The Detection and Consequences of Anxiety in Clinical Depression

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Anxiety symptoms and comorbid anxiety are common in depressive syndromes, and there is evidence they are associated with increased severity of depression and a poorer outcome. Anxiety and agitation symptoms also appear to be an acute risk factor for suicide in patients who have major affective disorder, an observation that has been supported by a number of biological correlates. Rapid and aggressive treatment of these anxiety/agitation symptoms with suitable antidepressants or benzodiazepines should be considered in order to avoid the immediate risk of suicide and to permit successful treatment of the affective disorder. *(J Clin Psychiatry 1997;58[suppl 8]:35–40)*

COMORBIDITY OF ANXIETY AND DEPRESSION: CONSEQUENCES OF SEVERE ANXIETY

Evidence suggests that anxiety is one of the most prevalent symptoms in clinical depression and that assessing and treating severe, persistent anxiety are of great importance in the successful treatment of depression. Anxiety is not required for the diagnosis of clinical depression—neither major depression, bipolar depression, nor dysthymia. It has long been realized, however, that anxiety disorders exist as comorbid conditions with clinical depression. Using the Schedule for Affective Disorders and Schizophrenia (SADS) interview, Fawcett and Kravitz[1] found symptoms of worry, psychic anxiety, and somatic anxiety of at least moderate severity in 42% to 72% of 200 patients with SADS-diagnosed major affective disorder. Moreover, 29% of these patients described a history of recent panic attacks. Clayton et al.[2] reported a similar presence of anxiety symptoms in 327 unipolar depressive patients and 31 bipolar depressive patients. The total anxiety scores were calculated by adding the severity scores for worry, psychic anxiety, somatic anxiety, and the presence of panic attacks. These total scores revealed that patients with a score above the median for the sample (> 15) of the severity distribution experienced a significantly longer time to recovery, a higher prevalence of multiple drug treatments (including lithium), a higher incidence of suicide in the first year of follow-up, and a more frequent history of depression.

Joffe et al.[3] found that a similar frequency severity scale (> 16) was present in 31% of outpatients with unipolar depression and that this correlated with higher depression scores and more functional disability that, in turn, accounted for poorer treatment outcome. Coryell et al.[4] showed that 10 depressive symptoms were significantly more severe in patients with major affective disorders who reported panic attacks in the present episode. In addition, there was a 3 to 4 times higher likelihood of developing major depression for non–affectively ill relatives of probands with major depression and a preexisting phobic or panic disorder, and a significantly higher likelihood of relapse of major depression over 6 years of follow-up for patients with phobic and panic disorder (> 50% relapse).[4] Coryell et al.[5] also reported a significant delay in recovery from major depression in patients with comorbid obsessions or compulsions who were followed over a 5-year period.

Analyses of the prominent symptoms of major depression that indicate severity have pointed toward the importance of anxiety symptoms. In an item analysis of the Hamilton Rating Scale for Depression (HAM-D), Bech and Allerup[6] concluded that depression severity was validly measured by just five items. One of these five items was psychic anxiety. More recently, Gibbons et al.[7] analyzed the HAM-D ratings obtained in two large collaborative treatment studies. Their item analysis resulted in six HAM-D items correlating with the severity of depressive illness. Of these six items, depressive mood correlated most strongly with the diagnosis, while the anxiety items (psychic anxiety, somatic anxiety, and agitation in increasing order) correlated with the severity of depression as measured by total HAM-D scores. Thus, the presence of anxiety symptoms as measures of severity of a depressive

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illness is supported by these item analyses, as well as by the clinical literature.

ANXIETY SYMPTOMS AND SUICIDE

There is mounting evidence that anxiety symptoms are not only associated with severity of depressive syndromes, but that severe anxiety, especially when associated with depression, may be a risk factor for suicide. Allebeck et al.[8] reported a significant number of suicides diagnosed as anxiety disorder in Sweden, while Coryell reported a significantly increased suicide rate in a follow-up study of patients with a diagnosis of panic disorder.[9] It would be of interest to determine how many patients who committed suicide in these two studies had comorbid clinical depression. In a study assessing the features associated with 1397 suicides in Finland over the period of 1 year, Isometsä et al.[10] reported that 17% of the suicide victims were retrospectively diagnosed as having unipolar depression with a comorbid anxiety disorder and 6% had bipolar diagnoses with a comorbid anxiety disorder.

Our prospective studies, which used the SADS research interview rating to investigate the presence and severity of anxiety symptoms in 954 patients with major affective disorder, also point to the role of severe anxiety symptoms in suicide.[11] The findings showed a significant association with suicide over a 1-year follow-up, but not in patients who committed suicide after 2 to 5 years of follow-up or in the majority of patients who did not commit suicide. An analysis of admission SADS severity ratings in 13 patients who were subsequently "short-term" suicides over a follow-up period of 1 year revealed both "short-term" (within 1 year) and "long-term" (2 to 5 year) correlations with suicide when compared with 12 suicides over the subsequent 2 to 5 years and with 929 patients who survived. Suicidal ideation, a history of past suicide attempts, and the severity of hopelessness did not correlate significantly with suicide over the subsequent year, while the severity of psychic anxiety and the presence of panic attacks did show a significant correlation.

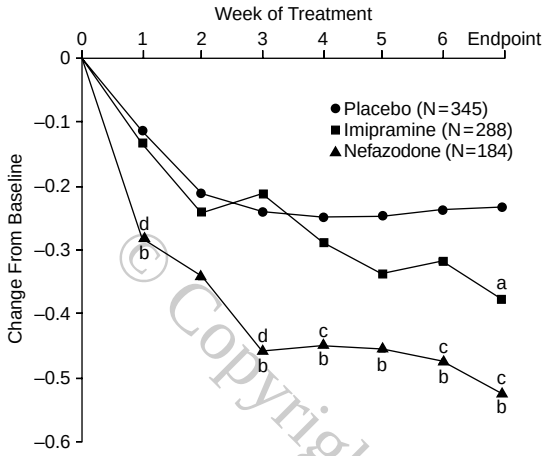
Although the Collaborative Depression Study had the advantage of being a large prospective study, the periods of follow-up (every 6 months) and the limited number of suicides precluded a truly acute time frame.[11] On the basis of prior findings, we have recently begun studies to look at acute clinical features by collecting inpatient and outpatient suicide cases. Thus far, we have rated the hospital records of 14 inpatient suicide cases by employing SADS ratings of each 24-hour clinical record for 1 week prior to the occurrence of suicide. These records (which are nonstandardized clinical hospital records) have demonstrated the presence of severe psychic anxiety in 13 of the 14 patients in the initial sample.[12] These cases were not rated blind to the knowledge that suicide was the outcome, nor were matched depressed patients who did not commit suicide rated blindly and compared with the suicide charts. In this sense, the findings can be considered only as a pilot study that extends the hypothesis of the anxiety-severity-suicide finding of the Collaborative Depression Study to the acute period (1 week) prior to the suicide. In preparing for a blinded study with matched comparison cases, we have collected an additional 75 inpatient suicide records from sources around the United States. A nonblinded analysis of the cases shows clear evidence of severe anxiety-agitation over the week before suicide in 78% of cases (Busch K, Fawcett J. 1995. Unpublished data). Blinded ratings of these cases, compared with matched cases in which suicide was not the outcome, are ongoing. Findings to date suggest not only that the presence of severe anxiety-agitation is associated with high acute suicide risk, but that aggressive treatment of anxiety symptoms might prevent an acute suicide, even in situations where the depression continues. It is hoped that controlled, blinded studies using inpatient records (which usually have complete clinical descriptions of the patient) will yield useful information.

BIOLOGICAL FACTORS ASSOCIATED WITH ANXIETY IN DEPRESSIVE ILLNESS

Biological correlates of suicide risk were first investigated in 1965.[13] Markers of both the hypothalamo-pituitary-adrenal axis (HPAA) and serotonin function have been associated with suicide risk.[14] The first such observation raised the possibility that evidence of hyperactive adrenal function (as measured by 17-hydroxycorticosteroid [17-OHCS] excretion) may be an acute marker for suicide risk.[13] Subsequently, Åsberg et al.[15] presented evidence suggesting that patients at risk for violent suicidal behavior showed evidence of decreased cerebrospinal fluid (CSF) levels of 5-hydroxyindoleacetic acid (5-HIAA), a final metabolite of serotonin. Ensuing postmortem studies of suicide cases have supported this notion[16] and, most recently, studies of serotonin receptors on blood platelets (which have the advantage of being readily obtainable) have suggested that down-regulation of serotonin receptors correlates with suicidal behavior.[17] It is not yet clear whether serotonin depletion is a state-related finding in temporal proximity to suicide risk, or a trait variable that correlates with chronic high suicide risk when depression is present. Interestingly, there have been a number of studies suggesting that acutely elevated, state-related adrenal cortical function may be associated with acute suicide risk.[18,19]

Based on the premise that acute increases in HPAA function are associated with overwhelming anxiety-agitation that may not always be expressed by a patient, the levels of 17-OHCS were determined in five patients who either committed suicide or made serious attempts subsequent to 1 week of sample collections. The results repli-

Figure 1. Improvement in Hamilton Rating Scale for Depression Item 9, Agitation: Mean Change From Baseline†*



†Data from reference 21, with permission.
*Intent-to-treat sample, last-observation-carried-forward data set.
[a]p ≤ .05 vs placebo.
[b]p ≤ .01 vs placebo.
[c]p ≤ .05 vs imipramine.
[d]p ≤ .01 vs imipramine.

cate earlier findings that related markers of adrenal hyperfunction in patients who committed suicide.[18] In four of the five patients, mean levels of 17-OHCS were more than two standard deviations from the mean of the whole patient sample. In addition, a Fisher's exact test comparing the suicides/serious attempters with the remaining sample was significant at the $p < .004$ level based on milligrams of 17-OHCS per 24 hours. All but one case had levels over 10 mg/24 hours; the remaining patient had an average level of 9.79 mg/24 hours. Clinical experience has shown that elevated levels normalize when the patient has been adequately treated and is less symptomatic. The elevated levels also appear to correlate with severe anxiety-agitation, "psychic pain," or "ego disintegration states."[20] As in the case of clinical indicators, decisive treatment successful in the modulation of severe anxiety-agitation appears to have the capacity to safely resolve the crisis and permit successful treatment of the episode.

Antidepressant medications that have the capacity to rapidly modulate anxiety-agitation symptoms may be suitable in this situation. Figure 1 illustrates the significant decrease in agitation items on the HAM-D scale obtained in a meta-analysis of five combined studies of nefazodone versus placebo and imipramine.[21] It is possible, however, that some antidepressants may initially increase anxiety or agitation in the first few days or first weeks of treatment, resulting in a worsening of the depressive syndrome in individual patients.[22–25] This situation requires great care, patient education, and close follow-up when initiating antidepressant treatment in severely ill, highly anxious or agitated patients. The use of relatively rapidly acting anxiolytic medications, such as short-acting benzodiazepines, in doses sufficient to modulate anxiety and agitation is useful in this situation. In the presence of psychotic agitation, or in anxious/agitated borderline patients, the use of sedating neuroleptics that have a low possibility of inducing akathisia may be indicated. In terms of the use of benzodiazepine anxiolytics, and the reported relationship with severe anxiety symptoms preceding suicide, it is interesting to note that Nemeroff et al.[26] have reported elevated corticotropin-releasing factor (CRF) levels in the CSF of suicide victims, and that Owens et al.[27] have shown that alprazolam is capable of rapidly lowering CRF in experimental animals. Many clinicians and health authorities have expressed misgivings regarding the use of benzodiazepines, especially in significant doses, in view of the risk of physical and psychological dependency. However, the risk associated with giving adequate anxiolytic doses of benzodiazepines should be balanced against the risk of suicide in the high risk patient, even in a hospital care setting. More than one suicide has taken place in a hospital setting during an attempt to withdraw benzodiazepines from a patient who was presumed to be abusing them, despite significant chronic anxiety symptoms, and several patients, both in and out of a hospital setting, who suffered extensive, often untreated, anxiety symptoms, in addition to the presence of clinical depression, have committed suicide (personal observations).

CASE REPORTS

Case 1

A 48-year-old white man presented with depression and anxiety of 6-month duration associated with many life stresses. Two weeks previously he had suffered severe panic and suicidal ideation. The patient described symptoms of poor appetite and sleep, as well as increased rumination. He conversed easily, was motivated to receive help and was hyperalert and oriented, although his speech was rambling and tangential. He was markedly anxious, agitated, depressed, unreassurable, and labile, but denied current suicidal ideation, expressing the belief that it was wrong. Treatment was started with imipramine, but 1 week later he had not improved and was admitted to the hospital. He described intense uncontrollable homicidal impulses that made him panic and he appeared to be in an agitated depressive state. He also described feeling overwhelmed, having no pleasure, feeling that nothing helped and that he was at his worst. The patient appeared extremely anxious and nervous and paced around during the interview and throughout the day. He held his forehead and wrung his hands, and appeared depressed and unable to rest, eat, or concentrate. He admitted to thoughts of a suicide plan prior to admission but denied any previous suicide attempts or current suicidal or homicidal thoughts. In the hospital, he sought contact but expressed fears that treatment was useless. He was labile in his affect with

mood changes from anger to depression, from anxiety to hopelessness; he also had anxious ruminations but contracted for safety with nursing staff.

At 10:00 p.m. on his first day in the hospital he was very anxious and expressed fears of his impulses, but stated that he would be afraid to hurt himself. He was described as anxious and restless, and although he paced around all evening he was open to reassurance. He denied suicidal ideation and made a verbal contract with the staff not to harm himself. He was given 5 mg of haloperidol at 10:10 p.m. and was checked every 15 minutes thereafter. He was subsequently found hanging 10 minutes after he was last seen on the unit.

This patient manifested symptoms of depression and severe ruminative anxiety, as well as agitation. He expressed feelings of loss of control, while at the same time denying suicidal thoughts and promising the staff he would not harm himself. Despite observations every 15 minutes and treatment with haloperidol, as well as a supportive unit staff, the patient hanged himself. The presence of severe anxiety-agitation, which was not responsive to the treatment given, appears highly related to the suicidal outcome in this case. The patient's denials of suicidal ideation in the face of continued anxiety-agitation meant nothing, except possibly to mislead the staff.

Case 2

A 47-year-old salesman with a 6-month history of depression unresponsive to trazodone (50 mg three times daily and 150 mg at bedtime) was seen for the first time following referral from a primary care physician. The patient was seen both alone and in the presence of his wife, a 40-year-old psychiatric social worker. Although the patient had been able to get to work regularly, his depression reduced his performance, resulting in dropping sales that concerned him. The patient complained of low energy, anhedonia, poor concentration, social withdrawal, decreased motivation, decreased appetite, irritability, and worry over his job performance. He denied suicidal ideation but, when questioned about his feelings of hopelessness, he emphasized his concern regarding his work performance. He was seen on a Wednesday, at which time he was instructed to begin treatment with nortriptyline (50 mg at bedtime, to be increased to 75 mg at bedtime after 2 days, and then to 100 mg at bedtime after 2 more days). Daytime trazodone doses were stopped and nighttime doses reduced initially to 100 mg and then to 50 mg. His wife agreed to call if the patient experienced any worsening of his condition, and a return appointment was scheduled for the following Tuesday. As the weekend progressed, the patient initially seemed more relaxed, but on Sunday afternoon he began to appear more anxious. By Sunday evening, the patient showed irritability with some pacing, and had become withdrawn and preoccupied. His wife had difficulty communicating with him, but concluded that he was upset about returning to work on Monday. She decided not to call his psychiatrist but to see how he was on Monday and discuss the situation on Tuesday at his next appointment. During Sunday night, the wife awoke upon hearing noises and found her husband had hanged himself by his workbench in the basement. A note in his handwriting stated that he loved her but that he was a total failure and that she was better off without him. Instructions for accessing insurance policies and financial records were spelled out.

This is a case of a patient who had apparently moderate depression, denoted by the fact that he continued to work and appeared relatively normal to his fellow workers, but this depression was probably more severe than initial appearances indicated. Within 4 days of starting a new medication and facing a return to work on Monday, he experienced increasing anxiety, fearful ruminations regarding work, and withdrawal, which progressed to agitation and further ruminations. He apparently killed himself rather than face his intractable fear of anticipated failure and being overwhelmed at work. The case is noteworthy in that his worsening was associated not with a serotonin selective reuptake inhibitor (SSRI), but with a tricyclic antidepressant. The rapidity of his decline (associated with progressively severe anxiety and fearful ruminations and leading to agitation with overwhelming fears and ruminations) and the difficulty in identifying his decline in time for intervention are particularly notable.

Case 3

A 43-year-old high school football and martial arts coach, who also was active in teaching at the Sunday school in his church, presented with mixed anxious and depressive symptoms. He was initially seen by a psychiatric social worker who made a presumptive diagnosis of depression and referred him to a psychiatrist who suspected dysthymia, possible panic attacks, and obsessive compulsive disorder. The patient had a reputation for being very organized and self-disciplined and for demanding that his students not only work hard but maintain a strong Christian ethic in their sports participation; he was feared and respected for this attitude.

Treatment consisted of a series of antidepressants aimed at symptoms of depression, recurrent anxiety, and recurrent obsessional ruminations concerning his success as a teacher and his modest finances. During 2 years of outpatient treatment, he underwent supportive psychotherapy, at approximately 2-week intervals, aimed at his depression, anxiety, and "obsessional" doubts. He also underwent several courses of treatment with SSRI and tricyclic antidepressants that were aimed at his symptoms of depression, recurrent anxieties, and "obsessional" or ruminative self-doubts. These treatments resulted in periods of apparent improvement, followed by recurrence of his symptoms. His medications were changed several times

and, after it was confirmed that he had no alcohol abuse problems, benzodiazepines were added to help modulate his anxiety attacks that had some features of panic attacks. At one point, the patient recovered sufficiently to taper himself off benzodiazepine treatment and to win distinction for his coaching efforts with his young students. Several months later, the patient again complained of feelings of self-doubt, depression, and recurrent episodes of anxiety. His medications were changed once more, and benzodiazepine treatment was reinstated in response to his increased complaints of depression, anxiety, and ruminations of self-doubt and failure. He expressed feelings of discouragement that his symptoms were still present after more than 2 years of treatment and, unless reminded, he did not seem to be able to recall the periods where he had been well and had achieved considerable successes. No evidence of suicidal thoughts was recorded at this time, despite past references to such thoughts in the absence of suicidal plans or impulses. The psychiatrist was next notified that the patient had called in sick to work and could not be found by his wife or family. Several days later, his body was found at a remote cabin owned by his in-laws. He had left the cabin in an orderly state, wrapped himself in a tarpaulin with a hunting rifle, in order to leave no mess and to be hidden from view, and shot himself. His suicide note professed love for his wife and sons, but stated he could no longer go on.

This case is notable for the long history of recurring depression, anxious ruminations, and anxiety attacks (despite treatment) that were interrupted by periods of improvement and high levels of functioning. No risk symptoms of suicide, apart from recurrent depression, occasional suicidal thoughts, recurrent anxious ruminations, and possible panic attacks, were uncovered before or after his suicide. His symptoms at the time of his suicide did not appear more severe than in the past, and no environmental stresses were found. The chronic recurring history in the face of sustained function and the absence of acute signs of more severe symptoms than in past recurrences is troubling in this case. The only acute risk factors that could be determined after review were the recurrent anxiety of panic attacks and anxious ruminations.

DISCUSSION

The presence of anxiety symptoms and comorbid anxiety in depressive syndromes has been well documented, and there is clear evidence that anxiety symptoms constitute severity factors in depressive illness as shown by findings that increased severity and poor outcomes of depression appear to be associated with the presence of anxiety symptoms or disorders. Studies relating the increased risk of suicide in the presence of severe anxiety/agitation in patients with major affective disorders have also emphasized anxiety symptoms as acute factors for suicide. Interestingly, a number of biological factors appear to be associated with both anxiety symptoms and suicide risk in depression.

The three case reports discussed provide a good illustration of the major role anxiety and agitation play in suicidal risk. The first case described the inpatient suicide of a patient who was extremely anxious and agitated on the first evening of admission. Despite close observation, administration of haloperidol, and denials of suicidal intent, including promises that he would not harm himself, the patient hung himself. This case serves to illustrate the importance of untreated severe anxiety/agitation. The second case described an outpatient who presented with depression that was unresponsive to treatment and perhaps masked in severity by continued function at work. There was a clear deterioration after starting treatment with a new antidepressant, and this was associated with rapidly escalating anxiety and fearful ruminations that progressed to severe agitation. This case shows how rapidly anxious deterioration and suicide can occur in a depressed patient after the initiation of treatment. The third case raises a troubling possibility; a patient who, having suffered from both recurrent depression and anxiety for almost 2 years despite treatment, committed suicide during a recurrence that was difficult to discriminate, in terms of severity of symptoms, from prior episodes. The fact that the patient had a history of continued exemplary performance, strong commitment to a set of values one would expect to deter suicide, and no evidence that these strengths were being overcome by his depressive illness, makes the case particularly difficult. However, no risk factors could be found other than depression, associated suicidal ideation on several occasions over the course of illness, and recurring anxious ruminations and anxiety of panic attacks. While it is certainly possible that unknown factors played a role, it is reasonable to consider that the recurring pain of anxiety (which was perhaps more severe than communicated to anyone by a highly “self-disciplined” and obsessional patient who may also have been alexithymic) associated with the hopelessness of depression in terms of expectation for relief was the major factor in this suicide. If so, the importance of aggressively addressing anxiety symptoms in some chronic, recurrent, depressed patients becomes a clear possibility. It is hoped that further studies of anxiety in depressed suicidal patients will help to clarify this possibility.

Drug names: alprazolam (Xanax), haloperidol (Haldol and others), imipramine (Tofranil and others), nortriptyline (Pamelor and others), trazodone (Desyrel and others).

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