Can Monoamine-Based Therapies Be Improved?

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Monoamine-based therapies that selectively target serotonin, norepinephrine, or dopamine uptake are effective as antidepressants. However, many depressed patients do not achieve remission with these single-action agents. Treatment strategies that target more than one neurotransmitter, either through augmentation, combination treatment, or the development of single agents with dual or triple reuptake mechanisms, may prove to be even more effective than traditional antidepressants and merit further research. *(J Clin Psychiatry 2002;63[suppl 2]:14–18)*

The monoamine hypothesis of depression implicates altered function of monoamine neuronal systems as a possible cause of depression. Strategies that increase the availability of any or all of the 3 classical monoamine neurotransmitters—serotonin (5-HT), norepinephrine, and dopamine—have been successful in the treatment of depression. However, the DSM-IV-TR[1] states that at least 60% of people who experience a single episode of major depressive disorder will probably have a second episode; risk increases with each subsequent episode. The National Comorbidity Survey[2] reports a 17% lifetime prevalence of major depression. The disease is both recurrent and widespread, and although the currently available antidepressants are effective for many patients, a sizeable minority—29% to 46%—will not respond to drug treatment or will have only a partial response.[3]

Among the most successful antidepressant strategies have been those that lead to enhanced serotonin availability via reuptake inhibition of the neuronal transport site for serotonin. Serotonin is a major neurotransmitter in the central nervous system. Serotonin neurons arise from at least 9 distinct nuclear groups, they show a broad distribution and innervate most of the brain and much of the spinal cord, and they differ in their anatomical and biochemical properties. At least 14 different receptor subtypes mediating serotonin action have been identified. These differences suggest the theoretical possibility of regionally selective manipulation of serotonin function, which, in turn, could allow clinicians to pinpoint the type of response needed and provide therapeutic intervention for a patient accordingly. The selective serotonin reuptake inhibitors (SSRIs) were a major step forward in the development of antidepressants because they combined the efficacy of the tricyclic antidepressants (TCAs) but did not display the anticholinergic side effects or the danger in overdose that the TCAs do.

In addition to the well-established action to alter the availability of the classical monoamine neurotransmitters, current research efforts are pointing to several potential biochemical targets for future antidepressant development (Table 1). These possible targets include direct action on postreceptor signaling events and, ultimately, specific, focused action on more precise gene targets. This brief commentary will explore the question: Can the clinical effect provided by currently available monoamine-based antidepressants be improved by further refinements on this mechanistic platform? This question will be addressed by considering examples of receptor-specific antidepressant augmentation (e.g., 5-HT$_{1A}$ receptor antagonism) and by examining data from the developing area of dual-reuptake inhibitors.

ANTIDEPRESSANT AUGMENTATION

Although it is clearly established that monoamine-based therapies such as the SSRIs and TCAs are clinically effective antidepressants, they are not without room for improvement. For example, the latency to onset of noticeable clinical effect is at least 2 to 4 weeks.[4] Furthermore, although many patients ultimately respond well to antidepressant treatment, many others have an incomplete response or do not respond at all.[3] Indeed, partial or nonresponse to treatment of first choice is the norm in clinical practice.

One of the more commonly employed strategies to enhance clinical response has been the use of adjuvant or augmentation treatment accompanying the initial antidepressant. For instance, lithium is often used to augment

Table 1. Potential Targets for Future Antidepressant
Development
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Altered neurotransmitter availability
   Serotonin, norepinephrine, dopamine
   Neuropeptides, neuromodulators
Receptor-specific modulation
   Autoreceptor blockade
Postreceptor targets
   Second messengers
      Cyclic adenosine monophosphate (cAMP)
      Phosphoinositide cascade
   Third messengers
      Kinases
      cAMP response element binding protein
      Calcium
      Fos
Genomic targets
   Gene expression (brain-derived neurotrophic factor,
     nerve growth factor)
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monoamine-based antidepressant therapies and improve the quality of the ultimate response. Heninger and coworkers[5] found lithium to be effective when added to desipramine, amitriptyline, or mianserin in patients with treatment-resistant depression. Interestingly, some patients improved quickly, within the first 2 days of beginning lithium treatment. It has been speculated that the efficacy of lithium as an augmenting agent may provide circumstantial clues to the relevance of second messenger targets or other postreceptor signaling events in the pharmacologic treatment of depression. It also clearly demonstrates that, as effective as the TCAs and SSRIs are, they do not define a ceiling of clinical effect.

The use of lithium represented to some extent a purely empirical approach to antidepressant augmentation. As our understanding of serotonin neurochemistry has evolved, it has been possible to propose an arguably more rational approach to augmentation. One of the more recent examples of this has been speculation that the concurrent action of an SSRI and a 5-HT$_{1A}$ antagonist would hasten the onset and perhaps increase the endpoint response to the SSRI. This speculation is based on the observation, in animals, of an acute reduction in the firing rate of the major serotonin-containing cell bodies in the dorsal raphe nucleus after SSRI administration. This reduction of cell firing rate is largely mediated by the somatodendritic 5-HT$_{1A}$ autoreceptors. Subsequent down-regulation of that receptor subpopulation over the ensuing 2 weeks is accompanied by a longer-term increase in serotonin neurotransmission. Because the time course of these neurochemical changes in animals parallels the observed clinical response latency to SSRI use in humans, it has been proposed that acute antagonism of the 5-HT$_{1A}$ receptor may avert this initial reduction in serotonin firing and hence may lead to a more rapid onset of clinical effect, and perhaps an even greater endpoint response than seen with SSRI treatment alone. Unfortunately, at this time few clinically available agents

possess 5-HT$_{1A}$ antagonist properties. One of these agents is the β-adrenoceptor antagonist pindolol. Several studies have found pindolol to be an effective and even rapidly acting adjuvant therapy. For example, Artigas and coworkers[6] studied 2 small groups of patients to determine the efficacy of pindolol, 2.5 mg t.i.d., added to 20 mg/day of paroxetine as a means to reduce the latency of response in one group of depressed patients and to increase degree of response in another group. They reported that 4 of 7 patients in the first group remitted completely within 1 week, and another recovered partially in that time. In the second group, 5 of 8 patients remitted completely in 1 week, and an additional patient partially recovered in that time period. The authors concluded that pindolol added to the SSRI was a quick and effective augmentation approach. Extending this work, in a larger placebo-controlled study of 111 patients with major depression, Perez and colleagues[7] found similar results. In that study, significantly more patients who took 2.5 mg t.i.d. of pindolol added to a regimen of 20 mg/day of fluoxetine experienced a response than those patients who had placebo added to fluoxetine (75% rate of response vs. 59% rate of response). This response happened more quickly and was sustained longer.

Unfortunately, not all reports of pindolol augmentation of antidepressant treatment have provided positive results. In a well-designed, double-blind, placebo-controlled study, Berman et al.[8] set out to confirm the results found by Artigas and others.[6] Patients were treated with 20 mg/day of fluoxetine plus pindolol, 7.5 or 10 mg/day, or placebo. At the end of study, no difference in response rate was observed in the pindolol-treated group versus the placebo-treated group. Another double-blind, placebo-controlled study[9] that added pindolol or placebo to current antidepressant treatment also failed to find a statistical difference in response rates. In a review of pindolol augmentation in depression, Olver and colleagues[10] found mixed results in both open-label and double-blind studies. They also discussed the possibility that a more complete interpretation of the clinical effects of pindolol coadministration must consider the potential for drug interaction if pindolol is used in conjunction with an antidepressant that is metabolized by the cytochrome P450 2D6 enzyme and warned that pindolol is potentially fatal in overdose.

What other considerations should be taken into account to interpret these disparate clinical results? One possible explanation for the inconsistent antidepressant effect of pindolol reported in the literature is provided by Martinez and others.[11] These authors have found that the dosage of pindolol normally used in augmentation studies (usually 7.5–15 mg/day) may produce an insufficient degree of occupancy at the presumably relevant central nervous system–located 5-HT$_{1A}$ receptor sites to permit a consistent response. In fact, at a dose as high as 30 mg/day, they found only a 64% occupancy of 5-HT$_{1A}$ receptors in the

dorsal raphe nucleus as measured by positron emission tomography in 9 healthy volunteers.

Clinical evidence to date, then, has provided inconsistent evidence that pindolol has an adjuvant antidepressant effect when used in conjunction with an SSRI antidepressant. Neuroimaging results suggest that the doses of pindolol employed may have provided insufficient central nervous system 5-HT$_{1A}$ receptor occupancy to induce an antidepressant effect. Furthermore, since pindolol is not itself a pure 5-HT$_{1A}$ antagonist, these results do not exclude the possibility that 5-HT$_{1A}$ antagonism may be a successful antidepressant therapy. Results from these two approaches and others underscore the reality that receptor-specific augmentation strategies remain a viable area for improvement on monoamine-based antidepressant treatments.

COMBINATION TREATMENTS WITH MIXED MONOAMINE ACTION

Consistent with the monoamine hypothesis of depression, dysregulated monoamine neurotransmitter function is presumed to cause a cascade of cellular and subcellular events ultimately leading to the development of depression. Although the idea of "monoamine-pure" depressive illness subtypes is a useful heuristic model, numerous pieces of evidence implicate a complex combination of roles for the classical monoamine neurotransmitters in the pathophysiology of depression. While amino acid depletion studies[12,13] have shown that serotonin and norepinephrine can be separately affected and induce remission in depressed patients who are effectively treated with either SSRIs or norepinephrine reuptake inhibitors, respectively, it is also recognized that concentrations of the metabolites of serotonin and norepinephrine in various body fluids may be concurrently disturbed in depression, suggesting a complex and interactive role for the neurotransmitters.[14] Clearly both systems play important roles. A relevant question that emerges from these observations is the degree to which a dual-action therapeutic intervention may have an additive or greater-than-additive effect on expanding the number of successfully treated patients and also potentially enhancing the response in those patients who may respond partially to agents active on only one neurotransmitter system alone. Several emerging lines of clinical evidence suggest that, indeed, therapeutic strategies that combine action on more than one neurotransmitter system may indeed have a greater clinical impact than single-action therapies.

It had been observed that coadministration of the TCA desipramine and the SSRI fluoxetine was associated with a down-regulation of β-adrenoceptors in rats in 4 days, before longer-term changes were observed in the relevant monoaminergic systems with either agent alone.[15] Based in part on these animal data, Nelson and others[16] studied the combination of those 2 drugs in depressed patients to determine whether the effect found in rats correlated with an increased, more rapid clinical response in depressed patients. Fourteen inpatients were given desipramine and fluoxetine in open-label fashion for 4 weeks, and their results were compared with those of retrospectively identified patients who took desipramine only. Patients receiving the combination responded more quickly than those receiving desipramine only, and 10 of 14 achieved remission within the 4-week period.

Other studies have confirmed that combination treatment with an SSRI and a TCA can enhance and hasten the onset of clinical response in depressed patients. In 8 cases of treatment-resistant, recurrent depression, Seth and coworkers[17] noted significant improvement with the combination treatment of an SSRI and nortriptyline. Weilburg and others[18] added fluoxetine to the treatment regimen of 30 depressed outpatients receiving antidepressant treatment; 26 (86.7%) improved. Unlike pindolol augmentation therapy, which specifically targets a specific serotonin receptor subtype to enhance response, combination treatment with an SSRI and a TCA targets a more expanded action on both serotonin and norepinephrine reuptake inhibition.

Perhaps even more compelling evidence to support the view that mixed-action antidpressants provide a superior clinical outcome is seen in the reports from the Danish University Antidepressant Group. For instance, this multisite group has provided evidence to suggest that the TCA clomipramine has greater clinical efficacy than does the SSRI citalopram.[19] In general, newer, more neurotransmitter-selective antidepressants appear to achieve equivalent or lower remission rates (20%–30%) than do broader-action agents such as the TCAs[20–24] when remission is typically considered a total score of 7 or less on the 17-item Hamilton Rating Scale for Depression (HAM-D).
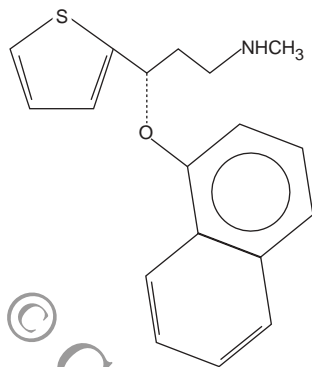
Unfortunately, the currently available antidepressant options that exhibit pharmacologic action on more than one monoamine neurotransmitter system also have notable drawbacks in use. For example, the TCAs are not monoamine selective; they have a considerable range of other pharmacologic actions that confer undesirable adverse effects. Therefore, opportunity clearly exists in the research and development of novel antidepressants that may improve upon the profile of existing agents.

SINGLE AGENTS WITH MIXED MONOAMINE ACTION

Venlafaxine

Venlafaxine has provided one of the first opportunities to examine the hypothesis that a specific dual-action antidepressant would provide a superior clinical response to single-action agents. Indeed, in a recently published meta-analysis of 8 randomized, double-blind studies of patients with major depressive disorder, venlafaxine was suggested

Figure 1. Chemical Structure of Duloxetine

Table 2. Relative Binding Affinity (K_i) of Duloxetine and Venlafaxine[a]

	K_i, nM		Norepinephrine/
Drug	Norepinephrine	Serotonin	Serotonin Ratio
Duloxetine	7.5	0.8	9
Venlafaxine	2480	82	30

[a]Data from Bymaster et al.[36]

to have a statistically significantly higher rate of remission than either SSRIs or placebo.[25] Preclinical studies of venlafaxine suggest that its affinity for the serotonin and norepinephrine reuptake transport sites is not equivalent. At lower plasma concentrations, the relatively higher affinity for the serotonin transport site results in a functional action virtually identical to that of an SSRI. It is only at higher plasma concentrations where the relatively lower affinity for the norepinephrine transport site is recruited, resulting in a more complete dual reuptake inhibition.[26–28] This dose-dependent action may explain why severely depressed patients may respond better to higher doses, up to 375 mg/day, the highest dose recommended by the manufacturer.[29] Unfortunately, it has also been reported that venlafaxine carries with it the risk of significant sustained increases in supine diastolic blood pressure at doses above 300 mg/day.[30,31] Venlafaxine clearly represents an important step forward in the development of mixed-action drugs. However, improvements in the relative balance of the dual action as well as an enhanced tolerability across the clinical dose range would be welcome advances.

Duloxetine

Duloxetine is a new dual-action antidepressant that inhibits the reuptake of both serotonin and norepinephrine (Figure 1). It has been demonstrated to be both safe and effective in depressed patients.[32,33]

Preclinical pharmacology. Wong and others[34] reported that duloxetine was associated with dose-dependent decreases of serotonin and norepinephrine reuptake in rat hypothalamus and cerebral cortex ex vivo. Those authors also showed similar results in vivo in rat hypothalamus and demonstrated that this inhibition remained constant for 6 hours. Using in vivo microdialysis, Kihara and Ikeda[35] studied the effects of duloxetine on extracellular levels of serotonin, norepinephrine, and dopamine in rat frontal cortex and nucleus accumbens. Extracellular levels of all 3 neurotransmitters were increased after oral administration of duloxetine. These increases were maintained over a 4-hour period. Again, these effects were more noticeable with higher doses of duloxetine. It has more recently been reported that duloxetine inhibits the reuptake of serotonin and norepinephrine more potently and more evenly than does venlafaxine in a similar in vitro model (Table 2).[36]

Duloxetine, then, is a potent and balanced inhibitor of serotonin and norepinephrine reuptake. It also has a low affinity for other neurotransmitter receptors, suggesting a reduced potential for undesirable effects compared with the TCAs. This pharmacologic profile is consistent with an agent expected to show antidepressant efficacy in a clinical setting.

Clinical experience with duloxetine. In an early report,[33] 79 patients with DSM-III-R major depression were treated with duloxetine in an open-label fashion. Response was defined as a 50% reduction from baseline in total HAM-D score, while remission was defined as a HAM-D score ≤ 6. Seventy-eight percent of patients responded to duloxetine, while 60% achieved remission. The authors report that the drug was well tolerated by these patients.

In a more recently completed double-blind study,[32] 179 male and female patients meeting DSM-IV criteria for nonpsychotic major depression were randomly assigned to treatment with duloxetine (N = 70), placebo (N = 70), or fluoxetine (N = 33). The primary outcome measure was change in score on the 17-item HAM-D. Duloxetine was provided in a forced-titration manner with an initial dose of 20 mg b.i.d., increasing in weekly increments up to 60 mg b.i.d. Overall, duloxetine was well tolerated as demonstrated by the observation that 76% of patients reached the maximum dose allowed. Duloxetine-treated patients experienced a significantly greater response than did the placebo-treated patients on the primary outcome measure (the HAM-D) and on nearly all the secondary outcome measures, including the Montgomery-Asberg Depression Rating Scale, the Clinical Global Impressions-Severity of Illness and Global Improvement scales, and the Patient Global Impressions-Improvement scale. In general, duloxetine was safe and well tolerated at doses up to and including 120 mg/day. A study currently underway compares duloxetine, 40 mg b.i.d. and 20 mg b.i.d., with placebo and paroxetine in patients with major depression. Again, duloxetine treatment has been associated with superior response compared with placebo and was well tolerated at doses of 40 or 80 mg/day (D. J. Goldstein, M.D., Ph.D.; Y. Lu, Ph.D.; M. J. Detke, M.D., Ph.D.; et al., manuscript submitted).

CONCLUSION

Monoamine-based antidepressants have been a mainstay and fundamental basis of therapeutic intervention in the management of depression and related conditions for over 20 years. Recent advances in our understanding of receptor subtypes accompanied by advances in medicinal chemistry resulting in molecules that combine action on reuptake inhibition and specific receptor subpopulations hold considerable promise for augmenting single neurotransmitter–based approaches and developing new single-agent, mixed-action strategies. In clinical practice, mixed reuptake inhibitors provide the best evidence that the efficacy of monoamine-based antidepressant therapies can indeed be improved.

Drug names: amitriptyline (Elavil and others), citalopram (Celexa), desipramine (Norpramin and others), fluoxetine (Prozac and others), nortriptyline (Pamelor and others), paroxetine (Paxil), venlafaxine (Effexor).

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