Depression With Anger Attacks

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A number of phenomenologic studies have demonstrated the marked heterogeneity of unipolar depressive disorders. We have recently identified a subtype of depression characterized by the presence of irritability and anger attacks. These attacks are sudden spells of anger accompanied by symptoms of autonomic activation such as tachycardia, sweating, flushing, and tightness of the chest. They are experienced by depressed patients as uncharacteristic of them and inappropriate to the situations in which they occur. Approximately one third of depressed outpatients present with anger attacks. Patients with unipolar depression and anger attacks frequently experience significant anxiety and somatic symptoms, and are relatively more likely to meet criteria for avoidant, dependent, borderline, narcissistic, and antisocial personality disorders than depressed patients without these attacks. Anger attacks subside in 53% to 71% of depressed outpatients treated with antidepressants, and the degree of improvement in depressive symptoms after antidepressant treatment is comparable in depressed patients with and without anger attacks. In addition, the rate of emergence of anger attacks after treatment with antidepressants (6%–10%) appears to be lower than the rate with placebo (20%). Finally, antidepressants that affect serotonergic neurotransmission, known to be involved in the modulation of aggressive behavior in animals and humans, may be particularly effective in this subtype of depression, but further studies are needed to support this hypothesis.

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A number of phenomenologic studies have demonstrated the marked heterogeneity of unipolar depressive disorders, which can be accompanied by mood states other than depression itself. The DSM-IV classification of major depressive disorder (MDD) includes irritable mood as 1 of the core symptoms of this form of unipolar depression in children and adolescents, although the criteria used for the diagnosis of major depression in adults do not make this association explicit. One can argue that it is highly unlikely that an adolescent with unipolar major depression characterized by marked irritability would spontaneously cease to experience irritable mood while depressed as an adult. In fact, moderate-to-severe outwardly directed irritability was found to be present in 37% of depressed inpatients, although there was no significant relationship between such irritability and severity of depressive symptoms.[1]

Irritability is typically defined as a mood state with reduced control over temper usually resulting in pathologic anger or aggression, manifested as strong feelings of displeasure and verbal or behavioral outbursts that are either unprovoked or inappropriate to the triggering situation. For this reason, it was not surprising that the Epidemiologic Catchment Area study found a significant association between depression and violent behavior in community samples.[2] A study of 1140 recently incarcerated male felons observed an association between a history of either dysthymia or recurrent depression and a robbery incarceration history and between dysthymia and multiple incidents of fighting since age 18 years.[3] Finally, a study by Pan et al.[4] showed that, for every 20% increase in depressive symptoms, the odds of being severely aggressive toward the spouse increased by 74%. All these studies suggest that the presence of depression may be actually associated with pathologic anger and aggression and may represent a risk factor for domestic abuse.

ARE PATHOLOGIC ANGER AND AGGRESSION IN UNIPOLAR DEPRESSION RELATED TO A COMORBID AGGRESSION DISORDER?

If one considers the broad spectrum of behaviors and affective states that characterize individuals with a history of pathologic anger and aggression, it is hard to conceptualize these emotional states and behaviors as a *disorder*. Anger outbursts and pathologic aggression may be more appropriately described as *syndromes*, which are accounted for by some specific psychiatric or neurologic disorders.

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The DSM-IV does include a diagnostic category of intermittent explosive disorder, which is applied to individuals who attack others and/or destroy property in the absence of an underlying psychiatric or medical condition. The main limitation of this diagnostic category is that it is an exclusionary diagnosis, and it is rarely applicable to populations seeking treatment for pathologic aggression. In addition, these criteria do not capture individuals with pathologic anger and/or irritability who do not commit acts of violence. For these reasons, it is unlikely that the presence of irritability and angry, violent outbursts in unipolar depression is due to the presence of a comorbid aggression disorder.

HOSTILE DEPRESSION

If irritability, anger outbursts, and violent behaviors are relatively common among patients with unipolar depression, and they are not related to the presence of a comorbid aggression disorder, are these specific features of a particular subtype of depression? Using an application of cluster analysis and related numerical taxonomy, Overall et al.[5] first proposed a subtype of depression called hostile depression and characterized it by a distinctly different Brief Psychiatric Rating Scale profile. This hostile depressive subtype was characterized by high levels of overt hostility, agitation, suspiciousness, anxiety, somatic concern, tension, and guilt,[5] and appeared with second greatest frequency among patients with depression, with an overall prevalence rate of 34%.[6] Subsequently, in a series of 2000 patients from a combined French and American sample of depressed patients, the hostile subtype of depression was identified again with the use of cluster analysis method.[7] Further support to the postulated existence of a hostile depression subtype came from subsequent studies, which showed that depressed patients reported significantly greater levels of anger and hostility than normal controls.[8,9]

The concept of hostile depression clearly challenged the psychodynamic hypothesis of a reciprocal relationship between depression and hostility. Such hypotheses had previously led to the development of a view that antidepressant treatment might actually mobilize hostility.[10] However, a longitudinal study by Klerman and Gershon[11] of 3 depressed women found no evidence of an increase in hostility following treatment with the tricyclic antidepressant, imipramine. On the contrary, anger/hostility levels in depressed patients were subsequently found to decrease with recovery after treatment with the tricyclic antidepressant, amitriptyline,[12] and the selective serotonin reuptake inhibitor, fluoxetine.[13] The latter findings were confirmed in a subsequent study with a different outpatient sample, where the reduction in hostility was significantly positively related to decreases in depressive symptoms, perceived stress, and negative thinking.[14] In the same study, the levels of hostility in depressed patients classified as responders to treatment with fluoxetine dropped quite dramatically with treatment, to the point of being almost identical to those of normal controls.[14] This apparent normalization of anger and hostility with successful antidepressant treatment provides further challenge to the notion that antidepressants mobilize hostility. Furthermore, Davidson et al.[15] found that the antidepressant monoamine oxidase inhibitor isocarboxazid was significantly superior to placebo in reducing depression and hostility among patients with hostile depression.

In summary, these studies support the hypothesis of a hostile depression subtype and suggest that high levels of hostility are actually quite common among depressed patients and that antidepressant treatment may significantly reduce such levels. However, the proposed subtype of hostile depression does not include irritability and pathologic anger and aggression, even though these 2 symptoms are frequently observed in unipolar depression.[1,2]

DEPRESSION WITH ANGER ATTACKS

My colleagues and I have recently identified a subtype of depression characterized by the presence of irritability and anger attacks. We had initially reported[16] a series of illustrative cases in which patients had presented with *anger attacks*, described as sudden spells of anger accompanied by symptoms of autonomic activation such as tachycardia, sweating, hot flashes, and tightness of the chest, which resembled panic attacks but lacked the predominant affective states of fear and anxiety. These anger attacks were experienced by the patients as uncharacteristic of them and inappropriate to the situations in which they had occurred.[16] Since treatment of these attacks with antidepressants produced, in each case, marked improvements in behavior, we hypothesized that these attacks were variants of major depressive disorder.[16] We subsequently developed the Anger Attacks Questionnaire,[17] a self-rating scale aimed at assessing the presence of anger attacks, and observed that depressed outpatients had significantly higher rates of anger attacks than healthy volunteers with no known psychiatric history.[17] Patients were classified as having anger attacks if they exhibited the following 4 criteria: (1) irritability during the previous 6 months; (2) overreaction to minor annoyances; (3) occurrence of at least 1 anger attack during the previous month; and (4) experience during at least 1 of the attacks of 4 or more of the following: tachycardia, hot flashes, chest tightness, paresthesia, dizziness, shortness of breath, sweating, trembling, panic, feeling out of control, feeling like attacking others, attacking physically or verbally, and throwing or destroying objects.[17] In a subsequent study in 56 depressed outpatients reporting anger attacks, the mean number of attacks per month was 7.4, and the most frequently reported symptoms or behaviors during the

attacks were feeling like attacking others, feeling out of control, tachycardia, and hot flashes.[13] In addition, 63% of these patients reported attacking others physically or verbally during the attacks, and 30% reported throwing or destroying property.[13] These findings suggested that perhaps the presence of these anger attacks was associated with an increased risk for violent behavior, and appeared to fit with the notion of an association between violence and depression.[2]

My colleagues and I then conducted a series of studies to evaluate whether the presence of these anger attacks in patients with unipolar depression was associated with a characteristic psychological profile. No significant age and/or gender differences were noted between depressed outpatients with and without anger attacks in 2 different patient samples.[13,18] On the other hand, depressed patients with anger attacks showed significantly higher scores of anxiety,[13] as well as somatic symptoms and hostility[13,18] than depressed patients without anger attacks. These findings were certainly consistent with the definition of the hostile depressive subtype previously proposed by Overall et al.[5]; the sample showed high levels of overt hostility, agitation, suspiciousness, anxiety, somatic concern, tension, and guilt. Depressed patients with anger attacks also reported greater levels of dysfunctional attitudes (i.e., "I am worthless") and negative thinking than depressed patients without these attacks.[19]

No significant relationship was found between the presence of atypical major depression and anger attacks,[13] consistent with findings of comparable prevalence rates of anger attacks between patients with atypical major depression and patients with unspecified major depression (see Prevalence of Depression With Anger Attacks). While no significant differences in rates of lifetime comorbid anxiety, eating, and substance use disorders were found between depressed patients with and without anger attacks, 8% of depressed patients with anger attacks met criteria for current comorbid panic disorder compared to 3% of depressed patients without anger attacks; there was a trend toward a statistically significant difference.[20] Finally, depressed patients with anger attacks were significantly more likely to meet criteria for borderline, histrionic, narcissistic, and antisocial personality disorders than depressed patients without anger attacks in a study in which a self-rated assessment of personality disorders was used.[13] A subsequent study using a clinician-rated instrument found that depressed patients with anger attacks had significantly higher rates of dependent, avoidant, narcissistic, borderline, and antisocial personality disorders than depressed patients without such attacks.[20] The increased rates of comorbid personality disorder diagnoses in depressed patients with anger attacks suggest that the behavior and attitudes of these patients may bias the clinician to view the attacks as secondary to a personality disorder as opposed to a unipolar depressive disorder.

PREVALENCE OF DEPRESSION WITH ANGER ATTACKS

My research group has conducted a series of studies to investigate the frequency of this depressive subtype. Two single-site studies on 127 and 164 medication-free outpatients with major depression showed rates of anger attacks of 44%[13] and 39%,[18] respectively. A subsequent multicenter study on depressed outpatients found that anger attacks were present in 38% of 94 patients with atypical major depression and in 28% of 74 patients with dysthymia, with an overall rate of anger attacks of 34%.[21] Therefore, it appears that the prevalence of anger attacks in depressed populations is approximately 30% to 40%, consistent with the 34% rate of hostile depression in the study by Overall et al.,[6] and with the 37% rate of moderate-to-severe outwardly directed irritability reported in depressed inpatients.[1]

ANGER ATTACKS IN OTHER PSYCHIATRIC POPULATIONS

Although, as mentioned earlier, the presence of irritable mood has been considered for many years as a core feature of major depressive disorder in children and adolescents, anger attacks and irritability in adults have been traditionally viewed as indicators of the bipolar nature of the depressive episode. For this reason, we have compared rates of anger attacks in bipolar and unipolar depression.[22] Patients with unipolar major depressive disorder were significantly more likely to report anger attacks than bipolar patients during a depressive (neither manic/hypomanic nor mixed) episode.[22] These findings, in addition to the fact that switches into mania or hypomania are extremely infrequent in patients diagnosed as having unipolar major depression with anger attacks and are not more frequent than among unipolar depressives without anger attacks,[20] clearly challenge the assumption that anger attacks in a depressed patient are characteristic of a bipolar diathesis.

Since pathologic anger and aggression are observed in a number of psychiatric disorders,[23] one would expect that anger attacks are not unique to depressed populations. In fact, in a study among women with eating disorders, the prevalence of anger attacks was 31% among the women with eating disorders and 10% among female normal volunteers.[24] However, patients with eating disorders and anger attacks had significantly more depressive symptoms than patients without these attacks.[24] In a 2-site study, the prevalence of anger attacks in panic disorder patients was approximately one third, with similar rates emerging for patients with other anxiety disorders.[25] Furthermore, the same authors found that patients with depressive disorders had twice the prevalence of anger attacks than did anxiety disorder patients.[25] At both sites, anxiety disorder patients with anger attacks were significantly more depressed than

those without anger attacks and had either current or past histories of major depression significantly more frequently than anxiety disorder patients without anger attacks.[25] These 2 studies suggest that anger attacks do not occur solely among depressed populations, but the severity of depressive symptoms appears to be the most significant predictor of the presence of anger attacks among eating disorder and anxiety disorder populations.

NEUROENDOCRINE STUDIES

A pilot study on outpatients with major depression found that depressed patients with anger attacks had a significantly blunted prolactin response to thyrotropin-releasing hormone (TRH) stimulation compared with depressed patients without anger attacks.[26] In addition, treatment with fluoxetine for 8 weeks was followed by a significant increase in the prolactin response to TRH among depressed patients with anger attacks, but not among those without anger attacks.[26] Given the inhibitory role played by central serotonergic neurotransmission in the hypothalamic release of TRH and the stimulating effect of TRH on the release of prolactin from the pituitary gland, these results were interpreted as suggesting that the subset of patients with major depression and anger attacks may have a relatively greater serotonergic dysregulation than depressed patients without such attacks.[26] My colleagues and I have recently completed a study[27] using a more specific probe of the central nervous system serotonergic neurotransmission, the fenfluramine challenge, among depressed patients with and without anger attacks. We have found that depressed patients with anger attacks have a significantly blunted prolactin response to fenfluramine challenge compared with depressed patients without these attacks.[27]

TREATMENT STUDIES

Eighty-five depressed outpatients completed at least 8 weeks of treatment with fluoxetine 20 mg/day, and 71% (N = 24) of 34 patients who had reported anger attacks at baseline stopped having them, while only 6% (N = 3) of 51 patients who had not reported them at baseline reported these attacks at the end of the treatment.[13] A subsequent study was conducted among 164 consecutive outpatients diagnosed as having major depression with the Structured Clinical Interview for DSM-IIII-R.[18] These patients were treated openly with fluoxetine 20 mg/day for 8 weeks, and the prevalence of anger attacks was assessed before and after treatment. Of the 64 patients who had reported having anger attacks at baseline, 41 (64%) did not report anger attacks after fluoxetine treatment, while only 7 (7%) of the 100 patients who had not reported having anger attacks at baseline were found to have anger attacks after treatment; this difference was statistically significant.[18] Furthermore, a French multicenter study of 50 patients with major depression found that fluoxetine treatment was followed by a 74% reduction in the anger attack/irritability subscale of the 58-item Hopkins Symptom Checklist in the group of depressives with agitated-anxious depression.[28] Finally, a U.S. multicenter study randomly assigned 168 outpatients with atypical major depression or dysthymia to treatment with sertraline (up to 200 mg/day), imipramine (up to 300 mg/day), or placebo for 12 weeks.[21] Among 57 patients reporting anger attacks at baseline, anger attacks ceased in 53% of patients receiving sertraline, 57% of those receiving imipramine, and 37% of those in the placebo group.[21] These studies suggest that anger attacks respond quite well to antidepressant treatment, consistent with previous studies showing marked improvement in hostility following antidepressant treatment.[14,15]

My colleagues and I were also interested in examining whether the subtype of depression with anger attacks was associated with a poorer antidepressant response. We therefore studied the degree of improvement in depressive symptoms and the response rates after treatment with fluoxetine 20 mg/day in a large sample of outpatients with major depression, and found no significant difference in outcome between depressed patients with and without anger attacks.[29] We also wanted to examine the risk of emergence of anger attacks after antidepressant treatment among patients without such attacks at baseline. Among 111 patients who did not report anger attacks pretreatment, the emergence of anger attacks was reported by 8% of sertraline-treated patients, 10% of imipramine-treated patients, and 20% of placebo-treated patients in a double-blind study.[21] In addition, the rate of emergence of anger attacks after open treatment with fluoxetine (6%–7%) in 2 large single-site studies[13,18] is no different from the rates observed after treatment with sertraline (8%) and imipramine (10%).[21] These findings are consistent with those of Heiligenstein et al.[30] of statistically significantly fewer fluoxetine-treated patients than placebo-treated patients experiencing events suggestive of aggression in a meta-analysis of clinical trials conducted in the United States with this antidepressant.

SUMMARY

My colleagues and I have recently identified a subtype of depression characterized by the presence of irritability and anger attacks. These attacks are sudden spells of anger accompanied by symptoms of autonomic activation such as tachycardia, sweating, flushing, and tightness of the chest. They are experienced by depressed patients as uncharacteristic of them and inappropriate to the situations in which they occur. Approximately one third of depressed outpatients present with anger attacks. Patients with unipolar depression and anger attacks frequently experience significant anxiety and somatic symptoms and are rela-

tively more likely to meet criteria for avoidant, dependent, borderline, narcissistic, and antisocial personality disorders than depressed patients without these attacks. Anger attacks subside in 53% to 71% of depressed outpatients treated with antidepressants, and degree of improvement in depressive symptoms after antidepressant treatment is comparable across depressed patients with and without anger attacks. In addition, the rate of emergence of anger attacks after treatment with antidepressants (6%–10%) appears to be lower than the rate with placebo (20%). All these studies suggest that antidepressant treatment of anger attacks in depression is safe and effective. Finally, antidepressants that affect serotonergic neurotransmission, known to be involved in the modulation of aggressive behavior in animals and humans,[31] may be particularly effective in this subtype of depression, as both serotonin reuptake inhibitors and antidepressants with significant serotonin 5-HT_2 receptor antagonism have shown antiaggressive effects in nondepressed patients with pathologic aggression.[23] Further studies, however, are needed to support this hypothesis. More specifically, large placebo-controlled studies comparing relatively serotonergic antidepressants with relatively noradrenergic antidepressants such as desipramine may help us understand whether depressed patients with anger attacks show a distinctive responsiveness to drug treatment.

Drug names: amitriptyline (Elavil and others), desipramine (Norpramin and others), fenfluramine (Pondimin), fluoxetine (Prozac), imipramine (Tofranil and others), isocarboxazid (Marplan), sertraline (Zoloft).

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