The Role of Norepinephrine in the Treatment of Depression

This ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *presents highlights of 2 symposia held at the 152nd annual meeting of the American Psychiatric Association, Washington, D.C., May 15–20, 1999, and supported by an unrestricted educational grant from Pharmacia & Upjohn Company, Bridgewater, N.J.*

The first symposium, "Spectrum of Depression: New Treatment Approaches," was chaired by Jack M. Gorman, M.D., Professor and Vice Chairman, Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, N.Y. The second symposium, "Norepinephrine: Neurotransmitter for the Millennium," was chaired by Charles B. Nemeroff, M.D., Ph.D., Reunette W. Harris Professor and Chairman, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Ga., and co-chaired by Dennis S. Charney, M.D., Professor and Deputy Chairman, Academic and Scientific Affairs, Department of Psychiatry, Yale University School of Medicine, New Haven, Conn.

Participants in the symposia are listed at the end of this section.

Current Challenges in the Management of Depression

Despite recent strides in treatment, depression remains a common, costly, and often deadly disease, Dr. Charles B. Nemeroff stated. More than 1.2 million persons are diagnosed with an affective disorder in the United States each year, an incidence of approximately 5% to 10%,[1,2] and depression is more prevalent than arthritis, diabetes, or heart disease.[3] Depression is also a costly disease: in 1990 it was estimated that in the United States alone the cost of depression approached $44 billion, including direct costs for medication, physician services, etc., as well as indirect costs such as increased morbidity, excessive absenteeism, and reduced productivity.[4] Depression also has a high mortality: up to 15% of severely depressed patients will ultimately commit suicide.[5]

Despite its prevalence, depression is often not recognized, Dr. Nemeroff pointed out. It is estimated that only about one third of those with affective disorders are in treatment.[5] Depression may be particularly likely to be underdiagnosed in the primary care setting and among the elderly.[6] When it is recognized, depression is often incorrectly treated with inappropriate medications or combinations of medications, insufficient dosages, and insufficient treatment duration.[6]

Even among patients who are appropriately treated for their depression, a third or more will not achieve or maintain a response.[7] Indeed, a meta-analysis of 36 clinical trials of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) in a double-blind comparison showed a similar response rate between the TCAs and SSRIs, 48.6% and 48.0%, respectively.[8] However, significantly more TCA-treated than SSRI-treated subjects dropped out due to either lack of efficacy or adverse reactions (30.0% vs. 24.7%, $p = .01$). Furthermore, as many as 30% to 50% of treated patients will suffer a relapse or recurrence during the 4 to 6 months following the cessation of antidepressant therapy.[9] In addition, 75% to 80% of patients will experience recurrent depression during their lifetime.[9] These statistics indicate that the management of depression remains a challenge for psychiatry, Dr. Nemeroff concluded.

Much of the challenge of depression management stems from the shortcomings of currently available antidepressants. Seventy-five percent of patients are not experiencing an optimal response with the current pharmacopoeia, according to Dr. Nemeroff. Although the availability of a wide variety of new antidepressants has clearly improved the treatment of major depression, there is unquestionably room for further advancements relative to tolerability. Patients still have significant trouble staying in antidepressant trials—as many as 20% drop out—because they cannot tolerate or do not want to be taking medications.[10] With the TCAs, fewer than 50% of patients are compliant. Although the compliance rate is considerably better with the SSRIs, it is a long way from 100%. According to Dr. Nemeroff, the goal of therapy should be to achieve total wellness, not just to convert severe depression to mild-to-moderate depression.

Dr. Nemeroff summarized some of the key issues about the current antidepressant therapies.

The "first-generation" therapeutic agents for depression—the TCAs and the monoamine oxidase inhibitors (MAOIs)—while producing clinically significant improvement in 65% to 75% of patients, have major drawbacks that limit their use.[11] Of particular importance are the side effects of these drugs. The TCAs are associated with cardiovascular effects such as orthostatic hypotension, tachycardia, worsening of conduction defects, negative inotropic effects, hypertension, electrocardiographic changes, and even

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congestive heart failure, as well as anticholinergic effects including dry mouth, urinary retention, blurred vision, constipation, and increased intraocular pressure. The TCAs may lower the seizure threshold; they also present a significant risk for suicide by overdose.[12] TCAs are the number one cause of suicide by overdose in the United States[13] and are especially lethal in children.[12] With the MAOIs, side effects such as orthostatic hypotension, palpitations, dizziness, insomnia, sexual dysfunction, tachycardia, constipation, agitation, and edema are common. In addition, dietary restrictions and concerns about drug-drug interactions and hypertensive crisis complicate administration of the MAOIs, Dr. Nemeroff noted.

The SSRIs, the dual serotonin/norepinephrine (5-HT/NE) inhibitors (venlafaxine), and the selective receptor antagonists (nefazodone and mirtazapine) all represent distinct advances over the TCAs and the MAOIs. These clear advantages include a greatly improved therapeutic index and side effect profile. The efficacy of these newer agents is generally considered equal to that of the TCAs, though there is some controversy on this matter. However, although the new antidepressants represent a clear improvement over the first-generation agents in side effect profile, they are not free of adverse effects, Dr. Nemeroff pointed out. The primary adverse effects seen with the SSRIs are decreased appetite, insomnia, nervousness and anxiety, and gastrointestinal symptoms (nausea, diarrhea).[12] Headache, sexual dysfunction, and somnolence have also been reported. Some of the agents may cause weight gain, dry mouth, sweating, or asthenia or may produce a discontinuation syndrome when treatment is abruptly terminated.

The atypical antidepressants are also associated with unwanted effects. Side effects of trazodone include orthostatic hypotension, sedation, dizziness, confusion, and priapism. Bupropion may cause anxiety, agitation, headache, dry mouth, gastrointestinal disturbances, tremor, insomnia, and, at high doses, seizures. Mirtazapine is associated with somnolence, dry mouth, and an increased appetite, which may lead to weight gain. Adverse effects of nefazodone include dry mouth, somnolence, nausea, and dizziness. Venlafaxine may produce the same side effects as nefazodone, plus insomnia, sexual dysfunction, and headache.

The hope for improvement in antidepressant pharmacotherapy lies in 2 major areas: improved efficacy and a better side effect profile, according to Dr. Nemeroff. In terms of efficacy, many patients treated with monotherapy exhibit only a partial response to any of the drugs in the classes of antidepressants listed above; moreover, approximately 20% to 40% of patients are treatment resistant or do not respond at all, depending on the definition of response.[7] In terms of tolerability, side effects of treatment remain the major cause of noncompliance. In addition to better efficacy and tolerability, a rapid onset of action remains a major goal of new antidepressant drug development.

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Differences in side effect profiles are only one of many reasons for our need for so many antidepressants. Depression is a broadly defined disorder with many different presentations. Symptoms range from being so mild that they barely fulfill DSM-IV criteria to those that are associated with severe melancholia and psychotic depression. Some patients will show tremendous irritability and anger; others, in contrast, show severe anergia and fatigue. Whether a given complex of symptoms is in fact a predictor of response to one or another antidepressant remains a topic of investigation, but what is clear is that patients who do not respond to an antidepressant from one class of medications may respond to an antidepressant from another.[14] Also under investigation is the growing recognition that there may be subtypes of depression for which certain medications may be more or less appropriate.[15] The availability of a wide range of medications with varying properties is also important for addressing the special needs of the significant numbers of patients with psychiatric and medical comorbidity.

The Role of Norepinephrine in Depression

Overcoming the current limitations of antidepressant therapy may require a better understanding of the role of the various monoamine neurotransmitters in depression, according to Dr. Jack M. Gorman. Abundant evidence exists that abnormalities of the serotonergic system are involved in many forms of depression. In recent years, the prominent role of the SSRIs in the treatment of depression has further substantiated this evidence. However, as discussed by Dr. Gorman, it is unlikely that any single neurotransmitter could explain the entire psychopathology associated with psychiatric illnesses as we currently understand them, and it is becoming increasingly clear that there are close functional relationships between the noradrenergic, dopaminergic, and serotonergic systems. Although the serotonergic system appears to play an important role in mood and the noradrenergic systems appears to affect drive and motivation, the effects overlap and are not mutually exclusive.

Because some antidepressant medications have multiple sites of action, Dr. Gorman suggested that an understanding of the functional and anatomical properties of the serotonergic and noradrenergic systems might provide additional insights into the broad-spectrum efficacy of many of the antidepressants. Serotonergic neurons originate in the brainstem raphe nuclei and send widespread projections throughout the brain. Projections to the prefrontal cortex may mediate mood, those to the hypothalamus may affect appetite and sleep, and projections to the amygdala may affect anxiety and fear. Serotonin also plays a role in aggression, sexual behavior, and pain. Noradrenergic neurons originate in the pontine nucleus locus ceruleus and also send widespread projections throughout the brain, including to the hypothalamus, hippocampus, amygdala, and frontal cortex. In addition to their overlapping distributions, the 2 transmitter systems are likely to have functional interactions, similar to the interactions between the serotonergic and dopaminergic systems.[16] Noradrenergic tracts innervate most of the major brain regions involved in psychiatric and neurologic disease. That the serotonergic and noradrenergic neurotransmission systems are functionally interactive has been demonstrated in a number of preclinical and clinical studies.[16–19] Therefore, current models of psychiatric illness suggest that the 3 systems have partially overlapping and interacting functions (Figure 1).

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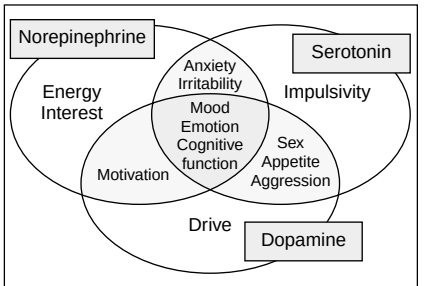
The evidence strongly suggests a role for norepinephrine in the pathophysiology and treatment of depression, according to Dr. Dennis S. Charney. Some of this evidence comes from the behavioral effects of reducing norepinephrine levels in patients with depression; other evidence has been developed in animal models.

Drs. Charney and Delgado have provided intriguing evidence that the serotonin and norepinephrine systems have unique pathways in the treatment of depression. They have performed experiments that involve depletion of serotonin or norepinephrine in patients who have responded to different antidepressant drugs.[21] In patients whose depression had been successfully treated with a norepinephrine reuptake inhibitor (NRI) (desipramine or mazindol), depleting norepinephrine and dopamine levels with an inhibitor of tyrosine hydroxylase (alpha-methylparatyrosine; AMPT) caused depressive symptoms to transiently return. In contrast, in patients whose depression had been treated successfully with an SSRI, AMPT did not cause a return of depressive symptoms.[22,23] These results support the hypothesis that therapeutic effects in depression may involve either noradrenergic or serotonergic pathways.[24]

The converse experiment revealed similar results.[21] Patients whose depression had been successfully treated with an SSRI had their serotonin levels depleted by administration of a tryptophan-free mixture of amino acids. Such treatment has been shown to reduce plasma tryptophan (the required precursor of serotonin) by 80% within 5 hours. In these patients, such depletion caused a return of depressive symptoms. In contrast, patients whose depression had been treated with desipramine showed a much weaker effect as a result of serotonin depletion.

Experiments with depletion of norepinephrine and serotonin suggest that depression could be induced in normal persons by depletion of these transmitters. However, the investigators found that this was not the case.[21] In contrast to patients who were receiving antidepressant therapy, normal subjects did not experience depression when their levels of serotonin or norepinephrine

Figure 1. Aspects of Functioning Attributed to Norepinephrine, Serotonin, and Dopamine[a]



[a]Modified from Healy and McMonagle.[20]

were depleted. This finding has led Dr. Delgado to propose a thought-provoking explanation. He suggests that perhaps depression is not caused by insufficient serotonin or norepinephrine, but that it is merely treatable by increasing the levels of these compounds.

Taken together, the studies with AMPT and tryptophan depletion suggest that norepinephrine and serotonin form independent pathways through which antidepressant drugs may mediate their therapeutic effects. What is becoming increasingly clear is that serotonin is not the only neurotransmitter involved in the pathophysiology of depression and that norepinephrine plays an important role.

Dr. Marc G. Caron described experiments in which he and colleagues disrupted expression of the norepinephrine transporter in mice in an attempt to mimic the effects of a selective NRI.[25] The researchers successfully generated mice in which the norepinephrine transporter (NET) was not expressed (NET-knockout mice). The NET-knockout mice were shown to have altered biochemical and psychological characteristics consistent with the expected effects of NRIs. For example, tissue concentrations of norepinephrine, which are believed to largely reflect transmitter stored in the presynaptic vesicle pool, were reduced in such mice. This result is consistent with an important role for the NET in clearing this neurotransmitter from the extracellular space and in maintaining releasable pools of transmitter. NET-knockout mice were also studied in behavioral models of depression. Overall, the behavior of NET-knockout mice was similar to the behavior of wild-type mice treated with antidepressants. Interestingly, the researchers also found changes in the dopamine system of the NET-knockout mice—changes that may have important behavioral implications. This finding also supports the concept that the neurotransmitter systems interact.

Alternatives to SSRIs in the Treatment of Depression

With the introduction of the SSRIs, norepinephrine has become the "forgotten" monoamine with regard to the mechanism of action of antidepressants, said Dr. Alan Frazer. However, agents that selectively and acutely alter norepinephrine function—desipramine, for example—are effective antidepressants. It is not clear whether these drugs maintain their selectivity for norepinephrine systems on repeated administration or, in addition, affect serotonergic function. However, repeated administration of NRIs to rats does not affect certain serotonergic parameters, (e.g., 5-HT_{1A} receptor sensitivity). Also, the clinical efficacy of NRIs does not seem to be dependent on the presence of 5-HT. By contrast, new in vivo voltametric data have demonstrated that NRIs alter the clearance of serotonin in certain brain areas. Also, administering desipramine to patients with depression causes a reduction over time in the affinity of the 5-HT transporter for serotonin and ultimately the concentration of serotonin in their platelets.[26]

Dr. Gorman stated that it is naive to believe that SSRIs or any other psychoactive medications could possibly have effects limited to only one neurotransmitter system. Interconnections among neurotransmitter circuits make it inevitable that influencing one neurotransmitter, such as 5-HT, will lead to changes in other neurotransmitters, such as norepinephrine. Most recently, for example, an agent that is highly selective for norepinephrine reuptake inhibition—reboxetine—has also been shown to be clinically efficacious for a broad range of depressive symptoms.

Dr. Charney pointed to emerging evidence, based on changes in norepinephrine and 5-HT metabolism in the central nervous system, that the primary disturbance in some depressed patients may be in serotonin function, while in others the primary disturbance may be in catecholamine function.[24] Patients in the former subtype may therefore respond better to an SSRI; those in the latter, to an NRI. Depressive symptoms for which a role for norepinephrine has been implicated include diminished pleasures in nearly all activities, significant weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, and diminished ability to think or concentrate. The development of a new, selective norepinephrine reuptake inhibitor without the side effects of the relatively norepinephrine-selective TCAs would be a major addition to our armamentarium of drugs to treat depression, he concluded.

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Clinical Efficacy of Reboxetine in Major Depression

To demonstrate the clinical effects of a selective norepinephrine reuptake inhibitor, Dr. Alan F. Schatzberg summarized the results of clinical studies of reboxetine, a new selective NRI that was recently introduced in Europe. This medication has only a minimal affinity for muscarinic acetylcholine receptors and thus causes less dry mouth, constipation, urinary retention,

Table 1. Percentage of Patients Reporting Treatment-Emergent CNS Symptoms in the Short-Term, Controlled, Reboxetine Trials[a]

Adverse Event	Reboxetine (N = 785)	Placebo (N = 402)
Agitation	22 (2.8%)	13 (3.2%)
Anxiety	13 (1.7%)	12 (3.0%)
Nervousness	8 (1.0%)	6 (1.5%)
Somnolence	24 (3.1%)	29 (7.2%)

[a]Data on file, Pharmacia & Upjohn Company.

and other such effects than do the TCAs. Reboxetine does not block serotonin reuptake or α_1-adrenergic receptors and therefore does not appear to produce significant nausea, diarrhea, or hypotension.[27] Unlike certain other antidepressants, reboxetine appears to be nonsedating.[28]

The efficacy and tolerability of reboxetine have been studied in 10 placebo-controlled and/or active treatment–controlled studies, as well as 4 open studies in patients with major depressive disorder (MDD) and dysthymia,[27] Dr. Schatzberg noted. Reboxetine was well tolerated in these studies, in which patients were followed for 4 weeks to 12 months. The most common side effects in the clinical trials were dry mouth, constipation, insomnia, and increased sweating. Adverse events were mainly mild to moderate, and no clinically significant changes in vital signs or laboratory parameters were noted.[27] Reboxetine has a negligible effect on psychomotor and cognitive function (as measured by Critical Flicker Fusion threshold, Choice Reaction Time, and tests of tracking ability and short-term memory).[29] Both in vivo and in vitro studies have demonstrated a lack of inhibition of most cytochrome P450 enzymes. As a result, there appears to be minimal risk of drug-drug interactions (data on file, Pharmacia & Upjohn Company). Of importance, in more than 25,000 patient exposures through October 1998, no fatal overdoses attributed to reboxetine were reported (data on file, Pharmacia & Upjohn Company).

While some existing therapies may lead to symptoms of anxiety or agitation in patients with depression, Dr. Schatzberg noted that patients in the short-term, controlled, reboxetine trials reported low levels of agitation, anxiety, or nervousness with reboxetine, often no greater than with placebo (Table 1). Similarly, with reboxetine, the level of treatment-emergent somnolence was less than with placebo.

— . . . reboxetine as the first selective norepinephrine reuptake inhibitor may have the same impact on the treatment of depression as the SSRIs. —

The efficacy of reboxetine was compared with placebo in a randomized, double-blind, multicenter trial in patients with MDD,[27] Dr. Schatzberg explained. After a placebo washout period of 7 days, patients were randomly assigned to reboxetine or placebo treatment and followed for 6 weeks. Clinical improvement, defined as a $\geq 50\%$ decrease in total Hamilton Rating Scale for Depression (HAM-D) score from baseline to last assessment, occurred in 74.1% of the reboxetine-treated patients, compared with 20% of the placebo group ($p < .001$). Efficacy of reboxetine was also evidenced by significantly greater improvement on the Severity of Illness item of the Clinical Global Impressions (CGI-S) scale. This effect was evident by day 14.

Reboxetine has been found to be effective not only in the acute phase but also in long-term treatment of depression, as shown in a 1-year, randomized, double-blind, placebo-controlled multicenter study in 358 patients with MDD,[30,31] Dr. Schatzberg pointed out. After an open, 6-week, run-in phase, patients who responded to reboxetine (as shown by a $\geq 50\%$ decrease in total HAM-D score) were then randomly assigned to reboxetine or placebo treatment. Reboxetine produced a significantly greater rate of remission, defined as total HAM-D score ≤ 10. More than 78% of the reboxetine patients were in remission at their last assessment, compared with 45% of the placebo group ($p < .001$). In the placebo group, 56% of the patients relapsed, whereas only 22% of the patients in the reboxetine group met the criteria for relapse. Reboxetine was also well tolerated over the 1-year study period.[31,32] In addition, 2 open studies showed that response to reboxetine was maintained over a 12-month period.[27]

Dr. Schatzberg also summarized studies comparing reboxetine with an active control. Reboxetine was compared with desipramine and placebo in 258 patients with MDD.[33] Most (> 80%) of the patients in this study, Dr. Schatzberg noted, were suffering recurrent episodes of depression. At 4 weeks, 60% of the reboxetine patients, compared with 48% of the desipramine patients and 35% of those receiving placebo, had achieved a $\geq 50\%$ reduction in the 17-item HAM-D score ($p < .05$, reboxetine vs. placebo). In addition, 51% of the reboxetine group had achieved a $\geq 50\%$ reduction in the CGI-S score, compared with 33% and 23% for the desipramine and placebo groups, respectively ($p < .05$, reboxetine vs. desipramine and reboxetine vs. placebo) (Figure 2).

A randomized, double-blind, multicenter study also compared the efficacy and tolerability of reboxetine and imipramine in 256 patients with MDD.[34] The 2 agents were similar in efficacy as measured by improvement on the HAM-D scale, the Montgomery-Asberg Depression Rating Scale (MADRS), and the CGI

scale. However, the cumulative risk of dry mouth, hypotension, or tremor was significantly lower with reboxetine than with imipramine ($p < .05$).

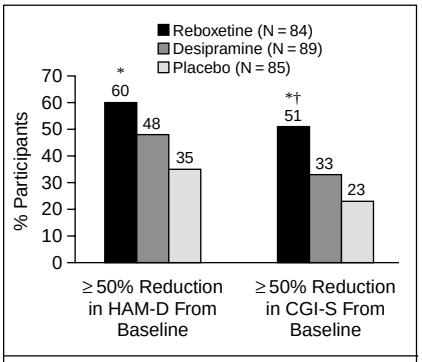
Two additional studies compared the efficacy and safety of reboxetine and fluoxetine in a total of 549 patients with MDD.[35,36] Patients were randomly assigned to receive one of these agents or, in one of the studies, placebo, for 8 weeks. In these studies, the percentage of patients who responded to treatment (as indicated by a ≥ 50% reduction in baseline total HAM-D score) was similar for the reboxetine and fluoxetine groups. Both active agents were significantly more effective than placebo. In addition, the frequency of newly reported adverse events was comparable for the 2 active treatment groups, and most of the reported adverse events were mild to moderate.[35,36]

To summarize the effects of reboxetine in treating depression, these studies indicate that reboxetine is significantly more effective than placebo and as effective as fluoxetine, imipramine, and desipramine in reducing depressive symptoms. Further, data from controlled clinical trials have shown that the side effect profile of reboxetine is relatively benign.

In addition to depression, reboxetine may play a role in the treatment of panic attacks. Dr. Schatzberg presented results from a multicenter, placebo-controlled study of 82 patients with panic and phobic symptoms. By week 5, there were significant reductions in the number of panic attacks and phobic symptoms in the reboxetine-treated patients compared with the placebo group ($p < .05$).[37] These are promising results that warrant more extensive study.

Reboxetine may have an influence beyond the treatment of individual patients; it may also improve our understanding of depression, according to Dr. Charney. Thus, reboxetine as the first selective NRI may have the same impact on the treatment of depression as the SSRIs.[24] Of particular interest are the effects of reboxetine on the social functioning of patients with depression, as well as its use in those with severe or refractory depression.

Figure 2. Response Rates With Respect to Reductions in Hamilton Rating Scale for Depression (HAM-D) and Clinical Global Impressions-Severity of Illness (CGI-S) Scores in a Double-Blind Study of Reboxetine, Desipramine, and Placebo[a]



[a]Data from Ban et al.[33]
*Significant difference ($p < .05$) from placebo.
†Significant difference ($p < .05$) from desipramine.

Assessment of Social Functioning of Patients With Depression

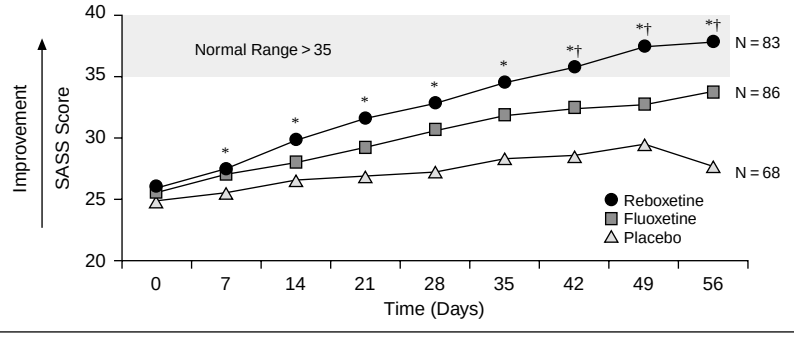
Dr. Myrna M. Weissman stated that there is increasing interest in assessments that capture a spectrum of outcomes beyond the typical clinical symptoms of depression. Traditional depression scales assess mainly the core biological features of the illness—mood, pessimism, and vegetative signs (e.g., appetite and sleep loss). However, assessments of drive, motivation, performance, and quality of interpersonal relations (e.g., the social context once the symptoms are improved) may not be captured in traditional symptom scales. More importantly, some depressed patients have social impairments that remain after overt depression symptoms resolve.

— Both noradrenergic and serotonergic antidepressant therapy affect social motivation and behavior. Noradrenergic therapy such as reboxetine may be more effective in improving negative self-perception and lack of motivation toward action. —

To assess social functioning, several scales have been developed, and 3 in particular have been used in clinical trials with depressed patients. These include the Social Adjustment Scale-Self Report (SAS-SR),[38] which assesses performance in roles (work, family, etc.); the Social Adaptation Self-Evaluation Scale (SASS),[39] which assesses self-perception, motivation, and behavior; and the Short Form Health Survey (SF-36),[40] which assesses activities of daily living (symptoms and physical and social functioning). To evaluate the effect of noradrenergic versus serotonergic therapy for depression on social functioning, reboxetine, fluoxetine, and placebo were compared using the SASS instrument in 302 depressed patients in a multicenter, randomized, double-blind trial conducted in Europe.[41]

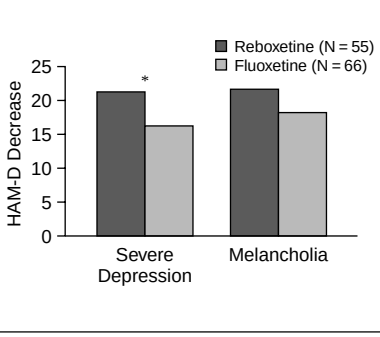
Mean SASS score improved over the course of the study for both the reboxetine and the fluoxetine patients (Figure 3).[41] There were also significant differences in negative self-perception and active social behavior as measured by the SASS between the patients receiving the NRI reboxetine compared with the SSRI fluoxetine favoring reboxetine. These differences

Figure 3. Effect of Reboxetine, Fluoxetine, and Placebo on Social Functioning of Depressed Patients as Measured by the Social Adaptation Self-Evaluation Scale (SASS)[a]



[a]Modified with permission from Dubini et al.[41] A total score > 35 is considered normal.
*p < .05 vs. placebo.
†p < .05 vs. fluoxetine.

Figure 4. A Comparison of Reboxetine and Fluoxetine in Patients With Severe Depression and Melancholia[a]



[a]Data on file, Pharmacia & Upjohn Company.
*Difference in HAM-D improvement statistically significant (p < .05).

were seen despite similar responses to the 2 antidepressants as indicated by HAM-D and MADRS scores.

Thus, both noradrenergic and serotonergic antidepressant therapy affect social motivation and behavior; however, noradrenergic therapy such as reboxetine may be more effective in improving negative self-perception and lack of motivation toward action. Much needs to be learned about these measures and further U.S. studies are needed to confirm these preliminary European findings. These findings may be important in improving outcomes for individual depressed patients; they also have implications with regard to pharmacoeconomic evaluation of old and new antidepressants, Dr. Weissman noted. Typically, new antidepressants are more expensive than older agents, particularly drugs like the TCAs. The current preoccupation with controlling health care expenditures has made it imperative that we justify the use of the new agents by gathering cost-effectiveness evidence that goes beyond a simple listing of the drug's side effect or safety profile. Health care payers want to know if these drugs improve compliance, result in fewer lost days at work, improve work performance, or provide other evidence for a reduced economic and social burden. Clearly, the assessment of social functioning can be important in determining the depressed patient's outcome on treatment, and instruments such as the SAS-SR, SASS, and SF-36 may be able to demonstrate significant improvements in quality of life and economic well-being associated with the newer agents.

New Approaches to Severe and Refractory Depression

The availability of an NRI with a benign side effect profile, such as reboxetine, may also be a benefit in the treatment of severe and/or refractory depression. Clinicians report that approximately 25% to 33% of patients with depression are classifiable as severely depressed, according to Dr. Michael E. Thase. Depression severity, however, is not a unitary construct, and clinical impressions are influenced by a number of factors other than symptoms. Such factors include psychiatric and medical comorbidity, personality pathology, suicidality, and inpatient status. Melancholia and psychotic depressions, the most classical forms of severe depression, are distinguished by a characteristic neurovegetative profile, a low rate of response to supportive/nonspecific interventions, and a greater "burden" of neurobiological dysfunction.[42] These distinguishing features may be the result of progressively greater disturbances of both serotonin and norepinephrine neurotransmission, said Dr. Thase.

Clinical findings with reboxetine as monotherapy indicate that this agent is efficacious in both moderately and severely depressed patients. Subset analysis of patients who were markedly to severely depressed, as assessed by the CGI-S scale, showed that reboxetine was significantly more effective than placebo ($p < .05$) (Figure 4) (data on file, Pharmacia & Upjohn Company). In addition, cumulative analysis of the 2 studies comparing reboxetine and fluoxetine showed that reboxetine was significantly more effective than fluoxetine in patients with marked-to-severe depression ($p < .05$).[35,36]

In patients with refractory depression—that is, depression that does not respond to antidepressant monotherapy—a number of new pharmacothera-

peutic approaches are currently being used, according to Dr. Maurizio Fava. In addition to the more traditional lithium and thyroid hormone augmentation strategies, the addition of or switch to another antidepressant may be beneficial. Augmentation and switching strategies are often selected to obtain a different neurochemical effect (e.g., adding a relatively noradrenergic agent to a relatively serotonergic antidepressant). Several studies have suggested that patients with depression that is refractory to treatment with SSRIs may show a good response to newer agents that have a pharmacologic profile distinct from that of the SSRIs.[15,36] Furthermore, preliminary studies have shown that the addition to SSRIs of a noradrenergic TCA such as desipramine or a dopaminergic agent may be efficacious, even though concerns about drug-drug interactions and tricyclic cardiac toxicity have limited the use of the TCA-SSRI combinations.[43] The introduction of reboxetine may increase the use of a combination of an SSRI and a noradrenergic agent because of its better safety profile compared with the TCAs, said Dr. Fava.

Conclusions

In the past 10 years, antidepressant therapy has been dominated by drugs that target the serotonergic neurotransmission system. These antidepressants have revolutionized psychiatry and psychopharmacology and enabled psychiatrists to successfully treat many patients who formerly could not be treated. However, while outcomes have improved in patients with depressive disorders, symptom remission is too often not fully achieved or side effects interfere with successful therapy. Recent studies of the pathophysiology and treatment of depression at both the neuroscience and clinical levels have documented that there is a close functional relationship between the noradrenergic, dopaminergic, and serotonergic systems and reason to look beyond the SSRIs. In particular, there is abundant evidence suggesting a role for norepinephrine in the pathophysiology and treatment of depression. In this regard, it is noteworthy that recent clinical trials comparing reboxetine, a new selective NRI, with imipramine, desipramine, and fluoxetine have shown comparable or improved efficacy and comparable or better tolerability favoring reboxetine. Its positive effects on social functioning and improvements in core depressive symptoms, especially anergia and anhedonia, without the introduction of anxiety, bode well for reboxetine becoming an important addition to the U.S. pharmacopoeia. Reboxetine is likely to have a role as monotherapy for moderately to severely depressed patients or as combination therapy with agents with different mechanisms of action for refractory depression. Studies with this highly selective norepinephrine reuptake inhibitor also provide an opportunity to increase our understanding of the role of norepinephrine in the treatment of a broad spectrum of depression-related illnesses.

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SYMPOSIA AND PRESENTERS

These highlights are derived from 2 symposia held at the 152nd annual meeting of the American Psychiatric Association, Washington, D.C., May 15–20, 1999, and funded by Pharmacia & Upjohn Company, Bridgewater, N.J. The first symposium, "Spectrum of Depression: New Treatment Approaches," was chaired by Jack M. Gorman, M.D., Professor and Vice Chairman, Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, N.Y. The participants were Pedro L. Delgado, M.D., Professor of Psychiatry, University of Arizona College of Medicine, and Associate Head and Director of Research, Department of Psychiatry, University Medical Center, Tucson; Maurizio Fava, M.D., Associate Professor of Psychiatry, Harvard Medical School, and Director, Depression Clinical and Research Program, Massachusetts General Hospital, Boston; Michael E. Thase, M.D., Professor of Psychiatry, Chief of Adult Academic Psychiatry, University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, Pittsburgh, Pa.; and Myrna M. Weissman, Ph.D., Professor, Epidemiology in Psychiatry, and Chief, Clinical, Genetic Epidemiology, Department of Psychiatry and Epidemiology, Columbia University College of Physicians and Surgeons, New York, N.Y. The chairperson of the second symposium, "Norepinephrine: Neurotransmitter for the Millennium," was Charles B. Nemeroff, M.D., Ph.D., Reunette W. Harris Professor and Chairman, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Ga. Dennis S. Charney, M.D., Professor and Deputy Chairman, Academic and Scientific Affairs, Department of Psychiatry, Yale University School of Medicine, New Haven, Conn., was cochairperson. The participants were Marc G. Caron, Ph.D., James B. Duke Professor, Department of Cell Biology, Duke University Medical Center, and Investigator, Howard Hughes Medical Institute, Duke University Medical Center, Durham, N.C.; Alan Frazer, Ph.D., Professor and Chairman, Department of Pharmacology, The University of Texas Health Science Center at San Antonio, San Antonio; and Alan F. Schatzberg, M.D., Professor and Chairman, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Chief of Psychiatry Service, Stanford University Hospital, Stanford, Calif. ❑

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