How Antidepressants Help Depression: Mechanisms of Action and Clinical Response

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The monoamine hypothesis of depression suggests that depressive symptoms can be moderated by enhancing monoamine neurotransmission. Targeted neurotransmitters include serotonin and norepinephrine, and a number of medications are available that can selectively enhance the actions of one or both of these substances. Although laboratory tests have validated the pharmacologic effects of these compounds, much less is known about how these effects translate into clinical response. Therapeutic research and experience show clearly that the medications help patients, although the individual and potential cooperative or complementary effects of stimulating each neurotransmitter system remain unclear. Depletion studies have reinforced the validity of targeting these systems and, at the same time, underscored that monoamines most likely are not the only factor driving the clinical presentation of depression.

A large body of data conclusively demonstrates that all medications currently approved by the U.S. Food and Drug Administration for use in the treatment of major depression have potent effects on monoamine neurotransmission. Furthermore, more than 30 years of clinical research strongly suggests that effects on monoamine neurotransmission are the essential pharmacologic properties for antidepressant response and that effects on acetylcholine and/or histamine neurotransmission are not necessary.1

Most antidepressants have potent pharmacologic effects that increase synaptic levels of the monoamine neurotransmitters norepinephrine and/or serotonin (5-HT) and, in some cases, dopamine. Monoamine concentrations can be increased by blocking reuptake as well as by inhibiting metabolism that occurs via the enzyme monoamine oxidase. Associated data reviewed by Owens2 and Lucki and O’Leary3 in this supplement show that, depending on the paradigm used, certain antidepressants appear to have relatively more selective effects on 5-HT or norepinephrine neurotransmission and others exhibit dual effects by increasing both 5-HT and norepinephrine. Much of this evidence is based on radioligand binding studies measuring the in vitro affinity of drugs for monoamine transporters. There are, however, relatively few direct human data with which to assess the pharmacologic effects most important for a particular drug.

Furthermore, many important questions regarding the interpretation of radioligand binding data remain unanswered. How accurately do measurements of binding affinity estimate the actual pharmacologic effects to be expected in a living person being treated for major depression? Even assuming that the binding data are an accurate reflection of relative pharmacologic selectivity, how do we know which, if any, of these pharmacologic effects is responsible for antidepressant efficacy? We have learned that antidepressant selectivity is relative and dose-dependent, so which drugs truly are 5-HT–selective or norepinephrine-selective at usual clinical doses? Which drugs are dual-acting at the usual clinical doses? Getting at these answers may still leave a central issue unresolved. What is the clinical significance, if any, of being more or less selective for norepinephrine or 5-HT or of having dual action? This article will review selected clinical data relevant to these questions.

**Evidence Supporting the Validity of Norepinephrine and Serotonin Antidepressant Mechanisms of Action**

**Drugs Selective for Norepinephrine or Serotonin Are Effective Antidepressants**

All available antidepressants increase monoamine neurotransmission by blocking reuptake or inhibiting metabolism of the neurotransmitter(s), or else blocking receptors that secondarily increase signal transduction through other...
receptors, increase neuronal firing rate, or stimulate release of neurotransmitters. These initial effects on monoamines are well characterized, and there are several converging lines of evidence supporting the view that they are essential for antidepressant efficacy.

First and foremost is the fact that drugs synthesized to selectively block 5-HT (i.e., selective serotonin reuptake inhibitors [SSRIs]) or norepinephrine reuptake (i.e., norepinephrine reuptake inhibitors [NRIs]) are effective in the treatment of major depression. Furthermore, the effects on histamine, acetylcholine, γ-aminobutyric acid (GABA), or ion channel blockade seen with older antidepressants have been eliminated in selective agents with no apparent reduction in efficacy. Thus, it is reasonable to conclude that although such effects might contribute directly or indirectly to antidepressant efficacy in some patients, they are not essential.

We now have a large number of selective 5-HT and norepinephrine reuptake inhibitors, some of which are listed in Table 1. The evolution of SSRIs has been in the direction of increasing selectivity and potency. The recently developed escitalopram is the most potent and selective 5-HT reuptake inhibitor, as listed in Table 1. The evolution of SSRIs has been in the direction of increasing selectivity and potency. The recently developed escitalopram is the most potent and selective 5-HT reuptake inhibitor, as listed in Table 1.

Table 1. Some Relatively Neurotransmitter-Selective Antidepressants

<table>
<thead>
<tr>
<th>Norepinephrine reuptake inhibitors</th>
<th>Desipramine</th>
<th>Nortriptyline</th>
<th>Protriptyline</th>
<th>Maprotiline</th>
<th>Atomoxetine</th>
<th>Reboxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT/Norepinephrine reuptake inhibitors</td>
<td>Imipramine</td>
<td>Doxepin</td>
<td>Amitriptyline</td>
<td>Trimipramine</td>
<td>Venlafaxine</td>
<td>Duloxetine</td>
</tr>
<tr>
<td>5-HT reuptake inhibitors</td>
<td>Fluoxetine</td>
<td>Sertraline</td>
<td>Paroxetine</td>
<td>Fluvoxamine</td>
<td>Citalopram</td>
<td>Escitalopram</td>
</tr>
</tbody>
</table>

Abbreviation: 5-HT = serotonin.

Depletion of Monoamines
Selectively Reverses Antidepressant Action

A second line of evidence supporting the primary role of increased levels of norepinephrine or 5-HT in antidepressant action comes from neurotransmitter depletion studies. Discovery of the synthetic pathways for monoamines in the early 1960s made it possible to deplete monoamines pharmacologically by either blocking a particular step in synthesis or limiting the availability of an essential amino acid precursor. Figure 1 shows a representation of the synthetic pathways for monoamines. The methods derived from this knowledge for neurotransmitter depletion in humans are relatively straightforward and safe.

Several reversible monoamine synthesis inhibitors have been developed and studied in humans. This work evolved from research exploring the various substrates for the key enzymes involved in monoamine synthesis. Experimentation revealed that chemical modification of some precursors caused them to act as inhibitors of key rate-limiting enzymes. The development of α-methyl-para-tyrosine (AMPT), a reversible inhibitor of tyrosine hydroxylase, the rate-limiting enzyme in norepinephrine and dopamine synthesis, has sharpened our understanding of the clinical differences between SSRIs and NRIs with regard to the symptom profiles that each improves is less clear. Nelson published a comprehensive review of 16 studies comparing an NRI and an SSRI in patients with major depression. Most of the agents listed in Table 1 and 1563 patients were involved in the studies. Response rates were similar for the SSRIs and NRIs (65% and 60%, respectively), and there were no consistent findings across studies when baseline symptoms that predict response were examined. Some research, however, has shown that baseline anxiety predicts preferential response to SSRIs versus NRIs, as shown by the lack of efficacy of NRIs for obsessive-compulsive disorder and posttraumatic stress disorder, as well as a generally held perception that SSRIs are more effective than NRIs in depressed patients with moderate-to-severe anxiety symptoms. Arguing against a significant class difference are the studies showing NRIs to be effective in panic disorder and a recent study showing that baseline Hamilton Rating Scale for Anxiety score did not predict response to either sertraline or bupropion during treatment of depression.

Whether or not clinical differences in the efficacy profiles of SSRIs and NRIs beyond obsessive-compulsive disorder are understood clearly, the bulk of evidence indicates that these drug classes are comparably effective in the treatment of major depression. Also supporting the notion that the primary mechanisms of these compounds are linked to antidepressant response is the fact that most of the newest compounds listed in Table 1 do not have clinically relevant effects on acetylcholine, histamine, or GABA but still are effective. The most parsimonious explanation from these data is that norepinephrine or 5-HT reuptake inhibition is the most important pharmacologic property underlying the antidepressant actions of these drugs.
synthesis, marked the advent of such an approach. AMPT treatment in man (600–4000 mg/day) decreases urinary excretion of catecholamine metabolites by up to 75%.

AMPT treatment occurs within 2 to 3 days of initiation of treatment, with levels returning to normal within 3 to 4 days after withdrawal of the drug. Since its development, AMPT has been used extensively in laboratory animals and humans to rapidly deplete norepinephrine and dopamine.

The synthesis of 5-HT can be inhibited similarly by ingestion of para-chlorophenylalanine (PCPA). PCPA inhibits the enzyme tryptophan hydroxylase, the rate-limiting step in 5-HT synthesis. In a study of nonpsychiatric patients with 5-HT–producing carcinoid tumors, PCPA led to a variety of acute behavioral changes ranging from lethargy, irritability, anxiety, and depression to psychosis, although many subjects demonstrated little behavioral change.

Two mid-1970s clinical studies reported that PCPA appeared to rapidly reverse the antidepressant effects of both imipramine and tranylcypromine in patients with major depression. Antidepressant-remitted subjects experienced a depressive relapse within 24 hours of the initiation of PCPA treatment and a return to remission within 24 hours of discontinuation. The studies were highly criticized for a lack of placebo control and the small number of patients tested, and no attempts at replication have been reported. PCPA use was discontinued in the late 1970s because of concerns over tolerability and safety, and the substance no longer is available.

Another strategy for 5-HT depletion arose from research on dietary requirements. The essential amino acid L-tryptophan is the direct precursor of 5-HT synthesis. By definition, an essential amino acid is one that cannot be synthesized by humans, making dietary intake the sole source of its availability. One implication is that 5-HT can be depleted by rapid dietary depletion of tryptophan.

L-Tryptophan depletion has become the most commonly used method for 5-HT depletion experiments.

L-Tryptophan–free or low-L-tryptophan diets administered to healthy humans cause reductions of plasma L-tryptophan levels. Maintenance for up to 1 month on such diets has been reported without serious medical or psychological consequences. Diets that reduce the plasma ratio of L-tryptophan to large neutral amino acids (LNAA) increase the competition of LNAA with L-tryptophan for passage across the blood-brain barrier, resulting in decreased levels of CSF 5-HIAA. A 200-mg/day, low-L-tryptophan diet maintained for 8 days enhanced the prolactin response to intravenous L-tryptophan in healthy humans, suggesting the development of postsynaptic 5-HT receptor supersensitivity.

Reduction in plasma L-tryptophan of up to 80% also can be accomplished within 3 to 5 hours reliably and consistently by administering an oral L-tryptophan–free amino acid solution. The drink induces hepatic protein synthesis and thereby depletes available plasma L-tryptophan, which is used in the production of new proteins. Additionally, the large increase in LNAA that occurs after ingestion of an L-tryptophan–free amino acid solution competitively blocks any remaining L-tryptophan from being transported into the brain.

Data from human studies using this paradigm have been highly consistent and show that the plasma changes are associated with changes in brain 5-HT synthesis. An L-tryptophan–free amino acid drink leads to a 25% decrease in CSF 5-HIAA in healthy volunteers during continuous CSF sampling, and similar data have been observed with single CSF sampling. A study using positron emission tomography in healthy subjects reported an 87% reduction in 5-HT synthesis in men and a 97% reduction in women within 5 hours of ingesting the drink.

Clinical research with neurotransmitter depletion relevant to antidepressant action has focused on 5 distinct groups: healthy people without personal or family history of depression, medication-free people with a history of depression who were not clinically depressed, symptomatic depressed patients, SSRI-treated depressed patients, and NRI-treated depressed patients.

The protocol is similar across studies and is composed of a double-blind, placebo-controlled sequence of 2 test periods 1 week apart. Figure 2 shows an overview of these procedures. Each test period is 3 to 4 days in duration and involves a baseline day, depletion day(s), and a follow-up period 1 week apart.
day. During one of the two test periods, a real depletion occurs and during the other, no depletion occurs. For 1-tyrptophan depletion, subjects are administered an amino acid drink that either has or does not have 1-tryptophan. For depletion of norepinephrine and dopamine, subjects are administered either AMPT or the “active” placebo diphenhydramine, 25 mg t.i.d.22

In studies of the relative importance of norepinephrine or 5-HT to maintaining the effects of antidepressants,21–23,27 patients received up to 12 weeks of antidepressant therapy and entered the depletion phase if they achieved and maintained a 50% reduction in Hamilton Rating Scale for Depression score from baseline for 2 consecutive weeks. For the duration of the studies, these subjects also continued taking antidepressant medication at dose levels that yielded response. Table 2 summarizes the study results.

One of the most striking findings from these studies is how swiftly subjects react to the depletions. Antidepressant response takes several weeks to occur, and yet in these patients depressive symptoms returned acutely during depletion and then disappeared quickly as the depletion wore off. Making the results all the more remarkable is the fact that these reactions occurred in spite of antidepressant medication maintenance. Mood changes that occurred typically lasted from 4 to 36 hours. In addition, the symptoms reported by patients during neurotransmitter depletion may be a reflection of the fragility of these neurons.

These results confirm that monoamines are necessary for maintaining antidepressant therapeutic response. Furthermore, in spite of the fact that interactions between norepinephrine and 5-HT in the brain are well known,22 these systems appear to be independent of one another in the context of maintaining antidepressant action. The ability to selectively deplete and reverse the antidepressant effects in people taking single-acting agents suggests that, at least in those patients, only one particular neurotransmitter had a role in the mechanism of action of that medication.

CONCLUSIONS

Basic science studies have shown that all current antidepressants have potent effects on monoamine systems, although the paths between these effects and clinical outcomes remain poorly understood. Two converging lines of evidence provide a convincing body of data supporting the primary role for norepinephrine and 5-HT in antidepressant actions: Drugs that selectively increase either norepinephrine or 5-HT are effective in the treatment of depression, and the effects of these agents can be reversed selectively by depleting norepinephrine or 5-HT.

The evidence proves that increasing monoamines is the initial, necessary step for antidepressant action. Identification of which biological change is most proximal to the actual therapeutic response, however, remains elusive. The answer may be related to the fact that, while not achieving full potential, monoamine levels increase by 100% to 300% within hours of the initial dose of medication,53 and yet therapeutic response lags by at least 2 to 4 weeks. Current theories aimed at explaining this discrepancy focus on the adaptive changes that occur in nonmonoamine neurons as a result of increased monoamine levels.54–56 More recent data suggest that vulnerability to major depression may relate to cellular dysfunction in key limbic areas of the brain.57 It is hypothesized that the effects of increased monoamines on dysfunctional neurons of the limbic system may partially restore their ability to function.23 The rapid return of depression in antidepressant-treated patients during neurotransmitter depletion may be a reflection of the fragility of these neurons.

Also unresolved is whether the separate effects of increasing norepinephrine and 5-HT could be additive in causing antidepressant action, or if perhaps they are 2 separate and distinct pathways to the same endpoint. A somewhat ancillary question is whether selective norepinephrine or 5-HT drugs have different profiles of symptom response. In spite of failed prior efforts5,20 to find differences in symptom profile between patients responding to SSRIs or NRIs, I would argue that such effects are likely to be present. To address these questions directly,
prospective studies that specifically focus on key symptoms thought to differ between patients responding to SSRIs and NRIs are required. Vital to such studies are rating scales that are more sensitive to changes in symptoms. Obtaining the answers to these and other questions will help us to refine antidepressant treatments to yield better outcomes.

**Drug names:** amitriptyline (Elavil and others), atomoxetine (Strattera), bupropion (Wellbutrin and others), cilostazol (Clexa), desipramine (Norpramin and others), doxepin (Sinequan and others), escitalopram (Lexapro), fluoxetine (Prozac and others), imipramine (Tofranil and others), maprotiline (Ludiomil and others), nortriptyline (Pamelor), paroxetine (Paxil and others), sertraline (Zoloft), tranylcypromine (Parnate), trimipramine (Surmontil), venlafaxine (Effexor).

**REFERENCES**

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