ORIGINAL ARTICLE

Lifetime Panic-Depression Comorbidity in the National Comorbidity Survey

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Background: The National Comorbidity Survey is a nationally representative survey of the prevalences and correlates of *DSM-III-R* disorders in the US household population.

Methods: Retrospective age-at-onset reports were used to study predictive relationships between lifetime panic and depression.

Results: Strong associations were found between the lifetime prevalences of panic and major depressive episodes (odds ratios: for panic attacks with depression, 6.2; for panic disorder with depression, 6.8). These associations were not significantly influenced by the inclusion or exclusion of respondents with mania. Temporally primary depression predicted a first onset of subsequent panic attacks but not of panic disorder. Temporally primary panic attacks, with or without panic disorder and whether or not the panic was persistent, predicted a first onset of subsequent major depression. The associations between panic attack and depression were attenuated in models that controlled for prior traumatic life experiences and histories of other *DSM-III-R* disorders.

Conclusions: Lifetime panic-depression comorbidity characterizes most community respondents with panic disorder and a substantial few of those with major depression. The absence of a dose-response relationship suggests that primary panic attack is a marker, rather than a causal risk factor, of subsequent depression. Primary depression, in comparison, appears to be a genuine risk factor for secondary panic attacks. That primary depression predicts panic attacks but not panic disorder suggests that secondary panic is a severity marker of depression rather than a comorbid condition. These results are far from definitive because they are based on retrospective reports, lay-administered diagnostic interviews, and only 1 survey. However, they raise important questions that could lead to a fundamental rethinking of panic-depression comorbidity if they are replicated in future epidemiological and clinical studies.

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EPISODE COMORBIDITY is of considerable importance because of its high prevalence[1,2] and association with impairment and chronicity.[3,4] Episode comorbidity between panic disorder and depression is one of the strongest psychiatric comorbidities[1,5] and the single strongest anxiety-mood episode comorbidity in treatment groups[6] and general population samples.[7] In this report, we present epidemiological data on panic-depression comorbidity in the National Comorbidity Survey (NCS).[8] Unlike clinical studies, we deal with lifetime comorbidity and focus on predictive priorities between the first onsets of these disorders to shed light on the influences that lead to panic-depression comorbidity.

Theoretical discussions generally focus on whether patients with both panic and depression have a single disorder or 2 disorders.[9,10] The most compelling evidence for the former comes from studies that document neurobiological similarities in patients with panic and those with depression.[11] The poor sensitivity and specificity of these biological measures,[12] coupled with disparate findings in recent neuroimaging studies,[13,14] suggest that the 2 disorders have substantially different neurobiological substrates. In addition, comorbid panic-depression generally does not aggregate separately from pure panic or pure depression in family studies.[15-17] As a result, most cases of panic-depression are thought to represent comorbidity, whereas a smaller number might represent a distinct disorder.[18,19]

The following 3 logical possibilities could explain this comorbidity: depression is a causal risk factor for panic disorder, panic disorder is a causal risk factor for depression, or panic disorder and

SUBJECTS AND METHODS

SUBJECTS

The NCS is a nationally representative household survey of persons aged 15 to 54 years along with a representative sample of students living in campus group housing. The NCS was administered to 8098 respondents in face-to-face in-home interviews. The response rate was 82.4%. The data reported here have been weighted to adjust for differential probabilities of selection and nonresponse. More details on the NCS design, field procedures, and sample weights are reported elsewhere.[8,29]

DIAGNOSTIC ASSESSMENT

National Comorbidity Survey diagnoses are based on a modified version of the Composite International Diagnostic Interview (CIDI),[30] a fully structured interview designed to generate diagnoses according to both *DSM-III-R*[31] and *ICD-10*.[32] The *DSM-III-R* criteria are used here. Although the focus is on panic attack, panic disorder with or without agoraphobia, and major depressive episode, we control for other *DSM-III-R* disorders assessed in the NCS, including anxiety disorders (phobias, generalized anxiety disorder, and posttraumatic stress disorder), mania, addictive disorders (alcohol and drug abuse and dependence), conduct disorder, adult antisocial behavior, and nonaffective psychosis.

The World Health Organization's CIDI field trials found good short-term test-retest reliability and validity of the CIDI compared with clinical reassessments.[33] Because most of these results came from clinical samples, a clinical reappraisal study was carried out in the NCS.[34] Good validity compared with blind clinical reappraisal interviews was found for almost all diagnoses and for the assessment of panic attacks. The exceptions were mania[35] and nonaffective psychosis,[36] neither of which was assessed with acceptable validity in the CIDI. Because separate clinical reappraisal interviews were carried out for each diagnosis, no data are available on the CIDI's accuracy in discriminating between unipolar and bipolar depression or between depression and panic. Data on the validity of the distinction between panic attacks and panic disorder are also not available because the validity study focused on panic attacks only. The distinction between panic attacks with and without panic disorder was based on respondents reporting 4 or more attacks in a single month or persistent worry for a month or longer about having another attack. The absence of such data is a limitation of the results reported in this article.

The World Health Organization field trials also found good test-retest reliability—but only marginally acceptable validity compared with clinician assessments—of retrospective diagnostic age-at-onset reports in the CIDI.[37] This is an important limitation because age-at-onset reports play a central role in the analysis of temporal priorities. To improve the accuracy of these reports in the NCS, the standard CIDI age-at-onset question, which simply asks respondents how old they were when they first had an episode of depression, a panic attack, or a cluster of 4 panic attacks in a single month, was elaborated into a series of 4 more-focused questions. For the first question, respondents were asked if they could "*clearly remember* [emphasis in original]" the exact age when they had their first episode, attack, or attack cluster. If they answered yes, that age was recorded. If they answered no, they were asked their approximate age at onset: "*about* [emphasis in original] how old were you the first time?" They were then asked for "the earliest age you can *clearly remember* [emphasis in original]" a particular episode or attack or attack cluster. The response was taken as an upper bound on the respondent's age at onset.

No data to assess the validity of the age-at-onset reports based on this 4-question series were obtained in the NCS clinical reappraisal study. However, substantively implausible associations between the age at interview and the reported age at onset found in surveys that used the standard CIDI age-at-onset question[38] do not exist in the NCS,[39] indirectly arguing for improved validity. Nonetheless, the likely existence of remaining errors in NCS retrospective

depression are both consequences of some other common disorder. The second and third possibilities have been the focus of most clinical research. Persistent anxiety has been postulated[20] to lead to an exhaustion response and depression, a finding consistent with panic causing depression. Furthermore, most anxious-depressed patients report that their anxiety started at an earlier age than their depression,[21,22] suggesting a dose-response relationship between panic disorder and subsequent depression. This prediction has not been examined in previous research.

Panic attacks without panic disorder are generally thought to be nonspecific severity markers of other psychiatric disorders,[23,24] a view codified in *DSM-IV*.[25] Previous studies have not attempted to determine whether it is panic attack or panic disorder that is associated with depression. If it is only panic attack, then the most plausible interpretation is that panic represents a severity marker of depression rather than a comorbid condition.

Furthermore, if secondary depression is the result of exhaustion or demoralization in the face of persistent anxiety, we would expect that it is persistent anxiety that leads to secondary depression. If this is the case, the risk of depression after panic attacks or panic disorder should increase with the duration of the panic. We would also expect that only current panic, rather than a history of remitted panic, would predict a first onset of depression. If, on the other hand, panic is merely a phase in a distinct biologically determined panic-depressive disorder, we would expect that the risk of a first episode of depression is associated as strongly with a history of panic as with active panic and is not related to duration. No previous epidemiological study has examined these patterns.

We also evaluate the possibility that panic-depression comorbidity is due, at least in part, to common causes. Several possibilities exist, including neurobiological vulnerabilities,[9] temperament,[26] and stressful life experiences.[27] Epidemiological research has been most

age-at-onset reports is a limitation of the results presented here.

RISK FACTORS

The NCS asked about the lifetime occurrence and ages of first occurrence of 22 traumatic experiences that might be risk factors for both panic and depression. These include early loss events (eg, early death of a parent or parental divorce), interpersonal traumas (eg, rape or combat experience in a war), parental psychiatric disorders as assessed by *Family History Research Diagnostic Criteria*[40] (eg, maternal depression or paternal alcoholism), and other traumatic experiences (eg, being in a life-threatening automobile accident or a natural disaster). Only ages of first occurrence, not of subsequent recurrences, were recorded, so the assessment of these experiences is incomplete. Nonetheless, the available data provide a useful way of assessing the role of traumatic experiences in bringing about panic-depression comorbidity. A detailed description of the traumatic life experiences, the measurement procedures used to assess them, and their associations with each of the disorders assessed in the NCS are presented elsewhere.[41]

ANALYSIS PROCEDURES

Conditional probabilities and odds ratios (ORs) were used to study comorbidity. Retrospective age-at-onset reports were used to study temporal priorities between first onsets of panic and of depression. Discrete-time survival analysis[42] with person-year as the unit of analysis was used to study predictive associations. In this method, each year in the life of each respondent up to and including the year of onset of the outcome disorder or the year of the interview, whichever comes first, is treated as a separate observational record. Logistic regression is used to predict a dichotomous measure of the onset of the outcome disorder (coded 1 for the year of onset and 0 for prior years) in this person-year file. When controls are introduced for age at the time of the observational record, the logistic regression coefficients can be interpreted as survival coefficients in a model that allows nonproportional hazards.[42] These coefficients can also be exponentiated to generate ORs. The predictors can be either unrelated to time, such as sex or race, or time-varying, such as marital status or a history of other disorders as of the age of the observational record.

In our use of this method, we estimated a separate series of discrete-time survival models to predict the lifetime first onset of 3 outcomes: panic attack, panic disorder, and major depressive episode. In each model, we included controls for age in the person-year, age at interview, sex, and race. The predictors of primary interest were time-varying measures of the prior onset and continuation of the other disorders. These were "time-varying" because they were coded as not present for the observational records for a particular respondent up to the age at onset of the predictor disorder and then coded as present in subsequent observational records. We also created predictor variables for time since the first onset of the predictor disorder. Furthermore, we used respondent data about the age of recency of each disorder to create predictor variables. This allowed us to distinguish between observational records with a history of the predictor disorder that had ended at an earlier age and records with a history of the disorder that had not ended.

Significance tests for individual ORs were computed using the method of jackknife repeated replications[43] to estimate SEs that adjusted for design effects introduced by clustering and weighting of observations. The jackknife repeated replication is one of several methods that use simulations of coefficient distributions in subsamples to generate empirical estimates of SEs and significance tests. The ratios of the coefficients to these adjusted SEs were used to compute z scores for the significance of the survival coefficients and 95% confidence intervals for the ORs. Tests for the significance of sets of predictors taken together were computed using Wald χ^2 tests. Design effects were introduced into these calculations by computing the Wald scores from coefficient variance-covariance matrices based on the jackknife repeated replication simulations.

concerned with the last, showing that distant events account for more than half of the observed episode comorbidity between anxiety and depression.[27,28] No previous research has looked at the effects of traumatic events on lifetime panic-depression comorbidity.

RESULTS

LIFETIME PREVALENCES AND COMORBIDITIES OF PANIC AND DEPRESSION

The lifetime prevalences of *DSM-III-R* panic and depression were reported previously[44,45] and include 7.2% (n = 422) for panic attack, 3.4% (n = 200) for panic disorder, and 16.9% (n = 995) for major depressive episode. About half of respondents with lifetime panic attack (50.9%) and panic disorder (55.6%) also meet lifetime criteria for depression, whereas about one fifth (21.6%) of the people with lifetime depression reported a lifetime panic attack and one tenth (11.2%) met lifetime criteria for panic disorder. The ORs between lifetime panic and depression are statistically significant and substantial in magnitude: for panic attack with depression, 6.2 (95% confidence interval, 5.0-7.6); for panic disorder with depression, 6.8 (95% confidence interval, 5.1-8.9) ($P<.001$ for both).

TEMPORAL PRIORITY OF FIRST ONSETS OF PANIC AND DEPRESSION

Retrospective age-at-onset reports were compared to assess the temporal priority of first onsets of panic attack, panic disorder, and depression. Among the 302 respondents who reported at least 1 lifetime panic attack and at least 1 lifetime episode of depression, 94 (31.1%) said their first episode of depression occurred at an earlier age than their first panic attack, 77 (25.5%) said their first episode of depression and first panic attack occurred in the same year, and 131 (43.4%) said their first panic attack occurred at an earlier age than their first depressive

Table 1. Odds Ratios (ORs) of Prior Lifetime Major Depression in Predicting Subsequent First Onset of Panic Attack as a Function of Time Since First Onset of Depression*

Time Since First Onset of Depression, y	Model, ORs (95% Confidence Interval)†‡			
	1	2	3	4
0	25.9 (17.4-38.3)	25.1 (16.9-37.3)	18.3 (12.5-26.7)	10.1 (7.0-14.5)
1-2	3.2 (1.8-5.7)	3.1 (1.8-5.9)	2.3 (1.3-4.2)	1.4 (0.8-2.4)
3-5	5.1 (3.1-8.5)	4.9 (3.0-8.2)	3.5 (2.1-5.9)	1.9 (1.1-3.3)
6-10	3.2 (1.7-6.1)	3.1 (1.6-5.9)	2.3 (1.2-4.4)	0.9 (0.4-1.8)
≥11	3.6 (2.2-6.1)	3.4 (2.0-5.9)	2.6 (1.5-4.4)	0.9 (0.5-1.5)

*The ORs are exponentiated discrete-time survival coefficients based on person-year models comparing the odds of a subsequent first onset of panic attack among people with a history of depression vs those who never had an episode of major depression. A total of 583 respondents in the National Comorbidity Survey reported a history of panic attack at the time of the interview. The data file comparing these respondents with all others in the National Comorbidity Survey contained a total of 173 931 person-years.

†See the text for a complete description of each model. The traumas that significantly predicted subsequent panic attack were paternal generalized anxiety disorder, maternal depression, exposure to extreme physical aggression from parents as a youngster, and witnessing a traumatic event as a child. More details on the measurement of traumatic experiences and the associations between these experiences and subsequent disorders are given elsewhere by Kessler et al.[41]

‡All ORs are significant at .05 (2-tailed test), except those in model 4 for 6 or more years since first onset of depression.

episode. Among the 157 respondents with lifetime panic disorder and depression, with the age at onset of panic disorder dated as the age of the first cluster of 4 attacks in a 4-week period or the first month of persistent worry about having another attack, 75 (48.0%) reported that the depression started at an earlier age than the panic disorder, 48 (30.6%) said that the depression and panic disorder started at the same age, and 34 (21.5%) said that the panic disorder started at an earlier age than the first depressive episode.

TEMPORALLY PRIMARY DEPRESSION AND SUBSEQUENT PANIC

We began by using information about prior depression to predict the first onset of a panic attack (with or without panic disorder) and then carried out a parallel analysis to predict the first onset of panic disorder in the subsample of observational records for persons with a history of panic attacks. No evidence was found for an effect of depression in predicting panic disorder after the onset of a first panic attack. Therefore, we focused further efforts on the prediction of a first panic attack. Two important results emerged. First, the persistence of depression is necessary to predict a panic attack. That is, people who reported a history of temporally primary depression but said that their last episode ended in, eg, year Y+5, had a significantly elevated risk of a first onset of panic attack in the 5-year interval between Y (signifies year) and Y+5 but (assuming they did not have an onset in this interval) no longer had an elevated risk beginning in year Y+6. This implies that active depression rather than a history of depression predicts a panic attack. Second, the effect of depression in predicting panic attack does not vary significantly with time since the first onset.

The parameter estimates in the final model are reported in the first column of **Table 1** (referred to as model 1). The effects of depression are differentiated by the time since onset. The OR for the first onset of depression in the same year as respondents had their first panic attack is large (25.9), and the ORs for the first onset of panic attack in subsequent years are smaller (between 3.2 and 5.1).

The results for model 2 in Table 1 are the ORs for the same predictor variables in a model that introduces a control for mania. These results suggest that mania does not play a major part in the association between depression and a subsequent first onset of panic attack. As stated previously, however, mania is not assessed with acceptable validity in the CIDI due to its substantial overdiagnosing of the disorder.[35] To address this problem, we replicated model 1 after excluding respondents who were classified by the CIDI as having a history of mania. The results (not shown) were similar to those reported in Table 1 for model 2.

The results for model 3 are the ORs for the same predictor variables in a model that introduces controls for mania and also for the 22 lifetime traumatic experiences described earlier (see the "Risk Factors" subsection of the "Subjects and Methods" section). Each of the ORs is smaller than those in model 2, which means that the experiences considered here explain part of the association between temporally primary depression and a subsequent panic attack. We also estimated models that distinguished the effects of traumatic life experiences that occurred before vs later than the first onset of depression and included multiplicative interactions between depression and the traumas. No more of these interactions were significant than we would expect on the basis of chance.

Finally, the results for model 4 are the ORs for the same predictor variables in a model that includes controls for mania, the 22 traumatic experiences, and all other NCS or *DSM-III-R* disorders that occurred before the first onset of panic attack. This model controls for such mediating processes as that linking primary depression to secondary panic attacks through addiction. The cross-sectional OR is statistically significant but considerably smaller than in model 1, whereas the time-lagged ORs are no longer statistically significant in panic with onset delays of 6 years or more. The aggregate time-lagged effect of between 1 and 5 years remains significant in a modified version of model 4 (OR, 1.7; 95% confidence interval, 1.1-2.0; $P = .04$) but is substantially smaller than the comparable coefficients in model 1.

Table 2. Odds Ratios (ORs) of Prior Lifetime Panic Attack and Panic Disorder in Predicting Subsequent First Onset of Major Depressive Episodes as a Function of Time Since First Onset of Panic*

Time Since First Onset of	Model, ORs (95% Confidence Interval)†‡			
	1	2	3	4
Panic attack, y				
0	16.5 (9.3-29.1)	15.6 (8.4-28.8)	11.6 (6.0-22.1)	7.2 (3.8-13.6)
1-2	3.5 (1.7-7.2)	3.1 (1.9-5.0)	2.3 (1.4-3.9)	1.5 (0.9-2.5)
3-5	2.8 (1.3-5.8)	2.3 (1.4-3.8)	1.8 (1.1-3.0)	0.9 (0.5-1.7)
6-10	4.8 (2.9-8.2)	3.9 (2.3-6.5)	3.1 (1.8-5.3)	1.6 (0.7-3.3)
≥11	3.9 (2.4-6.3)	2.8 (1.8-4.3)	2.1 (1.3-3.5)	0.8 (0.4-1.5)
Panic disorder, y				
0	3.1 (1.4-6.5)	3.0 (1.5-6.1)	3.1 (1.4-6.9)	2.3 (1.1-5.1)

*The ORs are exponentiated discrete-time survival coefficients based on person-year models comparing the odds of a subsequent first onset of a major depressive episode among people with a history of panic vs those who never had a panic attack or a panic disorder. A total of 1403 respondents in the National Comorbidity Survey reported a history of a major depressive episode at the time of the interview. The data file comparing these respondents with all others in the National Comorbidity Survey contained a total of 155 548 person-years.

†See the text for a complete description of each model. The traumas that significantly predicted subsequent major depression were paternal separation or divorce when the respondent was a child, maternal or paternal depression, maternal or paternal generalized anxiety disorder, maternal or paternal antisocial personality disorder, maternal or paternal alcohol or other drug dependence, sexual abuse or rape, exposure to extreme physical aggression from parents as a youngster, exposure to a natural disaster, and witnessing a traumatic event as a child. More details on the measurement of traumatic experiences and the associations between these experiences and subsequent disorders are given elsewhere by Kessler et al.[41]

‡All ORs are significant at .05 (2-tailed test), except all those in model 4 for 1 or more years since first onset of panic attack.

More detailed analyses found 3 potentially important elaborations of the significant time-lagged coefficients in model 4. First, a strong relationship was found between the severity of primary depression, as indicated by the number of symptoms, and the odds of subsequent panic. Second, approximately half of respondents with depression followed by panic attack had at least 1 other anxiety disorder before the depression. These earlier anxiety disorders are significant predictors of depression and of panic attack after depression. No evidence was found for a significant interaction between depression and prior anxiety in predicting panic attack. Third, a significant interaction was found between life stage and prior depression in predicting panic attack, with the effect of depression increasing with age.

TEMPORALLY PRIMARY PANIC AND SUBSEQUENT DEPRESSION

Parallel discrete-time survival models were used to study the time-lagged relationship between temporally primary panic and subsequent depression. The least complex models included controls plus separate time-varying effects of panic attack (with or without panic disorder) and panic disorder. The cross-sectional associations involving panic attack and disorder were significant, as was the time-lagged association for panic attack. No significant time-lagged association was found for panic disorder, however.

More detailed models were then estimated to explore the effects of persistence and time since the first onset of panic attacks. Three important results emerged. First, the persistence of panic attacks is not necessary to predict the subsequent first onset of depression. For instance, people who reported a history of temporally primary panic attack but said that their last attack was in year Y+5 not only had a significantly elevated risk of a first episode of depression in the interval between Y and Y+5 but (assuming that they did not have an onset in this interval) they also had the same elevated risk beginning in year Y+6. This implies that it is a history of panic rather than active panic that predicts a subsequent first onset of depression. Second, the time-lagged effect of panic attack does not vary with the time since the first onset. Third, no meaningful association was found between life stage and panic in predicting the subsequent first onset of depression.

The parameter estimates for the final model are reported in the first column of **Table 2** (referred to as model 1). The OR for the first onset of depression in the same year as a first panic attack is large (16.5), and the ORs for the onset of depression in the same year as panic disorder (3.1) and in the years after the onset of panic attack are smaller (between 2.8 and 4.8). Significance tests for time trends found no evidence that the time-lagged coefficients change significantly with the time since the onset.

The results for model 2 are the ORs for the same predictor variables in a model that introduces controls for mania. The ORs are consistently lower than in model 1, demonstrating that mania plays at least some role in the association between temporally primary panic and the subsequent first onset of depression. When all persons with mania according to the CIDI are excluded from the analysis and model 1 is estimated in this restricted sample, results (not shown) are similar to those shown in Table 2 for model 1.

The results for model 3 are the ORs for the same predictor variables in a model that controls for mania and for the 22 lifetime traumatic experiences described earlier. All of the ORs are somewhat smaller than in model 2 but remain consistently significant at .05. More detailed analyses were carried out to distinguish the effects of traumatic experiences before vs later than the first onset of panic attack and panic disorder and to examine multiplicative interactions between panic and these experiences, but no more of these interactions were significant than we would expect on the basis of chance.

The results for model 4 are the ORs for the same predictor variables in a model that controls for mania, the 22 traumatic experiences, and other NCS and *DSM-III-R* disorders. All of the ORs are lower than in model 3, and none but the cross-sectional OR is statistically significant at .05. No significant interactions were found between prior disorders and panic in predicting a subsequent first onset of depression.

COMMENT

We note 3 important limitations of this study. First, the NCS is a cross-sectional survey. This means that all inferences about temporal ordering are based on retrospective reports. Recall bias or sample selection bias could distort estimated relationships. That results hold up in subsamples differing in age at onset argues indirectly against a strong effect of recall bias. A definitive evaluation will require replication in a prospective study. Second, the CIDI is a lay-administered diagnostic interview that imperfectly captures the diagnostic distinctions made by experienced clinicians. The evidence of consistency in the CIDI with independent clinical diagnoses argues against a pervasive bias, but imprecision in distinguishing panic attack from panic disorder or panic from depression might play a part in the results. Third, the CIDI focuses largely on lifetime disorders. Consequently, we have been concerned here with the temporal ordering of first onsets, with no focus on the order of the onset of panic and depression in particular episodes. There is no indication that temporal priority in a first onset will tell us much about temporal priority in episodes.

In the context of these limitations, the pattern of lifetime comorbidity reported is similar to that found in previous epidemiological studies[7,46] in showing depression in most of those with panic and panic in a substantial few of those with depression. In addition, we find strong reciprocal predictive relationships between panic attack and depression. About half of respondents with lifetime panic-depression have at least 1 other prior anxiety disorder. This means that panic-depression is often part of a larger anxious-depression syndrome in which another anxiety disorder is temporally primary. This larger syndrome, which has not been examined in this report, warrants detailed examination in future research.

The results regarding temporal priority between panic and depression might appear to be at odds with most of the literature because previous studies[21,22] have consistently found that anxiety usually begins at an earlier age than depression among people with lifetime comorbidity. The NCS data yield the same result when anxiety is analyzed in the aggregate, as it has been in most previous epidemiological studies.[47] This is because early-onset phobias are the temporally primary disorders in most patients with lifetime comorbid anxiety and depression. The situation is different for panic-depression comorbidity both in the NCS and in the few other epidemiological surveys[7,22,48] that have focused on this particular type of anxiety-depression comorbidity. When we define the onset of panic as the age of the first attack, depression occurring before panic is only slightly less common than panic occurring before depression. Furthermore, when we focus on the age at onset of a panic disorder rather than the age at onset of a first panic attack, depression occurring before panic is much more common than panic occurring before depression.

Although the NCS results regarding temporal priority are consistent with previous research, they contradict the assumptions of earlier studies in 2 important ways. First, the temporal priority of anxiety before depression has been previously interpreted as meaning that the transition is stronger from pure anxiety than from pure depression to anxious-depression.[49,50] Our more subtle analysis shows that gross time-lagged effects are similar in magnitude for temporally primary panic attack predicting a subsequent first onset of depression and for temporally primary depression predicting a subsequent first onset of panic attack.

Second, the implicit assumption in all previous research on panic-depression comorbidity has been that panic disorder rather than panic attack is comorbid with depression. We found the opposite to be true. Because panic attacks are generally conceptualized as nonspecific severity markers, it is not clear that the association between panic attacks and depression should be conceptualized as a comorbidity. As a result, this finding, if it is replicated in independent data sets, will require a fundamental rethinking of the meaning of panic-depression comorbidity. There is an important exception to the general finding that depression is related to panic attack but not panic disorder. A significant cross-sectional relationship exists between panic disorder and depression. This pattern characterizes nearly a third of respondents with the lifetime co-occurrence of panic disorder and major depression, and these respondents conceivably represent a distinct subtype.

When we focus on the association between panic attacks and depression, important time-lagged asymmetries emerge that raise questions about whether the underlying causes might differ depending on which is temporally primary. In the case of depression before panic attack, that the time-lagged relationship is no longer significant for patients with remitted depression is consistent with treatment studies that have failed to document an association between remitted depression and the severity of current panic attacks.[51,52] This result, in conjunction with the relationship between the number of depressive symptoms and the risk of a subsequent panic attack, suggests that secondary panic might be a severity marker of depression rather than a comorbid condition. If this is true, it is not clear why there is no relationship between the number of years of depression and the risk of a subsequent panic attack. Further research needs to determine whether this specification replicates in other data sets and, if so, to look for explanatory or mediating variables that might make sense of this phenomenon.

The situation is different for panic before depression, where the data suggest that panic attack is a proxy for some other underlying causal risk factor. This conclusion is based on 3 observations indicating the

absence of a dose-response relationship. The first is that respondents with a history of panic attack have the same elevated risk of subsequent depression whether their panic is remitted or active. It is possible to make sense of this while maintaining the view that panic causes depression by suggesting that consequences of panic that persist after the attacks have ended, such as avoidance, secondary agoraphobia, and secondary substance abuse, lead to depression. This interpretation is also consistent with the finding that the time-lagged associations between a primary panic attack and subsequent depression are statistically insignificant in model 4 of Table 2, which controls for other disorders. It is more difficult to offer a similar interpretation of the observations that panic attack, but not panic disorder, predicts a subsequent first onset of depression and that the duration of the primary panic attack is unrelated to the risk of a subsequent first onset of depression. These results are more consistent with the view that panic attack is a marker of some cluster of risk factors of both panic and depression. These results demonstrate that clinicians should be aware that their patients with a history of panic attacks, whether or not the panic is active, are at risk of subsequent depression. More focused research, using longitudinal and family-genetic designs, is needed to sort out the causal pathways involved in this risk to develop a rational strategy for preventing subsequent depression.

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A complete list of all NCS publications, including abstracts, study documentation, interview schedules, and the raw NCS public-use data files, is available via the Internet (http://www.hcp.med.harvard.edu/ncs).

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