Conclusion

Depression and Its Subtypes: A Treatment Update

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In this Supplement, Andrew A. Nierenberg, M.D., has reviewed the large body of clinical trials that have demonstrated a specific pharmacologic response for the depressive subtype termed *atypical* depression, defined by the presence of mood reactivity combined with 2 of the following: hypersomnia, hyperphagia, leaden paralysis, and/or rejection sensitivity. For patients with this profile of depressive symptoms, the monoamine oxidase inhibitor (MAOI) phenelzine proved superior to the tricyclic antidepressant (TCA) imipramine. The combination of a well-defined symptom profile and evidence of a preferential response to one class of antidepressants over another gives important support to the impetus to identify subtypes of patients with major depression. These findings for atypical depression were perhaps more impressive, given that patients with the atypical profile were at one time those most likely to be viewed as characterological and less well suited to a pharmacotherapeutic as opposed to psychotherapeutic intervention. The psychiatric belief and tradition had been that patients with a more neurotic or mood reactive pattern were those for whom antidepressant medication was least likely to be useful or appropriate, and, yet, indeed, they turn out to be the first subtype to demonstrate a separation in efficacy between 2 previously established, effective antidepressant medication classes.

Patients with atypical depression were also observed, compared with those with nonatypical depression, to have an earlier onset of their mood symptoms and to suffer more relapses and shorter episodes. There is also a possibility that a similar superiority of response as seen with the MAOI over the TCA (but both superior to placebo) would also be evident for selective serotonin reuptake inhibitors (SSRIs) over TCAs as fluoxetine has appeared in preliminary studies[1] to be superior to a tricyclic comparator in atypical populations and equivalent to the MAOI phenelzine in one study.[2] As Nierenberg et al. point out, there are other suggestions of biological distinctions between atypical and nonatypical patients, in addition to treatment response, including the possibility of a diminished importance of the central norepinephrine system in this disorder and a distinctive pattern of corticotropin-releasing hormone release (diminished).

Despite the term *atypical*, Nierenberg et al. also point out that in ambulatory populations, the disorder is hardly atypical in that a substantial minority of depressed patients, 42% in one study at the Massachusetts General Hospital,[3] were classified as atypical and 14% met criteria for both melancholia and atypical depression. While the Axis I and Axis II comorbid disorders associated with atypical depression were not markedly different for patients with melancholia, those with atypical depression tended to have earlier age at onset, shorter episodes, and the suggestion of a link with social phobia and avoidant disorder. Treatment research with the SSRI fluoxetine, however, did not reveal an overall superior response for atypicals compared to melancholics.

Both "anxious" and "hostile" subtypes were first delineated in 1966 by Overall and colleagues.[4] Lydiard and Brawman-Mintzer have reviewed the diagnostic and clinical issues in understanding anxious depressions. Anxiety is certainly a common antecedent to depression, anxiety symptoms are extremely common (nearly universal) in major depressive episodes, and Axis I anxiety disorders are frequently comorbid with major depression. High levels of anxiety associated with depression typically predict greater impairment and a more chronic course. With respect to comorbid panic disorder, for example, the presence of the anxiety disorder with depression implies a poor prognosis and an additional risk factor for suicidal behavior. Panic attacks, the hallmark of panic disorder, are also common in the context of major depressive disorder even in the absence of diagnosable panic disorder, raising the possibility that panic attacks themselves may be as much a feature of mood disorder as of anxiety disorder.

Whether patients with significant anxiety and depression represent a valid subtype in terms of biological differences and important treatment response differences remains a question for further study. Nonetheless, it is a critical clinical task to identify anxiety disorders that are comorbid with major depression such as panic disorder, social phobia, obsessive-compulsive disorder, posttrau-

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matic stress disorder, and generalized anxiety disorder, inasmuch as not all therapies for major depression are equally effective for the comorbid condition.

Over the last several years, Maurizio Fava, M.D., and the Depression Clinical and Research Program at the Massachusetts General Hospital have further validated the initial Overall[4,5] observation that a substantial minority of depressive patients had a subtype featuring anger and hostility, termed *hostile depression*. Despite their recognition more than 3 decades ago and their high prevalence in ambulatory depressive populations, anger, hostility, and irritability are insufficiently recognized in the diagnostic criteria. One in 3 patients with major depression suffers sudden bursts of extreme anger and rage with considerable adverse impact on family members and the workplace. Despite an apparently increased comorbidity of personality disorders, at least as evaluated prior to antidepressant treatment, depressives with this profile turn out to be extremely treatable, particularly with serotonergic agents. Moreover, there is evidence that the subgroup of patients with anger attacks and irritability, compared with those without anger attacks, have lower levels of central serotonergic function. The association of major depression with outwardly directed anger and subsequent relief of this outwardly expressed and directed anger with antidepressant treatment certainly contrasts with the traditional belief that depression reflected the inability to outwardly direct anger. As it turns out, both outwardly and inwardly directed anger improves with the treatment of the depression. While further work needs to be done to demonstrate whether the hostile depressive subtype relapses into hostile depressive episodes and whether this subtype of depression is familial or genetically determined, this important line of clinical research already alerts clinicians to elicit reports of irritability and anger attacks and to consider a diagnosis of depression. Recognizing an Axis I underpinning and therapeutic target for dysregulation of anger permits greater therapeutic optimism when planning treatment for the patient.

The review by William Z. Potter, M.D., Ph.D., summarizes our understanding of the most clearly differentiated subtype of depression, bipolar depression. This distinct subtype has clear therapeutic importance with respect to concerns about the risk of switch into mania. MAOIs have appeared to be particularly useful for this state (although efficacy in both atypical and bipolar depression may well simply indicate that MAOIs are particularly good antidepressants). Other antidepressants may emerge as safer than others with respect to the risk of switch. In addition, novel therapeutic approaches, such as use of the anticonvulsant lamotrigine, suggest that some agents could serve as antidepressants for the bipolar patient without necessarily being efficacious for unipolars. If so, this would further differentiate bipolar from other types of depression. Work that Potter and colleagues have done over time with respect to α_2-adrenoceptor antagonists also raises the possibility of novel approaches to treating bipolar depression using α_2 antagonists. One currently available antidepressant, mirtazapine, has this pharmacologic profile, although evidence for particular usefulness of this newer antidepressant in bipolar depression is required.

Despite these suggestions that differentiating patients within the broad class of major depression is a valid pursuit and despite the availability of a diverse pharmacopoeia, the possibility of matching patient symptom profile with antidepressant mechanism to achieve more rapid response or greater efficacy remains elusive. The effort may yet prove useful as we continue to refine our use of diagnostic criteria, delineate subtypes, and test hypotheses involving treatment matching. Nonetheless, at this point, as comprehensively reviewed by Stephen M. Stahl, M.D., Ph.D., the best matching we can do with our therapeutic agents and our patients is to compare the mechanisms of action of the medication with the desired adverse event profile. That we have drugs with divergent mechanisms of action does encourage us to consider the possibility that initial nonresponders to one class of agents may benefit from an alternate route, but our priority goal of matching treatment with patients is not yet at hand. Stahl holds out the possibility that agents with multiple mechanisms of action may offer efficacy advantages, although more data to test this hypothesis are required.

Drug names: fluoxetine (Prozac), imipramine (Tofranil and others), mirtazapine (Remeron), phenelzine (Nardil).

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