The symptoms of depression are :

intense feelings of sadness, hopelessness, and despair as well as the inability to experience pleasure in usual activities, changes in sleep patterns and appetite, loss of energy, and suicidal thoughts.

MECHANISM OF ANTIDEPRESSANT DRUGS

Most clinically useful antidepressant drugs potentiate, either directly or indirectly, the actions of norepinephrine and/or serotonin in the brain.

This, along with other evidence, led to the biogenic amine theory, which proposes that depression is due to a deficiency of monoamines, such as norepinephrine and serotonin, at certain key sites in the brain.

Figure 12.1
Summary of antidepressants.
(Continued on next page)

DRUG	UPTAKE INHIBITION	
	Nor-epinephrine	Serotonin
Selective serotonin reuptake inhibitor		
Fluoxetine	0	++++
Selective serotonin/ norepinephrine reuptake inhibitors		
Venlafaxine	++*	++++
Duloxetine	++++	++++
Tricyclic antidepressant		
Imipramine	++++	+++

Figure 12.2
Relative receptor specificity of some antidepressant drugs. **Venlafaxine* inhibits norepinephrine reuptake only at high doses. ++++ = very strong affinity; +++ = strong affinity; ++ = moderate affinity; + = weak affinity; 0 = little or no affinity.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

The selective serotonin reuptake inhibitors (SSRIs) specifically inhibit serotonin reuptake, having 300- to 3000-fold greater selectivity for the serotonin transporter, as compared to the norepinephrine transporter.

This contrasts with the tricyclic antidepressants that nonselectively inhibit the uptake of norepinephrine and serotonin Both of these antidepressant drug classes exhibit little ability to block the dopamine transporter.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Moreover, the SSRIs have little blocking activity at muscarinic,α-adrenergic, and histaminic H1 receptors. Therefore, common side effects associated with TCAs, such as orthostatic hypotension, sedation, dry mouth, and blurred vision, are not commonly seen with the SSRIs.

Because they have fewer adverse eff ects and are relatively safe even in overdose, the SSRIs have largely replaced TCAs and monoamine oxidase inhibitors
(MAOIs) as the drugs of choice in treating depression.

Actions

The SSRIs block the reuptake of serotonin, leading to increased concentrations of the neurotransmitter in the synaptic cleft and, ultimately, to greater postsynaptic neuronal activity.

Antidepressants, including SSRIs, typically take at least 2 weeks to produce significant improvement in mood, and maximum benefit may require up to 12 weeks or more . However, none of the antidepressants are uniformly effective. Approximately 40 percent of depressed patients treated with adequate doses for 4 to 8 weeks do not respond to the antidepressant agent.

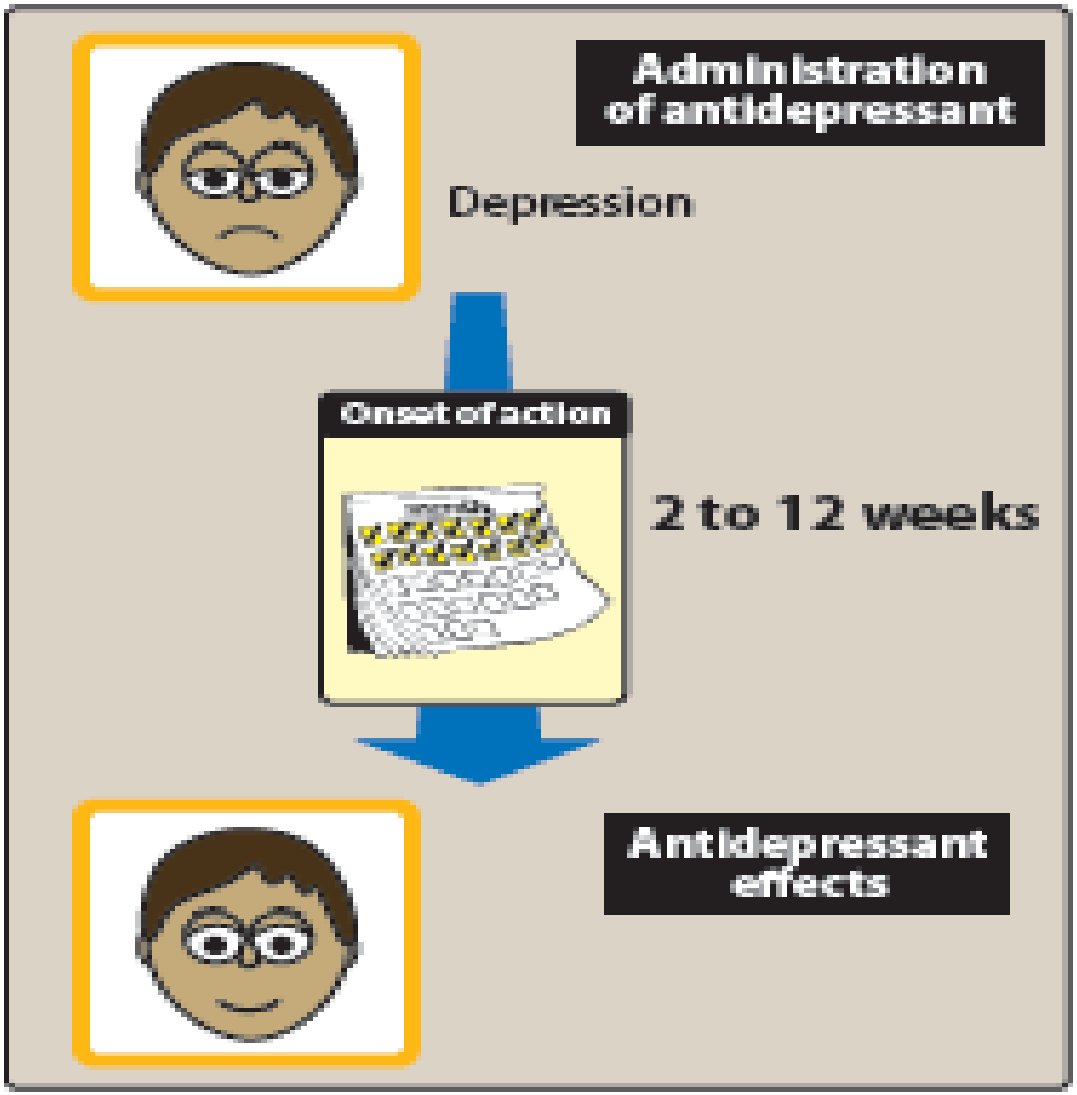


Figure 12.3
Onset of therapeutic effects of the major antidepressant drugs requires several weeks.

Therapeutic uses

The primary indication for SSRIs is depression, for which they are as effective as the TCAs.
A number of other psychiatric disorders also respond favorably to SSRIs, including:

- ✓ obsessive-compulsive disorder,
- ✓ panic disorder,
- ✓ generalized anxiety disorder,
- ✓ posttraumatic stress disorder,
- ✓ social anxiety disorder
- ✓ bulimia nervosa (only *fluoxetine is approved for this last indication).*

Pharmacokinetics

All of the SSRIs are well absorbed after oral administration. Peak levels are seen in approximately 2 to 8 hours on average. Food has little effect on absorption (except with *sertraline, for which food increases* its absorption).

Only *sertraline undergoes significant first-pass metabolism.*

The majority of SSRIs have plasma half-lives that range between 16 and 36 hours.

Metabolism by cytochrome P450 (CYP450)-dependent enzymes and glucuronide or sulfate conjugation occur extensively.

Fluoxetine diff ers from the other members of the class in two respects.

First, it has a much longer half-life (50 hours) and is available as a sustained-release preparation allowing once-weekly dosing.

Second, the metabolite of the S-enantiomer, S-norfluoxetine, is as potent as the parent compound. The half-life of the metabolite is quite long, averaging 10 days.

Fluoxetine and paroxetine are potent inhibitors of a hepatic CYP450 isoenzyme (CYP2D6) responsible for the elimination of TCAs, neuroleptic drugs, and some antiarrhythmic and β-adrenergic antagonist drugs.

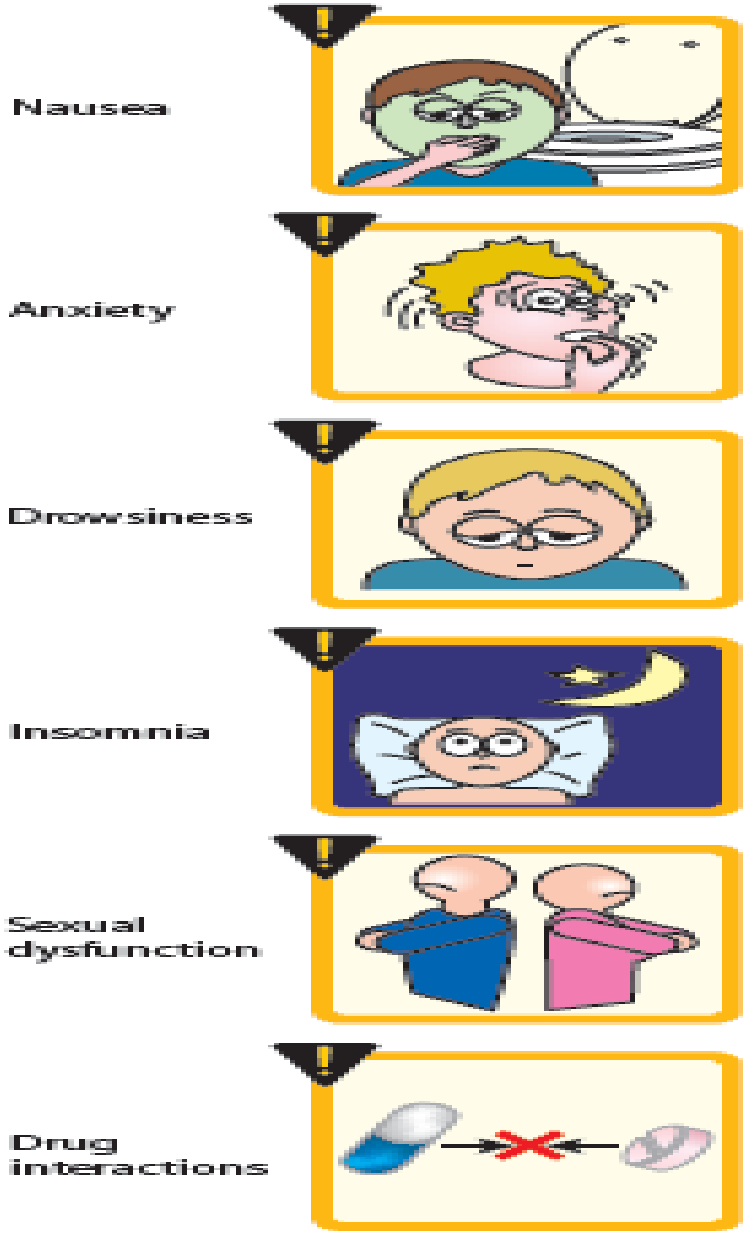


Figure 12.4
Some commonly observed adverse effects of selective serotonin reuptake inhibitors.

Adverse effects

Although the SSRIs are considered to have fewer and less severe adverse effects than the TCAs and MAOIs, the SSRIs are not without troublesome adverse effects, such as:

- ✓ headache,
- ✓ sweating, anxiety and agitation,
- ✓ gastrointestinal (GI) effects (nausea, vomiting, diarrhea),
- ✓ Weakness and fatigue,
- ✓ sexual dysfunction,
- ✓ changes in weight,
- ✓ sleep disturbances (insomnia and somnolence), and
- ✓ drug-drug interactions

Use in children and teenagers:
Antidepressants should be used cautiously in children and teenagers, because about 1 out of 50 children report suicidal ideation as a result of SSRI treatment.

Pediatric patients should be observed for worsening depression and suicidal thinking whenever any antidepressant is started or its dose is increased or decreased.

Fluoxetine, sertraline, and fluvoxamine are U.S. Food and Drug Administration (FDA)-approved for use in children to treat obsessive-compulsive disorder, and *fluoxetine is* approved to treat childhood depression.

Overdoses:
Large intakes of SSRIs do not usually cause cardiac arrhythmias (compared to the arrhythmia risk for the TCAs),

Seizures are a possibility because all antidepressants may lower the seizure threshold.

All SSRIs have the potential to cause a serotonin syndrome that may include the symptoms of hyperthermia, muscle rigidity, sweating, myoclonus (clonic muscle twitching), and changes in mental status and vital signs when used in the presence of a MAOI or other highly serotonergic drug.

Therefore, extended periods of washout for each drug class should occur prior to the administration of the other class of drugs.

Discontinuation syndrome:
Whereas all of the SSRIs have the potential for causing a discontinuation syndrome after their abrupt withdrawal, the agents with the shorter half-lives and having inactive metabolites have a higher risk for such an adverse reaction.

Fluoxetine has the lowest risk of causing an SSRI discontinuation syndrome.

Possible signs and symptoms of such a serotonin-related discontinuation syndrome include headache, malaise and flu-like symptoms, agitation and irritability, nervousness, and changes in sleep pattern

SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS

Venlafaxine , desvenlafaxine , and duloxetine inhibit the reuptake of both serotonin and norepinephrine

These agents, termed selective serotonin/norepinephrine reuptake inhibitors (SNRIs), may be eff ective in treating depression in patients in whom SSRIs are ineff ective.

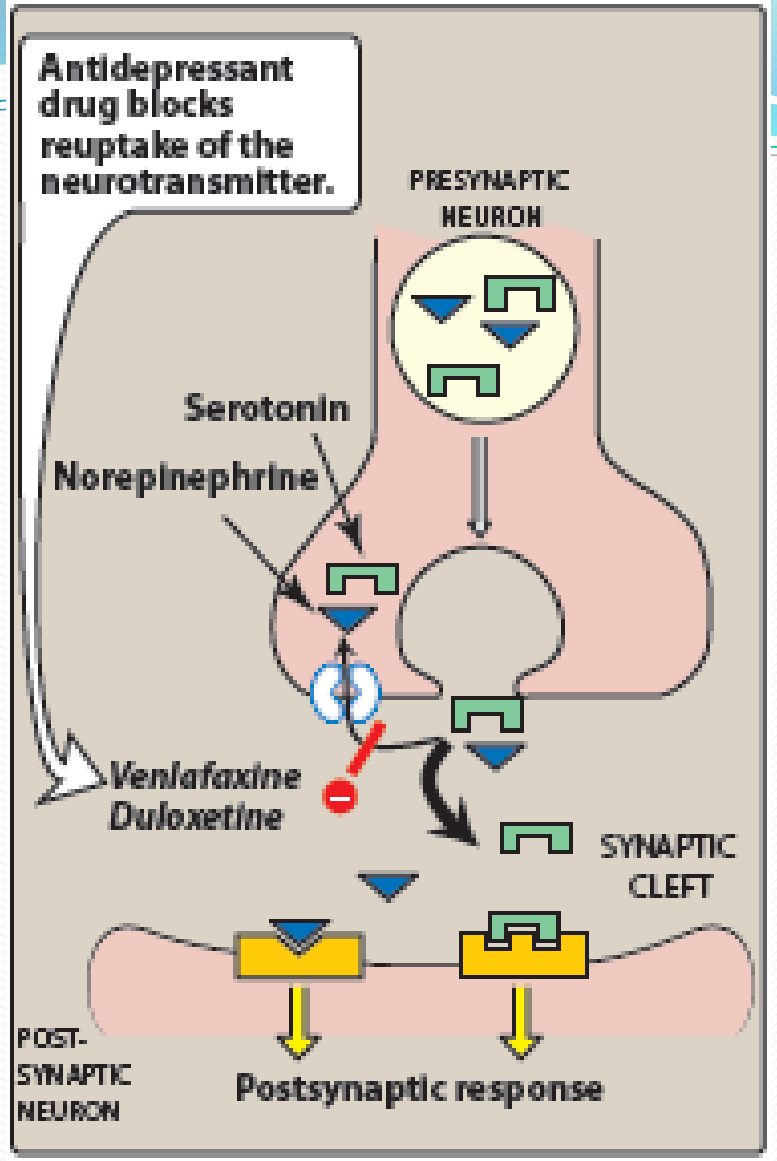


Figure 12.5
Proposed mechanism of action of selective serotonin/norepinephrine reuptake inhibitor antidepressant drugs.

Furthermore, depression is often accompanied by chronic painful symptoms, such as backache and muscle aches, against which SSRIs are also relatively ineffective.

Both SNRIs and TCAs, with their dual actions of inhibiting both serotonin and norepinephrine reuptake, are sometimes eff ective in relieving physical symptoms of neuropathic pain such as diabetic peripheral neuropathy.

However, the SNRIs, unlike the TCAs, have little activity at adrenergic, muscarinic or histamine receptors and, thus, have fewer of these receptor-mediated adverse eff ects than the TCAs

Venlafaxine, desvenlafaxine, and *duloxetine may precipitate a discontinuation syndrome if treatment* is abruptly stopped.

ATYPICAL ANTIDEPRESSANTS

The atypical antidepressants are a mixed group of agents that have actions at several different sites. They are not any more efficacious than the TCAs or SSRIs, but their side effect profiles are different.

Bupropion ,

This drug acts as a weak dopamine and norepinephrine reuptake inhibitor to alleviate the symptoms of depression.

also used in attenuating the withdrawal symptoms for nicotine in tobacco users trying to quit smoking.

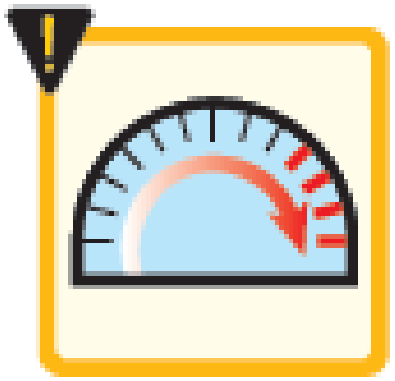
Side effects may include dry mouth, sweating, nervousness, tremor, a very low incidence of sexual dysfunction, and an increased risk for seizures at high doses.

Mirtazapine

This drug enhances serotonin and norepinephrine neurotransmission via mechanisms related to its ability to block presynaptic α2 receptors.

Additionally, it may owe at least some of its antidepressant activity to its ability to block 5-HT2 receptors.

It is a sedative because of its potent antihistaminic activity, which may be an advantage in depressed patients having difficulty sleeping



Weight gain

Sedation

Figure 12.6
Some commonly observed adverse effects of *mirtazapine*.

Nefazodone and trazodone

These drugs are weak inhibitors of serotonin reuptake. Their therapeutic benefit appears to be related to their ability to block postsynaptic 5-HT2A receptors.

With chronic use, these agents may desensitize 5-HT1A presynaptic autoreceptors and, thereby, increase serotonin release.

Both agents are sedating, probably because of their potent H1-blocking activity.

TRICYCLIC ANTIDEPRESSANTS

The TCAs block norepinephrine and serotonin reuptake into the neuron.

Imipramine (Desipramine), Amitriptyline (Nortriptyline), Clomipramine, Doxepin , Trimipramine ,Maprotiline and amoxapine .

All have similar therapeutic effi cacy

Patients who do not respond to one TCA may benefi t from a diff erent drug in this group.

These drugs are a valuable alternative for patients who do not respond to SSRIs.

Mechanism of action

1. Inhibition of neurotransmitter reuptake:

TCAs and *amoxapine are* potent inhibitors of the neuronal reuptake of norepinephrine and serotonin into presynaptic nerve terminals. At therapeutic concentrations, they do not block dopamine transporters.

2. Blocking of receptors:

TCAs also block serotonergic, α-adrenergic, histaminic, and muscarinic receptors. It is not known if any of these actions produce TCAs' therapeutic benefi t.

However, actions at these receptors are likely responsible for many of the adverse eff ects of the TCAs. *Amoxapine also blocks 5-HT2 and* D2 receptors.

Therapeutic uses

The TCAs are eff ective in treating moderate to severe depression.

Some patients with panic disorder also respond to TCAs.

Imipramine has been used to control bed-wetting in children (older than age 6 years) by causing contraction of the internal sphincter of the bladder.

At present, it is used cautiously because of the inducement of cardiac arrhythmias and other serious cardiovascular problems.

The TCAs, particularly *amitriptyline,* have been used to treat migraine headache and chronic pain syndromes (for example, neuropathic pain)

Low doses of TCAs, especially *doxepin, can be used to treat insomnia.*

Pharmacokinetics

TCAs are well absorbed upon oral administration.

Because of their lipophilic nature, they are widely distributed and readily penetrate into the CNS.

This lipid solubility also causes these drugs to have variable halflives (for example, 4 to 17 hours for *imipra mine). As a result of their* variable first-pass metabolism in the liver, TCAs have low and inconsistent bioavailability. Therefore, the patient's response and plasma levels can be used to adjust dosage.

The initial treatment period is typically 4 to 8 weeks. The dosage can be gradually reduced to improve tolerability, unless relapse occurs.

These drugs are metabolized by the hepatic microsomal system (and, thus, may be sensitive to agents that induce or inhibit the CYP450 isoenzymes) and conjugated with glucuronic acid.

Ultimately, the TCAs are excreted as inactive metabolites via the kidney.

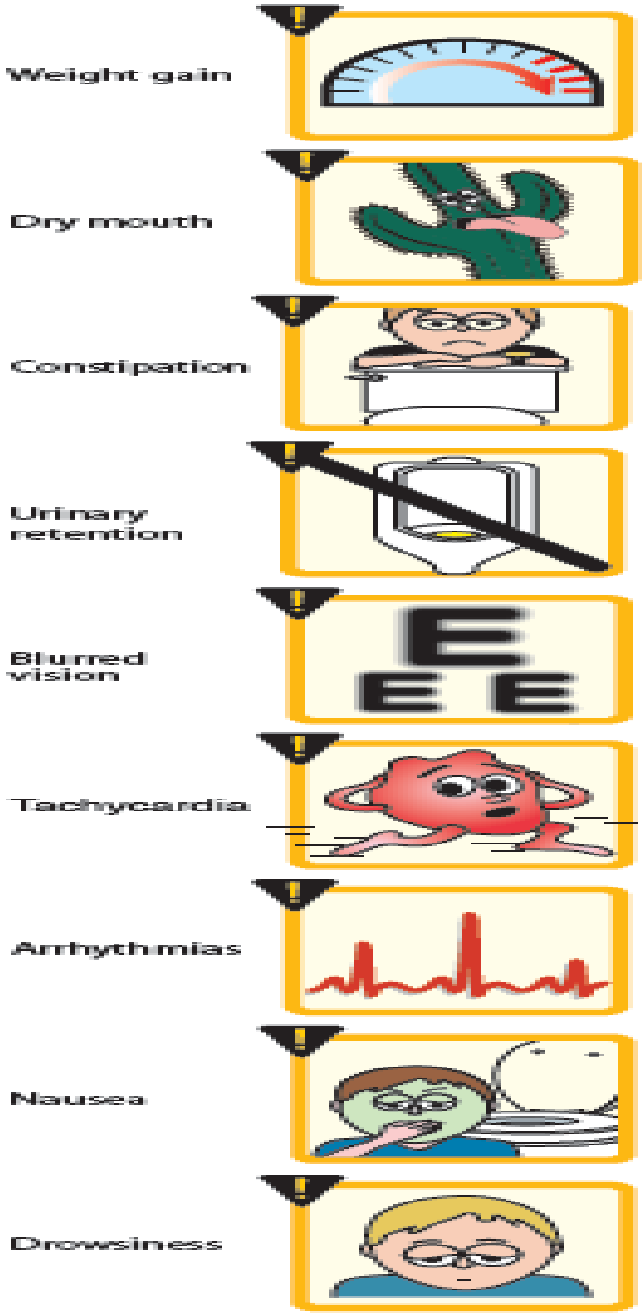


Figure 12.7
Some commonly observed adverse effects of tricyclic antidepressants.

Precautions :

The TCAs have a narrow therapeutic index (for example, five- to sixfold the maximal daily dose of *imipramine can be lethal).*

Depressed patients who are suicidal should be given only limited quantities of these drugs and be monitored closely.

Drug interactions with the TCAs

The TCAs may exacerbate certain medical conditions, such as unstable angina, benign prostatic hyperplasia, epilepsy, and preexisting arrhythmias.

Caution should be exercised with their use in very young or very old patients as well.

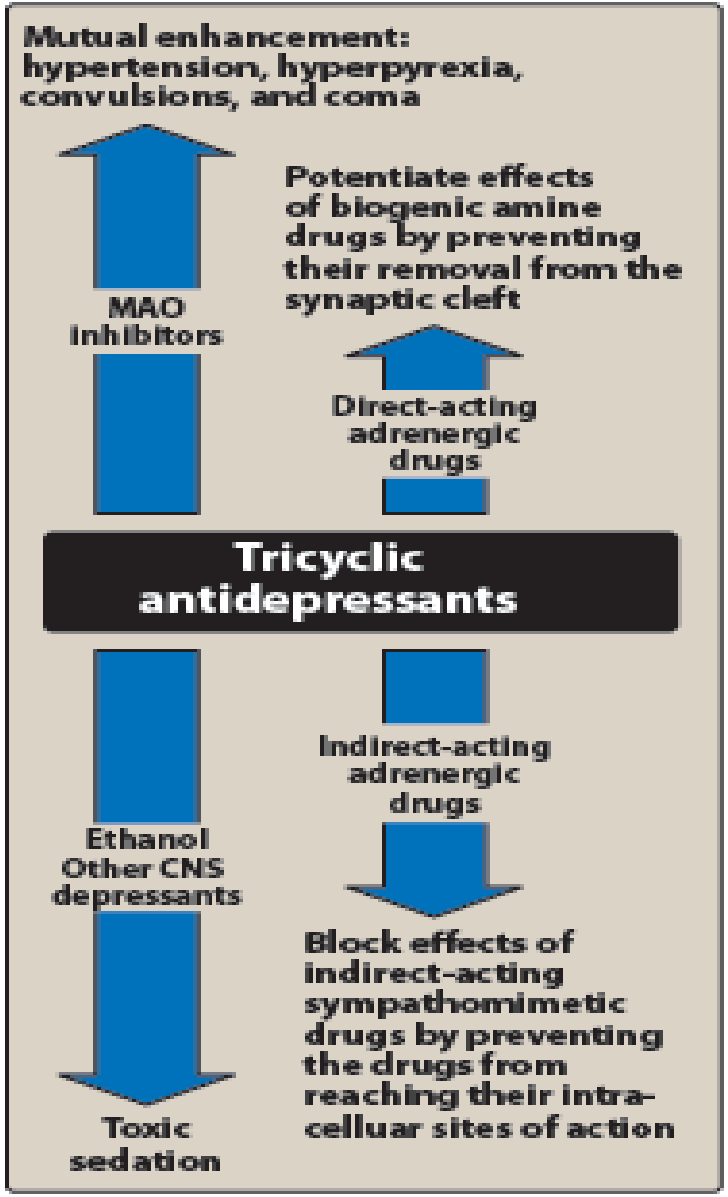


Figure 12.8

Drugs interacting with tricyclic antidepressants. CNS = central nervous system; MAO = mono-amine oxidase.

MONOAMINE OXIDASE INHIBITORS

Monoamine oxidase (MAO) is a mitochondrial enzyme found in nerve and other tissues, such as the gut and liver. In the neuron, MAO functions as a “safety valve” to oxidatively deaminate and inactivate any excess neurotransmitter molecules (norepinephrine, dopamine, and serotonin)

The MAO inhibitors (MAOIs) may irreversibly or reversibly inactivate the enzyme, permitting neurotransmitter molecules to escape degradation and, therefore, to both accumulate within the presynaptic neuron and leak into the synaptic space.

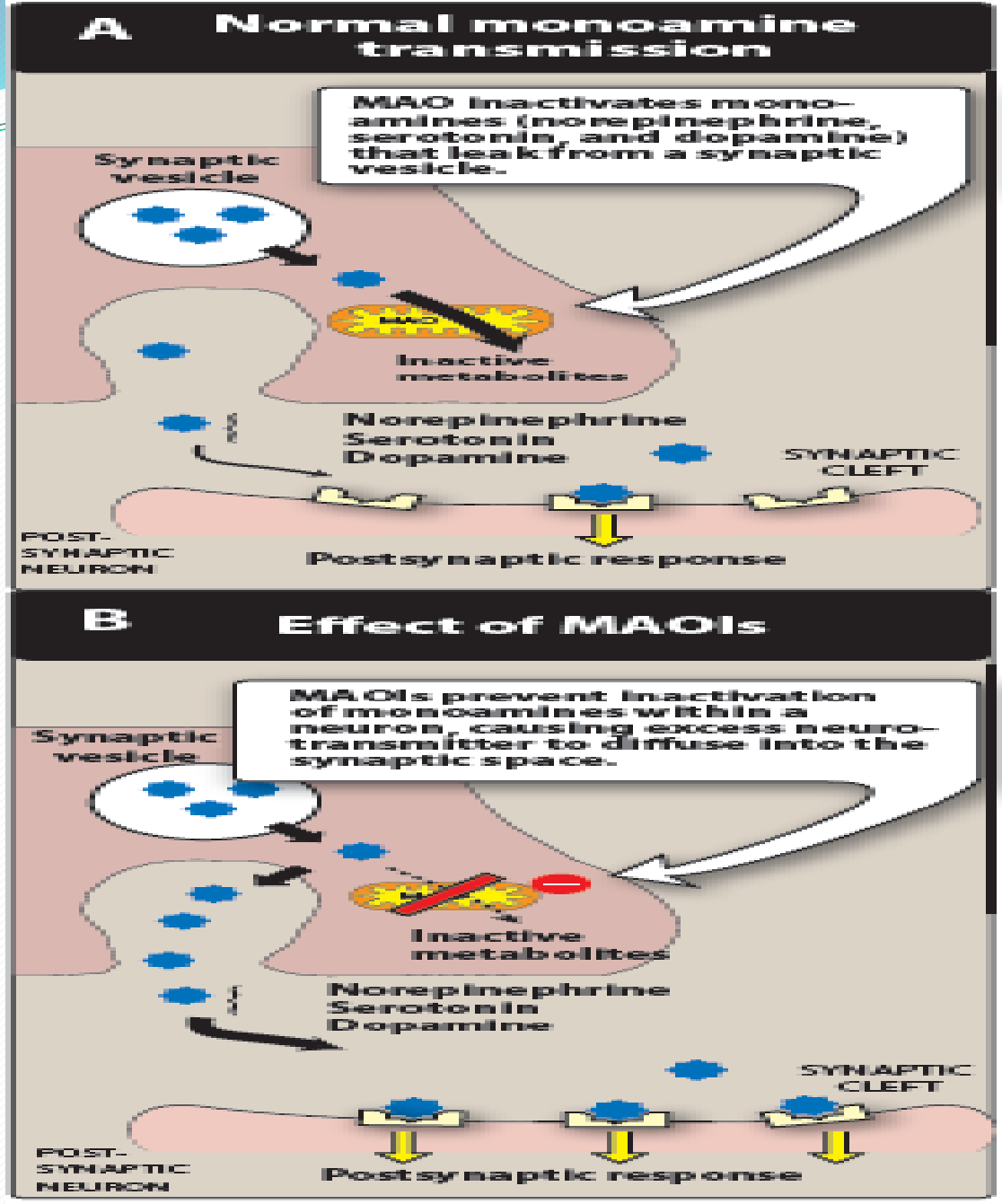


Figure 12.9
Mechanism of action of monoamine oxidase inhibitors (MAOIs).

Four MAO Is are currently available for treatment of depression:
Phenelzine ; tranylcypromine; isocarboxazid ; and

the agent that was prior-approved for Parkinson disease, but is now also approved for depression, *selegiline,*
which is the first antidepressant available in a transdermal delivery system.

Use of MAOIs is now limited due to the complicated dietary restrictions required of patients taking them.

Mechanism of action

Most MAOIs, such as *phenelzine, form stable complexes with the* enzyme, causing irreversible inactivation. This results in increased stores of norepinephrine, serotonin, and dopamine within the neuron and subsequent diff usion of excess neurotransmitter into the synaptic space .

These drugs inhibit not only MAO in the brain, but also MAO in the liver and gut that catalyze oxidative deamination of drugs and potentially toxic substances, such as tyramine, which is found in certain foods.

The MAOIs, therefore, show a high incidence of drug-drug and drug-food interactions.

Selegiline administered as the transdermal patch may produce less inhibition of gut and hepatic MAO at low doses because it avoids fi rst-pass metabolism.

Actions

Although MAO is fully inhibited after several days of treatment, the antidepressant action of the MAOIs, like that of the SSRIs and TCAs, is delayed several weeks.

*Selegiline and tranylcypromine have an amphetamine-*like stimulant effect that may produce agitation or insomnia.

Therapeutic uses

The MAOIs are indicated for depressed patients who are unresponsive or allergic to TCAs or who experience strong anxiety.

Because of their risk for drug-drug and drug-food interactions, the MAOIs are considered to be last-line agents in many treatment venues.

Pharmacokinetics

These drugs are well absorbed after oral administration, but antidepressant effects require at least 2 to 4 weeks of treatment.

Enzyme regeneration, when irreversibly inactivated, varies, but it usually occurs several weeks after termination of the drug.

Thus, when switching antidepressant agents, a minimum of 2 weeks of delay must be allowed after termination of MAOI therapy and the initiation of another antidepressant from any other class.

MAOIs are metabolized and excreted rapidly in urine.

Adverse eff ects

Severe and often unpredictable side eff ects, due to drug-food and drug-drug interactions, limit the widespread use of MAOIs.

Tyramine, which is contained in certain foods, such as aged cheeses and meats, chicken liver, pickled or smoked fish (such as anchovies or herring), and red wines, is normally inactivated by MAO in the gut.

Individuals receiving a MAOI are unable to degrade tyramine obtained from the diet. Tyramine causes the release of large amounts of stored catecholamines from nerve terminals, resulting in what is termed a "hypertensive crisis," with signs and symptoms such as occipital headache, stiff neck, tachycardia, nausea, hypertension, cardiac arrhythmias, seizures, and, possibly, stroke.

Patients must, therefore, be educated to avoid tyramine-containing foods. *Phentolamine and prazosin* are helpful in the management of tyramine-induced hypertension.

Other possible side effects of treatment with MAOIs include drowsiness, orthostatic hypotension, blurred vision, dry mouth, dysuria, and constipation.

MAOIs and SSRIs should not be coadministered due to the risk of the life-threatening "serotonin syndrome."

Both types of drugs require washout periods of at least 2 weeks before the other type is administered, with the exception of *fluoxetine, which should be discontinued at least 6 weeks* before a MAOI is initiated.

Combination of MAOIs and *bupropion can* produce seizures.

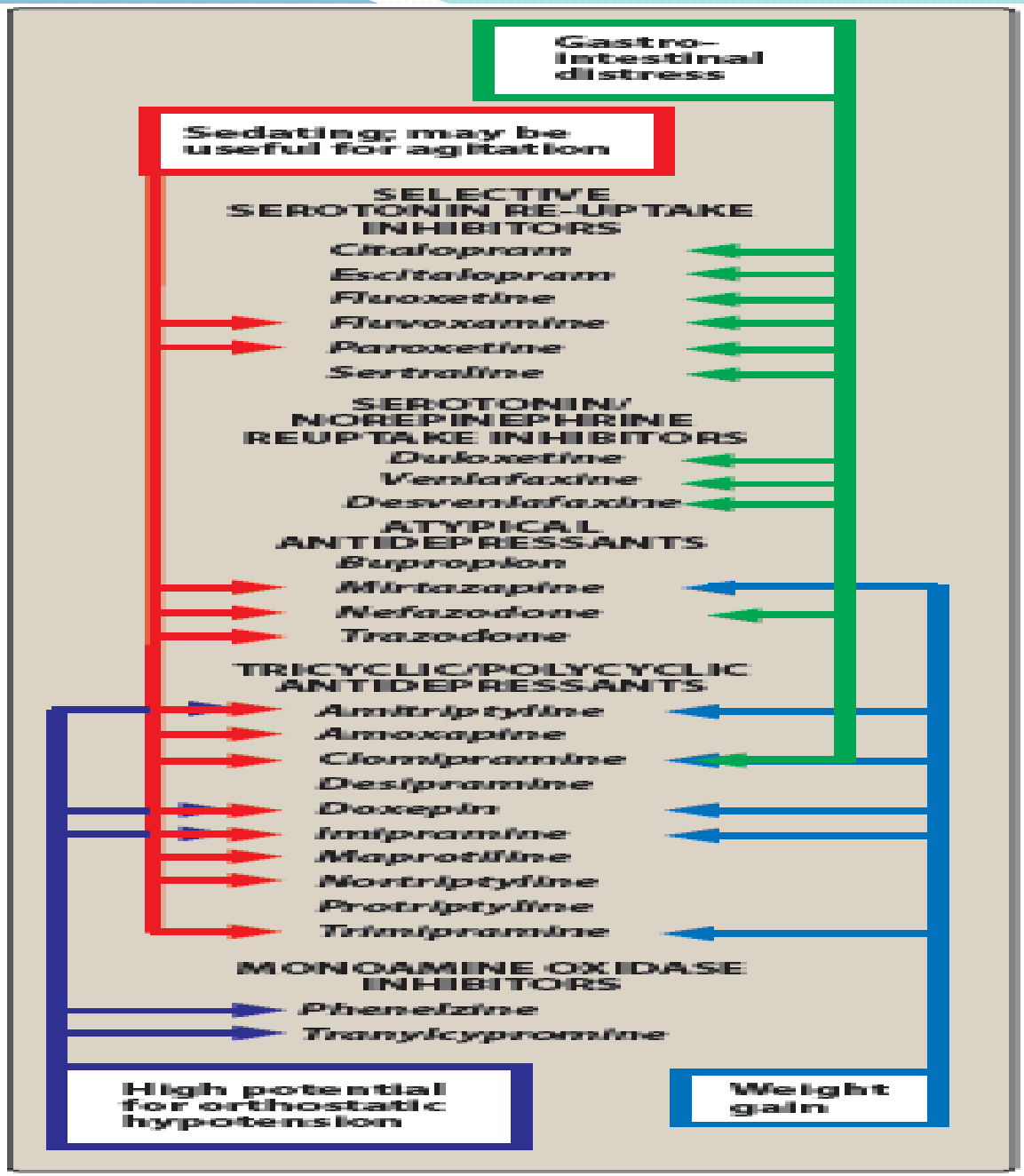


Figure 12.10
Side effects of some drugs used to treat depression.