

A History of the Concept of Atypical Depression

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The term *atypical depression* as a preferentially monoamine oxidase inhibitor (MAOI)–responsive state was first introduced by West and Dally in 1959. Further characterization of this syndrome and its responsiveness to antidepressants came to occupy the attention of many psychopharmacologists for the next 30 years. Different portrayals of atypical depression have emerged, for example, nonendogenous depression, phobic anxiety with secondary depression, vegetative reversal, rejection-sensitivity, and depression with severe chronic pain. Consistency across or within types has been unimpressive, and no coherent single type of depression can yet be said to be “atypical.” In successfully demonstrating superiority of MAOI drugs to tricyclics, the Columbia (or DSM-IV) criteria have established their utility and become widely adopted, but other criteria have also passed this test. In this “post-MAOI” era, no novel compound or group of drugs has been clearly shown to have good efficacy in atypical depression, leaving the treatment of atypical depression as an unmet need.

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DEVELOPING THE CONCEPT OF ATYPICAL DEPRESSION

The concept of atypical depression with respect to monoamine oxidase inhibitors (MAOIs) was first articulated in 1959 by West and Dally¹ upon recognizing a subgroup of depressed patients with atypical symptoms who responded preferentially to MAOIs after failing treatment with tricyclic antidepressants (TCAs) and electroconvulsive therapy. In their report of more than 500 depressed patients receiving the MAOI iproniazid, West and Dally described a group of patients exhibiting atypical depressive states that sometimes resembled anxiety hysteria with secondary depression. After other treatments had failed, iproniazid appeared to almost completely relieve their disabling symptoms. Interestingly, the response to iproniazid occurred within the first few days of treatment, with a rapid increase in energy levels and decrease in anxiety compared with a much slower response rate for patients with melancholic depression. Another unusual aspect of this report was that patients did not relapse when with-

drawn from the medication after a few months of treatment. This observation may reflect recovery from brief episodes of depression or possibly a set of patients with different atypical symptoms than those seen today; it is also possible that follow-up was not long enough to observe relapses. The results fueled debate as to whether atypical depression is a single condition and whether patients with this condition do indeed respond preferentially to MAOIs. Since the term was introduced in the early 1960s, *atypical depression* has been used variously to denote depression with the following characteristics: nonendogenous depression, anxiety state, reversed vegetative shift, chronic pain, bipolar disorder, and rejection sensitivity.

Anxiety

In 1972, Sargent and Slater² described atypical depression as being characterized more as a form of anxiety, with phobic symptoms and autonomic lability, which responded particularly well to the MAOI phenelzine. Sargent and Slater suggested that depression was of secondary importance to the primary anxiety disorder, which appeared first and was the predominant feature.

Reversed Vegetative Symptoms

Another view was put forward by Pollitt,³ who explored atypical depression as a reversal of the “typical” vegetative symptoms seen in depression. Pollitt and Young⁴ observed that in atypical depression, the symptoms may include increased appetite, weight, and libido. Moreover, patients with these symptoms were less obsessional and more hysterical than patients with melancholic

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depression. Atypical symptoms were also found to be more common in younger patients experiencing either depression or anxiety.

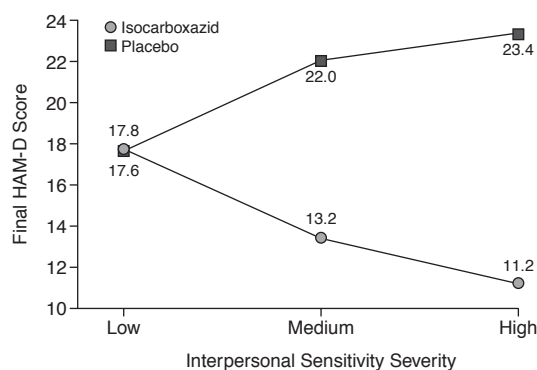
Chronic Pain

In 1966, Lascelles⁵ noted that patients with chronic facial pain often presented with atypical depression. In a 4-week, double-blind crossover study, Lascelles reported that the MAOI phenelzine was superior to placebo in patients with chronic facial pain and atypical depressive symptoms. In 1979, Raft et al.⁶ were the first to observe that phenelzine was superior to both a tricyclic drug, amitriptyline, and placebo in patients with atypical depression who were recruited from a pain clinic population. Davidson and Raft⁷ later reported in the same population that up to 74% of patients exhibited reversed vegetative symptoms. Although the aspect of chronic pain in atypical depression has been largely overlooked since that time, these studies suggest an important application of MAOIs that deserves further attention.

Bipolar Disorder

Research has also established a relationship between reversed vegetative symptoms and bipolar disorder. In a small (N = 84) questionnaire-based study, Detre et al.⁸ found that 78% of patients with bipolar depression experienced hypersomnia and postulated that such a symptom might be useful in the classification of affective disorders. Subsequently, Himmelhoch et al.⁹ examined the efficacy of the MAOI tranylcypromine versus imipramine for the acute treatment (first 6 weeks) and continuation treatment (next 10 weeks) of patients with bipolar depression with reversed vegetative features. In this double-blind, randomized study of 56 outpatients with anergic bipolar depression, the tranylcypromine-treated group had significantly fewer discontinuations (7% vs. 25% for imipramine, $p = .03$), greater response to acute treatment (81% vs. 48%, $p = .02$), less acute treatment failure (8% vs. 29%, $p = .06$), and greater sustained remission rates (71% vs. 20%, $p = .01$) compared with the imipramine-treated group. Study authors concluded that the presence of anergia and reversed vegetative symptoms contributed to the greater efficacy of tranylcypromine. In a study¹⁰ of patients with depression with or without atypical symptoms, those with atypical depression (N = 198) had a 3.6-times greater prevalence of bipolar disorder compared with patients without atypical symptoms (N = 122). The patients with atypical features also experienced an earlier onset of depressive episodes, had greater functional impairment, and were more likely to have a chronic course of illness than patients with nonatypical depression. Other studies^{11,12} have also reported a high association of bipolar disorder with atypical depression, with one study¹¹ reporting that 72% of patients with atypical depression had bipolar spectrum disorders.

Figure 1. Interpersonal Sensitivity Is Associated With Treatment Outcome in Depression^a



^aData from Davidson et al.¹⁶

Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

Rejection Sensitivity

Atypical depression has additionally been associated with rejection sensitivity. Klein and Davis¹³ introduced the term *hysteroid dysphoria* to describe a subgroup of depressed patients, mainly women, who exhibited an extreme response to admiration, approval, and personal rejection. These patients were prone to atypical symptoms such as oversleeping, overeating, and leaden paralysis.¹⁴ Liebowitz and Klein¹⁵ subsequently reported specific medication-response patterns to treatment with MAOIs in patients with hysteroid dysphoria. Because symptoms indicating interpersonal sensitivity showed responsiveness to MAOIs, Davidson et al.¹⁶ undertook post hoc analysis of a 6-week study of 174 outpatients receiving the MAOI isocarboxazid or placebo. In this analysis, patients were stratified by baseline levels of interpersonal sensitivity (low, medium, or high), and characteristics of the 3 groups, including their response to MAOI treatment, were described. The authors found that the degree of interpersonal sensitivity was a significant indicator of treatment response to the MAOI (Figure 1).¹⁶ Specifically, they found that for subjects with low levels of interpersonal sensitivity at study entry, final depression scores at week 6 were identical for drug and placebo. Conversely, for subjects with high baseline interpersonal sensitivity, the impact of drug therapy was substantial, and placebo was significantly less effective. The benefit of isocarboxazid was thus most apparent in subjects with marked rejection sensitivity.

When one term is used to represent different clinical phenomena, it becomes important to assess the extent to which symptoms may overlap. In a 1983 report by Paykel and colleagues,¹⁷ little nosologic coherence was found to exist among definitions. Such disparity and noninterrelatedness between symptom sets led the authors to suggest the need for agreement on a more precise definition.

VALIDATION OF MAOI RESPONSIVITY

Phenelzine

Throughout the 1970s, research continued to focus on validating the preferential MAOI response compared with TCAs in treating atypical depression. In 1973, Robinson et al.¹⁸ conducted a 6-week, double-blind, placebo-controlled trial of 87 outpatients with depression and anxiety. Researchers used a diagnostic index to characterize and measure patient symptomatology, and they used a biochemical assay of platelet monoamine oxidase inhibition as a measure of drug activity. At study end, phenelzine significantly improved patient scores on items from the Hamilton Rating Scale for Depression, including total depression ($p < .05$), total anxiety ($p < .05$), somatic anxiety ($p < .05$), hypochondriasis-agitation ($p < .001$), and psychomotor change ($p < .001$), compared with placebo. Dose was found to be an important variable in treatment with phenelzine. Another identical study by the same investigators¹⁹ was conducted to examine dose-response effects of phenelzine. They found that phenelzine 60 mg/day significantly improved responses compared with placebo, while phenelzine 30 mg/day was not significantly different from placebo. Robinson et al.^{18,20} reported optimal clinical response with phenelzine when monoamine oxidase was inhibited by at least 80%, reminding us of the importance of proper dosing, as well as helping define optimal use of phenelzine.

The efficacy of phenelzine has also been compared with that of the TCA amitriptyline in the treatment of panic attacks associated with depression. In a 6-week, double-blind study²¹ of 169 outpatients with depression, phenelzine treatment was associated with significant benefits compared with amitriptyline in patients with panic attacks. Specifically, phenelzine was associated with significantly less anxiety ($p = .002$), interpersonal sensitivity ($p = .02$), somatization ($p = .01$), and severity of panic attacks ($p = .006$) compared with amitriptyline. In contrast, in a study of 131 outpatients with depression or mixed anxiety-depression, Paykel et al.²² detected only a slight advantage of phenelzine over amitriptyline in patients with additional anxiety, as specifically defined by the *International Classification of Diseases, Ninth Revision*. A multiple regression analysis²³ of data from these outpatients found little evidence to support different responses to phenelzine and amitriptyline among patient subgroups.

Landmark efficacy trials²⁴⁻²⁹ of MAOIs were conducted by investigators at Columbia University during the 1980s and 1990s. All of their studies used a set of criteria for atypical depression that they had developed, requiring mood reactivity and at least 2 associated symptoms of hyperphagia, hypersomnolence, leaden fatigue, and rejection sensitivity as an enduring trait. As noted later in this article, this definition was adopted by DSM-IV as criteria for the atypical subtype of depression. In 1988, Liebowitz

et al.²⁴ reported on a 6-week, double-blind, randomized study of imipramine, phenelzine, and placebo in 119 patients who met the Columbia criteria for atypical depression. After a 10-day placebo run-in period, patients were randomly assigned to drug or placebo for 6 weeks, followed by a continuation phase in which responders could continue in the study for an additional 6 weeks. After the first 6 weeks, response rates were 50%, 71%, and 28% for imipramine, phenelzine, and placebo, respectively. Both drugs were significantly more efficacious than placebo, and phenelzine was also superior to imipramine.

At the same time, Quitkin et al.²⁵ demonstrated the superiority of phenelzine over placebo and imipramine in a group of patients with probable atypical depression, i.e., depression with reactive mood and only 1 of the 4 associated symptoms. Response rates were 47%, 71%, and 29% for imipramine, phenelzine, and placebo, respectively. Both drugs were significantly more effective than placebo ($p = .03$). Other studies²⁶⁻²⁹ by the Columbia group further established the superiority of phenelzine over imipramine in atypical depression.

In a crossover design study, McGrath et al.²⁹ compared the efficacy of phenelzine and imipramine in nonresponders. In this trial, patients who were previously unresponsive to double-blind administration of imipramine ($N = 46$) or phenelzine ($N = 22$) were switched to receive the other active drug in a double-blind fashion. At study end, 67% of patients switching from imipramine to phenelzine responded compared with only 41% of patients switching from phenelzine to imipramine ($p = .01$). Study findings suggested that patients with symptoms of atypical depression who were unresponsive to TCA treatment may gain significant clinical benefit from switching to MAOI treatment, but that the probability of responding to imipramine was reduced in patients who were recently nonresponsive to phenelzine.

Isocarboxazid

Davidson and colleagues³⁰ explored the efficacy of isocarboxazid, a less frequently used hydrazine MAOI drug, for the treatment of atypical depression. Isocarboxazid was superior to placebo on many measures, and in a linear regression analysis examining which particular aspects of atypical depression responded preferentially to the MAOI over placebo, the authors found that interpersonal sensitivity and phobic avoidance were the aspects most MAOI responsive.

CLASSIFICATION STUDIES

The concept of atypical depression has been further explored by the Duke University group^{31,32} using grade of membership multivariate analysis to explore the classification of depression. In the first study,³¹ 221 patients involved in double-blind trials of antidepressants were in-

cluded. Results of grade of membership analysis showed 5 distinct subsets of depressive symptoms: (1) melancholic depression, typically in older male patients, with modest response to MAOIs; (2) mild depression with panic attacks and agoraphobia, with a good response to MAOIs; (3) mild depression with anxiety, agitation, hypochondria, obsession, and atypical vegetative features, typically in young patients, with a good MAOI response; (4) severely agitated melancholia with panic attacks and agoraphobia (melancholia and neuroticism), with poor treatment response; and (5) depression with psychic anxiety, depersonalization, frequent somatization, low distress, and modest treatment response.

A confirmation study³² of 130 outpatients reported similar groupings with the last 2 types in reverse order: type 1 included mainly older male patients with melancholia who responded modestly to MAOIs; type 2 consisted of depression with obsessive-anxious symptoms in older patients who responded better to isocarboxazid than placebo; type 3 consisted of mild depression that responded well to placebo (65%) and better to drug (100%); type 4 consisted of depression with agitation, anorexia, and depersonalization, and responsiveness to MAOIs; and type 5 included mainly young females who had atypical vegetative symptoms and poor overall response, but significantly better outcome on isocarboxazid than on placebo (recovery rates for this type of depression were 33% and 0%, respectively). These studies explored the relationship between depression and anxiety and provided validation of the existence of characteristic subtypes of depression, including an atypical subtype that responded better to MAOI treatment than to placebo, albeit showing an overall low rate of response at 6 weeks.

In a study³³ of 1029 female-female twin pairs, latent class analyses of 14 DSM-III-R symptoms were analyzed to validate depressive symptoms. The study authors reported 3 depressive syndromes: mild typical, severe typical, and atypical. Atypical depression was associated with shorter depressive episodes, obesity, subsequent atypical depression episodes, and high concordance of depressive type between monozygotic twins. Study authors concluded that genetics contribute to the type of depression manifested and that the origins of depression may be divergent.

DSM-IV DEFINITION OF ATYPICAL DEPRESSION

Based upon extensive data from the Columbia University researchers, and others mentioned herein, the American Psychiatric Association established atypical depression as a separate subtype to the mood disorders category in the DSM-IV.³⁴ DSM-IV criteria for atypical depression require mood reactivity (i.e., the capacity for mood improvement when presented with positive events) in addition to the presence of at least 2 of the following symp-

toms: overeating, oversleeping, leaden paralysis, and a long-standing pattern of extreme sensitivity to perceived interpersonal rejection.

OTHER DRUGS IN ATYPICAL DEPRESSION

Studies have also suggested the utility of modafinil for the treatment of atypical depression. Modafinil is a wake-promoting agent approved by the U.S. Food and Drug Administration for reducing excessive sleepiness associated with sleep disorders, but it has also shown some utility for anergia in atypical depression and anergic depression. Vaishnavi et al.³⁵ studied 66 patients with atypical depression who entered a 12-week open-label study of modafinil, followed by randomization to modafinil (N = 24) or placebo (N = 26) for another 12 weeks. During the first 12 weeks, patients significantly improved from baseline on 29-item HAM-D scores (9.7 at week 12 vs. 34 at baseline, $p < .0001$). During the double-blind relapse-prevention second phase of the trial, there were no differences in rates of relapse between those who continued on the drug versus those who were randomly assigned to placebo. The open-label part of the study suggested the possible benefit of modafinil for atypical depression, although rates of relapse were no different in those remaining on drug versus those discontinuing it.

CLINICAL COURSE AND BIOLOGICAL ALTERATIONS IN ATYPICAL DEPRESSION

Studies have also examined the possible biological basis for depression with atypical symptoms. In a small (N = 19) study³⁶ of female patients with and without atypical depression, low-dose dexamethasone was administered and plasma cortisol levels were evaluated in efforts to understand the relationship between atypical depression and hypothalamo-pituitary-adrenal axis function. Levitan et al. found that a 0.5-mg dexamethasone challenge dose reduced morning cortisol secretion by 92% in women with atypical depression, compared with a 78% reduction in control women. Because these results were opposite to those observed in patients with melancholic depression, study authors proposed that atypical depression may represent a biologically distinct form of depression. The nature of this "super-suppression" of cortisol to low-dose dexamethasone suggests a hypersensitive feedback system and resembles the profile seen in posttraumatic stress disorder. It is therefore possible that, in some forms of atypical depression, the occurrence of early trauma could have some influence on the neurobiology of atypical depression.

An increased rate of such trauma in atypical depression has been reported by Matza and colleagues.³⁷ Using data from the U.S. National Comorbidity Survey, Matza et al.³⁷ identified patients as having atypical depression (N = 304)

if they met DSM-III-R criteria for depression with the added symptoms of hyperphagia and hypersomnia. They identified patients with typical depression (N = 523) and those without psychiatric disorders (N = 4071) as comparator groups. When weighted for the national population, atypical depression accounted for 39% of individuals with depression. Compared with typical depression, atypical depression was associated with significantly greater history of paternal depression ($p < .01$), childhood sexual abuse ($p < .01$), and childhood neglect ($p < .05$), suggesting both genetic and environmental contributions to atypical depression. In addition, atypical depression was associated with significantly more health care utilization, including emergency department visits and antidepressant use ($p < .05$), compared with typical depression.

It bears asking whether the symptoms of vegetative reversal remain constant across episodes. In a double-blind study by Nierenberg et al.,³⁸ 74 outpatients with atypical depression who responded to 12 weeks of open-label fluoxetine treatment were randomly assigned to placebo or 50, 38, or 14 weeks of fluoxetine (followed by placebo to equal 50 weeks total). Continuity of atypical vegetative symptoms was examined at relapse. Forty-three percent of all patients relapsed. Ninety percent of patients with reversed vegetative symptoms continued to have the same symptoms upon relapse, compared with 64% of patients with typical vegetative symptoms. The study highlighted the stability of reversed neurovegetative symptoms over time in patients with atypical depression.

CONCLUSION

First postulated on the basis of presumed preferential response to MAOI treatment, atypical depression has since been shown repeatedly to respond more robustly to phenelzine or tranylcypromine than to imipramine or amitriptyline. The Columbia criteria, as well as criteria from Pittsburgh (Thase and colleagues), Vermont (Robinson and colleagues), and North Carolina (Raft and Davidson), have all been used successfully to distinguish between an MAOI and a TCA. These have emphasized respectively, rejection sensitivity, anxiety/nonendogenicity, bipolarity with vegetative reversal, and pain with vegetative reversal. Although genetic and environmental elements certainly contribute to atypical depression, the full range of etiologic characteristics remains elusive, and the formative effect of trauma needs further clarification. The nature of atypical depression, though distinguishable from melancholic depression, is still the subject of debate.

Drug names: dexamethasone (Maxidex, Mymethasone, and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), isocarboxazid (Marplan), modafinil (Provigil), phenelzine (Nardil), tranylcypromine (Parnate and others).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, dexamethasone, iproniazid, and modafinil are

not approved by the U.S. Food and Drug Administration for the treatment of depression.

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