Novel Antidepressant Strategies to Optimize Outcome

This ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *presents highlights of a symposium held at the 1999 Institute on Psychiatric Services meeting, New Orleans, La., October 31, 1999, and supported by an unrestricted educational grant from Pharmacia Corporation, Peapack, N.J.*

The symposium, "Novel Antidepressant Strategies to Optimize Outcome," was chaired by J. Craig Nelson, M.D., Professor of Psychiatry, Yale School of Medicine, and Director of Psychiatric Inpatient Services, Yale-New Haven Hospital, New Haven, Conn.

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

Norephinephrine: A Driving Force Behind the Effects of Antidepressants

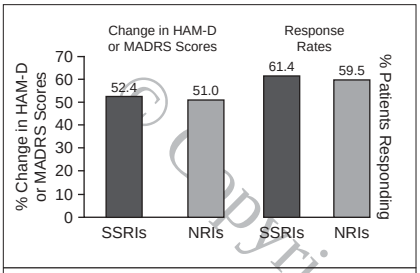
A resurgence of interest in the potent neurotransmitter norepinephrine (NE) and its role in depression has led investigators to realize that norepinephrine reuptake inhibitors (NRIs) may have a greater impact on drive, motivation, energy, and social functioning than selective serotonin reuptake inhibitors (SSRIs). This realization is the result of research on approaches to optimize the outcomes of patients with depression, whereby NE and serotonin have been compared with respect to their effects on antidepressant mechanisms of action and efficacy.

The introduction of fluoxetine more than 10 years ago spurred great interest in the role of serotonin in depression and subsequently resulted in the development of several new serotonergic antidepressants. As psychopharmacologists continued to focus on serotonin during this period, the SSRIs ultimately became first-line drugs for the treatment of depression. Nonetheless, the role of NE and its extensive history in the area of noradrenergically based antidepressant therapy cannot be overlooked, as early prescribers of nortriptyline and desipramine may appreciate. Offering a historical perspective on NE, J. Craig Nelson, M.D., reviewed the hypotheses of catecholamine depletion and β-adrenergic receptor down-regulation. In the 1960s, the hypothesis that depletion of NE from the brain could elicit depression while the administration of tricyclic antidepressants (TCAs) with NE-enhancing effects could reverse it was advanced by Schildkraut.[1] Later, Sulser and associates[2] found that β-adrenergic receptors in the brain were down-regulated by the chronic administration of antidepressants. Of particular interest is the finding that the down-regulation of the β-adrenergic receptors coincides with the onset of therapeutic effects.

Norepinephrine, like serotonin, is a neurotransmitter that is essential to the ability of the brain to regulate a variety of physiologic functions. Specifically, NE is released by neurons that innervate those regions of the brain involved with regulating mood, drive and motivation, learning and memory, sleep-wake cycle, eating, and hypothalamic-pituitary axis function. Interestingly, aberrations in the various functions influenced by NE—for example, difficulty in concentrating, insomnia, and poor appetite—overlap with the symptomatic criteria for depression as listed in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV).[3]

One of the research strategies used to determine the role of serotonin and NE during antidepressant treatment has been the depletion of critical monoamines involved in the synthesis of these 2 neurotransmitters. At issue was whether patients who had been successfully treated with a serotonergic or noradrenergic antidepressant would relapse when these amines were depleted. What was learned was that a reduction in tryptophan intake, which reduces the synthesis of serotonin, causes relapse in patients who have

Figure 1. Percent Change in Hamilton Rating Scale for Depression (HAM-D) and Montgomery-Asberg Depression Rating Scale (MADRS) Scores and Overall Response Rates in Comparative Study of Selective Serotonin Reuptake Inhibitors (SSRIs) and Norepinephrine Reuptake Inhibitors (NRIs) (N = 1563)[a]



[a]Adapted from Nelson,[9] with permission.

been successfully treated with a serotonergic agent without having any significant effect on patients treated with a noradrenergic agent.[4] Conversely, the administration of α-methylparatyrosine (AMPT), which blocks the synthesis of NE, causes relapse in patients treated with noradrenergic as opposed to serotonergic drugs.[5] While the results of amine depletion studies have not clarified the etiology of depression, they have confirmed that the antidepressant response achieved with the SSRIs and the NRIs is mediated by serotonin and NE, respectively, and to some extent have independent actions. Because both of these neurotransmitters are involved in mediating antidepressant actions, Dr. Nelson believes that one reasonably must ask whether the drugs that affect these neurotransmitters are relatively comparable or different in efficacy. While several reviews comparing SSRIs with NE-enhancing TCAs have been performed,[6–8] the heterogeneity and nonselectivity of the TCAs make efficacy comparisons of the 2 drug classes difficult to interpret.

Dr. Nelson reviewed a series of 15 double-blind, random-assignment, parallel comparison studies of selective SSRIs and a mixture of antidepressants with largely NE-reuptake inhibiting properties.[9] The SSRIs included fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, and zimelidine. The drugs with NE-reuptake inhibiting properties included desipramine, nortriptyline, maprotiline, lofepramine, and reboxetine, of which only reboxetine is truly selective for NE reuptake inhibition. Percent changes in the Hamilton Rating Scale for Depression (HAM-D) and the Montgomery-Asberg Depression Rating Scale (MADRS) were used to evaluate the antidepressant effect achieved with these agents, with response defined as a 50% improvement in symptom scores. Results showed that the SSRIs and the NRIs achieved nearly equivalent percent change on the HAM-D and MADRS (52.4% vs. 51.0%) as well as overall response rates (61.4% vs. 59.5%) (Figure 1). It is important to note that these comparisons are being made in a general population of depressed patients that are typically enrolled in such studies. It has not been clarified if the SSRIs and NRIs are interchangeable and therefore effective in the same patients or if they differ in efficacy depending on patient characteristics or depression subtype. Unfortunately, no studies have unequivocally identified clusters of symptoms that are predictive of a differential response to SSRIs or NRIs. The medical community, according to Dr. Nelson, is still in the process of learning about satisfactory symptom predictors of response to antidepressant treatment. The fact that many patients who are being treated for depression do not experience a complete response with a single agent suggests the potential importance of understanding which symptoms are most responsive to specific drugs.

A study performed by Dr. Nelson and colleagues[10] a few years ago pinpointed the specific symptoms of depression that improved in direct relation to achieving therapeutic plasma levels of desipramine, a potent TCA with extensive noradrenergic activity. Unfortunately, desipramine has a range of other receptor affinities with the result that it is also associated with unwanted cardiovascular and anticholinergic effects. A total of 43 patients with nonpsychotic, unipolar major depression were treated with a 2.5-mg/kg dose of desipramine. Patients who responded to desipramine experienced improvement in 8 symptoms—interest, pleasure, energy level, appetite, depressed mood, worthlessness, guilt, and somatic anxiety. The investigators concluded that primarily noradrenergic agents such as desipramine may be especially helpful for the amelioration of symptoms related to drive, energy, and motivation. Additional support for a differential response for noradrenergic agents comes from a study by Berman and colleagues,[11] in which previously euthymic patients with depression were evaluated to investigate the impact of catecholamine depletion. Catecholamine depletion was accomplished using AMPT, while a control group received diphenhydramine. Of note

Primarily noradrenergic agents such as desipramine may be especially helpful for the amelioration of symptoms related to drive, energy, and motivation.

was that loss of energy, decreased concentration, and loss of interest emerged as significantly more common in the catecholamine-depleted group than in the control group.

Because SSRIs and NRIs may treat different patient types or different symptoms, augmentation regimens might enhance the management of patients who have not achieved a satisfactory response to one or the other type of agent, according to Dr. Nelson.[12]

He added that, of course, one would need to weigh the benefits against the risks of additional adverse effects. Dual agents may be another option for patients who fail to respond to monotherapy with either a serotonergic or noradrenergic antidepressant or combination therapy. The results of a preliminary study by Dr. Nelson's group revealed that combination therapy with desipramine and fluoxetine was more effective than desipramine alone, and had a more rapid onset of action.[13] In a subsequent, prospective, double-blind comparison in inpatients with nonpsychotic unipolar major depression,[14] Dr. Nelson's group found the combination of desipramine and fluoxetine more effective than either drug alone but not more rapid. The difference between treatments was particularly marked when remission rates were examined. More than 50% of the patients receiving combined treatment remitted, while less than 10% of the patients receiving either drug alone achieved remission during the 6-week period. During the study, the fluoxetine dose was fixed at 20 mg/day, while the desipramine dose was adjusted to reach a therapeutic plasma level.

In view of the findings from the studies described above, Dr. Nelson reiterated that (1) both serotonin and NE are involved in mediating antidepressant effects, (2) drugs that affect these neurotransmitters have similar efficacy in a general depressed population, (3) predictors of patient response to these selective agents have not been identified, and (4) noradrenergic agents may be especially effective for improving drive and motivation. ❑

Selective Norepinephrine Reuptake Inhibition: The Unique Role of Reboxetine in Depression

Reboxetine, the first selective NRI, represents a novel weapon in the treatment of depression. By acting specifically at noradrenergic sites with minimal binding to receptors that cause troublesome effects, reboxetine achieves a higher level of NE reuptake inhibition, which translates into notable efficacy and tolerability when compared with placebo, desipramine and imipramine, and the SSRI fluoxetine. Patients with severe depression, anxiety, or panic attacks may benefit in particular from treatment with reboxetine.

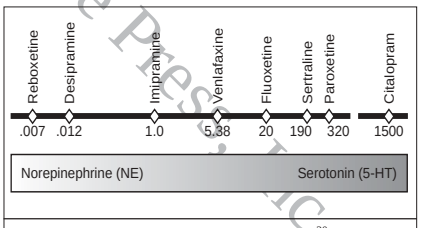
The emergence of reboxetine has resulted in a reexamination of and renewed interest in the role of NE in depression therapy. Misbeliefs coupled with unknowns may explain why NE has long been a neglected influence in antidepressant therapeutics. To date, knowledge of NE has been largely derived from depression models using the older TCAs such as desipramine, nortriptyline, or maprotiline, which have been associated with numerous side effects attributed to their binding to multiple receptors. With reboxetine, we now have the ability to study selective noradrenergic effects just as we have studied selective serotonergic effects with the SSRIs, according to Stuart A. Montgomery, M.D.

In the spectrum of antidepressants, significant variation exists in the selectivity of these agents for serotonin versus NE receptors (Figure 2). Among the SSRIs, fluoxetine is the least selective for serotonin while citalopram is the most selective. Regarding agents with NE-enhancing properties, imipramine is the least selective for NE reuptake inhibition with reboxetine being the most selective of all.

The potency of reboxetine, defined as an inhibition constant (k_i) of 50%, characterizes the drug as being highly selective overall. Norepinephrine reuptake is 8 nM (expressed as K_i). Differentials against 5-HT reuptake and dopamine reuptake are substantial to large—1070 nM and > 10,000 nM, respectively.[15,16] Studies of receptor binding report reboxetine's affinity for the α_1 and α_2 receptors as being very low, 10,000 nM and 43,000 nM, respectively.[15] The affinity of reboxetine for other receptors is minimal and includes histamine$_1$, 1400 nM; muscarinic, 3900 nM; and dopamine D_2, 8800 nM. At therapeutic concentrations, it appears that the sole impact of reboxetine will be on the noradrenergic system.

The minimal affinity of reboxetine for certain receptors may ameliorate potential side effects, which usually manifest with more intensity when agents with a higher affinity for these receptors are administered. Thus, the dry mouth, blurred vision, constipation, and urinary hesitancy that are experienced following drug/muscarinic receptor interaction may be less significant with reboxetine as compared to TCAs. Similarly, the lack of interaction between reboxetine and the histamine receptor may result in less sedation, drowsiness, and weight gain as compared to the TCAs and mirtazapine, which have high affinities for the histamine receptor. Antidepressants that increase NE rather than sero-

Figure 2. Relative Reuptake Selectivity: Ratio of Inhibition (NE:5-HT)[a]



[a]Reprinted from Gorman and Sullivan,[30] with permission. Figure 2 represents the ratios of inhibition constants of 8 antidepressants for norepinephrine reuptake vs. serotonin reuptake inhibition. Imipramine with a ratio of 1.0 has equal inhibition selectivity, whereas reboxetine and citalopram fall at either end of the spectrum of ratios. The inhibition constants were based on values derived by Richelson and Pfenning.[16]

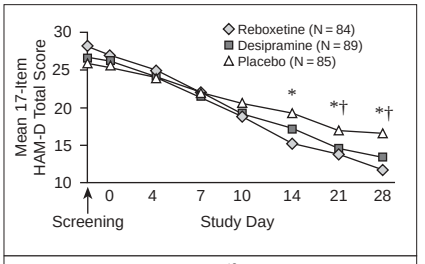
tonin are associated with fewer gastrointestinal and sexual side effects. According to Dr. Montgomery, both of these side effects are believed to result from enhanced serotonin activity.

To disentangle any conflicting issues surrounding the appropriateness of enhancing brain NE for the treatment of depression, Dr. Montgomery summarized the results of 8 randomized, multinational clinical studies on reboxetine (references 17–22 and data on file, Pharmacia Corporation, Peapack, N.J.). Over 2500 adult patients with major depressive disorder were enrolled, and efficacy data were obtained from close to 2000 hospitalized patients and outpatients. Agents administered to these patients included reboxetine, 8–10 mg/day; imipramine, 150–200 mg/day; desipramine, 200 mg/day; fluoxetine, 20–40 mg/day; and placebo.

Against placebo, reboxetine was clearly more effective in a 6-week study of hospitalized patients with severe depression.[17] Fifty-six patients were enrolled, with 28 patients randomly assigned to each group. Mean HAM-D_{21} scores at the time of enrollment were in the region of 36, which is indicative of severe depression. By the conclusion of the study, the HAM-D_{21} scores of the patients given reboxetine were approximately 12, whereas the scores of the patients given placebo were 32. Investigators concluded that reboxetine was effective for the treatment of severe depression. This finding is important, stressed Dr. Montgomery, in light of the special concerns with patients with severe depression (i.e., high rate of suicide, greater morbidity, need for hospitalization, modest response with SSRIs).

In a head-to-head comparison of reboxetine (4–8 mg/day) versus desipramine (100–200 mg/day) versus placebo in hospitalized patients, reboxetine was significantly more effective than placebo, while results for desipramine-treated patients were comparable to placebo (Figure 3).[18] Although the protocol specified the administration of desipramine in maximally tolerated dosages, Dr. Montgomery believed the dosage for desipramine might not have been high enough. The reticence to administer a higher dose may have represented an attempt to avoid dropouts due to the known side effects of high-dose desipramine. Nevertheless, the study suggests that obtaining a better tolerated and more effective dose of antidepressant is easier with reboxetine than with desipramine.

Figure 3. Response Rates for Desipramine, Reboxetine, and Placebo in a 4-Week Study of Major Depression[a]



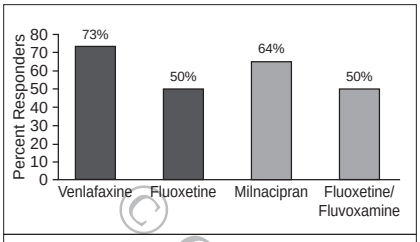
[a]Reprinted from Ban et al.,[18] with permission.
*Reboxetine < placebo, p < .006.
†Desipramine < placebo, p < .006.

In a head-to-head study with imipramine, reboxetine was more effective and better tolerated than imipramine.[19] In this 6-week study of 256 hospitalized patients and outpatients, responses were seen in 69% (90/130) of the reboxetine-treated patients compared with 56% (70/126) of the imipramine-treated patients. The dropout rate caused by the non–treatment-related side effects of imipramine probably compromised the effectiveness of the drug, commented Dr. Montgomery. As is the case with the SSRIs, administration of a selective NRI (reboxetine) versus a nonselective TCA with NE-reuptake inhibition properties (imipramine) may enhance effectiveness because of a cleaner side effect profile.

Another study comparing the administration of reboxetine with that of imipramine in a population of 218 elderly patients showed little difference in the efficacy of the 2 drugs during an 8-week study.[20] In one analysis in which a response was defined as a ≥ 50% decrease in the HAM-D total score, 55% (60/109) of the patients treated with reboxetine versus 56% (61/109) of the patients treated with imipramine were responders. In a separate analysis using the Clinical Global Impressions (CGI) scale, in which improvement was described as "much to very much improved," 59% (64/109) of the patients receiving reboxetine versus 52% (57/109) of the patients receiving imipramine met the criteria for response. As the 2 treatment arms were set up to have equivalent requirements, one may conclude with confidence that reboxetine was as effective as imipramine in the treatment of elderly outpatients—a group that is deemed clinically difficult to manage—commented Dr. Montgomery. He added that reboxetine may be a more advantageous antidepressant to administer to these patients given their sensitivity to the anticholinergic, cardiovascular, and sedative side effects of many of these drugs.

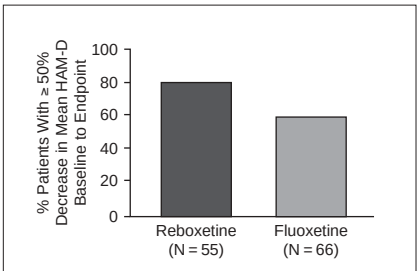
There were two 8-week comparator studies with fluoxetine, one with a placebo control (data on file, Pharmacia Corporation, Peapack, N.J.) and the other without.[21] Closely equivalent levels of efficacy were noted between reboxetine and fluoxetine administered to the general population of patients with depression.[23] In the study without placebo, 78% (62/79) of patients in the reboxetine arm versus 74% (66/89) of patients in the fluoxetine arm were responders.[21] The study that included a placebo control showed response rates of 56% for both drugs (70/126 reboxetine-treated patients and 71/127 fluoxetine-treated patients) and 34% for placebo (43/128 patients) (data on file, Pharmacia Corporation, Peapack, N.J.). Dr. Montgomery cautioned that the admittance

Figure 4. Response Rates Associated With Noradrenergic vs. Serotonergic Antidepressants for Treatment of Severe Depression[a]



[a]Data from Clerc et al.[24] and Lopez-Ibor et al.[25] More noradrenergic antidepressants (mirtazapine, venlafaxine, milnacipran) have been shown to have higher response rates than SSRIs in severe depression.

Figure 5. Reboxetine vs. Fluoxetine in a Subset of Patients With Severe Depression[a]



[a]Data from Versiani et al.[22] and data on file, Pharmacia Corporation, Peapack, N.J.

of a placebo into any study causes patient dropout among those individuals who are concerned about not responding without receiving an active drug, which is an important factor to consider in any discussion of the differential effects of 2 drugs.

The long-term efficacy of reboxetine was convincingly demonstrated in a double-blind, placebo-controlled study extending 350 days.[22] Cumulative probability of relapse was reduced to 20% (27/133 patients relapsing) in the reboxetine treatment arm versus 58% (77/132 patients relapsing) in the placebo arm. All patients were required to be responders to reboxetine during the acute phase of treatment before being randomly assigned to receive reboxetine or placebo.

Considerable discussion has surrounded the efficacy of the NRIs and the SSRIs for depression. Dr. Montgomery reviewed the results of studies showing the superior efficacy of antidepressants with potent noradrenergic reuptake inhibition, whether selective or not, versus the SSRIs in patients with severe depression, suggesting that the noradrenergic component may be an important factor in achieving a more potent effect. In a head-to-head comparison, venlafaxine achieved a significantly higher response rate than fluoxetine in severely depressed patients[24]; likewise, milnacipran was significantly more effective than both fluoxetine and fluvoxamine in a meta-analysis of the data from separate studies (Figure 4).[25]

A more exacting assessment of the impact of noradrenergic antidepressant therapy requires an examination of patients with severe depression separate from that of the general population of depressed patients. Adopting this approach, one subset analysis of outpatients with severe depression who were enrolled in an 8-week study showed that reboxetine was more effective than fluoxetine as evidenced by the higher percentage of patients who experienced a ≥ 50% decrease in the mean HAM-D total score from baseline to endpoint—that is, 80% (44/55) of reboxetine-treated patients versus 61% (40/66) of fluoxetine-treated patients (Figure 5) (reference 22 and data on file, Pharmacia Corporation, Peapack, N.J.). Such retrospective analyses also have shown that reboxetine is significantly more effective than fluoxetine and equally as effective as imipramine in cases of severe depression (reference 26 and data on file, Pharmacia Corporation, Peapack, N.J.). The results of prospective studies are still necessary to confirm the effects of selective NRIs in severe depression beyond those already demonstrated for reboxetine against placebo.[17]

Whether selective NRIs are effective in the treatment of anxiety has been raised periodically. From the data comparing reboxetine, fluoxetine, and placebo, Dr. Montgomery reported on specific analyses of the psychic anxiety and somatic anxiety items from the HAM-D (data on file, Pharmacia Corporation, Peapack, N.J.). From these analyses, fluoxetine proved to be significantly better than placebo; reboxetine also was significantly better than placebo and actually showed a slight advantage over fluoxetine. Dr. Montgomery concluded that because reboxetine, like fluoxetine, is effective in treating the symptoms of anxiety, NE may have a direct effect on anxiety.

Not only are symptoms of depression modulated by NE, but benefits are also noted on the symptoms of panic disorder—a finding that has largely been substantiated by studies with reboxetine. Data from a recent, short-term, randomized, double-blind study of 82 patients with panic disorder achieved a significant ($p < .05$) reduction in the mean number of panic attacks for reboxetine when compared with placebo.[27]

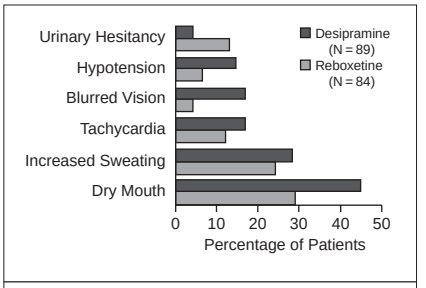
The effectiveness of reboxetine is accompanied by a fairly distinct tolerability profile. As a selective NRI, reboxetine has been associated with a significantly lower rate of side effects than desipramine or imipramine.[18–20] Although urinary hesitancy occurs more frequently with reboxetine than with desipramine, other side effects such as hypotension, blurred vision, tachycardia, increased sweating, and dry mouth occur less often (Figure 6). Compared with the SSRIs, reboxetine causes less nausea and fewer gastrointestinal disturbances.[22] Also, the reported incidence of sexual dysfunction has been low with reboxetine (data on file, Pharmacia Corporation, Peapack, N.J.). Like the SSRIs, reboxetine appears to be safe in overdose. To date, there have been no known fatalities attributed solely to reboxetine (data on

file, Pharmacia Corporation, Peapack, N.J.). With regard to discontinuation effects, none have been noted in any of the studies in which abrupt discontinuation was part of the protocol (data on file, Pharmacia Corporation, Peapack, N.J.).

In elderly patients, who are in general an at-risk population, antidepressants that favor the noradrenergic pathway may offer specific advantages. To date, this has been hard to evaluate because of the additional burden of side effects associated with nonselective agents such as the TCAs. In addition, the TCAs pose a cardiovascular risk in elderly patients with ischemic coronary disease and are fatal in overdose.[28]

The risk of suicide or attempted suicide in the course of antidepressant therapy was lowest with reboxetine (0.4%; N = 1622) when compared with desipramine and imipramine (0.6%; N = 501), fluoxetine (0.9%; N = 216), and placebo (0.6%; N = 542) in a cumulative analysis of clinical trials involving these agents (data on file, Pharmacia Corporation, Peapack, N.J.). Calculations were based on the number of attempts per 100 patient years. Dr. Montgomery considered the results to offer reassurance, as they suggest a possible role for NE in conferring protection against suicidal ideation.

Figure 6. Tolerability Profile of Reboxetine vs. Desipramine[a]



[a]Adapted from Ban et al.[18] and data on file, Pharmacia Corporation, Peapack, N.J. Adverse events listed are those that occurred significantly more frequently with desipramine or reboxetine.

Using reboxetine as a model, Dr. Montgomery found it was more difficult to explain the effects of NE on adverse effects than on antidepressant efficacy. In the clinical trials, patients reported experiencing more dry mouth with reboxetine than with placebo (30.6% vs. 14%) (data on file, Pharmacia Corporation, Peapack, N.J.). In a trial comparing reboxetine with desipramine, the incidence of dry mouth was lower for reboxetine compared with desipramine (26% vs. 45%).[29] This side effect is difficult to explain because evidence of a direct effect of reboxetine on the muscarinic receptors is lacking. While reboxetine has virtually no affinity for α_1-adrenoceptors in the salivary glands that regulate secretion, its effects may be directly attributed to central noradrenergic activity. The higher incidence of urinary hesitancy with reboxetine versus placebo (5% vs. 2%) is probably due to the effect of the drug on the α_1-adrenoceptors in the bladder (data on file, Pharmacia Corporation, Peapack, N.J.).

In Dr. Montgomery's final assessment of the data, he considered the cumulative clinical evidence to be good for the efficacy and tolerability of reboxetine in adult patients with severe depression, anxiety, and panic attacks in panic disorder. Although formal studies to accrue data on the use of reboxetine in children and adolescents are needed, anecdotal reports from Europe indicate the effectiveness of this selective NRI in these populations. ❑

Melancholia and Severe Depression: Controversies in Clinical Trial Data

The heterogeneous nature of depression necessitates the administration of different pharmacologic agents for optimal treatment of the various subtypes of this illness. While the favorable safety and tolerability profile of the SSRIs has positioned these agents as first-line treatment for depression in general, the subtype of melancholic depression may be more responsiveness to the more noradrenergic agents, according to Steven P. Roose, M.D.

Recognition that subtyping of depressive illness has implications for treatment first came from the documentation that patients with nondelusional unipolar depression responded to TCAs at significantly higher rates than patients with the delusional subtype. Patients with delusional depression respond best to electroconvulsive therapy or a combination of antidepressant and antipsychotic agents.[31,32] Further appreciation that depressive subtypes require different treatment approaches came from studies of atypical depression, which is characterized by patients who oversleep and overeat, experience "leaden paralysis," and display rejection sensitivity.[33] Comparisons of the differential response of patients with atypical depression to placebo, imipramine, and the monoamine oxidase inhibitor phenelzine reveal that patients with atypical depression respond at a higher rate to phenelzine than either imipramine or placebo.

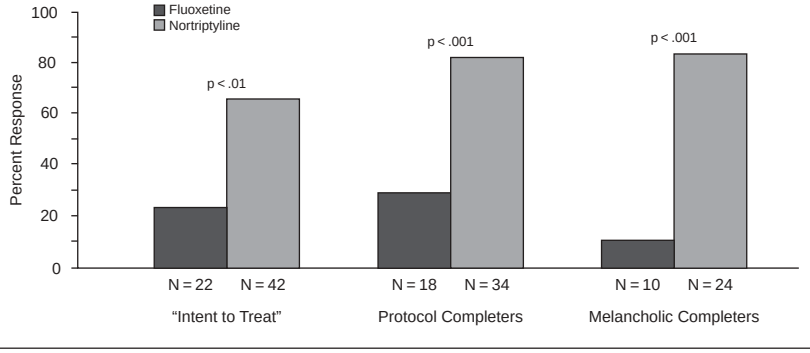
The first suggestion that the SSRIs and TCAs may be preferential in different subtypes of depression came from a study by Reimherr and colleagues,[34] who initially reported that neither imipramine nor fluoxetine had a high response in patients with depression. However, a second analysis of the data, which categorized patients as having the atypical or endogenous subtype, revealed that fluoxetine was significantly more effective than imipramine in the treatment of atypical depression and there was a strong trend for the greater effectiveness of the

TCAs versus the SSRIs in endogenous depression.[35]

Two studies from Denmark further substantiated the greater effectiveness of the TCAs compared with the SSRIs in refraction.[7,8] A study from the Danish University Antidepressant Group compared the SSRI citalopram (40 mg/day) with the TCA clomipramine (150 mg/day) in hospitalized patients who met the endogenous criteria using the Newcastle II Scale (i.e., comparable to DSM-IV criteria for the melancholic subtype).[7] To set the stage for the first study, Dr. Roose prefaced that the investigators had the expectation that citalopram would be as effective as clomipramine in the treatment of this patient population. After 5 weeks of treatment, only 28% (14/50) of patients in the citalopram cell versus 60% (31/52) of patients in the clomipramine cell met the criteria for a complete response. To see whether these unanticipated results were specific to citalopram, a second double-blind, randomized study was undertaken by the same group to compare the SSRI paroxetine (30 mg/day) with clomipramine (150 mg/day).[8] This study used DSM-III criteria for major depressive disorder and melancholia subtype. The second study had results similar to the first. The complete response rate in the paroxetine cell was 22% (11/50 patients) versus 58% (30/52 patients) in the clomipramine cell. As the only 2 randomized studies comparing an SSRI with a TCA in patients with melancholic subtypes of depression, the importance of these studies cannot be underestimated.

The findings of the Danish University Antidepressant Group were extended in an important study by Tignol and colleagues,[36] who analyzed the worldwide database on paroxetine versus placebo in outpatients with a diagnosis of melancholia based on DSM-III criteria. With a response rate defined as a HAM-D score < 10 at the end of treatment, 31% (55/178) of patients in the paroxetine arm versus 15% (10/66) of patients in the placebo arm were responders. This study did find that paroxetine was significantly more effective than placebo in the treatment of melancholia. From a clinical perspective, however, Dr. Roose noted that the most striking result of this study was the relatively low response rate of melancholic patients treated with paroxetine.

Figure 7. Treatment Response to Nortriptyline at 4 Weeks vs. Fluoxetine at 6 Weeks[a]



[a]Data from Roose et al.[37]

For many years, Dr. Roose has studied the cardiovascular effects and safety of antidepressant medications. Most of these studies included patients with severe depression, mostly melancholic, who had gone untreated because of the presence of cardiovascular disease. Antidepressant protocols lasted 7 to 12 weeks and required hospitalization.

Although the TCAs have a reputation of being robustly effective, the severe cardiovascular effects noted by Dr. Roose's group led them to study the cardiovascular safety of fluoxetine. These studies were begun under the presumption that all antidepressant medications were equally effective. In one study,[37] open treatment was given to 22 patients, with a mean age of 73 years. Sixty-three percent met criteria for melancholic subtype (i.e., baseline HAM-D > 26) and cardiovascular disease. The study found that the SSRIs had significant cardiovascular safety compared with the TCAs—an important advantage of this drug class; however, they also found that the SSRIs were surprisingly ineffective in this particular patient population.[37] Fluoxetine treatment was given in dosages of up to 60 mg/day for 7 weeks. At 6 weeks, the response rate, defined as a HAM-D score of < 8, was only 28% (5/18) among completers; among melancholic patients, the rate was only 10% (1/10).

A historical comparison of the findings from the fluoxetine study with those of an earlier open study of nortriptyline treatment in a similar population of patients revealed a significantly higher response rate with the TCA.[37] The effect of a therapeutic plasma level of nortriptyline at 4 weeks was compared with the fluoxetine-generated response at 6 weeks. The nortriptyline response rate in melancholic patients was 83% (20/24) versus 10% (1/10) in the fluoxetine-treated melancholic patients (Figure 7). Those patients who failed to respond to fluoxetine were not treatment refractory, Dr. Roose emphasized. Among 7 fluoxetine nonresponders who subsequently received nortriptyline, 71% (5/7) improved. Among 6 who received ECT, including the 2 patients who did not respond to nortriptyline, all responded. Thus, the recovery rate was 100% for the 11 non-

responders to fluoxetine who later received nortriptyline and/or ECT.

Another study involving patients with melancholia reported that nefazodone (neither an SSRI nor NRI) was comparable in efficacy to paroxetine.[38] A particularly intriguing study is reported by Clerc et al.,[24] in which venlafaxine (both a serotonin and NE reuptake inhibitor [SNRI]) was compared to fluoxetine (an SSRI) in hospitalized patients with melancholia. Venlafaxine, with its noradrenergic mechanism of action, achieved a significantly better response than fluoxetine.

While the database on TCAs versus SSRIs is substantial, the flaws in study design must be considered, according to Dr. Roose. One could argue that the SSRI treatment arm in some studies should have called for higher doses administered for a longer duration. Also, too few studies used a double-blind, randomized design. Despite the flaws, Dr. Roose believes that the existing database suggests 2 major points: First, the SSRIs are not as effective as other agents in the treatment of melancholia, and second, the drugs that have been found to be effective in the treatment of melancholia—for example, the classic TCAs, venlafaxine, and reboxetine—all have significant noradrenergic activity. ❑

Outcome Assessments in Depression: Implications for Patient and Practice Management

Measurements of symptom reduction and functional improvement in patients receiving antidepressants can yield invaluable information at critical points in decision making related to clinical care. Several assessment tools are available to assist clinicians in determining an optimal treatment strategy, ranging from those that indicate the predictive value of pretreatment symptoms in the selection of antidepressant therapy to those that track the efficacy and tolerability of an agent following administration. Practice management issues such as physician staffing and reimbursements also may be defined more clearly with the application of these tools, which provide the rationale necessary to support clinical decisions.

Several reasons for measuring outcome were outlined by A. John Rush, M.D. First, outcome measurements encourage clinicians to create a treatment plan for their patients, which includes a course of treatment. Such a plan provides a basis for making tactical decisions (e.g., changing dosages, extending the trial). Second, outcome measurements provide documentation of results. Before a treatment strategy can be intelligently modified for those patients not experiencing full benefits, Dr. Rush explained that the clinician needs to know if that strategy was first fully implemented and, in addition, to know what benefits have been obtained.

Clinically relevant outcomes that need to be measured include symptoms of depression and function, which are interrelated. Specific depressive symptoms for assessment include mood, vegetative, cognitive, and motivational. Function is gauged in the context of work, marriage, family, and friends. Symptoms require more frequent measurement than function; function responds to treatment more slowly than symptoms.

Function plays a critical role in outcomes assessments because the aims of treatment are both functional restoration and complete remission of symptoms.

Symptoms need to be measured because they are, in essence, a manifestation of the depressive illness. Through symptom measurement, commented Dr. Rush, the clinician can assess the degree of disease control being achieved, determine whether symptom response or remission has occurred, provide a basis for selecting among treatment strategies (e.g., switching to a new drug, augmenting treatment with a second antidepressant) and using specific tactics (e.g., new dose), and teach disease management to patients and families. Function plays a critical role in outcomes assessments because the aims of treatment are both functional restoration and complete remission of symptoms. Medications that result in some degree of symptom control may improve function. Rehabilitative or psychotherapeutic interventions will improve function above and beyond that obtained by medication alone.[39] Finally, antidepressants may well differ in their effect on function, based either on a difference in side effect burden or possibly on pharmacologic differences (e.g., NE vs. serotonin effects).

Emphasis on the relationship between function and symptoms, especially in the United States, has emanated from several sources, according to Dr. Rush. Patients have appropriately begun to push for organized, consistent treatment plans that target both symptom reduction and functional restoration. Health care providers are requiring documentation that supplies a clear basis for treatment-related decisions in the form of guidelines or algorithms. Purchasers for formularies, as well as managed care administrators, are also interested in knowing that patients actually experience improved function, as well as better symptomatic relief.

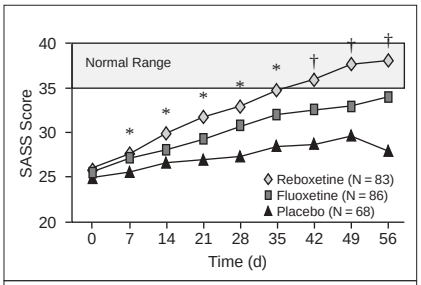
Interest in the extent to which treatment can alter the symptoms and function of a patient with depression is understandably high, given that depression is the leading cause of disability in

Table 1. Improvement in Social Adaptation Self-Evaluation Scale Item Scores: Reboxetine vs. Fluoxetine vs. Placebo[a]

Reboxetine Superior to Fluoxetine	Reboxetine Equivalent to Fluoxetine
Social attractiveness	Work enjoyment
External relationship appreciation	Social inquisitiveness
Control of surroundings	Family relationship quality
Interest in hobbies	Communication difficulties
Rejection sensitivity	External relationship quality
Gregariousness	Intellectual interest
Vainness	Job interest
Community involvement	Difficulties in coping with resources
Social compliance	Home work interest
Family-seeking behavior	

[a]Adapted from Dubini et al.[48]

Figure 8. Reboxetine vs. Fluoxetine vs. Placebo in Major Depressive Disorder: Improvement in Social Functioning as Determined by 21-Item Social Adaptation Self-Evaluation Scale (SASS) Scores[a]



[a]Reprinted from Dubini et al.,[49] with permission. $p < .05$ vs. placebo*/fluoxetine†.

the world.[40] Social functioning is affected more adversely by depression than by general medical conditions such as hypertension, coronary artery disease, arthritis, and diabetes.[41] Likewise, subtypes of depression, including subthreshold depression, major depression, dysthymia, and double depression, are associated with lower levels of emotional functioning than are general medical conditions.[42]

To study the response of social functioning in patients administered antidepressant treatment, a number of assessment scales have been developed. Weissman and Bothwell[43] created the Social Adjustment Scale Self-Report (SAS-SR) to monitor social performance in various roles (e.g., work, family). Tracking a group of 76 depressed patients with their assessment scale, Weissman and Bothwell found that once patients were stabilized with an antidepressant and interpersonal therapy, functional improvements were maintained over the 20 months of the trial.

Other scales have slightly different emphases, Dr. Rush pointed out, but they all aim at defining domains of function and the capacity of patients to participate fully in different domains of daily function. The SAS-SR is the only scale to consider family, marital, and parental domains in addition to work. The section of the scale specifically related to the work domain includes a series of questions about the number of days and hours worked per week, attitudes about work and coworkers, sense of satisfaction derived from work, and ability to function. Another social adjustment scale recently coming into use in Europe is known as the Social Adaptation Self-Evaluation Scale (SASS), which again assesses occupational or work function through a similar battery of questions.[44] Finally, the Medical Outcomes Study (MOS) Short-Form with 36 items (SF-36) typically examines the patient's self-report of his or her capacity to work for the previous 4 weeks, including any disabilities related to emotional problems affecting time spent, level of accomplishment, and diligence on the job.[45]

On the basis of outcome assessments, the relevancy of symptom resolution on functional restoration in depressed patients has been questioned and represents an area meriting more comparative studies, according to Dr. Rush. A large, randomized, double-blind trial comparing imipramine with sertraline administration during the acute phase of depression showed that the 2 drugs achieved an equivalent reduction in symptoms as noted by the HAM-D score at 12 weeks; however, a somewhat differential effect on social functioning as assessed by the SAS-SR revealed that sertraline was slightly more effective.[46]

In the selection of an antidepressant agent, the clinician should evaluate not only the available clinical data but also the mechanism of action. As the different dimensions of functioning have been attributed to different neurotransmitters—that is, energy and interest are influenced by NE, impulse by serotonin, and drive by dopamine—the different neurochemical actions of different antidepressant medications may impact differently on both symptom targets and function.

A report compared the SASS scores of patients treated with the selective NRI reboxetine versus placebo versus the SSRI fluoxetine.[47] The mean SASS scores were compared at baseline and at the final measurement for the overall population and for patients in remission. In each instance, the SASS scores that were achieved with reboxetine statistically exceeded the scores achieved with fluoxetine. No significant improvement was seen in the patients receiving placebo. These results, said Dr. Rush, raise the question as to whether different neurotransmitter systems might have differential effects on function over and above that which can be accounted for by the differential effects on symptoms.

Reboxetine was noted to achieve a substantial effect across a number of domains of function using the 21-item SASS scores to compare the agent with

fluoxetine and placebo for major depressive disorder (Table 1).[48] Only those patients administered reboxetine experienced significant improvement resulting in normal social functioning (SASS score ≥ 35) (Figure 8).[49] All but one item discriminated reboxetine from placebo, while only 12 items discriminated fluoxetine from placebo. In the reboxetine-fluoxetine comparison, 9 items showed a positive association with reboxetine, while the opposite was never seen. The association was maximal in the area of negative self-perception and lack of motivation toward action. Dubini and colleagues suggest that these results support, at the social functioning level, a differential effect of selective manipulation of the noradrenergic or serotonergic system in keeping with the long-debated hypothesis on the specific involvement of serotonin in regulating mood and/or NE sustaining drive.

Recently published evidence[50] indicates that a global assessment of a patient's response to treatment is not nearly as accurate as a symptom rating scale, which is why Dr. Rush advocates the regular use of symptom measurement in clinical practice. These more specific gauges can determine if patients are merely better or fully asymptomatic. Dr. Rush stressed that *better* does not mean *well; better* only means *improved*. The goal of therapy in depression should be full remission—getting better and staying well. The HAM-D, the MADRS, or even a self-report scale may provide an accurate assessment of symptom severity. The implications of outcome assessments on clinical practice could be modifications in the treatment plans (tactical changes such as adjustment in the dose or strategic choices such as adding a second medication or replacing one antidepressant with another) or adding or switching to psychotherapy to improve symptomatic response or to further improve day-to-day function. Assessment of function after maximal symptom benefits may be performed less frequently but nonetheless carefully. Without these measurements, future therapeutic advancements in psychiatry and clinical psychology may well be impeded.

The goal of therapy in depression should be full remission—getting better and staying well.

Conclusion

With the introduction of reboxetine, a selective norepinephrine reuptake inhibitor, norepinephrine has once again become one of the driving forces in the treatment of depression. Reboxetine represents a significant advance in the evolution of treatments for depression, equivalent to the discovery of the SSRIs for serotonin-directed treatments. It enables clinicians, for the first time, to increase the actions of norepinephrine in the brain without recourse to the potential problems of the TCAs. ❑

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Symposium and Presenters

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