

# Relationship of Neurotransmitters to the Symptoms of Major Depressive Disorder

David J. Nutt, M.D., Ph.D.

A relationship appears to exist between the 3 main monoamine neurotransmitters in the brain (i.e., dopamine, norepinephrine, and serotonin) and specific symptoms of major depressive disorder. Specific symptoms are associated with the increase or decrease of specific neurotransmitters, which suggests that specific symptoms of depression could be assigned to specific neurochemical mechanisms, and subsequently specific antidepressant drugs could target symptom-specific neurotransmitters. Research on electroconvulsive therapy has supported a correlation between neurotransmitters and depression symptoms. A 2-dimensional model of neurotransmitter functions is discussed that describes depression as a mixture of 2 separate components—negative affect and the loss of positive affect—that can be considered in relation to the 3 amine neurotransmitters. Owing to the different methods of action of available antidepressant agents and the depression symptoms thought to be associated with dopamine, serotonin, and norepinephrine, current treatments can be targeted toward patients' specific symptoms.

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Research over the years has attempted to define the relationships between specific neurotransmitters in the brain and specific symptoms of major depressive disorder (MDD), and the idea has developed that different neurotransmitters may regulate different brain functions. The available antidepressant agents belong to drug classes that target different neurotransmitters, and electroconvulsive therapy (ECT) also affects neurotransmitters in such a way as to affect different symptoms of MDD. Therefore, specific treatments for MDD could be used to target specific neurotransmitters and, consequently, patients' specific symptoms.

## EVOLUTION OF PHARMACOTHERAPY FOR MDD

Monoamine oxidase inhibitors (MAOIs) were the first group of antidepressant agents, introduced about 50 years

ago.<sup>1,2</sup> The efficacy of MAOIs for MDD was discovered accidentally. Iproniazid was being studied as treatment for tuberculosis, and patients' moods were found to improve independent of the progression of their disease.<sup>2</sup> Subsequent studies of iproniazid<sup>3,4</sup> confirmed that monoamine oxidase inhibition could be used to treat depression. Other MAOI agents—i.e., phenelzine and tranylcypromine—were developed and found to be effective in treating MDD. However, MAOIs have limitations related to side effect burden resulting from increased risk for hypertensive crisis<sup>2</sup> and toxicity in overdose.<sup>5</sup> Iproniazid was eventually discontinued due to hepatotoxicity.<sup>2</sup>

As with MAOIs, the mood-elevating effects of tricyclic antidepressants (TCAs), such as imipramine, amitriptyline, and clomipramine, were discovered accidentally while researchers were studying new treatments for schizophrenia.<sup>6</sup> Chlorpromazine had neuroleptic effects, but its derivative imipramine unexpectedly had antidepressant properties instead.<sup>7</sup> However, like MAOIs, TCAs have limitations due to their side effect burden (e.g., anticholinergic effects and toxicity in overdose). Tricyclic antidepressants in particular are associated with a high incidence of seizures<sup>8</sup> and even death,<sup>9</sup> especially in overdose.<sup>10</sup>

Because of the side effect burden and potential for toxicity in overdose with MAOIs and TCAs, researchers investigated safer and equally effective antidepressants, and a breakthrough came with the discovery of the selective serotonin reuptake inhibitors (SSRIs).<sup>11</sup> Tricyclic antidepressants block many neurotransmitter receptors, including muscarinic, adrenergic, histaminic, noradrenergic, and serotonergic receptors,<sup>12</sup> and thus have many effects on patients, some beneficial and some adverse. It was reasoned

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*From the Psychopharmacology Unit, University of Bristol, United Kingdom.*

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*Corresponding author and reprints: David J. Nutt, M.D., Ph.D., Psychopharmacology Unit, Dorothy Hodgkin Bldg., Whitson St., Bristol, BS1 3NY, UK (e-mail: david.j.nutt@bristol.ac.uk).*

that if an agent blocked only serotonin uptake, it could have antidepressant qualities without as many side effects. A pure serotonin uptake blocker was developed called zimelidine; this proved to be efficacious but had side effects such as Guillain-Barré syndrome and hepatitis, so its use was banned worldwide. Subsequently, a series of SSRIs was developed that remain currently available, namely fluvoxamine, fluoxetine, paroxetine, sertraline, citalopram, and escitalopram. The SSRIs have an advantage over TCAs in terms of efficacy for anxiety disorders as well as MDD.<sup>11</sup> Because SSRIs have a different chemical structure than TCAs, they do not have the same problems with adverse effects, such as anticholinergic effects, or overdose toxicity.<sup>13</sup> Common side effects include gastrointestinal problems and sexual dysfunction. In parallel with the development of SSRIs, drugs that can be called *receptor antagonists*, including trazodone, mianserin, and mirtazapine, were discovered serendipitously. These drugs work by disinhibiting either the norepinephrine or the serotonin systems in the brain, so they indirectly increase amine availability, whereas the TCAs and SSRIs increase amine availability by blocking reuptake, and MAOIs work by preventing the breakdown of amine.<sup>14</sup>

Receptor antagonists, therefore, provide physicians with a third method of increasing amine availability. Their mode of action is probably somewhat more noradrenergic than serotonergic, but they also interact with the histamine receptor and the 5-HT<sub>2</sub> serotonin receptor. They have a benign side effect profile but are probably most extensively used in patients with depression who need sedative effects.<sup>15</sup>

Serotonin-norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine, milnacipran, and duloxetine, block both serotonin and norepinephrine uptake. By blocking these neurotransmitters, serotonin-norepinephrine reuptake inhibitors have a similar mode of action as the TCAs and similar efficacy to TCAs when used to treat patients with depression. The noradrenergic component gives them some added benefit over the SSRIs in terms of efficacy.<sup>16</sup> However, unlike TCAs, SNRIs do not have interactions with cholinergic,  $\alpha$ -adrenergic, and histaminic receptors. Without the adverse effects caused by interaction with those receptors, SNRIs are better tolerated than TCAs. In addition, SNRIs do not block sodium channels, which means that they are associated with less overdose toxicity.

Reboxetine is a selective norepinephrine reuptake inhibitor that has no effect on serotonin.<sup>17,18</sup> Reboxetine mimics, to some extent, the more adrenergic tricyclics, such as desipramine and nortriptyline, in that it causes a degree of activation and tends to energize patients and improve attention.

Bupropion is a norepinephrine-dopamine reuptake inhibitor that has a moderate impact to block the reuptake of the norepinephrine and dopamine transmitters.<sup>19,20</sup> Bupropion is the only antidepressant with a dopaminergic

component as well as some action to enhance norepinephrine function. Overdose toxicity is not a problem as with MAOIs and TCAs; seizures are the main risk but are rare.

## ECT

Electroconvulsive therapy is a nonpharmacologic treatment alternative for patients who have poor response to antidepressant treatment. Treatment with ECT produces behavioral changes that are similar to the changes produced by antidepressants. These changes are produced to a greater extent and faster than antidepressants.

Nutt and Glue<sup>21</sup> reviewed the effects of a full course of ECT treatment (6–8 seizures) and described how ECT enhanced monoamine neurotransmitters at each stage of treatment. Following seizures 1 to 2, dopamine receptor function is enhanced, and patients experience increased appetite and drive. After the initial electroconvulsive seizures (even as few as a single seizure), patients with depression will sometimes experience a short period during which they will accept water or food and then return to a depressive stupor. Following additional seizures, a period of increased brightening will occur. Patients' interest in activities becomes longer and, over time, appetite and drive are restored. It appears that there is a direct link between this change in dopamine function and these behaviors.

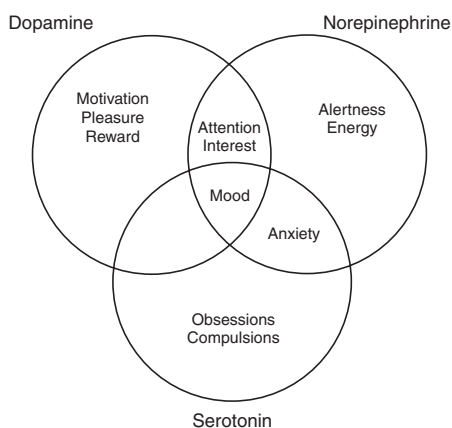
By seizures 3 to 5, synaptic norepinephrine is increased.<sup>21</sup> The mechanisms for this increase are probably due to some change in the autoinhibitory regulatory receptors that inhibit norepinephrine release, which seem to become desensitized after a few seizures. This desensitization leads to an increase in norepinephrine, which in turn leads to an increase in energy and attention. At this point, patients become more active (e.g., they get out of bed, walk around, and engage in groups) despite still having a lot of depressive ideation.

Toward the end of the treatment course of ECT, between seizures 6 and 8, the full benefit to the patients can be seen when the symptoms of depression fully lift.<sup>21</sup> Serotonin function is increased at this stage of treatment, which is believed to be associated with a positive change in cognition, the loss of negativity in cognition, and the resolution of the anxiety that often coexists with depression.

## MONOAMINE NEUROTRANSMITTER REGULATION OF MOOD AND BEHAVIOR

Based on the findings from studies of antidepressants and ECT treatment,<sup>21–24</sup> it may be possible to assign specific symptoms of depression to specific neurochemical mechanisms (Figure 1). Knowing which particular neurotransmitters are associated with which particular symptoms of depression may help physicians prescribe treatments that target specific mechanisms that in turn target

Figure 1. Monoamine Neurotransmitter Regulation of Mood and Behavior<sup>a</sup>



<sup>a</sup>Based on Stahl,<sup>22,23</sup> Foote and Aston-Jones,<sup>25</sup> Argyropoulos et al,<sup>26</sup> and Shelton and Tomarken.<sup>27</sup>

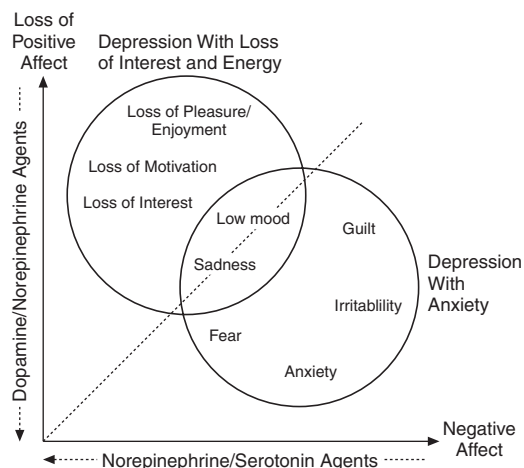
specific depression symptoms. Norepinephrine may be related to alertness and energy as well as anxiety, attention, and interest in life; serotonin to anxiety, obsessions, and compulsions; and dopamine to attention, motivation, pleasure, and reward, as well as interest in life. Increasing any of these 3 neurotransmitters will elevate mood, but the other elements of depression may be particularly responsive to a certain neurotransmitter.

### Two-Dimensional Model of Neurotransmitter Functions in Depression

A well-known psychological concept describes depression as a mixture of 2 components: an increase in negative affect and a loss of positive affect (Figure 2).<sup>24</sup> Negative affect means viewing the world as a hostile, unpleasant, disturbing, and threatening place. Loss of positive affect means having an inability to enjoy rewards from normal activities such as family, work, or hobbies that normally give one pleasure. These 2 dimensions have some overlap in feelings of low mood and sadness. Evidence from psychological studies suggests that elements of these 2 components are found in many forms of depression, and, therefore, may be used to define the nature of the depression. For example, some patients may experience a particularly unresponsive depression with an increased loss of positive affect, while other patients may experience depression with increased negative affect, such as symptoms of anxiety.

If the nature of the depression can be clinically established by cataloging a patient's symptoms and determining whether the patient is experiencing increased negative affect or loss of positive affect, then it could be possible to use symptom-specific pharmacologic agents to treat the patient (see Figure 2).<sup>24</sup> Patients experiencing symptoms associated with negative affect can be returned to normal

Figure 2. Hypothetical Model Showing Differential Actions of Antidepressant Agents on Symptoms of Positive and Negative Affect<sup>a</sup>



<sup>a</sup>Reprinted with permission from Nutt et al.<sup>24</sup>

functioning by using norepinephrine- and/or serotonin-acting drugs to ease or eliminate the symptoms of anxiety, fear, irritability, and guilt. Patients experiencing symptoms of loss of positive affect can be returned to normal functioning with an agent that has a dopaminergic and/or noradrenergic component to treat loss of motivation, interest, and enjoyment.

### Dopaminergic Systems and Possible Regions of Symptom Generation in Depression

The role of serotonin in MDD has been the focus of much research since the development and success of the SSRIs.<sup>18</sup> However, many people who take SSRIs for depression do not fully recover, and that may partly be because they have more loss of positive affect than increased negative affect.<sup>24</sup> Therefore, they may benefit from drugs with dopaminergic and noradrenergic action. While noradrenergic action has been investigated since the 1960s with the advent of the TCAs,<sup>28</sup> the relationship between decreased positive affect and dopamine has only more recently been explored.<sup>29</sup> Correlating the neuroanatomy of dopaminergic systems in the brain with specific symptoms of depression is one way to help physicians implement symptom-specific antidepressant treatment for patients.

The 3 main projection areas of the mid-brain dopamine system are the striatum, the nucleus accumbens (ventral striatum), and the prefrontal cortex.<sup>24</sup> Most of the dopamine in the striatum is produced by projections from the substantia nigra, whereas the dopamine in the nucleus accumbens and the prefrontal cortex derives from projections from the ventral tegmental area.

It is well known that, in Parkinson's disease, the substantia nigra is damaged and a loss of dopamine in the stri-

atum is a characteristic pathologic finding of the illness. Because patients with Parkinson's disease experience loss of energy and retardation, these symptoms in depression are believed to be partly driven by a relative dysfunction of dopamine in the striatum.<sup>30</sup>

The nucleus accumbens, which is innervated from the ventral tegmental area, is associated with positive sensations of reward. Thus, a defective dopamine system might be associated with a dysfunctional response to normal rewards.<sup>24</sup> The reward value of particular activities that normally are pleasurable is devalued in depression, which could be explained by reduced dopamine function in the nucleus accumbens leading to a loss of pleasure or interest.

In the prefrontal cortex, dopamine has a defined role in regulating attention and directing behavior. Despite a lack of strong evidence, a relative dysfunction of dopamine in the prefrontal cortex is believed to contribute to the loss of mental energy, the loss of drive, and the fatigue that commonly accompanies depression.<sup>24</sup> The loss of interest experienced by patients with depression is probably exacerbated by dysfunction of both the nucleus accumbens, the location of the reward system in the brain, and the prefrontal cortex, the location for the motivational system in the brain.

## CONCLUSION

Growing evidence suggests that different neurotransmitters may regulate different brain functions in patients with depression. Different antidepressants with different pharmacologies target different neurotransmitters, and these different neurotransmitters may affect different symptoms of depression. Therefore, when treating patients with depression in a clinical setting, physicians should consider selecting an antidepressant based on the symptom profile of the patient. Selecting the appropriate antidepressant for a patient's particular symptoms may provide the best chance of treatment response.

**Drug names:** bupropion (Wellbutrin and others), citalopram (Celexa and others), chlorpromazine (Thorazine, Sonazine, and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), mirtazapine (Remeron and others), nortriptyline (Pamelor and others), paroxetine (Paxil and others), phenelzine (Nardil), sertraline (Zoloft and others), tranylcypromine (Parnate and others), venlafaxine (Effexor and others).

**Disclosure of off-label usage:** The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

## REFERENCES

- López-Muñoz F, Alamo C, Juckel G, et al. Half a century of antidepressant drugs: on the clinical introduction of monoamine oxidase inhibitors, tricyclics, and tetracyclics, pt 1: monoamine oxidase inhibitors. *J Clin Psychopharmacol* 2007;27:555–559
- Baumbacher G. Abuse of monoamine oxidase inhibitors: antidepressants. *Am J Drug Alcohol Abuse* 1992;18:399–406
- Kline N. Clinical experience with iproniazid (Marsilid). *J Clin Exp Psychopathol* 1958;19(suppl 1):72–78
- Crane GE. Iproniazid (Marsilid) phosphate, a therapeutic agent for mental disorders and debilitating diseases. *Psychiatr Res Rep Am Psychiatr Assoc* 1957;135:142–152
- Sarko J. Antidepressants, old and new: a review of their adverse effects and toxicity in overdose. *Emerg Med Clin North Am* 2000;18:637–654
- Fangmann P, Assion HJ, Juckel G, et al. Half a century of antidepressant drugs: on the clinical introduction of monoamine oxidase inhibitors, tricyclics, and tetracyclics, pt 2: tricyclics and tetracyclics. *J Clin Psychopharmacol* 2008;28:1–4
- Kuhn R. The treatment of depressive states with G22355 (imipramine hydrochloride). *Am J Psychiatry* 1958;115:459–464
- Montgomery SA. Antidepressants and seizures: emphasis on newer agents and clinical implications. *Int J Clin Pract* 2005;59:1435–1440
- Thanacoody HK, Thomas SH. Tricyclic antidepressant poisoning: cardiovascular toxicity. *Toxicol Rev* 2005;24:205–214
- Nutt DJ. Death by tricyclic: the real antidepressant scandal? *J Psychopharmacol* 2005;19:123–124
- Montgomery SA. Selective serotonin reuptake inhibitors in the acute treatment of depression. 2000. Available at <http://www.acnp.org/g4/GN401000102/CH100.html>. Accessed Feb 4, 2008
- Carlsson A. Some current problems related to the mode of action of antidepressant drugs. *Acta Psychiatr Scand Suppl* 1981;290:63–66
- Peretti S, Judge R, Hindmarch I. Safety and tolerability considerations: tricyclic antidepressants vs selective serotonin reuptake inhibitors. *Acta Psychiatr Scand* 2000;403:17–25
- Slattery DA, Hudson AL, Nutt DJ. Invited review: the evolution of antidepressant mechanisms. *Fundam Clin Pharmacol* 2004;18:1–21
- Thase ME. Antidepressant treatment of the depressed patient with insomnia. *J Clin Psychiatry* 1999;60(suppl 17):28–31
- Lambert O, Bourin M. SNRIs: mechanism of action and clinical features. *Expert Rev Neurother* 2002;2:849–858
- Hajós M, Fleishaker JC, Filipiak-Reisner JK, et al. The selective norepinephrine reuptake inhibitor antidepressant reboxetine: pharmacological and clinical profile. *CNS Drug Rev* 2004;10:23–44
- Montgomery SA. Predicting response: noradrenaline reuptake inhibition. *Int Clin Psychopharmacol* 1999;14(suppl 1):s21–s26
- Foley KF, DeSanty KP, Kast RE. Bupropion: pharmacology and therapeutic applications. *Expert Rev Neurother* 2006;6:1249–1265
- Fava M, Rush AJ, Thase ME, et al. 15 years of clinical experience with bupropion HCl: from bupropion to bupropion SR to bupropion XL. *Prim Care Companion J Clin Psychiatry* 2005;7:106–113
- Nutt DJ, Glue P. The neurobiology of ECT: animal studies. In: Coffey CE, ed. *ECT: From Research to Clinical Practice*. Washington, DC: American Psychiatric Association; 1992:241–265
- Stahl SM. *Essential Psychopharmacology*. 2nd ed. New York, NY: Cambridge University Press; 2000
- Stahl SM. Deconstructing psychiatric disorders, pt 2: an emerging, neurobiologically based therapeutic strategy for the modern psychopharmacologist [BRAINSTORMS]. *J Clin Psychiatry* 2003;64:1145–1146
- Nutt DJ, Demyttenaere K, Janka Z, et al. The other face of depression, reduced positive affect: the role of catecholamines in causation and cure. *J Psychopharmacol* 2007;21:461–471
- Foote SL, Aston-Jones GS. Pharmacology and physiology of central noradrenergic systems. In: Bloom FE, Kupfer DJ, eds. *Psychopharmacology: The Fourth Generation of Progress*. 2nd ed. New York, NY: Raven Press Ltd; 1995:335–345
- Argyropoulos SV, Ploubidis GB, Wright TS, et al. Development and validation of the Generalized Anxiety Disorder Inventory (GADI). *J Psychopharmacol* 2007;21:145–152
- Shelton RC, Tomarken AJ. Can recovery from depression be achieved? *Psychiatr Serv* 2001;52:1469–1478
- Axelrod J, Whitby LG, Hertting G. Effect of psychotropic drugs on the uptake of H<sup>3</sup>-norepinephrine by tissues. *Science* 1961;133:383–384
- Nutt DJ. The role of dopamine and norepinephrine in depression and antidepressant treatment. *J Clin Psychiatry* 2006;67(suppl 6):3–8
- Flint AJ, Black SE, Campbell-Taylor I, et al. Abnormal speech articulation, psychomotor retardation, and subcortical dysfunction in major depression. *J Psychiatr Res* 1993;27:309–319