Introduction

New Directions in the Treatment of Atypical Depression

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In this supplement, each article focuses on a different aspect of atypical depression. First, Jonathan R. T. Davidson, M.D., examines the evolution of the concept of atypical depression; second, Gordon B. Parker, M.D., Ph.D., D.Sc., discusses the validity of the current concept and suggests a new model for viewing atypical depression from a personality spectrum perspective; third, Jonathan W. Stewart, M.D., presents a review of the treatment literature, focusing on established therapies and ending with the work on selective serotonin reuptake inhibitors (SSRIs); and finally, Mark H. Rapaport, M.D., considers newer perspectives on treatment of atypical depression and evaluates recent therapy developments. This brief overview touches on the topics that each author addresses.

HISTORY OF THE CONCEPT

The concept of atypical depression has been part of the depression nomenclature for almost as long as there have been effective antidepressant medications. As Dr. Davidson explains elsewhere in this supplement, modern use of the term *atypical depression* began with West and Dally,[1] investigators in London in the 1950s, who used the term to describe a subgroup of patients who were not particularly responsive to electroconvulsive therapy or to the tricyclic antidepressant (TCA) imipramine, but who were responsive to the monoamine oxidase inhibitor (MAOI) iproniazid.[1] Soon after the discovery of the therapeutic potential of the first MAOI, iproniazid,[2,3] clinical observers attempted to compare iproniazid with the first TCA, imipramine, and to cross-tabulate meaningful heterogeneity in antidepressant response with meaningful heterogeneity in patients' clinical presentation.[1,4–6] Prior to the introduction of these treatments, depression was only subdivided into endogenous (now known as melancholia) and nonendogenous states.

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Although the concept of atypical depression was anchored to preferential response to MAOIs, the criteria used to define the diagnosis have been and remain subject to debate, as Dr. Parker discusses elsewhere in this supplement. West and Dally[1] did not describe reverse vegetative symptoms, such as overeating, weight gain, and hypersomnia, in coining the term atypical depression. They emphasized that these patients were atypical in that they not only did not respond to the treatments of choice for melancholia but also did not have classic features of endogenous depression, including autonomous mood disturbance. West and Dally's criteria did, however, include prominent anxiety and multiple phobias, with the anxiety and phobias both preceding the depression as well as intensifying during the depression.

It was not until the late 1960s that the current concept of vegetative reversal was pushed to the forefront of the criteria for atypical depression. In the work on treatment of nonmelancholic depressions by the Columbia group[6] and by Robinson and colleagues,[7] the emphasis on vegetative reversal increased, particularly oversleeping and hypersomnolence, and overeating with weight gain over time.

Klein and Davis[8] linked atypical depression to a particular interpersonal style using the term *hysteroid dysphoria*. In the language of the 1960s, the term described atypical depression that was present predominantly in younger, nonmelancholic women who were likely to experience vegetative reversal symptoms and early onset.

In retrospect, an unfortunate aspect of this increased emphasis on vegetative reversal in atypical depression was to diminish the importance of some kinds of anxieties in the natural history of this presentation of depression. Recent work of Parker and colleagues[9] has suggested that some features of atypical depression are more strongly linked than others to some kinds of anxiety, perhaps most particularly social phobia.

DSM Criteria

The current definition of atypical depression is a direct result of the research of investigators at Columbia University, although their definition is slightly modified.[6] Lack of broad acceptance of an operational definition of atypical depression delayed the official introduction of a definition until the publication of the DSM-IV.[10] The current

definition in the DSM-IV-TR[11] describes the essential features of depression with the specifier "With Atypical Features" as:

> . . . mood reactivity (Criterion A) and the presence of at least two of the following features (Criterion B): increased appetite or weight gain, hypersomnia, leaden paralysis, and a long-standing pattern of extreme sensitivity to perceived interpersonal rejection. These features predominate during the most recent 2-week period (or the most recent 2-year period for Dysthymic Disorder). The specifier With Atypical Features is not given if the criteria for With Melancholic Features or With Catatonic Features have been met during the same Major Depressive Episode.[11(p420)]

The DSM-IV definition of atypical depression begins with the threshold or entry symptom of preserved mood reactivity. An operational definition of preserved mood reactivity, used sometimes by the Columbia group, has been that the individual retains at least 50% of his or her normal reactivity to positive events as well as significant reactivity to negative events. My colleagues and I attempted to apply this definition prospectively to a group of patients with recurrent major depressive disorder and found that, according to this definition, more than 80% of our patients with recurrent major depressive disorder had significant mood reactivity.[12] Preserved mood reactivity seemed, at least in our hands, to be a broadly inclusive entry point, and lack of mood reactivity appeared to be a relatively uncommon feature of depressed outpatients.

In addition to preserved mood reactivity, patients meeting the DSM-IV-TR definition of atypical depression must have at least 2 of 4 classic features of atypical depression: hyperphagia, hypersomnia, leaden paralysis, or rejection sensitivity. Defining vegetative reversal is problematic. In practice, some patients may only oversleep on the weekend (i.e., their hypersomnolence is alarm-clock dependent), and other patients may show fluctuating levels of vegetative disturbance during the same depressive episode.

The definition of leaden paralysis has been even more problematic. Perhaps changes in the use of language have resulted in *leaden paralysis* no longer being a natural way to describe the experience. Whereas psychopathologists from 20, 30, or 40 years ago could identify leaden paralysis in their patients, today, patients seldom spontaneously report this experience, and attempts to apply these criteria retrospectively have been fraught with difficulty. Leaden paralysis is not synonymous with marked fatigue, although in contemporary practice that is often how the term is used.

Rejection sensitivity is the fourth classic feature of atypical depression. While significant mood reactivity is the entry symptom, extreme sensitivity to rejection, which is a dependent on preserved mood reactivity, is an additional descriptor.

Finally, the exclusionary symptoms are that the patient is neither melancholic nor catatonic (implicitly not psychotic) in his or her presentation. A strong case could be made for reversing the order of these factors so that the entry criterion would become: not being melancholic, catatonic, or psychotic, with the rest to follow. Dr. Parker examines these criteria in more detail elsewhere in this supplement.

VALIDITY OF THE SYNDROME

Atypical depression is common and occurs in almost all clinical settings; at least one seventh of patients, and sometimes as many as one third, have been shown to have atypical depression according to DSM-IV criteria.[13] Atypical depression is not atypical in the 21st century; it is one of the more common subtype presentations of major depressive disorder and is perhaps the predominant subtype presentation of the patient who is neither melancholic nor psychotic. In nongeriatric populations, atypical depression is probably a more common presentation of depression than melancholia, so the historical term *atypical* is hardly apt in the context of the current formulation of depressive disorders.

Several attempts have been made to validate atypical depression.[14,15] One method is to use modern psychometric techniques to look for the inherent structure of the expression of symptoms of depression, and these efforts have consistently reinforced the reverse vegetative symptoms. In a twin study,[14] for example, about a quarter of the patients with depression met criteria for atypical depression on the basis of reverse vegetative symptoms, and atypical depression was not a mild presentation but rather was apparent across the severity dimensions. Similarly, in the National Comorbidity Survey,[15] which interviewed a nationally representative sample of young to mid-life adults, nearly 40%[13] of all those with DSM-III-R[16] major depressive disorder manifested one or more reverse vegetative features, and as in the twin study, the atypical presentation was distributed across the severity dimensions.

Parker and colleagues[9] and Posternak and Zimmerman[17] have pointed out that the syndrome as it is defined in the DSM-IV has relatively weak internal consistency. If a patient has one of the symptoms, the probability that he or she will have another is relatively low, and the coefficient alphas typically range in the 0.1 to 0.25 zone.[9,17] A tighter definition of atypical depression would be preferable. In the work of Parker et al.[9] and Posternak and Zimmerman,[17] as well as in the 2 epidemiologic studies,[14,15] mood reactivity (criterion A) does not appear to be essentially tied to reverse vegetative symptoms (criterion B). Mood reactivity appears to arbitrarily impose a severity cap, which may not be useful in defining the term *atypical depression* because some patients who are more severely depressed have at least 2, if not more, of the

DSM-IV B-level criteria, but these patients do not show mood reactivity.

Studies[9,18,19] of the biology of atypical depression have relatively consistently confirmed that, as currently defined, atypical depression differs from melancholia. Atypical depression may not be characterized by a unique pathophysiologic profile, although extensive studies using modern neuroimaging techniques, both resting and using various provocation techniques, have not yet been undertaken. The strongest validator of the DSM-IV definition remains the consistent evidence that patients meeting these criteria are less responsive to TCAs and show significantly better response to MAOIs, both in relation to placebo as well as in relation to TCAs.

TREATMENT

Paradoxically, the concept of atypical depression diminished in its day-to-day utility almost immediately upon its official inclusion in the DSM-IV in 1994. The importance of the differential therapeutics between MAOIs and TCAs lessened dramatically with the introduction of the SSRIs and other newer antidepressants in the 1990s. Since then, SSRIs have risen to be almost universally the first-choice antidepressant in the United States. Dr. Stewart and Dr. Rapaport examine therapy options in more detail elsewhere in this supplement.

MAOIs Versus TCAs

Differential therapeutic response to MAOIs and TCAs has been examined in several studies.[6,20,21] A meta-analysis[6] of original data from randomized controlled trials conducted by the Columbia group demonstrated that, across their studies of atypical depression, the TCA imipramine was less effective than the MAOI phenelzine. Phenelzine offered almost a 3-fold advantage compared with placebo, whereas imipramine was solidly intermediate. Imipramine was not ineffective; it was simply less effective than phenelzine.

Dr. Stewart discusses subanalyses[20] of the Columbia group's studies in greater detail elsewhere in this supplement. Briefly, the subanalyses showed that the advantage of MAOIs compared with TCAs in patients with atypical depression consistently depended upon 2 characteristics: early onset and a chronic course. Since chronicity and early onset may each suggest genetic vulnerability, in future research it would be worthwhile to look for potential genetic mediators or moderators of antidepressant response that are linked to early onset and chronicity.

Before turning attention to more contemporary therapeutic options, it is important to clarify one frequent misunderstanding. Because MAOIs were typically reserved for second-line use in the 1970s and 1980s, it was widely believed that MAOIs were selectively effective for patients with atypical depression. As my colleagues and I demonstrated more than a decade ago,[22] the MAOIs were, indeed, less effective than the TCAs in comparative studies of more severely depressed inpatients, but they were more effective than placebo. Moreover, the MAOIs were slightly more effective than the TCAs in studies of ambulatory patients, including studies that contained patients with more typical depressive syndromes. Thus, it is more accurate to say that atypical depression is relatively less responsive to TCAs than it is to say that atypical depression is preferentially responsive to MAOIs.

SSRIs and Bupropion

Since the introduction of SSRIs, reports have indicated that in atypical depression the SSRI fluoxetine appears to be comparable to the MAOI phenelzine,[23] but that fluoxetine does not appear to be superior to the TCA imipramine.[24] This latter finding is problematic because the meta-analysis[6] of the Columbia group's work demonstrated convincingly that phenelzine is superior to imipramine. These results suggest problems with underpowered studies and difficulties with trying to conduct qualitative summaries of literature in which there are not enough studies to make informed judgments of what may be relatively modest differences. Although more data comparing SSRIs with the MAOIs are needed to resolve this issue,[25] it is extremely unlikely that such studies will be forthcoming. However, practitioners clearly found the SSRIs to be more useful for treatment of atypical depression than TCAs and, for more than a decade, the role of MAOIs progressively declined as more and more alternatives were introduced.

Bupropion is one of the most widely used treatments today for atypical depression, but despite promising open-label case series, for example, Rye and colleagues' study,[26] efficacy was never established in prospective studies. Controlled trials of differential efficacy for bupropion in relation to placebo or other antidepressants in atypical depression have not been published. It may be possible to "mine" some data from the controlled studies comparing bupropion and various SSRIs, but to date no such reports have surfaced.

To summarize, the current standard treatments for atypical depression—the SSRIs and bupropion—have not been rigorously tested in large comparative studies of patients with well-diagnosed atypical depression. We thus have no confidence that these treatments actually show the same magnitude of benefit that the MAOIs did compared with the TCAs.

Future Directions

One possible future direction for treatment of atypical depression could be the continued use of older MAOIs in patients who have not responded to SSRIs and bupropion. Another future option is the use of newer MAOIs. The only modern MAOI to be systematically studied to date in

atypical depression is the reversible inhibitor of monoamine oxidase-A, moclobemide. Moclobemide is not approved for use in the United States, but it has been demonstrated to be more effective in atypical depression than placebo[27] and as effective as SSRIs.[28,29] However, data suggesting moclobemide's equivalence to the older MAOIs such as phenelzine have not arisen, and one meta-analysis[28] suggested that moclobemide was actually a weaker antidepressant than the older MAOIs. Recently, a new transdermal patch form of the older MAOI selegiline became available in the United States, and the low dose can be used without the dietary restrictions of other MAOIs.[30] This patch showed efficacy in placebo-controlled studies[30] of major depression and was well tolerated. We have yet to discover whether, compared with the older MAOIs, it has a particular utility in atypical depression.

Lastly, a consistent undercurrent in the literature indicates that atypical depression, as formulated in the DSM-IV, is linked to the so-called soft side of the bipolar spectrum. Benazzi[31] found, in a large clinical series in Italy, that patients with bipolar II disorder were about twice as likely to have DSM-IV atypical depression as patients with unipolar depression. If patients did not meet criteria for bipolar II depression, they were still likely to have multiple features of the bipolar spectrum, including briefer, sub–DSM-level hypomanic episodes. Perhaps some of the newer treatments used in bipolar depression—including the novel anticonvulsant lamotrigine and the atypical antipsychotic medications—may provide additional options for patients who are not responsive to newer antidepressant medications.

Drug names: bupropion (Wellbutrin and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), lamotrigine (Lamictal and others), phenelzine (Nardil), selegiline transdermal system (EMSAM).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, lamotrigine is not approved by the U.S. Food and Drug Administration for the acute treatment of depression.

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