

## Introduction

# Spectrum of Depression: New Treatment Approaches

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© Since the introduction of the selective serotonin reuptake inhibitors (SSRIs) in the 1980s, we have lived in a “serotonin age” with respect to the treatment of depression and anxiety disorders. So successful have the SSRIs been that we even believe that abnormalities in serotonin neurotransmission must be central to the etiopathophysiology of these conditions.

In support, there is now robust evidence for abnormalities in the serotonin system in patients with depression. Still, clinicians remember well that there was a time when we treated depression and anxiety disorders with a great deal of success with relatively selective norepinephrine reuptake inhibitors (NRIs), like desipramine and nortriptyline. The problem with those treatments rested not with lack of efficacy but rather with serious anticholinergic side effects.

More recently, medications that have potent effects on noradrenergic neurotransmission have proved to be highly effective antidepressants. This has once again focused our attention on the role of the noradrenergic system in mood and anxiety disorders. In a recent symposium at the annual meeting of the American Psychiatric Association, speakers examined the evidence for the involvement of norepinephrine in depression. The following articles reflect those presentations.

My colleague Gregory Sullivan, M.D., and I first note that preclinical neuroscience has clearly shown us that neurotransmitter systems are highly interrelated in the central nervous system. It is fair to say that all NRIs ultimately affect the serotonin system and that all SSRIs affect the noradrenergic system. Calling a drug a specific reuptake blocker for one neurotransmitter only tells us its first activity. Beyond that, influencing one system inevitably influences others.

Pedro L. Delgado, M.D., and Francisco A. Moreno, M.D., develop this theme further by reviewing data based largely on depletion studies. These studies show us that NRIs appear to be dependent on available concentrations of norepinephrine to work, while SSRIs need serotonin. Mixed effect drugs—like mirtazapine and venlafaxine—may need both. But depleting a healthy volunteer of either transmitter does not cause depression, suggesting that mere deficiency of one chemical neurotransmitter or another cannot be the proximate cause of depression.

Is knowledge about the effects of antidepressants on specific neurotransmitter systems useful in treating patients with severe depression or patients who do not respond to conventional therapy? These issues are addressed by Michael E. Thase, M.D., and Maurizio Fava, M.D., respectively. While most antidepressants are effective for the majority of patients, severely ill patients and those who do not respond to the first course of treatment raise particular challenges. Having a wide

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range of medication and psychotherapy options available has made the treatment of these patients somewhat less daunting. In both cases, drugs that affect norepinephrine, either in combination with effects on serotonin or exclusively, as is the case with the new agent reboxetine, may offer particular advantages for the treatment of some patients.

Although it may not seem obvious at first glance, perhaps the most provocative article in this issue is provided by my Columbia colleague, Myrna M. Weissman, Ph.D. Since the beginning of chemotherapy for depression, we have used symptom rating scales to evaluate the efficacy of antidepressants. Now, however, we increasingly realize that a decrement in score on the Hamilton Rating Scale for Depression brought about by an antidepressant, while clearly desirable, is not sufficient. Many patients who are judged responders after an acute trial of an antidepressant nevertheless remain substantially depressed and are still not in remission. What is needed are not only better antidepressants but also rating scales that capture more than just changes in vegetative symptoms. Weissman discusses the use of measures that assess social functioning and illustrates the point with a recent clinical trial involving reboxetine. In this effort, she is clearly challenging psychiatrists to hold themselves to a very high standard: the use of the full range of available antidepressant therapies to help patients not only get better but actually get well.

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