33 Drugs Used in Mood Disorders

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DRUG LIST

The most common mood disorders are major depression (unipolar depression) and manic-depressive illness (bipolar disorder). Major depression is a common disorder that continues to result in considerable morbidity and mortality despite major advances in treatment. Approximately 1 in 10 Americans will be depressed during their lifetime. Of the 40,000 suicides occurring in the United States each year, 70% can be accounted for by depression. Antidepressants are now the mainstay of treatment for this potentially lethal disorder, with patients showing some response to treatment 65 to 80% of the time.

Both major depression and manic-depressive disorders are characterized by exaggerated mood associated with physiological, cognitive, and psychomotor disturbances. Major depression generally presents as depressed mood, diminished interest in normal activities, anorexia with significant weight loss, insomnia, fatigue, and inability to concentrate. By contrast, manic episodes associated with manic-depressive illness are characterized by expansive mood, grandiosity, inflated self-esteem, pressured speech, flight of ideas, and poverty of sleep. While each condition is a diagnostic entity unto itself, it can also be secondary to specific

medical problems (e.g. hypothyroidism), neurological disease (e.g., Parkinson's disease), and chronic administration of specific medications (e.g., antihypertensives). Attempting to rule out an underlying medical cause for the mood disturbance is essential before additional treatment is initiated.

This chapter covers the basic and clinical pharmacology of each class of agents demonstrating efficacy in the treatment of major depression and manic-depressive illness. The distinguishing features among agents for the treatment of each illness are their side effect profiles and relative toxicity. Physicians should understand both the appropriate agent for the treatment of specific mood disorders and pharmacological factors that allow for the individualization of medication to meet the patient's needs. A list of drugs and their half-lives are shown in Table 33.1.

TABLE 33.1 Half-Lives of Antidepressant Drugs

Drug (trade name)	Half-life (hr)
Heterocyclics	
Amitriptyline (Elavil)	16–26
Nortriptyline (Pamelor)	19–45
Imipramine (Tofranil)	11–25
Desipramine (Norpramin)	20–25
Protriptyline (Vivactil)	67–89
Trimipramine (Surmontil)	8
Doxepin (Sinequan)	11–23
Maprotiline (Ludiomil)	27–58
Amoxapine (Asendin)	8
SSRIs	
Fluoxetine (Prozac)	168–216[a]
Sertraline (Zoloft)	25
Paroxetine (Paxil)	21
Citalopram (Celexa)	35
MAOIs	
Phenelzine (Nardil)	1.5–4.0
Tranylcypromine (Parnate)	1.5–3.5
Isocarboxazid (Marplan)	–4
Miscellaneous agents	
Trazodone (Desyrel)	5–9
Bupropion (Wellbutrin SR)	21[a]
Nefazodone (Serzone)	18[a]
Venlafaxine (Effexor XR)	11[a]
Mirtazapine (Remeron)	30

SSRI, selective serotonin reuptake inhibitor; MAOI, monoamine oxidase inhibitor.
[a]Parent compound and active metabolite.

TREATMENT OF MAJOR DEPRESSION

It is often surprising for the student to learn that mood-elevating agents do not act as stimulants of the central nervous system (CNS). With the exception of varying degrees of sedation, the antidepressants have little effect on behavior early in treatment. During this period patients will, however, have side effects specific to the class and agent being used. Only after 2 to 3 weeks of dosing will a therapeutic benefit on depression emerge. At this point the patient begins to demonstrate elevation in mood and self-esteem. In addition, many of the vegetative signs of the illness (e.g., insomnia, anorexia) abate, and the patient regains an interest in daily activities. Failure to continue the medication, however, will result in an immediate relapse into the depressive state. Therefore, maintenance therapy must be continued for at least 6 months.

The Selective Serotonin Reuptake Inhibitors

In 1987, the FDA approved the drug fluoxetine (*Prozac*) for use in the treatment of major depression. Fluoxetine belongs to a class of agents referred to as *selective serotonin reuptake inhibitors* (SSRIs). The SSRIs now include sertraline (*Zoloft*), fluvoxamine (*Luvox*), paroxetine (*Paxil*), and citalopram (*Celexa*). Fluvoxamine is approved for use only in obsessive-compulsive disorder and is not discussed in this chapter.

With the introduction of the SSRIs, the safety and tolerability of antidepressants improved remarkably. As a class, these medications have little or no affinity for cholinergic, β-adrenergic or histamine receptors and do not interfere with cardiac conduction. They are well tolerated by patients with heart disease and by the elderly, who are especially sensitive to the anticholinergic and orthostatic effects of the tricyclic antidepressant agents (TCAs) and monoamine oxidase inhibitors (MAOIs).

The high degree of selectivity of SSRIs for the nerve terminal serotonin reuptake system has supported the hypothesis that these agents produce their therapeutic action through an ability to modulate serotonin neurotransmission in the brain. Chronic studies in animals have provided evidence for a cascade of altered synaptic events, beginning with inhibition of 5-hydroxytryptamine (5-HT) neuronal reuptake (Fig. 33.1). Increased 5-HT levels activate 5-HT_{1A} autoreceptors and result in a decrease in neuronal firing. Desensitization of this receptor results in enhanced serotonin release. The terminal 5-HT_{1B} autoreceptors normally inhibiting release of serotonin also become desensitized. These events, triggered by a sustained inhibition of the nerve terminal serotonin reuptake system, ultimately cause a potentiation of serotonin neurotransmission at central synaptic

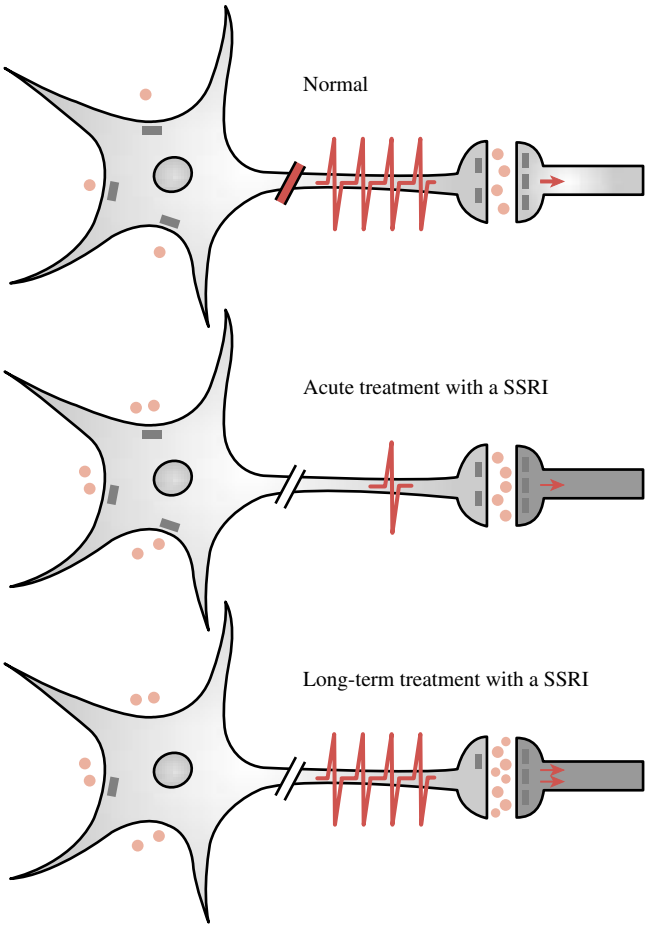

FIGURE 33.1
5-HT neurons depicting the impact of an SSRI on 5-HT neurotransmission. The cell bodies of 5-HT neurons are in the brainstem and give rise to 5-HT projections reaching all brain structures. The rectangles on the cell bodies of 5-HT neurons represent the 5-HT_{1A} autoreceptors, and the ones on the terminals represent the 5-HT_{1B} autoreceptors; their disappearance after long-term treatment is meant to illustrate their desensitization. The rectangles on the postsynaptic neurons represent 5-HT_{1A} receptors in the hippocampus that do not desensitize after long-term treatment. The number of zigzags on the axons and dots represent the firing frequency of the 5-HT neurons and the level of synaptic 5-HT, respectively. (Reprinted with permission from Blier P and Ward H. CNS Spectrum 2002;7:148–153.)

sites. The development of these synaptic events shares the time frame of the delayed appearance of the therapeutic benefit of these agents in depression.

With initiation of therapy with an SSRI, some patients describe anxiety or agitation. This can usually be overcome by reducing the dose and titrating upward more slowly. Insomnia can be a persistent activating side effect that can limit therapy or require the addition of a sedating agent at bedtime. Nausea and loose stools are a frequent side effect and may be lessened by taking the medication with food. As many as one-third of patients taking SSRIs may complain of sexual dysfunction, including decreased libido, delayed ejaculation, and anorgasmia. The SSRIs tend to be weight neutral with the exception of paroxetine (*Paxil*), which is associated with weight gain. No correlation has been made between plasma levels of the SSRIs and efficacy.

Fluoxetine

Fluoxetine (*Prozac*) is given in the morning because of its potential for being activating and causing insomnia. Food does not affect its systemic bioavailability and may actually lessen the nausea reported by some patients. Fluoxetine is highly bound to serum proteins and may interact with other highly protein bound drugs. It is demethylated in the liver to form an active metabolite, norfluoxetine. Inactive metabolites are excreted by the kidney. Doses must be reduced in patients with liver disease.

The slow elimination of fluoxetine and norfluoxetine lead to special clinical concerns when adjusting doses and discontinuing this medication. Steady state is not reached until 4 to 6 weeks, and similarly, complete elimination takes 4 to 6 weeks after discontinuation of the medication. A 4- to 6-week waiting period should be permitted before starting a medication with potential for an interaction with fluoxetine, such as a monoamine oxidase inhibitor (MAOI). Additionally, fluoxetine is a potent inhibitor of cytochrome P450 2D6 and can significantly elevate levels of drugs metabolized by this route. Thus, coadministration of drugs with a narrow therapeutic index, such as TCAs and type 1C antiarrhythmics, including flecainide and propafenone, are a particular concern.

Sertraline

Sertraline (*Zoloft*) has an elimination half-life of 25 hours and can be administered once a day, usually in the morning to avoid insomnia. Sertraline undergoes extensive hepatic metabolism, and doses must be reduced in patients with liver disease. Sertraline may produce more gastrointestinal side effects, such as nausea and diarrhea, than does fluoxetine and is generally thought to be less activating than fluoxetine. It is highly bound to serum proteins (98%) and may alter plasma protein binding of other medications. A 14-day washout period is recommended before starting a MAOI. Sertraline is a weak inhibitor of cytochrome P450 2D6. Intensive therapeutic drug monitoring is indicated when combining sertraline with drugs metabolized by this route that have a narrow therapeutic index, such as the TCAs and the type 1C antiarrhythmics propafenone, encainide, and flecainide.

Paroxetine

Paroxetine (*Paxil*) has an elimination half-life of 21 hours and is also highly bound to plasma proteins, so it requires special attention when administered with drugs such as warfarin. Paroxetine is a potent inhibitor of the cytochrome P450 2D6 isoenzyme and can raise the plasma levels of drugs metabolized via this route. Of particular concern are drugs with a narrow therapeutic index, such as TCAs and the type 1C antiarrhythmics flecainide, propafenone, and encainide. Additionally, paroxetine itself is metabolized by this enzyme and inhibits its own metabolism, leading to nonlinear kinetics. Weight gain is higher with paroxetine than with the other SSRIs, and it tends to be more sedating, presumably because of its potential anticholinergic effects. Additionally, patients have had difficulty with abrupt discontinuation with this agent, reporting a flulike syndrome; this symptom can be avoided by tapering the medication.

Citalopram

Citalopram (*Celexa*) has an elimination half-life of 35 hours and is 80% bound to plasma proteins. Of all of the SSRIs it has the least effect on the cytochrome P450 system and has the most favorable profile regarding drug–drug interactions.

Miscellaneous Antidepressants

Venlafaxine

Venlafaxine (*Effexor*) inhibits the reuptake of both serotonin and norepinephrine at their respective presynaptic sites. This drug does not have significant effects at muscarinic, histamine, or α-adrenergic receptors and therefore is devoid of many of the side effects associated with the TCAs. Venlafaxine and its active metabolite, *O*-desmethyl-venlafaxine, have half lives of 5 and 11 hours respectively, so dosing twice a day is necessary. However, an extended release preparation (*Effexor XR*) now allows for once-daily dosing and better tolerance. Venlafaxine has a side effect profile similar to that of the SSRIs (Table 33.2). Higher doses of venlafaxine result in modest increases in blood pressure in approximately 5% of patients. Venlafaxine has minimal effects on the cytochrome P450 enzyme system.

Bupropion

Bupropion (*Wellbutrin*) is a pharmacologically unique antidepressant, since it is a weak inhibitor of both dopamine and norepinephrine neuronal reuptake. However, its actual antidepressant activity is not well understood. Bupropion is generally well tolerated and does not block muscarinic, histaminergic, or adrenergic receptors. Unlike the SSRIs and venlafaxine, bupropion does not cause sexual side effects. However, it can cause CNS stimulation, including restlessness and insomnia. High doses of bupropion, given as its original formulation, were associated with a risk of seizures in 0.4% of patients. However, this risk is lower with slow-release bupropion (*Wellbutrin SR*). This formulation still requires dosing twice a day, and bupropion is contraindicated in patients with a history of seizures. Bupropion inhibits the cytochrome P450 2D6 isoenzyme and may elevate blood levels of drugs metabolized by this route.

Mirtazapine

Mirtazapine (*Remeron*) enhances both serotonergic and noradrenergic neurotransmission. By blocking presynaptic α_2-adrenoceptors, mirtazapine causes release of norepinephrine. Indirectly, through noradrenergic modulation of serotonin systems, mirtazapine also causes increased release of serotonin. It is an antagonist

TABLE 33.2 Common Side Effects of Therapeutic Doses of Antidepressants

Agent	Sedation	Anticholinergic	Orthostasis	Weight Gain	Sexual Dysfunction
SSRIs	+/−	0	0	+/−	+++
TCAs	+ + +	+ + +	+ + +	++	++
Miscellaneous					
Trazodone	+++	0	++	++	+[a]
Bupropion	0	0	0	0	0
Nefazodone	++	0	0	0	0
Venlafaxine	+/-	0	0[b]	0	++
Mirtazapine	++	0	0	++	0
MAOIs	0	+	+++	++	+

TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; MAOI, monoamine oxidase inhibitor.
0, no effect; +, + +, +++ indicate increasing effect.
[a]Priapism.
[b]Venlafaxine can cause a dose-dependent increase in blood pressure.

at the 5-HT_{2A}, $5HT_{2C}$, 5-HT_3, and histamine receptors but has minimal affinity for muscarinic or α_1-receptors. Mirtazapine does not inhibit neuronal reuptake of serotonin or norepinephrine. Weight gain and sedation are common side effects (Table 33.2); sedation necessitates dosing at bedtime. Mirtazapine does not have significant effects on cytochrome P450 isoenzymes.

Trazodone

Trazodone (*Desyrel*) was introduced in the early 1980s as a second-generation antidepressant. It blocks the neuronal reuptake of serotonin and is an antagonist at the $5HT_2$-receptor. Also, its major metabolite, *m*-chlorophenylpiperazine (mCPP), is a postsynaptic serotonin receptor agonist. When compared to the TCAs, trazodone is relatively free of antimuscarinic side effects, but it does block the α-adrenoceptor. Common side effects include marked sedation, dizziness, orthostatic hypotension, and nausea (Table 33.2). Priapism is an uncommon but serious side effect requiring surgical intervention in one-third of the cases reported. Because of trazodone's sedating quality, it is often used in low doses to counter the insomnia associated with the newer antidepressants, such as the SSRIs.

Nefazodone

Although nefazodone (*Serzone*) is structurally related to trazodone, it is less sedating. It does not block α_1-adrenoreceptors, and its use is not associated with priapism. Nefazodone inhibits the neuronal reuptake of serotonin and blocks $5HT_{2A}$ receptors. Its short half-life requires dosing twice a day (Table 33.1). Nefazodone is not associated with weight gain or sexual dysfunction. It inhibits the cytochrome P450 3A4 isoenzyme that is responsible for 50% of known oxidative metabolism, and therefore, nefazodone can elevate levels of drugs dependent on this pathway for metabolism.

Tricyclic Antidepressants

In the late 1950s, imipramine was noted to be effective for the symptomatic treatment of depression. A number of chemical congeners of imipramine have been synthesized and tested for antidepressant properties; they are collectively known as TCAs. The TCAs are no longer considered first-line agents in the treatment of depression because of their prominent side effects and the need to monitor drug blood levels to avoid toxicity.

Seven TCA drugs are available in the United States for treatment of major depression. They are generally categorized as tertiary or secondary amines. Tertiary amines include imipramine (*Tofranil*), amitriptyline (*Elavil*), trimipramine (*Surmontil*), and doxepin (*Sinequan*). Desipramine (*Norpramin*), nortriptyline (*Pamelor*), and protriptyline (*Vivactil*) are secondary amines. Clomipramine (*Anafranil*) also a member of the tricyclic family, possesses similar pharmacology and antidepressant efficacy. This agent, however, has Food and Drug (FDA) approval only for use in the treatment of obsessive-compulsive disorder and is not included in this discussion of antidepressant drugs.

Maprotiline (*Ludiomil*) and amoxapine (*Asendin*) are heterocyclic antidepressant agents that are not members of the tricyclic family. However, their pharmacology is so similar to that of the tricyclic amines that they are included for discussion purposes with this class of agents. Desipramine and nortriptyline are major metabolites of imipramine and amitriptyline, respectively.

Mechanism of Action

The precise molecular mechanism responsible for the antidepressant action of the TCA drugs is unknown, although a number of hypotheses have been generated. Many of these involve alterations in neurotransmission of norepinephrine or serotonin or both.

β-Adrenoceptor down-regulation at central noradrenergic synapses is one popular theory used to explain the antidepressant properties of TCA drugs and other antidepressants. This theory focuses on a cascade of adaptive changes at the noradrenergic synapse that appears to be triggered by inhibition of norepinephrine neuronal reuptake by TCA drugs (Fig. 33.2). Subsensitivity in the β-adrenoceptor–coupled adenylyl cyclase system and associated reductions in β-adrenoceptor density appear to be common features of the antidepressants and of electroconvulsant treatment. Moreover, the time-dependent changes in β-adrenoceptor

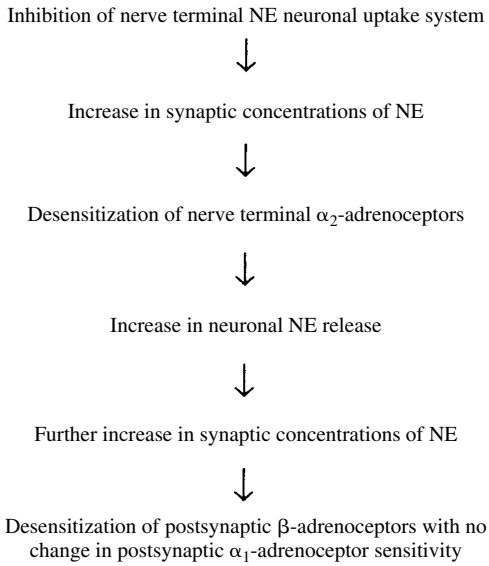

FIGURE 33.2
Cascade of adaptive changes occurring at norepinephrine (NE) synapses following chronic TCA drug treatment.

function parallel the time delay associated with clinical efficacy of these drugs (2–3 weeks). These latter findings have added to the attractiveness of this theory. However, at noradrenergic synapses with multiple adrenoceptors (i.e., α_1-, α_2-, and β-adrenoceptors), synaptic transmission through α_1-adrenoceptors will likely be enhanced at the same time that synaptic transmission through α_2- and β-adrenoceptors is reduced (Figure 33.3).

While much emphasis has been placed on alterations in noradrenergic neurotransmission, TCA drugs are not without effect on serotonin (5-HT) neurotransmission. Long-term studies with TCA drugs in animals have demonstrated postsynaptic supersensitivity to serotonin (5-HT_{1A}) receptor agonists at serotonin synapses, with an associated enhancement of serotonergic neurotransmission. The sensitization to 5-HT_{1A} agonists is mediated in part by an increase in the density of postsynaptic 5-HT_{1A} receptors. Enhancement of transmission through 5-HT_{1A} receptors appears to be a common phenomenon after chronic administration of all clinically effective antidepressants and electroconvulsive treatment. The occurrence of this 5-HT_{1A} supersensitivity parallels the delayed onset of the therapeutic actions of these agents (2–3 weeks). These observations lend strong support to the hypothesis that enhanced serotonergic neurotransmission is required for the therapeutic benefit from TCA drugs.

It is likely that TCA drugs produce their therapeutic benefits by acting at both serotonin and norepinephrine synapses. The literature also supports the notion of an interdependence of these two monoamine systems in the treatment of depression. The time-dependent changes in the flow of synaptic information through individual receptor subtypes within the norepinephrine and serotonin synapses following chronic TCA administration are summarized in Figure 33.3.

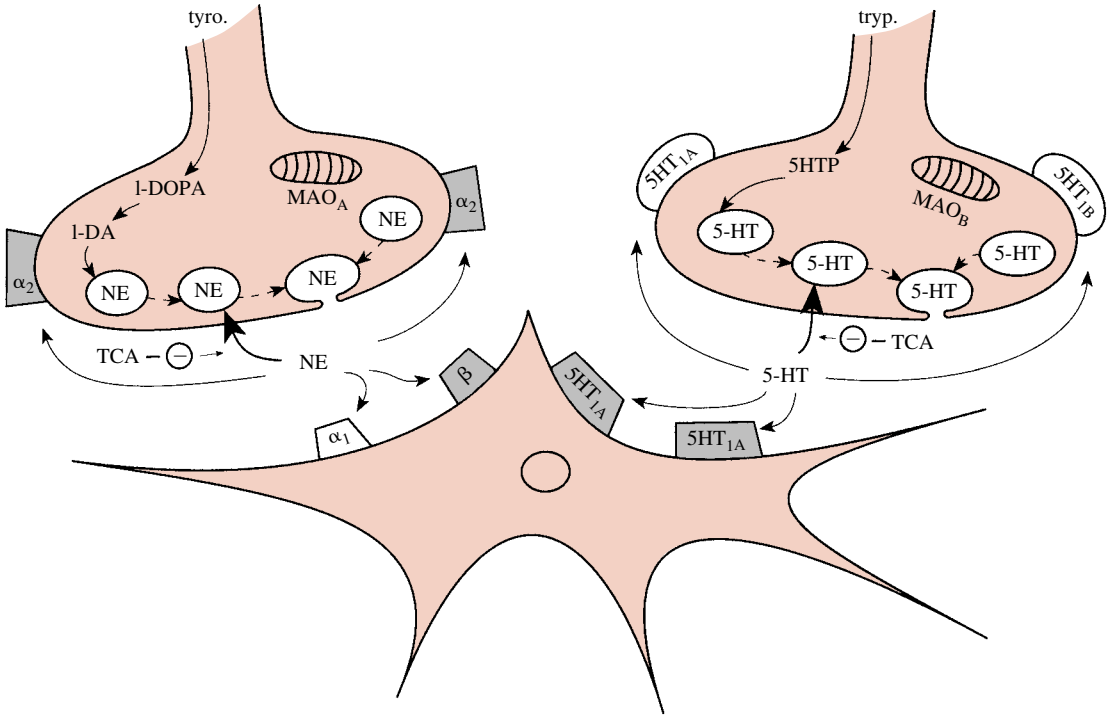

FIGURE 33.3
Flow of information through receptor subtypes at norepinephrine and serotonin synapses following chronic TCA drug administration. A cascade of events leads to altered receptor-mediated physiology of the norepinephrine (NE) and serotonin (5-HT) synapses of the brain following long-term TCA drug administration. The adaptive changes in synaptic physiology are triggered by selective inhibition of the NE and/or 5-HT neuronal reuptake systems. Responses at β- and α_2-adrenoceptors are depressed, whereas responses at 5-HT_{1A} receptors are enhanced. Responses at α_1-adrenoceptors and 5-HT_{1B} receptors remain unchanged. Accordingly, the postsynaptic flow of information at NE and 5-HT synapses will be reduced through β-adrenoceptors but enhanced through 5-HT_{1A} receptors. Although the responsiveness of α_1-adrenoceptors remains unchanged, it is likely that transmission through these postsynaptic sites will be enhanced. In this regard, desensitization of α_2-adrenoceptors will provide greater concentrations of synaptic NE to activate normosensitive postsynaptic α_1-adrenoceptors.

Pharmacokinetics

The TCA drugs are well absorbed from the gastrointestinal tract, are extremely lipid soluble, and bind extensively to plasma proteins. Their half-lives range from 8 to 89 hours (Table 33.1). Several days to weeks are required both to achieve steady-state serum levels and for complete elimination of these agents from the body. Long half-lives make most of these agents amenable to dosing once a day, generally at bedtime.

Drug inactivation generally occurs through oxidative metabolism by hepatic microsomal enzymes. Tertiary amines are converted to secondary amines, which generally possess biological activity and are frequently in serum at levels equal to or greater than that of the parent tertiary amine. A second route of inactivation includes conjugation of hydroxylated metabolites with glucuronic acid.

Adverse Effects

The TCA drugs have lost their place as first-line therapy for depression because of their bothersome side effects (Table 33.2) at therapeutic doses and lethal effects in toxic doses. In addition to their presynaptic effects on the neuronal uptake of norepinephrine and serotonin, they block several postsynaptic receptors. They are potent cholinergic muscarinic receptor antagonists, resulting in symptoms such as dry mouth, constipation, tachycardia, blurred vision and urinary retention. Blockade of histamine receptors (H_1) often results in sedation and weight gain. Antagonism of α_1-adrenoceptors in the vasculature can cause orthostatic hypotension.

TCA drugs have potent membrane-stabilizing properties similar to those of quinidine. Conduction is slowed throughout the heart, and serious ventricular arrhythmias may develop in patients with preexisting conduction abnormalities at therapeutic doses and in all patients at toxic doses. At therapeutic doses, the TCA drugs lower the seizure threshold and at toxic doses can cause life-threatening seizures. Maprotiline has a greater potential for reducing the seizure threshold and should not be used in patients with a seizure disorder. Amoxapine has dopamine receptor antagonist properties (see Chapter 31) and can induce extrapyramidal side effects, gynecomastia, lactation, and neuroleptic malignant syndrome. To increase tolerance to the anticholinergic and orthostatic effects of the TCA drugs, the dose is usually titrated with increasing increments over the first few weeks of therapy.

Drug Interactions

Multiple drug interactions can occur with the TCA drugs. Because of their high degree of binding to plasma proteins, competition for binding sites can exist between TCAs and phenytoin, aspirin, phenothiazines, and other agents that also display avid plasma protein-binding characteristics. Elevation in the serum level of TCAs (with corresponding toxicity) can occur following the administration of one of these second drugs. Elevations in the serum TCA level also can occur following inhibition of hepatic TCA metabolism by antipsychotics, methylphenidate, oral contraceptives, and some SSRIs.

Tricyclic antidepressant drugs can prevent the action of antihypertensive drugs, such as guanethidine and clonidine. This antagonistic action is related to the primary (inhibition of neuronal reuptake) and secondary (adaptive changes) effects of TCA drugs at noradrenergic synapses. A more serious but rare interaction exists between TCA drugs and MAOIs. While both classes of drugs are effective in the treatment of major depression, simultaneous administration of a drug from each class can result in severe CNS toxicity (hyperpyrexia, convulsions, and coma). In TCA-resistant patients, it is advisable to discontinue the TCA drug for 2 to 3 weeks before initiation of a MAOI agent. Finally, TCA drugs potentiate the sedative effects of alcohol, and patients must be cautioned about this interaction.

Therapeutic Drug Monitoring

Safe and effective use of the TCA drugs requires monitoring of serum levels. The importance of this monitoring is based on the relatively narrow range between therapeutic and toxic doses (therapeutic index of 3) of each agent. While annoying side effects (sedation, dry mouth, constipation) begin to occur at subtherapeutic serum concentrations, life-threatening cardiac and CNS effects develop in a dose dependent fashion above serum levels of 500 ng/mL. The metabolism and elimination rates vary 10- to 30-fold among individuals taking TCA drugs. For this reason, it is estimated that only 50% of the patients receiving a standard dose of a TCA drug would achieve an optimal therapeutic serum concentration. Of additional concern, 3 to 5% of patients will be deficient in hepatic enzymes that metabolize the TCA drugs and may develop life-threatening serum levels on standard doses. Therefore, steady-state serum levels of TCA drugs (drawn 10 to 12 hours after the last dose) are monitored to avoid toxicity, monitor compliance, and optimize the therapeutic response.

Monoamine Oxidase Inhibitors

Iproniazid, originally developed for the treatment of tuberculosis, exhibited mood-elevating properties during clinical trials in tuberculosis patients with depression. The distinguishing biochemical feature between iproniazid and other chemically similar antituberculosis compounds was the ability of the former to inhibit MAO. Thus, a series of hydrazine and non–hydrazine-related

MAOI agents was synthesized and tested for antidepressant properties. Three MAOI agents are approved in the United States for use in major depression: isocarboxazid (*Marplan*), phenelzine (*Nardil*), and tranylcypromine (*Parnate*).

The MAOIs are as effective as the heterocyclic antidepressants and the newer agents, such as the SSRIs. However, at least two forms of life-threatening toxicity (hepatotoxicity and dietary tyramine–induced hypertensive crisis) have been associated with their chronic use. For this reason, the MAOIs are not considered first-line agents in the treatment of depression. They are generally reserved for treatment of depressions that resist therapeutic trials of the newer, safer antidepressants. However, a new transdermal formulation of selegiline undergoing clinical trials demonstrates antidepressant efficacy without concerns of liver toxicity or dietary tyramine-induced hypertension.

Mechanism of Action

Monoamine oxidase exists in the human body in two molecular forms, known as type A and type B. Each of these isozymes has selective substrate and inhibitor characteristics. Neurotransmitter amines, such as norepinephrine and serotonin, are preferentially metabolized by MAO-A in the brain. MAO-B is more likely to be involved in the catabolism of human brain dopamine, although dopamine is also a substrate for MAO-A.

Isocarboxazid, phenelzine, and tranylcypromine are irreversible nonselective inhibitors of both MAO-A and MAO-B. However, it appears that inhibition of MAO-A, not MAO-B, is important to the antidepressant action of these agents.

Therapeutic efficacy by selective MAO-A inhibitors (such as clorgyline or moclobemide) in major depressions strongly suggests that MAO inhibition at central serotonin or norepinephrine synapses or both is responsible for the antidepressant properties of these agents. However, since complete MAO-A inhibition is achieved clinically within a few days of treatment, while the antidepressant effects of these drugs are not observed for 2 to 3 weeks, suggests that additional actions must be involved.

In a manner similar to that of the TCAs and SSRIs, MAOIs are known to induce adaptive changes in the CNS synaptic physiology over 2 to 3 weeks. These changes result in both down-regulation of synaptic transmission mediated through noradrenergic α- and β-adrenoceptors and up-regulation or enhancement of synaptic transmission at serotonin synapses ($5HT_{1A}$-receptors). This action on serotonin neurotransmission is the result of desensitized somatodendritic autoreceptors responsible for the regulation of the firing rate of serotonin-containing neurons of the forebrain. Accordingly, these neurons fire at elevated rates, releasing large quantities of serotonin into the synapse. This serotonin is protected from degradation by inhibition of synaptic MAO-A. It is believed that the development of these physiological changes at norepinephrine and serotonin synapses, which parallel the time delay associated with the antidepressant properties of the MAOIs, is the mechanism of action for these agents in the treatment of major depression.

Adverse Effects

The potential for toxicity that is associated with the administration of the MAOIs restricts their use in major depression. Hepatotoxicity is likely to occur with isocarboxazid or phenelzine, since hydrazine compounds can cause damage to hepatic parenchymal cells. This is true particularly for patients identified as slow acetylators (see Chapter 4) of hydrazine compounds. Fortunately, the incidence of hepatotoxicity is low with the available agents.

A greater concern is the potentially lethal cardiovascular effects that can occur in patients who do not comply with their dietary restrictions. Patients who take a MAOI should not eat food rich in tyramine or other biologically active amines. Normally, these amines are rapidly metabolized by MAO-A during gastric absorption by the mucosal cells of the intestinal wall and by MAO-A and MAO-B during passage through the liver parenchyma. If both isozymes of MAO are inhibited, elevated circulating levels of tyramine will be free to interact with the sympathetic noradrenergic nerve terminals innervating cardiac and vascular smooth muscle tissue to produce a pressor effect (see Chapter 10). In these conditions, tyramine can cause an acute elevation in blood pressure, sometimes leading to a hypertensive crisis. Cheeses, wine, and a whole host of other foods rich in tyramine must be avoided. A number of other bothersome side effects, such as tremors, orthostatic hypotension, ejaculatory delay, dry mouth, fatigue, and weight gain, are common at therapeutic doses of MAOIs (Table 33.2).

Drug Interactions

Serious hypertension can occur with concomitant administration of over-the-counter cough and cold medications containing sympathomimetic amines. When switching from a MAOI to another antidepressant, such as a SSRI, a drug-free period of 2 weeks is required to allow for the regeneration of tissue MAO and elimination of the MAOI. When switching from an antidepressant, such as an SSRI, to a MAOI, sufficient time should be allowed for the SSRI to be cleared from the body (at least 5 half-lives) before starting the MAOI. Special note should be taken of fluoxetine's long half-life, requiring at least 5 weeks after discontinuation of fluoxetine at a 20-mg dose and longer at higher doses, before

initiation of MAOI therapy. Coadministration of a MAOI and an SSRI or venlafaxine can overstimulate the serotonin receptors in the brainstem and spinal cord (serotonin syndrome), which can be lethal. Serotonin syndrome consists of a constellation of psychiatric, neurological, and cardiovascular symptoms that may include confusion, elevated or dysphoric mood, tremor, myoclonus, incoordination, hyperthermia, and cardiovascular collapse.

TREATMENT OF MANIC-DEPRESSIVE ILLNESS

Lithium

For more than 40 years, Li^+ has been used to treat mania. While it is relatively inert in individuals without a mood disorder, lithium carbonate is effective in 60 to 80% of all acute manic episodes within 5 to 21 days of beginning treatment. Because of its delayed onset of action in the manic patient, Li^+ is often used in conjunction with low doses of high-potency anxiolytics (e.g., lorazepam) and antipsychotics (e.g. haloperidol) to stabilize the behavior of the patient. Over time, increased therapeutic responses to Li^+ allow for a gradual reduction in the amount of anxiolytic or neuroleptic required, so that eventually Li^+ is the sole agent used to maintain control of the mood disturbance.

In addition to its acute actions, Li^+ can reduce the frequency of manic or depressive episodes in the bipolar patient and therefore is considered a mood-stabilizing agent. Accordingly, patients with bipolar disorder are often maintained on low stabilizing doses of Li^+ indefinitely as a prophylaxis to future mood disturbances. Antidepressant medications are required in addition to Li^+ for the treatment of breakthrough depression.

Mechanism of Action

Lithium is a monovalent cation that can replace Na^+ in some biological processes. It can be argued that competition by Li^+ for active Na^+ sites may lead to altered neuronal functions that may account for its antimanic and mood-stabilizing actions. In this regard, the failure of Li^+ to maintain a normal membrane potential because of its lower affinity for the Na^+ pump has been demonstrated. However, this action of Li^+ would not explain its relatively selective effects on the CNS, sparing comparable excitable tissues (e.g. cardiac muscle) in the periphery. Moreover, an action on membrane polarity would be so general that the entire pool of brain neurons would be affected by Li^+. It seems more reasonable that Li^+ produces its psychotropic actions by perturbation of molecular events common to a few CNS synapses that might have been disturbed during the course of the manic-depressive illness.

Recently, attention has focused on the actions of Li^+ on receptor-mediated second-messenger signaling systems of the brain. In this regard, interactions between Li^+ and guanine nucleotide (GTP) binding proteins (G proteins) have been the target of many studies, since G proteins play a pivotal role in the function of many second-messenger signaling systems. Lithium is capable of altering G-protein function. It can diminish the coupling between the receptor recognition site and the G protein. The molecular mechanism involves the competition for Mg^{++} sites on the G protein, which are essential for GTP binding. Guanine nucleotide activates the G protein. Accordingly, in the presence of Li^+, receptor-mediated activation of these G proteins is attenuated. This action of Li^+ has been selectively demonstrated for G proteins associated with β-adrenoceptors and M_1 muscarinic receptors of the CNS (Fig. 33.4).

While it is not possible at present to assign a therapeutic role to this action of Li^+, it is a step toward explaining the stabilizing actions of this drug. Since several neurotransmitter receptors share common G protein–regulated second-messenger signaling systems, Li^+ could simultaneously correct the alterations at individual synapses associated with depression and mania by a single action on the function of specific G proteins.

An additional action of Li^+ is interruption of the phosphatidylinositide cycle through an inhibitory action on inositol phosphate metabolism. By this mechanism, depletion of membrane inositol and the phosphoinositide-derived second-messenger products diacylglycerol and inositol triphosphate ultimately reduces signaling through receptor systems dependent on the formation of these products. It is presently unclear to what extent inhibition of inositol phosphate metabolism contributes to the therapeutic properties of Li^+ in bipolar patients.

Pharmacokinetics and Therapeutic Drug Monitoring

Lithium is readily absorbed from the gastrointestinal tract, reaching a peak plasma level in 2 to 4 hours. Distribution occurs throughout the extracellular fluid with no evidence of protein binding. Passage through the blood-brain barrier is limited, so that cerebrospinal fluid levels are 50% of plasma levels at steady state.

The elimination half-life of Li^+ is estimated at 24 hours, and more than 90% of the dose of Li^+ is excreted into the urine. Renal clearance, however, is only 20%, since Li^+ is actively reabsorbed in the proximal tubule at sites normally used for the conservation of Na^+. Thus, competition between Li^+ and Na^+ for uptake sites can alter the elimination of Li^+ and its concentration in total body water. Na^+ loading enhances Li^+ clearance, while Na^+ depletion promotes Li^+ retention. This important relationship explains the appearance of Li^+ toxicity (discussed later) associated with diet (low Na^+),

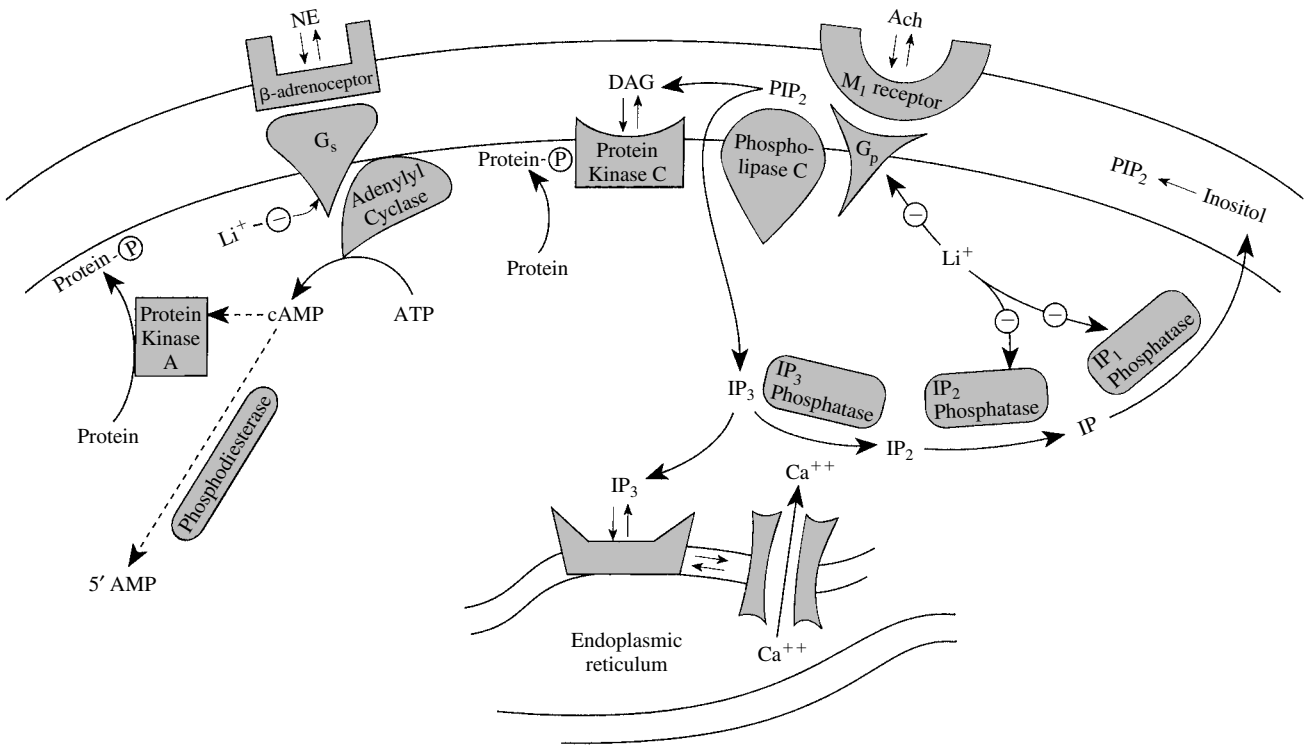

FIGURE 33.4
The actions of Li^+ on postsynaptic receptor-mediated second-messenger signaling systems. Lithium can simultaneously alter the flow of synaptic information through several receptor-mediated systems by diminishing coupling between the receptor recognition site and its specific G proteins. This model explains the stabilizing actions of Li^+ at both ends of the mood spectrum through a single action at the G-protein level. Attenuating actions of Li^+ have been demonstrated through G-protein interactions at the β-adrenoceptor and the acetylcholine M_1 muscarinic receptor systems of the CNS. A second action of Li^+ as an inhibitor of inositol diphosphate (IP_2) phosphatase may further attenuate the flow of synaptic information through the M_1 muscarinic receptor by the eventual depletion of membrane phosphatidyl inositol-bis-phosphate (PIP_2). IP_3, inositol triphosphate; DAG, diacylglycerol; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; 5′-AMP, 5′-adenosine monophosphate; NE, norepinephrine; ACh, acetylcholine.

drugs (diuretics), medical conditions (diarrhea), or physical activities (those that induce sweating) that deplete the body of Na^+.

The elimination rate of Li^+ from the body is variable. It is quite rapid during the first 10 hours after ingestion, and this period accounts for about 40% of the total Li^+ excretion. However, the remaining portion of the Li^+ dose is excreted very slowly over 14 days. Because of this biphasic elimination rate, clinically useful serum Li^+ concentrations are usually determined 12 hours after the last dose. This period assures a relatively accurate reflection of the Li^+ concentration, since it is beyond the most variable portion (rapid elimination phase) of the Li^+ elimination profile.

Adverse Effects

The frequency and severity of adverse reactions associated with Li^+ therapy are directly related to serum levels. Since Li^+ has a low therapeutic index (approximately 3) and a narrow therapeutic window (0.5–1.5 mEq/L), the frequent measurement of serum steady-state concentrations is standard practice in the treatment of bipolar patients.

Adverse reactions occurring at serum trough levels (12 hours after the last dose) below 1.5 mEq/L are generally mild, whereas those seen above 2.5 mEq/L are usually quite severe. Mild toxicity is usually expressed as nausea, vomiting, abdominal pain, diarrhea, polyuria, sedation, and fine tremor. If the serum concentration of Li^+ progressively rises above 2 mEq/L, frank neurological toxicity appears, beginning with mental confusion and progressing to hyperreflexia, gross tremor, dysarthria, focal neurological signs, seizures, progressive coma, and even death.

Adverse effects sometimes seen during chronic maintenance of bipolar patients with Li^+ include hypothyroidism (approximately 5%) and nephrogenic dia-

betes insipidus. Both conditions are readily reversible by discontinuation of Li^+. Routine laboratory monitoring includes TSH (thyroid-stimulating hormone) and serum creatinine measurements to detect hypothyroidism and any change in renal capacity to clear the drug.

Other Mood-Stabilizing Agents

Several anticonvulsant medications have mood-stabilizing properties. Valproic acid and carbamazepine are the best studied to date. In 1995, valproic acid was approved by the FDA for treatment of acute mania and is now considered a first-line agent. Other anticonvulsants under investigation include lamotrigine and topiramate, which are covered in Chapter 32. The atypical antipsychotic agent olanzapine received FDA approval in 2000 for use in acute mania and mixed episodes associated with bipolar disorder; it is covered in Chapter 34.

Study Questions

1. Which of the following antidepressants is most selective for inhibition of neuronal reuptake of serotonin?
(A) Mirtazapine (*Remeron*)
(B) Venlafaxine (*Effexor*)
(C) Bupropion (*Wellbutrin*)
(D) Sertraline (*Zoloft*)
(E) Imipramine (*Tofranil*)

2. In a patient with a seizure disorder, which antidepressant is contraindicated?
(A) Nefazodone (*Serzone*)
(B) Fluoxetine (*Prozac*)
(C) Venlafaxine (*Effexor*)
(D) Mirtazapine (*Remeron*)
(E) Bupropion (*Wellbutrin*)

3. Mr. Smith is 28 years old and has no active medical problems. He has been treated with Li^+ for manic-depressive illness for 1 year, and his mood has been stable. He now reports the gradual onset of fatigue, weight gain, and cold intolerance. Which single laboratory test is most likely to lead to the correct diagnosis?
(A) TSH (thyroid-stimulating hormone)
(B) Hepatic function panel
(C) Glucose tolerance test
(D) Hematocrit
(E) Serum prolactin level

4. Which of the following antidepressants requires therapeutic blood monitoring for safe use?
(A) Paroxetine (*Paxil*)
(B) Phenelzine (*Nardil*)
(C) Nortriptyline (*Pamelor*)
(D) Venlafaxine (*Effexor*)
(E) Bupropion (*Wellbutrin*)

5. Which of the following statements about antidepressant medications is most appropriate?
(A) They all have a delay of approximately 48 hours for onset of benefit.
(B) There are large differences in efficacy among individual agents.
(C) Some benefit is expected in 65 to 80% of patients treated with an antidepressant for major depression.
(D) The major contribution of the newer antidepressants lies in the marked improvement in duration of action.

ANSWERS

1. D. Mirtazapine acts at serotonin and adrenergic receptors and does not effect reuptake of neurotransmitters. Venlafaxine is a mixed serotonin–norepinephrine reuptake inhibitor. Bupropion inhibits norepinephrine and dopamine reuptake. Imipramine is a TCA with mixed serotonin and norepinephrine properties. Sertraline belongs to the class of antidepressants know as the SSRIs and selectively blocks neuronal reuptake of serotonin.

2. E. Nefazodone, fluoxetine, mirtazapine, and venlafaxine have minimal effects on seizure threshold. Bupropion in its original formulation caused seizures in 4 in 1000 patients. Although this has been reduced with the slow release form of the medication (*Wellbutrin SR*), it remains a contraindication to prescribe this medication to patients with a history of seizures.

3. A. Approximately 5% of patients taking lithium over the long term develop hypothyroidism, and thyroid status should be followed as routine care for these patients. Mr. Smith's symptoms are classic for hypothyroidism. Impairment in glucose metabolism, hepatic function, red blood cell production, and prolactin secretion are not typical complications of lithium therapy.

4. C. Nortriptyline (*Pamelor*) is a TCA, and as a class these drugs require at least one steady-state blood level to safely and effectively use the medication. Paroxetine, venlafaxine, and bupropion have not had blood levels correlated to response, and their relatively low toxicity does not require therapeutic blood monitoring. Nardil is a MAOI, which can be

lethal in overdose, but blood levels are not used to monitor for efficacy or toxicity.

5. **C.** All agents have a delay of approximately 48 hours. There are no significant differences in efficacy among the individual agents. The major contribution of the newer antidepressants is in their improved safety and tolerability.

SUPPLEMENTAL READING

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CASE Study Treatment of Depression

Mary Smith is a 46-year-old secretary who complains to her primary care physician mainly of fatigue. She reports having low energy over the past 2 months and finding it more and more difficult to maintain her home and work responsibilities. Although tired, she is unable to sleep through the night and awakens several times each night. Her appetite has been low and she has lost 10 pounds over this time. Her husband has noticed that she has lost interest in her hobbies and has withdrawn from their friends. He is concerned that she now has to bring office work home because her impaired attention and concentration make it impossible for her to complete her assignments during the workday. On this visit, Ms. Smith is neatly dressed, appropriate in conversation, but worried about why she has become unable to execute her tasks at work and enjoy her family and friends. She becomes tearful when describing this, feels guilty, and describes her mood as down. She expresses concern that she may not get better and has had thoughts of death but no actual plan or intent to end her life. She drinks no alcohol and doesn't use recreational drugs. She has no active medical problems and takes no prescription medications. Ms. Smith has one sister with a history of major depression, successfully treated with sertraline. Her mother was treated for depression with imipramine and phenelzine. Physical examination produces normal findings. Thyroid testing, blood counts, and blood chemistry are normal. Ms. Smith meets the DSM-IV criteria for major depression (depressed mood, loss of interest in pleasurable activities, decreased attention and concentration, fatigue, sleep disturbance, low appetite, weight loss, ideas of death). What pharmacological approach would you recommend?

ANSWER: Because of sertraline's favorable side effect profile and no need for dietary restrictions, it probably should be chosen over the older agents (TCAs and MAOIs). She should be warned about nausea and possibly loose stools, anorgasmia, and insomnia before she begins therapy. It also should be explained that the medication will take at least 2 weeks to begin working and that a complete trial of the medication to assess its efficacy will take 4 to 6 weeks. Since this is her first episode of depression, she should take the medication for 6 to 12 months after her symptoms have remitted before considering discontinuation of drug therapy.