Review

# Pharmacology of Antidepressants

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**Presently in the United States, 21 compounds have been approved by the Food and Drug Administration as antidepressants. Two additional drugs marketed outside the United States as antidepressants have been approved for obsessive-compulsive disorder. Nearly one half of all these compounds became available within the past 12 years, whereas the first antidepressant was available more than 40 years ago. After the clinical aspects of depression are introduced in this article, the pharmacology of the newer generation drugs is reviewed in relationship to the older compounds. The information in this review will help clinicians treat acute depression with pharmacological agents.**

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**CYP = cytochrome P-450; 5-HT = serotonin (5-hydroxytryptamine); MAOI = monoamine oxidase inhibitor; OCD = obsessive-compulsive disorder; PET = positron emission tomography; SSRI = serotonin selective reuptake inhibitor**

Depression is one of the most common illnesses in the US adult population. Nearly 19 million American adults, or in a given year about 10% of the US population older than 18 years, have a depressive disorder.[1,2] However, depression remains underdiagnosed and undertreated[3] for various reasons but not because of a lack of safe and effective drugs.

From early 1988 to the present, nearly one half of all antidepressants currently available for clinical use in the United States were approved by the US Food and Drug Administration. Thus, the total number of approved antidepressants in the United States is 21. In addition, during that time, 2 other drugs (clomipramine and fluxovamine) marketed outside the United States as antidepressants were marketed in the United States for the treatment of obsessive-compulsive disorder (OCD). Progress in the availability of antidepressants has been substantial in the relatively recent past, especially since the first antidepressant, imipramine, was discovered about 40 years ago.[4]

With all these compounds, including the monoamine oxidase inhibiting class and the 2 antidepressants approved for other purposes, in theory 23 drugs are available in the United States to treat depression. Reboxetine (Figure 1) may be the next antidepressant approved for marketing in the United States. Are these drugs pharmacologically different from one another, or are they similar? On what basis can a clinician decide which drug is best for his or her patient? This review, which will be of interest to psychiatrists and primary care physicians who treat most patients with depression, attempts to answer these questions by primarily exploiting the vast amount of in vitro information on the pharmacology of these drugs. Although I assume that all antidepressants are equally efficacious in treating depression, some studies suggest otherwise. This article's brief introduction on depression will benefit readers who are not psychiatrists. (Clinical research on the specificity of certain antidepressants for treating certain subtypes of depression is not provided.)

## DIAGNOSIS OF DEPRESSION AND ITS PREVALENCE

Despite extensive research to find a diagnostic test, the diagnosis of depression remains clinical. The criteria for the diagnosis of major depression[5] are the core signs and symptoms, including depressed mood, diminished pleasure or interest in activities, pronounced change in appetite or weight, alterations in sleep (insomnia or hypersomnia), psychomotor agitation or retardation, fatigue or loss of energy, inability to concentrate, indecisiveness, and thoughts of death, dying, or suicide.

A clinician's index of suspicion about the diagnosis of depression should be raised if a patient presents with a chief complaint of fatigue, pain, sleep disturbances, anxiety, irritability, or gastrointestinal problems.[6] If unable to find a physical reason for these complaints, the clinician should then evaluate the patient for depression.

Patients with other psychiatric disorders, such as schizophrenia, schizoaffective disorder, and anxiety disorders, may have depression. Depression is relatively common among patients with the diagnosis of dementia[7] and may be

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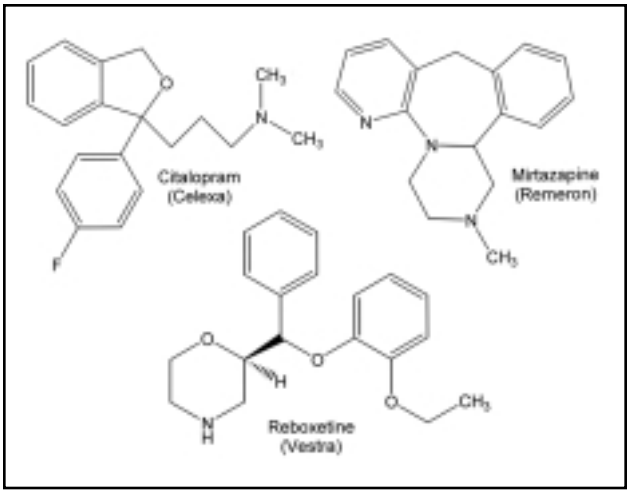


Figure 1. Some newer generation antidepressants.

a risk factor for developing dementia.[8] Many nonpsychiatric disorders can present with complaints of fatigue, insomnia, and difficulty concentrating. Disorders that suggest depression[9] include endocrinopathies (hypothyroidism, hyperparathyroidism, Cushing and Addison diseases), subcortical dementias (Huntington and Parkinson diseases), frontal lobe disease, right hemisphere stroke, occult tumors outside the brain, and infections of the brain. In addition, anemia, hypoglycemia, and hyperglycemia may appear clinically like depression.

Each year about 10% of the US population age 18 years and older has a depressive disorder.[1,2] Over a lifetime, about 10% to 20% of the adult population will have experienced depression.[10] The risk of depression is 2 to 3 times higher among women compared with men. In addition, depression is 2 to 3 times higher in first-degree relatives of depressed persons. Although earlier studies suggested that the rates of depression were increasing in association with a decrease in the age at onset,[11] more recent work suggests that both rate of depression and age at onset have remained stable over time.[10] The lifetime probability of suicide in patients with major affective disorder has an estimated incidence rate of 25% to 30%,[12] although this figure may be overestimated based on more recent work.[13,14] However, suicide attempts by patients with major depression are severalfold higher than those in a control population.[15] Data from the Centers for Disease Control and Prevention on suicide in the United States in 1997 show that almost 31,000 suicides were reported. Depression is the eighth leading cause of death in the United States, which ranks 24th worldwide in the rate of suicide.

Suicide by the depressed patient is not the only concern about mortality in depressed patients. Many studies suggest that depressed patients with medical problems have higher morbidity and mortality rates compared with nondepressed patients with medical problems. For example, in 1 study,[16] the mortality rate at 6 months after a myocardial infarction was more than 5-fold higher in depressed patients than in nondepressed patients. Furthermore, depression may be a risk factor for the development of coronary artery disease[17] and may predict mortality in patients receiving long-term hemodialysis.[18]

The economic effect of depression is substantial. The estimated cost of depression in the United States in 1990 was $44 billion.[19] This amount includes direct costs of treatment, as well as costs associated with depression-related suicides and lost productivity in the workplace. Additionally, depressed patients seek medical attention frequently. Thus, their medical care costs are higher than those for nondepressed patients.[20] The cost of medical treatments for depressed patients far exceeds the cost of treating their depression.

Despite the clear evidence that depression is a treatable illness that affects health care beyond psychiatry, it remains underdiagnosed and undertreated for various reasons.[3] Surveys by the National Institute of Mental Health show that about 70% of depressed patients do *not* receive treatment. To alter this finding, a decade ago, the National Institute of Mental Health initiated the Depression Awareness, Recognition, and Treatment Program (D/ART),[21] and other organizations have followed. Fortunately, about 80% to 90% of depressed patients can be treated successfully.[22]

About 65% of patients ultimately respond to antidepressant drug therapy[23] and completely recover. Electroconvulsive therapy, an efficacious type of treatment, can help patients whose depression is refractory to antidepressants (about another 20% of patients).[24] In about 15% of depressed patients, the disorder is resistant to all known types of therapy.[22]

## PHARMACOTHERAPY FOR DEPRESSION

Antidepressant drugs are the mainstay for the treatment of depression. Usually, antidepressants are given in combination with some form of limited supportive psychotherapy. For mild depression, psychotherapy alone may be of use. However, evidence is accumulating that the combination of antidepressant treatment and some form of psychotherapy may be superior to either treatment alone, especially for more severe and recurrent depression.[25-27]

Over the past decade, the so-called tricyclic antidepressants (eg, imipramine or desipramine) have been supplanted by the so-called serotonin selective reuptake inhibitor (SSRI) antidepressants as first-line medications, primarily because of the tolerability and safety of the newer compounds.[28,29] However, whether the newer antidepressants are more or less efficacious than the older gen-

eration compounds, especially for severe depression, is controversial.[23,29]

## CLASSIFICATION OF AVAILABLE ANTIDEPRESSANTS

When fewer antidepressant compounds were available, the drugs were classified either as tricyclic antidepressants or as monoamine oxidase inhibitors (MAOIs), a classification that mixes a structural criterion with a functional one. At present, a broad range of structures make up the antidepressant pharmacopoeia, but there are only a few known functional (possibly therapeutic) effects of these compounds. Therefore, a functional classification of antidepressants is more useful than a structural one. Although not a completely satisfactory strategy, all currently available antidepressants can be classified into 1 of 3 classes: (1) MAOIs, (2) biogenic amine neurotransmitters (serotonin, norepinephrine, and dopamine) reuptake blockers, or (3) serotonin type 2A (5-$HT_{2A}$) receptor blockers (Table 1). This review focuses on reuptake blockers and 5-$HT_{2A}$ receptor blockers.

This functional classification eliminates the confusion in the literature from the incorrect use of terms such as *heterocyclic*, *tricyclic*, and *tetracyclic*.[30] For example, imipramine is both a heterocyclic and a tricyclic antidepressant. Therefore, using *heterocyclic* and *tricyclic* to describe antidepressants in mutually exclusive terms is incorrect.

Table 1. **Functional Classification of Antidepressants***

| Function | Antidepressant |
|---|---|
| Monoamine oxidase inhibitor | Isocarboxazid<br>Phenelzine<br>Tranylcypromine |
| Norepinephrine transport blocker | Amoxapine<br>Desipramine<br>Doxepin<br>Maprotiline<br>Nortriptyline<br>Protriptyline<br>Reboxetine† |
| Serotonin transport blocker | Amitriptyline<br>Citalopram<br>Clomipramine‡<br>Fluoxetine<br>Fluvoxamine‡<br>Imipramine<br>Paroxetine<br>Sertraline<br>Trimipramine<br>Venlafaxine |
| Dopamine transport blocker | Bupropion |
| Serotonin 5-$HT_{2A}$ receptor blocker | Mirtazapine<br>Nefazodone<br>Trazodone |

*5-$HT_{2A}$ = 5-hydroxytryptamine.
†Not approved for use in the United States.
‡Approved for use in the United States for the treatment of obsessive-compulsive disorder.

## CLINICAL PHARMACOLOGY OF ANTIDEPRESSANTS

### Onset of Activity

Practicing clinicians know that the mood-elevating effect of antidepressant medication usually begins about 1 to 2 weeks after initiation of treatment. The clinical rule of thumb is that a patient must be treated with an adequate dosage for at least 6 weeks before the clinician considers changing the treatment. However, the synaptic effects of these drugs occur within hours after the patient ingests the drug.[31] Because many of the early adverse effects have the same time course as the early synaptic effects, such synaptic effects of antidepressants can be related to certain adverse effects and drug interactions (as discussed subsequently).

In treating a patient with severe depression, the clinician would like to prescribe a drug that begins to work in the same time course as the synaptic effects. This rapid onset of activity would be one characteristic of the ideal antidepressant.[32] However, no drug appears to work more rapidly than another, and the time course is generally prolonged. Nonetheless, some data[33,34] suggest that drugs that have actions on both serotonergic and noradrenergic systems ("dual-action" compounds) have a quicker onset of action than that of other available antidepressants. However, dual-action compounds do not appear to have increased efficacy.[35]

### Elimination Half-Life

A drug's elimination half-life (the time it takes to eliminate one half the amount of drug in the plasma) provides information about its dosing schedule. Antidepressants can be rank-ordered according to their elimination half-lives (Figure 2).[36-44] Of importance, the data in Figure 2 are primarily derived from studies of healthy young men. (No information is provided about active metabolites, which are known to exist for most of these compounds.) Ideally, both the parent compound and the active metabolite should have an intermediate half-life. This is an important issue concerning fluoxetine, with its active metabolite norfluoxetine having a half-life of 7 to 15 days.[44]

The ideal antidepressant should have a half-life consistent with once-a-day dosing or a half-life of about 24 hours. The shorter half-life drug reaches steady state sooner than the longer half-life compound and also is eliminated quicker. A pharmacokinetic rule of thumb is that it takes about 4 to 5 times the elimination half-life with a constant dosing interval to achieve steady-state levels. With a drug that has a half-life of 1 day, this steady state is reached after 4 to 5 days. For a drug with the elimination half-life of 4

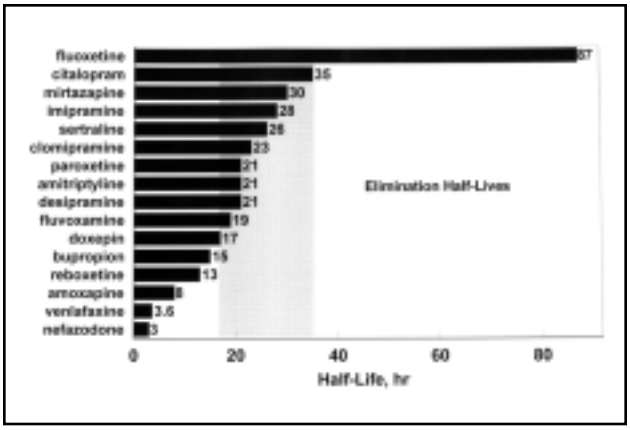


Figure 2. Elimination half-lives of antidepressants.[36-43] Fluoxetine's active metabolite norfluoxetine has a half-life of 7 to 15 days.[44] The shaded area highlights the half-life range for dosing once per day with immediate-release compounds to maintain good steady-state levels.

days, the time to steady state with once-a-day dosing is 16 to 20 days. Additionally, the phenomenon of cumulation or accumulation occurs when a drug is given at an interval shorter than 4 to 5 times its half-life. In this case, the blood level at steady state is much higher than that after the first dose. This is because the drug is given at an interval that is shorter than the time necessary for the body to eliminate most of the previous dose.

Another pharmacokinetic rule of thumb based on the elimination half-life is that it takes about 4 to 5 times the elimination half-life to have more than 90% of the drug eliminated from the body after the medication is discontinued. Thus, a drug with an intermediate half-life shortens the time to steady state and shortens the time for elimination. This knowledge is important when therapy is initiated, when dosages are adjusted, when a medication is discontinued because of an adverse effect, or when one drug is discontinued before another drug is initiated that might cause a drug interaction.

From a theoretical standpoint, the compounds with a half-life between about 17 and 36 hours can be given once per day to maintain good steady-state levels. Drugs with lesser half-lives must be given more frequently, and those with greater half-lives can be given less often than once per day, although this approach is generally not used. However, fluoxetine with its half-life of several days and a longer half-life for its metabolite may be efficacious when given once per week in the continuation phase of the treatment of depression.[45] An extended-release form of venlafaxine allows once-daily dosing.[46]

## Therapeutic Blood Levels

Interindividual variations in the blood levels of an antidepressant with a given dose can be substantial.[47-49] These variations are likely explained by individual differences in the activity of drug-metabolizing enzymes. Clinically, these differences likely underlie the observed differences in the rates of response and of adverse effects. If a defined therapeutic blood level were known, the dose of the medication could be tailored to the patient to achieve therapeutic effects and avoid adverse effects. However, concentration-response relationships have been established for only a fraction of the currently available antidepressants, namely, several tricyclic antidepressants.[50,51] Therefore, for the vast majority of antidepressants, this relationship is under investigation. Nonetheless, currently for tricyclic antidepressants, therapeutic drug monitoring is the standard of care to avoid toxicity with these compounds.[51] For most of the other classes of antidepressants, therapeutic drug monitoring may help to avoid toxicity and to increase response rates.[48,49,51]

## Adverse Effects

Most adverse effects of antidepressants can be explained by their synaptic effects. That is, the effects of these drugs on some important components of the synapse in the brain and elsewhere in the body result in some adverse effects and certain drug interactions, all of which are subsequently discussed in depth. The 2 most important synaptic effects of antidepressants are blockade of transport of certain neurotransmitters (norepinephrine, serotonin, and dopamine) back into the nerve ending and blockade of certain receptors for some neurotransmitters. The most clinically relevant receptor blockade is at the $\alpha_1$-adrenergic, dopamine $D_2$, histamine $H_1$, muscarinic acetylcholine, and, possibly, 5-$HT_{2A}$ receptors. Some of these synaptic effects may be required for the therapeutic effects of antidepressants. If so, the currently available antidepressants can never be devoid of certain adverse effects caused by interactions with neurotransmitters or their receptors.

Tricyclic antidepressants have effects on cardiac action potentials typical of class IA antiarrhythmics,[52] which include drugs such as quinidine and procainamide. Class I antiarrhythmics have been implicated to increase mortality after myocardial infarction, leading to concern about the use of tricyclic antidepressants in patients with cardiovascular disease.[53] However, in general, this property of tricyclic antidepressants accounts for a serious risk of cardiotoxicity and contributes toward the narrow therapeutic index of tricyclic antidepressants. This property is a major pharmacological distinction between the older tricyclic compounds and the newer generation compounds. This may partly explain the high toxicity of tricyclic antidepres-

sants and similar compounds with an overdose compared with the newer generation compounds (Table 2).

## Drug Interactions

The interactions of one drug with another can be divided into 2 categories: pharmacodynamic and pharmacokinetic. Pharmacodynamic drug interactions relate to the effect of drug A on the *mechanism* of action of drug B, which the patient is already taking. Pharmacokinetic drug interactions relate to the effect of drug A on the *metabolism* of drug B. Most of the pharmacodynamic effects of antidepressants relate to their synaptic effects (discussed subsequently). The likelihood of an antidepressant causing a clinically meaningful pharmacodynamic drug interaction is shown in Table 3.

Most of the pharmacokinetic drug interactions of antidepressants relate to their inhibitory effects on drug-metabolizing enzymes.[54] The class of enzymes inhibited by antidepressants are of the cytochrome P-450 (CYP) category, of which there are a multitude. However, probably only 3 enzymes are of concern—CYP1A2, CYP2D6, and CYP3A4. Nearly all the drugs that are prescribed to patients are metabolized by these 3 enzymes. Based on both basic[55-68] and clinical[69-75] research, the antidepressants that are especially potent inhibitors of these enzymes are fluvoxamine at CYP1A2, paroxetine and fluoxetine at CYP2D6, and nefazodone at CYP3A4. The likelihood of the newer generation antidepressants causing a pharmacokinetic drug interaction is ranked in Table 4. Of importance, pharmacokinetic drug interactions are a likely consequence when one drug is combined with another drug, which might inhibit drug-metabolizing enzymes. Additionally, even drugs in the low-risk category might cause a pharmacokinetic drug interaction. Thus, the clinician must be vigilant when adding an antidepressant medication to a patient's current treatment regimen.

## Synaptic Effects of Antidepressants

Most of the effects of antidepressants in the body, whether therapeutic or adverse, occur at the level of the synapse—the site in the nervous system where one neuron communicates with another neuron or another type of cell (eg, smooth muscle cell). By blocking uptake of neurotransmitters, blocking certain neurotransmitter receptors, or inhibiting the mitochondrial enzyme monoamine oxidase, antidepressants alter the magnitude of the effects of neurotransmitters at these synapses.

Neurotransmitters, the chemicals that neurons use to communicate with one another, are generally small molecules (usually amino acids or their derivatives) and are released from the nerve ending to bind to specific receptors on the outside surface of cells. These receptors are highly specialized proteins, which often have been molecularly cloned by researchers. Each neurotransmitter has at least 1 unique receptor that selectively binds it. However, there are many examples (eg, for the neurotransmitter serotonin, which is 5-hydroxytryptamine) of multiple subtypes of receptors for the neurotransmitter.

When the chemical messenger binds to its postsynaptic receptor on the receiving neuron, this neuron is changed electrically and biochemically because of the coupling of the neurotransmitter-receptor complex to other components of the membrane in which the receptor resides. Neurons can also regulate their own activity by feedback mechanisms involving receptors called *autoreceptors*,

Table 2. **Relative Toxicity of Antidepressants With Overdose**

| Relative toxicity with overdose | Antidepressant |
|---|---|
| Very high | Amoxapine<br>Maprotiline<br>Tricyclic antidepressants |
| High | Monoamine oxidase inhibitors |
| Low | Bupropion<br>Fluoxetine<br>Fluvoxamine<br>Mirtazapine<br>Nefazodone<br>Paroxetine<br>Reboxetine<br>Sertraline<br>Trazodone<br>Venlafaxine |

Table 3. **Pharmacodynamic Drug Interactions of Antidepressants**

| Interaction | Antidepressant |
|---|---|
| With serotonin selective reuptake inhibitors—lethal | Monoamine oxidase inhibitors |
| With monoamine oxidase inhibitors—lethal | Citalopram<br>Clomipramine<br>Fluoxetine<br>Fluvoxamine<br>? Nefazodone*<br>Imipramine<br>Paroxetine<br>Sertraline<br>Venlafaxine |
| With most drugs—little | Bupropion<br>Mirtazapine<br>Reboxetine |

*Nefazodone has some serotonin receptor blocking properties that might protect against the development of the serotonergic syndrome.

Table 4. **Likelihood of an Antidepressant Causing Clinically Meaningful Pharmacokinetic Drug Interactions at Cytochrome P-450 Enzymes**

| Likelihood | Antidepressant |
|---|---|
| Most | Fluoxetine<br>Fluvoxamine<br>Nefazodone<br>Paroxetine |
| Less | Sertraline<br>Bupropion |
| Least | Citalopram<br>Mirtazapine<br>Reboxetine<br>Venlafaxine |

which are present on their cell bodies and on terminals (Figure 3).[76]

An example of an autoreceptor is the 5-$HT_{1A}$ receptor on the somatodendritic region of the raphe nucleus serotonergic neuron (Figure 3). Activation of this autoreceptor with the overflow of serotonin inhibits the firing rate of action potentials of this neuron ("negative feedback loop").

For some biogenic amine neurotransmitters (eg, norepinephrine, serotonin, and dopamine), after release they are taken back into the nerve ending (Figure 3). This process is called *uptake*, *reuptake*, or *transport*. Reuptake occurs through transport proteins (transporters), which have been molecularly cloned from humans and other species. This transport is a mechanism that prevents overstimulation of receptors in the synapse.[77]

One mechanism of enhancing neurotransmission early (in the absence of any presynaptic, negative feedback loops) is to block this transport with a drug. However, with long-term treatment, adaptive mechanisms come into play that can affect this outcome. Specifically, desensitization, which is often followed by down-regulation, can occur with many types of receptors after long-term treatment with a transport blocker. As a result, neurotransmission can ultimately be diminished (or be increased if, as discussed subsequently, the desensitized and down-regulated receptors are inhibitory receptors).

*Desensitization* is the loss of sensitivity of the cell to the neurotransmitter, and *down-regulation* is the loss of the receptor protein from the cellular surface. These processes may be the mechanisms of tolerance to certain drugs, such as opioids. In addition, desensitization and down-regulation may explain therapeutic effects and reversal of gastrointestinal side effects of SSRIs. In particular, desensitization and down-regulation may explain the reversal of SSRI appetite-suppressing effects, which can ultimately lead to weight gain late during therapy.[78] Of importance, adaptive mechanisms of receptors may not occur with all receptors. A given receptor possibly adapts or does not adapt depending on the cell type in which it resides.

Antidepressants of many types acting by different mechanisms can desensitize certain receptors for catecholamines and serotonin. These effects, which can occur in the absence of down-regulation, are the basis of a hypothesis of their mechanism of action.[76,79,80] In contrast, the antidepressant mirtazapine (Figure 1) may cause its therapeutic effects by directly blocking presynaptic $\alpha_2$-adrenoceptors and some postsynaptic receptors (eg, 5-$HT_{2A}$).[81,82]

By blocking a receptor with an antagonist, the effects of the neurotransmitter can be abolished early and selectively. Often with long-term blockade, the receptor undergoes another type of compensatory change and becomes more sensitive (supersensitive) to the neurotransmitter. Supersensitivity, which can be accompanied by up-regulation of receptor concentration, may be the mechanism of adaptation to some receptor-related adverse effects of antidepressants and other drugs, and it may be related to the development of tardive dyskinesia after long-term treatment with dopamine $D_2$ receptor blocking neuroleptics.[83]

Antidepressants can block uptake of biogenic amine neurotransmitters and antagonize certain receptors. In addition, some antidepressants inhibit the activity of monoamine oxidase, a ubiquitous enzyme that is important in the degradation of catecholamines and serotonin. Because this enzyme is present in mitochondria, which are found in the nerve ending, and in most cells in the body, its inhibition results in an increase in the concentration of neurotransmitter available for release at the synapse.

## Mechanism of Action of Antidepressants: Focus on Serotonergic Neurons

The mechanism of the therapeutic action of antidepressants remains uncertain. However, there are reasonable theories that can explain the time lag (up to 6 weeks) for the onset of therapeutic action of antidepressants.[76] Although this time lag exists, adverse effects occur quickly. These adverse effects can be explained by early synaptic effects of antidepressants, and therapeutic effects can be explained by slow-to-develop adaptive mechanisms, namely, desensitization and, possibly, down-regulation of certain receptors.

More recent theories about the mechanism of action of antidepressants focus on events beyond receptors, at the level of gene expression.[84] However, these theories are not mutually exclusive. The effects of antidepressants on neurotransmitter receptors are likely necessary for these drugs to affect gene expression.

Long before these receptor theories of the mechanism of action of antidepressants were proposed, studies of tricy-

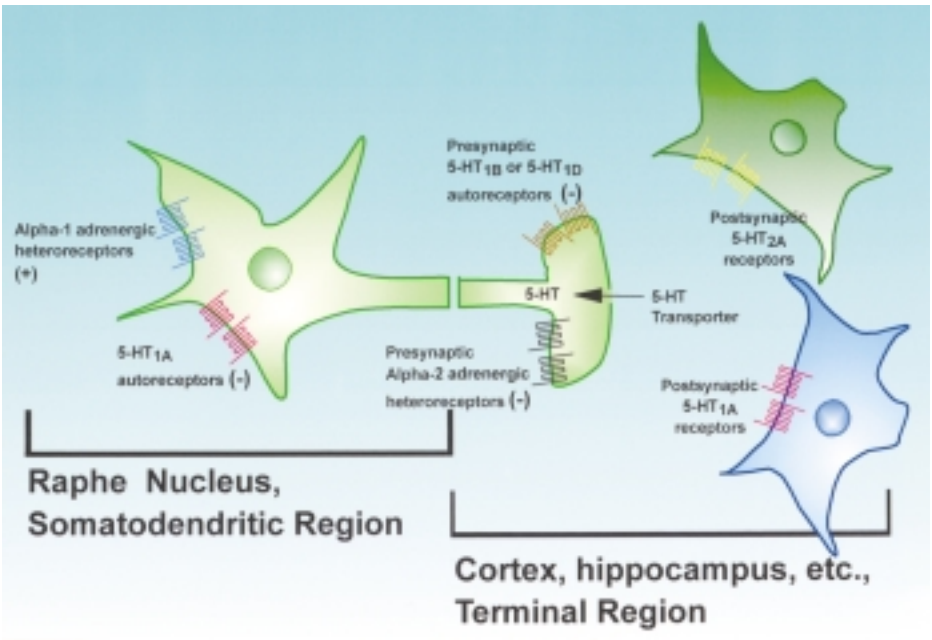


Figure 3. Schematic of a raphe nucleus serotonergic neuron. Receptors are illustrated with 7 transmembrane-spanning segments. 5-HT = 5-hydroxytryptamine (adapted with permission from Briley and Moret[76]).

clic antidepressants and MAOIs strongly suggested that serotonin and norepinephrine had important roles in the mechanism of action of antidepressants.[85] Because of this early evidence, researchers have performed animal studies focusing on the neurons in the brain that synthesize and release serotonin and norepinephrine.

Virtually all neurons in the brain that synthesize serotonin are located in the raphe nucleus; an example of such a neuron is shown in Figure 3. All neurons that synthesize norepinephrine are localized either in the locus coeruleus or in the lateral ventral tegmental fields. Of importance, a reciprocal relationship exists between noradrenergic neurons of the locus coeruleus and serotonergic neurons of the raphe nucleus[86] because these neurons project to one another.[87,88]

The neuron in Figure 3 synthesizes and releases serotonin. On the surface of this cell are either autoreceptors for serotonin or heteroreceptors for other neurotransmitters. In Figure 3, the heteroreceptors are for norepinephrine. All these receptors belong to the class of receptors that are thought to span the membrane 7 times (Figure 3) and are known to couple to proteins within the cells to cause the synthesis of second messengers, such as cyclic adenosine monophosphate (previously reviewed[89]).

These different receptors are important because most of those illustrated in Figure 3 are inhibitory. Somatodendritic autoreceptors inhibit the rate of firing of action potentials, and presynaptic autoreceptors inhibit the synthesis and release of serotonin. Additionally, the presynaptic $\alpha_2$-adrenergic heteroreceptors, when activated by norepinephrine, inhibit the release of serotonin, whereas the somatodendritic $\alpha_1$-adrenergic heteroreceptors activate this neuron on binding norepinephrine.

**Serotonin Receptor Changes With Treatment With an SSRI.—**With short-term treatment with an SSRI, elevation of serotonin in the synapse is modest because of negative feedback loops that prevent accumulation of excessive amounts of serotonin.[76] However, with long-term treatment with an SSRI, changes occur that involve first desensitization and then down-regulation.[76] Thus, long-term treatment of animals with an SSRI results in desensitization and down-regulation of serotonergic, somatodendritic, and presynaptic inhibitory autoreceptors that cause (1) an increased firing rate of raphe neurons (somatodendritic autoreceptors), (2) an increased synthesis of serotonin (presynaptic autoreceptors), and (3) an increased release of serotonin (presynaptic autoreceptors).

As a result of removing negative feedback loops by desensitization and down-regulation of these autoreceptors, synaptic levels of serotonin are increased substantially in the continued presence of the uptake blockade.[76] Not all animal studies support this theory,[90] and it has not yet been shown to occur in humans. However, the concept of presynaptic 5-$HT_{1A}$ autoreceptors involved in the nega-

tive feedback of serotonergic neurons has led to the clinical use of antagonists of this receptor in combination with antidepressants to treat depression. The aim of these studies is to increase the rate of onset of therapeutic effects of the antidepressant or enhance its efficacy.[91,92] Most of these studies have used pindolol, which blocks both serotonergic and adrenergic receptors. Results have been mixed.[93] One possible reason for these mixed results is that the dose of pindolol, which usually is 2.5 mg 3 times daily, is too low to occupy a substantial percentage of brain serotonin receptors in all persons, as demonstrated in a recent positron emission tomography (PET) study.[94] Another possibility (discussed subsequently) is that 5-$HT_{1A}$ autoreceptors are already reduced in patients with depression.

**Serotonin Receptors in Brains of Living Depressed Patients.—**There are numerous studies, with often conflicting results, of levels of serotonin receptors in brain tissue of patients who were depressed at the time of death or of suicide victims who were not always suffering from depression. However, it is interesting to review briefly some recent PET studies measuring concentrations of brain serotonin receptors in living humans. Data from these studies do not seem to support the previously outlined theories, which are based on animal studies.

In a study measuring brain levels of 5-$HT_{1A}$ receptors in depressed patients,[95] researchers found modestly decreased levels in both untreated and treated depressed patients compared to controls. No difference was noted in the concentration of binding sites between responders and nonresponders to antidepressant medication. In a study of patients with either major depressive disorder or bipolar depressed disorder and a first-degree relative with affective illness, similar results were obtained,[96] with reductions in binding potential in the raphe and in limbic and neocortical regions. These data are inconsistent with the previously outlined hypothesis that antidepressants are desensitizing and down-regulating presynaptic 5-$HT_{1A}$ autoreceptors. Perhaps other subtypes (eg, 5-$HT_{1D}$ receptors) are involved in the mechanism of action of antidepressants, or perhaps the theory based on animal studies is incorrect.

More PET scanning studies have measured brain levels of 5-$HT_{2A}$ receptors than of 5-$HT_{1A}$ receptors. Early animal studies show that the postsynaptic 5-$HT_{2A}$ receptors are down-regulated by antidepressant treatment.[97] These results suggest that depression is associated with an increase or up-regulation of 5-$HT_{2A}$ receptors. However, PET scanning studies, although findings are inconsistent, do not support the hypothesis of up-regulated 5-$HT_{2A}$ receptors in brains of depressed patients. Thus, in untreated depressed patients, brain 5-$HT_{2A}$ receptors are unchanged[98,99] or decreased.[100-102]

Consistent with animal studies,[97] 2 PET studies showed that antidepressants down-regulate 5-$HT_{2A}$ receptors in brains of depressed patients.[100,103] However, 1 study suggested that antidepressant treatment up-regulates these receptors.[104] In the studies showing down-regulation of 5-$HT_{2A}$ receptors,[100,103] no correlation was noted between clinical response and down-regulation because reduced receptor numbers were found in both responders and nonresponders to the antidepressant medication.

## Specific Synaptic Effects of Antidepressants and Their Possible Clinical Consequences

**Blockade of Neurotransmitter Transport by Antidepressants.—**The vast majority of available antidepressants block the transport of neurotransmitters back into the cells from which they were released. Most of these drugs are more potent at blocking transport of serotonin than transport of norepinephrine (Figures 4-6).[105] Newer antidepressants (SSRIs) are generally more selective and more potent than the older compounds at blocking transport of serotonin over norepinephrine. In addition, some antidepressants (eg, mirtazapine) weakly block transport of norepinephrine, serotonin, and dopamine. Reboxetine, which is marketed as an antidepressant outside the United States and may be marketed in the United States in the next few years, is selective for norepinephrine. Bupropion (also marketed for smoking cessation under the trade name Zyban) is the only antidepressant more selective for blocking transport of dopamine than for blocking transport of other neurotransmitters. However, bupropion may be more noradrenergic than dopaminergic because of effects of a metabolite, which is present in the body at much higher concentrations than is the parent compound.[106]

Paroxetine is the most potent blocker of serotonin transport (Figure 5), but citalopram (Figure 1) is by far the most selective (Figure 6). Selectivity cannot be equated with potency because selectivity is derived from a ratio of potencies. Thus, although citalopram is more than 10-fold more selective (ie, more specific) at blocking transport of serotonin than is paroxetine (Figure 6), it is only about one tenth as potent as paroxetine at this blockade (Figure 5). Finally, sertraline is the most potent of the antidepressants at blocking transport of dopamine (Figure 7), being about as potent as methylphenidate at this blockade.

Venlafaxine has been called a serotonin and norepinephrine reuptake inhibitor based on animal data.[107] However, it is much weaker at the human norepinephrine transporter than at the rat homologue. Therefore it is an SSRI at low dosages (likely <200 mg/d). At high dosages (eg, 375 mg/d), effects on the norepinephrine transporter can be achieved.[31]

**Blockade of Neurotransmitter Receptors by Antidepressants.—**Most of the newer generation antidepressants

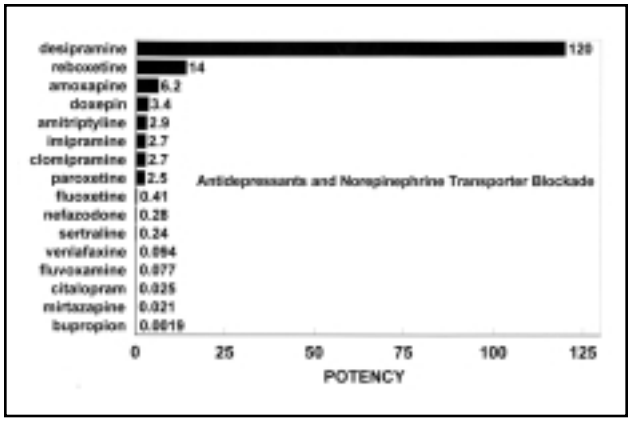


Figure 4. Antidepressant inhibition of the human norepinephrine transporter. Potency (affinity) data are expressed as the inverse of the equilibrium dissociation constant $K_d$, multiplied by a factor of $10^{-7}$. The $K_d$ is in molarity. Data derived from radioligand binding studies of the molecularly cloned human norepinephrine transporter.[105]

are weaker than the older compounds (especially, tricyclic antidepressants) at blocking receptors for neurotransmitters. This fact predicts an adverse-effect profile for these newer compounds different from and more favorable than that for older drugs.

At the $\alpha_1$-adrenoceptor, the most potent compounds (mainly, older generation tricyclic antidepressants), although a little weaker than the antihypertensive drug phentolamine, are likely to have effects clinically at these receptors (Figure 8). Of the currently marketed antidepressants in the United States, mirtazapine is the only one that is relatively potent at binding to the $\alpha_2$-adrenoceptor (data not shown). Additionally, with the exception of amoxapine, a demethylated derivative of the neuroleptic loxapine, antidepressants are also weak competitive antagonists of dopamine $D_2$ receptors (Figure 9).

Overall, as receptor blockers, the most potent interaction of antidepressants (especially the classic tricyclic drugs) is at the histamine $H_1$ receptor (Figure 10). Histamine is a putative neurotransmitter in the brain[110] where, like elsewhere in the body, it causes its effects by acting at 3 types of receptors, histamine $H_1$, $H_2$, and $H_3$. The newest histamine receptor $H_3$ affects the presynaptic synthesis and release of histamine and other neurotransmitters.[111-113] Histamine $H_2$ receptors are present in the brain, but classically these receptors are involved with gastric acid secretion. Also outside the nervous system, histamine $H_1$ receptors are classically involved with allergic reactions.

Some antidepressants are exceedingly potent histamine $H_1$ antagonists (Figure 10) and are more potent than any of the newer generation histamine $H_1$ antagonists marketed recently in the United States. As a result, clinicians are using them to treat allergic and dermatological problems.[114] Interestingly, a topical antipruritic agent with the active ingredient of doxepin was reported to cause a tricyclic antidepressant overdose in a child with eczema.[115] The child never ingested the drug, but it was absorbed through the skin.[114,116]

The next most potent, clinically relevant receptor blocking effect is at the muscarinic acetylcholine receptor. Such receptors are the predominant type of cholinergic receptors in the brain, where they are involved with memory and learning, among other functions.[117] In addition, some evidence suggests that these brain receptors are involved in the pathophysiology of affective illness.[118] Antidepressants have a broad range of affinities for human

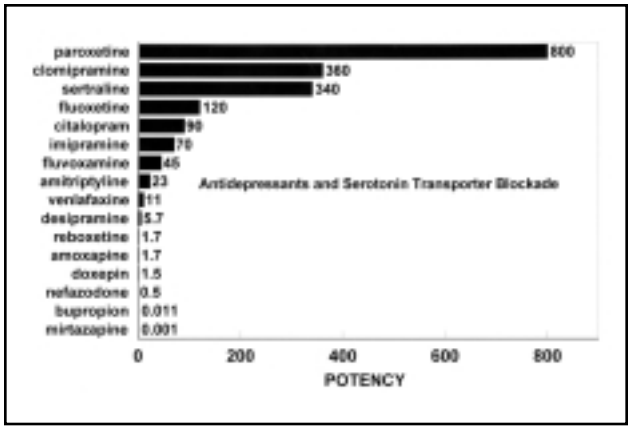


Figure 5. Antidepressant inhibition of the human serotonin transporter. Potency data are expressed as in the legend to Figure 4. Data from reference 105.

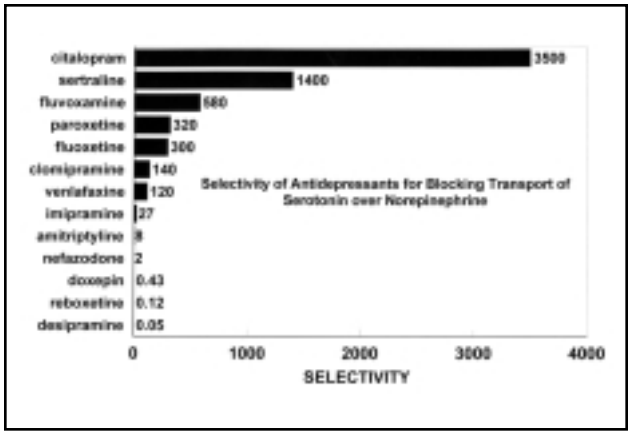


Figure 6. Selectivity of antidepressants for blocking uptake of serotonin over norepinephrine. Data are ratios of numbers presented in Figures 4 and 5.

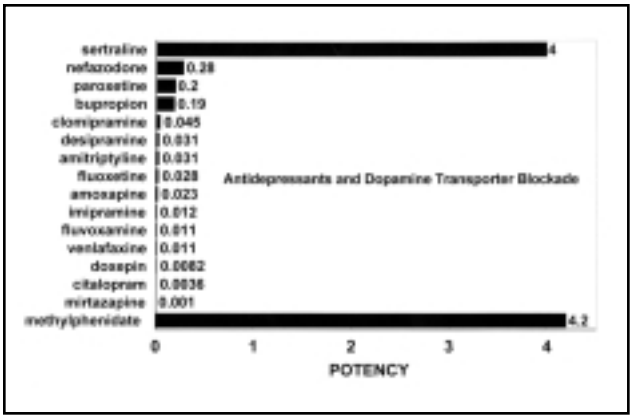


Figure 7. Antidepressant inhibition of the human dopamine transporter. Potency data are expressed as in the legend to Figure 4. Methylphenidate is the reference compound. Data from reference 105.

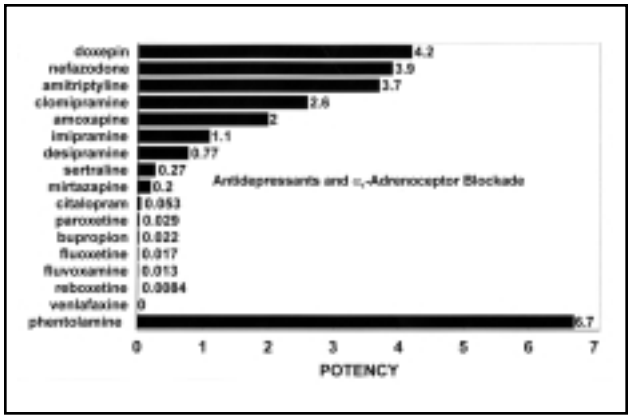


Figure 8. Antidepressant blockade of human $\alpha_1$-adrenoceptors. Affinity data are expressed as in the legend to Figure 4. Phentolamine is the reference compound. Data derived from radioligand binding studies of human brain tissue.[108,109]

brain muscarinic receptors (Figure 11). The most potent is amitriptyline. The SSRI paroxetine is unique among the newer compounds for having appreciable antimuscarinic potency, similar to that for imipramine (Figure 11). Studies with the molecularly cloned human muscarinic receptors, of which there are 5, show that paroxetine has highest affinity for the m3 subtype of this receptor.[119] This subtype is found predominantly in the brain, glandular tissue, and smooth muscle. Overall, antidepressants vary little in their affinities for the 5 subtypes of the human muscarinic receptor.[119]

Antidepressants also antagonize the 5-$HT_{2A}$ receptor, which is 1 of about 15 molecularly cloned subtypes of receptors for serotonin. In general, antidepressants are weak at this blockade, except for amoxapine, nefazodone, and mirtazapine (Figure 12).

Monoamine oxidase inhibitors have weak direct effects on neurotransmitter receptors and almost no clinically important pharmacological activity on them (data not shown).

**Clinical Importance of Early Synaptic Effects of Antidepressants.—**All the pharmacological effects of the drugs discussed previously occur shortly after a patient has ingested a dose of the medication. Thus, most of the possible clinical effects discussed subsequently occur early in the treatment of patients. However, with long-term administration of the drug, adaptive changes may occur. These changes can result in an adjustment to certain adverse effects, the development of new adverse effects, and the onset of therapeutic effects. The pharmacological properties and their possible clinical consequences are listed in

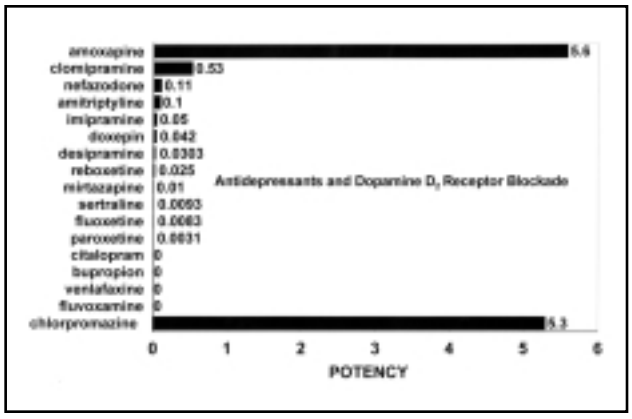


Figure 9. Antidepressant blockade of human dopamine $D_2$ receptors. Affinity data are expressed as in the legend to Figure 4. Chlorpromazine is the reference compound. Data from references 108 and 109.

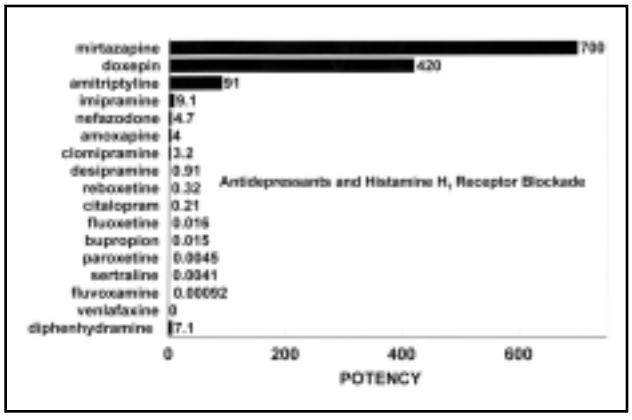


Figure 10. Antidepressant blockade of human histamine $H_1$ receptors. Affinity data are expressed as in the legend to Figure 4. Diphenhydramine is the reference compound. Data from references 108 and 109.

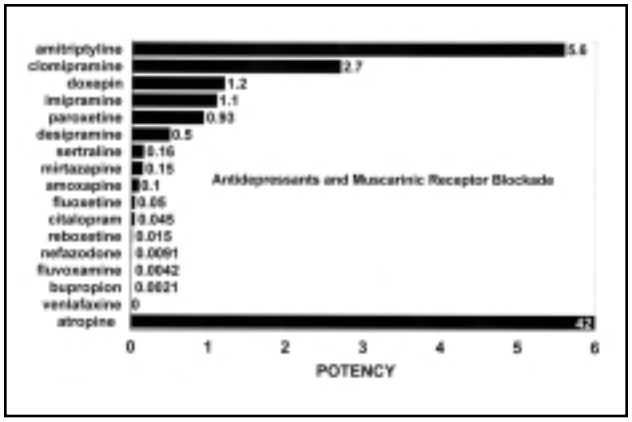


Figure 11. Antidepressant blockade of human muscarinic receptors. Affinity data are expressed as in the legend to Figure 4. Atropine is the reference compound. Data from references 108 and 109.

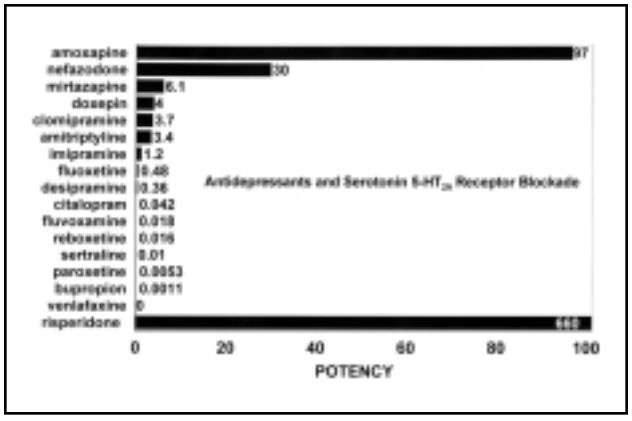


Figure 12. Antidepressant blockade of human serotonin 5-hydroxytryptamine$_{2A}$ (5-HT$_{2A}$) receptors. Affinity data are expressed as in the legend to Figure 4. Risperidone is the reference compound. Data from references 108, 109, and 120.

Table 5. Of note, as a first approximation, the drugs that are most potent at the properties discussed are more likely to cause these possible effects than the drugs that are weak at these properties (Figures 4, 5, and 7-12).

*First approximation* refers to the fact that there are more variables to consider, other than affinity for a transporter or receptor, in predicting the likelihood that a drug will cause an adverse effect. In fact, true prediction is based on knowledge of variables, which at present cannot be measured readily. More specifically, the concentration of the drug at the site of action, relative to its affinity for the site, determines how much of the drug will be bound to its target. However, this is true only in the absence of neurotransmitters competing for binding to the same site and in the absence of biological variability of the target (ie, structural differences affecting binding affinity).[121] Assuming no biological variability, the clinician needs to know the concentration not only of the drug but also of the neurotransmitter at the target. With the current technology, clarification of these issues is difficult, except in a limited way with PET scanning.

Although transporter blockade may be related to the mechanism of therapeutic effects of antidepressants (Table 5), evidence to date suggests otherwise. Specifically, antidepressants do not seem to differ in clinical efficacy,[29,35] although the range of potencies of antidepressants at blocking this transport is broad (Figures 4, 5, and 7). However, clinical data suggest that potent uptake blockade of serotonin is necessary for the treatment of panic disorders and OCD.[122-124]

Blockade of neurotransmitter transport likely relates to certain adverse effects of these antidepressant drugs and to some of their drug interactions (Table 5). For example, serotonin transport blockade is the property that causes sexual adverse effects, including anorgasmy and decreased libido, more commonly associated with the SSRIs than with other types of antidepressants.[125] In support of the hypothesis relating serotonin to anorgasmy is the use of a serotonin receptor antagonist to treat this problem.[126]

Serotonin transport blockade causes a clinical syndrome (serotonergic syndrome) when an MAOI is combined with an antidepressant that blocks the transport of serotonin.[127] In addition, researchers have reported adverse interactions between tryptophan, the precursor of serotonin, and fluoxetine.[128]

Rarely, SSRIs can also cause extrapyramidal adverse effects,[129-132] paranoid reactions,[133] and intense suicidal preoccupation,[134] which may be secondary to akathisia.[135,136] The extrapyramidal adverse effects are not due to blockade of dopamine receptors because SSRIs are weak at this binding site (Figure 9). Instead, such adverse effects are likely due to increased synaptic levels of serotonin, mediating inhibition of release of dopamine through one of the serotonin receptor subtypes.[132,137,138]

Such effects on the extrapyramidal system suggest that there may be risks associated with use of SSRIs in patients with Parkinson disease. However, retrospective studies seem to show that use of SSRIs does not worsen the underlying motor system disease.[139] In addition, a recent prospective study of paroxetine supports this theory, although the dropout rate due to adverse effects was 20%.[140] Nonetheless, caution is advised when this class of antidepressant drugs is used in patients with Parkinson disease, not only because of the potential for worsening the disease but also because of the potential for a drug interaction with selegiline.[141]

Blockade of the dopamine transporter, as of the other transporters, may relate to antidepressant effects of drugs. It may also be of benefit to patients with Parkinson disease.

Table 5. **Possible Therapeutic and Adverse Effects of Transporter and Receptor Blocking Effects of Antidepressant Drugs***

| | Possible effects | |
|---|---|---|
| | Therapeutic | Adverse |
| Norepinephrine transporter | Antidepressant | Tremors<br>Tachycardia<br>Blockade of antihypertensive effects of guanethidine and guanadrel<br>Augmentation of pressor effects of sympathomimetic amines |
| Serotonin transporter | Antidepressant | Gastrointestinal disturbances (including weight loss early in treatment, weight gain late in treatment)<br>Increase or decrease in anxiety (dose dependent)<br>Sexual dysfunction (including decreased libido)<br>Extrapyramidal adverse effects<br>Interactions with tryptophan, monoamine oxidase inhibitors, and fenfluramine |
| Dopamine transporter | Antidepressant<br>Antiparkinsonian | Psychomotor activation<br>Precipitation or aggravation of psychosis |
| $\alpha_1$-Adrenoceptors | Unknown | Potentiation of antihypertensive effect of prazosin, terazosin, doxazosin, and labetalol<br>Postural hypotension and dizziness<br>Reflex tachycardia |
| Dopamine $D_2$ receptor | Amelioration of signs and symptoms of psychosis | Extrapyramidal movement disorders—dystonia, parkinsonism, akathisia, tardive dyskinesia, rabbit syndrome<br>Endocrine effects—prolactin elevation (galactorrhea, gynecomastia, menstrual changes, sexual dysfunction in men) |
| Histamine $H_1$ receptor | Sedation | Sedation<br>Drowsiness<br>Weight gain<br>Potentiation of central depressant drugs |
| Muscarinic receptor | Antidepressant | Blurred vision<br>Attack or exacerbation of narrow-angle glaucoma<br>Dry mouth<br>Sinus tachycardia<br>Constipation<br>Urinary retention<br>Memory dysfunction |
| 5-$HT_{2A}$ receptor | Antidepressant<br>Reduction of anxiety<br>Promotion of deep sleep<br>Prophylaxis of migraine headaches<br>Antipsychotic | Unknown |

*5-$HT_{2A}$ = 5-hydroxytryptamine$_{2A}$.

However, this property could cause psychomotor activation and precipitation or aggravation of psychosis, seen rarely with bupropion[142] and sertraline.[143]

$\alpha_1$-Adrenergic receptor blockade by antidepressants may be responsible for orthostatic hypotension, a serious, common cardiovascular effect.[52] This adverse effect can cause dizziness and reflex tachycardia. In addition, this property of antidepressants results in the potentiation of several antihypertensive drugs that potently block $\alpha_1$-adrenoceptors (Table 5).

Antidepressants are weak competitive antagonists of dopamine $D_2$ receptors (Figure 9). The most potent com-

pound, amoxapine, is a demethylated derivative of the neuroleptic loxapine. The in vitro activity of amoxapine likely explains its extrapyramidal adverse effects[144] and its ability to elevate prolactin levels.[145] Interestingly, because of its affinity for 5-$HT_{2A}$ receptors relative to its affinity for $D_2$ receptors, some investigators consider amoxapine an atypical neuroleptic,[146] at least at lower dosages. Because of its dopamine receptor blocking property, amoxapine should be given only to patients with psychotic depressions.

Potentiation of the effects of central depressant drugs, which cause sedation and drowsiness, is a pharmacodynamic drug interaction of antidepressants related to histamine $H_1$ receptor antagonism. This antagonism is probably responsible for the adverse effects of sedation and drowsiness. Sedation, however, may be a desired effect in agitated, depressed patients. This property also may be responsible for weight gain because this mechanism of antipsychotic drugs has been strongly correlated with weight gain.[147]

Although blockade of muscarinic receptors may be related to therapeutic effects,[118] more likely this receptor blockade by some antidepressants is responsible for several adverse effects (Table 5). The relatively high affinity of paroxetine for these receptors distinguishes it from the other newer compounds. In addition, it may explain the common complaint of dry mouth and constipation reported in some published clinical trials with paroxetine.[148] Vigilance is especially important with the elderly patient to avoid or reduce these antimuscarinic effects of antidepressants and other drugs.[149]

Antidepressants also block 5-$HT_{2A}$ receptors (Figure 12). Blockade of 5-$HT_{2A}$ receptors may be a mechanism of antidepressant effects. However, because of the lack of selectivity of drugs blocking 5-$HT_{2A}$ receptors,[150] many of the clinical effects ascribed to 5-$HT_{2A}$ receptors may actually involve 5-$HT_{2C}$ receptors or a combination of both receptors. Nonetheless, activation of 5-$HT_{2A}$ receptors may cause anxiety, sleep disturbances, and sexual dysfunction.[126,151,152] Therefore, blockade of these receptors may reduce anxiety, promote deep sleep, prevent migraine headaches, and alleviate depression. In addition, blockade of the 5-$HT_{2A}$ receptor and the 5-$HT_{2C}$ receptor may be involved in the alleviation of psychosis.[150,153,154]

With respect to blockade of 5-$HT_{2A}$ receptors possibly causing antidepressant effects, newer atypical neuroleptics with potent 5-$HT_{2A}$ blocking effects, such as risperidone and olanzapine, occasionally induce mania in patients.[155] These compounds are being used in combination with antidepressants to treat patients with refractory depression.[156,157]

Antidepressants that are relatively potent at 5-$HT_{2A}$ receptors (eg, amoxapine, nefazodone, and mirtazapine) are not likely to cause the types of sexual adverse effects seen with SSRIs.[158,159] Such drugs could potentially be used either in combination with an SSRI to reduce SSRI-induced sexual adverse effects or as an alternative antidepressant medication in patients with intolerable sexual adverse effects from an SSRI.[158,159]

## CONCLUSION: THE FUTURE, PAST, AND PRESENT

What might the future bring with respect to the pharmacological treatment of depression in the United States? Compounds that block transporters are still under development. For example, reboxetine, a compound selective for the norepinephrine transporter, may be marketed in the United States within the next few years, several years after the marketing of this compound outside the United States. Drugs that potently block more than 1 transporter are also under development. An example of this class of compounds is duloxetine, which potently blocks both the norepinephrine and the serotonin transporters.[160] In addition, pharmaceutical companies are actively seeking compounds that potently block all 3 transporters (norepinephrine, serotonin, and dopamine), the acronym of which is *SNUB* or *super neurotransmitter uptake blocker*. Such compounds are in early stages of development.[161] Finally, agonists of 5-$HT_{1A}$ receptors, such as gepirone, are being used in clinical trials for treatment of depression.[162]

Representing a major departure from the focus on norepinephrine, serotonin, and dopamine, drugs are under development that target some neuropeptide receptors. Specifically, at present researchers are studying in depressed patients novel and potentially breakthrough compounds that are antagonists of receptors for the neuropeptides substance P[163] and corticotropin-releasing factor.[164] Unfortunately, the follow-up clinical studies of the substance P antagonist showed, once again, how powerful placebo is as an antidepressant.[165]

Pharmacogenetics has a role in the treatment of depression. Intriguing studies being published suggest that the response to an SSRI is predicted by the genotype of the patient with respect to his or her serotonin transporter. The serotonin transporter exists in several forms based on the structure of the gene. Two of these polymorphisms in the promoter region give either a short ("s") form, which is expressed at a low level, or a long ("l") form, which is expressed at a high level.[166,167] One group showed that individuals homozygous ("ll") or heterozygous ("ls") for the long form have a better response to SSRIs than those homozygous for the short form ("ss").[168,169] However, these results were not replicated in a study by another group.[170] Nonetheless, in the future, genotyping for various polymorphisms will be performed to help with dosing (eg, CYP polymorphisms) or selection of an antidepressant drug.

In the meantime, the information presented in this review will help clinicians select the appropriate antidepressant for their patients to avoid or minimize certain adverse effects and drug interactions. The data show that the newer generation compounds offer clear advantages over the tricyclic antidepressants and other older generation compounds.

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