Does Interpersonal Loss Preceding Panic Disorder Onset Moderate Response to Psychotherapy? An Exploratory Study

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Background: Little research has addressed moderators of treatment outcome for anxiety disorders, and none has considered interpersonal loss as a predictor of outcome.

Purpose: To examine the effect of interpersonal loss events within the 6 weeks preceding panic disorder onset as a moderator of outcome in a randomized controlled trial of Panic-Focused Psychodynamic Therapy (PFPP) and Applied Relaxation Therapy (ART). Researchers hypothesized that such loss events would predict better outcome in PFPP but would not affect ART outcome.

Method: Forty-nine subjects with panic disorder were randomly assigned to a 12-week course of PFPP or ART. Independent raters blinded to treatment condition and study hypotheses rated subjects on the Panic Disorder Severity Scale (PDSS) and Sheehan Disability Scale. Exploratory analyses assessed between-group effect size for PFPP and ART following standard moderator analytic procedures. The trial was conducted between February 2000 and January 2005.

Results: Three quarters of subjects reported a narrowly defined interpersonal loss (LOSS) in the 6 weeks preceding panic disorder onset. These subjects had a mean (SD) duration of panic disorder of 8.2 (9.5) years. PFPP was more efficacious than ART, but LOSS did not moderate PFPP outcome. An unexpected finding was that LOSS moderated ART outcome: subjects without LOSS showed no response to ART (PDSS mean (SD) change score = 0.00 [2.90]), whereas LOSS had a pre-post mean (SD) change score of 4.29 (5.60). Neither examination of potential confounding variables nor sensitivity analyses of assumptions regarding attrition altered these findings.

Conclusions: Interpersonal loss events preceding onset of panic disorder were more common even than in prior studies. These losses moderated outcome in ART, a therapy that does not focus on such losses. Implications and the need for future research before incorporating these findings into clinical practice are discussed.

Trial Registration: clinicaltrials.gov Identifier: NCT00128388

J Clin Psychiatry 2009;70(3):406–411

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Funded by National Institute of Mental Health (NIMH) grant K23-MH01849-01/05 and a fund by the New York Community Trust established by DeWitt Wallace.

Dr. Leon is a consultant to the U.S. Food and Drug Administration and NIMH and is a member of the data safety monitoring boards for Pfizer and Organon. Drs. Klass, Milrod, Schwalberg, and Markowitz, Ms. Kay, and Mr. Li report no additional financial or other relationships relevant to the subject of this article.

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By DSM-IV definition, patients perceive panic attacks in panic disorder as arising uncued, "out of the blue."[1] Yet the DSM-IV also notes that panic disorder often arises in the context of interpersonal loss, when interpersonal bonds are disrupted.[1(p389)] The few research studies to have appraised interpersonal loss in the context of panic disorder have found interpersonal loss events to be associated with onset of panic disorder in a substantial proportion of panic disorder patients, ranging from 25%[2] to 67%[3] within the year preceding panic disorder onset. Interpersonal loss in childhood (severe disruption of the relationship with a significant other, as through divorce or death) has been widely recognized as a risk factor for the subsequent development of panic disorder in adulthood.[4,5]

In one study of members of a self-help group for panic disorder patients (N = 55), in the year before panic disorder onset, 38.2% experienced the death of a significant other and an additional 29.1% reported other interpersonal losses.[3] In a naturalistic treatment sample (N = 223), Manfro et al.[2] found that 25% reported an interpersonal loss in the year before panic disorder onset. In a sample of 100 treatment-seeking patients diagnosed with panic disorder with agoraphobia, 62% reported interpersonal loss in the year before panic disorder onset.[6] Faravelli and Pallanti[7] compared pre-onset life events (in the year before the interview) reported by patients with recent-onset panic disorder (N = 64) with events reported by a healthy convenience sample (N = 78) matched for

sex, age, marital status, education, and social class. Of the panic disorder patients, 64.1% reported a stressful life event (not necessarily an interpersonal loss), in contrast to 28.2% of the comparison group. In a sample derived from 1 completed and 1 ongoing study, our group found that 47% of 51 panic disorder patients participating in our psychotherapy-only treatment studies reported an interpersonal loss event in the 6 weeks preceding panic disorder onset.[8] The researchers reporting these findings have not all defined "interpersonal loss" identically, further obscuring its frequency.

Do patients who report developing panic disorder in the context of interpersonal loss events differ from those who do not? Of greater clinical relevance, does the context in which DSM-IV panic disorder emerges affect treatment outcome? To date, no outcome study of panic disorder treatment has evaluated the effect of interpersonal loss as a precipitant to panic disorder onset on subsequent treatment response. The present exploratory study examined whether interpersonal loss proximal to panic disorder onset moderates current treatment response in the context of a randomized controlled trial[9] of Panic-Focused Psychodynamic Psychotherapy (PFPP) and Applied Relaxation Training (ART).

Because of the flexible approach inherent in PFPP, and because of its focus on emotional meanings underlying the panic experience, we hypothesized that interpersonal loss events closely predating panic disorder onset would moderate PFPP such that subjects who experienced interpersonal losses antecedent to developing panic disorder would derive added benefit of PFPP relative to ART. We hypothesized that interpersonal losses preceding panic onset would not affect ART outcome, as ART does not focus on life events.

METHOD

Design

This study was a randomized controlled trial of two 12-week, 24-session psychotherapies, PFPP and ART, for subjects with primary DSM-IV panic disorder. Standard assessments were administered before and after treatment, and at intervals of 2 months over the ensuing 12 months of follow-up. Details of the trial, conducted between February 2000 and January 2005, are reported elsewhere.[9]

Subjects

Forty-nine subjects aged 18 to 55 years with primary DSM-IV panic disorder, diagnosed on the Anxiety Disorders Interview Schedule for DSM-IV-Lifetime Version (ADIS-IV-L),[10] were enrolled in a randomized controlled trial of PFPP and ART.[9] Subjects reported events preceding the onset of their panic disorder, if they recalled any, as part of the comprehensive ADIS-IV-L baseline assessment. Two raters (S.J.K., B.L.M.) independently assessed and coded subjects' responses for the presence of interpersonal loss events within the 6 weeks preceding initial panic onset, which often predated study entry by years. *Interpersonal loss events* were narrowly defined as death of a close love object, divorce or rupture of a love relationship, moving away from family/parents, miscarriage, or abortion. All subjects signed informed, written consent; the Weill Medical College Institutional Review Board approved the protocol.

Subjects were randomly assigned to PFPP or ART for 24 twice-weekly sessions for 12 weeks. The primary dependent variable was the Panic Disorder Severity Scale (PDSS),[11] a standard measure in panic disorder outcome studies, chosen because it is a diagnosis-based, composite, global rating of panic severity, the only specific measure of its kind. Independent, trained evaluators, blinded to patient treatment group, therapist orientation, and study hypotheses, performed all outcome assessments. The moderating effect of interpersonal loss events within the 6 weeks preceding panic disorder onset was also assessed on the Sheehan Disability Scale (SDS),[12,13] a self-rated measure of psychosocial function. Outcome was assessed at treatment termination.

Therapeutic Interventions

Panic-Focused Psychodynamic Psychotherapy. Panic-Focused Psychodynamic Psychotherapy was a 12-week, 24-session (twice weekly) manualized psychoanalytic psychotherapy that preserves a psychoanalytically oriented, transference-focused framework while consistently attending to physical symptoms of panic disorder and agoraphobia.[14,15] Focus on unconscious emotional significance of panic is central to the treatment, which emphasizes identifying and decoding underlying psychological meanings of physical symptoms. Treatment explores and interprets the emotional significance of panic. Panic-Focused Psychodynamic Psychotherapy consistently focuses on helping patients to understand their internal emotional states. Because of its patient-directed, therapist-assisted format, and its focus on underlying emotional meaning of anxiety symptoms, PFPP appears suited to help patients address the emotional impact engendered by interpersonal losses. Panic-Focused Psychodynamic Psychotherapy focuses on psychological significance of events preceding panic, thus interpersonal loss events that patients experienced as emotionally connected with panic onset would likely become central areas of therapy exploration. Panic-Focused Psychodynamic Psychotherapy involves no exposure.

Applied Relaxation Training. Applied Relaxation Training was a 12-week, 24-session intervention, delivered twice weekly. This study adapted the Anxiety Treatment Project Relaxation Treatment Manual of Cerny and colleagues (J. A. Cerny, Ph.D., et al; available from the

authors on request). Progressive muscle relaxation training involves focusing attention on particular muscle groups, tensing the muscle group for 5–10 seconds, attending to the sensations of tension, relaxing the muscle group, attending to differences between sensations of tension and relaxation, and therapist suggestions of deepening relaxation. The number of muscle groups is gradually reduced from 16 to 8 to 4. Discrimination training, generalization, relaxation by recall, and cue-controlled relaxation (pairing the relaxed state to the word "relax") follow.

Home practice is required twice daily. By week 8, subjects apply relaxation skills to anxiety-provoking situations (in vivo exposure) in a graduated fashion. Trained to identify early stages of anxiety, subjects are instructed to use relaxation as an active coping strategy whenever they become aware of tension and to practice relaxation regularly throughout the day in various situations to maximize generalization. Applied Relaxation Training uses no interoceptive exposure, analysis of situational cues for panic, or cognitive restructuring. It is not designed specifically to address interpersonal loss events associated with panic disorder, but uses relaxation skills to cope with incipient and full-blown panic attacks. Relaxation skills are viewed as providing a method to unlearn panic-related associations.

Therapists

PFPP therapists. All 8 PFPP therapists were postresidency psychiatrists or Ph.D. psychologists with 21 mean years of experience (SD = 8.6; range, 2–40 years).

ART therapists. The 6 ART therapists were postresidency psychiatrists or Ph.D. psychologists with 16 mean years of experience (SD = 11.3; range, 5–35 years) (Mann-Whitney p = .66 between therapist groups).

Adherence. Adherence to treatments was monitored by trained raters in each condition, who rated 3 videotaped sessions per patient/therapist dyad. Both therapist groups were adherent to their administered treatment. For additional details on therapists, please see Milrod et al.[9]

Data Analytic Procedures

The hypothesized moderator is the presence/absence at baseline of the report of an interpersonal loss event, as defined above, within the 6 weeks preceding initial panic disorder onset. The analysis was guided by the general strategy for exploratory moderator analyses in randomized controlled trials described by Kraemer et al.,[16] whose criteria for treatment moderators require that (1) the potential moderator precede treatment; (2) because of randomization, the potential moderator be uncorrelated with form of treatment; and (3) a moderator of treatment "…must be shown to have an interactive effect with treatment on the outcome."[16(p879)] That is, the treatment effect must be shown to vary across levels of the moderator.

At the recommendation of Kraemer et al.[16] our analyses focused on magnitude of the effect on the primary randomized controlled trials endpoint measure, the PDSS,[11] not on significance testing. These exploratory analyses examined differential effects of treatment by comparing subjects with and without antecedent interpersonal loss events on the between-group (PFPP vs. ART) effect size. Cohen d, for PDSS change (baseline to posttreatment) was estimated separately for subjects with and without interpersonal loss events within the 6 weeks preceding panic onset.

The intention-to-treat principle was employed in data analyses in accordance with the study protocol by carrying forward the last observation (LOCF), which was the baseline assessment for study dropouts if they refused assessment at dropout. Supplemental analyses examined the sensitivity of this strategy to attrition by only including subjects who were willing to provide follow-up data (N = 42). Alternative strategies for analysis of repeated assessments over the course of the trial using mixed-effects linear regression models, for example, were not possible because the study design only included baseline and endpoint assessments.

RESULTS

Baseline Demographics

Subjects were a mean (SD) of 33 (9.1) years old. Seventy-one percent (N = 35) were Caucasian, 27% (N = 13) African American, and 2% (N = 1) Asian; 18% (N = 9) were Hispanic. Twenty-six subjects were randomly assigned to PFPP and 23 to ART. The demographic and clinical characteristics of patients assigned to the 2 treatments did not significantly differ, except that the ART sample had significantly more men (47%) than the PFPP sample (15%) (2-tailed Fisher exact p = .03). Linear regression analysis found no association between gender and the primary outcome measure at baseline, the PDSS, (F = 5.16, df = 46, p = .89), nor was there a treatment by gender interaction (F = 0.30, df = 45, p = .58).

Interpersonal Loss Events Within 6 Weeks of Panic Disorder Onset

Overall, 36 subjects (73%) reported a proximal interpersonal loss event (LOSS) and 13 (27%) reported no loss (no LOSS). Of the patients receiving PFPP, 19 (73%) reported LOSS, and 7 (27%) did not; in ART, 17 (74%) reported LOSS and 6 (26%) did not. The proportion of patients in the 2 treatments with and without LOSS did not differ (2-tailed Fisher exact = 0, df = 1, p = 1.00). Of those experiencing LOSS (N = 36), 15 (42%) experienced a break-up, divorce, or separation, 11 (31%) were mourning the death of a close relation, 9 (25%) had just moved away from family/parents, and 1 (3%) had an abortion.

Potential Confounds

Before conducting moderator analyses, we compared LOSS and no-LOSS groups on potentially confounding

Table 1. Moderator Effects of Loss on Panic-Focused Psychodynamic Psychotherapy (PFPP) and Applied Relaxation Training (ART) for Panic Disorder: LOCF Used for Dropouts

	PDSS			SDS		
Loss Status[a]	N	Change Score, Pre-Post, Mean (SD)	Between-Group Effect Size	N[b]	Change Score, Pre-Post, Mean (SD)	Between-Group Effect Size
No loss						
PFPP	7	7.71 (5.41)	1.32	7	8.36 (6.59)	1.34
ART	6	0.00 (2.90)		6	–1.17 (3.56)	
Loss						
PFPP	19	8.26 (5.16)	0.70	19	6.95 (7.63)	0.46
ART	17	4.29 (5.60)		16	3.59 (6.65)	

[a]Loss status: No loss = no interpersonal loss reported in the 6 weeks prior to panic disorder onset; Loss = interpersonal loss reported in the 6 weeks prior to panic disorder onset.
[b]One subject did not correctly fill out SDS, hence differences in N.
Abbreviations: LOCF = last observation carried forward, PDSS = Panic Disorder Severity Scale, SDS = Sheehan Disability Scale.

Table 2. Moderator Effects of Loss on Panic-Focused Psychodynamic Psychotherapy (PFPP) and Applied Relaxation Training (ART) for Panic Disorder: Dropouts Without Termination Data Eliminated From Analysis

	PDSS			SDS		
Loss Status[a]	N	Change Score, Pre-Post, Mean (SD)	Between-Group Effect Size	N[b]	Change Score, Pre-Post, Mean (SD)	Between-Group Effect Size
No loss						
PFPP	6	9.00 (4.60)	1.45	6	9.75 (5.98)	1.49
ART	3	0.00 (4.58)		3	–2.23 (5.25)	
Loss						
PFPP	19	8.26 (5.16)	0.55	18	7.33 (7.65)	0.39
ART	14	5.21 (5.78)		13	4.42 (7.16)	

[a]Loss status: No loss = no interpersonal loss reported in the 6 weeks prior to panic disorder onset; Loss = interpersonal loss reported in the 6 weeks prior to panic disorder onset.
[b]Ns differ due to missing data from dropouts.
Abbreviations: PDSS = Panic Disorder Severity Scale, SDS = Sheehan Disability Scale.

variables: severity of panic disorder (mean [SD] change score) on the PDSS (LOSS = 7.0 [5.6]; no LOSS = 6.0 [6.2]; 2-tailed Mann-Whitney U = 202; p = .431), presence of comorbid depression (LOSS = 25% [N = 9]; no LOSS = 15% [N = 2]; Fisher exact = 0.73), other Axis I (LOSS = 92% [N = 33]; no LOSS = 92% [N = 12]; Fisher exact = 1.00), Axis II comorbidity (LOSS = 47% [N = 17]; no LOSS = 62% [N = 8]; Fisher exact = 0.52), and mean (SD) duration of panic disorder (LOSS = 8.2 [9.5] years; no LOSS = 9.3 [10.2] years; Mann-Whitney U = 269; p = .539). LOSS and no-LOSS groups did not differ on these variables.

Evaluation of the Moderator Effect

We evaluated differential treatment response to PFPP and ART for subjects whose panic disorder appeared to be precipitated by LOSS in comparison with those reporting no LOSS. Treatment outcome was assessed using the PDSS, with additional analyses using the SDS to assess panic-related psychosocial function. Clinically meaningful, moderate to large between-group effects favoring PFPP over ART were observed in subjects with panic disorder precipitated by LOSS (Cohen d = 0.70) (Table 1), and this was magnified in subjects not reporting proximal interpersonal loss (Cohen d = 1.32).

Outcome in the domain of psychosocial functioning, as captured by the SDS, showed similar response patterns. The between-group difference favoring PFPP over ART in subjects reporting LOSS lay in the moderate range (Cohen d = 0.46), while for those with no LOSS, between-group differences were very large (Cohen d = 1.34).

Patients in the ART condition with LOSS showed greater improvement in panic disorder symptomatology (mean (SD) PDSS pre-post change score = 4.29 [5.60]) and in psychosocial functioning (mean [SD] SDS change score = 5.21 [5.78]) than ART patients with no LOSS. Indeed, patients with no LOSS did not benefit from ART (mean (SD) PDSS change score in ART condition = 0.00 [2.90] in the no-LOSS group). In contrast, PFPP patients showed equivalent improvements on the PDSS and SDS whether or not their panic was preceded by interpersonal loss events (Table 1). In other words, over and above general agreement with the LOCF findings, the effect sizes among no-LOSS subjects were somewhat higher and those among LOSS subjects were slightly lower.

Sensitivity analyses compared the results from the above LOCF-imputed and the non-LOCF data sets. Ten subjects dropped out, of whom 3 provided assessments at dropout (Table 2). The apparent moderator effect of LOSS persisted and maintained the same pattern when analyses

were limited to the 42 subjects who completed termination ratings. For the PDSS, among no-LOSS subjects, Cohen d = 1.45, substantially favoring PFPP over ART; whereas for subjects with LOSS, Cohen d = 0.55. For the SDS, the comparison of treatments for no-LOSS subjects indicated very large between-group differences favoring PFPP, Cohen d = 1.49; in contrast, for LOSS subjects, Cohen d = 0.39. Thus, over and above general agreement with the LOCF findings, the effect sizes among no-LOSS subjects were somewhat higher and those among LOSS subjects were slightly lower.

DISCUSSION

This study explored whether interpersonal loss as a precursor to onset of panic disorder moderated treatment response in the first randomized controlled study of psychoanalytic therapy for panic disorder.[9] Our findings support the DSM-IV observation that interpersonal loss often provides the context for onset of panic disorder, as nearly three quarters of the study patients reported developing panic disorder in the 6-week period immediately following interpersonal loss events. The rate was even higher than those reported for the prior year in previous studies.[2–7]

We had hypothesized that PFPP, which showed an overall advantage in outcome relative to ART,[9] would have a particular advantage for subjects whose panic disorder was associated with interpersonal loss. It appeared understandable that patients with LOSS would respond to PFPP, with its patient-directed, flexible frame and transference focus that permits articulation of problematic aspects of relationships, including those that have ended. Yet contrary to our hypothesis, outcome in PFPP did not vary with or without loss events prior to panic onset.

Strikingly, patients with panic associated with interpersonal loss events responded to ART, whereas those with no loss did not. Only ART patients with interpersonal loss responded. This was a surprising and unanticipated result.

Our preliminary findings suggest recall of interpersonal loss may have a clinically meaningful role as an initial precipitant to panic disorder. While a large literature exists concerning putative mechanisms for observed therapeutic gains in psychotherapies, few such mechanisms have been adequately distinguished from epiphenomena.[17] The mechanisms by which precipitating loss may affect treatment response in Applied Relaxation Training are unclear. Why should ART, focused on skill development, practice, and in vivo exposure, help patients who recalled having suffered interpersonal losses to recover from panic disorder, while those patients without such precipitants to panic did not benefit?

Nothing in the ART protocol explicitly addresses interpersonal loss or any historical context for panic onset. As ART strictly focused on relaxation therapy, patients were much less likely than in PFPP to discuss panic antecedents. Therapists were directed to discuss panic attacks in terms of physiologic symptoms and the use of relaxation for coping, with purposeful inattention to internal cognitive and emotional experiences during ongoing panic and to analysis of the situational antecedents and context of the panic. If patients raised non-panic issues, brief reflective listening was permitted, but was followed by directing the interaction back to the ART framework.

It seems unlikely that this ART effect is attributable to "common factor"[18] elements of this psychotherapy: i.e., empathic listening, the sense that a knowledgeable professional cares and understands, and the strength of the therapeutic alliance. Applied Relaxation Training adherence was uniformly high, with no differences between LOSS and no-LOSS ART treatments. Alternatively, LOSS might be confounded by some other, as yet undetermined clinical variable. Our analyses ruled out some obvious confounds. Currently, these counterintuitive findings cannot be easily explained.

Several limitations of this study deserve notice. Most importantly, ascertainment of proximal interpersonal loss was coded from the answer to an interview question about circumstances in the 6 weeks prior to panic disorder onset. Responses may have been subject to retrospective and explanatory (*post hoc, ergo propter hoc*) bias. Even if the sequence of events occurred as patients reported approximately 8 years later, such losses have certainly not been shown to "cause" panic disorder. It is possible that panic disorder vulnerability sensitizes individuals to the effects of interpersonal loss, or that interpersonal losses can trigger an underlying panic diathesis, or that interpersonal loss makes patients more amenable to some psychotherapeutic interventions (i.e., ART) than they otherwise would be. In the absence of prospective longitudinal studies, which do not yet exist for panic disorder, researchers must perforce rely on patients' retrospective reporting of stressors that occurred at the time of illness onset in evaluating psychosocial component variables. Despite this drawback, some data do suggest that, for example, depressed patients can accurately recall past depressive episodes 4 years and longer before being interviewed.[19]

Thus, patients' retrospective reports of interpersonal loss proximal to panic disorder onset may be construed either as actual events or as reflecting differing psychological organization of experience. We lack prospective and adequately fine-grained data to distinguish between these alternatives. The phenomenology of panic and the experience of interpersonal loss may at least partially overlap. The feeling of panic is often described as an overwhelming sense of helplessness and need for help, potentially mimicking feelings common in interpersonal loss situations.

The treatment sample had some distinctive characteristics. The rate of reported proximal interpersonal loss was higher (74% in the 6 weeks prior to panic onset) than re-

ported in other panic disorder samples, in which rates ranged from 25%[2] to 67%[3] in the prior year. This was true even though we defined interpersonal loss more narrowly, and within a briefer time frame, than did some other studies. It is unclear whether our subjects' higher loss reporting reflects a clinically meaningful difference from previously reported samples of panic disorder patients, as this variable has rarely been followed in the panic disorder clinical trials literature. The overall response rate to ART (39%) was higher than reported elsewhere,[10] potentially reflecting the ART therapists' high degree of experience or the unusually intense, twice-weekly ART treatment, which included an active in vivo exposure protocol, in addition to the relatively high rate of patients in this sample who reported interpersonal loss.

Interpersonal loss may be a meaningful clinical marker in panic disorder, an anamnestic target for clinicians, and a variable for future moderation research. Life events and traumas are a complex area of psychopathology[20]: many patients report them, yet not all develop symptoms.[21,22] It will be interesting to determine whether reports of proximal interpersonal loss moderate other, more commonly recommended treatments, such as cognitive behavior therapy[23,24] or psychopharmacologic interventions. Cognitive behavior therapy is more flexible than ART, addresses more levels of the panic attack experience, and uses a wider range of techniques.

This panic disorder trial has now yielded 2 preliminary moderators of treatment: Axis II cluster C comorbidity predicted improved PFPP outcome,[25] and LOSS predicts better ART outcome. To our knowledge, the current report is the first moderator analysis of any anxiety disorder treatment to assess a psychosocial variable. The clinical importance of this variable can only be determined on the basis of future research in this area.

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