Course and Treatment of Atypical Depression

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Atypical depression is the most common form of depression in outpatients, but compared with melancholia, little is known about its comorbidity, course, and treatment. Beyond the well-characterized constellation of symptoms that define atypical depression (mood reactivity, hypersomnia, leaden paralysis, hyperphagia, and rejection sensitivity), specific Axis I and II comorbid conditions may differentiate atypical from other depressed patients. Similarly, age at onset, duration of episodes, frequency of relapses and recurrences, and frequency of complete remission in atypical depression may be different. It has not even been established if atypical depression is a stable subtype or if it is just one of several forms of depression that an individual may express during a lifetime of recurrent depressions. Monoamine oxidase inhibitors (MAOIs) are superior to tricyclic antidepressants (TCAs) for the treatment of atypical depression, but few studies have compared MAOIs to the newer generation of antidepressants (SSRIs, bupropion, venlafaxine, nefazodone, and mirtazapine). Because of the favorable benefit/risk ratio, clinicians tend to use these newer antidepressants for all outpatients, including those with atypical depression, even though the literature is limited. A review and critique of the relevant literature on atypical depression will be presented.

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DEFINITIONS AND HISTORY OF ATYPICAL DEPRESSION

Typical, melancholic, or endogenous depression was the prototypical form of depression until patients were observed to have core depressive symptoms (depressed mood, decreased interest and pleasure, feelings of worthlessness and guilt, decreased concentration, and suicidal ideation) but without insomnia or decreased appetite. Patients with alternative presentations of depression included those who were labeled neurasthenics (anxious neurotics), those with sleep and appetite changes opposite to those found in melancholics (i.e., hypersomnia and hyperphagia or reversed neurovegetative symptoms,[1] dramatic displays of distress in response to the loss of relationships, also known as hysteroid dysphoria,[2] and lifelong traits of increased sensitivity to interpersonal criticism or rejection[3–5]). Leibowitz, Quitkin, and colleagues at Columbia University operationalized the definition of atypical depression to include mood reactivity as the sine qua non.[6,7] By mood reactivity, they meant that patients, while depressed, could feel at least 50% better if they were exposed to a positive event, in effect the opposite of hypersensitivity to criticism or rejection. Feeling better with positive events and feeling worse with negative events can be viewed as opposite sides of the same phenomenon, that is, mood responds to changes in the environment. In addition to mood reactivity, to meet Columbia criteria for atypical depression, patients require at least 2 of the following symptoms: hyperphagia, hypersomnia, physical fatigue of extremities (arms and legs feel heavy, as though they were made of lead, i.e., leaden paralysis), or rejection sensitivity.

Part of these criteria for atypical depression arose from the search for predictors of response to monoamine oxidase inhibitors (MAOIs), as first proposed by West and Dally,[8] and reviewed by Stewart et al.[4] The result of almost 20 years of investigation by the Columbia group confirmed what they refer to as a pharmacologic dissection of depressive subtypes: typical melancholic depressives respond to the full range of available antidepressants, while those with atypical depression respond preferentially to MAOIs and SSRIs as compared with TCAs.[6,9] While some have failed to confirm the findings of the Columbia group,[1,10,11] the atypical distinction is among the few accepted depressive subtypes that might predict treatment response, or more accurately, treatment nonresponse to TCAs.

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CLINICAL AND EPIDEMIOLOGIC ASPECTS OF ATYPICAL DEPRESSION

Clinically, atypical depression is distinctive beyond a unique symptom cluster. Those patients with atypical depression tend to have an earlier age at onset of their first depressive episode as compared with nonatypical patients in some,[1,4,12] but not all studies.[13] While some data suggest that the duration of the current episode is shorter for atypical, as compared with nonatypical depression,[12] others have shown the index episode to be longer.[13] Lagomosino et al. found the gender mix to be the same, but the findings of Asnis and colleagues were different with more women than would be expected in the atypical group.[12,13] As one would expect, the score on the traditional Hamilton Rating Scale for Depression (HAM-D),[14] which omits ratings of hypersomnia and hyperphagia, tends to be lower in atypicals.[13] Atypical depressives tend to have a more chronic, phasic course with a family history of increased rates of dysthymia and alcoholism compared with nonatypical patients in clinical[3,15,16] but not epidemiologically derived samples.[17,18]

Kendler and colleagues[17] studied a community sample of over 1000 female twins and found, by using latent class analysis, a syndrome of atypical depression characterized by depression with increased appetite and weight gain, hypersomnia, and psychomotor retardation, without the benefit of measures of mood reactivity. These atypically depressed patients had shorter episodes of depression compared with more typical depression, consistent with data from Lagomosino et al.,[12] but in contrast to the findings from Asnis and colleagues.[13] The atypicals in the community twin sample also had moderate concordance for developing an atypical syndrome when they relapsed, consistent with data from Stunkard et al.,[19] Stewart et al.,[4] and Nierenberg and colleagues.[20] Even though Kendler and colleagues[17] omitted measures of mood reactivity, they found that atypical depressives were least likely to have experienced a stressful life event preceding the onset of depression. A lower rate of stressful life events implies that either mood reactivity may not necessarily be the sine qua non of the atypical syndrome as proposed by the Columbia group or at least, for atypical depression, a stressful life event may not necessarily be causal. In the Kendler et al. cohort, atypically depressed females with a monozygotic twin sister had a high likelihood of having the same subtype of depression and those with dizygotic twin sisters had less concordance across depressive subtypes. Increased monozygotic compared with dizygotic concordance suggests genetic stability of depressive subtypes.

Horwath and colleagues[18] used a similar definition of atypical depression as Kendler et al.[17] to analyze data from the Epidemiologic Catchment Area study and found that patients with atypical depression had higher rates of comorbid panic, drug abuse and dependence, and somatization disorder. In contrast, Kendler et al.[17] found that patients with atypical depression, compared with nonatypical depression, had lower rates of panic, similar rates of social phobia, similar rates of alcoholism, and higher rates of bulimia. Note that the Kendler et al. sample was a female twin registry while the Horwath et al. sample was a broad epidemiologic study. These differences in gender mix may account for the differences observed in comorbidity rates. As reviewed above, more substantial differences exist between clinical and epidemiologic samples.

Why are the findings from clinical samples at variance from findings in epidemiologic samples? Comorbidity rates in clinical samples tend to be higher than epidemiologic samples because of Berkson's bias.[21] Berkson's bias states that people who tend to seek medical care will do so because they experience distress and disability. This distress and disability will be higher for those with more than 1 disorder as compared to those with only 1 disorder. Therefore, those who seek clinical care (clinical samples) will tend to have higher rates of co-occurring disorders compared with epidemiologic samples.

BIOLOGICAL ASPECTS OF ATYPICAL DEPRESSION

Biologically, while patients with atypical depression have decreased response to TCAs, they appear to have normal tyramine excretion tests, normal dichotic listening, and normal sleep studies.[6,16] The cortisol response to intramuscular desipramine is increased in atypical depression, indicating less of a norepinephrine dysregulation as compared with nonatypical depression.[13,22] If confirmed in other studies, these findings may explain the lack of response of patients with atypical depression to TCAs, which have mostly noradrenergic effects. Less dysregulation of noradrenergic function would respond less frequently to those agents (TCAs) that have a noradrenergic mechanism of action. In another set of studies of seasonal affective disorder in patients with winter atypical depression, ovine corticotropin-releasing hormone (oCRH) was found to cause a less robust and delayed increase in adrenocorticotropic hormone (ACTH), but normal plasma cortisol concentrations before oCRH was administered.[22] These findings suggest diminished activity of the hypothalamic-pituitary-adrenal axis at the level of the hypothalamus with normal pituitary corticotrophs and normal adrenal glands. Patients with melancholic depression have, in contrast to atypical depression, an attenuated ACTH response to oCRH plus elevated baseline plasma cortisol levels and normal levels of ACTH. These findings suggest that in nonatypical depression the pituitary is responsive to the negative feedback of high circulating glucocorticoids, which in turn may be caused by an abnormality at or above the hypothalamus and hyperresponsiveness of adrenal glands to ACTH. Gold and colleagues[22]

hypothesized that, in contrast to melancholic depression, CRH was diminished in atypical depression and that diminished CRH is associated with hyperphagia, hypersomnia, fatigue, and leaden paralysis. Ravindran and colleagues[23] found that in patients with atypical depression, there was an increase in ACTH levels along with higher interleukin-1β serum levels and normal mitogen-induced cell proliferation. Based on the data reviewed above, patients with atypical depression appear, overall, to be biologically distinct from those with nonatypical depression.

ATYPICAL DEPRESSION IN BIPOLAR AND UNIPOLAR DEPRESSION

Clinical lore has long held that those patients with atypical depression are more likely to be bipolar.[24] Mitchell and colleagues[25] challenged this assumption in a study that found, in contrast to those with unipolar depression, melancholic bipolar patients had less psychomotor retardation and more agitation. By selecting only those with melancholia, these investigators argue that they decreased the probability of spurious differences that could arise from heterogeneity. Alternatively, they may have erred on the side of overmatching and missed important differences in the frequency of certain symptom clusters, e.g., differences in prevalence of atypical depressive subtypes in unipolar compared with bipolar patients. Other studies that contrast unipolar and bipolar patients have been inconsistent, with studies showing either increased or similar psychomotor retardation, and increased, similar, and decreased rates of agitation in bipolar patients.[25–31] The most definitive study to date contrasted 79 unipolar patients with 30 bipolar patients.[32] Similar proportions of unipolar and bipolar patients were atypical. About 30% of each group met Columbia University criteria for definite atypical depression and about 20% met criteria for probable atypical depression. When these investigators compared patients with atypical versus nonatypical depression, the only significant difference was that, consistent with other studies, atypical depressives had more lifetime episodes. One caveat that the investigators fail to discuss is that the power to detect differences is limited because of the small sample size of the bipolar group. Together, these studies suggest that the atypical depressive syndrome per se fails to differentiate bipolar and unipolar depression, but more methodologically rigorous studies are needed to clarify this difference or lack thereof.

STUDIES OF ATYPICAL DEPRESSION AT MASSACHUSETTS GENERAL HOSPITAL

To better understand atypical depression, the group at the Depression Clinical and Research Program at Massachusetts General Hospital (MGH) has examined several large cohorts of patients who were drug free and were then entered into clinical trials. The MGH group examined the prevalence, clinical characteristics, comorbidity, and course of atypical depression (Nierenberg AA, Alpert JE, Rosenbaum J, unpublished data).

Eligible subjects consisted of depressed outpatients between the ages of 18 to 65 years. Subjects met criteria for major depression as determined by the Structured Clinical Interview for DSM-III-R-Patient Edition (SCID-P)[33] and had a 17-item HAM-D[14] score greater than 16 both at screen and after a 1-week washout period. The presence of atypical depression was determined by semistructured interview using the Atypical Depression Diagnosis Scale[4] prior to open treatment with fluoxetine. Patients were classified as having a definite atypical depression if they had mood reactivity and any 2 of the following symptoms: hypersomnia, leaden paralysis, increased appetite, increased eating or weight gain, or rejection sensitivity. Mood reactivity plus 1 of the above symptoms was classified as probable atypical depression, while mood reactivity alone constituted simple mood reactive depression.

Exclusion criteria included pregnancy or breast feeding, serious suicidal risk, serious or unstable medical illness, seizure disorder, organic mental disorders, substance abuse disorders (including alcohol) active within the year prior to the study, schizophrenia, delusional disorder, psychotic disorders not otherwise specified, mood congruent or incongruent psychosis, bipolar disorder, significant antisocial personality disorder, history of multiple adverse drug reactions or allergy to fluoxetine, current use of other psychotropic drugs, and clinical or laboratory evidence of hypothyroidism. Routine laboratory tests included complete blood count, urinalysis, SMA-20, and electrocardiogram.

Out of 396 depressed patients, 42% were atypical, 12% melancholic, 14% both atypical and melancholic (with the combination called either atypicholics or melatypicals), and 32% met neither criteria. The rates of atypical depression seen by the MGH group were much higher than reported by Asnis and colleagues.[13] Asnis reported that 29% (33/114) of outpatients who had mostly major depression (but 15 of 114 had either minor depression or intermittent depressive disorder) met Columbia criteria for atypical depression. Atypicals had similar demographics as melancholics, but some differences in the course of their depression, most notably an earlier age at onset with shorter, but more frequent episodes.

As for comorbidity, when atypicals were compared to melancholics, no significant differences were found for rates of Axis I disorders, but there were increased rates of Axis II obsessive-compulsive and passive-aggressive personality disorders. Alpert and colleagues[34] assessed combined comorbid clusters of social phobia and avoidant personality disorder and found that, of those who met criteria for both social phobia and avoidant personality disorder, about 55% met criteria for atypical depression, in contrast

to about 31% of those who failed to meet criteria for either social phobia or avoidant personality disorder. Reciprocally, about 26% of patients with atypical depression met criteria for both social phobia and avoidant personality disorder in contrast to 10% of those with nonatypical depression. Similarly, Nierenberg and colleagues[20] found that about 15% of atypicals met lifetime criteria for body dysmorphic disorder while only about 7% of those without atypical depression did so. When patients with atypical depression were compared with those who had nonatypical depression (including those with melancholia), those with atypical depression had higher rates of bulimia, consistent with the hyperphagia seen in atypical depression.[12] By putting these findings together, a picture of atypical depression emerges of an earlier more recurrent mood disorder with brief episodes superimposed on a socially inhibited cluster of comorbid problems (social phobia, avoidant personality disorder, obsessive-compulsive personality disorder, and passive-aggressive personality disorders).

No differences in response rates were found between atypical and nonatypical depression in a clinical trial of fluoxetine 20 mg/day for 8 weeks. When patients with atypical depression were compared specifically with those who had melancholia, no statistically significant differences in response or nonresponse rates were observed.

To assess the stability of depressive symptoms across episodes, we studied 74 outpatients with atypical unipolar major depression before response to fluoxetine treatment and again after relapse while taking either fluoxetine or placebo. Patients were assessed at baseline with the ADDS and at baseline and during follow-up with the 17-item HAM-D. Thirty-two (43%) of responders had a relapse or recurrence, of whom 21 (66%) had a predominance of reversed or positive neurovegetative symptoms at baseline. Nine of 10 (90%) patients with reversed symptoms at baseline had the same symptoms when they relapsed; 7 of 11 (64%) of those with positive symptoms at baseline had positive symptoms again at relapse (kappa = .557). Overall, 5 of 21 (24%) had changes in their disturbances in sleep, appetite, or weight when they relapsed. This suggests that the atypical subtype is relatively stable across episodes and is consistent with the genetic epidemiology data of Kendler and colleagues.[17]

SUMMARY

Atypical depression is a common subtype with between 29% and 42% of depressed outpatients meeting criteria. Most studies show that patients with atypical depression have an earlier age at onset, shorter but more frequent episodes, similar patterns of Axis I comorbidity with the exception of bulimia, increased rates of obsessive-compulsive and passive-aggressive personality disorders, increased rates of body dysmorphic disorder, and coexisting avoidant personality disorder and social phobia. Specificity for bipolar depression is questionable. Most studies show that MAOIs are more effective than TCAs, SSRIs are as effective as MAOIs, and the newer generation of antidepressants need more study in this prevalent subtype.

Drug names: bupropion (Wellbutrin), fluoxetine (Prozac), mirtazapine (Remeron), nefazodone (Serzone), venlafaxine (Effexor).

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