

# Basic Psychopharmacology of Antidepressants, Part 1: Antidepressants Have Seven Distinct Mechanisms of Action

Stephen M. Stahl, M.D., Ph.D.

Distinct pharmacologic mechanisms allow the antidepressants to be separated into seven different classes. These basic pharmacologic concepts can explain not only the therapeutic actions, but also the side effects of the wide range of antidepressants currently available. The two classical mechanisms are those of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). The most widely prescribed agents are the serotonin selective reuptake inhibitors (SSRIs). Three other classes of antidepressants, like the SSRIs, increase serotonergic neurotransmission, but they also have additional actions, namely dual serotonin and norepinephrine reuptake inhibition (venlafaxine); serotonin-2 antagonism/reuptake inhibition (nefazodone); and  $\alpha_2$  antagonism plus serotonin-2 and -3 antagonism (mirtazapine). The selective norepinephrine and dopamine reuptake inhibitor bupropion defines a novel class of antidepressant that has no direct actions on the serotonin system. (*J Clin Psychiatry 1998;59[suppl 4]:5-14*)

There are more than two dozen antidepressant agents, which work by seven distinct pharmacologic mechanisms (Figure 1).<sup>1,2</sup> The seven mechanisms include two that are classical and five that are new. The classical mechanisms of action are those shared by tricyclic antidepressants (TCAs) or by monoamine oxidase inhibitors (MAOIs). The five newer categories include (1) the serotonin selective reuptake inhibitors (SSRIs); (2) a dual serotonin and norepinephrine reuptake inhibitor (SNRI; i.e., medium- to high-dose venlafaxine); (3) serotonin-2 antagonist/reuptake inhibitors (SARIs; e.g., nefazodone); (4) a norepinephrine and dopamine reuptake inhibitor (NDRI; i.e., bupropion); and (5) noradrenergic and specific serotonergic antidepressants (NaSSAs; exemplified by mirtazapine, with  $\alpha_2$  antagonist properties). There are many other treatments for depression, including forms of psychotherapy, electroconvulsive therapy, and various augmenting agents. However, only the first-line monotherapies will be considered here.

## THE MONOAMINE HYPOTHESIS OF DEPRESSION

For over 30 years, the leading theory to explain the biological basis of depression has been the monoamine hy-

pothesis of depression.<sup>1-4,6</sup> This theory proposes that depression is due to a deficiency in one or another of three biogenic monoamines, namely serotonin, norepinephrine, and/or dopamine. A corollary to this hypothesis is that every known antidepressant increases neurotransmission of serotonin, norepinephrine, and/or dopamine. Six of the seven classes of antidepressants accomplish this by blocking one or more of the reuptake pumps<sup>7</sup> or receptors for these three monoamines. The seventh class inhibits an enzyme, namely MAO.<sup>1</sup>

Increasing neurotransmission seems to be the result of desensitization (or down-regulation) of certain key neurotransmitter receptors (see below for details). Interestingly, this desensitization has a delayed onset, just like the therapeutic actions of antidepressants.<sup>8</sup> The development of tolerance to side effects of antidepressants also occurs with delayed onset.<sup>8</sup> Thus, the monoamine receptor hypothesis has evolved from the monoamine hypothesis and proposes that the increases in neurotransmission—which all the antidepressants share—are translated into receptor desensitization in order to effect an antidepressant response as well as to allow tolerance to develop to acute side effects.<sup>1,2,8,9-11</sup>

## THREE KEY NEUROTRANSMITTER RECEPTOR SYSTEMS: NOREPINEPHRINE, DOPAMINE, AND SEROTONIN

The noradrenergic neuron is regulated by a multiplicity of receptors for norepinephrine (NE) (Figure 2). This includes the NE transporter, and several NE receptors, including  $\alpha_1$ -,  $\alpha_2$ -, and  $\beta_1$ -adrenergic receptors. Postsynaptic NE receptors generally act by recognizing when NE is released from the presynaptic neuron and reacting by setting up a molecular cascade in the postsynaptic neuron. This

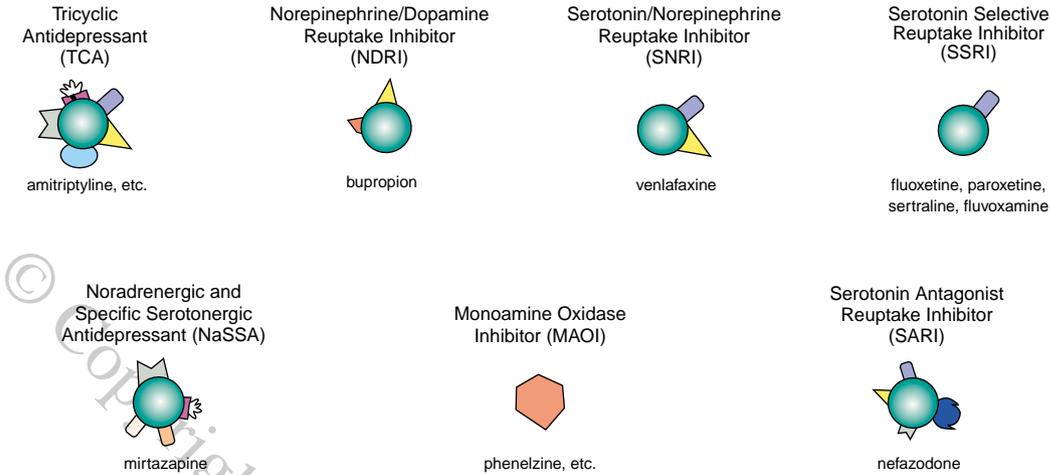
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*From the Clinical Neuroscience Research Center and the Department of Psychiatry, University of California, San Diego.*

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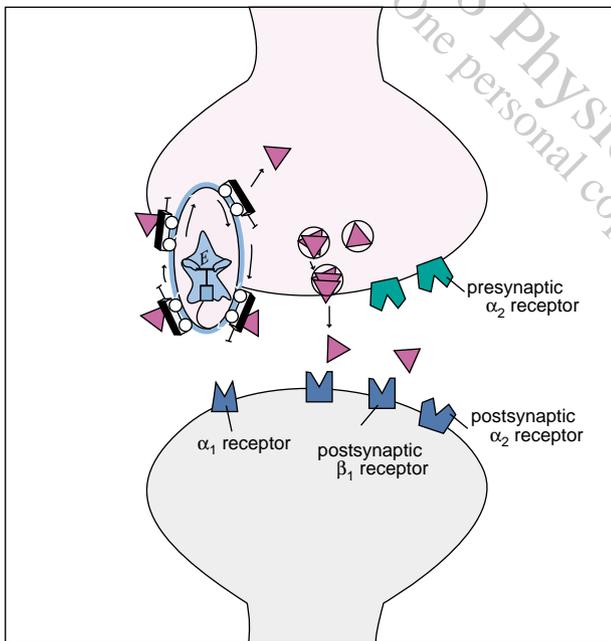
*Reprint requests to: Stephen M. Stahl, M.D., Ph.D., Clinical Neuroscience Research Center, 8899 University Center Lane, Suite 130, San Diego, CA 92122.*

**Figure 1. The Seven Classes of Antidepressants\***



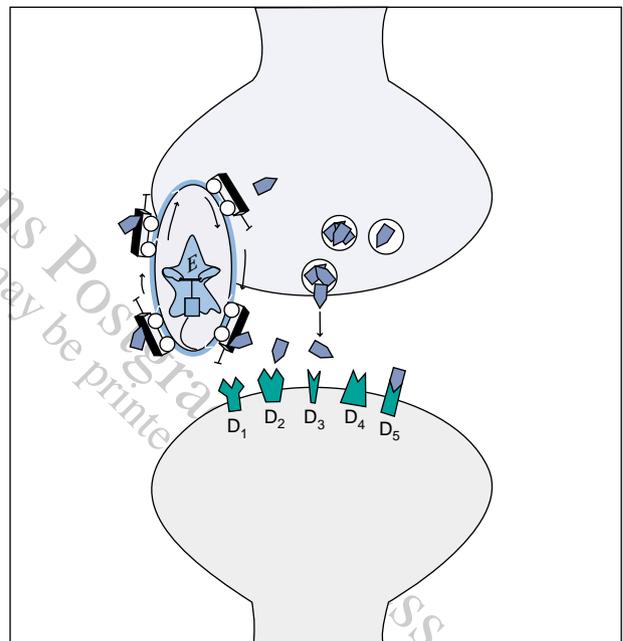
\*From reference 1, with permission.

**Figure 2. Several Norepinephrine Receptor Subtypes\***



\*From reference 1, with permission. Triangles represent norepinephrine and can interact with various norepinephrine receptors, including the circular reuptake pump.

**Figure 3. Several Dopamine Receptor Subtypes\***



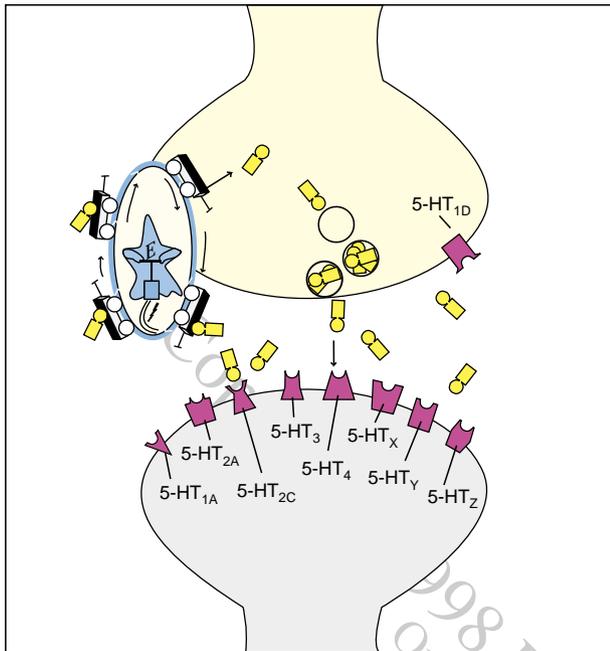
\*From reference 1, with permission. Pentagons represent dopamine and can interact with various dopamine receptors, including the circular reuptake pump.

causes neurotransmission to pass from the presynaptic neuron to the postsynaptic neuron. The presynaptic  $\alpha_2$  receptor is important because it is an autoreceptor; that is, when the presynaptic  $\alpha_2$  receptor recognizes synaptic NE, it turns off further release of NE. Thus the presynaptic  $\alpha_2$  terminal autoreceptor acts as a brake for the NE neuron. Stimulating this receptor (i.e., stepping on the brake) stops the neuron from firing; this probably occurs physiologically to prevent overfiring of the NE neuron, since it can

shut itself off once the firing rate gets too high and the autoreceptor becomes stimulated.

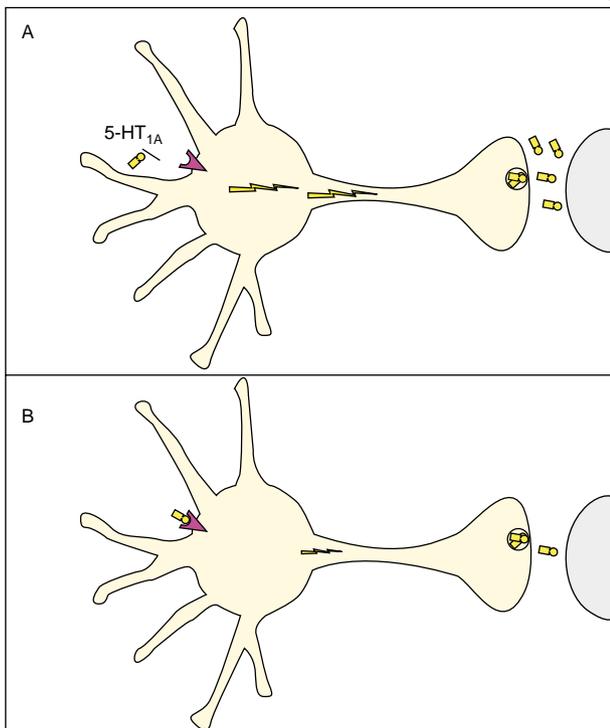
Receptors for dopamine (DA) regulate dopaminergic neurotransmission. A plethora of dopamine receptors exist, including the presynaptic DA transporter and at least five pharmacologic subtypes and several more molecular isoforms (Figure 3). Perhaps the most extensively investigated dopamine receptor is the D<sub>2</sub> receptor, as it is stimulated by dopaminergic agonists for the treatment of

Figure 4. Several Serotonin Receptor Subtypes\*



\*From reference 1, with permission. The circle-on-square icons represent serotonin (5-HT) and can interact with numerous 5-HT receptors, including the circular reuptake pump.

Figure 5. Serotonin-1A Receptors Located on the Cell Body and Dendrites\*



\*From reference 1, with permission. Serotonin-1A receptors located on the cell body (soma) and dendrites are called somatodendritic (A). Since they inhibit the release of serotonin, they are also called autoreceptors (B).

Parkinson's disease and blocked by dopamine antagonist neuroleptics for the treatment of schizophrenia.<sup>1</sup>

Receptor subtyping for the serotonergic neuron has proceeded at a very rapid pace, with the designation of several major categories of serotonin (5-hydroxytryptamine or 5-HT) receptors, each further subtyped depending upon pharmacologic properties or molecular properties (Figure 4). In addition to the serotonin transporter, there is a key presynaptic serotonin receptor (the 5-HT<sub>1D</sub> receptor) and several postsynaptic serotonin receptors (5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, 5-HT<sub>3</sub>, 5-HT<sub>4</sub>, and many others). Presynaptic 5-HT<sub>1A</sub> receptors are autoreceptors, are located on the cell body and dendrites, and are therefore called somatodendritic autoreceptors (Figure 5A, B). These 5-HT<sub>1A</sub> somatodendritic autoreceptors detect the presence of 5-HT, causing a shutdown of 5-HT neuronal impulse flow (Figure 5B). Presynaptic 5-HT<sub>1D</sub> receptors are also a type of autoreceptor, but are located on the presynaptic axon terminal, and are therefore called terminal autoreceptors. They are also regulators of 5-HT release, so if the 5-HT<sub>1D</sub> receptor is stimulated, the release of 5-HT is blocked.

Two key postsynaptic 5-HT receptors with clinical implications are the 5-HT<sub>2A</sub> receptor and the 5-HT<sub>3</sub> receptor. When the postsynaptic 5-HT<sub>2A</sub> receptor is occupied by 5-HT, it causes neuronal impulses in the postsynaptic neuron to be altered via the production of second messengers, whereas stimulation of the 5-HT<sub>3</sub> receptor opens an ion channel.

### CLASSICAL ANTIDEPRESSANTS: MAO INHIBITORS AND TRICYCLIC ANTIDEPRESSANTS

The first antidepressants were discovered 40 years ago by serendipity. Only much later was it determined that these early agents worked either by inhibiting the enzyme MAO<sup>1,2</sup> or by blocking the reuptake of norepinephrine and serotonin.<sup>1,2,8</sup> Interestingly, no subsequent antidepressant can surpass the classical agents in overall efficacy in clinical trials. However, the newer agents are far safer and better tolerated. The classical agents dominated the treatment of depression for almost 30 years, from the late 1950s until the late 1980s when the SSRIs were introduced.

The action of an MAOI is to increase the availability of the monoamine neurotransmitters NE, DA, and 5-HT by blocking their metabolism.<sup>1</sup> The classical MAOIs are non-selective and irreversible, but the newer MAOIs are selective for MAO-A or MAO-B as well as reversible for MAO-A (Table 1).<sup>1</sup> Several reversible inhibitors of MAO-A are in development, but only moclobemide is marketed (not in the United States).<sup>12</sup>

TCAs are actually *five or more drugs in one*: (1) a serotonin reuptake inhibitor (SRI); (2) a norepinephrine reuptake inhibitor (NRI); (3) an anticholinergic-antimuscarinic drug (M<sub>1</sub>); (4) an  $\alpha_1$ -adrenergic antagonist; and (5) an antihistamine (H<sub>1</sub>).<sup>1,13</sup> They also inhibit sodium channels at

**Table 1. Monoamine Oxidase Inhibitors (MAOIs)**

Classical MAO Inhibitors—Irreversible and Nonselective
Phenelzine
Tranylcypromine
Isocarboxazid
RIMA—Reversible Inhibitor of MAO-A
Moclobemide
Selective Inhibitor of MAO-B
Deprenyl

overdose levels, causing potentially lethal cardiac arrhythmias and seizures.

Therapeutic actions of the TCAs are due to serotonin reuptake inhibition as well as norepinephrine reuptake inhibition.<sup>1,2,13</sup> The degree and selectivity of inhibition of the 5-HT versus NE transporters differ across the family of TCAs, with clomipramine being a preferential inhibitor of the 5-HT reuptake pump, and desipramine and maprotiline being preferential inhibitors of the NE reuptake pump.<sup>13</sup>

Side effects of the TCAs can be explained by their (unwanted) blockade of neurotransmitter receptors. H<sub>1</sub> (antihistamine) blockade of histamine receptors causes weight gain and drowsiness; M<sub>1</sub> (anticholinergic/antimuscarinic) blockade of acetylcholine receptors causes constipation, blurred vision, dry mouth, and drowsiness;  $\alpha_1$  blockade causes the side effects of dizziness, decreased blood pressure, and drowsiness.<sup>1,13</sup>

### SEROTONIN SELECTIVE REUPTAKE INHIBITORS

The SSRIs are the most widely prescribed antidepressants in the United States, accounting for well over half of all antidepressant prescriptions.<sup>1,2</sup> Five separate agents form the members of the SSRI class, differing in chemical structure, secondary pharmacologic properties, and pharmacokinetics. Four of these agents are on the United States market (fluoxetine, sertraline, paroxetine, fluvoxamine), with the fifth to become available in the United States soon (citalopram).<sup>2,14</sup>

#### Benefits of SSRI Administration

The SSRIs have revolutionized the treatment of depression for a number of reasons.<sup>14</sup> The principal advantage of these drugs over the classical MAOIs and TCAs is their much improved safety and tolerability. Whereas the classical antidepressant agents are lethal in overdose, the SSRIs are not. Also, the cardiac toxicity and troublesome anticholinergic side effects are absent from the SSRIs. This improved tolerability profile arrived on the scene just as new data have demonstrated the value of long-term treatment in preventing relapse of future depressive episodes. Thus, the acceptability of long-term treatment is much greater with the SSRIs than with the TCAs, and compliance is much higher.

Another advantage of the SSRIs is the breadth of their therapeutic profile, extending far beyond antidepressant actions.<sup>1,14</sup> Thus, SSRIs have proven efficacy in panic disorder, obsessive-compulsive disorder (OCD), and bulimia, with encouraging findings in social phobia, posttraumatic stress disorder, premenstrual dysphoric disorder, migraine, dysthymia, and many other conditions.

#### Mechanism of Action

The mechanism of action of SSRIs is usually explained simply by selective inhibition of the serotonin transporter.<sup>7</sup> However, a more precise statement of SSRI therapeutic action is “delayed disinhibition of serotonin neurotransmission in at least four key pathways.”<sup>1,9,15–23</sup>

When an SSRI is administered, it indeed blocks the serotonin reuptake pump, and this happens immediately.<sup>1,7</sup> However, this action causes a sudden increase in serotonin *predominately in the somatodendritic area*, and not at the axon terminals where serotonin is presumably needed in order to exert therapeutic actions (Figure 6A).<sup>1,9,15</sup> Perhaps this explains why SSRIs do not have rapid onset of therapeutic actions.

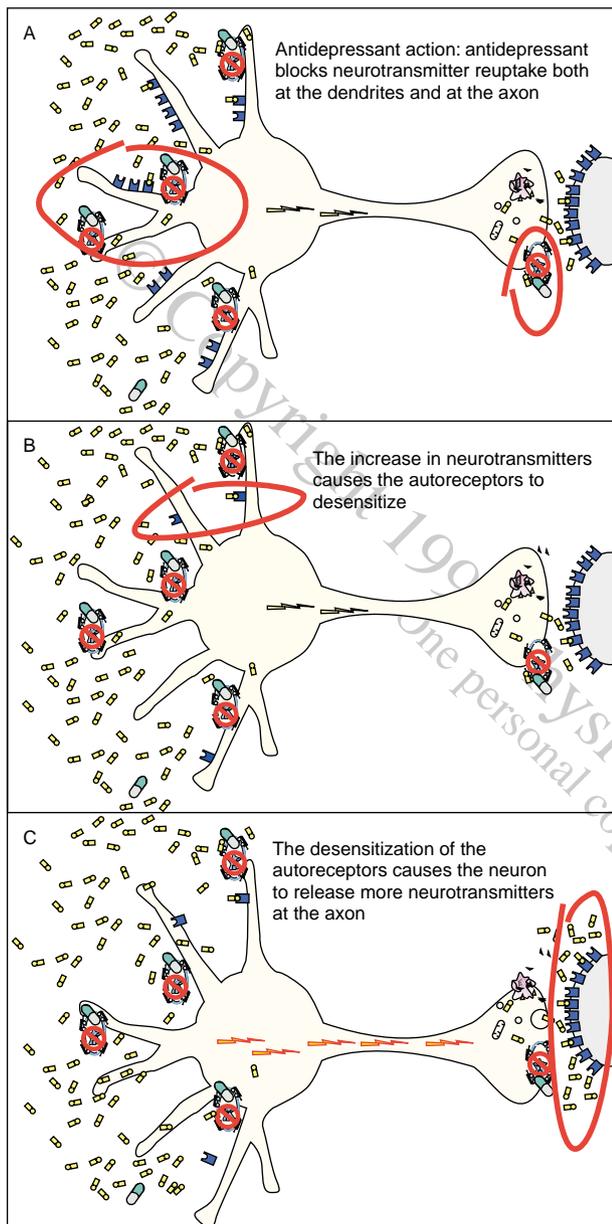
If SSRIs are administered chronically, the sustained increases of serotonin in the somatodendritic area of the serotonin neuron cause the somatodendritic serotonin-1A autoreceptors to desensitize (Figure 6B).<sup>1,9,14–25</sup> Once the somatodendritic autoreceptors desensitize, neuronal impulse flow is no longer as readily inhibited by serotonin. Thus, *neuronal impulse flow is turned on*. Another way to say this is that serotonergic neurotransmission is *disinhibited*, and more *serotonin is released from the axon terminal*.<sup>16–25</sup> (Figure 6C).

However, *this increase is delayed* compared with the increase of serotonin in the somatodendritic areas of the serotonin neuron. This delay is the result of the time it takes for somatodendritic serotonin to desensitize the serotonin-1A autoreceptors, and turn on (i.e., disinhibit) neuronal impulse flow in the serotonin neuron. As mentioned earlier, this delay may account for why SSRIs do not relieve depression immediately.

Finally, once SSRIs have blocked the reuptake pump, increased somatodendritic serotonin, desensitized somatodendritic serotonin-1A autoreceptors, disinhibited neuronal impulse flow, and increased release of serotonin from axon terminals, the final step is the desensitization of postsynaptic serotonin receptors (Figure 6C).<sup>1,10,26,27</sup> Desensitization of these receptors may contribute to the therapeutic actions of SSRIs, or it could account for the development of tolerance to acute side effects of SSRIs.<sup>1,2,9,10,15,26,27</sup>

In summary, the pharmacologic profile of an SSRI is to cause powerful if delayed disinhibition of 5-HT neurotransmission, presumably from every 5-HT pathway in the central nervous system (CNS).

**Figure 6. Adaptive Changes of the Serotonin Neuron to Chronic SSRI Administration\***



\*From reference 1, with permission. First (A), SSRIs increase serotonin predominantly in the raphe (that is, the somatodendritic area, located on the left) and not in the axon terminal areas on the right. Next (B), the somatodendritic serotonin-1A autoreceptors (on the left) are desensitized over time by this increased serotonin. Finally (C), the serotonin neuron is disinhibited, turning on serotonin release in the axon terminal.

Since different 5-HT pathways are known to mediate different CNS functions,<sup>29-51</sup> the various therapeutic effects of SSRIs may be mediated by disinhibition in different pathways. Thus disinhibition of serotonergic neurotransmission in the pathway from midbrain raphe to prefrontal cortex could hypothetically help mediate the antidepressant effects of SSRIs.<sup>2,51-65</sup>

Similarly, disinhibition of the pathway from midbrain raphe to basal ganglia could hypothetically mediate therapeutic actions of SSRIs in OCD<sup>2,51,52,66,67</sup>; disinhibition of the pathway to limbic cortex and hippocampus, therapeutic actions in panic disorders<sup>2,51,68,69</sup>; and disinhibition of the pathway to hypothalamus, therapeutic actions in bulimia and binge-eating disorder.<sup>51,70</sup> In each case, SSRI-induced disinhibition of serotonergic neurotransmission theoretically delivers neurotransmitter where it is needed, hypothetically in different places for different psychiatric disorders.

Clinical observations support the notion that different pathways mediate the different therapeutic actions of SSRIs, since SSRIs act so differently depending on which psychiatric disorder is being targeted.<sup>1,2,14</sup> Thus, the antidepressant profile of SSRIs is to frequently cause complete recovery; the usual maintenance dose is the same as the starting dose; the usual onset of response is in 3 to 8 weeks; and target symptoms do not worsen at first.

On the other hand, the anti-OCD profile of SSRIs is to cause on average less than 50% reduction of symptoms; the usual onset of response can be delayed as long as 12 to 26 weeks; the usual maintenance dose is often higher than the starting dose because of less than complete therapeutic response at the starting dose; and target symptoms do not worsen at first.

Still different is the antipanic profile of SSRIs, namely with starting doses usually less than starting doses for other indications and also lower than eventual maintenance dosing, because target symptoms often worsen at first before they improve after a 3- to 8-week delay.

Finally, the clinical profile of SSRI actions in bulimia is for the starting dose to be higher than that for any other indication and for the therapeutic onset of action to be faster than for the other indications. At present, bulimia is the only indication for which it is not proven that chronic treatment not only reduces symptoms, but prevents recurrence with long-term maintenance therapy.<sup>71-74</sup>

### Problems Associated With SSRI Administration

However, the SSRIs are not without their problems. Although efficacy is obviously quite broad, there is a nagging feeling among many investigators that SSRIs are not as effective for severe depression as other agents with dual mechanisms such as TCAs, venlafaxine, or mirtazapine.<sup>75</sup>

The SSRIs can also have side effects that are bothersome, such as anxiety, sleep disturbances, sexual dysfunction, and gastrointestinal disturbances.<sup>1,2,14</sup> In order to understand the mechanism of these side effects, it is helpful to know the functions of 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors. As already mentioned, stimulation of some 5-HT<sub>2</sub> receptors by serotonin when serotonergic neurons are disinhibited may play a role in some of the therapeutic effects of SSRIs.<sup>27</sup> Stimulation of other 5-HT<sub>2</sub> receptors hypothetically mediates several of the side effects of the SSRIs,

including anxiety, sleep disturbances, and sexual dysfunction.<sup>1,2,14,35-37</sup> The 5-HT<sub>2</sub> receptor may also mediate the hallucinogenic effects of LSD and other psychotomimetics.<sup>35-37</sup> The 5-HT<sub>2</sub> receptor may even mediate some of the behavioral changes in psychosis since blocking this receptor with the new “designer” antipsychotics such as risperidone and olanzapine improves psychosis.<sup>1</sup>

In considering the side effects of SSRIs, there also appears to be a neuroanatomic topography since stimulation of 5-HT<sub>2</sub> receptors in specific locations within the CNS may cause different side effects.<sup>37</sup> The topographical representation of these side effects follows the same rationale as that discussed above for the therapeutic effects, namely that different side effects are mediated by different 5-HT receptors in different 5-HT pathways.<sup>51</sup>

For example, a particularly troublesome side effect of SSRIs is the development of sexual dysfunction in long-term treatment.<sup>76,77</sup> Sexual function has a complex physiology and psychology. Some forms of sexual dysfunction can be caused by the illnesses that SSRIs treat, especially depression.<sup>76-78</sup> This usually takes the form of decreased libido and reduced pleurability, leading even to reduction in arousal. These aspects of sexual functioning may be mediated by mesolimbic dopamine pathways.<sup>2,14,37,79</sup> This pathway, which may be inhibited by serotonergic input to 5-HT<sub>2</sub> receptors, is hypothesized to control pleasure and reward.<sup>1,79</sup> Abnormalities in this pathway may be associated with conditions such as anhedonia in depression and craving from withdrawal of substances of abuse.<sup>1,79</sup> Simply put, there is a reciprocal relationship between serotonin and dopamine, with serotonin tending to inhibit sexual functioning and dopamine tending to enhance sexual functioning. That is why the SSRIs, which disinhibit serotonergic pathways that innervate mesolimbic dopamine systems, can cause sexual dysfunction. This is also why agents that promote dopamine, such as bupropion or stimulants, can often reverse SSRI-induced loss of libido.<sup>14,76-78</sup>

Another key serotonin pathway that controls sexual function is the descending pathway from brain stem down the spinal cord to spinal neurons that mediate various spinal reflexes such as ejaculation and orgasm. Disinhibiting this descending spinal pathway for serotonin causes increased serotonin release, which in turn inhibits sexual functioning.<sup>2</sup> Evidence that serotonin mediates its negative effects on sexual functioning via 5-HT<sub>2</sub> receptors comes both from observations that 5-HT<sub>2</sub> antagonists can occasionally reverse SSRI-induced sexual dysfunction<sup>76,77</sup> and from the fact that those antidepressants that are 5-HT<sub>2</sub> antagonists do not seem to induce sexual dysfunction.<sup>1,2,76,77</sup> Likewise, bupropion, which promotes dopamine but not serotonin, not only fails to produce ejaculatory and orgasmic disturbances, but can reverse those caused by the SSRIs.<sup>2,76,77</sup> Thus, some antidepressant agents (such as bupropion, nefazodone, and mirtazapine)

improve upon the SSRI side effect of sexual dysfunction because of their differing mechanisms of action.<sup>2,76,77</sup>

SSRI-induced akathisia and agitation are hypothetically mediated by stimulating 5-HT<sub>2</sub> receptors in the serotonin pathway that projects to the basal ganglia.<sup>80-82</sup> This may be due in part to the fact that serotonin inhibits dopamine release there.<sup>1,81,82</sup> Thus, increasing serotonin can produce a mild pseudo-dopamine deficiency state and the concomitant symptoms of akathisia and agitation.<sup>80-82</sup> Overt extrapyramidal effects can even be caused in rare cases.

SSRI-induced anxiety and even occasional panic attacks are hypothetically mediated by stimulating 5-HT<sub>2</sub> receptors in the serotonin pathway that projects to the hippocampus and limbic cortex.<sup>68,69,83,84</sup> Although the production of anxiety is often seen at the initiation of treatment with an SSRI, it usually subsides over time, and the SSRIs eventually are long-term anxiolytics.

SSRI-induced insomnia is hypothetically mediated by stimulating 5-HT<sub>2</sub> receptors in brain stem sleep centers, particularly the serotonergic pathway that projects to the cholinergic neurons in the lateral tegmentum.<sup>85-87</sup> Stimulating 5-HT<sub>2</sub> receptors can disrupt both rapid eye movement (REM) and, particularly, slow-wave sleep.<sup>88,89</sup> 5-HT<sub>2</sub> receptor stimulation can also induce nocturnal myoclonus, which can increase the frequency of nocturnal awakenings.<sup>1,2,14,88,89</sup>

Stimulation of the 5-HT<sub>3</sub> receptor appears to be responsible for various gastrointestinal side effects of the SSRIs.<sup>2,90-93</sup> These effects are mediated not only in CNS pathways such as the brain stem vomiting center and the pathway to hypothalamus, but also outside the brain in the gut itself, which also has 5-HT<sub>3</sub> receptors. Thus, SSRIs can cause nausea, gastrointestinal distress, and diarrhea. The brain stem vomiting center, also known as the chemoreceptor trigger zone, can be triggered by 5-HT<sub>3</sub> agonists, such as serotonin itself, or even cancer chemotherapy. Blocking this receptor can prevent cancer chemotherapy from inducing vomiting.<sup>90-93</sup>

Disinhibition of the serotonin pathway from brain stem to hypothalamus, which mediates aspects of appetite and eating behaviors, may be responsible for the reduced appetite, nausea, and even weight loss associated with SSRIs.<sup>2,35,36,90-93</sup>

Finally, there are 5-HT<sub>3</sub> receptors located right in the wall of the gut, and, when stimulated, they increase gastrointestinal motility. Thus, increases in serotonin in the gut that are induced by SSRIs may be responsible for the gastrointestinal cramps and diarrhea associated with SSRI administration.<sup>2,90-93</sup>

### NOREPINEPHRINE AND DOPAMINE REUPTAKE INHIBITION (BUPROPION)

The only antidepressant that ignores the serotonin system and acts selectively on the noradrenergic and dopa-

minergic systems is bupropion.<sup>1,2,94</sup> This property renders the actions of bupropion to be unique not only from the SSRIs, but from all the other classes of antidepressants, all of which cause serotonergic interactions of one type or another. Not surprisingly, the therapeutic profile, side effects, and clinical applications of bupropion are different from and indeed often complementary to those of the widely used SSRIs.

The pharmacology of bupropion suggests clinical actions in areas where boosting norepinephrine and dopamine would be especially desired. Both preclinical studies and empiric clinical observations suggest that symptoms of dopamine deficiency could include psychomotor retardation, anhedonia, hypersomnia, cognitive slowing, inattention, pseudodementia, and craving.<sup>95</sup> Not surprisingly, such symptoms may be preferably targeted by bupropion.

In addition, when patients do not respond to or do not tolerate SSRIs, bupropion can be substituted because of its "mirror image" pharmacology or added as an augmenting agent either to amplify therapeutic effects or to eliminate side effects, particularly SSRI-induced sexual dysfunction.<sup>1,2,76-78</sup>

Other novel applications of the noradrenergic and dopaminergic pharmacology of bupropion include use in attention deficit disorder<sup>96,97</sup> and in the treatment of smoking cessation,<sup>98</sup> where craving during nicotine withdrawal may be mitigated by boosting dopamine.

On the other hand, the pro-adrenergic pharmacology of bupropion can also go too far, with overstimulation, agitation, insomnia, or nausea as possible adverse effects.<sup>2,99</sup> However, seizures, which with the original, immediate-release formulation of bupropion are increased about four-fold over other antidepressant classes, may occur with the new, controlled-release formulation of bupropion with only the same frequency as other antidepressant classes.<sup>99</sup>

#### SEROTONIN/NOREPINEPHRINE/DOPAMINE REUPTAKE INHIBITION (VENLAFAXINE)

The pharmacology of venlafaxine is dose dependent: namely, at low doses it is essentially an SSRI; at medium to high doses, additional NE reuptake inhibition occurs; and at high to very high doses, some DA reuptake inhibition also occurs.<sup>1,2,100,101</sup> Thus, at low doses, the actions of venlafaxine are similar to those explained above for the SSRIs, and as the dose increases, the actions explained above for bupropion progressively kick in.

#### SEROTONIN-2 RECEPTOR ANTAGONISM WITH SEROTONIN REUPTAKE BLOCKADE (NEFAZODONE)

The pharmacology of nefazodone can be thought of as that of the SSRIs explained above with one important difference: 5-HT<sub>2</sub> receptors are blocked with nefazodone,

**Table 2. Serotonin-2 Antagonists in Psychiatric Practice\***

Trazodone
Nefazodone
Several tricyclic antidepressants (eg, amoxapine, amitriptyline, nortriptyline)
Cyproheptadine (used predominantly as an antihistamine)
Clozapine (the classical atypical antipsychotic)
Methysergide (used to treat migraine)
New atypical antipsychotics (eg, risperidone, olanzapine)
*All have additional important pharmacologic actions.

whereas they are stimulated with the SSRIs.<sup>1,2</sup> This leads to a difference in the therapeutic and side effect profiles between nefazodone and SSRIs. Perhaps the biggest differences are that serotonin-2 receptor blockade *reduces* whereas SSRIs may *cause* short-term increases in anxiety, and insomnia due to nocturnal awakenings and myoclonus. In addition, serotonin-2 receptor blockade may not increase the incidence of akathisia or sexual dysfunction nearly to the degree that serotonin-2 receptor stimulation does. Agents with serotonin-2 antagonist properties (plus additional pharmacologic actions) are shown in Table 2.

#### ALPHA-2 ANTAGONISM PLUS SEROTONIN-2 AND SEROTONIN-3 ANTAGONISM (MIRTAZAPINE)

Mirtazapine is a "designer" antidepressant with four principal actions that combine to make a novel compound. Although it could be classified simply as an  $\alpha_2$  antagonist, this designation does not do justice to its other important pharmacologic properties.

One name used in the literature on mirtazapine is NaSSA, or noradrenergic and specific serotonergic antidepressant.<sup>2,102-105</sup> By this, it is implied that mirtazapine has both pro-adrenergic and pro-serotonergic actions and that its serotonergic actions are selectively directed away from the 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors to the 5-HT<sub>1A</sub> receptor. The pro-adrenergic and pro-serotonergic actions are due to its  $\alpha_2$  antagonist properties.<sup>102-105</sup>  $\alpha_2$  Antagonism disinhibits both serotonin and norepinephrine neurotransmission. Because mirtazapine has serotonin-2 antagonist properties, its profile changes from that of an SSRI to that of other serotonin-2 antagonists as discussed above for nefazodone.<sup>106,107</sup> Since mirtazapine is also a serotonin-3 antagonist, it does not share the actions of SSRIs that lead to 5-HT<sub>3</sub> stimulation. Thus, mirtazapine is not associated with the gastrointestinal disturbances associated with the SSRIs.<sup>106,107</sup> Finally, mirtazapine has strong antihistamine properties, which explains its side effects of weight gain and sedation, as previously explained for the TCAs.<sup>102-107</sup>

#### CONCLUSION

Although all antidepressants increase the neurotransmission of serotonin, norepinephrine, and/or dopamine,

the currently marketed drugs do this by seven pharmacologically distinct mechanisms of action. It is not yet possible to determine which mechanism to match with which patient on the basis of objective laboratory tests or clinical criteria. However, these mechanisms can explain side effects in many cases. In addition, clinicians can use knowledge of these mechanisms to increase the chances of successful and well-tolerated antidepressant treatment when one agent with a given mechanism fails by switching to another mechanism or by making rational combinations of mechanisms.

*Drug names:* amitriptyline (Elavil and others), amoxapine (Asendin), bupropion (Wellbutrin), clomipramine (Anafranil), clozapine (Clozaril), cyproheptadine (Periactin and others), desipramine (Norpramin and others), fluoxetine (Prozac), fluvoxamine (Luvox), isocarboxazid (Marplan), maprotiline (Ludiomil), methysergide (Sansert), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Pamelor and others), olanzapine (Zyprexa), paroxetine (Paxil), phenelzine (Nardil), risperidone (Risperdal), sertraline (Zoloft), tranylcypromine (Parnate), trazodone (Desyrel and others), venlafaxine (Effexor).

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