Follow-Up and Family Study of Anxious Depression

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Objective: The failure of the concept of anxious depression to find its way into DSM-III-R led the authors to conclude that a further report on the occurrence of anxiety symptoms in depressed subjects is indicated. Method: The subjects were 327 consecutively evaluated inpatients and outpatients with primary unipolar depressive disorder at five university medical centers participating in the National Institute of Mental Health Collaborative Program on the Psychobiology of Depression—Clinical Studies. The authors restricted their sample selection to patients with primary depressive disorder so that patients with other preexisting psychiatric disorders, especially anxiety disorders, would not contaminate the symptom picture, family studies, or follow-up. They examined six anxiety symptoms and derived a new anxiety summary score to show the effect of anxiety in depression on family data and 5-year outcome. Results: Depressed subjects with higher ratings for anxiety took longer to recover. There was also a significant relationship between anxiety in depressed probands and the risk for primary unipolar depressive disorder, but not anxiety disorders or alcoholism, among 832 blindly interviewed first-degree relatives. Conclusions: These data confirm the usefulness of subdividing depressed patients according to anxiety symptoms: psychic and somatic symptoms of anxiety, taken together, significantly predict family illness and course. The data also emphasize the wisdom of requiring that generalized anxiety disorder not be diagnosed in the presence of a mood disorder. Clearly, symptoms of anxiety coexist with depression and need to be recognized for the effective treatment of the underlying depressive disorder.


DSM-III and DSM-III-R do not allow clinicians to attach “anxious mood” as a modifying descriptor when diagnosing the depressive syndrome. Nor do they include other features of anxiety in the description of depressive disorders. Nonetheless, clinicians and investigators have long recognized the overlap of anxiety and depressive symptoms.

In 1970 Sir Aubrey Lewis (1) published a review of the ambiguous word “anxiety.” He proposed that in psychiatry the technical term “anxiety” had passed through two main phases: first as a qualifying term for the agitated depression of melancholia, then as a qualifying term for a neurosis in which subjective feelings of alarm were associated with visceral disturbances. From his perspective, the first use of the term had little acceptance outside of German psychiatry, so only the second, “anxiety neurosis” as christened by Freud, was examined. This paper, however, concerns the first use of the term.

Contrary to Lewis’ beliefs at the time, rating scales for depression in fact emphasized the prominence of anxiety in depression. From such scales, Overall et al. (2) derived three and Paykel (3) four subtypes of depression, the largest group in each being the anxious/tense subtype. In addition, from these reports, the association between anxious and agitated depression to which Lewis referred was confirmed.

Further review of the literature on anxiety symptoms in depressed patients leads us to conclude that many patients with depression can be described as having “anxious depression.” The following findings emerge.

1. Between 15% and 33% of depressed patients have frank panic attacks (4–10).

2. A far larger proportion have other anxiety symptoms. Symptoms that seem to cluster with anxious depression are agitation, obsessive-compulsive symptoms, anorexia, weight loss, gastrointestinal symptoms, hypochondriasis, depersonalization, and diurnal variation (2, 4, 6, 7, 11–14).

3. Despite anecdotal data from clinical writings implying that anxious depression is milder, almost all...
studies that compared anxious with nonanxious depressed patients found the former to be more severely ill at index, as measured by Hamilton rating scales or by an incapacitated or endogenous subtype diagnosis (5, 7).

4. Naturalistic studies with follow-ups found depressed patients with anxiety to be more chronically ill and to have a poorer response to treatment (8, 14). In one treatment study comparing depressed patients with panic and patients with pure depression given either 150 mg or more of imipramine or desipramine or 60 mg or more of phenelzine (10), the group with panic had a significantly poorer response at 6 weeks. In another treatment study with tricyclic antidepressants (15), nonresponders had significantly higher baseline anxiety ratings on the Hamilton Rating Scale for Anxiety. Psychiatric anxiety and panic attacks also predicted an outcome of suicide in the first year (16, 17).

5. Most studies comparing anxious and nonanxious depressed patients that included family data found no difference in the family histories for primary depressive disorder. Four (7, 8, 14, 18) reported more alcoholism in the families of depressed patients with panic attacks, and two (8, 18) reported more of all types of depressive disorder (primary and secondary) in this group.

The failure of the concept of anxious depression to find its way into DSM-III-R despite these findings leads us to conclude that a further report on the occurrence of anxiety symptoms in depressed subjects is indicated. We report on inpatients and outpatients with primary depressive disorder and their naturalistic treatments before and after their inclusion into the study. (We define “primary” explicitly in the Method section of this paper.) We restricted our selection to patients with primary depressive disorder so that patients with other preexisting psychiatric disorders, especially anxiety disorders, would not contaminate the symptom picture, family studies, or follow-up. We examined six anxiety symptoms and derived a new anxiety summary score to show the effect of anxiety depression on family data and 5-year outcome.

METHOD

The probands are participants in the National Institute of Mental Health Collaborative Program on the Psychobiology of Depression—Clinical Studies. Screening procedures and inclusion and exclusion criteria are described elsewhere (19). This is a naturalistic longitudinal study of affective disorders; treatments were carefully recorded but were not controlled by study design. The patients reported on in this paper are the 327 patients who met Research Diagnostic Criteria (RDC) (20) for both lifetime and current definite primary unipolar depressive disorder at update (at discharge or, for outpatients, 2 months after intake).

“Primary” means that the depression was not antedated by an RDC diagnosis of panic disorder, obsessive-compulsive disorder, phobic disorder, alcoholism, drug abuse, sociopathy, or Brier’s disorder at the definite or probable level. Further, these patients never met RDC for mania, hypomania, or a schizophrenic or schizoaffective episode in the past or during the index hospitalization (or after 2 months in the study as outpatients). Generalized anxiety disorder, as defined by the RDC, could have been present either as a previous disorder or as a present disorder if it preceded the current episode of depression by more than 2 months; only 13 (4.6%) of our patients had ever met RDC for generalized anxiety disorder, and only four (1.2%) exhibited so-called comorbidity in the index episode.

The Schedule for Affective Disorders and Schizophrenia (SADS) (21), the interview used to characterize probands’ episodes, includes six symptoms that are frequently considered to be associated with anxiety states such as phobic disorder, generalized anxiety disorder, panic disorder, and obsessive-compulsive disorder. Each symptom is rated from 1 to 6; 1=not at all, 4=moderate, 5=severe, and 6=extreme. However, panic attacks are rated on a 3-point scale on which 1=not present and 3=definite. The six symptoms examined are 1) worry, brooding, painful preoccupation, and inability to get rid of unpleasant thoughts (may or may not be accompanied by depressive mood), 2) panic attacks (circumscribed periods of intense anxiety with at least two physical symptoms not associated with physical exertion or life-threatening situations), 3) somatic anxiety (one or more physiological concomitants of anxiety other than during a panic attack, including the items listed as associated with panic attacks as well as headaches, stomach cramps, diarrhea, or muscle tension, all scored whether or not the subject has had panic attacks), 4) psychic anxiety (subjective feelings of anxiety, fearfulness, or apprehension, excluding panic attacks, whether or not accompanied by somatic anxiety and whether focused on specific concerns or not), 5) phobia (irrational fear of a specific object, activity, or situation that the subject tends to avoid), 6) obsessions or compulsions (recurrent or persistent ideas, images, feelings, impulses, or movements that generally are accompanied by a sense of subjective compulsion and a desire to resist the event and are usually recognized by the individual as foreign to his or her personality or nature, i.e., “ego alien”).

Group comparisons of patients with high versus low anxiety ratings were made in several ways. In looking at the time to recovery from the index episode of illness, log-rank chi-square and Cox proportional hazards models were used (22). In examining the rates of nonanxiety depressive symptoms or risk to relatives as a function of proband anxiety, chi-square was used. When examining risks to relatives controlling for proband age at onset, logistic regression was used (23). All statistical analyses were conducted with the Statistical Analysis System (24).

RESULTS

Two hundred eleven (65%) of the 327 subjects were women, their mean±SD age at intake was 41±16.0 years, 74 (23%) were outpatients, and 126 (39%) were...
TABLE 1. Anxiety Symptom Ratings in 327 Patients With Primary Unipolar Depression

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Moderate Rating</th>
<th>Severe Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N %</td>
<td>N %</td>
</tr>
<tr>
<td>Worrying</td>
<td>100 30.6</td>
<td>143 43.7</td>
</tr>
<tr>
<td>Panic attacks</td>
<td>—</td>
<td>88 26.9</td>
</tr>
<tr>
<td>Somatic anxiety</td>
<td>69 21.1</td>
<td>67 20.5</td>
</tr>
<tr>
<td>Psychiatric anxiety</td>
<td>89 27.2</td>
<td>124 37.9</td>
</tr>
<tr>
<td>Phobia</td>
<td>35 10.7</td>
<td>16 4.9</td>
</tr>
<tr>
<td>Obsessive-compulsive features</td>
<td>11 3.4</td>
<td>5 1.5</td>
</tr>
</tbody>
</table>

*The range of ratings was 1–3 (1=not present, 2=probable, and 3=definite); ratings of 2 or 3 were scored as severe.

The range of ratings was 1–6 (1=not at all, 2=moderate, 3=severe, and 6=extreme); ratings of 5 or 6 were scored as severe.

experiencing their first depressive episode. The mean age at first episode of major depressive disorder was 29.7 ± 15.2. The mean age at first outpatient care for any mental disorder was 30.9 ± 15.3, and the mean age at first hospitalization (if any) was 34.3 ± 15.7. One hundred sixty-two (50%) had previously received medications, and 60 (18%) had had ECT for major depressive disorder. To summarize, the subjects represented a mixture of inpatients and outpatients with or without previous episodes who had been identified as having unipolar depressive disorder and were being treated at tertiary care centers.

Table 1 shows the high frequency of the anxiety symptoms in these depressed patients. Worrying occurred at a moderate or severe degree in almost 75% of these patients. Psychiatric anxiety, somatic anxiety, and panic attacks also occurred in a large number of patients. The frequencies of these symptoms were equal in both sexes except that phobic symptoms were reported by more women. None of these symptoms occurred for a sufficient duration before the onset of depression to qualify as a preexisting diagnosis of anxiety disorder. For instance, 55 patients had panic attacks for less than 6 weeks and 33 had panic attacks for more than 6 weeks but only during the depressive episode.

An unrotated principal components analysis of correlations among the anxiety items was performed to determine how these symptoms sorted together. One component explained much of the variance. (Only one eigenvalue was over 1.0; a scree test [24] indicated that there was only one factor.) On this component, all the items had positive loadings of about the same magnitude. For worrying, the first component was 0.53; for panic attacks it was 0.63, for somatic anxiety, 0.63; for psychic anxiety, 0.66; for phobias, 0.66; and for obsessive-compulsive features, 0.48. The eigenvalue was 2.17. Therefore, we decided to total the anxiety symptoms to yield a single score for each depressed patient, thus using a summary dimensional approach to these symptoms. The range of the anxiety summary score was from 6 (no anxiety symptoms present) to 33 (the highest possible rating on each item) because 1 means “not at all” on the SADS.

For simplicity and as an heuristic approach, we divided patients into those with high (16 or more) (N=172) and low (15 or less) (N=155) anxiety ratings in all further analyses. This is a split at the median. When we did this and looked at treatment before intake, we found that those depressed patients with high anxiety ratings were significantly more likely to receive psychotherapy (58% [N=100] versus 47% [N=73]) and antidepressants (69% [N=119] versus 57% [N=88]). This was true even though there was no difference in the severity of their illnesses as measured by the Global Assessment Scale (GAS), a 100-point scale combining symptom severity with functional impairment. Each group had a median GAS score of 35. In the first 6 months after admission to the study, patients with high anxiety ratings were significantly more likely to be receiving lithium (17% [N=29] versus 9% [N=14]).

We tested the difference between probands with high and low anxiety ratings on scores for 39 other SADS-assessed symptoms that are diagnostic of or often associated with depression. If one considers a t test with p<0.0013 to be significant (corresponding to an overall type I error rate of 0.05 by Bonferroni correction), then the following symptoms were significantly more intense in highly anxious depressed patients: depressed mood, negative self-evaluation, discouragement, diurnal variation, depersonalization, somatic overconcern, difficulty concentrating, insomnia, lack of energy, psychomotor agitation, subjectively experienced anger, distrustfulness, and nonreactivity of mood to changes in circumstances. No symptom was significantly more frequent or intense in the low-anxiety group.

Next we examined the relationship among high versus low anxiety, gender, and age. We found no appreciable or statistically significant relationship between either sex or age on the one hand and the anxiety classification on the other.

Blind lifetime version of the SADS (SADS-L) (21) interviews were conducted with 832 first-degree relatives (parents, siblings, children) of the 327 probands. The dichotomized anxiety symptom score was considered in relation to psychiatric diagnoses in first-degree relatives. Table 2 indicates that a strong positive association occurred only between proband anxiety status and the risk of unipolar depressive disorder, chiefly primary depressive disorder. Note that most of the relatives with major depressive disorder had unipolar depressive disorder. Hence, the test for a relationship between proband anxiety and the risk to relatives for major depressive disorder essentially duplicates that for unipolar major depressive disorder.

The association between anxiety and risk for primary unipolar depressive disorder remained when proband age at onset of major depressive disorder was simultaneously used as a predictor (logistic regression parameter x²=6.52, df=1, p<0.02). The association also persisted when the RDC subtype of recurrent unipolar depressive disorder was simultaneously used as a predictor (logistic regression partial x²=7.28, df=1, p<0.007). These facts are important to interpreting the association between anxiety and risk for primary unipolar depressive disorder.
between anxiety and familial risk, since familial risk is sometimes positively correlated with both early age at onset and recurrent major depressive disorder in the proband.

Finally, the relationship between anxiety and outcome was examined. We used survival analysis (SAS PROC LIFETEST) for this comparison. Time to recovery was dated from time of entry into the study. The patients with higher anxiety ratings were slower to recover from their index episodes of major depressive disorder (log-rank χ² = 6.76, df = 1, p < 0.01). Median recovery time for those with lower anxiety ratings was 13 weeks, compared with 26 weeks for those with higher ratings (estimated by interpolation in Kaplan-Meier curves).

**DISCUSSION**

These data confirm the usefulness of subdividing depressed patients according to anxiety symptoms: psychic and somatic symptoms of anxiety, taken together, significantly predict family illness and course. Inpatients and outpatients with primary unipolar depressive disorder who have higher anxiety ratings define a subgroup of patients who have a higher familial prevalence of unipolar primary depressive disorder and a poorer 5-year outcome. They do not have higher familial rates of any of the RDC anxiety disorders or RDC alcoholism, drug abuse, secondary depressive disorder, or bipolar disorders.

The additional symptoms that highly anxious depressed patients are more likely to exhibit are negative self-evaluation, discouragement, more depressed mood, diurnal variation with mood worse in the morning, somatic overconcern (including gastrointestinal symptoms), lack of energy, insomnia, agitation, less ability to concentrate, depersonalization and derealization, subjective anger, distrustfulness, and lack of reactivity of mood to changes in circumstances. These symptoms are similar to those described by Hamilton (11), Rassaby and Paykel (12), Overall and Rhoades (13), Van Valkenburgh et al. (6, 14), and Garvey et al. (7).

Symptoms that are essentially uncorrelated with anxiety score are retardation, a distinct quality to the depressed mood, weight loss, suicidal tendencies, delusions, hallucinations, and bizarre behavior. Thus, this identifies a group of worried, anxious patients rather than a retarded or psychotic group. Kettering et al. (25), in following up delusional depressed patients, also identified a second group of non-delusional, anxious depressed patients.

To illustrate this further, the frequencies of all depressive symptoms in the patients with primary unipolar depressive disorder were examined. Of the 10 most common symptoms (depressed mood, discouragement, loss of interest, trouble concentrating, fatigue, insomnia, worry, negative self-evaluation, social withdrawal, and psychic anxiety), two are anxiety symptoms. These, unlike the others, are not symptoms used to make the diagnosis. This is consistent with the position taken by Cassidy et al. (4), who in their classic paper on 100 patients with manic-depressive disorder and 50 medically ill control subjects designated the mood change necessary for depression as blue, worried, discouraged, depressed, anxious, low, scared, fearful, angry, afraid, gloomy, hopeless, despondent, not caring, empty, and disgusted. They reported that many anxiety symptoms were significantly more frequent in the depressed patients than the control subjects.

The data also emphasize the wisdom, fortunately exercised in DSM-III-R, of requiring that generalized anxiety disorder not be diagnosed in the presence of a mood disorder. Given our data showing high rates of anxious symptoms in depressive disorder without much coexisting RDC generalized anxiety disorder (about 1%), we would conclude that such symptoms frequently represent an anxious aspect of depression rather than comorbidity. The place of anxiety symptoms in the definition of depression will be clarified by further work.

The finding of a higher familial prevalence for depression in anxious depressed patients supports the results and conclusions of Angst (26). Although his sample was small, he found, like Stenstedt (27) and Hopkinson (28), a higher morbid risk among relatives of anxious, agitated depressed patients than among relatives of patients with inhibited endogenous depression. He also found more schizoaffective in these relatives.

The theoretical implications of our family data are unclear. There may be a distinct, anxious depressive subtype with higher familial risk. Coryell et al. (8) reported a higher frequency of total major depression but only a trend for primary major depression in the relat-
tives of depressed patients with panic attacks. This may still be consistent with the hypothesis that there are two types of depression because panic attacks alone would not be expected to be as predictive as would all anxiety symptoms taken together.

Another possibility is that these anxiety symptoms measure a pathologic factor. Relatives who, by virtue of genes or a common rearing environment, have higher anxiety ratings may be at higher risk for depression. According to this model, the greater risk of depression in relatives should be gradual and roughly proportional to increasing proband anxiety score. A direct test of this theory would require anxiety ratings for all relatives, even those without histories of major depression, which we unfortunately lack.

These anxious depressed patients did not have higher familial rates of other anxiety disorders or alcoholism. The former is consistent with the bulk of the literature but contradicts reports derived from a single epidemiologic sample of depressed patients and their families (18, 29). Not finding higher rates of alcoholism in these families is difficult to explain. It may be that panic attacks (but not more general anxiety symptom scores) in depression (7, 8, 14, 18) predict that association. This needs further study.

These findings also have clinical implications. The patients with higher levels of anxiety were treated with more psychotherapy and antidepressants before entry into the study than were those with lower levels. During the initial phase of the study, they received significantly more lithium. These treatments probably reflect the treatment-resistant nature of anxious depression, also confirmed by the fact that at follow-up they were less likely to have recovered than were their less anxious counterparts. The treatment cannot be related to the presence of psychotic symptoms because these symptoms negatively correlated with high anxiety. The poor outcome is also reflected in the additional finding from the Collaborative Program study (16, 17) that anxiety in the index episode correlated with completed suicide in the first year. It may be that, as Fawcett and Kravitz (5) postulated, if anxiety symptoms are not attended to early in the treatment of the depression, the rates of noncompliance and premature termination may be higher. Or the best treatment has not yet been devised. Both adequacy of antidepressant treatment and compliance need to be reviewed. The presence of anxiety symptoms in depression represents an aspect of drug and ECT trials that needs to be considered. Clearly, anxiety symptoms coexist in depression and need to be recognized for the effective treatment of the underlying depressive disorder.

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REFERENCES