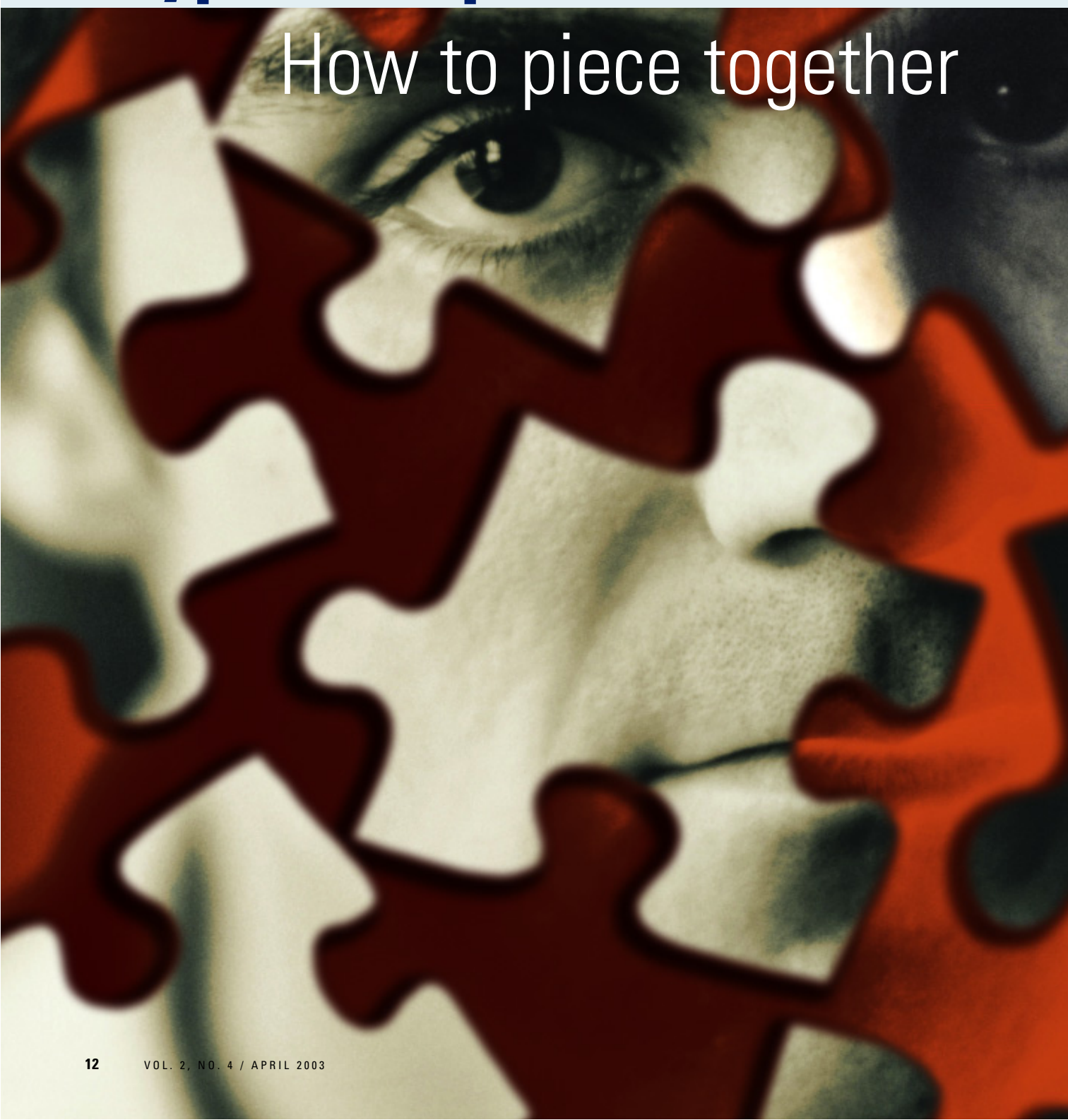
Current Psychiatry

Atypical depression Puzzled?

How to piece together



symptoms and treatments

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When do depressive symptoms become 'atypical,' and which antidepressants are most effective? Though evidence is incomplete, these authors recommend a clinical approach.

Deciding if a patient's depressive episodes are "atypical" can be difficult because key pieces of the diagnostic puzzle are missing. Notwithstanding DSM-IV criteria, atypical depression's definition remains unclear. This creates a therapeutic dilemma because we know that patients with atypical depression respond differently to antidepressants:

- Monoamine oxidase inhibitors (MAOIs) may be most effective, but their side effects can be troublesome.
- Tricyclics are clearly less effective than MAOIs, but the newer antidepressants' role in treating atypical depressive symptoms has not been adequately explored.

We offer recommendations for diagnosing and treating atypical depression and address issues that may affect your clinical approach. These include possible overemphasis on mood reactivity in DSM-IV, shortcomings in studies defining the atypical depressive syndrome, and the potential role of biological markers in clarifying this challenging diagnosis.

Features of atypical depression

Atypical depression, as defined in DSM-IV,[1] is characterized by mood reactivity and two or more of the following criteria:

- hypersomnia
- increased appetite or weight gain
- leaden paralysis (heavy, leaden feeling in arms or legs)
- longstanding sensitivity to interpersonal rejection that results in significant social or occupational impairment (*Table 1*).

An estimated 16 to 23% of patients with unipolar depression present with atypical features.[2] These rates are higher among patients with bipolar disorder.[2,3]

Distinctive features. Studies comparing atypical depression with typical or melancholic depression suggest that atypical depression may be distinct in epidemiology, family history, comorbidity, and course of illness (*Table 2*). Specifically, atypical depression has a higher female-to-male ratio and earlier age of onset.[4] Patients with atypical depression have higher rates of comorbid panic disorder,[4,5] social phobia,[4,5] bipolar II disorder,[5] and bulimia[6] than do those with typical depression.

MAOIs are almost twice as effective as tricyclics in patients with atypical depression

Family members of patients with atypical depression are more likely to have atypical features during a depressive episode than are family members of patients with melancholic depression.[7] These findings suggest a genetic component to atypical depression. Atypical depressive episodes also may be more likely to become chronic.[4,8]

Not all patients are alike. Studies of the diagnostic stability of atypical depression over time suggest that patients exhibiting atypical features are heterogeneous.[9] Some longitudinal studies report reasonable diagnostic stability, with 59% to 100% of patients with an index episode of atypical depression exhibiting atypical features 12 to 24 months later.[9,10] In a follow-up study of patients in remission from an episode of atypical depression, 64% of patients suffering a relapse were again found to have atypical features.[11]

Although numerous studies have failed to replicate one or more of these findings,[4,8] several investigators have concluded that atypical depression is a distinct and valid subtype of major depression.[4,7,8]

Antidepressant dilemmas

Unlike typical or melancholic depression, atypical depression responds more robustly to MAOIs than to tricyclic antidepressants (TCAs).[12] MAOIs are roughly twice as effective as TCAs (response rate 72% vs. 44%, respectively), according to a meta-analysis of six studies comparing MAOIs and TCAs in patients with atypical depression.[13]

Clinicians rarely use MAOIs as first-line antidepressants, however, because of side effects and potential dietary and drug interactions. A depressed patient is thus unlikely to receive MAOIs unless the clinician strongly suspects that the presentation is atypical.

SSRIs. Few studies have evaluated how patients with atypical depression respond to newer antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs). This lack of evidence creates a dilemma when treating atypical depression, as SSRIs are widely used in depressed patients, including those with atypical features.

One study found fluoxetine and phenelzine comparably effective in atypical depression,[14] while another found sertraline works as well as moclobemide.[15] However, the fluoxetine study was limited by a relatively small sample size (n=42), and both studies lacked placebo controls.

Some studies have suggested that SSRIs are less effective than MAOIs[16] or as effective as TCAs in depressed patients with atypical features.[17,18] However, one of these trials was limited by a small sample size (n=28),[18] and only one was placebo-controlled.[17]

Bupropion. Studies of other antidepressants in atypical depression also are limited. In two separate trials, depressed patients with atypical features showed a

Table 1

MOOD EPISODES: DSM-IV CRITERIA FOR ATYPICAL FEATURES SPECIFIER

The following criteria must be present in the last 2 weeks of the episode

Criterion A.

Mood reactivity (ie, mood brightens in response to positive events)

Criterion B. Two or more of the following:

Increased appetite or weight gain

Hypersomnia

Leaden paralysis

Longstanding sensitivity to interpersonal rejection

greater response to bupropion than did depressed patients with typical features.[19,20]

Bupropion—a combined dopaminergic-noradrenergic antidepressant—appears to have stimulating properties that may help patients with hypersomnia and hyperphagia. Like MAOIs, bupropion also appears to have a greater effect on dopaminergic systems than either TCAs or SSRIs.

Recommendation. The most prudent approach appears to be using SSRIs or bupropion as first-line treatment for atypical depression and reserving MAOIs for patients who do not respond.

Table 2

HOW ATYPICAL DEPRESSION COMPARES WITH MELANCHOLIC OR 'TYPICAL' DEPRESSION

Feature	Atypical depression	Melancholic (MEL)/ typical (TYP) depression
Symptom		
Sleep	Increased	Decreased
Appetite	Increased	Decreased
Age of onset	Late teens to early 20s	Mid to late 30s
Female:male ratio	> 2:1	Between 1:1 and 2:1
Frequency of bipolar II disorder	Increased compared with MEL/TYP	
Duration of episodes	Increased compared with MEL/TYP	
Biology		
HPA axis activity	Low to normal	High
Comorbidity		
Panic disorder, social phobia, bulimia	Frequency increased compared with MEL/TYP	

Attempts to define atypical depression

Although atypical depression responds differently to MAOIs than to TCAs, it is unclear which patients will respond preferentially to MAOIs. Early attempts to classify this subgroup recognized that these patients display symptom clusters, including:

- anxious depression (prominent anxiety symptoms)
- anergic depression (prominent fatigue and/or psychomotor retardation)
- and depression with reversed vegetative symptoms (hypersomnia and increased weight/appetite).[7,21]

Researchers have focused on patients with different combinations of these symptom profiles when defining the atypical depressive syndrome. Some have defined atypical depression as anxious temperament and reactive mood; others, as depression with reversed vegetative symptoms and severe fatigue; still others employ aspects of both profiles, as does DSM-IV.[21] As a result of this confusion, investigators have demonstrated the preferential response to MAOIs in groups that exhibit different "atypical" symptoms.

Mood reactivity. The importance of mood reactivity in the diagnosis of atypical depression has been debated. DSM-IV requires mood reactivity for the diagnosis, perhaps to clearly differentiate melancholia from atypical depression.[7] Yet some studies have demonstrated the preferential MAOI response in patients without this symptom.

The Columbia group, from whose work the DSM-IV definition was adopted, performed several convincing studies showing clear superiority of MAOIs in patients who had reactive mood and displayed at least two additional atypical features, such as reversed vegetative symptoms and anergia.[22] Patients with reactive mood and only one additional atypical symptom (classified as "probable" atypical depression) also displayed the preferential response to MAOIs, whereas patients who displayed mood reactivity alone did not.[12]

Thase et al,[23] however, reported that reversed vegetative symptoms were more common with nonreactive mood (48%) than with reactive mood (16%) in patients with highly recurrent depression. Moreover, patients who displayed reversed vegetative symptoms without mood reactivity showed the

Table 3

HOW ANTIDEPRESSANTS COMPARE IN CLINICAL TRIALS OF ATYPICAL DEPRESSION

MAOIs	8 controlled trials found MAOI > placebo 6 controlled trials found MAOI > TCA
TCAs	6 controlled trials found MAOI > TCA
SSRIs	2 controlled trials found SSRI = MAOI 1 trial found MAOI > SSRI 2 trials found SSRI = TCA
Bupropion	1 open-label trial found bupropion more effective in atypical depression than in typical depression 1 open-label trial found bupropion effective in depression with hypersomnia 1 retrospective study found bupropion > fluoxetine in atypical depression

> more effective than
= as effective as

same preferential response to MAOIs as the mood-reactive group. Patients with typical vegetative symptoms did not show this differential response.

More evidence suggests that mood reactivity should not be given the hierarchical importance it holds in the DSM-IV definition of atypical depression. In studies using latent class and cluster analyses, mood reactivity did not correlate with any other atypical feature,[4,21] whereas hyperphagia, hypersomnia, leaden paralysis, and rejection sensitivity appear to be associated with one another.

Recommendation. Mood reactivity's uncertain status in atypical depression's definition makes it difficult to predict which patients may respond preferentially to MAOIs, as many patients present with other atypical features and nonreactive mood. Most recently, it has been suggested that atypical depression's diagnostic criteria should be modified so that mood reactivity is not required but is one of five atypical features, of which three must be present for the diagnosis.[24]

Biological markers of depression

Atypical depression's definition might be clarified if specific depressive symptoms could be linked to any biological markers. One proposed marker is decreased HPA axis activity, possibly caused by a central deficiency of corticotropin-releasing hormone (CRH),[25] a potent HPA axis stimulator.

- HPA axis hyperactivity—presumably caused by increased CRH activity in the central nervous system—has been linked to melancholic depressive symptoms—particularly insomnia and reduced appetite.[26]
- Normal or diminished HPA axis activity—suggested by normal cortisol levels, low levels of CRH in cerebrospinal fluid, and increased frequency of dexamethasone suppression—has been associated with some atypical depressive features—specifically reversed vegetative symptoms.[27-29]

However, no studies have examined whether low HPA axis activity is associated with other atypical symptoms listed in DSM-IV. Research is needed to determine whether HPA axis hypoactivity is associated only with reversed vegetative symptoms or with atypical depression per se.

Obesity and eating disorders. Depressed patients who are obese or present with eating disorders may overlap with the atypical subtype and may respond better to some drug interventions than to others. Evidence suggests that depression—particularly the atypical subtype—is associated with increased rates of obesity[8,29] and eating disorders.[8,30]

In our clinical experience, the combination of venlafaxine and bupropion can be effective for both depression and excessive eating in these patients, many of whom also exhibit other atypical features. A possible explanation is that the combined pharmacologic effect of venlafaxine and bupropion resembles that of the MAOIs (increased synaptic availability of serotonin, norepinephrine, and dopamine) without many MAOI side effects, such as weight gain.

We have, however, also observed treatment-emergent hypomania when using this drug combination, which is consistent with:

- the idea that mood reactivity and rejection sensitivity may be markers for bipolar disorder
- the often-reported high rate of bipolar II disorder among patients with atypical depression.[5]

In obese patients with bipolar II disorder, we have found that adding topiramate to mood stabilizer therapy can help treat both mood instability and overeating.[31,32]

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Related resources

- Parker G, Roy K, Mitchell P, Wilhelm K, Malhi G, Hadzi-Pavlovic D. Atypical depression: a reappraisal. *Am J Psychiatry* 2002;159(9):1470-9.
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DRUG BRAND NAMES

Bupropion • Wellbutrin
Fluoxetine • Prozac
Moclobemide • Manerix
Phenelzine • Nardil
Sertraline • Zoloft
Topiramate • Topamax
Venlafaxine • Effexor

DISCLOSURE

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Bottom Line

Mood reactivity's uncertain status in atypical depression's definition makes it difficult to predict which patients may exhibit a preferential response to MAOIs. The most prudent approach appears to be using SSRIs or bupropion as first-line treatments and reserving MAOIs for patients who do not respond.