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THE IMPACT OF STRESSFUL LIFE EVENTS ON RELAPSE OF GENERALIZED ANXIETY DISORDER

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Abstract

Background—Stressful life events (SLEs) are associated with the onset of psychiatric disorders but little is known about the effects of SLEs on individuals already diagnosed with an anxiety disorder, particularly generalized anxiety disorder (GAD) in which worry about life events is a defining characteristic. This study examined the impact of SLEs on relapse in adults already diagnosed with GAD.

Methods—Data are obtained from the Harvard/Brown Anxiety Research Project (HARP), a naturalistic longitudinal study of adults with a current or past history of anxiety disorders. One hundred and twelve adults recovered from an episode of GAD and 27 subsequently relapsed during the study. Eight categories of SLEs were assessed via interview and were examined as predictors of GAD relapse.

Results—An increased total number of SLEs was associated with a higher cumulative probability of relapse into episode of GAD and there was a nonsignificant statistical trend indicating specific categories of SLEs including health, death, and family/friends/household were related to an increased probability of relapse into episodes of GAD.

Conclusions—SLEs impact the course of GAD and certain types of stressors may be more relevant to symptomatology than others. The change and uncertainty associated with SLEs may exacerbate existing worry tendencies even among those who have recovered from GAD.

Keywords

anxiety; course; adults; longitudinal; psychiatric

INTRODUCTION

Numerous studies support the connection between stressful life events (SLEs) and the development and course of depressive symptoms.^[1–3] Despite high comorbidity between depression and anxiety,^[4] less research attention has been paid to examining if SLEs

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similarly impact anxiety conditions. Of the anxiety disorders, SLEs are particularly relevant to generalized anxiety disorder (GAD). Worry about life events^[5] is a defining characteristic of the disorder and etiological theories suggest that SLEs are important to the development and maintenance of GAD.^[6]

GAD is one of the more common anxiety disorders, with a lifetime prevalence of 5.7% in the general population.^[7] It is characterized by a chronic course^[8, 9] and is associated with significant personal, economic, and societal burdens.^[10, 11] Individuals diagnosed with GAD endorse more potentially traumatizing events during their lifetime^[12] and more minor life events than nonanxious controls.^[13] Among community and twin samples, the presence of one SLE predicted increased risk for new onset of GAD, and there was also an increased risk as a greater number of SLEs were endorsed.^[2, 14] Additionally, university students with GAD were more likely to report SLEs than those without GAD and there was a positive association between SLEs and being in episode of GAD.^[15] In sum, these data indicate SLEs are influential in the development of GAD. However, these studies fail to address the temporal relationship between SLEs and symptoms among individuals already diagnosed with GAD.

It would seem likely that the presence of SLEs, which typically leads to change and uncertainty, would be problematic for a worrier, and could lead to a relapse of GAD symptoms. The objective of this study was to examine the effect of SLEs on GAD relapse in a sample of participants enrolled in the Harvard/Brown Anxiety Disorders Research Program (HARP). HARP's prospective, longitudinal design allowed for a closer examination of the impact of life stressors on GAD symptoms. We investigated the relationship between total number of SLEs and GAD relapse, predicting that a greater number of SLEs would be predictive of relapse. We also examined the relationship between specific categories (e.g. work, health) of SLEs and GAD relapse to gain insight into what type of SLE was most likely to precipitate relapse. Improved understanding of factors that affect the course of GAD would be beneficial to assist clinicians in recognizing risks for symptom change and to assist patients in utilizing coping strategies to reduce the potential impact of SLEs.

METHOD

PARTICIPANTS

Participants were recruited for the Harvard/Brown Anxiety Research Program (HARP), a prospective longitudinal observational multicenter study of adults with a current or past history of anxiety disorders. Seven hundred and eleven participants entered into the study from over 30 clinicians' practices at 11 different clinical treatment facilities in the New England area. These methods are described in detail elsewhere.^[16] Inclusion criteria were a past or current DSM-III-R (Diagnostic and Statistical Manual of Mental Disorders) diagnosis of at least one of the following at intake: Panic Disorder without Agoraphobia, Panic Disorder with Agoraphobia, Agoraphobia without Panic Disorder, Social Phobia, or GAD. Participants must have been at least 18 years of age at intake, willing to voluntarily participate in the study, and sign a written consent form. Exclusion criteria consisted of the presence of an organic brain syndrome, a history of schizophrenia, or current psychosis at intake.

Of the 711 participants enrolled in HARP, a total of 170 were diagnosed with GAD at intake. For the purposes of this paper, in order to have a GAD relapse, a participant had to have recovered first. Of the 170 diagnosed with GAD, 112 (65.9%) relapsed during the study period. Because we collect weekly data on illness severity and because relapse and

recovery could occur within the same 12-month follow-up period or less, we had sufficient data for analyses on all 112 individuals.

PROCEDURES

Participants were interviewed in person for the initial assessment and then subsequent interviews were conducted by telephone. Follow-up interviews were assessed at 6-month intervals for the first 2 years of HARP and then annually thereafter. SLE data collection occurred during years 10–17 of the study for a total of 7 years. Interviews were conducted by bachelors- and masters-level trained, experienced clinical interviewers. All received careful and rigorous training from an intensive training program that has been developed and successfully used for the past 30 years. Participants were paid \$50 for their participation at each interview.

MEASURES

Structured Clinical Assessment (SCALUP)^[17]—The SCALUP is a structured clinical interview used to assess diagnoses at intake. The Structured Clinical Interview for DSM-III-R Non-affective Disorders, Patient Version (SCID-P) and the Research Diagnostic Criteria (RDC) Schedule for Affective Disorders-Lifetime (SADS-L) were combined to create the SCALUP. The instrument yielded both present and past RDC diagnoses for affective disorders and DSM-III-R diagnoses for nonaffective (including anxiety) disorders. The DSM-III-R exclusion of a diagnosis of GAD during the course of a mood disorder was set aside for this study. Interviews usually took place in single sessions lasting 2–4 hr.

Longitudinal Interval Follow-Up Evaluation-Upjohn (LIFE-UP)^[18]—The LIFE-UP is a follow-up interview used to assess monthly psychosocial functioning and the weekly course of psychiatric disorders using psychiatric status ratings (PSRs). Thus, the LIFE-UP facilitated measurement of weekly symptom severity of each participant's individual diagnoses. PSRs measure the severity of illness on a six-point scale (Table 1). The greatest severity of GAD, a PSR six, requires full DSM-III-R criteria in addition to major disruption in functioning. A PSR of three includes three to five symptoms of GAD and worry less than 50% of the time, whereas occasional worry is designated by a PSR of two. PSRs are assessed on a weekly basis, generating change points.

DEFINITIONS OF RECOVERY AND RELAPSE

Consistent with previous research from this sample (e.g.^[19, 20]), recovery and relapse in this study were defined prospectively. Full recovery was defined as occasional or no symptoms (PSR of 1 or 2) for eight consecutive weeks, a time period that can detect noticeable changes in morbidity and minimize transient changes in psychopathological state. Participants who experienced a full recovery were designated as relapsed if their PSR score increased to either 5 or 6 (full criteria) for 4 weeks or longer.

Assessment of interrater reliability of all anxiety disorder PSRs found good-to-excellent reliability, with intraclass correlation coefficients ranging from .78 to .84 for GAD. The long-term test–retest conducted to assess the reliability of using subjects' retrospective recall to assess PSRs over 1 year found very good to excellent reliability for the anxiety disorders and major depression. For GAD, the reliability of retrospective symptom recall ranged from .97 to 1.00. A more detailed description of the interrater reliability, subject recall, and validity of the LIFE-UP is reported in Warshaw et al.^[21, 22]

Stressful Life Events (SLE)^[23,24]—The SLE interview is a rater administered interview modified from the Psychiatric Epidemiology Research Interview (PERI^[25]). The SLE is used to assess the presence of 111 different stressors during the preceding year, including

the start and end dates of the events, ratings of perceived stress, and whether the impact on the subject's life was good or bad. Eleven categories were assessed and the number of items within each domain include school ($n = 7$), work ($n = 25$), love ($n = 17$), health ($n = 11$), crime and legal ($n = 11$), money and financial ($n = 7$), friends/family/household ($n = 11$), residence ($n = 6$), personal ($n = 2$), death ($n = 7$), and childbirth ($n = 7$). Perceived stress was measured on a four-point scale from "not stressful" to "very stressful." Only those events that the participant endorsed as "somewhat" or "very stressful" were included in these analyses.

STATISTICAL ANALYSES

Statistical analyses were conducted using SAS Version 9.1 (SAS Institute Inc., Cary, NC). Kaplan–Meier estimates were used to examine relapse of GAD. Cox proportional hazard regression models were used to examine the independent effects of SLEs (number of events from eight categories) on the risk of GAD relapse over a 7-year follow-up period. We did not examine the childbirth, personal, and school SLE categories due to the low number of endorsements. Subject selection required having met full criteria GAD at entry to the study or to have a GAD onset at a later time in the study. From this sample, we required the subject to have had at least 1 week of GAD PSR. Thus, if someone met criteria at study inclusion and then quickly recovered, we were still able to capture their data.

A relapse event was identified and an SLE was included in the analyses if it occurred in the month prior to GAD relapse. The 1-month timeframe was based on prior research in anxiety and depression indicating that the highest risk for onset of the disorders was within the month of SLE occurrence.^[2] Additionally, the analyses of time to relapse used the time-varying predictor of whether the participant experienced stress in the 4 weeks preceding the relapse and assessed the entire span of time each participant had both stress data and GAD PSRs. Analyses for our manuscript controlled for age, gender, and presence/absence of major depression as a weekly time-varying covariate. However, because the covariates were nonsignificant they were not included in the final models. Significance of $P < .006$ was used to correct for the multiple comparisons and Benjamini–Hochberg multiple testing adjustments^[26] were used to control for Type I error.

RESULTS

PARTICIPANTS

Of the 112 individuals who recovered from an episode of GAD, a majority were female (64.3%; $n = 72$), had at least a high school education (92.9%; $n = 104$), and were married (54.5%; $n = 61$). Their average age at baseline was 39.5 ($SD = 12.2$) years. Comorbid diagnoses included panic disorder with agoraphobia (46.4%), social phobia (28.6%), major depressive disorder (25.9%), and panic disorder (8.9%).

GAD RELAPSE

Of the 112 participants who recovered from GAD, we examined the impact of SLEs on those who went on to experience a relapse. Twenty-seven out of one hundred and twelve (24.1%) individuals experienced a relapse at some point during the 8 years of life events data collection. The mean length of time from GAD recovery to relapse was 648.2 weeks ($SD = 56.3$ weeks; 12.5 years) with a range of 548 weeks (10.54 years) to 766 weeks (14.73 years).

STRESSFUL LIFE EVENTS

The average number of stressors and the frequency of stressors reported per year across each year of SLE data collection are presented in Table 2. For example, of the 38 participants

who had SLE and PSR data during Year 1 of life event data collection, the average number of stressors reported was 1.29 ($SD = 1.18$). Additionally, 12 of 38 participants (31.6%) reported one stressor during Year 1. Table 3 presents the frequency of SLE by category across the 8 years of data collection for the 112 participants who had recovered from GAD. The most frequently reported category of stressors was health (e.g. hospitalization for a life-threatening physical illness, injury, or major surgery; $n = 97$; 86.7%), followed by death (e.g. spouse/mate died; $n = 70$; 62.5%), and work (e.g. had trouble with a boss, fired from work; $n = 68$; 60.7%). Residential stressors (e.g. lost a residence through a disaster, moving) were the least frequently reported stressors ($n = 27$, 24.1%).

IMPACT OF SLES ON GAD RELAPSE

The total number of SLEs experienced (in the previous 4 weeks) was related to GAD relapse ($HR = 1.63$; 95% CI, 1.18–2.26; $P < .003$). After adjustment of the data using Benjamini–Hochberg corrections, there was a nonsignificant trend for the following stressors predicting GAD relapse: health ($HR, 1.55$; 95% CI: 1.03–2.32, $P = .03$), death ($HR = 5.42$, 95% CI: 1.22–24.03, $P = .03$), and family friends or household ($HR = 3.76$; 95% CI: 1.27–11.13, $P = .02$), meaning that the occurrence of these stressors was associated with a worsening of GAD symptoms. GAD relapse was not related to stressors involving work, money, love, crime, or residential matters (P s $> .006$), as results showed these SLEs did not precipitate symptom worsening.

Initial statistical analyses examined main effects for depression, age, and gender but there were no significant effects for these variables; therefore, they were not included in the final analyses.

DISCUSSION

This study examined the effects of SLEs on relapse of GAD among participants in a naturalistic, longitudinal study of adults with anxiety disorders. Results revealed that in the 4 weeks prior to a relapse, the total number of SLEs predicted the relapse, indicating that SLEs impact the course of GAD. This is consistent with evidence that SLEs also impact the course of other disorders such as depression,^[2] panic disorder,^[27] and hoarding.^[28] We examined presence/absence of depression as a covariate predicting GAD relapse. Our findings suggested that depression did not account for any unique variance in the prediction of GAD relapse.

In the case of GAD, where worry about minor, miscellaneous, and future events is a hallmark symptom, it seems likely that SLEs (e.g. serious illness) would exacerbate existing worry tendencies. SLEs create change and uncertainty, and intolerance of uncertainty is considered to play a role in the development and maintenance of GAD.^[29] The Intolerance of Uncertainty Model posits that individuals with GAD find uncertain or ambiguous situations to be stressful, which leads to chronic worry, cognitive avoidance, and impaired problem orientation.^[30] Additionally, individuals who are intolerant of uncertainty tend to overestimate the probability of occurrence for highly unlikely future events and worry about how to handle them “if” they happen.^[31] Thus, it is possible that the occurrence of SLEs creates new worry, reinforces the use of worry as a coping strategy because the “unlikely” event actually happened, and further increases overall GAD symptomatology leading to relapse.

We did not find strong evidence for differential impact of specific types of SLEs on GAD relapse. Correcting for multiple comparisons, there was a statistical trend for SLEs related to death, health, or family/ friends/household to be associated with a worsening of GAD symptoms. These findings are consistent with smaller studies that have examined worry

content in clinical populations, in which those diagnosed with GAD tend to worry more about future events and more about health and interpersonal/family issues compared to those without GAD.^[32, 33] However, large community studies examining worry content reported that GAD-related worry is diverse and can fluctuate depending on a variety of factors including age, gender, and marital status.^[34, 35] Data from the experimental literature also report significant variance in worry themes across individuals with GAD.^[34] Thus, it may be that GAD worry is diffuse and idiosyncratic suggesting that particular categories of SLEs are less important than individual differences.

Treatment interventions that have integrated a focus on interpersonal functioning are not significantly more effective than standard GAD treatments.^[36] Thus, from a clinical perspective, individual differences in response to particular life events, rather than the events themselves, likely need to be taken into consideration. Future research should investigate potential moderators in the relationship between SLEs and GAD including intolerance of uncertainty, coping strategies, and social support that would help inform theoretical models of GAD and improve understanding of who is most impacted by SLEs.

Several limitations of this study will need to be addressed in future research.

First, we only examined relapses that occurred during later years of the study (i.e. years 10–17) because this is when SLE data collection started. Our analyses did not include those individuals who had already relapsed in the first 9 years of the study or who remained in recovery throughout the years of SLE administration. There may be differences in response to SLEs between those individuals that relapse shortly after remission from GAD and those who experience a longer period of remission. Second, our relapse sample size was small, making definitive conclusions about the relationships between symptoms and events more difficult. Third, a potential confound in our approach may be that those with GAD have a tendency to report more SLEs than nonanxious controls^[13, 36] due to attentional biases in which anxious individuals are more likely to interpret neutral events as threatening.^[37] It has been argued that GAD worry tendencies might “create” SLEs, which leads to worsening of GAD. From a purely methodological approach, this could be problematic; but from a clinical perspective, we suggest it is reasonable and crucial to examine events that were personally relevant. Thus, although we did not control for this issue, the SLE interview in our study may assist in providing some increased objectivity over pure self-report ratings. The interview requires careful probing of endorsed events to fully assess the significance and impact of the event. For instance, interviewers were trained to ask the following questions when participants endorsed experiencing a change in their health status: How serious was the problem? Was it life-threatening? Did he/she need someone to care for them? Did he/she stay in the hospital? Did he/she lose time from work? These factors were used to inform the interviewer’s perspective on the significance of the event(s). Fourth, we did not control for the effects of treatment on course of illness. Previous HARP research^[19] did not find any relationship between treatment and the course of GAD, social phobia, or panic disorder. This is not an unusual finding for a naturalistic study as treatment bias effects are significant and those who have the most severe symptoms receive the most treatment. Lastly, participants were diagnosed with GAD using DSM-III-R diagnostic criteria rather than the more current DSM-IV. Given the changes in GAD criteria from the third to fourth editions of the DSM, participants included in this study met more stringent criteria to be diagnosed with GAD^[37] than individuals diagnosed using DSM-IV criteria, suggesting results can also apply to those who meet DSM-IV criteria.

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TABLE 1

Psychiatric status ratings (PSRs) for generalized anxiety disorder

Code	Definition
6	Experiences worry and anxiety more days than not, accompanied by at least six of 18 DSM-III-R symptoms for GAD, and these symptoms cause a major disruption in functioning
5	Experiences worry and anxiety more days than not, accompanied by at least six of 18 DSM-III-R symptoms for GAD, but these symptoms cause no major disruption in functioning. Impairment not required to make full criteria.
4	Experiences worry and anxiety more days than not, but only has three to five symptoms associated with GAD or has at least six symptoms associated with GAD but does not experience worry and anxiety more days than not
3	Has only three to five symptoms associated with GAD and does not experience worry and anxiety more days than not
2	Experiences only occasional worry and anxiety, and may or may not be bothered by one or two symptoms associated with GAD
1	None of the above

TABLE 2

Mean and frequency of stressors by year of data collection for participants who recovered from GAD

Year	n	Mean (SD)	Number of stressors			
			0	1	2	3–6
1	38	1.29 (1.18)	11 (28.95%)	12 (31.6%)	11 (28.9%)	4 (11%)
2	99	1.43 (1.13)	23 (23.2%)	32 (32.3%)	26 (26.3%)	18 (18.2%)
3	109	1.52 (1.28)	24 (22.0%)	39 (35.8%)	23 (21.1%)	23 (21.1%)
4	103	1.74 (1.26)	18 (17.5%)	32 (31.1%)	22 (21.4%)	31 (30.1%)
5	96	1.71 (1.36)	20 (20.8%)	29 (30.2%)	20 (20.8%)	27 (28.1%)
6	85	1.53 (1.26)	19 (22.4%)	29 (34.1%)	19 (22.4%)	18 (21.2%)
7	52	1.50 (1.31)	13 (25.0%)	17 (32.7%)	11 (21.2%)	11 (21.2%)
8	8	2.25 (1.75)	2 (25.0%)	1 (12.5%)	1 (12.5%)	4 (50.0%)

TABLE 3

Frequency of stressor categories across 7 years of SLE data collection

Type of stressor	Frequency	%
Health	97	86.61
Death	70	62.5
Work	68	60.71
Friends, family, household	51	45.54
Love	42	37.5
Crime	37	33.04
Money	36	32.14
Residential	27	24.11