# Noradrenergic Approaches to Antidepressant Therapy

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A decade of remarkable research in neuroscience has given us a much more complete picture of how the central nervous system works and, in some instances, how the brain does not work when patients develop depression. Preclinical and clinical studies have shown that stimulation of the serotonergic system leads to noradrenergic effects and vice versa, confirming that the serotonin and norepinephrine systems are intimately connected in the central nervous system. Although medications that target the serotonergic neurotransmitter system have recently dominated antidepressant therapy, atypical antidepressants—with either mixed serotonergic and noradrenergic effects or exclusively noradrenergic effects—have been shown to be clinically efficacious medications. This increased understanding of the interrelationship between neurotransmitter systems has renewed interest in the role of neurotransmitters other than serotonin in the treatment of depression. With the introduction of reboxetine, a very selective norepinephrine reuptake inhibitor, researchers have had an opportunity to study the unique effects of norepinephrine in the etiology and treatment of depression. Ultimately, differences in neurotransmitter profiles may influence therapeutic potentials of antidepressants. For example, influencing norepinephrine may affect the expression of energy and interest, while influencing serotonin may affect impulse control and influencing dopamine may affect drive. Clinicians now have a range of antidepressants with variable neurotransmitter effects, different side effect profiles, and some interesting differences in functional utility in their armamentarium for treating depression.

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Until the introduction of the selective serotonin reuptake inhibitor (SSRI) class of antidepressants more than a decade ago, antidepressant therapy relied on tricyclic (TCA) and tetracyclic medications and, to a lesser extent, the monoamine oxidase inhibitors (MAOIs).[1] Most of these drugs influence the reuptake of both serotonin (5-HT) and norepinephrine (NE), although some TCAs have relative specificity for the NE reuptake mechanism.[2] These medications proved to be effective in the treatment of a range of mood and anxiety disorders, but adverse side effects often limited their use. Indeed, renewed concerns about the cardiovascular effects of TCAs and potential pro-arrhythmic properties have been recently voiced.[3]

## CURRENTLY AVAILABLE ANTIDEPRESSANTS

### Selective Serotonin Reuptake Inhibitors

SSRIs work acutely to inhibit the 5-HT reuptake protein and therefore increase synaptic levels of serotonin. Four SSRIs are now available in the United States for the treatment of depression: fluoxetine, sertraline, paroxetine, and citalopram. These medications have largely replaced the TCAs as first-line medications for the treatment of depression, mainly because of their improved side effect profile and reduced toxicity. SSRIs do not have anticholinergic properties of clinical significance, do not affect cardiac rate or rhythm, and are not lethal in overdose. In general, they are more convenient, tolerable, and safer than TCAs or MAOIs.[4]

In terms of efficacy, SSRIs are generally shown in comparison trials to be equivalent to TCAs. However, a controversy exists about whether TCAs, perhaps by virtue of their ability to influence the noradrenergic system, may be more effective than SSRIs in more severely depressed patients, such as those who are hospitalized or meet criteria for melancholia.[5] Many studies, however, have shown that SSRIs are effective for these more severely ill patients, and most show that they are better tolerated than TCAs.[6]

It is also important to note that SSRIs vary in their selectivity for the 5-HT reuptake transport protein. As shown in Figure 1, there is a wide range of NE reuptake–blocking properties with even fluoxetine, sertraline, and paroxetine having some effect on the NE system. The question has arisen, therefore, whether NE reuptake–blocking properties are relevant to the antidepressant effects of SSRIs.[7] It has also been shown by several investigators that the addition of a TCA to an SSRI improves response,[8–10] presumably because of the addition of NE reuptake–blocking effect to the 5-HT reuptake–blocking effect of the SSRIs.

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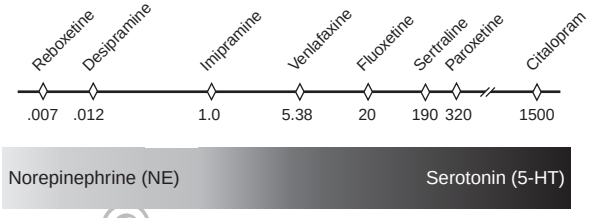
**Figure 1. Relative Reuptake Selectivity: Ratio of Inhibition (NE:5-HT)[a]**




[a]Figure 1 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.[26]

Because of the clinical success of SSRIs, theories have evolved linking the pathophysiology of mood and anxiety disorders to putative abnormalities in 5-HT neurotransmission. It is important to recognize, however, that the 5-HT and NE systems are intimately connected in the central nervous system (CNS). Most NE-producing neurons in the CNS originate in the pontine nucleus locus ceruleus (LC). Projections from the LC innervate widespread areas of the brain, including the hypothalamus, hippocampus, amygdala, and frontal cortex. Preclinical[11] and clinical studies[12] have shown that chronic (i.e., several weeks) stimulation of the 5-HT system leads to NE effects and vice versa. It is, indeed, 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 a neurotransmitter like 5-HT will lead to changes in other neurotransmitters like NE.

## Atypical Antidepressants

Several antidepressants available to physicians in the United States have demonstrable effects on neurotransmitter systems in addition to 5-HT that do not significantly increase adverse side effect profiles. These medications are sometimes referred to as "atypical" antidepressants, because of the difficulty in finding a unifying theme among them for classification. They include bupropion, nefazodone, venlafaxine extended release (XR), and mirtazapine. Reboxetine, a selective norepinephrine reuptake inhibitor (selective NRI), is currently available in some European countries, and an application has been submitted for Food and Drug Administration approval in the United States. The pharmacodynamic mechanisms of these medications, as with the tricyclic and tetracyclic antidepressants, suggest that NE neurotransmission effects are highly relevant to the antidepressant action of drugs.

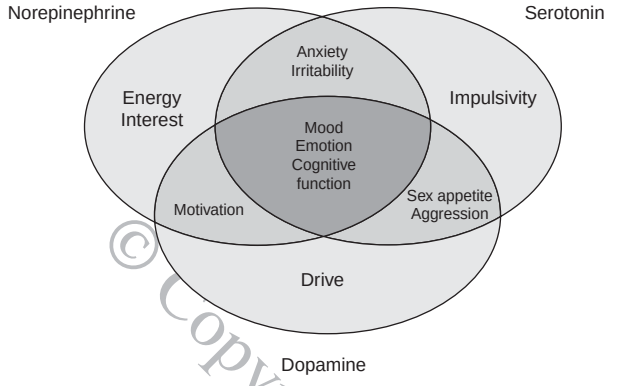
The exact transmitter effects of the antidepressant bupropion are unclear, but studies have shown effects on both dopamine (DA) and NE reuptake.[2,7] Bupropion appears to have efficacy equal to other antidepressants[13] and has been reported to be less likely to induce mania in bipolar depressed patients, although there are few empirical data for this claim.[14] Bupropion can produce an increase in anxiety and insomnia in some patients, but it is also associated with a lower rate of sexual side effects than the SSRIs.[13] Although the drug was originally associated with an increased seizure rate, this does not appear to be a pressing clinical issue when the medication is correctly administered.

Nefazodone works primarily by blocking a postsynaptic serotonin receptor, the 5-$HT_2$ receptor, but also has 5-HT and NE reuptake inhibition properties. In clinical trials, nefazodone has been proved equal in efficacy to several SSRIs,[15] with a low incidence of sexual side effects and a positive effect on insomnia and comorbid anxiety symptoms. Its inhibition of the 3A4 isoenzyme of the cytochrome P450 enzymatic system requires caution when coprescribing nefazodone with certain other medications.[16]

Venlafaxine XR has both 5-HT and NE reuptake–blocking properties,[17] although the latter may not be clinically meaningful until doses of at least 150 mg/day have been reached. Venlafaxine XR has been proved effective across a broad range of depression severities, suggesting that its dual 5-HT and NE receptor effects may confer some additional benefit as severity worsens.[18] Venlafaxine XR also recently became the first medication approved for the specific treatment of generalized anxiety disorder. A meta-analysis[19] suggested that venlafaxine XR might be more effective than SSRIs (success rate 73.7% vs. 61.1%). The medication is generally as well tolerated as SSRIs, but it can produce blood pressure increases in a small percentage of patients and, as with the SSRIs, is also associated with sexual side effects.

Mirtazapine has complex receptor effects that ultimately result in stimulating both the 5-HT and NE systems. By acutely blocking the $\alpha_2$-noradrenergic receptor, mirtazapine results in both a release from negative feedback of the NE neuron and a release of inhibition of the 5-HT neuron. In addition, mirtazapine blocks 2 postsynaptic serotonin receptors, 5-$HT_2$ and 5-$HT_3$, and has antihistaminic effects. The result is an antidepressant with efficacy comparable to other antidepressants but with reduced sexual side effects compared with the SSRIs.[20] Mirtazapine also relieves anxiety in depressed patients and has little potential to produce nausea, probably by virtue of its 5-$HT_3$ blocking properties. In one study, mirtazapine had sustained antidepressant effects comparable to amitriptyline (both superior to placebo) at 20 weeks, and antidepressant effects superior even to amitriptyline (and placebo) at the endpoint of the study, a mean of 2 years from initiation.[21] Again, the suggestion has been that mirtazapine may have a favorable efficacy profile by virtue of its dual 5-HT and NE effects. Mirtazapine has been found to be sedating and to cause an increase in appetite in some patients.

**Figure 2. Aspects of Functioning Attributed to Norepinephrine, Serotonin, and Dopamine[a]**




[a]Adapted from Healy and McMonagle,[24] with permission.



### Norepinephrine Reuptake Inhibitors

Reboxetine is a novel selective NRI that has been available in certain European countries. It has no active metabolites or effects on the P450 enzymatic system. Reboxetine has almost no acute effects on serotonergic, dopaminergic, cholinergic, or histaminic systems and is a slightly more potent NE reuptake inhibitor than desipramine.[22] Clinical studies have shown that reboxetine is an effective antidepressant with little potential for sexual side effects. A recent study compared reboxetine to the TCA desipramine in 258 patients with major depression.[23] Reboxetine proved more effective than placebo and, on some measures, more effective than desipramine. Its adverse side effect profile includes dry mouth, constipation, headache, sweating, insomnia, and dizziness.

## RATIONALE FOR LOOKING BEYOND SEROTONERGIC ANTIDEPRESSANTS

Healy and McMonagle[24] have presented an interesting theory about the domains of function affected by drugs that influence the NE, 5-HT, and DA systems. The Venn diagram (Figure 2) presents their ideas. According to this view, influencing NE affects levels of energy and interest, influencing 5-HT affects impulse control, and influencing DA affects drive. All 3 systems affect mood, emotion, and cognitive function. Serotonin and NE overlap in effects on anxiety and irritability. This interesting approach suggests that clinicians may consider tailoring their choice of antidepressants based on the specific symptoms and functional deficits of the individual and also on different adverse side effect profiles.

In the end, however, it will always be perilous to make judgments about the mechanism of action of antidepressant medications based on their acute effects on neurotransmitter receptors, both presynaptically and postsynaptically. As Hyman and Nestler[25] have convincingly argued, these effects occur rapidly when an antidepressant is first administered, but weeks are generally required before patients with mood and anxiety disorders respond clinically. The implication is that effects downstream from those on neuronal membrane receptors must occur before antidepressants become effective and that many of these downstream effects may represent final common pathways through which antidepressants of many different classes are ultimately effective. The cascade of events outlined by Hyman and Nestler[25] occur over weeks following the start of antidepressant therapy and include influences on second messenger systems, phosphorylation of protein kinases within the cytoplasm of the postsynaptic neuron, activation of transcription factors, and, ultimately, binding of these factors to promoter regions of genes inside the nucleus of the postsynaptic cell. These factors ultimately affect gene expression. Modern neuroscience now focuses on these intraneuronal events with an eye to identifying the true mechanism of action of antidepressant drugs.

Until recently, we might say that the 1990s have been a "serotonin" era for our focus on antidepressant medications. However, it is now recognized that even SSRIs have NE effects. Also, the 5-HT and NE systems are intimately connected in the CNS, and the "atypical" antidepressants that have either mixed 5-HT and NE effects or even exclusive NE effects are clinically efficacious medications. These revelations have led to a renewed interest in the role of the NE system in the treatment of depression, as well as an understanding that the ultimate mechanism of action of antidepressants probably rests well beyond membrane reuptake protein inhibition. Although it will take years of intensive laboratory examination to understand these mechanisms, clinicians now have available a range of antidepressants with variable neurotransmitter effects, different side effect profiles, and some interesting potential differences in functional utility.

*Drug names:* amitriptyline (Elavil and others), bupropion (Wellbutrin), citalopram (Celexa), desipramine (Norpramin and others), fluoxetine (Prozac), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), reboxetine (Vestra), sertraline (Zoloft), venlafaxine (Effexor).

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