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Diagnostic Comorbidity in Panic Disorder: Effect on Treatment Outcome and Course of Comorbid Diagnoses Following Treatment

Timothy A. Brown
Center for Stress and Anxiety Disorders University at Albany, State University of New York
Martin M. Antony
Center for Stress and Anxiety Disorders University at Albany, State University of New York
David H. Barlow
Center for Stress and Anxiety Disorders University at Albany, State University of New York

ABSTRACT

The impact and course of additional diagnoses was examined in 126 patients undergoing cognitive—behavioral treatment for panic disorder. With the Anxiety Disorders Interview Schedule–Revised, a high comorbidity rate (51%) was observed at pretreatment. Pretreatment comorbidity was not predictive of premature termination, nor did it have a substantial impact on short-term treatment outcome. However, patients with comorbidity at posttreatment were more likely to have sought additional treatment over the follow-up interval. Although a significant and dramatic decline in the overall comorbidity rate was found at posttreatment (17%), at 24-month follow-up this rate had increased to a level (30.2%) that was no longer significantly different from pretreatment. This was despite the fact that patients maintained or improved on treatment gains for panic disorder over this interval. The implications of these findings for the treatment, conceptualization, and classification of emotional disorders are discussed.

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Correspondence may be addressed to Timothy A. Brown, Phobia and Anxiety Disorders Clinic, Center for Stress and Anxiety Disorders, State University of New York at Albany, 1535 Western Avenue, Albany, New York, 12203.
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Studies published within the past 5 years indicate that the majority of patients presenting with an anxiety disorder (as diagnosed by the *Diagnostic and Statistical Manual of Mental Disorders* [3rd ed., rev.; *DSM—III—R;* American Psychiatric Association, 1987]) have at least one additional disorder (Brown & Barlow, 1992 ; de Ruiter, Rijken, Garssen, van Schaik, & Kraaimaat, 1989 ; Sanderson, Di Nardo, Rapee, & Barlow, 1990 ; cf. Maser & Cloninger, 1990). The high degree of comorbidity observed among anxiety disorders is partly attributable to the expansion of the *DSM* classification system over the past several decades. Whereas only three anxiety disorders existed in the second edition of the *DSM* (*DSM—II;* American Psychiatric Association, 1968), there are 12

diagnostic categories for adults in the fourth edition of the *DSM* (*DSM—IV;* American Psychiatric Association, 1994). Citing the high rates of comorbidity among the anxiety and mood disorders as one piece of supporting evidence, many researchers have raised the possibility that current classification systems such as the *DSM* and the International Classification of Diseases are erroneously distinguishing phenomena on the basis of differing manifestations of common pathophysiology (e.g., Andrews, in press ; Andrews, Stewart, Morris-Yates, Holt, & Henderson, 1990 ; Hudson & Pope, 1990 ; Tyrer, 1989). Thus, whereas the rise in the number of diagnostic categories within these systems might imply greater precision in the organization and understanding of psychopathology, high rates of comorbidity may be indicative of nosologies that are artificially differentiating symptomatology that would be more parsimoniously merged. This issue was quite salient throughout the process of developing *DSM—IV* particularly for certain diagnoses such as generalized anxiety disorder (GAD; cf. Brown, Barlow, & Liebowitz, 1994). Although controversy remains regarding how classification should be approached, most researchers concede that these nosologies should be regarded more for their heuristic value rather than as a "final word" on the nature of mental disorders (cf. Brown, in press ; Maser, Kaelber, & Weise, 1991).

An important indicator of the usefulness of a classification system is the extent to which it guides the selection of the optimal treatment (Tyrer, 1989). In recent years, substantial advances have been achieved in the development and evaluation of successful psychosocial treatments for every anxiety disorder specified by the *DSM—III—R* (cf. Barlow, 1994 ; Brown, Hertz, & Barlow, 1992). These treatments typically contain therapeutic procedures that have been designed to address the specific features of the disorder (Barlow, 1989). For example, an intervention of choice for blood—injection phobia includes applied muscle tension, a therapeutic component that is not found in treatments for other anxiety disorders, or other types of specific phobias (Öst & Sterner, 1987). Treatments for panic disorder involve eliciting specific somatic sensations while attending to relevant cognitions (Craske & Barlow, 1993). Nevertheless, cognitive—behavioral treatments for anxiety disorders possess many overlapping elements such as therapeutic exposure and the restructuring of cognitions pertaining to the overestimation of threat risk and catastrophic perceptions of the impact of feared events. These overlapping treatment components address features that are common to all anxiety disorders.

Despite the significant strides taken in the documentation of effective treatments for anxiety disorders, relatively little research has been conducted on the role of comorbidity in treatment outcome. This lack of research can be attributed to such factors as (a) the infancy of many treatments for anxiety disorders, (b) failure to assess comorbid diagnoses, (c) use of comorbid diagnoses as study exclusion criteria, and (d) use of small sample sizes that prevent the examination of the impact of specific patterns of comorbidity (Brown & Barlow, 1992). One important issue is whether the presence of certain comorbid diagnoses affects short- and long-term treatment efficacy. The fact that information regarding comorbidity is reported infrequently in treatment outcome studies precludes the examination of what may be a mediating factor of differential treatment outcome across studies. Interestingly, the majority of research that has been conducted to date on this issue has come from pharmacological outcome studies of panic disorder, with equivocal results (Coryell & Noyes, 1988 ; Green & Curtis, 1988 ; Grunhaus, 1988 ; Lesser et al., 1988 ; Mavissakalian & Hamann, 1987 ; Noyes et al., 1990 ; Pyke & Kraus, 1988 ; Reich, 1988). Many of these studies assessed comorbidity with questionnaires (e.g., Personality Disorders Questionnaire) rather than structured interviews.

The few psychosocial treatment outcome studies that have examined the impact of pretreatment comorbidity on treatment outcome have produced generally weak or nonsignificant findings. For example, although an initial study (Foa, Grayson, & Steketee, 1982) found that depression was

associated with less favorable improvement and higher rates of relapse in the treatment of obsessive—compulsive disorder (OCD), later studies did not corroborate this finding (Basoglu, Lax, Kasvikis, & Marka, 1988 ; Foa, Steketee, Kozak, & McCarthy, 1990). Studies have produced some evidence that certain comorbid Axis II disorders are associated with poorer response to behavioral treatment of social phobia (Turner, 1987) and panic disorder with agoraphobia (Chambless, Renneberg, Goldstein, & Gracely, 1992). However, in the latter study, which assessed personality disorders using the Millon Clinical Multiaxial Inventory, contradictory findings were reported. Whereas avoidant personality disorder was associated with less favorable outcome, two personality disorders (dependent and histrionic) were unexpectedly associated with an enhanced response to treatment. In addition, Steketee (1990) found that dependent personality traits were associated with a better initial response to a short-term treatment for OCD.

Another related issue accorded even less research attention involves examining what influence the treatment of one disorder has on the course of its co-occurring diagnoses. The extent to which the treatment of one condition leads to the reduction or elimination of the symptomatology of comorbid conditions that have not been the target of treatment has relevance to such issues as the evaluation of treatment efficacy and the validity of the classification and assessment of these disorders (Brown & Barlow, 1992). On the one hand, the reduction of comorbid disorders through the treatment of another disorder may speak to the robustness of the treatment package for promoting therapeutic change and treatment generalization. Additionally, one disorder may precipitate another (e.g., restriction in mobility from agoraphobia may result in major depression), thus successful treatment may produce an amelioration of the symptoms of both disorders. On the other hand, concurrent reduction of two disorders through the treatment of one may be indicative of a lack of independence of the diagnoses because they share overlapping definitional features (i.e., diagnostic criteria) or represent different features within one larger underlying syndrome or dimensions of psychopathology (cf. Blashfield, 1990 ; Frances, Widiger, & Fyer, 1990).

Thus, the initial step to address this issue is to determine what effect treatment has on comorbid diagnoses. In the only studies published to date, Mavissakalian and his colleagues (Mavissakalian & Hamann, 1987 ; Mavissakalian, Hamann, & Jones, 1990) found that antidepressant and combined antidepressant—behavioral treatment produced significant reductions in personality disorder symptomatology in patients with OCD and panic disorder with agoraphobia. However, in these studies, personality disorders were assessed with questionnaires rather than structured interviews. Thus, the extent to which these patients simply evidenced the features of these disorders, rather than met the diagnostic threshold for a *DSM—III—R* personality disorder, is not known.

With these issues in mind, we examined the impact and course of comorbidity in 126 patients participating in a treatment outcome study for panic disorder. Comorbidity was evaluated using a structured interview designed to establish *DSM—III—R* diagnoses for anxiety, mood, and selected somatoform disorders. The main questions addressed were (a) Do comorbidity and specific diagnoses that frequently co-occur with panic disorder affect short- and long-term treatment outcome? and (b) Is treatment of panic disorder associated with a reduction in comorbidity?

Method

Participants

One hundred twenty-six patients participated in a large, comparative treatment outcome study for panic disorder (cf. Barlow et al., 1991 ; Margraf, Barlow, Clark, & Telch, 1993). They were selected

from a large pool of patients presenting for assessment and treatment at the Center for Stress and Anxiety Disorders. Patients came from many sources, including referrals by primary care physicians and mental health professionals and self-referrals. Potential participants were required to satisfy the following criteria: (a) principal diagnosis (*DSM—III—R;* American Psychiatric Association, 1987) of panic disorder with no more than mild agoraphobic avoidance, (b) age between 18 and 65 years, and (c) a record of at least one panic attack or limited symptom attack in the 2-week self-monitoring period before the initial treatment session. Participants were excluded if any of the following were present: (a) current or recent (within the past 6 months) alcohol or drug abuse or dependence or (b) evidence of psychosis, bipolar disorder, or organic brain syndrome. Participants were required to meet certain medication and alternative psychotherapy stabilization or wash-out criteria as well (cf. Di Nardo, Moras, Barlow, Rapee, & Brown, 1993). The largest portion of the sample comprised female participants (69.8%); the average age of the sample was 33.99 (*SD* = 8.70, range, 20 to 64).

Diagnoses were established using the Anxiety Disorders Interview Schedule–Revised (ADIS-R; Di Nardo & Barlow, 1988), a structured diagnostic interview designed to comprehensively evaluate the *DSM—III—R* anxiety disorders and mood disorders and to screen for other major disorders (e.g., somatoform, substance use, psychotic). Interrater agreement (based on two independent interviews for principal *DSM—III—R* anxiety disorders) using the ADIS-R ranges from moderate to excellent (kappa coefficients range from .46 to .82). The kappa for panic disorder (pooling across no and mild agoraphobic avoidance) is .71 (Di Nardo et al., 1993).

Interviewers were PhD-level clinical psychologists and advanced doctoral-level students who had received extensive training in ADIS-R administration and had met strict reliability criteria (cf. Di Nardo et al., 1993). In instances in which the patient was deemed as meeting criteria for two or more diagnoses, the "principal" diagnosis was the one that received the highest ADIS-R clinical severity rating (on a scale ranging from 0 to 8) that indicated the diagnostician's judgment of the degree of distress and interference in functioning associated with the diagnosis. To be included in the study, patients were required to have a principal diagnosis of panic disorder (no or mild avoidance) that was assigned an ADIS-R clinical severity rating of 4 or higher. Additional diagnoses were assigned as either (a) clinical (deemed to meet formal *DSM—III—R* criteria for the diagnosis [i.e., ADIS-R clinical severity ratings of 4 i.e., moderate, or higher]); or (b) subclinical (presence of diagnostic features that do not meet *DSM—III—R* criteria for distress or functional impairment [e.g., a marked fear of spiders that does not meet the distress or interference criterion of *DSM—III—R* simple phobia]). Subclinical diagnoses, per conventions used at the clinic, were assigned ADIS-R clinical severity ratings below 4 on the scale from 0 to 8.

Measures ADIS-R.

In addition to diagnoses and their respective clinical severity ratings (ranging from 0 to 8) mentioned earlier, the following information from the ADIS-R was used in the study: (a) demographic variables (e.g., age and sex); and (b) frequency of panic attacks in the past month.

At posttreatment and each follow-up assessment, patients were administered a condensed version of the ADIS-R that excluded research questions but included items covering each of the diagnostic criteria necessary to establish five-axis *DSM—III—R* diagnoses for the anxiety and mood disorders. This version of the ADIS-R also contained questions pertaining to current and past medication use and utilization of alternative treatments. For some of the initial patients enrolled in the treatment protocol, this "mini-ADIS" comprised only the panic disorder, agoraphobia, generalized anxiety disorder, and Hamilton scale sections. For the majority of patients, however, the posttreatment and

follow-up ADIS-Rs contained sections to evaluate all of the *DSM—III—R* anxiety disorders and mood disorders (i.e., major depression and dysthymia).

Questionnaires.

Measures administered at each assessment point included (a) the *Anxiety Sensitivity Index* (ASI; Peterson & Reiss, 1987), a 16-item scale designed to assess fear of the symptoms of anxiety, and (b) the *Subjective Symptoms Scale* (SSS), which is a modification of a scale introduced by Hafner and Marks (1976) containing point ratings (ranging from 0 to 8) of the extent that anxiety symptoms interfered with five different areas of daily functioning during the past week (work, home management, private leisure, social leisure, family relationships). Analyses of item correlations and internal consistency using the present sample supported the scoring of the items that constitute the SSS into a single scale (Cronbach's alpha = .83; item *r* s ranged from .41 to .67).

Assessment points.

Posttreatment assessment (ADIS-R, questionnaires) occurred 2 weeks after the patient's final treatment session. Follow-up assessments occurred at 3, 6, 12, and 24 months. For purposes of brevity, only data from the posttreatment, 3-month, and 24-month assessment points are presented here (see Brown & Barlow, in press , for a full presentation of follow-up findings).

Composite and Categorical Measures of Clinically Significant Change

A composite measure was developed for evaluation of patients' absolute level of functioning (i.e., endstate functioning) after treatment. To be classified as having achieved high endstate functioning, patients were required to meet both of the following criteria: (a) an ADIS-R clinical severity rating of panic disorder of 2 or below and (b) a report of having no panic attacks in the previous month on the basis of the ADIS-R interview. These criteria were viewed as being more conservative than those used in previous studies (e.g., Barlow, Craske, Cerny, & Klosko, 1989), given that this classification was conjunctive and was based solely on interview data collected by an independent evaluator (cf. Barlow, Brown, & Craske, 1994 ; Craske, Brown, & Barlow, 1991). In addition, one component of the criteria for endstate functioning was analyzed separately: panic-free status (i.e., reporting no panic attacks in the previous month on the basis of the ADIS-R interview).

Treatment Conditions

The treatment outcome study (Barlow et al., 1991) entailed dismantling the Panic Control Treatment package developed at the Center for Stress and Anxiety Disorders (cf. Craske & Barlow, 1993). Accordingly, patients were randomly assigned to one of four treatment conditions: (a) cognitive restructuring, (b) cognitive restructuring and breathing retraining, (c) cognitive restructuring and interoceptive exposure, or (d) a combination of all three treatment components. In all four conditions, therapy was delivered in 11 individual hourly sessions, with Sessions 1—3 occurring within a period of 10 days, Sessions 4—9 occurring on a weekly basis, and Sessions 10 and 11 occurring on a biweekly basis. A detailed description of the Panic Control Treatment protocol can be found in Craske and Barlow's (1993) work. As noted in earlier reports (Barlow et al., 1991 ; Margraf et al., 1993), patients who completed the active treatment phase evidenced substantial reductions in panic and associated symptomatology across the pre- to posttreatment and follow-up periods (also see Results). However, differences in the four active treatment conditions were not significant. Because of this lack of differential efficacy, as well as the lack of differential attrition rates, treatment

conditions were collapsed in the present study.

Results

Patterns and Impact of Pretreatment Comorbidity

Of the 126 patients entering the study, 87 completed the active treatment phase, 23 discontinued treatment before the 11th session (for a variety of reasons, including remission of symptoms), and 16 patients were removed from the study (e.g., irregular attendance beyond protocol requirements, noncompliance with monitoring, change in diagnostic status). Half (51%) of the patients had at least one additional diagnosis at pretreatment. Of the 64 patients with comorbidity, 41 had one additional diagnosis, 20 had two additional diagnoses, and 3 had three additional diagnoses. As shown in Table 1, the most frequent additional diagnoses were generalized anxiety disorder (GAD; 32.5%), social phobia (13.5%), and depression (12.7%, collapsing across major depression and dysthymia). The three groups (i.e., completers, dropouts, and removals) did not differ in terms of the presence or number of comorbid diagnoses at pretreatment, $\chi^2 2, N = 126 = .023., ns$, nor did the groups differ in the distributions of specific diagnoses. For example, as shown in Table 1, the rates of comorbid depression were 12.6%, 13.0%, and 12.5% for completers, dropouts, and removals, respectively. These results did not change when dropouts and removals were collapsed into a single category.

Analyses of variance (ANOVAs) indicated that, relative to patients with no comorbid diagnoses ($M = 5.06$, $SD = 0.85$), patients with comorbidity at pretreatment were assigned significantly higher ADIS-R clinical severity ratings of their panic disorder ($M = 5.80$, $SD = 0.74$), F (1, 124) = 26.82, $p < .001$. Because this finding may have been due in part to interviewer bias (i.e., interviewers may have elevated severity ratings of panic disorder to assign additional diagnoses with severity ratings of 4 or higher), we examined the impact of comorbidity on pretreatment panic symptomatology using two questionnaire measures: the ASI and the SSS. Results indicated that patients with pretreatment comorbidity obtained significantly higher ASI scores ($M = 36.96$, $SD = 11.62$) than patients with no additional diagnoses ($M = 30.21$, $SD = 10.15$), F (1, 122) = 11.84, $p < .001$. In addition, pretreatment comorbidity was associated with significantly higher SSS scores ($M = 3.59$, $SD = 1.75$) than when additional diagnoses were absent ($M = 2.77$, $SD = 1.55$), F (1, 116) = 7.28, $p < .01$.

Impact of Comorbidity on Treatment Outcome Impact of pretreatment diagnoses on short-term outcome.

To examine whether the presence of additional diagnoses affected short-term treatment outcome (i.e., posttreatment and 3-month follow-up), we conducted a series of chi-square analyses using the categorical measures of treatment outcome (i.e., endstate status, panicfree status). Pretreatment comorbidity was analyzed as a two-level variable (i.e., presence vs. absence of additional diagnoses; subclinical diagnoses were assigned to the latter category).

The results of these analyses are presented in Figure 1. These analyses indicated that patients with an additional diagnosis at pretreatment (regardless of type) were not significantly less likely to achieve high endstate or panicfree status at either posttreatment or 3-month follow-up (all χ^2 s < 1). For example, whereas 43.6% of patients without comorbid diagnoses at pretreatment met high endstate criteria at posttreatment, these criteria were met by 35% of patients with at least one comorbid diagnosis.

Given the low rates of co-occurrence of many diagnoses at pretreatment, the impact of specific

diagnoses could be examined for only three categories: GAD, social phobia, and depression (collapsing across major depression and dysthymia). As seen in Figure 1 , the presence of comorbid GAD was not associated with differential outcome at either short-term assessment point (all χ^2 s < 1). Counter to expectation, a larger proportion of patients (77.8%) with an additional diagnosis of social phobia met high endstate criteria at posttreatment than those without comorbid social phobia (34.3%), χ^2 1, N = 79 = 6.33, $p < .05$. This difference approached significance at 3-month follow-up (70.0% and 38.2% for patients with and without comorbid social phobia, respectively), χ^2 1, N = 78 = 3.60, $p < .06$. Similarly, relative to patients without social phobia, more patients with social phobia at pretreatment were classified as panicfree at posttreatment, although this difference only approached significance, χ^2 1, N = 79 = 3.37, $p < .07$. and was no longer evident at 3-month follow-up χ^2 s < 1 .

There was some indication that the presence of comorbid depression was associated with differential outcome at posttreatment. Only 11.1% of patients with an additional mood disorder at pretreatment met high endstate criteria at posttreatment, in contrast to 42.9% of patients without comorbid depression. This difference approached significance, χ^2 1, N = 79 = 3.37, $p < .07$. However, a statistically significant effect was obtained for panicfree status in that fewer (22.2%) patients with comorbid depression were classified as panicfree than patients without a comorbid mood disorder (65.7%), χ^2 1, N = 79 = 6.32, $p < .05$. Neither of these effects was evident at the 3-month follow-up (both χ^2 s < 1).

Impact of posttreatment diagnoses on long-term outcome.

To determine whether additional diagnoses that were still present at the 3-month follow-up affected long-term outcome (i.e., 24-month follow-up), we conducted chi-square analyses using endstate status and panicfree status as dependent measures. Because of the low overall frequency of additional diagnoses remaining at the 3-month follow-up, statistical analyses could not be performed for specific diagnoses. Thus, 3-month follow-up comorbidity was analyzed, collapsing across diagnostic categories (i.e., presence vs. absence of additional diagnoses). To ensure that the largest possible N was used in these analyses, we included patients who were unavailable at the 3-month follow-up in the analyses using data from the posttreatment assessment, if these patients had received the full ADIS-R at posttreatment (this was done for 7 patients). All patients available for the 24-month follow-up assessment received the full ADIS-R.

Although 64 patients completed the 24-month follow-up assessment, 8 were not included in the analysis because they did not receive the full ADIS-R at either posttreatment or the 3-month follow-up. These analyses indicated that the presence of an additional diagnosis at the 3-month follow-up was not associated with less favorable long-term outcome as measured by high endstate or panicfree criteria. Whereas 29 (65.9%) of the 44 patients with no additional diagnoses at the 3-month follow-up met high endstate criteria at the 24-month follow-up, these criteria were met by 5 (41.7%) of the 12 patients with comorbidity at the 3-month follow-up, χ^2 1, N = 56 = 2.32, *ns* Differences in outcome at the 24-month follow-up were even less evident using the panicfree measure; 77.3% (34 of 44) and 75.0% (9 of 12) for patients with and without additional diagnoses at the 3-month follow-up respectively, χ^2 1, N = 56 = 0.03, *ns*

Treatment seeking over the 24-month follow-up interval was analyzed as another index of long-term outcome. Treatment seeking was analyzed in two ways: (a) whether patients sought additional treatment (psychosocial, pharmacological, etc.) specifically for panic attacks at any time during the

24-month follow-up interval and (b) whether patients sought additional treatment during the 24-month interval, regardless of the purpose of treatment (including panic treatment). If a patient was unavailable at the 24-month follow-up but had indicated during a previous follow-up assessment that they had sought additional treatment, they were included in these analyses ($n = 4$). Patients who had additional diagnoses still present at the 3-month follow-up were significantly more likely to have sought further treatment for panic during the 24-month follow-up period, χ^2 1, $N = 60 = 4.22$, $p < .05$. Specifically, whereas 10 (21.7%) of the 46 patients without comorbid diagnoses at the 3-month follow-up had sought additional treatment for panic, 7 (50%) of the 14 patients with comorbid diagnoses had done so. In addition, comorbidity at the 3-month follow-up was associated with a significantly greater likelihood (64.3%; 9 of 14 patients) of seeking treatment of any type during the follow-up period (32.6% '15 of 46] for patients without additional diagnoses at the 3-month follow-up), χ^2 1, $N = 60 = 4.49$, $p < .05$.

As elaborated on in Brown and Barlow's (in press) work, the 17 patients who sought additional treatment for panic were most likely to have received pharmacotherapy ($n = 7$) or to have received counseling or psychotherapy ($n = 6$); the remaining 4 patients received additional cognitive—behavioral treatment. All but 2 of these patients received more than a month of additional treatment. The 7 patients who received further treatment for problems other than panic did so for the following reasons: interpersonal problems ($n = 3$), anxiety disorder ($n = 2$), stress management ($n = 1$), and dysthymia ($n = 1$). Whereas 2 of these patients reported fewer than 4 sessions of additional treatment, 5 reported more than a month of treatment ("counseling or psychotherapy" was the most common; $n = 4$).

Course of Additional Diagnoses After Treatment

The issue of whether cognitive—behavioral treatment for panic disorder resulted in the reduction of additional diagnoses was addressed initially by examining the frequency of comorbid diagnoses assigned at pretreatment and various posttreatment assessment points (using the presence or absence of any additional diagnosis and the diagnoses of GAD, social phobia, and depression in the analyses). Because the aforementioned findings indicate that many patients received additional treatment between the 3- and 24-month follow-up points (only 2 patients had sought treatment before the 3-month follow-up), one should remember that any changes in comorbidity between these follow-up points would be difficult to associate directly to the study treatment. [1] To ensure that changes in the rate and patterns of additional diagnoses were not affected by variations in sample compositions, we performed these analyses by using patients who completed all of the assessments used in the analysis.

Change in comorbid GAD was examined first because all patients were administered a version of the ADIS-R at posttreatment and follow-up that evaluated this diagnosis. Figure 2 presents data pertaining to the change in the rate in which GAD was assigned for the 57 patients who were available at all four assessment points: pretreatment, posttreatment, 3-month follow-up, and 24-month follow-up. Whereas GAD was present in 15 (26.3%) of these patients at pretreatment, only 4 (7.0%) were assigned GAD at posttreatment; subclinical GAD increased from 7.0% to 15.8% from pre- to posttreatment, perhaps because of the fact that a few patients with clinical GAD at pretreatment moved to the subclinical category at posttreatment. These posttreatment breakdowns remained quite stable at the 3-month follow-up and the 24-month follow-up. Indeed, McNemar tests indicated a statistically significant reduction in the frequency in which GAD was assigned from pretreatment to posttreatment, to the 3-month follow-up, and to the 24-month follow-up (p s < .01, .01, and .05, respectively; subclinical GAD was collapsed into the category of "no GAD"); there were no differences in the rate in which GAD was assigned among the posttreatment, 3-month, and 24-

month follow-up assessments.

For the remaining diagnostic categories, these analyses were performed using the pretreatment, 3-month, and 24-month follow-up assessment points. As with the previously reported analyses involving the prediction of treatment seeking and functioning at the 24-month follow-up, the 3-month follow-up assessment was used instead of the posttreatment assessment because a larger number of patients had been administered the full ADIS-R at the 3-month follow-up than at posttreatment. [2] Thus, 53 patients were used in these analyses because they had been administered the full ADIS-R at pretreatment and at the 3- and 24-month follow-up points.

Whereas 5 (9.4%) of patients received an additional mood disorder (major depression or dysthymia) at pretreatment, 3 (5.7%) were assigned this diagnosis at the 3-month follow-up (1 patient was assigned a subclinical mood disorder at pretreatment and at the 3-month follow-up). However, at the 24-month follow-up, the comorbidity rate of mood disorders returned to the pretreatment level (9.4%; subclinical = 5.7%). Thus, the rate in which comorbid mood disorders were assigned across these three assessment points did not differ, as confirmed by nonsignificant McNemar tests. The number of patients given clinical and subclinical diagnoses of social phobia at pretreatment was 6 (11.3%) and 13 (24.5%), respectively. At the 3-month follow-up, only 1 (1.9%) patient was assigned this diagnosis (subclinical = 22.6%). A McNemar test indicated that this reduction approached significance ($p < .07$). However, 4 (7.5%) patients were assigned social phobia at the 24-month follow-up (subclinical = 15.1%); McNemar tests revealed that comorbidity rates of social phobia did not differ between pretreatment and the 24-month follow-up point and between the 3- and 24-month follow-up points.

Next, these analyses were conducted to determine if the overall comorbidity rate changed significantly from pretreatment to the 3- and 24-month follow-up points. As noted in Figure 3 , 21 (39.6%) patients at pretreatment were assigned at least one additional diagnosis. This rate had decreased to 17.0% at the 3-month follow-up, a change that was significant (McNemar test $p < .01$). However, 16 (30.2%) of patients were assigned at least one diagnosis other than panic disorder at the 24-month follow-up. Accordingly, McNemar tests indicated that the overall comorbidity rate did not significantly differ between pretreatment and the 24-month follow-up ($p < .30$) or between the 3- and 24-month follow-up points ($p < .12$). Despite the increase in the rate comorbidity, albeit nonsignificant, from the 3-month follow-up to the 24-month follow-up, these patients maintained or improved on their treatment gains for panic disorder symptomatology over the same interval. Whereas 41.5% patients met high endstate criteria at the 3-month follow-up, this increased to 62.3% at the 24-month follow-up, a change that was significant ($p < .05$). The percentage of patients panicfree was 71.7% and 77.4% at the 3- and 24-month follow-up points, respectively, an increase that was not significant ($p < .65$).

Longitudinal Analysis of the Course and Impact of Comorbid Diagnoses

As the previous analyses provide the cross-sectional comorbidity rates at selected assessment points, they do not specifically indicate the longitudinal course of additional diagnoses. For example, the 5 patients who were assigned a mood disorder at the 24-month follow-up may or may not have been the same 5 patients who had a mood disorder diagnosis at pretreatment. To address this issue, we performed longitudinal comparisons using the 64 patients who completed the 24-month follow-up assessment (74% of patients completing the active treatment phase). [3] Of the 64 patients available at the 24-month follow-up, 28 (43.8%) had received at least one additional diagnosis at pretreatment. Of these 28 patients, 15 (53.6%) continued to have at least one comorbid diagnosis at the 24-month

follow-up. Interestingly, 7 of the 15 patients that continued to carry one or more comorbid diagnosis at the 24-month follow-up were assigned a diagnosis that was different from any of the comorbid diagnoses they received at pretreatment (the new diagnoses were major depression [$n = 2$], simple phobia [$n = 2$], GAD, social phobia, and sexual arousal disorder). As seen in Figure 4 , the continued presence of comorbid diagnoses was associated with poorer treatment outcome for panic disorder at the 24-month follow-up. Relative to the 13 patients who had been assigned an additional diagnosis at pretreatment but who no longer evidenced comorbidity at the 24-month follow-up, the 15 patients with continued comorbidity were significantly less likely to have achieved high endstate status at the 24-month follow-up, respectively; χ^2 1, $N = 28 = 5.32$, $p < .05$. Specifically, whereas 76.9% of patients who no longer had any comorbid diagnoses met high endstate criteria, only 33.3% of patients with continued comorbidity met these criteria. This difference approached significance for panicfree status: 92.3% and 66.7% for patients without and with comorbid diagnoses, respectively; χ^2 1, $N = 28 = 2.72$, $p < .09$.

Of the 36 patients who had not received any additional diagnoses at pretreatment, 6 (16.7%) were assigned a diagnosis other than panic disorder at the 24-month follow-up. The diagnoses assigned to these 6 patients were major depression ($n = 2$), GAD ($n = 2$), anxiety disorder not otherwise specified, and OCD. The emergence of additional diagnoses in patients who previously had no comorbidity was associated with poor long-term outcome for panic disorder, as noted in Figure 4 . Whereas 20 (66.7%) of the 30 patients who continued to have no comorbid diagnoses at the 24-month follow-up met high endstate functioning criteria at this assessment point, only 1 (16.7%) of the 6 patients with a new additional diagnosis met these criteria, χ^2 1, $N = 36 = 5.14$, $p < .05$. This difference was also obtained on the panicfree status measure, χ^2 1, $N = 36 = 9.45$, $p < .01$. Of the 30 patients who continued to have no additional diagnoses at the 24-month follow-up, 24 (80.0%) were classified as panicfree, compared with only 1 (16.7%) of the 6 patients who were no longer considered to be without comorbid disorders at the 24-month follow-up.

As previous analyses demonstrated the association between comorbidity and greater panic disorder symptomatology at pretreatment, an ANOVA was conducted to determine whether pretreatment clinical severity of panic disorder was associated with comorbidity at the 24-month follow-up. This analysis was significant, F (1, 62) = 6.48, $p < .05$. Results indicated that patients with additional diagnoses at the 24-month follow-up had been assigned significantly higher ADIS-R clinical severity ratings for panic disorder ($M = 5.81$, $SD = 0.98$) than patients with no comorbid diagnoses at the 24-month follow-up ($M = 5.23$, $SD = 0.78$). Similarly, a significant effect was obtained for the SSS, F (1, 57) = 11.78, $p < .01$. Patients with comorbidity at the 24-month follow-up had obtained significantly higher pretreatment SSS scores ($M = 3.73$, $SD = 1.46$) than patients with no comorbidity ($M = 2.46$, $SD = 1.28$). No between-groups differences were obtained for the pretreatment ASI (M s = 33.19 and 32.01 for the comorbid and noncomorbid groups, respectively, $F < 1$).

Discussion

Consistent with prior findings (e.g., Brown & Barlow, 1992 ; de Ruiter et al., 1989), a high rate of comorbidity was observed at pretreatment in the present sample of patients with panic disorder. Indeed, 51% of the 126 patients enrolled in the study were assigned at least one additional diagnosis, the most common being GAD, social phobia, and mood disorder. Another finding that was generally consistent with the few other studies that exist in this area was the observation that pretreatment comorbidity was not strongly associated with short-term treatment efficacy. Pretreatment comorbidity

was not predictive of premature termination of treatment, nor were certain comorbid patterns (any diagnosis or GAD) associated with high endstate or panicfree status at posttreatment and at the 3-month follow-up. Patients with a mood disorder at pretreatment were less likely to be panicfree at posttreatment (and somewhat less likely to be classified as high endstate); however, there was no association between pretreatment depression and treatment outcome at the 3-month follow-up. Whereas it might be concluded that the presence of a mood disorder does not have a substantial impact on treatment outcome for panic disorder, these findings should be considered keeping in mind that the small number of patients with pretreatment depression and the reliance on nonparametric statistics mitigated the statistical power of these and similar analyses (on the other hand, the fact that alpha was not adjusted to control for the influence of experimentwise error in these analyses should be considered as well).

Similar to the findings of Chambless et al. (1992) who noted that the presence of pretreatment dependent and histrionic personality disorders were associated more favorable outcome for panic disorder with agoraphobia, one comorbid pattern was somewhat predictive of treatment outcome in the direction opposite to expectation. Patients with social phobia at pretreatment were significantly more likely to meet high endstate status criteria at posttreatment, an effect that approached significance at the 3-month follow-up. In interpreting their findings, Chambless et al. (1992) speculated that dependent personality was associated with more favorable outcome because these patients may have been more apt to comply with treatment. Although this interpretation could be offered for the present study's findings (e.g., patients with social phobia may be more compliant because of a fear of negative evaluation), it is noteworthy that Chambless et al. (1992) found no association between social phobia and treatment outcome (however, social phobia was measured only by questionnaires in that study).

Interestingly, whereas comorbidity at the 3-month follow-up was not associated with high endstate or panicfree status at the 24-month follow-up, the presence of additional diagnoses at the 3-month follow-up was predictive of treatment seeking during the follow-up interval, both for additional treatment of panic disorder and for additional treatment of any kind of emotional problem. Thus, a possible reason why the presence of comorbid diagnoses after treatment for panic was not associated with poorer outcome at the 24-month follow-up was the fact that nearly two thirds (64.3%) of the patients with comorbidity at the 3-month follow-up had sought additional treatment before the 24-month follow-up assessment.

Cognitive—behavioral treatment for panic disorder resulted in a significant decline in the percentage of patients with additional diagnoses at the 3-month follow-up. For specific diagnoses, this reduction was most evident for GAD, the disorder that was most frequently assigned at pretreatment. Whereas 26.3% of patients had GAD at pretreatment, only 8.8% received this diagnosis at posttreatment. The rate in which GAD was assigned remained significantly below pretreatment levels at the 3- and 24-month follow-up points. Other diagnoses (depression, social phobia) also evidenced a decline from pretreatment to the 3-month follow-up, although these reductions were either nonsignificant or only approached significance, in part, because of the lower rate in which these diagnoses were assigned at pretreatment. As noted earlier, although the mechanisms responsible for the decrease in comorbidity are unclear, they are potentially of great importance to the evaluation of treatment efficacy and the validity of classification systems for emotional disorders.

In terms of their relevance to treatment efficacy, the decrease in comorbid diagnoses may be indicative of the robust nature of treatment, perhaps because the treatment is successfully addressing processes that are common to all anxiety and mood disorders or because the additional disorder was

causally related to the principal disorder. For instance, in the case of the decline in GAD, perhaps patients were able to apply effectively the cognitive restructuring skills learned as part of the panic treatment package to their nonpanic-related worries. However, this explanation might be countered with the observation that when GAD is treated as the principal diagnosis, some studies have found this disorder to be much more resistant to change through cognitive—behavioral or pharmacological intervention (e.g., Barlow, Rapee, & Brown, 1992 ; Blowers, Cobb, & Mathews, 1987). Thus, alternative explanations for the dramatic decline in GAD and overall comorbidity from pre- to posttreatment might relate to diagnostic difficulties either because of vague or overlapping criteria or because the co-occurring diagnoses do not represent separate entities.

For example, researchers who have argued that there is insufficient empirical support for the degree of differentiation found in *DSM—III—R* and *DSM—IV* might interpret the present findings as supporting the position that panic disorder treatment did not produce a reduction in multiple disorders but an amelioration of different features of one larger, underlying syndrome. Moreover, the weak effect that pretreatment comorbidity had on treatment outcome in this and other studies might also be considered as supporting evidence. Additional arguments for this position have been prompted by drug studies that suggest that various disorders respond favorably to antidepressant medication (Hudson & Pope, 1990), although this conclusion is controversial (cf. Liebowitz et al., 1988). In one of the few studies, if not the only study, involving psychosocial treatments to directly examine this issue, Tyrer et al. (1988) found that patients with panic disorder, GAD, or dysthymia responded similarly to the same cognitive—behavioral, self-help, or drug treatment.

Related to this argument, researchers in the area of comorbidity and classification have called for increased attention to the severity dimension of psychopathology (Blashfield, 1990 ; Sturt, 1981). Quite evident in factor-analytic studies, this dimension refers to findings indicating that patients can be distributed along a severity continuum ranging from those who score high and who evidence a large number of symptoms to those who score low and have relatively few symptoms (Blashfield, 1990). Several findings in the present study could be viewed as evidence for this phenomenon, including the findings that (a) pretreatment comorbidity was associated with greater panic disorder severity, (b) presence of continued comorbidity at the 24-month follow-up was associated with poorer outcome of panic disorder at this assessment point, and (c) greater severity of panic disorder at pretreatment was associated with comorbidity at the 24-month follow-up. Thus, given the cross-sectional relation between comorbidity and panic disorder symptomatology, it could be argued that treatment simply promoted a shift down this severity continuum so that panic and all associated symptoms were reduced accordingly. The lack of temporal stability in the type of diagnosis in cases when comorbidity was present at both pretreatment and the 24-month follow-up might also be lend support to this position. Moreover, the temporal instability in the type and presence of diagnoses may be reflective of low diagnostic reliability of these categories, which would be expected if diagnosticians were artificially distinguishing (i.e., diagnosing) a unitary dimension of psychopathology (cf. Brown & Barlow, 1992).

Counter to the severity dimension position is the finding that patients continued to improve on their treatment gains for panic disorder symptomatology (e.g., 62.3% met high endstate criteria at the 24-month follow-up, compared with 41.5% at the 3-month follow-up), despite the fact that the rate of comorbid diagnoses increased at the 24-month follow-up (30.2%) to the point that it was no longer significantly different from pretreatment. This result addresses the fact that there was a considerable degree of independence between panic disorder symptomatology and comorbid syndromes, at least at the 24-month follow-up assessment. This finding might also support the position that, although cognitive—behavioral treatment was successful in eliminating the maintaining processes of panic

disorder, common diatheses remained that had etiological significance in the emergence or resilience of other disorders. Barlow (1988) has offered an intermediary position that might account for these findings. Specifically, his model asserts that anxiety and depression share common diatheses (i.e., biological vulnerabilities) but differ on important dimensions (e.g., focus of attention, degree of psychological vulnerability to experiences of unpredictability and uncontrollability) to the extent that increased differentiation of these pathological phenomena is warranted (e.g., has implications for treatment).

Similar to most initial studies, the present findings raise as many issues as they resolve. As mentioned earlier, the few studies of this nature completed to date have been conducted largely at the descriptive level. Consequently, these studies are limited in their ability to provide conclusive evidence as to whether changes in additional diagnoses after treatment are indicative of (a) the effectiveness of the treatment intervention; (b) depending on the theoretical model, problems in (or support for) the manner in which psychopathological phenomena are conceptualized and classified; or (c) miscellaneous factors (e.g., demand characteristics that result in the clinician or patient underreporting symptomatology at posttreatment assessments; cf. Brown & Barlow, 1992). As we have elaborated on elsewhere (Brown & Chorpita, in press), the application of large-sample, longitudinal designs used in tandem with causal modeling procedures may be the optimal approach for determining the extent to which these and other interpretations are operative. Nevertheless, regardless of the specific methodological approach, further study of the longitudinal course and interrelationship of co-occurring syndromes and symptoms (both treated and untreated) should have substantial implications to the understanding and organization of the emotional disorders.

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1

Interestingly, additional treatment did not appear to have a substantial influence on comorbidity changes between the 3- and 24-month follow-up points. With patients who had at least one additional diagnosis at the 3-month follow-up, comorbidity at the 24-month follow-up remained in 57% of patients who sought further treatment, compared with 60% of patients who did not.

2

As with the analyses involving GAD, the rates of comorbidity did not differ appreciably between posttreatment and the 3-month follow-up for any diagnosis. For example, of patients who received the full ADIS-R at posttreatment and the 3-month follow-up, 22.2% and 20.0% had at least one additional diagnosis at posttreatment and the 3-month follow-up, respectively.

3

Patients completing the 24-month follow-up assessment did not differ from noncompleters on any salient measure (e.g., treatment response and pretreatment clinical characteristics; cf. Brown & Barlow, in press).

Table 1.

Figure 1. Percentage of patients with and without pretreatment comorbidity meeting high endstate and panicfree status criteria at posttreatment and 3-month follow-up. ANY DX = presence of additional diagnosis regardless of type; MOOD = mood disorder (major depression or dysthymia); GAD = generalized anxiety disorder; SOC = social phobia.

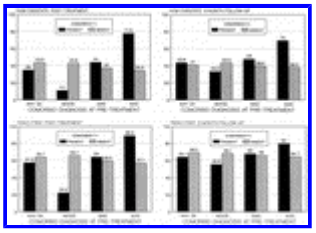

Figure 2. Course of generalized anxiety disorder after cognitive—behavioral treatment for panic

disorder. PRE-TX = pretreatment; POST-TX = posttreatment; 3MFU = 3-month follow-up; 24MFU = 24-month follow-up.

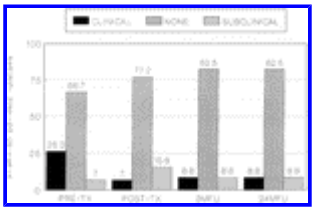

Figure 3. Change in overall comoribidity rate after cognitive behaviroal treatment for panic disorder. PRE-TX = Pretreatment; 3MFU = 3-month follow-up; 24MFU = 24-month follow-up.

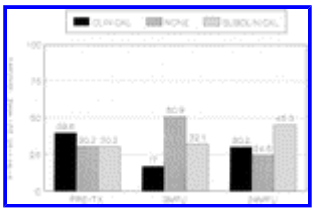

Figure 4. Relation of longitudinal changes in comorbidity to treatment outcome at 24-month follow-up. PRE+ AND 24MFU+ = comorbidity present at both pretreatment and 24-month follow-up; PRE+ AND 24MFU – = comorbidity present at pretreatment but not present at 24-month follow-up; PRE – AND 24MFU – = comorbidity not present at either pretreatment or 24-month follow-up; PRE – AND 24MFU+ = comorbidity not present at pretreatment but present at 24-month follow-up.