors that began during follow-up and recurrence approached significance, partial $r(64) = .23$, $P = .06$. In contrast, total number of chronic stressors that started prior to the follow-up were not significantly associated with either residual symptoms, partial $r(64) = .17$, $P = .17$, or recurrence, partial $r(64) = .17$, $P = .18$. A final Cox regression modeling time to recurrence from

residual Ham-D scores, severe independent events, and only those difficulties that started during follow-up indicated that acute life events were still a robust mediator, such that they continued to predict recurrence at a trend, OR = 1.03, Wald = 3.78, $P = .05$, CI₉₅: 1.00, 1.06, whereas residual symptoms again failed to significantly predict time to recurrence, OR = 1.03, Wald = .15, $P = .70$, CI₉₅: .90, 1.17. Eighty percent of the effect of residual symptoms on recurrence was mediated through the stress variables. Chronic stress during follow-up did not significantly predict recurrence in this full model, OR = 1.15, Wald = 1.64, $P = .20$, CI₉₅: .93, 1.43.

DISCUSSION

Residual depression symptoms following acute treatment had a strong zero-order effect on time to recurrence in follow-up. Our definition of response was strict, necessitating a minimum symptom criterion maintained for 3 weeks. It is compelling that residual symptoms were such strong predictors of recurrence in this sample of rigorously treated patients. Therefore, these results add to a growing literature suggesting that one of the most important steps to preventing relapse and recurrence may be to ensure complete remission of symptoms.^[59]

Consistent with our hypothesized mechanism of recurrence, stressful life events mediated the relation of residual symptoms to recurrence, even after controlling for chronic stressors that spanned the acute treatment and follow-up periods. Over 90% of the effect of residual symptoms on recurrence was mediated through the stress variables, suggesting strong mediation. To our knowledge, this is the first study to examine stress exposure as a mechanism of recurrence risk in those with residual symptoms following acute treatment.

The primacy of severe *independent* life events in the current analyses is consistent with research demonstrating increased prospective exposure to independent events in individuals with severe vegetative symptoms of depression (e.g., sleep disturbance).^[31] Intriguingly, these are the very symptoms that are most likely to remain following treatment in those with residual symptoms.^[11,60] Therefore, it is possible that patients whose syndrome of depression does not fully remit with treatment, and perhaps particularly those with lingering vegetative symptoms following treatment, live in contexts in which particular independent events are more likely to occur. Although not the focus of the current study, future research could examine the specific residual symptoms, or clusters of symptoms, that best predict life event exposure and subsequent recurrence.

To further understand the life contexts of those with residual symptoms, we examined the specific life events to which these individuals were exposed during the follow-up phase. Interestingly, we found that almost all of the events coded as severe and independent had happened to other people. For instance, one patient's teenage son needed surgery after he mutilated his arm, another patient's mother with psychosis attempted to

strangle her father, another patient's sister died of a drug overdose, and two patients had close relatives hospitalized for suicide attempts (note that details in these examples have been altered to protect patient confidentiality). Although it is hard to imagine how these patients could have *caused* these events (i.e., they were correctly coded as independent in the LEDS system), it is possible that the types of patients who fail to attain full remission of their depression live in family contexts that have high levels of disturbance.^[48] That is, these events are independent of the person, but they may not be independent of the network context in which all family members are interconnected.^[61,62]

Chronic stressors were strongly associated with both residual symptoms and recurrence risk. The chronic environmental context is important in forming the backdrop of exposure to acute life events.^[21] The chronic stressors most central in the current analyses were dependent in nature, and overwhelmingly involved ongoing support of friends or family members in their crises, or chronic conflict/tension with friends or family members. It is easy to see how these sorts of chronic stressors are complementary with the independent life events listed above. Again, this suggests a context of chronic network stress in those with residual symptoms.

There are at least two possible, complementary temporal models relating these chronic and acute stressors to recurrence. First, residual symptoms may lead to prospective exposure to acute and chronic stress that triggers recurrence.^[21] Second, preexisting chronic stressors may portend incomplete remission from acute treatment, which then leads to exposure to acute and chronic stress, that then trigger recurrence. There is also the possibility that acute life events and chronic difficulties interact to predict recurrence. Testing these possible models was beyond the scope of the current paper, particularly given the time-varying nature of the life event variables, which necessitates more targeted study with larger samples.

Nevertheless, we sought to provide a preliminary investigation of the above issue by separately analyzing those chronic stressors that began only after the onset of follow-up (and, thus, were relevant to the first proposed model), and those that began prior to the end of acute treatment (and, thus, were relevant to the second proposed model). Residual symptoms were only significantly associated with chronic stressors that began after the onset of the follow-up period, and only these stressors significantly predicted recurrence. Based on these results, we tentatively suggest that the presence of residual symptoms following treatment may prospectively heighten exposure to both acute and chronic stress. In the final mediation model only acute life events significantly mediated the relation of symptoms to recurrence. Therefore, the mediating role of acute life events in this model is robust even when controlling for those chronic stressors most relevant to incomplete symptom remission. Nevertheless, the failure of the effect of chronic stressors to reach statistical significance in this model

should be interpreted with caution given the low number of patients reporting these types of stressors. Overall, however, our results provide important preliminary support for the role of stress exposure in mediating the effect of residual symptoms on recurrence risk.

The current results should be interpreted in the context of the following limitations. First, our final sample was small due to attrition and missing life event data. However, our results were unlikely to have been biased by attrition as the final sample did not differ significantly from those who were excluded in terms of recurrence rates, level of residual symptoms, or treatment assignment. Further, our attrition rates were wholly consistent with those found in similar randomized trials. Second, our small sample resulted in low frequencies of patients reporting severe life events and chronic difficulties. Therefore, replication of our results in a larger sample is warranted. Third, it was beyond the scope of the current study to examine additional variables, such as high trait neuroticism,^[63] that may further mediate the relation of residual symptoms, acute and chronic stress, and depression recurrence, and this remains an important area of future research. Finally, the LEDS relies on retrospective reporting of stress, which raises concerns about memory bias. The LEDS addresses the issue of bias by having interviewers query only about the practical details of participants' experiences and *not* about the participants' emotional reaction to stressors or the relation of stressors to depression. In addition, blind ratings are based on manualized examples to ensure standardization. The LEDS is widely regarded as a gold standard for assessing life events, and has shown superior reliability and validity in the study of depression than questionnaire measures of stress.^[64,65]

CONCLUSIONS

Residual depression symptoms following treatment with CBT, IPT, or ADM significantly predicted exposure to severe life events. Further, severe stress significantly mediated the relation of residual symptoms to recurrence even controlling for chronic stress. Our results suggest that heightened exposure to stress may be an important mechanism through which residual depression symptoms cause recurrence. As such, recurrence rates may be decreased by incorporating strategies targeting stress coping into acute and/or continuation psychotherapy, or employing these treatments as a sequential strategy following symptom remission with ADM.^[66] Incomplete remission adds significantly to the burden of MDD, and thus rigorous follow-up aimed at dampening reactivity to stress has the potential to prevent a lifelong pattern of illness.

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