

# Noradrenergic Versus Serotonergic Antidepressants: Predictors of Treatment Response

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© Serotonin selective reuptake inhibitors (SSRIs) have generally proven to be as effective as tricyclic antidepressants (TCAs) in the treatment of major depression and have an improved side effect profile. However, data suggest that the SSRIs are not as effective as the TCAs in certain subsets of depressed patients, indicating the importance of norepinephrine reuptake inhibition for such patients. Evidence for the role of norepinephrine in depression comes from early studies on excretion of catecholamines and more recent studies on receptor function, second messenger systems, and gene modification. These data are reviewed in this article. Data from a multicenter, randomized, controlled clinical trial comparing desipramine, a relatively norepinephrine-selective TCA, and the SSRI fluoxetine in moderate to marked major depression suggest a differential response depending on the antidepressant. The 2 drugs were overall similar in efficacy; however, in severely ill patients, there was a suggestion that desipramine was more likely to induce remission than fluoxetine. Urinary metabolite 3-methoxy-4-hydroxyphenylglycol levels were a better predictor of likelihood of remission than severity of episode or drug treatment. Desipramine and fluoxetine produced different longitudinal effects in catecholamine excretion, indicating that the 2 agents act through different mechanisms. Given the good therapeutic profile but relative risks associated with TCA therapy, selective norepinephrine reuptake inhibitors, such as reboxetine, which has a good safety profile, could be a major step forward in the treatment of depression. (*J Clin Psychiatry* 1998;59[suppl 14]:15-18)

The 2 major classes of antidepressants in use in current pharmacologic practice are the tricyclic antidepressants (TCAs) and the more recently developed serotonin selective reuptake inhibitors (SSRIs). Although some TCAs, such as desipramine, are relatively selective for norepinephrine, most TCAs also block other receptor systems, leading to significant side effects.<sup>1</sup> In particular, TCAs affect  $\alpha_1$ -noradrenergic receptor systems, resulting in orthostasis and dizziness, and block cholinergic receptors, with muscarinic side effects such as dry mouth and constipation. In addition, TCAs may have antihistaminic effects leading to dry mouth and sedation, with paradoxical stimulation occurring at high doses and in children.

SSRIs are generally as effective as TCAs in the treatment of major depression and have an improved side effect profile.<sup>2</sup> However, evidence suggests that SSRIs may

not be as effective as TCAs in certain subsets of depressed patients.<sup>3</sup> Thus, the inhibition of norepinephrine reuptake may be an important, even necessary, pharmacologic effect for reversing somatic symptoms in some patients, and an antidepressant drug that selectively targets the noradrenergic system could have significant benefits for the treatment of depression without the adverse events associated with TCAs.

Until recently, pure noradrenergic uptake blockers have not been available. Agents such as the relatively norepinephrine-selective antidepressant desipramine have been used in studies to assess the different roles of norepinephrine and serotonin in depression. This article reviews some of these data.

The introduction of reboxetine, a unique, selective norepinephrine reuptake inhibitor with a good safety profile,<sup>4</sup> could, in the light of data indicating a clear role for norepinephrine in depression, alter current treatment strategies for the management of depression.

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## MONOAMINE THEORIES OF THE BIOCHEMICAL BASIS OF MAJOR DEPRESSION: THE ROLE OF NOREPINEPHRINE

Biological theories of depression have revolved for many years around 2 monoamine systems, norepinephrine and serotonin. It is apparent, however, that these 2 systems do not completely explain the pathophysiology of

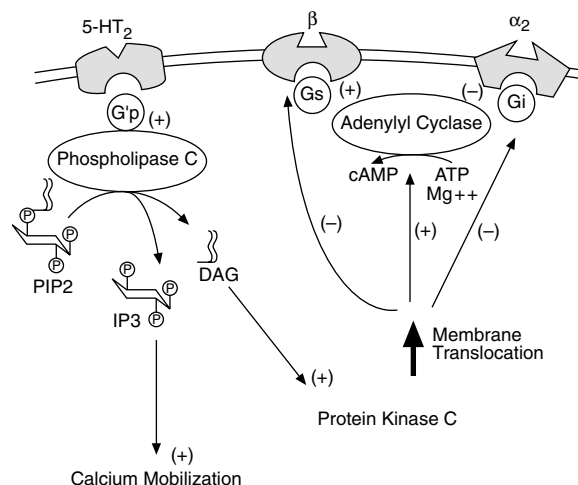
depression. The hypothalamic-pituitary-adrenal (HPA) axis, including the effects of corticotropin-releasing hormone (CRH) and cortisol, plays an important role in the pathophysiology of depression as do second and third messenger systems.

Major theories of depression involving norepinephrine are centered on (1) a decrease in release or production from presynaptic neurons; (2) an increase in presynaptic  $\alpha_2$ -adrenergic autoreceptor activity, which results in a decreased release of norepinephrine; and (3) a disregulated noradrenergic system in which there is normal or even enhanced production of norepinephrine but subsensitive postsynaptic receptor activity or second and/or third messenger activity.

There is considerable pathophysiologic evidence that is supportive of noradrenergic theories of depression.<sup>5</sup> It has been known for some time that there is a gross abnormality in central and peripheral noradrenergic function in patients with depression, anxiety disorders, and panic attacks, and recent evidence also shows that the noradrenergic system is involved in posttraumatic stress disorder. Among the biochemical data supportive of a role for norepinephrine in depression is the finding that patients with bipolar depression and a subset of patients with unipolar depression exhibit a low urinary output of the norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG).<sup>6</sup> In addition, patients with low urinary MHPG levels have been reported to be responsive to the relatively norepinephrine-selective antidepressant imipramine.<sup>7</sup> Blunted cyclic adenosine monophosphate (AMP) and growth hormone responses to the  $\alpha_2$ -adrenoceptor agonist clonidine in depressed patients have also been observed,<sup>8,9</sup> indicating a disorganized or subnormal processing of neuronal signaling. In suicide victims, there is an increased density of central  $\alpha_2$ -adrenergic receptors and an up-regulation of postsynaptic  $\beta$ -adrenergic receptors.<sup>10</sup> This suggests a decrease in the release and/or production of norepinephrine in depressed individuals. Furthermore, there is a relapse of depressive symptoms when blockers of norepinephrine synthesis, such as  $\alpha$ -methylparatyrosine (AMPT), are given to patients whose depression is successfully managed with drugs, such as desipramine, that inhibit norepinephrine uptake.<sup>11</sup>

In terms of the serotonergic system, most evidence supports a decrease in transport and/or release of serotonin, or a decreased efficacy of serotonergic transmission. The role of serotonin in the pathophysiology of depression has been investigated by a number of groups, including those of Coppen, Åsberg, and Curzon.<sup>12</sup> A relationship between low levels of the metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA), in cerebrospinal fluid and violent suicide has been established.<sup>13</sup> The platelet concentration of serotonin is decreased,<sup>14</sup> as is the binding of <sup>3</sup>H-imipramine to the serotonin transporter in platelets.<sup>15</sup> The density of 5-HT<sub>2</sub> receptors has been found to be

Figure 1. Mediation of Receptor-Effector Cross-Talk in the Central Nervous System by G Proteins\*†



\*From reference 18, with permission.

†Abbreviations: ATP = adenosine triphosphate, cAMP = cyclic adenosine monophosphate, DAG = diacylglycerol, IP3 = inositol triphosphate, PIP2 = phosphatidylinositol 4,5-biphosphate.

increased in the brains of suicide victims,<sup>13</sup> a phenomenon that can be reversed by antidepressant treatment. Furthermore, the successful treatment of depression with SSRIs is reversed in patients depleted of the serotonin precursor tryptophan.<sup>16,17</sup>

### SUBRECEPTOR ACTIVITY IN DEPRESSION

In recent years, the emphasis of research into depression has shifted away from simple monoaminergic theories toward the investigation of subreceptor activities.<sup>18</sup> Manji<sup>18</sup> hypothesized cross-talk between transmitter systems, and there is evidence that various monoamines or monoaminergic receptors are able to alter cyclic AMP levels through the same G protein (Figure 1).<sup>19</sup> An abnormality in such a G protein or in the responsivity of cyclic AMP to any of the receptors will result in an alteration in noradrenergic and/or serotonergic neurotransmission. The molecular biology of the subreceptor components, including cyclic AMP, protein kinases, and nerve growth factors, such as brain-derived neurotrophic factor (BDNF), is currently under investigation.<sup>20-23</sup> The cross-talk hypothesis suggests that some patients may be responsive to multiple types of medication, although the mechanism by which changes in the biology of the individual may occur could vary between classes of drug. Thus, it is important to have alternative treatment strategies in our armamentarium to optimize the response of individual patients.

### PREDICTORS OF TREATMENT RESPONSE

In order to optimize the treatment regimen for a particular patient, a method for predicting the response of

**Table 1. Changes in Catecholamine and Metabolite Levels After 6 Weeks' Treatment With Either Desipramine or Fluoxetine\***

	Desipramine	Fluoxetine
Norepinephrine	↑	—
3-methoxynorepinephrine (NMN)	—	↓
3-methoxy-4-hydroxymandelic acid (VMA)	↓	↓
3-methoxy-4-hydroxyphenylglycol (MHPG)	↓	↓
Sum of metabolites	↓	↓
Norepinephrine/sum of metabolites	↑	—

\*Data from reference 26.  
Symbols: ↑ = increase, ↓ = decrease, — = no change.

patients to different classes of antidepressant drug is required. There is evidence that low urinary excretion of MHPG predicts a positive (rapid) response to relatively norepinephrine-selective drugs such as imipramine, nortriptyline, desipramine, or maprotiline.<sup>24,25</sup> Individuals with high levels of urinary MHPG tend to respond poorly to these drugs.

In an investigation by our group comparing the efficacy and safety of desipramine and fluoxetine in moderate to severe major depression,<sup>19</sup> we aimed to identify predictive biochemical factors for patient response and remission, i.e., does the excretion of the catecholamine metabolite MHPG predict differential responses to desipramine or fluoxetine? The hypothesis was that individuals with high MHPG excretion levels would respond to fluoxetine and those with low urinary excretion of MHPG would respond to desipramine.

Sixty patients (hospitalized and outpatients) diagnosed with major depression (HAM-D  $\geq$  20) entered the study.<sup>19</sup> The patients received 6 weeks' treatment with desipramine (up to 250 mg/day) or fluoxetine (up to 60 mg/day). Major baseline and posttreatment biological measurements included urinary and plasma catecholamines and metabolites, plasma urinary and free cortisol, platelet tritiated imipramine binding, and blood levels of treatment drug. In terms of efficacy, the 2 treatments were similar. There was a suggestion from the data that the severity of depression at baseline could be a predictor of differential response. Using chi-square or Fisher exact tests, remission appeared to be more likely in desipramine-treated, severely ill patients (e.g., HAM-D > 25) than in fluoxetine-treated patients, although, when regression analysis was applied, drug and severity of depression did not predict remission.<sup>26</sup>

Using logistic regression analysis, we addressed the question of whether disease severity, drug treatment, or urinary MHPG levels predicted a response to antidepressant therapy.<sup>27</sup> In these patients, we found that low pretreatment MHPG levels predicted a response to either desipramine or fluoxetine. Furthermore, high excretors of catecholamines tended to be nonresponders or partial responders to either drug. No significant link to either disease severity or drug treatment was found. Although

catecholamine excretion did not differentiate fluoxetine and desipramine responders, these data suggest that catecholamine excretion patterns may predict the likelihood of treatment response to antidepressant agents. The positive response in low MHPG patients and the lack of response in high MHPG excretors is consistent with the cross-talk hypothesis,<sup>18</sup> in that low MHPG patients may respond to either a serotonergic or a noradrenergic agent and high catecholamine excretors may exhibit a postsynaptic post-receptive abnormality that is not corrected by blocking the uptake of either norepinephrine or serotonin.

### Longitudinal Analysis of Urinary Catecholamine Excretion

Longitudinal analysis of urinary catecholamine and metabolite excretion has revealed interesting data regarding the mechanism of action of various antidepressants.<sup>27-29</sup> Patients who received the norepinephrine reuptake blocker desipramine were monitored over time and exhibited a decrease in catecholamine metabolite excretion and an increase in norepinephrine excretion.<sup>25,27</sup> This is because the reuptake of norepinephrine into the presynaptic neuron is prevented, and so it is excreted largely unchanged. Furthermore, free norepinephrine excretion was significantly increased, whereas all the metabolites, including 3-methoxy-4-hydroxymandelic acid (VMA) and MHPG, and the sum of the metabolites were significantly decreased (Table 1).

Interestingly, with fluoxetine treatment, excretion of all metabolites was decreased, but free norepinephrine excretion remained unchanged (Table 1). Thus, fluoxetine does alter catecholamine excretion in responders, as has been reported previously.<sup>30-32</sup> However, the mechanism of action is apparently not through blockade of norepinephrine uptake; rather, it is more likely to be through an indirect effect via second messengers or an indirect effect of serotonin on norepinephrine.

### FUTURE PERSPECTIVES

Norepinephrine and serotonin both have a role to play in the etiology of depression. Biochemical predictors of treatment response have so far failed to identify definite parameters that could identify patients more likely to respond to either a noradrenergic or serotonergic antidepressant.

Part of this research has been hampered by the lack of a purely noradrenergic agent; however, the development of reboxetine, the first selective norepinephrine reuptake inhibitor, should greatly improve our understanding of the role of norepinephrine in depression. Reboxetine now gives clinicians a choice of antidepressant based on selectivity to brain hormones. The challenge for the future is to link selectivity to brain hormones with the symptomatology of depressive illness.

*Drug names:* clonidine (Catapres), desipramine (Norpramin and others), fluoxetine (Prozac), imipramine (Tofranil and others), maprotiline (Ludomil), nortriptyline (Pamelor and others).

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