Mirtazapine is sometimes called a noradrenergic and specific serotonergic antidepressant (NaSSA). Its primary therapeutic action is alpha 2 antagonism, as shown in Figures 12-51 through 12-54. It also blocks three serotonin (5HT) receptors: 5HT2A, 5HT2C, and 5HT3. Finally, it blocks histamine 1 (H1) receptors.

5HT2A/5HT2C antagonism for anxiety are discussed later, in Chapter 14, on anxiety; the therapeutic benefits of 5HT2A/5HT2C antagonism for sleep are also discussed later, in Chapter 16, on sleep. In terms of antidepressant effects, 5HT2A antagonist action can be difficult to separate from 5HT2C antagonist actions. Both may contribute to increasing dopamine and norepinephrine release, as discussed extensively in Chapter 10 for atypical antipsychotics and illustrated in Figures 10-22, 10-26, and 10-28; also discussed in Chapter 11 for antidepressants and illustrated in Figure 11-40.

5HT2C antagonist action as a mechanism for increasing both NE and DA release in prefrontal cortex may be more important than 5HT2A antagonist actions for a drug such as mirtazapine, which lacks the D2 antagonism of an atypical antipsychotic. It turns out that 5HT2A regulation of dopamine release is quite complex and depends on the specific circuit, the area of the brain where 5HT2A receptors are located, and the baseline amount of dopamine and serotonin release as well as the presence of other simultaneous pharmacological mechanisms, such as D2 antagonism. However, 5HT2C antagonism may be more consistently linked to norepinephrine and dopamine disinhibition in the prefrontal cortex regardless of these various factors. The bottom line is that in addition to being an SNDI (serotonin norepinephrine disinhibitor; Table 12-2) due to alpha 2 antagonist properties, mirtazapine is also an NDDI (norepinephrine and dopamine disinhibitor; Table 12-2) due to 5HT2C (and possibly 5HT2A) antagonist properties. Both of these concepts of SNDI and NDDI are novel explanations for the pharmacological actions of this established antidepressant (Table 12-2). These novel concepts may also help to explain the antidepressant actions not only of some atypical antipsychotics but also of several new drugs in development (discussed in the section on future antidepressants, below).

Although it is not clear that 5HT2C antagonist properties alone can cause weight gain, when combined with mirtazapine's simultaneous H1 antihistamine properties (Figure 12-55), weight gain appears more likely (see discussion in Chapter 10 and Figure 10-59).
5HT3 antagonist action should theoretically reduce any nausea or gastrointestinal problems caused by mirtazapine’s ability to increase serotonin release (Figure 12-56).

H1 antihistamine actions of mirtazapine (Figure 12-57) should theoretically relieve insomnia at night and improve anxiety during the day, but they could also cause drowsiness during the day. Combined with the 5HT2C antagonist properties described above, the H1 antihistamine actions of mirtazapine could also cause weight gain (Figure 12-57). Interestingly, the histamine 1 antagonist properties of mirtazapine are so potent that both mirtazapine and its active enantiomer esmirtazapine can be given in such low doses that they are essentially selective histamine 1 antagonists. The active enantiomer at very low doses is under investigation as a novel hypnotic and is discussed in Chapter 16, on sleep.

So, there you have it. Mirtazapine is a molecule with very complex pharmacology that does not block any monoamine transporter yet is a very effective antidepressant. In summary, the therapeutic actions of mirtazapine are thought to be mainly mediated through its alpha 2 antagonist and 5HT2C antagonist properties. The other properties add to
FIGURE 12-57 Mirtazapine at histamine 1 receptors. When mirtazapine blocks histamine 1 receptors, it can cause anxiolytic actions and possibly reduce nighttime insomnia, but it may also contribute to weight gain and daytime drowsiness.

therapeutic actions, cause some side effects, but probably allow patients to tolerate the powerful alpha 2 and 5HT2C antagonist actions that boost serotonin, norepinephrine, and possibly dopamine. An integrated view of mirtazapine's pharmacological actions is shown in Figure 12-58. Because of these unique pharmacological properties, it is worthwhile to understand this molecule and add it to the therapeutic armamentarium for depression, especially as an augmenting agent for difficult cases.

Two other alpha 2 antagonists are marketed as antidepressants in some countries (but not the United States), namely mianserin (worldwide except in the United States) and setiptilene (Japan). Unlike mirtazapine, mianserin has potent alpha 1 antagonist properties that tend to mitigate its ability to enhance serotonergic neurotransmission, so that this drug enhances predominantly noradrenergic neurotransmission yet with associated 5HT2A, 5HT2C, 5HT3, and histamine 1 antagonist properties. Yohimbine is also an alpha 2 antagonist, but its alpha 1 antagonist properties similarly mitigate its pro-serotonergic actions. Several selective alpha 2 antagonists, including idazoxan and fluparoxan, have been tested, but they have not demonstrated sufficiently robust antidepressant efficacy with sufficient tolerability, as they may provoke panic, anxiety, and prolonged erections in men, side effects that are not generally observed with alpha 2 antagonists such as mirtazapine, which have additional pharmacological properties that tend to block these side effects.

**Serotonin antagonist/reuptake inhibitors (SARIs)**

Several antidepressants share the ability to block serotonin 2A and 2C receptors as well as serotonin reuptake. The prototype drug with this antidepressant mechanism is trazodone (Figure 12-59), which is classified as a serotonin antagonist/reuptake inhibitor (SARI) (Table 12-2) or, more fully, as a serotonin 2A/2C antagonist and serotonin reuptake inhibitor (Figure 12-60). However, moderate to high doses of trazodone are required to inhibit SERT and 5HT2C receptors as well as 5HT2A receptors sufficiently for trazodone to be an effective antidepressant.
Doses of trazodone lower than those effective for antidepressant action are frequently used for the effective treatment of insomnia. Low doses exploit trazodone’s potent actions as a 5HT2A antagonist and also its properties as an antagonist of histamine 1 and alpha 1 adrenergic receptors, but they do not adequately exploit its SERT or 5HT2C inhibition properties, which are weaker (Figure 12-59). As discussed in Chapter 10 and illustrated in Figure 10-71, blocking the brain’s arousal system with histamine 1 and alpha 1 antagonism can cause sedation or sleep; along with 5HT2A antagonist properties, this may explain the mechanism of how a low dose of trazodone works as a hypnotic. Since insomnia is one of the most frequent residual symptoms of depression after treatment with an SSRI (discussed earlier in this chapter and illustrated in Figure 12-9), a hypnotic is often necessary for patients with a major depressive episode. A hypnotic can not only potentially relieve the insomnia itself but— as recent data suggest— treating insomnia in patients with major depression also increases remission rates due to improvement of other symptoms, such as loss of energy and depressed mood. This ability of low doses of trazodone to improve sleep...
FIGURE 12-59 Serotonin antagonist/reuptake inhibitors. Shown here are icons for two serotonin 2A antagonist/reuptake inhibitors (SARIs): trazodone and nefazodone. These agents have a dual action, but the two mechanisms are different from the dual action of the serotonin norepinephrine reuptake inhibitors (SNRIs). The SARIs act by potent blockade of serotonin 2A (5HT2A) receptors as well as dose-dependent blockade of serotonin 2C (5HT2C) receptors and the serotonin transporter (SRI). SARIs also block alpha 1 adrenergic receptors. In addition, trazodone has the unique property of histamine 1 receptor antagonism and nefazodone has the unique property of norepinephrine reuptake inhibition (NRI).

FIGURE 12-60 SARI actions at serotonin (5HT) synapses. This figure shows the dual actions of a serotonin 2A antagonist/reuptake inhibitor (SARI). This agent acts both presynaptically and postsynaptically. Presynaptic actions are indicated by the serotonin reuptake inhibitor (SRI) portion of the icon, which is inserted into the serotonin reuptake pump, blocking it. Postsynaptic actions are indicated by the serotonin 2A receptor antagonist portion of the icon (5HT2A) inserted into the 5HT2A receptor and by the serotonin 2C antagonist portion of the icon (5HT2C) inserted into the 5HT2C receptor. It is believed that all three blocking actions contribute to the antidepressant effects of SARIs. The 5HT2A antagonist actions are more potent than the serotonin reuptake properties or 5HT2C antagonism.
Mechanism of Action of SARIs: Baseline Postsynaptic Action

in depressed patients may thus be an important mechanism whereby trazodone can augment the efficacy of other antidepressants. The use of trazodone as a general hypnotic is discussed further in Chapter 16, on sleep.

Beyond the treatment of insomnia associated with depression, recruiting SERT inhibition with trazodone by increasing the dose is an important pharmacological mechanism that can be potentially synergistic with 5HT2A/5HT2C antagonism for broader antidepressant actions (Figures 12-61 through 12-64). However, in order to get this synergy of multiple mechanisms with trazodone monotherapy, a moderate to high dose must be used, which can often be attained without unacceptable daytime sedation by slow dose titration, allowing tolerance to develop, or giving the dose mostly at night to avoid unacceptable daytime sedation. Controlled-release formulations of trazodone are also in testing to reduce peak-dose sedation. Alternatively, low to moderate doses of trazodone can be added to a full dose of a known SERT inhibitor such as an SSRI or an SNRI to exploit 5HT2A/SERT synergy, as shown in Figures 12-60 through 12-63. An interesting aspect of trazodone's actions is the relative lack of sexual side effects at any dose, something it shares with mirtazapine, another 5HT2A/5HT2C antagonist.

How does 5HT2A/2C antagonism synergize with SERT inhibition to enhance the treatment of depressive symptoms other than insomnia? There are four possible ways in which this happens; these are illustrated in Figures 12-61 through 12-64.
Serotonin 2A antagonism potentiates the inhibitory action of serotonin at 5HT1A receptors (Figure 12-61A)

Recall that serotonin 1A receptors in general can have the opposite actions of serotonin 2A receptors (see discussion in Chapter 10 and Figures 10-21 and 10-30). Thus, serotonin itself is excitatory at 5HT2A receptors (compare Figures 12-61A and 12-61B) and inhibitory at 5HT1A receptors (compare Figures 12-61A and 12-61C). Whether serotonin excites or inhibits the neuron depends on the density of each receptor at a given synapse and the amount of serotonin released. If the excitatory action of serotonin at 5HT2A receptors is blocked, this potentiates the inhibitory action of 5HT1A receptors (compare Figure 12-61D with Figures 12-61C and 12-61A).

Trazodone will cause 5HT2A inhibition at essentially any clinical dose, but to get the potentiation of serotonin's inhibition at 5HT1A receptors, there must be SERT inhibition that raises serotonin in the synapse and therefore increases serotonin levels so serotonin itself can interact at 5HT1A receptors at the same time that trazodone is blocking 5HT2A receptors (Figure 12-61D). This can be accomplished either by raising the trazodone dose or by adding a SERT inhibitor. The potentiation of 5HT1A inhibition of serotonin neurons may also be useful in relieving anxiety and in reducing overactivity in neuronal circuits in some brain regions associated with the various symptoms of depression (see reduction in...
Mechanism of Action of SARIs:
Serotonin Is Inhibitory at 5HT1A Receptors

Stimulation of 5HT1A receptors by 5HT (red circle) decreases firing of the postsynaptic 5HT neuron compared to baseline.

 nerve impulse flow shown in Figure 12-61D and hypothetical areas of neuronal hyperactivity in depression in Figure 11-64).

Serotonin 2A antagonism potentiates gene expression stimulated by 5HT1A receptors (Figure 12-62)

Another action of serotonin at 5HT1A receptors that is opposed by serotonin actions at 5HT2A receptors is the stimulation of gene expression. That is, 5HT1A receptors stimulate gene expression by signal transduction through a second messenger system that utilizes cAMP (Figure 12-62A). Serotonin blocks this signal cascade system through actions downstream from 5HT2A receptors (Figure 12-62B). When this action of serotonin at 5HT2A receptors is blocked, the stimulation of gene expression by serotonin actions at 5HT1A receptors is potentiated (Figure 12-62C). Again, any clinical dose of trazodone will block 5HT2A receptors, but a higher dose of trazodone or a concomitantly administered SERT inhibitor is necessary to increase serotonin levels so that there is stimulation of 5HT1A receptors and thus 5HT2A/SERT synergy (Figure 12-62C). Potentiation of gene expression may be helpful in facilitating the regulation of neurotransmitter receptors or neurotrophic factors associated with improvement in the symptoms of depression.
Mechanism of Action of SARIs:
Serotonin 2A Antagonism Potentiates the Inhibitory Action of Serotonin at 5HT1A Receptors

**Serotonin 2A antagonism potentiates the inhibitory action of serotonin 1A on glutamate release from cortical pyramidal neurons (Figure 12-63)**

Serotonin stimulates glutamate release from pyramidal neurons in prefrontal cortex by its actions at 5HT2A receptors (Figure 12-63A) but inhibits glutamate release from these same neurons by its actions at 5HT1A receptors (Figure 12-63B). When 5HT2A receptors are blocked, it potentiates the inhibitory actions of serotonin at 5HT1A receptors (Figure 12-63C), but this can occur only if trazodone’s potent 5HT2A antagonist properties are coupled with simultaneous SERT inhibition. Preventing the release of too much glutamate from dysfunctional pyramidal neurons that have inefficient information processing may improve information processing and reduce symptoms of depression in patients who have abnormal pyramidal cell functioning in various prefrontal cortex areas that mediate specific symptoms of depression (Figure 12-63C and Figure 11-64).

**Serotonin 2A/2C potentiation of NE and DA disinhibition at serotonin 1A receptors (Figure 12-64)**

Finally, as already discussed above in the sections on fluoxetine (Figure 12-25) and mirtazapine, serotonin’s actions at 5HT2C receptors inhibit both DA and NE release (Figure 12-64). This same inhibition may also occur under certain circumstances at 5HT2A...
Mechanism of Action of SARs:
Serotonin Stimulates Gene Expression at 5HT1A Receptors

FIGURE 12-62A Serotonin (5HT) stimulates gene expression through 5HT1A receptors. The molecular consequences of 5HT1A stimulation alone, shown here, result in a certain amount of gene expression corresponding to the pharmacological actions shown in Figure 12-61C. 5HT occupancy of its 5HT1A receptor (top red circle) causes a certain amount of gene transcription (see bottom red circle on the right). The 5HT1A receptor is coupled to a stimulatory G protein (Gs) and adenylate cyclase (AC), which produces the second messenger cyclic AMP from ATP. This, in turn, activates protein kinase A (PKA), so that transcription factors such as cyclic AMP response element binding protein (CREB) can activate gene expression (mRNAs).

receptors, as discussed in Chapter 10 for atypical antipsychotics. Also already discussed is how stimulation of serotonin 1A receptors acutely reduces the serotonergic inhibition of DA and NE release at 5HT2C receptors and possibly at 5HT2A receptors, thus disinhibiting DA and NE release (Figure 12-64). Because this 5HT1A mechanism tends to desensitize, it may be important to potentiate this action of serotonin at 5HT1A receptors by simultaneously blocking 5HT2C and/or 5HT2A receptors, leading to release of both DA and NE in prefrontal cortex (Figure 12-64). The bottom line is that producing disinhibition of NE and DA in prefrontal cortex by whatever mechanism could theoretically help to enhance the efficiency of information processing there and lead to a reduction in the symptoms of depression mediated in this brain region.

Nefazodone is another SARI with robust 5HT2A antagonist actions and weaker 5HT2C antagonism and SERT inhibition, but it is no longer commonly used because of rare liver toxicity (Figure 12-59). Several tricyclic antidepressants—such as amitriptyline, nortriptyline, doxepin, and amoxapine—also have a combination of serotonin 2A and 2C antagonism with serotonin reuptake inhibition along with several other pharmacological actions; these are discussed later in this chapter in the section on tricyclic antidepressants. Since the potency of blockade of serotonin 2A and 2C receptors varies considerably among
Mechanism of Action of SARIs:
Serotonin at 5HT2A Receptors Blocks Signal Transduction and Gene Expression From 5HT1A Receptors

**FIGURE 12-62** Serotonin (5HT) at 5HT2A receptors blocks gene expression from 5HT1A receptors. The molecular consequence of 5HT2A receptor stimulation concomitant with 5HT1A receptor stimulation is to reduce the gene expression of 5HT1A stimulation alone (i.e., that shown in Figure 12-62A). These molecular consequences correlate with the pharmacological actions of simultaneous 5HT1A and 5HT2A stimulation. Simultaneous activation of the 5HT2A receptor by 5HT (top right red circle) will alter the consequences of activating 5HT1A receptors (top left red circle) in a negative way and reduce the gene expression of 5HT1A receptors acting alone (Figure 12-62A). Thus, occupancy of 5HT2A receptor (top circle) causes coupling of a stimulatory G protein (Gs) with the enzyme phospholipase C (PLC). This, in turn, activates calcium flux and converts phosphatidylinositol (PI) into diacylglycerol (DAG). This activates the enzyme phosphokinase C (PKC), which has an inhibitory action on phosphokinase A (PKA). This reduces the activation of transcription factors such as cyclic AMP response element binding protein (CREB) and leads to a decrease in gene expression (bottom red circle).

In the tricyclics, it is not clear how important this action is to the therapeutic actions of tricyclic antidepressants in general.

Many other drugs are 5HT2A/2C antagonists, including mirtazapine, just discussed in the previous section, and the atypical antipsychotics discussed in Chapter 10, all of which are potent 5HT2A antagonists and some of which are also potent 5HT2C antagonists (Figures 10-90 to 10-101). The use of atypical antipsychotics as augmenting agents for treatment-resistant depression is discussed later in this chapter in the section on antidepressants in clinical practice; their use for treatment of bipolar depression is discussed in Chapter 13, on mood stabilizers.

YM992 is another SARI (serotonin 2A/2C antagonist with moderately potent serotonin reuptake inhibition properties) that is in testing as an antidepressant. Selective 5HT2A antagonists, however, do not appear to be effective antidepressants. On the other hand, drugs
Mechanism of Action of SARIs:
Serotonin Blockade at 5HT2A Receptors Potentiates Gene Expression Stimulated by 5HT1A Receptors

5HT1A receptor

\[ \text{AC} \rightarrow \text{cAMP} \rightarrow \text{PKA} \rightarrow \text{CREB} \]

5HT2A receptor

\[ \text{Gs} \rightarrow \text{PLC} \rightarrow \text{ATP} \rightarrow \text{PI} \rightarrow \text{DAG} \rightarrow \text{PKC} \rightarrow \text{mRNAs} \]

FIGURE 12-62C Serotonin (5HT) blockade at 5HT2A receptors potentiates gene expression from 5HT1A receptors. The molecular consequence of 5HT1A receptor disinhibition by 5HT2A receptor blockade is shown here – namely, enhanced gene expression. These molecular events are the consequence of the pharmacological actions shown in Figure 12-61D. Simultaneous inhibition of the 5HT2A receptor (top right circle) can stop the negative consequences that 5HT2A receptor stimulation by 5HT can have on gene expression, as shown in Figure 12-62B. Thus gene expression of the 5HT1A receptor is enhanced when 5HT2A receptors are blocked (bottom red circle) rather than diminished when they are stimulated (Figure 12-62B).

with 5HT2A/2C antagonist properties plus direct-acting 5HT1A agonist properties are in testing as potential novel antidepressants and disinhibitors of DA release for improving sexual dysfunction, including the agents flibanserin, adatanserin, BMS181,101, and others. One particularly novel agent with 5HT2C antagonist properties in testing as an antidepressant is agomelatine, discussed in the section on future antidepressants below.

**Classic antidepressants: monoamine oxidase inhibitors**

The first clinically effective antidepressants to be discovered were inhibitors of the enzyme monoamine oxidase (MAO). They were discovered by accident when an antituberculosis drug, iproniazid, was observed to help depression that coexisted in some of the patients who had tuberculosis. This antituberculosis drug was eventually found to work in depression by inhibiting the enzyme MAO. However, inhibition of MAO was unrelated to its antituberculosis actions.

This discovery soon led to the synthesis of more drugs in the 1950s and 1960s that inhibited MAO but lacked unwanted additional properties (such as antituberculosis properties and liver toxicity). Although best known as powerful antidepressants, the MAOIs are
SARs: Serotonin Stimulates Glutamate Release at 5HT2A Receptors

**Mechanism of Action:**

- Serotonin stimulates glutamate release at 5HT2A receptors.
- 5HT2A accelerator stimulates glutamate release.
- 5HT projections from the midbrain raphe synapse with pyramidal glutamate neurons in the prefrontal cortex.
- Binding of 5HT to 5HT2A receptors stimulates glutamate release from pyramidal neurons.

**FIGURE 12-63A Serotonin (5HT) stimulates glutamate release at 5HT2A receptors.** 5HT projections from the midbrain raphe synapse with pyramidal glutamate neurons in the prefrontal cortex. Binding of 5HT to 5HT2A receptors stimulates glutamate release from pyramidal neurons.

**Three of the original MAO inhibitors that are still available for clinical use today are phenelzine, tranylcypromine, and isocarboxazid (Table 12-4). These are all irreversible enzyme inhibitors and thus bind to MAO covalently and irreversibly and destroy its function forever. Enzyme activity returns only after new enzyme is synthesized. Sometimes such**
Serotonin Inhibits Glutamate Release at 5HT1A Receptors

Mechanism of Action of SARIs:

Enzyme inhibitors are called "suicide inhibitors," because once this kind of inhibitor binds to the enzyme, the enzyme essentially commits suicide in that it can never function again until a new enzyme protein is synthesized by the neuron's DNA in the cell nucleus. This is an unfortunate terminology for a very effective class of antidepressants and perhaps is a concept better utilized by enzymologists, not by clinicians.

Amphetamine is itself a weak MAO inhibitor (Table 12-5). Some MAO inhibitors, such as tranylcypromine, have chemical structures modeled on amphetamine; thus, in addition to MAO inhibitor properties, they also have amphetamine-like dopamine-releasing properties (Tables 12-4 and 12-5). Amphetamine's actions on the dopamine transporter (DAT) that trigger dopamine release are discussed in Chapter 4 and illustrated in Figure 4-15. Tranylcypromine has these same actions on DAT as well. Selegiline itself does not have amphetamine-like properties but is metabolized to both L-amphetamine and 1-methamphetamine, which do have inhibitory actions on DAT and dopamine-releasing properties (Tables 12-4 and 12-5). Thus there is a close mechanistic link between some MAO inhibitors and DAT inhibition as well as between the MAO-inhibiting properties and DAT-inhibiting properties of amphetamine itself (Tables 12-4 and 12-5). It is therefore not surprising that one of the augmenting agents utilized to boost MAO inhibitors...
Mechanism of Action of SARIs:
Serotonin 2A Antagonism Potentiates Inhibitory Action at Serotonin 1A Receptors

FIGURE 12-63C Serotonin (5HT) 2A antagonism potentiates inhibitory action at 5HT1A receptors. Blockade of 5HT2A receptors can potentiate the inhibitory actions of serotonin at 5HT1A receptors on glutamate release (left).

Antidepressants
in treatment-resistant patients is amphetamine, administered by experts with great caution while monitoring blood pressure.

MAO subtypes
MAO exists in two subtypes, A and B (Table 12-6). Both forms are inhibited by the original MAO inhibitors, which are therefore nonselective (Table 12-4). The A form preferentially metabolizes the monoamines most closely linked to depression (i.e., serotonin and norepinephrine), whereas the B form preferentially metabolizes trace amines such as phenethylamine (Table 12-6). Both MAO-A and MAO-B metabolize dopamine and tyramine (Table 12-6). Both MAO-A and MAO-B are in the brain (Table 12-6). Noradrenergic neurons (Figure 11-31) and dopaminergic neurons (Figure 9-19) are thought to contain both MAO-A and MAO-B, with perhaps MAO-A activity predominant, whereas serotonergic neurons are thought to contain only MAO-B (Figure 10-16). With the exception of platelets and lymphocytes, which have MAO-B, MAO-A is the major form of this enzyme outside of the brain (Table 12-6).
Mechanism of Action of SARIs:
Serotonin Stimulation of 5HT1A Receptors Potentiates the NE and DA Disinhibition of 5HT2A and 5HT2C Antagonism

Indirect stimulation of presynaptic 5HT1A receptors via SERT inhibition by high doses of trazodone can reduce this inhibition of NE and DA by 5HT via reducing the concentrations of 5HT at postsynaptic sites on NE and DA neurons. Furthermore, if 5HT2C and 5HT2A receptors are blocked, this may potentiate the disinhibiting effects of 5HT1A stimulation on NE and DA.
TABLE 12-4 Currently approved MAO inhibitors

<table>
<thead>
<tr>
<th>Name (trade name)</th>
<th>Inhibition of MAO-A</th>
<th>Inhibition of MAO-B</th>
<th>Amphetamine properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>phenelzine (Nardil)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>tranylcypromine (Parnate)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>isocarboxazid (Marplan)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>amphetamines (at high doses)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>selegiline transdermal system (Emsam)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>brain</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>gut</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>selegiline low dose oral (Deprenyl, Eldepryl)</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>rasagiline (Agilect/Azilect)</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>moclobemide (Aurorix, Manerix)</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

TABLE 12-5 MAO inhibitors with amphetamine actions or amphetamines with MAO inhibition?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>amphetamine</td>
<td>MAOI at high doses</td>
</tr>
<tr>
<td>tranylcypromine (Parnate)</td>
<td>also called phenylcyclopropylamine</td>
</tr>
<tr>
<td>selegiline</td>
<td>metabolized to L-methamphetamine</td>
</tr>
<tr>
<td></td>
<td>metabolized to L-amphetamine</td>
</tr>
<tr>
<td></td>
<td>less amphetamine formed transdermally</td>
</tr>
</tbody>
</table>

TABLE 12-6 MAO enzymes

<table>
<thead>
<tr>
<th></th>
<th>MAO-A</th>
<th>MAO-B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substrates</td>
<td>5-HT</td>
<td>Pheny lethylamine</td>
</tr>
<tr>
<td></td>
<td>NE</td>
<td>DA</td>
</tr>
<tr>
<td></td>
<td>DA</td>
<td>Tyramine</td>
</tr>
<tr>
<td>Tissue distribution</td>
<td>Brain, gut, liver, placenta, skin</td>
<td>Brain, platelets, lymphocytes</td>
</tr>
</tbody>
</table>

Brain MAO-A must be inhibited for antidepressant efficacy to occur (Figure 12-65). This is not surprising, since this is the form of MAO that preferentially metabolizes serotonin and norepinephrine, two of the three components of the trimonoaminergic neurotransmitter system linked to depression and to antidepressant actions, both of which demonstrate increased brain levels after MAO-A inhibition (Figure 12-65). MAO-A, along with MAO-B, also metabolizes dopamine, but inhibition of MAO-A alone does not appear to lead to robust increases in brain dopamine levels, since MAO-B can still metabolize dopamine (Figure 12-65).

Inhibition of MAO-B is not effective as an antidepressant, as there is no direct effect on either serotonin or norepinephrine metabolism and little or no dopamine accumulates owing to the continued action of MAO-A (Figure 12-66). What, therefore, is the therapeutic value of MAO-B inhibition? When this enzyme is selectively inhibited, it can boost the action of concomitantly administered levodopa in Parkinson’s disease. Evidently, in the presence
MAO-A is Inhibited

Antidepressant Action

FIGURE 12-65 Monoamine oxidase A (MAO-A) inhibition. The enzyme MAO-A metabolizes serotonin (5HT) and norepinephrine (NE) as well as dopamine (DA) (left panels). Monoamine oxidase B (MAO-B) also metabolizes DA, but it metabolizes 5HT and NE only at high concentrations (left panels). This means that MAO-A inhibition increases 5HT, NE, and DA (right panels) but that the increase in DA is not as great as that of 5HT and NE because MAO-B can continue to destroy DA (bottom right panel). Inhibition of MAO-A is an efficacious antidepressant strategy.
FIGURE 12-66 Monoamine oxidase B (MAO-B) inhibition. Selective inhibitors of MAO-B do not have antidepressant efficacy. This is because MAO-B metabolizes serotonin (5HT) and norepinephrine (NE) only at high concentrations (top two left panels). Since MAO-B's role in destroying 5HT and NE is small, its inhibition is not likely to be relevant to the concentrations of these neurotransmitters (top two right panels). Selective inhibition of MAO-B also has somewhat limited effects on dopamine (DA) concentrations, because MAO-A continues to destroy DA. However, inhibition of MAO-B does increase DA to some extent, which can be therapeutic in other disease states, such as Parkinson's disease.
of a large load of dopamine derived from administration of a large dose of its precursor levodopa, selective MAO-B inhibition is sufficient to boost dopamine action in the brain. MAO-B is also thought to convert some environmentally derived amine substrates, called protoxins, into toxins that may cause damage to neurons and possibly contribute to the cause or decline of function in Parkinson’s disease. Inhibition of MAO-B may thus halt this process, and there is speculation that this might slow the degenerative course of various neurodegenerative disorders, including Parkinson’s disease. Thus, two MAO inhibitors in Table 12-4, selegiline and rasagiline, when administered orally in doses selective for inhibition of MAO-B, are approved for use in patients with Parkinson’s disease but are not effective at these selective MAO-B doses as antidepressants.

Perhaps the most important role of MAO-B in psychopharmacology is when it is inhibited simultaneously with MAO-A (Figure 12-67). In that case, there is a triple and very robust monoaminergic boost of dopamine as well as serotonin and norepinephrine (Figure 12-67). This would theoretically provide the most powerful antidepressant efficacy across the range of depressive symptoms, from diminished positive affect to increased negative affect (see Figure 11-55). Thus MAO-A plus B inhibition is one of the few therapeutic strategies available to increase dopamine in depression and therefore to treat refractory symptoms of diminished positive affect. This is a good reason for specialists in psychopharmacology to become adept at administering MAO inhibitors, so that they can have an additional strategy within their armamentarium for patients with treatment-resistant symptoms of diminished positive affect, which is a very common problem in a referral practice.

Tyramine reactions and dietary restrictions

One of the biggest barriers to utilizing MAO inhibitors has traditionally been the risk that a patient taking one of these drugs might develop a hypertensive reaction after ingesting tyramine in the diet. How does the combination of tyramine in the diet plus MAO-A inhibition in the gut lead to a dangerous elevation in blood pressure? Tyramine works to elevate blood pressure because it is a potent releaser of norepinephrine. Normally, NE is not allowed to accumulate to dangerous levels, owing in part to efficient destruction of NE by MAO-A once NE is released during neurotransmission (Figure 12-68). Thus there is no vasoconstriction and no elevated blood pressure because there is no excessive stimulation of postsynaptic alpha 1 or other adrenergic receptors (Figure 12-68). When foods high in tyramine content - such as tap beers, smoked meat or fish, fava beans, aged cheeses, sauerkraut, or soy - are ingested (Table 12-7), MAO-A in the intestinal wall goes to work, safely destroying tyramine before it is absorbed; MAO-A in the liver safely destroys any tyramine that gets absorbed; and even if any tyramine reaches the noradrenergic sympathetic neuron (Figure 12-69), the MAO-A there destroys any synaptic norepinephrine that this tyramine would release. The body thus has a huge capacity for processing tyramine, and the average person is able to handle around 400 mg of ingested tyramine before blood pressure is elevated. A high-tyramine meal, by contrast, represents only around 40 mg of tyramine.

However, when MAO-A is inhibited, this capacity to handle dietary tyramine is much reduced, and a high-tyramine meal is sufficient to raise blood pressure when a substantial amount of MAO-A is irreversibly inhibited (Figure 12-70). In fact, it may take as little as 10 mg of dietary tyramine to increase blood pressure when MAO-A is essentially knocked out by high doses of an MAO inhibitor. Some blood pressure elevations can be very large, sudden, and dramatic, causing a condition known as a hypertensive crisis (Table 12-8), which can rarely cause intracerebral hemorrhage or even death. This risk is normally controlled
MAO-A and MAO-B are Inhibited

Robust Antidepressant Action
Including Dopamine Action

MAO-A and MAO-B inhibition

Combined inhibition of monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B).

FIGURE 12-67 Combined inhibition of monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B).

Combined inhibition of MAO-A and MAO-B may have robust antidepressant actions owing to increases not only in serotonin (5HT) and norepinephrine (NE) but also dopamine (DA). Inhibition of both MAO-A, which metabolizes 5HT, NE, and DA, and MAO-B, which metabolizes primarily DA (left panels), leads to greater increases in each of these neurotransmitters than inhibition of either enzyme alone.
**TABLE 12-7** Suggested tyramine dietary modifications for MAO inhibitors

<table>
<thead>
<tr>
<th>Food to avoid</th>
<th>Food allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dried, aged, smoked, fermented, spoiled, or</td>
<td>Fresh or processed meat, poultry, and fish</td>
</tr>
<tr>
<td>improperly stored meat, poultry, and fish</td>
<td></td>
</tr>
<tr>
<td>Broad bean pods</td>
<td>All other vegetables</td>
</tr>
<tr>
<td>Aged cheeses</td>
<td>Processed and cottage cheese, ricotta cheese, yogurt</td>
</tr>
<tr>
<td>Tap and nonpasteurized beers</td>
<td>Canned or bottled beers and alcohol (have little tyramine)</td>
</tr>
<tr>
<td>Marmite, sauerkraut</td>
<td>Brewer's and baker's yeast</td>
</tr>
<tr>
<td>Soy products/tofu</td>
<td></td>
</tr>
</tbody>
</table>

*No dietary modifications needed for low doses of transdermal selegiline or for low oral doses of selective MAO-B inhibitors.

**FIGURE 12-68 Normal destruction of norepinephrine.** Monoamine oxidase A (MAO-A) is the enzyme that normally acts to destroy norepinephrine (NE) to keep it in balance. Since accumulated NE can cause vasoconstriction and elevated blood pressure via increased binding at alpha 1 and other adrenergic receptors, its normal destruction by MAO-A helps prevent these negative effects.

by restricting the diet so that foods dangerously high in tyramine content are eliminated (Table 12-7). Until recently, the risk of hypertensive crisis and the hassle of restricting diet have generally been the price that a patient has had to pay in order to get the therapeutic benefits of the MAO inhibitors in treating depression.

Because of the potential danger of a hypertensive crisis from a tyramine reaction in patients taking irreversible MAO inhibitors, a certain mythology has grown up around how
Tyramine, as in cheese, increases the release of NE (1) and the excess is destroyed by MAO-A (2) in NE neurons.

FIGURE 12-69 Tyramine increases norepinephrine release. Tyramine is an amine present in various foods, including cheese. Indicated in this figure is how a high-tyramine meal (40 mg, depicted here as cheese) acts to increase the release of norepinephrine (NE) (1). However, in normal circumstances the enzyme monoamine oxidase A (MAO-A) readily destroys the excess NE released by tyramine (2), and no harm is done (i.e., no vasoconstriction or elevation in blood pressure).

much tyramine is in various foods and therefore what dietary restrictions are necessary. Since the tyramine reaction is sometimes called a "cheese reaction," there is a myth that all cheese must be restricted. However, that is true only for aged cheeses such as English Stilton, but not for most processed cheese (Figure 12-71) or for most cheeses utilized in most commercial chain pizzas (Figure 12-72). Thus, it is not true that a patient on an MAO inhibitor must avoid all ingestion of any cheese. Also, it is not true that such patients must avoid all wine and beer. Canned and bottled beer are low in tyramine; generally only tap and nonpasteurized beers must be avoided (Table 12-8), and many wines, including Chianti, are actually quite low in tyramine (Figure 12-73). Thus, unless someone taking an irreversible inhibitor of MAO-A is going to eat 25 to 100 pieces of pizza or drink 25 to 100 glasses of wine or beer at a party, it is likely that he or she can still have a moderate amount of fun. Of course, every prescriber should counsel patients taking the classic MAO inhibitors about diet and keep up to date with the tyramine content of foods their patients wish to eat.

New developments for MAO inhibitors
Two developments have occurred with MAO inhibitors in recent years that appear to mitigate the risk of tyramine reactions. One is the production of inhibitors that are not only selective for MAO-A but also reversible. The other is the production of an MAO
### TABLE 12-8 Hypertensive crisis

Defined by diastolic blood pressure > 120 mm Hg

Potentially fatal reaction characterized by:
- Occipital headache which may radiate frontally
- Palpitation
- Neck stiffness or soreness
- Nausea
- Vomiting
- Sweating (sometimes with fever)
- Dilated pupils, photophobia
- Tachycardia or bradycardia, which can be associated with constricting chest pain

---

**FIGURE 12-70** Inhibition of monoamine oxidase A (MAO-A) and tyramine. Here tyramine is releasing norepinephrine (NE) (1) just as shown in Figure 12-69. However, this time MAO-A is also being inhibited by an irreversible MAO-A inhibitor (2). This results in MAO-A stopping its destruction of NE (2). As indicated in Figure 12-65, such MAO-A inhibition in itself causes accumulation of NE. When MAO-A inhibition is taking place in the presence of tyramine, the combination can lead to a very large accumulation of NE (3). Such a great NE accumulation can lead to excessive stimulation of postsynaptic adrenergic receptors (3) and therefore dangerous vasoconstriction and elevation of blood pressure.

Inhibitor that can be delivered through a skin patch such that both MAO-A and MAO-B are inhibited in the brain but much less MAO-A is inhibited in the gut. Neither of these innovations enhances the efficacy of MAO inhibition in depression, but both reduce the risk of hypertensive crisis, which can occur when tyramine is ingested in the diet after MAO-A is inhibited in the gut. One of these innovations is listed in Table 12-4 as moclobemide, a
selective and reversible inhibitor of MAO-A, sometimes also called a RIMA (or reversible inhibitor of MAO-A). This agent is approved in Canada, Mexico, and many European and other countries but not in the United States.

The other innovation listed in Table 12-4 is the transdermal delivery system for selegiline, cleverly dosed high when delivered to the brain to inhibit both MAO-A and MAO-B there for antidepressant actions yet simultaneously dosed low when delivered to the gut to inhibit, preferentially, MAO-B so as to reduce hypertensive reactions to tyramine. Transdermal selegiline is currently available only in the United States. How it attains this clever differential inhibition of brain versus gut MAO-A is explained below.

**RIMAs**

The RIMAs are a nifty development in new drug therapeutics for depression because they have the potential of providing MAO-A inhibition yet with decreased risk of a tyramine reaction (Figure 12-74). How can one inhibit MAO-A to have antidepressant actions yet not inhibit MAO-A to avoid tyramine reactions? Enter the reversible inhibitors of MAO-A. If someone taking a RIMA eats aged cheese with high tyramine content in a meal, as the tyramine is absorbed it will release norepinephrine, but this will chase the reversible inhibitor off the MAO-A enzyme, reactivating MAO-A in the intestine, liver, and sympathomimetic neurons and therefore allowing the dangerous amines to be destroyed.

---

**Figure 12-71 Tyramine content of cheese, part 1.** The tyramine content of different types of cheeses varies. Aged cheeses such as English Stilton are high in tyramine; however, most processed cheeses are quite low in tyramine.

<table>
<thead>
<tr>
<th>Cheese</th>
<th>mg per 15 g serving</th>
</tr>
</thead>
<tbody>
<tr>
<td>English STILTON</td>
<td>17.3</td>
</tr>
<tr>
<td>Kraft® grated PARMESAN</td>
<td>0.2</td>
</tr>
<tr>
<td>Philadelphia® CREAM CHEESE</td>
<td>0</td>
</tr>
</tbody>
</table>

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Antidepressants | 587
Tyramine Content of Commercial-Chain Pizzas

<table>
<thead>
<tr>
<th>Serving</th>
<th>mg per serving</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2 medium double cheese, double pepperoni</td>
<td>0.378</td>
</tr>
<tr>
<td>1/2 medium double cheese, double pepperoni</td>
<td>0.063</td>
</tr>
<tr>
<td>1/2 medium double cheese, double pepperoni</td>
<td>0</td>
</tr>
</tbody>
</table>

FIGURE 12-72 Tyramine content of cheese, part 2. The tyramine content of several commercial chain pizzas is shown here. As can be seen, these types of cheese are actually quite low in tyramine content.

(Figures 12-74 and 12-75). This is sort of like having your cake – or cheese – and eating it too. The RIMAs may thus have the same therapeutic profile as the irreversible inhibitors of MAO, particularly when they are adequately dosed, but without the same likelihood of a cheese reaction if a patient inadvertently eats otherwise dangerous dietary tyramine. However, many regulators in different countries still post a warning about tyramine reactions associated with moclobemide; thus some degree of dietary caution or restriction of tyramine intake is generally still recommended with this drug.

Transdermal delivery of selective MAO-B inhibitor
In the case of selective MAO-B inhibitors administered at low doses, no significant amount of MAO-A is inhibited and there is very little risk of hypertension from dietary amines. Patients taking MAO-B inhibitors to prevent the progression of Parkinson's disease, for example, do not require any special diet. On the other hand, MAO-B inhibitors are not effective antidepressants at doses that are selective for MAO-B. Only when the MAO-B inhibitor selegiline is given orally in doses that make it lose its selectivity and inhibit MAO-A as well is this agent effective orally as an antidepressant. However, these oral doses also cause tyramine reactions.

How can selegiline be administered so that it irreversibly inhibits MAO-A and MAO-B in the brain to provide robust antidepressant actions yet inhibits MAO-B only in the gut to avoid tyramine reactions? The answer is to deliver selegiline by a transdermal patch...
Tyramine Content of Wine

<table>
<thead>
<tr>
<th>Wine</th>
<th>mg per 4 oz serving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruffino CHIANTI</td>
<td>0.36</td>
</tr>
<tr>
<td>Blue Nun ® WHITE</td>
<td>0.32</td>
</tr>
<tr>
<td>Cinzano VERMOUTH</td>
<td>0</td>
</tr>
</tbody>
</table>

**FIGURE 12-73 Tyramine content of wine.** Although patients taking a monoamine oxidase inhibitor (MAOI) have historically been told to avoid all wine and beer because of the risk of a tyramine reaction, canned and bottled beers as well as many wines are actually low in tyramine.

That is, transdermal administration through a skin patch is like an intravenous infusion without the needle, delivering drug directly into the systemic circulation, hitting the brain in high doses, and avoiding a first pass through the liver (Figure 12-76). By the time drug recirculates to the intestine and liver, it has much decreased levels and significantly inhibits only MAO-B in these tissues. This action is sufficiently robust that, at least for low doses of transdermal selegiline, no dietary restrictions are necessary (Figure 12-77).

To show the profound reduction in risk of tyramine reactions with transdermal selegiline, it is useful to compare how much tyramine it takes to make blood pressure rise when patients take various MAO inhibitors, remembering that a high-tyramine diet is 40 mg of tyramine and that normals can handle around 400 mg of tyramine before blood pressure is increased (Figure 12-77). As stated earlier, perhaps as little as 10 mg of dietary tyramine is all that it takes for a traditional nonselective and irreversible oral MAO inhibitor to cause a tyramine reaction (Figure 12-77, first column). In that case, MAO-A and MAO-B are both inhibited in the brain for antidepressant actions, and they are also both inhibited in the gut, which increases the risk of tyramine reactions.

Contrast this with the patient taking an oral selective MAO-B inhibitor, who has only MAO-B inhibited in the brain and in the gut and can ingest as much tyramine as someone not taking any MAO inhibitor (Figure 12-77, the two far right columns). No tyramine reaction, but also no antidepressant action.
How RIMAs Reduce the Risk of Tyramine Reactions

**The Dilemma:**
- Must inhibit MAO-A in brain for antidepressant action.
- Simultaneous inhibition of MAO-A in liver and intestinal mucosa causes risk of tyramine reactions.

**The Solution:**
- When tyramine increases NE release, this reverses MAO-A inhibition and NE can be destroyed, reducing risk of tyramine reactions.

**FIGURE 12-74** Reversible inhibitors of monoamine oxidase A (RIMAs). Inhibition of monoamine oxidase A (MAO-A) in the brain is necessary for an antidepressant effect. However, MAO-A is present not only in the brain but also in the gut. Inhibition of MAO-A in the liver and intestinal mucosa poses the risk of a tyramine reaction. How can the effects in the brain be preserved while those in the gut are avoided? Reversible inhibitors of monoamine oxidase A (RIMAs) can be removed from the enzyme by competitors. Thus when tyramine increases norepinephrine (NE) release, it is increasing the competition for MAO-A, which leads to the reversal of MAO-A inhibition; thus NE can be destroyed, reducing risk of a tyramine reaction.

**FIGURE 12-75** Reversible inhibition of monoamine oxidase A (MAO-A). Shown in this figure is the combination of an MAO-A inhibitor and tyramine. However, in this case the MAO-A inhibitor is of the reversible type (reversible inhibitor of MAO-A, or RIMA). The accumulation of norepinephrine (NE) released by tyramine (1) can displace the RIMA (2), allowing for normal destruction of the extra NE (3).
How Transdermal Selegiline Reduces the Risk of Tyramine Reactions

**The dilemma:**
- must inhibit MAO-A and MAO-B in brain for antidepressant action
- simultaneous inhibition of MAO-A in liver and intestinal mucosa causes risk of tyramine reactions

**The solution:**
- antidepressant actions
- no risk of tyramine reactions at low dose
- high brain delivery
- bypasses gut delivery (first pass)

**FIGURE 12-76 Transdermal selegiline.** The selective monoamine oxidase B (MAO-B) inhibitor selegiline has antidepressant efficacy only when given at doses high enough also to inhibit monoamine oxidase A (MAO-A); yet when it is administered orally at these doses, it can also cause a tyramine reaction. How can selegiline inhibit both MAO-A and MAO-B in the brain to have antidepressant effects while inhibiting MAO-B only in the gut, so as to avoid a tyramine reaction? Transdermal administration of selegiline delivers the drug directly into the systemic circulation, hitting the brain in high doses and thus having antidepressant effects but avoiding a first pass through the liver and thus reducing risk of a tyramine reaction.

What is interesting are the two columns in Figure 12-77 for transdermal selegiline, showing that the average patient can take in much more than 40 mg of tyramine in a meal before showing a hypertensive reaction. At low doses of transdermal selegiline, there is substantial inhibition of both MAO-A and MAO-B in the brain but sufficiently selective inhibition of MAO-B in the gut such that no dietary restrictions are currently warranted. At high doses of transdermal selegiline, there is probably some MAO-A inhibition in the gut, with less tyramine therefore needed to raise blood pressure but still about twice as much as in a high-tyramine meal. Thus, at high doses of transdermally administered selegiline, some dietary caution against very high dietary intake of tyramine may be prudent.

**Dangerous drug interactions: decongestants and drugs that boost sympathomimetic amines**

Although the MAO inhibitors are famous in any pharmacology textbook for their notorious tyramine reactions, the truth is that drug–drug interactions are potentially more important clinically than dietary interactions because drug interactions are potentially more common, and some drug interactions can be much more dangerous and even lethal. Thus, when drugs that boost adrenergic stimulation by other mechanisms are added to MAO inhibitors that boost adrenergic stimulation by MAO inhibition, dangerous hypertensive reactions can ensue (Table 12-8). These interactions are generally well recognized; but, as for tyramine reactions, a certain mythology has grown up around what drugs can be given safely with MAO inhibitors.

It is true, for example, that many decongestants can adversely interact with MAO inhibitors to elevate blood pressure (Table 12-9 and Figure 12-78). However, that does
How Much Tyramine Is Dangerous With Irreversible MAO-A Inhibitors?

FIGURE 12-77 Dangerous tyramine levels with irreversible monoamine oxidase A (MAO-A) inhibitors. When it contains 40 mg of tyramine, a meal is considered high in this substance; however, in normal individuals (i.e., those not taking an MAO-A inhibitor) it takes as much as 400 mg of tyramine to elevate blood pressure (far right column). Patients taking low dose oral selegiline, which inhibits monoamine oxidase B (MAO-B) only, may ingest as much tyramine as someone not taking any MAO inhibitor; however, they also will not experience antidepressant effects (fourth column). In contrast, patients who take nonselective irreversible MAO inhibitors such as tranylcypromine or phenelzine may be able to ingest as little as 10 mg of tyramine before experiencing a tyramine reaction (first column). These patients experience antidepressant effects but are highly at risk for a tyramine reaction. Transdermal selegiline, on the other hand, inhibits MAO-A and MAO-B in the brain but only MAO-B in the gut; this means that it achieves antidepressant efficacy but is less likely to cause tyramine reactions. Patients taking transdermal selegiline may be able to ingest a high-tyramine meal of 40 mg or more with safety.

not mean that a patient can never take any cold preparation with an MAO inhibitor. What must be avoided are agents that add to the pro-noradrenergic actions of MAO inhibition to stimulate alpha 1 postsynaptic vascular receptors excessively (Figure 12-78). Currently, this applies mostly to phenylephrine, a relatively selective alpha 1 agonist, since three other related agents have been withdrawn from the U.S. and some other
TABLE 12-9 Potentially dangerous hypertensive combos: agents when combined with MAOIs that can cause hypertension (theoretically via adrenergic stimulation)

<table>
<thead>
<tr>
<th>Decongestants</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>phenylephrine (alpha 1 selective agonist)</td>
<td></td>
</tr>
<tr>
<td>ephedrine* (ma huang, ephedra) (alpha and beta agonist; central NE and DA releaser)</td>
<td></td>
</tr>
<tr>
<td>pseudoephedrine* (active stereoisomer of ephedrine - same mechanism as ephedrine)</td>
<td></td>
</tr>
<tr>
<td>phenylpropanolamine* (alpha 1 agonist; less effective central NE/DA releaser than ephedrine)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stimulants</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>amphetamines</td>
<td></td>
</tr>
<tr>
<td>methylphenidate</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antidepressants with NRI</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TCAs</td>
<td></td>
</tr>
<tr>
<td>NRI s</td>
<td></td>
</tr>
<tr>
<td>SNRI s</td>
<td></td>
</tr>
<tr>
<td>NDRI s</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Appetite suppressants with NRI</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>sibutramine</td>
<td></td>
</tr>
<tr>
<td>phentermine</td>
<td></td>
</tr>
</tbody>
</table>

*withdrawn from markets in the United States and some other countries.

Markets - namely ephedrine, pseudoephedrine, and phenylpropanolamine (Table 12-9). Another ingredient in cold preparations that should be avoided is the cough suppressant and opiate derivative dextromethorphan, discussed in more detail in the following section.

Stimulants such as methylphenidate, which potentiate NE at adrenergic synapses by blocking NE reuptake, and amphetamines, which do not only this but also release NE and DA, can elevate blood pressure; in combination with MAO inhibitors, they should either be avoided or used with the utmost caution and monitoring in heroic cases (Table 12-10). Any drugs that block norepinephrine reuptake, from antidepressants to ADHD drugs to appetite suppressants, should also be avoided or utilized only by experts when the risks and benefits are justified in an individual patient who is given adequate monitoring.

The mechanism of excessive noradrenergic stimulation when MAO inhibitors are combined with these various agents mentioned in Table 12-9 is illustrated in Figure 12-78. Specifically, decongestants work by vasoconstricting nasal blood vessels. When topically applied or given in reasonable oral doses, however, they generally do not have sufficient systemic actions to elevate blood pressure by themselves (Figure 12-78A). Nevertheless, in some vulnerable patients, these agents can elevate blood pressure even by themselves. MAO inhibitors given by themselves do potentiate norepinephrine, but this generally is not sufficient to cause hypertension, as shown in Figure 12-78B and as already discussed above. In fact, if anything, MAO inhibitors administered by themselves may be more likely to cause hypotension, especially orthostatic hypotension. The problem comes when the two mechanisms of decongestants and MAO inhibitors are combined, especially in vulnerable patients, in whom the pro-noradrenergic actions of MAO inhibition in concert with the direct stimulation of alpha 1 receptors by an agent such as phenylephrine can result in elevated blood pressure or even a hypertensive crisis (Figure 12-78C).
Interaction of Decongestants and MAO Inhibitors

**nasal decongestant alone**

- MAO-A destroys NE
- MAO-B destroys NE

**MAO inhibition alone**

- MAO-A destroys NE
- MAO-B destroys NE

**combined actions of decongestant and MAOI**

- Vasoconstriction
- Hypertension

---

**FIGURE 12-78A, B, and C Interaction of decongestants and monoamine oxidase (MAO) inhibitors.**

Decongestants that stimulate postsynaptic alpha 1 receptors, such as phenylephrine, may interact with MAO inhibitors to increase risk of a tyramine reaction. Decongestants work by constricting nasal blood vessels, but they do not typically elevate blood pressure at the doses used (A). An MAO inhibitor given alone (and without the ingestion of tyramine) increases norepinephrine but does not usually cause vasoconstriction or hypertension (B). However, the noradrenergic actions of an MAO inhibitor combined with the direct alpha 1 stimulation of a decongestant may be sufficient to cause hypertension or even hypertensive crisis (C).
TABLE 12-10 Potentially lethal combos: agents when combined with MAOIs that can cause hyperthermia/serotonin syndrome (theoretically via SERT inhibition)

<table>
<thead>
<tr>
<th>Antidepressants</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNRIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCAs (especially clomipramine)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other TCA structures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cyclobenzaprine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>carbamazepine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appetite suppressants with SRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sibutramine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dextromethorphan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>meperidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tramadol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>methadone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>propoxyphene</td>
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</tbody>
</table>

**Dangerous drug interactions: combining MAO inhibition with serotonin reuptake blockade**

More dangerous than the combination of adrenergic stimulants with MAO inhibitors may be the combination of agents that inhibit serotonin reuptake with MAO inhibitors. Although experts can sometimes cautiously administer some of the agents listed in Table 12-9 concomitantly with MAO inhibitors under heroic circumstances, one can essentially never combine agents that have potent serotonin reuptake inhibition (listed in Table 12-10) with agents given in doses that cause substantial MAO inhibition. This includes certainly any SSRI (serotonin selective reuptake inhibitor), any SNRI (serotonin norepinephrine reuptake inhibitor, including the appetite suppressant sibutramine), and the tricyclic antidepressant clomipramine (Table 12-10). Occasionally, tricyclics with weak serotonin reuptake inhibition can be combined with MAO inhibitors for heroic cases by experts, but this is rarely done any more because of the presence of many powerful and less dangerous therapeutic options. Opioids that block serotonin reuptake, especially meperidine but also methadone and even propoxyphene, dextromethorphan, and tramadol, especially at high doses, must be avoided when an MAO inhibitor is being given. Coadministration of an MAO inhibitor with an injection of meperidine may be the drug combination from the lists in Tables 12-9 and 12-10 that most frequently causes serious complications and even death. In fact, any agent with serotonin reuptake blockade has the potential to cause a fatal “serotonin syndrome,” noted by hyperthermia, coma, seizures, brain damage, and death. Theoretically, agents with a tricyclic structure such as carbamazepine and cyclobenzaprine are put on this list as a precautionary measure, but they are not known for potent serotonin reuptake blockade (Table 12-10).

The mechanism whereby serotonin reuptake inhibition combined with MAO-A inhibition causes the serotonin syndrome and its complications is illustrated in Figure 12-79. Already discussed extensively and illustrated many times is the serotonin reuptake pump, or serotonin transporter, also known as SERT, and the consequences of SERT inhibition (see Figure 12-79A as well as Figures 4-7 and 4-8, Figure 10-16, and Figure 12-17). We have also discussed the actions of irreversible MAO-A and B inhibitors in increasing synaptic...
serotonin levels after SERT inhibited

serotonin levels after MAO-A and MAO-B inhibited

~ = 5HT
~ = 5HT2A

FIGURE 12.79A, B, and C Interaction of serotonin reuptake inhibitors (SRIs) and monoamine oxidase (MAO) inhibitors. Inhibition of the serotonin transporter (SERT) leads to increased synaptic availability of serotonin (A). Similarly, inhibition of MAO leads to increased serotonin levels (B). These two mechanisms in combination can cause excessive stimulation of postsynaptic serotonin receptors, which may lead to hyperthermia, seizures, coma, cardiovascular collapse, or even death.
TABLE 12-11 Some tricyclic antidepressants still in use

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
</tr>
</thead>
<tbody>
<tr>
<td>clomipramine</td>
<td>Anafranil</td>
</tr>
<tr>
<td>imipramine</td>
<td>Tofranil</td>
</tr>
<tr>
<td>amitriptyline</td>
<td>Elavil, Endep, Tryptizol, Loroxyl</td>
</tr>
<tr>
<td>nortriptyline</td>
<td>Pamelor, Endep, Aventyl</td>
</tr>
<tr>
<td>protriptyline</td>
<td>Vivactil</td>
</tr>
<tr>
<td>maprotiline</td>
<td>Ludiomil</td>
</tr>
<tr>
<td>amoxapine</td>
<td>Asendin</td>
</tr>
<tr>
<td>doxepin</td>
<td>Sinequan, Adapin</td>
</tr>
<tr>
<td>desipramine</td>
<td>Norpramin, Pertofran</td>
</tr>
<tr>
<td>trimipramine</td>
<td>Surmontil</td>
</tr>
<tr>
<td>dothiepin</td>
<td>Prothiaden</td>
</tr>
<tr>
<td>lofepramine</td>
<td>Deprimyl, Gamanil</td>
</tr>
<tr>
<td>tianeptine</td>
<td>Coaxil, Stablon</td>
</tr>
</tbody>
</table>

Concentrations of serotonin by the mechanism of MAO inhibition (see Figure 12-79B as well as Figures 12-65 to 12-67). When these two mechanisms are combined, dangerous consequences can ensue (Figure 12-79C).

Theoretically, excessive stimulation of postsynaptic serotonin receptors, possibly the most important of which is the 5HT2A receptor in the hypothalamus, causes, among other things, a disruption in thermoregulation, resulting in dangerous hyperthermia and temperatures ≥106°F or over 40°C. Perhaps because the serotonin neuron has MAO-B (the “wrong” form of MAO for a substrate that is metabolized preferentially by MAO-A), preventing excessive concentrations of serotonin from accumulating may be quite dependent on the serotonin reuptake pump. In contrast, norepinephrine and dopamine neurons are equipped with the “right” form of MAO (namely, MAO-A). Thus, blocking SERT alone elevates 5HT robustly at 5HT neurons, and when the extrasynaptic removal of 5HT by MAO-A is also inhibited, a potentially disastrous accumulation of 5HT can occur. The consequences can range from migraines, myoclonus, diarrhea, agitation, and even psychosis on the milder end of the spectrum of potential symptomatology to hyperthermia, seizures, coma, cardiovascular collapse, permanent hyperthermic brain damage, and even death at the severe end of the spectrum of symptoms. For this reason, it is important to monitor closely all concomitant medication for patients on MAO inhibitors, even in patients taking the new RIMAs or the selegiline patch, where these drug interactions also apply.

**Classic antidepressants: tricyclic antidepressants**

The tricyclic antidepressants (Table 12-11) were so named because their chemical structure contains three rings (Figure 12-80). The tricyclic antidepressants were synthesized about the same time as other three-ringed molecules that were shown to be effective tranquilizers for schizophrenia (i.e., the early antipsychotic neuroleptic drugs such as chlorpromazine) (Figure 12-80). The tricyclic antidepressants were a disappointment when tested as antipsychotics. Even though they had a three-ringed structure, they were not effective in the treatment of schizophrenia and were almost discarded. However, during testing for schizophrenia, they were discovered to be antidepressants. That is, careful clinicians detected
antidepressant properties in schizophrenic patients, although not antipsychotic properties in these patients. Thus, the antidepressant properties of the tricyclic antidepressants were serendipitously observed in the 1950s and 1960s and eventually the TCAs were marketed for the treatment of depression.

Long after their antidepressant properties were observed, the tricyclic antidepressants were discovered to block the reuptake pumps for norepinephrine or for both norepinephrine and serotonin (Figures 5-16, 6-5, 6-6, 12-81, 12-82, and 12-83). Some tricycles have much more potency for inhibition of the serotonin reuptake pump (e.g., clomipramine) (Figures 12-81A and 12-82); others are more selective for norepinephrine over serotonin (e.g., desipramine, maprotiline, nortriptyline, protriptyline) (Figures 12-81B and 12-83). Most, however, block both serotonin and norepinephrine reuptake to some extent. The molecular action of monoamine transporters was discussed in detail in Chapter 4 and illustrated in Figures 4-4 through 4-8.

In addition, some tricyclic antidepressants have antagonist actions at 5HT2A and 5HT2C receptors. Although these properties have not been emphasized in classic explanations of the mechanism of action of these drugs, recent developments showing the importance of blocking 5HT2A and 5HT2C receptors in mediating the mechanism of therapeutic action of other drugs strongly suggest that these properties could contribute to the therapeutic profile of those tricycles that have such pharmacologic actions (Figures 12-84 and 12-85). Specifically, blocking 5HT2A receptors is associated with improvement of sleep and has a potential antidepressant action in its own right (Figure 12-84), possibly linked to the ability of 5HT2A/5HT2C receptor blockade to disinhibit both DA and NE release. This was discussed extensively above in relation to SARI action and trazodone and illustrated in Figure 12-64.

The major limitation to the tricyclic antidepressants has never been their efficacy; these are quite efficacious agents. The problem with drugs in this class is the fact that all of them share at least four other unwanted pharmacological actions shown in Figure 12-81, namely,
All tricyclic antidepressants block reuptake of norepinephrine and are antagonists at histamine 1, alpha 1 adrenergic, and muscarinic cholinergic receptors; they also block voltage-sensitive sodium channels (A, B, and C). Some tricyclic antidepressants are also potent inhibitors of the serotonin reuptake pump (A), and some may additionally be antagonists at serotonin 2A and 2C receptors (C).

Blockade of muscarinic cholinergic receptors, histamine 1 receptors, alpha 1 adrenergic receptors, and voltage-sensitive sodium channels (see Figures 12-86 through 12-88).

Blockade of histamine 1 receptors, also called antihistaminic action, causes sedation and may cause weight gain (Figure 12-86). Blockade of M1 muscarinic cholinergic receptors, also known as anticholinergic actions, causes dry mouth, blurred vision, urinary retention,
and constipation (Figure 12-87). To the extent that these agents can block M3 cholinergic receptors, they may interfere with insulin action, as discussed in Chapter 10 and illustrated in Figure 10-64. Blockade of alpha 1 adrenergic receptors causes orthostatic hypotension and dizziness (Figure 12-88). Tricyclic antidepressants also weakly block voltage-sensitive sodium channels in the heart and brain; in overdose, this action is thought to be the cause...
FIGURE 12-84 Therapeutic actions of tricyclic antidepressants (TCAs), part 3. In this figure, the icon of the TCA is shown with its 5HT2A portion inserted into the 5HT2A receptor, blocking it and causing an antidepressant effect as well as potentially improving sleep.

FIGURE 12-85 Therapeutic actions of tricyclic antidepressants (TCAs), part 4. In this figure, the icon of the TCA is shown with its 5HT2C portion inserted into the 5HT2C receptor, blocking it and causing an antidepressant effect.
FIGURE 12-86 Side effects of tricyclic antidepressants (TCAs), part 1. In this figure, the icon of the TCA is shown with its antihistamine (H1) portion inserted into histamine receptors, causing the side effects of weight gain and drowsiness.

FIGURE 12-87 Side effects of tricyclic antidepressants (TCAs), part 2. In this figure, the icon of the TCA is shown with its anticholinergic/antimuscarinic (M1) portion inserted into acetylcholine receptors, causing the side effects of constipation, blurred vision, dry mouth, and drowsiness.

of coma and seizures due to central nervous system (CNS) actions as well as cardiac arrhythmias and cardiac arrest and death due to peripheral cardiac actions (Figure 12–89).

The term “tricyclic antidepressant” is archaic in today’s pharmacology. First, the antidepressants that block monoamine transporters are not all tricyclic anymore: the new agents can have one, two, three, or four rings in their structures. Second, the tricyclic antidepressants are not merely antidepressants, since some of them have anti–obsessive compulsive
disorder effects and others have anti-panic effects (as discussed in Chapter 14, on anxiety). Because of their side effects and potential for death in overdose, tricyclic antidepressants have fallen into second-line use for depression. However, there remains considerable use of these agents for difficult-to-treat patients, and the cost of these agents is quite low.

**Antidepressant pharmacokinetics**

The CYP450 enzymes and the pharmacokinetic actions they represent must be contrasted with the pharmacodynamic actions of antidepressants discussed in the previous sections of this chapter, focusing on the various mechanisms of action of antidepressants. Although most of this book deals with the pharmacodynamics of psychopharmacological agents, especially how drugs act on the brain, the following section provides a quick overview of the pharmacokinetics of antidepressants. Some of the general principles of pharmacokinetics are discussed in Chapter 10 and illustrated in Figures 10-78 through 10-80; specific issues of antipsychotic pharmacokinetics are illustrated in Figures 10-81 through 10-89.

**CYP450 1A2**

One CYP450 enzyme of specific relevance to antidepressants is 1A2 (Figures 12-90, 12-91, and 12-92). Certain tricyclic antidepressants (TCAs) are substrates for this enzyme, especially the secondary amines like clomipramine and imipramine (Figure 12-90). CYP450 1A2 demethylates such TCAs but does not thereby inactivate them. In this case, the desmethyl metabolite of the TCA is still an active drug (e.g., desmethylclomipramine, desipramine, and nortriptyline; see Figure 12-90).

CYP450 1A2 is inhibited by the serotonin selective reuptake inhibitor (SSRI) fluvoxamine (Figure 12-91). Thus, when fluvoxamine is given concomitantly with other drugs
that use 1A2 for their metabolism, those drugs can no longer be metabolized as efficiently. Two instances of potentially important drug interactions are seen when fluvoxamine is given along with either duloxetine or theophyllin (Figure 12-92). In those cases, the duloxetine (or theophyllin) dose must often be lowered or else the blood levels of drug will rise and possibly cause side effects or even be toxic. The same may occur with caffeine.

**CYP450 2D6**

Another important CYP450 enzyme for antidepressants is 2D6. Tricyclic antidepressants are substrates of 2D6, which hydroxylates and thereby inactivates the TCAs. Several other antidepressants from the SSRI class are substrates of CYP2D6, and some are both substrates and inhibitors. We have already discussed venlafaxine as an important substrate of CYP2D6, as this antidepressant is converted into its active metabolite desvenlafaxine by CYP2D6, as shown in Figure 12-37. Most antidepressants that are substrates for CYP2D6, however, are converted into inactive metabolites, (e.g., the metabolites of duloxetine, paroxetine, atomoxetine, and tricyclic antidepressants are inactive) (Figure 12-93). There is a wide range of potency for 2D6 inhibition by many antidepressants, with paroxetine, fluoxetine,
FIGURE 12-90 Substrates for CYP450 1A2. Certain tricyclic antidepressants, especially secondary amines such as clomipramine and imipramine, are substrates for CYP450 1A2. By demethylation, this enzyme converts the tricyclics into active metabolites to form desmethyliclophramine and desipramine, respectively.

FIGURE 12-91 Inhibitors of CYP450 1A2. The serotonin selective reuptake inhibitor (SSRI) fluvoxamine is a potent inhibitor of the enzyme CYP450 1A2.

and duloxetine among the more potent inhibitors and reboxetine, bupropion, fluvoxamine, sertraline, and citalopram among those that are less potent (Figure 12-94).

One of the most important drug interactions that antidepressants can cause through inhibition of 2D6 is to raise plasma drug levels of tricyclic antidepressants (TCAs) when TCAs are given concomitantly with SSRIs or when there is switching between TCAs and SSRIs. Since TCAs are substrates for 2D6 and various antidepressants are inhibitors of
FIGURE 12-92 Consequences of CYP450 1A2 inhibition. Theophylline and duloxetine are substrates for CYP450 1A2. Thus, in the presence of the CYP450 1A2 inhibitor fluvoxamine, their levels will rise; therefore their dose must often be lowered in order to avoid side effects.

FIGURE 12-93 Substrates for CYP450 2D6. Venlafaxine, duloxetine, paroxetine, and atomoxetine are substrates for CYP450 2D6, which converts these antidepressants to active (desvenlafaxine) or inactive metabolites.

2D6 (Figure 12-94), concomitant administration will raise TCA levels, perhaps to toxic levels (Figure 12-95). Concomitant administration of an SSRI and a TCA thus requires monitoring of the plasma drug concentrations of the TCA and probably requires a dose reduction of the TCA.
FIGURE 12-94 Inhibitors of CYP450 2D6. Some antidepressants (paroxetine, fluoxetine, duloxetine) are inhibitors of CYP450 2D6.

![Diagram showing inhibitors of CYP450 2D6]

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCA</td>
<td>Paroxetine</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Codeine</td>
<td>Duloxetine</td>
</tr>
<tr>
<td>Some beta blockers</td>
<td>Atomoxetine</td>
</tr>
</tbody>
</table>

No Hydroxylation

![Diagram showing consequences of CYP450 2D6 inhibition]

FIGURE 12-95 Consequences of CYP450 2D6 inhibition. If a tricyclic antidepressant (a substrate for CYP450 2D6) is given concomitantly with a serotonin selective reuptake inhibitor or a serotonin norepinephrine reuptake inhibitor that is an inhibitor of CYP450 2D6, this will cause the levels of the tricyclic antidepressant to increase, which can be toxic. Therefore either monitoring of tricyclic plasma concentration with dose reduction or avoidance of this combination is required.

Other substrates of 2D6 whose plasma drug levels can be raised by antidepressants that are 2D6 inhibitors include venlafaxine, duloxetine, paroxetine, and atomoxetine; however, clinical experience suggests that only atomoxetine commonly requires dosage reduction when administered with a 2D6 inhibitor. These interactions among antidepressants are important to bear in mind for prescribers who commonly use one antidepressant to augment...
another or who switch patients from one antidepressant to another without a full washout of the first antidepressant. Concomitant administration of an antidepressant that is a 2D6 inhibitor could theoretically interfere with the analgesic actions of codeine (which must be converted to an active metabolite by 2D6 in order to work) and could theoretically raise the plasma drug levels of some beta blockers, as well as thioridazine, and cause dangerous arrhythmias.

### CYP450 3A4

A third important CYP450 enzyme for antidepressants is 3A4 (Figure 12-96). Some antidepressants are substrates for 3A4 and others are inhibitors of this enzyme. Many drugs, including some antidepressants that are substrates for 3A4, are also substrates for several other metabolic pathways; in these cases, inhibition of 3A4 does not necessarily raise the plasma drug levels of such agents. Generally, the most important thing for a clinician to know is which drugs can have clinically important increases in their plasma drug levels when 3A4 is inhibited. It is thus important to know which of these drugs are substrates and which are inhibitors of 3A4.

Among psychotropic drugs, the antipsychotic pimozide, the anticonvulsant and mood stabilizer carbamazepine, the benzodiazepines alprazolam and triazolam, and the anxiolytic buspirone are all substrates of 3A4 (Figure 12-96). Among nonpsychotropic drugs, certain cholesterol-lowering HMG-CoA reductase inhibitors (e.g., simvastatin, atorvastatin, and lovastatin but not pravastatin or fluvastatin) are also substrates for 3A4 (Figure 12-96).

Among the antidepressants, fluvoxamine, fluoxetine, and nefazodone are moderately potent 3A4 inhibitors, with reboxetine and sertraline weaker 3A4 inhibitors.
Among nonpsychotropic drugs, certain protease inhibitors for the treatment of human immunodeficiency virus (HIV) infection, certain azole antifungals (e.g., ketoconazole), and macrolide antibiotics (e.g., erythromycin) are all potent 3A4 inhibitors.

**Clinically important consequences of combining 3A4 substrates with 3A4 inhibitors**

Combining a 3A4 inhibitor with the 3A4 substrate pimozide can result in elevated plasma pimozide levels, with consequent QTc prolongation and dangerous cardiac arrhythmias. Combining a 3A4 inhibitor with carbamazepine, alprazolam, or triazolam can cause significant sedation due to elevated plasma drug levels of the latter agents. Combining a 3A4 inhibitor with certain cholesterol-lowering drugs that are 3A4 substrates (e.g., simvastatin, atorvastatin, and lovastatin but not pravastatin or fluvastatin) can increase the risk of muscle damage and rhabdomyolysis from elevated plasma levels of these statins.

Drug interactions mediated by CYP450 enzymes are constantly being discovered; the active clinician who combines drugs must be alert to these and thus remain continually up to speed on what drug interactions are important. Here we present only the general concepts of drug interactions at CYP450 enzyme systems, but the specifics should be found in a comprehensive and up-to-date reference source before prescribing.

**CYP450 inducers**

Finally, drugs can not only be substrates or inhibitors for CYP450 enzymes; they can also be inducers. An inducer increases the activity of the enzyme over time because it induces the synthesis of more copies of the enzyme. One example of this is the effects of the anticonvulsant and mood stabilizer carbamazepine, which induces 3A4 over time (discussed in Chapter 10 and illustrated in Figure 10-88). Another example of CYP450 enzyme induction is cigarette smoking, which induces 1A2 over time (discussed in Chapter 10 and illustrated in Figure 10-82). The consequence of such enzyme induction is that substrates for the induced enzyme will be more efficiently metabolized over time, and thus their levels in the plasma will fall. Doses of such substrate drugs may therefore need to be increased over time to compensate for this.

For example, carbamazepine is both a substrate and an inducer of 3A4. Thus, as treatment becomes chronic, 3A4 is induced and carbamazepine blood levels fall (Figures 10-88 and 10-89). Failure to recognize this and to increase carbamazepine dosage to compensate may lead to a failure of anticonvulsant or mood stabilizing efficacy, with breakthrough symptoms occurring as a result.

Another important thing to remember about a CYP450 inducer is what happens if the inducer is stopped. Thus, if one stops smoking, levels of drugs that are 1A2 substrates will rise. If one stops carbamazepine, levels of drugs that are 3A4 substrates will rise.

In summary, many antidepressant drug interactions require dosage adjustment of one of the drugs. A few combinations must be strictly avoided. Many drug interactions are statistically but not clinically significant. By following the principles outlined here, the skilled practitioner will learn whether any given drug interaction is clinically relevant.

**Trimonoaminergic modulators (triple monoamine modulators, or TMMs)**

An increasing number of agents now appear to modulate the trimonoaminergic neurotransmitter system of 5HT, NE, and DA by mechanisms other than inhibition of monoamine transporters and in a manner that may be more effective when given with a monoamine
transport inhibitor rather than as a monotherapy (Tables 12-2 and 12-12). These therapeutic interventions range from hormones to vitamins, medical foods, ions, electrical and magnetic brain stimulation, and even psychotherapy (Table 12-12). A few of these key therapeutics are reviewed here very briefly to provide a quick overview of this evolving concept. All are categorized as "trimonoaminergic modulators," or TMMs (Tables 12-2 and 12-12), because their various mechanisms of action are all postulated to share in common the modulation of one or more of the monoamines. Thus, TMMs theoretically boost the action of antidepressants in the treatment of depressive episodes, particularly when given as augmenting agents for the treatment of depressive episodes that fail to remit with traditional antidepressant treatment.

### Estrogen as a trimonoaminergic, GABA, and glutamate modulator

The hormone estrogen has a profound impact on mood and on the trimonoamine neurotransmitter system and thus can be considered a trimonoaminergic modulator (TMM). Estrogen also modulates the activity of other neurotransmitters, including GABA (gamma-aminobutyric acid) and glutamate, as will be discussed below. Many of estrogen's effects upon various neurotransmitter systems appear to be the result of estrogen binding to nuclear hormone receptors, known as estrogen receptors (Figure 12-97). Receptors for estrogen may also exist in neuronal cell membranes, but these are not yet well characterized. However, it is well established that nuclear ligand receptors specifically for estrogen are transformed into nuclear ligand-activated transcription factors when estrogen binds to them. This concept is discussed in Chapter 3 and illustrated in Figure 3-11, as an example of one of the major signal transduction systems for hormones.

#### Estrogen and nuclear hormone receptors

Estrogen modulates gene expression by binding to nuclear hormone receptors for estrogen—i.e., "estrogen receptors" (Figure 12-97A). Receptors for estrogen differ from tissue to tissue and may differ from brain region to brain region. In addition to various subtypes of estrogen receptors, there are also nuclear hormone receptors for progesterone and androgens as well as for other steroids such as glucocorticoids and mineralocorticoids (Chapter 3 and Figure 3-11; Chapter 5 and Figure 5-50). Unlike neurotransmitter receptors located on neuronal membranes, nuclear ligand-activated receptors for estrogen are located in the neuronal cell nucleus, so estrogen must penetrate the neuronal membrane and the nuclear membrane to find its receptors, which are located near the genes that estrogen influences (Figure 12-97). These genes are called estrogen response elements (Figure 12-97B). Activation of estrogen response elements by estrogen requires receptor "dimerization" (i.e., the coupling of two copies of the estrogen receptor) when estrogen binds to them; this forms an active

### TABLE 12-2 Trimonoamine modulators (TMMs)

- folate
- L-MTHF (L-methyl-tetrahydrofolate)
- estrogen
- estrogen replacement therapy
- thyroid hormones (T3/T4)
- lithium
- brain stimulation
- psychotherapy
Estrogen Acts at Nuclear Hormone Receptors: A Nuclear Ligand–Activated Transcription Factor

FIGURE 12-97A, B, and C
Estrogen and nuclear hormone receptors. Estrogen modulates gene expression by binding to estrogen receptors. Estrogen receptors differ from tissue to tissue and may differ from brain region to brain region. (A) Unlike neurotransmitter receptors located on neuronal membranes, receptors for estradiol are located in the neuronal cell nucleus, so estradiol must penetrate the neuronal membrane and the nuclear membrane to find its receptors, which are therefore located near the genes to be influenced. These genes are called estrogen response elements. (B) The expression of estrogen response elements within the DNA of the neuron must be initiated by estrogen and its receptor. Activation of these genes by estradiol requires "dimerization" (i.e., coupling of two copies of the estrogen receptor) when estrogen binds to the receptor to form an active transcription factor (TF) capable of "turning on" the estrogen response element. (C) Once the estrogen receptors are activated by estradiol into transcription factors, they activate gene expression by the estrogen response elements in the neuron's DNA. The gene products expressed include direct trophic factors such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), which can facilitate synaptogenesis and prevent apoptosis and neurodegeneration.

transcription factor capable of “turning on” estrogen response elements (Figure 12-97B). The formation of transcription factors is discussed in Chapter 3 and illustrated in Figures 3-22 through 3-34. Once estrogen receptors are activated as transcription factors, they activate gene expression in the neuron by binding to estrogen response elements in the neuron’s DNA (Figure 12-97C).
Gene products that are regulated by estrogen include trophic factors such as brain-derived neurotrophic factor (BDNF) as well as neurotransmitter synthesizing and metabolizing enzymes and various neurotransmitter receptors. Dramatic evidence of estrogen’s trophic properties can be observed in hypothalamic and hippocampal neurons in adult female experimental animals within days and across a single menstrual (estrus) cycle (Figures 12-98 and 12-99). During the early phase of the cycle, estradiol levels rise, causing dendritic spines to form specifically in the ventromedial hypothalamus and on pyramidal neurons in the hippocampus of female rats. Progesterone administration rapidly potentiates this, so spine formation is at its greatest when both estrogen and progesterone peak just after the first half of the cycle (Figure 12-98). However, once estrogen levels fall significantly and progesterone continues to rise, the presence of progesterone without estrogen triggers downregulation of these spines by the end of the estrus cycle (Figure 12-98).

Estrogen as a GABA (gamma-aminobutyric acid) inhibitor

One hypothesis to explain the mechanism of this cyclical formation and then loss of dendritic spines is that estrogen regulates a type of spine formation that occurs when neurons are active and that reverses when neurons are inactive, known as “activity-dependent” dendritic spine formation (Figure 12-99). As estrogen levels rise and fall during the menstrual cycle, estrogen can cause a corresponding cyclical rather than continuous activation of neurons in certain brain areas. The cyclical activation of these neurons is explained by the fact that estrogen exerts a cyclical inhibitory influence on GABA interneurons (Figure 12-99). Inhibitory actions of GABA interneurons on pyramidal neurons are discussed in Chapter 7 and illustrated in Figure 7-23. Estrogen inhibits this inhibition. This is not psychopharmacological double talk but a well-known phenomenon called disinhibition, just a fancy way of saying “activated.”

By inhibiting GABAergic inhibition, estrogen thus activates pyramidal neurons (Figure 12-99B). Estrogen does this by downregulating and thus reducing the synthesis of glutamic acid decarboxylase (GAD), the enzyme that synthesizes GABA. This, in turn, reduces the synthesis of GABA itself, which diminishes the release of GABA from GABAergic interneurons. No GABA, no inhibition; no inhibition, pyramidal neurons are activated.

Estrogen as a glutamate activator

When estrogen activates pyramidal neurons, these neurons release glutamate (Figures 12-99B and 12-99C). As estrogen levels rise during the first half of the menstrual cycle, so does pyramidal neuron activation by glutamate from other pyramidal neurons (Figure 12-99B); as estrogen levels fall during the last half of the menstrual cycle, pyramidal cells lose their activation (Figure 12-99C).

The cyclical formation of dendritic spines that is the consequence of these cyclical changes in estrogen levels is shown for a single menstrual (estrus) cycle in Figure 12-99A, B, and C. Thus, at the beginning of the cycle, estrogen levels are low, so GABA interneurons are active. When GABA interneurons are active, they inhibit pyramidal neurons (Figure 12-99A). However, as estrogen levels rise during the first half of the cycle, GABA interneurons are progressively inhibited, causing progressive disinhibition of pyramidal neurons (Figure 12-99B).

Disinhibited pyramidal neurons release glutamate (Figure 12-99B). Glutamate then interacts at a number of glutamate receptors, including postsynaptic NMDA receptors on other pyramidal neurons (Figure 12-99B). Sustained activation of NMDA receptors can
Reproductive Hormones and Synaptogenesis
Across the Menstrual Cycle

FIGURE 12-98 Reproductive hormones and synaptogenesis across the menstrual cycle. Dramatic evidence of estrogen’s trophic properties can be observed in hypothalamic and hippocampal neurons in adult female experimental animals within days and across a single menstrual (estrus) cycle. During the early phase of the cycle, estradiol levels rise, and this trophic influence induces dendritic spine formation and synaptogenesis. Progesterone administration rapidly potentiates this, so spine formation is at its greatest when both estrogen and progesterone peak just after the first half of the cycle. However, once estrogen levels fall significantly and progesterone continues to rise, the presence of progesterone without estrogen triggers downregulation of these spines and removal of the synapses by the end of the estrus cycle.

trigger long-term potentiation and trophic changes in postsynaptic neurons, including the formation of dendritic spines by the middle of the cycle (Figure 12-99C). This concept of NMDA actions of glutamate upon long-term potentiation and activation of trophic changes is also discussed in Chapter 5 and illustrated in Figure 5-43. Once estrogen levels fall by the end of the cycle, glutamate neurons again become inactive, and activity-dependent dendritic spine formation is not maintained (back to Figure 12-99A).
Activity-Dependent Spine Formation by Estradiol

FIGURE 12-99 Activity-dependent spine formation by estradiol. Estrogen exerts a cyclical inhibitory influence on gamma-aminobutyric acid (GABA) interneurons, which in turn regulate pyramidal neurons. When estrogen levels are low, GABA interneurons are active; thus pyramidal neurons are inhibited (A). As estrogen levels rise early in the menstrual cycle, GABA inhibition is reduced, thus disinhibiting pyramidal neurons and leading to glutamate release (B). Sustained activation of N-methyl-d-aspartate (NMDA) receptors by glutamate, achieved by the middle or late cycle, can trigger long-term potentiation and trophic changes that include the formation of dendritic spines (C). As estrogen levels fall by the end of the menstrual cycle, GABA interneurons become active again and resume inhibition of pyramidal neurons, preventing the maintenance of dendritic spine formation (A).

Estrogen regulation and major depression over a woman's life cycle

Estrogen levels shift rather dramatically across the female life cycle in relation to various types of reproductive events (Figure 12-100). Such shifts are also linked to the onset or recurrence of major depressive episodes (Figures 12-100 and 12-101). In men, the incidence of depression rises in puberty and then is essentially constant throughout life, despite a slowly declining testosterone level from age twenty-five onward (Figure 12-102). By contrast, in