

# The Dual-Action Hypothesis: Does Pharmacology Matter?

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With treatment to remission as the gold standard for depression treatment, there is considerable reassessment of treatment approaches with the view to finding and employing agents capable of rapidly eliminating all symptoms and returning patients to normalcy. The mechanisms of action intrinsic to different classes of antidepressants are at the center of this review. The selective serotonin reuptake inhibitors (SSRIs), the most commonly prescribed antidepressants, have a single-action mechanism involved in modulating the reuptake of the neurotransmitter serotonin. The selectivity of the SSRIs renders them safer and more tolerable than the earlier multi-acting monoamine oxidase inhibitors (MAOIs) and the tricyclic antidepressants (TCAs). However, because serotonin is not the only neurotransmitter implicated in the pathophysiology of depression, the selectivity that bestows safety to SSRIs may limit somewhat the antidepressant effect in some patients. A newer class of dual-action antidepressants acts by inhibiting the reuptake of both serotonin and norepinephrine. These serotonin-norepinephrine reuptake inhibitors (SNRIs) have improved side effect profiles compared with the earlier multi-action antidepressants, compare favorably with the SSRIs on safety and tolerability, and reduce depression and its associated symptoms with greater rapidity. This review compares the neurobiology of single- and dual-action mechanisms.

*(J Clin Psychiatry 2004;65[suppl 17]:5-10)*

**M**ajor depressive disorder (MDD) is a complex and heterogeneous disorder. Although a diagnosis of MDD requires the presence of specific core symptoms,<sup>1</sup> patients can present with countless combinations of these and other symptoms. For example, depending on the particular constellation of symptoms present, depression can be categorized as a specific subtype, such as atypical (characterized by hypersomnia, hyperphagia, mood reactivity, leaden paralysis, and rejection sensitivity) or melancholic (characterized by psychomotor retardation, lack of mood reactivity, pervasive anhedonia, etc.).<sup>1-3</sup> Further, regardless of the subtype, patients with MDD can experience a wide range of emotional and physical symptoms to varying degrees. A significant proportion of patients with MDD experience anxiety symptoms.<sup>4,5</sup> Others, par-

ticularly patients encountered in primary care settings, experience and present with physical symptoms as their primary complaint.<sup>6,7</sup> Finally, depression is frequently associated with comorbid anxiety disorders, substance abuse, or other disorders.<sup>8</sup>

For many patients, depression represents a lifelong episodic condition, with each subsequent episode raising the chance of future recurrence.<sup>9</sup> Evidence of neurobiological changes in the brains of depressed patients suggests that these changes are important factors in determining the course of an individual's depressive illness.<sup>10,11</sup> Specifically, findings from studies using precise and time-lapse imaging techniques have revealed that depression affects specific neuroanatomic regions, such as the amygdala, cingulate cortex, and hippocampus of the brain. Shelton et al.<sup>11</sup> demonstrated that the volume of the hippocampus, which has functional ties to learning, memory, contextual fear conditioning, and neuroendocrine regulation, was reduced in depressed patients compared with healthy subjects. The data also revealed a correlation between volumetric reduction in the hippocampus and the duration of depression as well as the number of days the condition went untreated. There is also evidence to suggest neurobiological changes that occur during early depressive episodes, which may be partly responsible for sensitization or "kindling" to the depressive condition (i.e., the onset of subsequent depressive episodes becomes progressively more self-directing and less associated with environ-

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*This article was derived from a series of teleconferences held in June 2004 and was supported by funding from Wyeth Pharmaceuticals.*

*Dr. Shelton has received grant/research support from or been a consultant or speaker for Abbott, Bristol-Myers Squibb, Eli Lilly, Glaxo, Janssen, Pfizer, Roehm-Polenc-Rorer, Sanofi, SmithKline Beecham, Solvay, Wyeth-Ayerst, and Zeneca.*

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mental stress).<sup>10</sup> Collectively, these findings point to the need to detect and treat depression as early as possible and, along with support from clinical evidence,<sup>9,10,12</sup> underscore the importance of achieving remission as the goal of treatment.<sup>13,14</sup>

It has long been believed that, although there may be differences in individual response to treatment, overall, all antidepressants are comparably effective. However, it has been suggested that different subtypes of depression respond preferentially to certain antidepressants (e.g., atypical depression tends to respond better to monoamine oxidase inhibitors [MAOIs] vs. tricyclic antidepressants [TCAs]) and that some individual symptoms of depression have varying degrees of response to different classes of antidepressants. Indeed, there may be differences in efficacy among classes of antidepressants with differing mechanisms of action. Specifically, there is some controversy over the issue of whether dual- or multiple-action antidepressants offer advantages over single-action medications. This article explores the issue in terms of neurobiological evidence of the roles of serotonin (5-HT) and norepinephrine (NE) and provides a basis for understanding how differences in pharmacology might translate to differences in clinical outcomes.

## EVOLUTION OF ANTIDEPRESSANT TREATMENT

Antidepressant pharmacotherapy is widely accepted as an effective treatment option for MDD. The development of antidepressant treatment began with agents that act on multiple neurotransmitters (e.g., MAOIs and TCAs), followed by those that are more selective (i.e., selective serotonin reuptake inhibitors [SSRIs]). Most recently, interest has returned to dual- or multiple-acting antidepressants, such as the serotonin and norepinephrine reuptake inhibitors (SNRIs) and mirtazapine, which affect multiple neurotransmitters.

The MAOIs block the metabolism of multiple monoamine neurotransmitters: 5-HT, NE, and dopamine. The origins of the MAOIs can be traced back to the early 1950s when it was discovered that the antimycobacterial agent iproniazid, then being investigated as a likely treatment for tuberculosis, also had psychoactive properties. Early tests with terminally ill patients showed that they became cheerier, more optimistic, and more physically active when given the drug.<sup>15</sup> Shortly after iproniazid was developed, it was demonstrated that compounds in this class, which includes isocarboxazid, phenelzine, and tranylcypromine, interfered with the enzymatic breakdown of the monoamines by inhibiting the mitochondrial enzyme monoamine oxidase. The MAOIs were first used to treat patients in the 1960s.

About then, too, another class of antidepressants was in development. Molecular modifications of phenothiazine resulted in the synthesis of imipramine, the first clini-

cally usable TCA. Later, other members of this class such as amitriptyline, clomipramine, desipramine, and maprotiline were developed. These drugs exert their effect by blocking the removal of 5-HT and NE from synapses, in effect raising the concentrations of these transmitters, which bind with receptors.

The MAOIs and the TCAs represented significant advances in the treatment of depression. However, their use was restricted by notable safety and toxicity concerns, stemming from their undesirable affinity for a range of receptors, including muscarinic,  $\alpha$ -adrenergic, and histaminergic, and potentially dangerous interactions between these drugs and other substances.

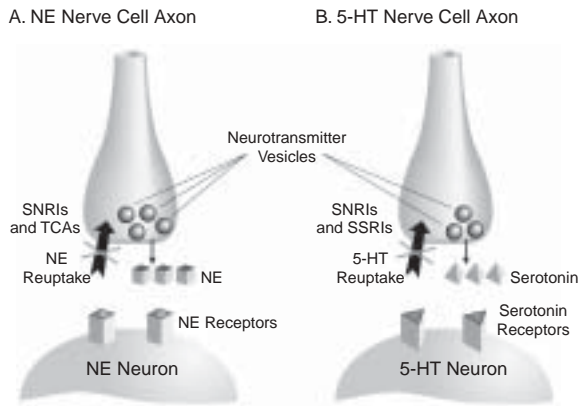
The SSRIs, which include citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline, have become the most widely used antidepressants over the past decade. The overriding factor in their acceptance among both clinicians and patients is their comparatively advantageous safety and tolerability profiles over the preceding antidepressants. While the selectivity of the SSRIs renders these agents safer than both the MAOIs and the TCAs, there is a concern that it may also render them less broadly effective than dual-action antidepressants. This concern ignited strong interest that led to substantial success in the development of safer dual-action antidepressants.

The dual-action antidepressants include bupropion (which is presumed to exert antidepressant effects via noradrenergic and dopaminergic mechanisms), the norepinephrine- and serotonin-releasing antidepressant (NaSSA) mirtazapine, and the SNRIs venlafaxine and duloxetine. Venlafaxine gained regulatory approval for MDD in 1993 (immediate release) and in 1997 (extended release); duloxetine was recently released for treatment of MDD in August 2004. Like the TCAs, the SNRIs block both serotonergic and noradrenergic reuptake, thereby increasing the concentration of both NE and 5-HT in neuronal synapses (Figure 1). However, compared with the TCAs, the SNRIs are more selective; they have limited affinity for the receptors associated with the troublesome side effects associated with TCAs (i.e., muscarinic,  $\alpha$ -adrenergic, and histaminergic). Thus, the tolerability and safety profile of SNRIs is more favorable than that of TCAs and comparable to that of SSRIs.

## DUAL-ACTION RATIONALE: PATHOPHYSIOLOGY OF DEPRESSION

From a treatment standpoint, a thorough comprehension of the neurochemical underpinnings of depression is of benefit. Over the past several decades, evidence has accumulated that shows that depression involves monoaminergic pathways. Depression appears to be caused, at least in part, by interferences to brain circuits that carry signals of certain monoamine neurotransmitters.<sup>16</sup> At this time, converging lines of evidence from multiple lines of re-

**Figure 1. Schematic Showing the Mechanisms of Action of TCAs and SNRIs (A) and SSRIs and SNRIs (B)**



Abbreviations: 5-HT = serotonin, NE = norepinephrine, SNRIs = serotonin-norepinephrine reuptake inhibitors, SSRIs = selective serotonin reuptake inhibitors, TCAs = tricyclic antidepressants.

search illustrate the importance of NE and 5-HT circuits in MDD.

Some NE pathways project into the same areas of the brain as the 5-HT pathways: in the frontal cortex to regulate mood, in the limbic areas to control anxiety and emotions, and in the hypothalamus to regulate eating, appetite, weight, sex drive, and pleasure. In addition, there are unique NE projections: to the frontal cortex to regulate cognition and attention and to the cerebellum to modulate motor movements. It is hypothesized that diminished activities of specific pathways for 5-HT and NE are linked to depression.<sup>17</sup> This notion is supported by evidence demonstrating that administration of reserpine (which depletes NE levels) to healthy individuals induced depressive symptoms.<sup>18</sup>

A series of studies through the 1990s examined the effects of neurotransmitter depletion to further elucidate the roles of 5-HT and NE in depression. The results showed that the therapeutic effects of SSRIs could be reversed with the rapid depletion of 5-HT but not NE. Conversely, the therapeutic effects of an NE reuptake inhibitor could be reversed with NE depletion, but not when 5-HT was depleted.<sup>19</sup> Specifically, in one study, depressed patients were randomly assigned to either desipramine or fluoxetine treatment arms.<sup>20</sup> Once remission was achieved, responders were given  $\alpha$ -methyl-*p*-tyrosine (AMPT), to block synthesis of NE and dopamine, thus depleting NE levels. A majority of desipramine responders (13/16 or 81%) relapsed during AMPT tests, in contrast to fluoxetine responders, who showed a lower rate of relapse from AMPT (4/21 or 19%). Similarly, results of 2 studies<sup>21,22</sup> demonstrated that depletion of serotonin induced by tryptophan depletion resulted in relapse for a greater propor-

tion of patients who had remitted with SSRIs or MAOIs than those remitters who had taken desipramine. These findings provide further evidence that enhancing trans-synaptic signaling with both serotonin and norepinephrine is involved in mediating antidepressant activity.<sup>19</sup>

Enhancement of neurotransmission in normal monoamine neurons appears to be at least part of the way that antidepressants produce their effects. However, because it is unlikely that depression results solely from a monoamine deficiency, there is interest in the actions of antidepressants beyond increasing neurotransmitter levels. Recent studies have begun to explore the potential of these drugs in restoring neuronal activity in the areas of the brain that they modulate. For example, preclinical and clinical studies have shown that stress may result in neuronal atrophy and cell death, which may be associated with the development of depression or other mood disorders.<sup>23</sup> The action of antidepressants may be related to their effects on the signal transduction cascades that control these responses.<sup>23</sup> Specifically, antidepressant treatment increases the levels of norepinephrine and serotonin at the synapse, which increases receptor binding events and activates intracellular signal transduction cascades such as those coupled to adenylyl cyclase (AC). In this case, chronic treatment increases coupling of receptors to stimulatory guanosine triphosphate (GTP)-binding protein ( $G_s$ ), resulting in the activation of AC. This, in turn, results in the synthesis of cyclic adenosine monophosphate (cAMP), which activates protein kinase A (PKA), a phosphorylation enzyme. One substrate phosphorylated by PKA is cyclic AMP response element binding protein (CREB), which binds to specific elements in the promoters of genes such as the neurotrophins, increasing their expression. Thus, by indirectly affecting these pathways, antidepressants may enhance the functioning and survival of neurons.<sup>25</sup>

The activation of these pathways appears to be related to the fact that 5-HT and NE may affect survival and growth of neurons by decreasing glucocorticoid levels and increasing brain-derived neurotrophic factor (BDNF) levels. The period between the attainment of effective plasma antidepressant levels and the onset of clinical improvement may be the duration needed for the enhancement or suppression of specific gene products and both the growth of neurons and sustained survival of neurons. Preliminary data from animal models suggest that the time elapsing before new neurons are produced following the start of antidepressant treatment was similar to the time preceding the onset of therapeutic effects as seen in the clinic.<sup>24</sup> Moreover, the findings point to different mechanisms for NE and 5-HT in neurogenesis.<sup>24</sup> Specifically, the effects of serotonergic and noradrenergic antidepressants were assessed in normal wild type mice and in mice without the 5-HT<sub>1A</sub> receptor, a receptor that has been linked to modulation of mood- and anxiety-related behaviors. Both

**Table 1. Clinical Benefits of Dual-Acting Antidepressants**

Efficacious in treating broad range of populations with MDD <sup>25-37</sup>
Rapid onset of action <sup>38-49</sup>
Greater overall efficacy compared with SSRIs <sup>32-37</sup>
Effective in treating broad range of symptoms, including somatic and painful physical symptoms <sup>46,50-62</sup>
Abbreviations: MDD = major depressive disorder, SSRIs = selective serotonin reuptake inhibitors.

groups were treated with the SSRI fluoxetine, the predominantly noradrenergic antidepressant imipramine, or vehicle for a period of 28 days. The researchers discovered that, following an appropriate lag time, the imipramine promoted the development of neurogenesis in both types of mice. Conversely, the fluoxetine treatment no longer promoted neurogenesis in the mice lacking the 5-HT<sub>1A</sub> receptor. This is an indication that 5-HT<sub>1A</sub> receptors are required for neurogenesis with fluoxetine treatment but not imipramine treatment. The findings of these experimental animal models suggest that during chronic antidepressant treatment, noradrenergic and serotonergic neurotransmitter systems work via independent molecular pathways to induce neurogenesis.

#### DUAL-ACTION RATIONALE: CLINICAL BENEFITS

Clearly, then, both serotonergic and noradrenergic systems are involved in the pathophysiology and treatment of depression. Therefore, it might be expected that treatments affecting both 5-HT and NE systems may have greater efficacy with a broader spectrum of symptoms. This hypothesis is supported by evidence derived from clinical practice—where prescribing trends show physicians augmenting partial responders to SSRIs with the NE and dopamine modulator bupropion to create dual-action treatment—and from findings of antidepressant comparison studies.

More detailed discussions of the clinical evidence of the efficacy of SNRIs in treating depression and anxiety are included elsewhere in this supplement. Briefly, there are a number of clinical benefits that have been associated with dual reuptake inhibition (Table 1).<sup>25-62</sup> Proof-of-concept studies have suggested advantages, including greater efficacy and a shorter time to improvement, when patients are treated with a combination of an SSRI and a noradrenergic TCA versus treatment with either agent alone.<sup>63,64</sup> Additional support for these and other advantages is provided by the results of numerous clinical trials. Specifically, several clinical trials and meta-analyses have demonstrated an advantage for dual reuptake inhibitors (including TCAs and SNRIs) over SSRIs in treating a broad range of depressed patients, including those with more severe depression, such as depressed inpatients,<sup>25-31</sup> as well as in general populations of depressed outpatients.<sup>32-37</sup> Evidence also suggests that a dual mechanism

of action, such as that associated with SNRIs or mirtazapine, is associated with a time to onset of action of 1 to 2 weeks,<sup>38-49</sup> which may represent an advantage over SSRIs. Finally, dual reuptake inhibitors, specifically the SNRIs venlafaxine and duloxetine, have been shown to effectively treat a broad range of depressive symptoms, including somatic or painful physical symptoms<sup>46,50-53</sup> and symptoms of anxiety associated with depression<sup>54,55</sup> or anxiety disorders.<sup>56-62</sup>

#### CONCLUSIONS

Although the precise mechanisms underlying the pathophysiology of depression and the therapeutic effects of antidepressants have not been completely elucidated, it is clear that serotonin and norepinephrine are an important part of these processes. The single-action SSRIs persist as the most widely prescribed antidepressants, but there is renewed neurobiological, pharmacologic, and clinical interest in the dual-action antidepressants catalyzed by the favorable safety and efficacy profiles of mirtazapine and the SNRIs. While the SSRIs are an indispensable class of antidepressants, there is considerable evidence in clinical practice and from a variety of clinical trials to suggest that the dual-acting antidepressants may have therapeutic advantages, for at least some patients.

*Drug names:* amitriptyline (Elavil and others), bupropion (Wellbutrin and others), citalopram (Celexa), clomipramine (Anafranil and others), desipramine (Norpramin and others), duloxetine (Cymbalta), escitalopram (Lexapro), fluoxetine (Prozac and others), imipramine (Tofranil, Surmontil, and others), isocarboxazid (Marplan), mirtazapine (Remeron), paroxetine (Paxil and others), phenelzine (Nardil), reserpine (Serpalan and others), sertraline (Zoloft), tranylcypromine (Parnate), venlafaxine (Effexor).

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