Introduction

The Dual-Action Debate: Does Pharmacology Matter?

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Major depressive disorder (MDD) is a common, often chronic, and not infrequently disabling condition. Remission has been established as the goal of short-term treatment of depression[1,2] and has become the standard by which treatment efficacy is evaluated. Moreover, achieving remission early in the course of illness can lead to improved long-term outcomes.[3,4] Pharmacotherapy, psychotherapy, and a combination of these approaches have been shown to be effective in the ambulatory management of MDD. Although antidepressant pharmacotherapy is the mainstay of treatment for patients with moderate-to-severe MDD, a significant number of patients who receive adequate treatment in clinical trials do not achieve remission. Thus, even modest, but statistically significant, differences in the likelihood of antidepressants to result in remission in clinical trials could translate into improved outcomes for patients that are seen in practice.

The past quarter century has given rise to newer drug classes, including the selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). These medications offer several therapeutic advantages relative to "first-generation" antidepressants (i.e., the tricyclic antidepressants [TCAs] and monoamine oxidase inhibitors [MAOIs]), particularly in terms of ease of use, improved overall tolerability, and substantially greater safety in overdose. The availability of such safer, better-tolerated agents has facilitated treatment of depression in primary care.

The question of whether there are differences in efficacy among newer antidepressants remains controversial. Although it is widely understood that both serotonin and norepinephrine are involved in mediating symptoms of depression, there is considerable disagreement as to whether differences in antidepressant pharmacology are associated with differences in treatment outcomes. There is some evidence to suggest that dual-acting agents may be more effective than SSRIs, although these differences in efficacy are often difficult to detect in clinical trials. Meta-analyses using all available studies do, however, suggest potential efficacy advantages, including a greater likelihood of remission, [5,6] efficacy in treating a broad range of psychic and somatic symptoms, [7–10] and a potentially more rapid onset of action,[11,12] for SNRIs relative to some SSRIs. It is unclear if these potential advantages apply universally to all antidepressants in these classes. Further, it is not known if differences observed during acute-phase treatment persist into a continuation phase of therapy. Finally, these potential advantages might be limited to certain subpopulations of depressed patients. This supplement reviews the currently available evidence of the relationship between antidepressant pharmacology and clinical efficacy.

We begin with a discussion of antidepressant pharmacology by Richard C. Shelton, M.D. A brief review of the history of antidepressant development, from early dual-acting agents (i.e., MAOIs, TCAs) to the SSRIs, to the second generation of dual-acting agents (e.g., SNRIs, mirtazapine), is provided. The rationale for potential differences between antidepressant classes is examined, highlighting findings from neurobiological research supporting the involvement of serotonin and norepinephrine in the pathophysiology and treatment of depression.

Despite this evidence demonstrating the importance of both serotonin and norepinephrine in depression, debate remains as to whether there is a correlation between antidepressant effects on both neurotransmitters and improved clinical outcomes. Drs. Zajecka and Albano continue the discussion with an assessment of the clinical benefits of SNRIs in the acute treatment of MDD. The discussion includes a review of evidence from clinical trials demonstrating the efficacy of SNRIs in treating depression. Findings that suggest clinical advantages of dual-acting agents over more selective antidepressants are considered, and potential factors contributing to these apparent advantages are proposed.

The overlap of depression and anxiety underscores the importance of identifying differences between antidepressants in their efficacy in treating anxiety disorders. Peter H. Silverstone, M.D., examines the role of norepinephrine and noradrenergic antidepressants in the treat-

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ment of symptoms of anxiety and anxiety disorders. Evidence from randomized controlled trials of SNRIs and other antidepressants with noradrenergic activity (e.g., desipramine, reboxetine) in the treatment of various anxiety disorders and of depression with concomitant anxiety is summarized. Finally, potential advantages of these agents over other anxiety treatments are evaluated.

Many depressed patients will require long-term treatment with antidepressants to maintain remission. The discussion concludes with a review of the use of antidepressants in the long-term treatment of depression. Charles Shelton, D.O., describes the factors that contribute to an increased risk for relapse or recurrence, and therefore the need for long-term treatment, in some patients. Clinical trials of the efficacy of SNRIs during long-term treatment, including studies of relapse and recurrence prevention, are reviewed. This article also discusses antidepressant tolerability issues, which are frequently the reason cited by patients for treatment discontinuation, and therefore are an important consideration with long-term treatment.

It is clear that additional clinical trials are necessary to more accurately clarify the extent of the differences in treatment outcomes between antidepressant classes and to determine whether differences in efficacy observed during short-term treatment ultimately result in improved long-term outcomes. Perhaps more importantly, further examination and elucidation of the mechanisms involved in the pathophysiology of depression and anxiety will provide a clearer understanding of the clinical outcomes that can be expected with various antidepressants based on their pharmacology and mechanisms of action.

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