OBJECTIVES

After studying this chapter, you will be able to
1. Describe major features of depression and bipolar disorder.
2. Discuss characteristics of antidepressants in terms of mechanism of action, indications for use, adverse effects, principles of therapy, and nursing process implications.
3. Compare and contrast selective serotonin reuptake inhibitors with tricyclic antidepressants.
4. Discuss selected characteristics of bupropion, mirtazapine, and venlafaxine.
5. Describe the use of lithium in bipolar disorder.
6. Discuss interventions to increase safety of lithium therapy.
7. Describe the nursing role in preventing, recognizing, and treating overdoses of antidepressant drugs and lithium.
8. Analyze important factors in using antidepressant drugs and lithium in special populations.

INTRODUCTION

Mood disorders include depression, dysthymia, bipolar disorder, and cyclothymia (Box 10-1). Depression is estimated to affect 5% to 10% of adults in the United States and to be increasing in children and adolescents. It is associated with impaired ability to function in usual activities and relationships. The average depressive episode lasts about 5 months, and having one episode is a risk factor for developing another episode. Depression and antidepressant drug therapy are emphasized in this chapter, and bipolar disorder and mood-stabilizing drugs are also discussed.

Etiology of Depression

Despite extensive study and identification of numerous potential contributory factors, the etiology of depression is unclear. It is likely that depression results from interactions among several complex factors. Two of the major theories of depression pathogenesis are described in the following sections.

Monoamine Neurotransmitter Dysfunction

Depression is thought to result from a deficiency of norepinephrine and/or serotonin. This hypothesis stemmed from studies demonstrating that antidepressant drugs increase the amounts of one or both of these neurotransmitters in the central nervous system (CNS) synapse by inhibiting their reuptake into the presynaptic neuron. Serotonin received increased attention after the selective serotonin reuptake inhibitor (SSRI) antidepressants were marketed. Serotonin helps regulate several behaviors that are disturbed in depression, such as mood, sleep, appetite, energy level, and cognitive and psychomotor functions.

Emphasis shifted toward receptors because the neurotransmitter view did not explain why the amounts of neurotransmitter increased within hours after single doses of a drug, but relief of depression occurred only after weeks of drug therapy. Researchers identified changes in norepinephrine and serotonin receptors with chronic antidepressant drug therapy. Studies demonstrated that chronic drug administration (ie, increased neurotransmitter in the synapse for several weeks) results in fewer receptors on the postsynaptic mem-
bran. This down-regulation of receptors, first noted with beta-adrenergic receptors, corresponds with therapeutic drug effects. All known treatments for depression lead to the down-regulation of beta receptors and occur in the same period as the behavioral changes associated with antidepressant drug therapy.

Alpha2-adrenergic receptors (called autoreceptors), located on presynaptic nerve terminals, may also play a role. When these receptors are stimulated, they inhibit the release of norepinephrine. There is evidence that alpha2 receptors are also down-regulated by antidepressant drugs, thus allowing increased norepinephrine release. With serotonin receptors, available antidepressants may increase the sensitivity of postsynaptic receptors and decrease the sensitivity of presynaptic receptors.

Physiologically, presynaptic receptors regulate the release and reuptake of neurotransmitters; postsynaptic receptors participate in the transmission of nerve impulses to target tissues. It seems apparent that long-term administration of antidepressant drugs produces complex changes in the sensitivities of both presynaptic and postsynaptic receptor sites.

Overall, there is increasing awareness that balance, integration, and interactions among norepinephrine, serotonin, and possibly other neurotransmission systems (eg, dopamine, acetylcholine) are probably more important etiologic factors than single neurotransmitter or receptor alterations. For example, animal studies indicate that serotonin is required for optimal functioning of the neurons that produce norepinephrine. Changes in neurons may also play a major role.

### Neuroendocrine Factors

In addition to monoamine neurotransmission systems, researchers have identified nonmonoamine systems that influence neurotransmission and are significantly altered in depression. A major nonmonoamine is corticotropin-releasing factor or hormone (CRF or CRH), whose secretion is increased in people with depression. CRF-secreting neurons are widespread in the CNS, and CRF apparently functions as a neurotransmitter and mediator of the endocrine, autonomic, immune, and behavioral responses to stress as well as a releasing factor for corticotropin. Hypothalamic CRF is part of the hypothalamic–pituitary–adrenal (HPA) axis, which becomes hyperactive in depression. As a result, there is increased secretion of CRF by the hypothalamus; adrenocorticotropic hormone (ACTH) by the anterior pituitary; and cortisol by the adrenal cortex. The increased cortisol (part of the normal physiologic response to stress) is thought to decrease the numbers or sensitivity of cortisol receptors (down-regulation) and lead to depression. This view is supported by animal studies indicating that antidepressant drugs restore the ability of cortisol receptors to bind with cortisol. This alteration of cortisol receptors takes
about 2 weeks, the approximate time interval required for the drugs to improve symptoms of depression. Extrahypothalamic CRF is also increased in depression. Secretion of both hypothalamic and extrahypothalamic CRF apparently returns to normal with recovery from depression.

Other neuroendocrine factors in clients with depression are thought to include abnormalities in the secretion and function of thyroid and growth hormones.

Additional Factors

Additional factors thought to play a role in the etiology of depression include the immune system, genetic factors, and environmental factors.

Immune cells (eg, T lymphocytes, B lymphocytes) produce cytokines (eg, interleukins, interferons, tumor necrosis factor), which affect neurotransmission. Possible mechanisms of cytokine-induced depression include increased CRF and activation of the HPA axis; alteration of monoamine neurotransmitters in several areas of the brain; or cytokines functioning as neurotransmitters and exerting direct effects on brain function.

Genetic factors are considered important mainly because close relatives of a depressed person are more likely to experience depression.

Environmental factors include stressful life events, which apparently change brain structure and function and contribute to the development of depression in some people. Changes have been identified in CRF, the HPA axis, and the noradrenergic neurotransmission system, all of which are activated as part of the stress response. These changes are thought to cause a hypersensitive or exaggerated response to later stressful events, including mild stress or daily life events. Most studies have involved early life trauma such as physical or sexual abuse in childhood.

Etiology of Bipolar Disorder

Like depression, mania and hypomania may result from abnormal functioning of neurotransmitters or receptors, such as a relative excess of excitatory neurotransmitters (eg, norepinephrine) or a relative deficiency of inhibitory neurotransmitters (eg, gamma-aminobutyric acid [GABA]). Drugs that stimulate the CNS can cause manic and hypomanic behaviors that are easily confused with schizophreniform psychoses.

Mechanisms of Action

Although the actions of antidepressant drugs are still being studied in relation to newer information about brain function and the etiology of mood disorders, these drugs apparently normalize abnormal neurotransmission systems in the brain by altering the amounts of neurotransmitters and the number or sensitivity of receptors. They may also modify interactions among neurotransmission systems and affect endocrine function (eg, the HPA axis and cortisol activity).

After neurotransmitters are released from presynaptic nerve endings, the molecules that are not bound to receptors are normally inactivated by reuptake into the presynaptic nerve fibers that released them or metabolized by MAO. Most antidepressants prevent the reuptake of multiple neurotransmitters; SSRIs selectively inhibit the reuptake of serotonin, and MAO inhibitors prevent the metabolism of neurotransmitter molecules. These mechanisms thereby increase the amount of neurotransmitter available to bind to receptors.

With chronic drug administration, receptors adapt to the presence of increased neurotransmitter by decreasing their number or sensitivity to the neurotransmitter. More specifically, norepinephrine receptors, especially postsynaptic beta receptors and presynaptic alpha receptors, are down-regulated. The serotonin receptor, a postsynaptic receptor, and cortisol (glucocorticoid) receptors may also be down-regulated.

Thus, antidepressant effects are attributed to changes in receptors rather than changes in neurotransmitters. Although some of the drugs act more selectively on one neurotransmission system than another initially, this selectivity seems to be lost with chronic administration.

With lithium, the exact mechanism of action is unknown. However, it is known to affect the synthesis, release, and reuptake of several neurotransmitters in the brain, including acetylcholine, dopamine, GABA, and norepinephrine. For example, the drug may increase the activity of GABA, an inhi-
bitary neurotransmitter. It also stabilizes postsynaptic receptor sensitivity to neurotransmitters, probably by competing with calcium, magnesium, potassium, and sodium ions for binding sites.

**Indications for Use**

Antidepressant therapy may be indicated if depressive symptoms persist at least 2 weeks, impair social relationships or work performance, and occur independently of life events. In addition, antidepressants are increasingly being used for treatment of anxiety disorders. TCAs may be used in children and adolescents in the management of enuresis (bedwetting or involuntary urination resulting from a physical or psychological disorder). In this setting, TCAs may be given after physical causes (eg, urethral irritation, excessive intake of fluids) have been ruled out. TCAs are also commonly used in the treatment of neuropathic pain. MAO inhibitors are considered third-line drugs, largely because of their potential for serious interactions with certain foods and other drugs.

**Contraindications to Use**

Antidepressants are contraindicated or must be used with caution in clients with acute schizophrenia; mixed mania and depression; suicidal tendencies; severe renal, hepatic, or cardiovascular disease; narrow-angle glaucoma; and seizure disorders.

**APPLYING YOUR KNOWLEDGE 10-1: HOW CAN YOU AVOID THIS MEDICATION ERROR?**

Mr. Mehring is talking with his pastor when you arrive to administer his medication. He asks you to just leave the medication and he will take it when he finishes his visit. You leave the medication with Mr. Mehring and chart it as given.

**TYPES OF ANTIDEPRESSANTS AND INDIVIDUAL DRUGS**

Additional characteristics of antidepressants and lithium are described in the following sections. Names, indications for use, and dosage ranges of individual drugs are listed in Table 10-1.

**Tricyclic Antidepressants**

TCAs, of which imipramine is the prototype, are similar drugs that produce a high incidence of adverse effects such as sedation, orthostatic hypotension, cardiac dysrhythmias, anticholinergic effects (eg, blurred vision, dry mouth, constipation, urinary retention), and weight gain. They are well absorbed after oral administration, but first-pass metabolism by the liver results in blood level variations of 10- to 30-fold among people given identical doses. After they are absorbed, these drugs are widely distributed in body tissues and metabolized by the liver to active and inactive metabolites. Because of adverse effects on the heart, especially in overdose, baseline and follow-up electrocardiograms (ECGs) are recommended for all clients. **Amitriptyline** (Elavil) is a commonly used TCA.

**Selective Serotonin Reuptake Inhibitors**

SSRIs, of which fluoxetine (Prozac, Sarafem) is the prototype, produce fewer serious adverse effects than the TCAs. They are well absorbed with oral administration, undergo extensive first-pass metabolism in the liver, are highly protein bound (56%–95%), and have a half-life of 24 to 72 hours, which may lead to accumulation with chronic administration. Fluoxetine also forms an active metabolite with a half-life of 7 to 9 days. Thus, steady-state blood levels are achieved slowly, over several weeks, and drug effects decrease slowly (over 2 to 3 months) when fluoxetine is discontinued. Sertraline (Zoloft) and citalopram (Celexa) also have active metabolites, but fluoxetine and paroxetine (Paxil) are more likely to accumulate. Escitalopram (Lexapro), paroxetine, sertraline, and fluvoxamine (Luvox) reach steady-state concentrations in 1 to 2 weeks. SSRIs are usually given once daily.

Because SSRIs are highly bound to plasma proteins, they compete with endogenous compounds and other medications for binding sites. Because the drugs are highly lipid soluble, they accumulate in the CNS and other adipose-rich tissue.

Adverse effects include a high incidence of gastrointestinal (GI) symptoms (eg, nausea, diarrhea, weight loss) and sexual dysfunction (eg, delayed ejaculation in men, impaired orgasmic ability in women). Most SSRIs also cause some degree of CNS stimulation (eg, anxiety, nervousness, insomnia), which is most prominent with fluoxetine. Because serotonin release from platelets is essential for hemostasis and psychotropic drugs interfere with serotonin reuptake, these agents are associated with increased risk of GI bleeding. Concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDS), aspirin, or warfarin increases this risk.

Serious, sometimes fatal, reactions have occurred due to combined therapy with an SSRI and an MAO inhibitor, and an SSRI and an MAO inhibitor should not be given concurrently or within 2 weeks of each other. In most cases, if a client taking an SSRI is to be transferred to an MAO inhibitor, the SSRI should be discontinued at least 14 days before starting the MAO inhibitor. However, fluoxetine should be discontinued at least 5 weeks before starting an MAO inhibitor.

**APPLYING YOUR KNOWLEDGE 10-2**

On his return visit to the physician 2 weeks later, Mr. Mehring’s wife complains that she sees no improvement in her husband’s mood and that he is taking too much medication. How would you respond?
### Tricyclic Antidepressants

<table>
<thead>
<tr>
<th>GENERIC/TRADE NAME</th>
<th>CLINICAL INDICATIONS</th>
<th>ROUTES AND DOSAGE RANGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline (Elavil)</td>
<td>Depression</td>
<td>PO 50–100 mg once daily at bedtime, gradually increased to 150 mg daily if necessary; IM 80–120 mg daily in 4 divided doses. Adolescents and older adults: PO 10 mg 3 times daily and 20 mg at bedtime.</td>
</tr>
<tr>
<td>Amoxapine (Asendin)</td>
<td>Depression</td>
<td>PO 50 mg 2 or 3 times daily, increased to 100 mg 2 or 3 times daily by end of 1 wk. Give maintenance dose in a single dose at bedtime. Older adults: PO 25 mg 2 or 3 times daily, increased to 50 mg 2 or 3 times daily by end of 1 wk. Give maintenance dose in a single dose at bedtime.</td>
</tr>
<tr>
<td>Clomipramine (Anafranil)</td>
<td>Obsessive-compulsive disorder</td>
<td>PO 25 mg daily, increased to 100 mg daily by end of 2 wk, in divided doses, with meals. Give maintenance dose in a single dose at bedtime. Maximum dose, 250 mg daily. Children and adolescents: PO 25 mg daily, increased to 3 mg/kg or 100 mg, whichever is smaller, over 2 wk. Give maintenance dose in a single dose at bedtime. Maximum dose, 3 mg/kg or 200 mg, whichever is smaller.</td>
</tr>
<tr>
<td>Desipramine (Norpramin)</td>
<td>Depression</td>
<td>PO 100–200 mg daily in divided doses or as a single daily dose. Give maintenance dose once daily. Maximum dose, 300 mg/d. Adolescents and older adults: PO 25–100 mg daily in divided doses or as a single daily dose. Maximum dose, 150 mg/d.</td>
</tr>
<tr>
<td>Doxepin (Sinequan)</td>
<td>Depression</td>
<td>PO 75–150 mg daily, in divided doses or a single dose at bedtime. Maximum dose, 300 mg/d.</td>
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<tr>
<td>Imipramine (Tofranil)</td>
<td>Depression; Childhood enuresis</td>
<td>PO 75 mg daily in 3 divided doses, gradually increased to 200 mg daily if necessary. Maintenance dose, 75–150 mg daily. Adolescents and older adults: PO 30–40 mg daily in divided doses, increased to 100 mg daily if necessary. Children &gt;6 y: Enuresis, PO 25–50 mg 1 h before bedtime</td>
</tr>
<tr>
<td>Nortriptyline (Aventyl, Pamelor)</td>
<td>Depression</td>
<td>PO 25 mg 3 or 4 times daily or in a single dose (75–100 mg) at bedtime. Maximum dose, 150 mg/d. Adolescents and older adults: 30–50 mg/d, in divided doses or a single dose once daily.</td>
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<tr>
<td>Protriptyline (Vivactil)</td>
<td>Depression</td>
<td>PO 15–40 mg daily in 3 or 4 divided doses. Maximum dose, 60 mg. Adolescents and older adults: PO 5 mg 3 times daily; increase gradually if necessary</td>
</tr>
<tr>
<td>Trimipramine maleate (Surmontil)</td>
<td>Depression</td>
<td>PO 75 mg daily, in divided doses or a single dose at bedtime, increased to 150 mg/d if necessary. Maximum dose, 200 mg/d. Adolescents and older adults: PO 50 mg daily, increased to 100 mg/d if necessary</td>
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<tr>
<td>Selective Serotonin Reuptake Inhibitors (SSRIs)</td>
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<tr>
<td>Citalopram (Celexa)</td>
<td>Depression</td>
<td>PO 20 mg once daily, morning or evening, increased to 40 mg daily in 1 wk, if necessary. Elderly/hepatic impairment: PO 20 mg daily</td>
</tr>
<tr>
<td>Escitalopram (Lexapro)</td>
<td>Depression; Generalized anxiety disorder</td>
<td>PO 10 mg once daily. May increase to maximum dose of 20 mg after minimum of 1 wk of therapy</td>
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<tr>
<td>Fluoxetine (Prozac, Prozac Weekly, Sarafem)</td>
<td>Depression; Obsessive-compulsive disorder; Bulimia nervosa; Premenstrual dysphoric disorder; (Sarafem)</td>
<td>PO 20 mg once daily in the morning, increased after several weeks if necessary. Give doses larger than 20 mg once in the morning or in 2 divided doses, morning and noon; maximum daily dose 80 mg. Prozac Weekly (delayed-release capsules), PO 90 mg once each wk, starting 7 days after the last 20-mg dose Children and adolescents 8–17 y for depression: PO 10 mg/d. May increase to 20 mg/d if necessary.</td>
</tr>
<tr>
<td>GENERIC/TRADE NAME</td>
<td>CLINICAL INDICATIONS</td>
<td>ROUTES AND DOSAGE RANGES</td>
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<tr>
<td>Fluvoxamine (Luvox)</td>
<td>Obsessive-compulsive disorder</td>
<td>PO 50 mg once daily at bedtime, increased in 50-mg increments every 4–7 d if necessary. For daily amounts above 100 mg, give in 2 divided doses. Maximum dose, 300 mg/d. <strong>Children 8–17 y:</strong> PO 25 mg once daily at bedtime, increased in 25-mg increments every 4–7 days if necessary. For daily amounts above 50 mg, give in 2 divided doses. Maximum dose 200 mg/d.</td>
</tr>
<tr>
<td>Paroxetine (Paxil, Paxil CR)</td>
<td>Depression, Generalized anxiety disorder</td>
<td>PO 20 mg once daily in the morning, increased at 1 wk or longer intervals, if necessary; usual range, 20–50 mg/d; maximum dose, 60 mg/d. <strong>Elderly or debilitated adults:</strong> PO 10 mg once daily, increased if necessary. Maximum dose, 40 mg. <strong>Severe renal or hepatic impairment:</strong> Same as for older adults</td>
</tr>
<tr>
<td>Sertraline (Zoloft)</td>
<td>Depression, Obsessive-compulsive disorder (OCD)</td>
<td>Depression, OCD, PO 50 mg once daily morning or evening, increased at 1-wk or longer intervals to a maximum daily dose of 200 mg</td>
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<td></td>
<td>Social anxiety disorder</td>
<td>Panic, PTSD, PO 25 mg once daily, increased after 1 wk to 50 mg once daily</td>
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<tr>
<td></td>
<td>Panic disorder</td>
<td><strong>Children:</strong> OCD, 6–12 y, 25 mg once daily; 13–17 y, 50 mg once daily</td>
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<tr>
<td></td>
<td>Post-traumatic stress disorder (PTSD)</td>
<td></td>
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<tr>
<td>Monoamine Oxidase (MAO) Inhibitors</td>
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<tr>
<td>Isocarboxazid (Marplan)</td>
<td>Depression</td>
<td>PO 10 mg twice daily</td>
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<tr>
<td>Phenelzine (Nardil)</td>
<td>Depression</td>
<td>PO 15 mg 3 times daily</td>
</tr>
<tr>
<td>Tranylcypromine (Parnate)</td>
<td>Depression</td>
<td>PO 30 mg daily in divided doses</td>
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<tr>
<td>Other Antidepressants</td>
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<tr>
<td>Buproprion (Wellbutrin, Wellbutrin SR, Wellbutrin XL, Zyban)</td>
<td>Depression (Wellbutrin) Smoking cessation (Zyban)</td>
<td>Immediate-release tablets, PO 100 mg twice daily, increased to 100 mg 3 times daily (at least 6 h apart) if necessary. Maximum single dose, 150 mg. Sustained-release (SR) tablets, PO 150 mg once daily in the morning, increased to 150 mg twice daily (at least 8 h apart). Maximum single dose, 150 mg. Wellbutrin XL: PO 150 mg once daily in the morning. May increase to target dose of 300 mg on or after fourth day of therapy. Maximum single dose, 450 mg.</td>
</tr>
<tr>
<td>Maprotiline</td>
<td>Depression</td>
<td>PO 75 mg daily in single or divided doses</td>
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<tr>
<td>Mirtazapine (Remeron)</td>
<td>Depression</td>
<td>PO 15 mg/d</td>
</tr>
<tr>
<td>Trazodone (Desyrel)</td>
<td>Depression</td>
<td>PO 100–300 mg daily, increased to a maximum dose of 600 mg daily if necessary</td>
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<tr>
<td>Venlafaxine (Effexor, Effexor XR)</td>
<td>Depression, Generalized anxiety disorder (XR form)</td>
<td>Immediate-release tablets, PO initially 75 mg/d in 2 or 3 divided doses, with food. Increase by 75 mg/d (4 d or longer between increments) up to 225 mg/d if necessary. Extended-release (XR) capsules, PO initially 37.5 or 75 mg/d in a single dose morning or evening. Increase by 75 mg/d (4 d or longer between increments) up to 225 mg/d if necessary. <strong>Hepatic or renal impairment:</strong> Reduce dose by 50% and increase very slowly.</td>
</tr>
<tr>
<td>Mood-Stabilizing Agent</td>
<td>Bipolar disorder (mania)</td>
<td>PO 600 mg 3 times daily or 900 mg twice daily (slow-release forms) Maintenance dose, PO 300 mg 3 or 4 times daily to maintain a serum lithium level of 0.6–1.2 mEq/L</td>
</tr>
</tbody>
</table>

PO, oral.
Monoamine Oxidase Inhibitors

MAO inhibitors are infrequently used, mainly because they may interact with some foods and drugs to produce severe hypertension and possible heart attack or stroke. Foods that interact contain tyramine, a monoamine precursor of norepinephrine. Normally, tyramine is deactivated in the GI tract and liver so that large amounts do not reach the systemic circulation. When deactivation is blocked by MAO inhibitors, tyramine is absorbed systemically and transported to adrenergic nerve terminals, where it causes a sudden release of large amounts of norepinephrine. Foods that should be avoided include aged cheeses and meats, concentrated yeast extracts, sauerkraut, and fava beans. Drugs that should be avoided include CNS stimulants (eg, amphetamines, cocaine), adrenergics (eg, pseudoephedrine), antidepressants (SSRIs, venlafaxine), buspirone, levodopa, and meperidine.

Other Antidepressants

Bupropion (Wellbutrin, Zyban) inhibits the reuptake of dopamine, norepinephrine, and serotonin. It was marketed with warnings related to seizure activity. Seizures are most likely to occur with doses above 450 milligrams per day and in clients known to have a seizure disorder.

After an oral dose, peak plasma levels are reached in about 2 hours. The average drug half-life is about 14 hours. The drug is metabolized in the liver and excreted primarily in the urine. Several metabolites are pharmacologically active. Dosage should be reduced in clients with impaired hepatic or renal function. Acute episodes of depression usually require several months of drug therapy. Bupropion is also used as a smoking cessation aid.

Bupropion has few adverse effects on cardiac function and does not cause orthostatic hypotension or sexual dysfunction. However, in addition to seizures, the drug has CNS stimulant effects (agitation, anxiety, excitement, increased motor activity, insomnia, restlessness) that may require a sedative during the first few days of administration. These effects may increase the risk of abuse. Other common adverse effects include dry mouth, headache, nausea and vomiting, and constipation.

Maprotiline is similar to the TCAs in therapeutic and adverse effects. Mirtazapine (Remeron) blocks presynaptic alpha2-adrenergic receptors (which increases the release of norepinephrine), serotonin receptors, and histamine H1 receptors. Consequently, the drug decreases anxiety, agitation, insomnia, and migraine headaches as well as depression.

Mirtazapine is well absorbed after oral administration, and peak plasma levels occur within 2 hours after an oral dose. It is metabolized in the liver, mainly to inactive metabolites. Common adverse effects include drowsiness (with accompanying cognitive and motor impairment), increased appetite, weight gain, dizziness, dry mouth, and constipation. It does not cause sexual dysfunction.

Mirtazapine should not be taken concurrently with other CNS depressants (eg, alcohol, benzodiazepine anxiolytics or hypnotic agents) because of additive sedation. In addition, it should not be taken concurrently with an MAO inhibitor or for 14 days after an MAO inhibitor is stopped. An MAO inhibitor should not be started until at least 14 days after mirtazapine is stopped.

Trazodone (Desyrel) is used more often for sedation and sleep than for depression because high doses (>300 mg/day) are required for antidepressant effects and these amounts cause excessive sedation in many clients. The drug is often given concurrently with a stimulating antidepressant, such as bupropion, fluoxetine, sertraline, or venlafaxine.

Trazodone is well absorbed with oral administration, and peak plasma concentrations are obtained within 30 minutes to 2 hours. It is metabolized by the liver and excreted primarily by the kidneys. Adverse effects include sedation, dizziness, edema, cardiac dysrhythmias, and priapism (prolonged and painful penile erection).

Venlafaxine (Effexor) inhibits the reuptake of norepinephrine, serotonin, and dopamine, thereby increasing the activity of these neurotransmitters in the brain. The drug crosses the placenta and may enter breast milk. It is metabolized in the liver and excreted in urine. It is contraindicated during pregnancy, and women should use effective birth control methods while taking this drug. Adverse effects include CNS (anxiety, dizziness, dreams, insomnia, nervousness, somnolence, tremors), GI (anorexia, nausea, vomiting, constipation, diarrhea), cardiovascular (hypertension, tachycardia, vasodilation), genitourinary (abnormal ejaculation, impotence, urinary frequency), and dermatologic (sweating, rash, pruritus) symptoms. Venlafaxine does not interact with drugs metabolized by the cytochrome P450 system, but it should not be taken concurrently with MAO inhibitors because of increased serum levels and risks of toxicity. If a client taking venlafaxine is to be transferred to an MAO inhibitor, the venlafaxine should be discontinued at least 7 days before starting the MAO inhibitor. If a client taking an MAO inhibitor is to be transferred to venlafaxine, the MAO inhibitor should be discontinued at least 14 days before starting venlafaxine.

Mood-Stabilizing Agents

Lithium carbonate (Eskalith) is a naturally occurring metallic salt that is used in clients with bipolar disorder, mainly to treat and prevent manic episodes. It is well absorbed after oral administration, with peak serum levels in 1 to 3 hours after a dose and steady-state concentrations in 5 to 7 days. Serum lithium concentrations should be monitored frequently because they vary widely among clients taking similar doses and because of the narrow range between therapeutic and toxic levels.

Lithium is not metabolized by the body; it is entirely excreted by the kidneys, so adequate renal function is a prerequisite for lithium therapy. Approximately 80% of a lithium
dose is reabsorbed in the proximal renal tubules. The amount of reabsorption depends on the concentration of sodium in the proximal renal tubules. A sodium deficit causes more lithium to be reabsorbed and increases the risk of lithium toxicity. A sodium excess causes more lithium to be excreted (ie, lithium diuresis) and may lower serum lithium levels to nontherapeutic ranges.

Before lithium therapy is begun, baseline studies of renal, cardiac, and thyroid status should be obtained because adverse drug effects involve these organ systems. Baseline electrolyte studies are also necessary.

Anticonvulsants (see Chap. 11) are also used as mood-stabilizing agents in bipolar disorder because they modify nerve cell function. Carbamazepine (Tegretol) and valproate (Depakene) are commonly used. Newer drugs (eg, gabapentin, lamotrigine, topiramate, oxcarbazepine) are being used and studied regarding their effects in bipolar disorder, but none are approved by the Food and Drug Administration (FDA) for this purpose. Thus far, most of the drugs seem to have some beneficial effects but additional studies are needed.

Antipsychotics (see Chap. 9) are increasingly being used to treat bipolar disorder. Currently, quetiapine, risperidone, and olanzapine in combination with fluoxetine are approved by the FDA for this indication.

**Herbal Supplement**

St. John’s wort (*Hypericum perforatum*) is an herb that is widely self-prescribed for depression. Several studies, most of which used about 900 milligrams daily of a standardized extract, indicate its usefulness in mild to moderate depression, with fewer adverse effects than antidepressant drugs. A 3-year, multicenter study by the National Institutes of Health concluded that the herb is not effective in major depression.

Antidepressant effects are attributed mainly to hypericin, although several other active components have also been identified. The mechanism of action is unknown, but the herb is thought to act similarly to antidepressant drugs. Some herbalists refer to St. John’s wort as “natural Prozac.”

Adverse effects, which are usually infrequent and mild, include constipation, dizziness, dry mouth, fatigue, GI distress, nausea, photosensitivity, restlessness, skin rash, and sleep disturbances. These symptoms are relieved by stopping the herb.

Drug interactions may be extensive. St. John’s wort should not be combined with alcohol, antidepressant drugs (eg, MAO inhibitors, SSRIs, TCAs), nasal decongestants or other over-the-counter cold and flu medications, bronchodilators, opioid analgesics, or amino acid supplements containing phenylalanine and tyrosine. All of these interactions may result in hypertension, possibly severe.

Most authorities agree that there is insufficient evidence to support the use of St. John’s wort for mild to moderate depression and that more studies are needed to confirm the safety and effectiveness of this herb. Most of the previous studies were considered flawed.

Overall, both consumers and health care professionals seem to underestimate the risks of taking this herbal supplement. For clients who report use of St. John’s wort, teach them to purchase products from reputable sources because the amount and type of herbal content may vary among manufacturers; to avoid taking antidepressant drugs, alcohol, and cold and flu medications while taking St. John’s wort; to avoid the herb during pregnancy because effects are unknown; and to use sunscreen lotions and clothing to protect themselves from sun exposure.

**NURSING PROCESS**

**Assessment**

Assess the client’s condition in relation to depressive disorders.

- Identify clients at risk for current or potential depression. Areas to assess include health status, family and social relationships, and work status. Severe or prolonged illness, impaired interpersonal relationships, inability to work, and job dissatisfaction may precipitate depression. Depression also occurs without an identifiable cause.
- Observe for signs and symptoms of depression. Clinical manifestations are nonspecific and vary in severity. For example, fatigue and insomnia may be caused by a variety of disorders and range from mild to severe. When symptoms are present, try to determine their frequency, duration, and severity.
- When a client appears depressed or has a history of depression, assess for suicidal thoughts and behaviors. Statements indicating a detailed plan, accompanied by the intent, ability, and method for carrying out the plan, place the client at high risk for suicide.
- Identify the client’s usual coping mechanisms for stressful situations. Coping mechanisms vary widely, and behavior that may be helpful to one client may not be helpful to another. For example, one person may prefer being alone or having decreased contact with family and friends, whereas another may find increased contact desirable.

**Nursing Diagnoses**

- Dysfunctional Grieving related to loss (of health, ability to perform usual tasks, job, significant other, and so forth)
- Self-Care Deficit related to fatigue and self-esteem disturbance with depression or sedation with antidepressant drugs
● Sleep Pattern Disturbance related to mood disorder or drug therapy
● Risk for Injury related to adverse drug effects
● Risk for Violence: Self-Directed or Directed at Others
● Deficient Knowledge: Effects and appropriate use of antidepressant and mood-stabilizing drugs

Planning/Goals
The client will
● Experience improvement of mood and depressive state
● Receive or self-administer the drugs correctly
● Be kept safe while sedated during therapy with the TCAs and related drugs
● Be assessed regularly for suicidal tendencies. If present, caretakers will implement safety measures.
● Be cared for by staff in areas of nutrition, hygiene, exercise, and social interactions when unable to provide self-care
● Resume self-care and other usual activities
● Avoid preventable adverse drug effects

Interventions
Use measures to prevent or decrease the severity of depression. General measures include supportive psychotherapy and reduction of environmental stress. Specific measures include the following:
● Support the client’s usual mechanisms for handling stressful situations, when feasible. Helpful actions may involve relieving pain or insomnia, scheduling rest periods, and increasing or decreasing socialization.
● Call the client by name, encourage self-care activities, allow him or her to participate in setting goals and making decisions, and praise efforts to accomplish tasks. These actions promote a positive self-image.
● When signs and symptoms of depression are observed, initiate treatment before depression becomes severe. Institute suicide precautions for clients at risk. These usually involve close observation, often on a one-to-one basis, and removal of potential weapons from the environment. For clients hospitalized on medical-surgical units, transfer to a psychiatric unit may be needed.
● Provide client teaching regarding drug therapy (see accompanying display).

Evaluation
● Observe for behaviors indicating lessered depression.
● Interview regarding feelings and mood.
● Observe and interview regarding adverse drug effects.
● Observe and interview regarding suicidal thoughts and behaviors.

PRINCIPLES OF THERAPY
Drug Selection
Because the available drugs seem similarly effective, the choice of an antidepressant depends on the client’s age; medical conditions; previous history of drug response, if any; and the specific drug’s adverse effects. Cost also needs to be considered. Although the newer drugs are much more expensive than the TCAs, they may be more cost effective overall because TCAs are more likely to cause serious adverse effects; they require monitoring of plasma drug levels and ECGs; and clients are more likely to stop taking them. The SSRIs are the drugs of first choice. These drugs are effective and usually produce fewer and milder adverse effects than other drugs. Guidelines for choosing one SSRI over another have not been established.

TCAs are second-line drugs for the treatment of depression. Initial selection of TCAs may be based on the client’s previous response or susceptibility to adverse effects. For example, if a client (or a close family member) responded well to a particular drug in the past, that is probably the drug of choice for repeated episodes of depression. The response of family members to individual drugs may be significant because there is a strong genetic component to depression and drug response. If therapeutic effects do not occur within 4 weeks, the TCA probably should be discontinued or changed, because some clients tolerate or respond better to one TCA than to another. For potentially suicidal clients, an SSRI or another newer drug is preferred over a TCA because the TCAs are much more toxic in overdoses.

MAO inhibitors are third-line drugs for the treatment of depression because of their potential interactions with other drugs and certain foods. An MAO inhibitor is most likely to be prescribed when the client does not respond to other antidepressant drugs or when electroconvulsive therapy is refused or contraindicated.

Criteria for choosing bupropion, mirtazapine, and venlafaxine are not clearly defined. Bupropion does not cause orthostatic hypotension or sexual dysfunction. Mirtazapine decreases anxiety, agitation, migraines, and insomnia, as well as depression. In addition, it does not cause sexual dysfunction or clinically significant drug–drug interactions. Venlafaxine has stimulant effects, increases blood pressure, and causes sexual dysfunction, but it does not cause significant drug–drug interactions.

For clients with certain concurrent medical conditions, antidepressants may have adverse effects. For clients with cardiovascular disorders, most antidepressants can cause hypotension, but the SSRIs, bupropion, and venlafaxine are rarely associated with cardiac dysrhythmias. Venlafaxine and MAO inhibitors can increase blood pressure. For clients with seizure disorders, bupropion, clomipramine, and maprotiline should be avoided. SSRIs, MAO inhibitors, and desipramine are less likely to cause seizures. For clients with diabetes

(text continues on page 184)
General Considerations

- Take antidepressants as directed to maximize therapeutic benefits and minimize adverse effects. Do not alter doses when symptoms subside. Antidepressants are usually given for several months, perhaps years. Lithium therapy may be lifelong.
- Therapeutic effects (relief of symptoms) may not occur for 2–4 weeks after drug therapy is started. As a result, it is very important not to think the drug is ineffective and stop taking it prematurely.
- Do not take other prescription or over-the-counter drugs without consulting a health care provider, including over-the-counter cold remedies. Potentially serious drug interactions may occur.
- Do not take the herbal supplement St. John’s wort while taking a prescription antidepressant drug. Serious interactions may occur.
- Inform any physician, surgeon, dentist, or nurse practitioner about the antidepressant drugs being taken. Potentially serious adverse effects or drug interactions may occur if certain other drugs are prescribed.
- Avoid activities that require alertness and physical coordination (eg, driving a car, operating other machinery) until reasonably sure the medication does not make you drowsy or impair your ability to perform the activities safely.
- Avoid alcohol and other central nervous system depressants (eg, any drugs that cause drowsiness). Excessive drowsiness, dizziness, difficulty breathing, and low blood pressure may occur, with potentially serious consequences.
- Learn the name and type of a prescribed antidepressant drug to help avoid undesirable interactions with other drugs or a physician prescribing other drugs with similar effects. There are several different types of antidepressant drugs, with different characteristics and precautions for safe and effective usage.
- Escitalopram (Lexapro) is a derivative of citalopram (Celexa), and the two medications should not be taken concomitantly.
- Bupropion is a unique drug prescribed for depression (brand name Wellbutrin) and for smoking cessation (brand name Zyban). It is extremely important not to increase the dose or take the two brand names at the same time (as might happen with different physicians or filling prescriptions at different pharmacies). Overdoses may cause seizures, as well as other adverse effects. When used for smoking cessation, Zyban is recommended for up to 12 weeks if progress is being made. If significant progress is not made by approximately 7 weeks, it is considered unlikely that longer drug use will be helpful.
- Do not stop taking any antidepressant drug without discussing it with a health care provider. If a problem occurs, the type of drug, the dose, or other aspects may be changed to solve the problem and allow continued use of the medication.
- Counseling, support groups, relaxation techniques, and other nondrug treatments are recommended along with drug therapy.

Self-Administration

- Notify your physician if you become pregnant or intend to become pregnant during therapy with antidepressant drugs.

With a selective serotonin reuptake inhibitor (eg, Celexa, Lexapro, Luvox, Paxil, Prozac, Zoloft), take in the morning because the drug may interfere with sleep if taken at bedtime. In addition, notify a health care provider if a skin rash or other allergic reaction occurs. Allergic reactions are uncommon but may require that the drug be discontinued.
- With a tricyclic antidepressant (eg, amitriptyline), take at bedtime to aid sleep and decrease adverse effects. Also, report urinary retention, fainting, irregular heartbeat, seizures, restlessness, and mental confusion. These are potentially serious adverse drug effects.
- With venlafaxine (Effexor), take as directed or ask for instructions. This drug is often taken twice daily. Notify a health care provider if a skin rash or other allergic reaction occurs. An allergic reaction may require that the drug be discontinued.
- There are short-, intermediate-, and long-acting forms of bupro- pion that are taken 3 times, 2 times, or 1 time per day, respectively. Be sure to take your medication as prescribed by your physician.
- With lithium, several precautions are needed for safe use:
  1. Take with food or milk or soon after a meal to decrease stomach upset.
  2. Do not alter dietary salt intake. Decreased salt intake (eg, low-salt diet) increases risk of adverse effects from lithium. Increased intake may decrease therapeutic effects.
  3. Drink 8–12 glasses of fluids daily; avoid excessive intake of caffeine-containing beverages. Caffeine has a diuretic effect and dehydration increases lithium toxicity.
  4. Do not take diuretic medications without consulting a health care provider. Diuretics cause loss of sodium and water, which increases lithium toxicity.
  5. Minimize activities that cause excessive perspiration, such as sweating during heavy exercise, sauna use, or outdoor activities during hot summer days. Loss of salt in sweat increases the risk of adverse effects from lithium.
  6. Report for measurements of lithium blood levels as instructed, and do not take the morning dose of lithium until the blood sample has been obtained. Regular measurements of blood lithium levels are necessary for safe and effective lithium therapy. Accurate measurement of serum drug levels requires that the sample has been obtained. Regular measurements of blood lithium levels are necessary for safe and effective lithium therapy. Accurate measurement of serum drug levels requires that the blood be drawn approximately 12 hours after the previous dose of lithium.
  7. If signs of overdose occur (eg, vomiting, diarrhea, unsteady walking, tremor, drowsiness, muscle weakness), stop taking lithium and contact the prescribing physician or other health care provider.
mellitus, SSRIs may have a hypoglycemic effect. Bupropion and venlafaxine have little effect on blood sugar levels.

Lithium is the drug of choice for clients with bipolar disorder. When used therapeutically, lithium is effective in controlling mania in 65% to 80% of clients. When used prophylactically, the drug decreases the frequency and intensity of manic cycles. Carbamazepine (Tegretol), an anticonvulsant, may be as effective as lithium as a mood-stabilizing agent. It is often used in clients who do not respond to lithium, although it is not approved by the FDA for this purpose.

**Drug Dosage and Administration**

Dosage of antidepressant drugs should be individualized according to clinical response. Antidepressant drug therapy is usually initiated with small, divided doses that are gradually increased until therapeutic or adverse effects occur.

With SSRIs and venlafaxine, therapy is begun with once-daily oral administration of the manufacturer’s recommended dosage. Dosage may be increased after 3 or 4 weeks if depression is not relieved. As with most other drugs, smaller doses may be indicated in older adults and in clients taking multiple medications.

**APPLYING YOUR KNOWLEDGE 10-3**

Mr. Mehring reports he is having difficulty sleeping. What measures should be initiated?

With TCAs, therapy is begun with small doses, which are increased to the desired dose over 1 to 2 weeks. Minimal effective doses are approximately 150 milligrams per day of imipramine (Tofranil) or its equivalent. TCAs can be administered once or twice daily because they have long elimination half-lives. After dosage is established, TCAs are often given once daily at bedtime. This regimen is effective and well tolerated by most clients. Elderly clients may experience fewer adverse reactions if divided doses are continued. With TCAs, measurement of plasma levels is helpful in adjusting dosages.

With bupropion, seizures are more likely to occur with large single doses, large total doses, and large or abrupt increases in dosage. Recommendations to avoid these risk factors are as follows:

- Give bupropion in equally divided doses, three times daily (at least 6 hours apart) for immediate-release tablets, twice daily for sustained-release tablets, and once a day for extended-release forms of bupropion XL.
- The maximal single dose of immediate-release tablets is 150 mg (sustained-release, 200 mg; XL, 450 mg).
- The recommended initial dose is 200 mg, gradually increased to 300 mg. If no clinical improvement occurs after several weeks of 300 mg/day, the dosage may be increased to 450 mg, the maximal daily dose for immediate-release tablets (sustained-release, 400 mg; XL, 450 mg).
- The recommended maintenance dose is the lowest amount that maintains remission.

With lithium, dosage should be based on serum lithium levels, control of symptoms, and occurrence of adverse effects. Measurements of serum levels are required because therapeutic doses are only slightly lower than toxic doses and because clients vary widely in rates of lithium absorption and excretion. Thus, a dose that is therapeutic in one client may be toxic in another. Lower doses are indicated for older adults and for clients with conditions that impair lithium excretion (eg, diuretic drug therapy, dehydration, low-salt diet, renal impairment, decreased cardiac output).

When lithium therapy is being initiated, the serum drug concentration should be measured two or three times weekly in the morning, 12 hours after the last dose of lithium. For most clients, the therapeutic range of serum drug levels is 0.5 to 1.2 milliequivalents per liter (mEq/L; SI units, 0.5 to 1.2 mmol/L). Serum lithium levels should not exceed 1.5 milliequivalents per liter, because the risk of serious toxicity is increased at higher levels.

After symptoms of mania are controlled, lithium doses should be lowered. Serum lithium levels should be measured at least every 3 months during long-term maintenance therapy.

**Duration of Drug Therapy**

Guidelines for the duration of antidepressant drug therapy are not well established, and there are differences of opinion. Some authorities recommend 9 months of treatment after symptoms subside for a first episode of depression; 5 years after symptoms subside for a second episode; and long-term therapy after a third episode. One argument for long-term maintenance therapy is that depression tends to relapse or recur, and successive episodes often are more severe and more difficult to treat.

Maintenance therapy for depression requires close supervision and periodic reassessment of the client’s condition and response. With the use of TCAs for acute depression, low doses have been given for several months, followed by gradual tapering of the dose and then drug discontinuation. However, recent studies indicate that full therapeutic doses (if clients can tolerate the adverse effects) for as long as 5 years are effective in preventing recurrent episodes. The long-term effects of SSRIs and newer agents have not been studied.

With lithium, long-term therapy is the usual practice because of a high recurrence rate if the drug is discontinued. When lithium is discontinued, most often because of adverse effects or the client’s lack of adherence to the prescribed regimen, gradually tapering the dose over 2 to 4 weeks delays recurrence of symptoms.

**Effects of Antidepressants on Other Drugs**

The SSRIs are strong inhibitors of the cytochrome P450 enzyme system, which metabolizes many drugs, especially
those metabolized by the 1A2, 2D6, and 3A4 groups of enzymes. Inhibiting the enzymes that normally metabolize or inactivate a drug produces the same effect as an excessive dose of the inhibited drug. As a result, serum drug levels and risks of adverse effects are greatly increased. Specific interactions include the following:

- Fluvoxamine inhibits both 1A2 and 3A4 enzymes. Inhibition of 1A2 enzymes slows metabolism of acetaminophen, caffeine, clozapine, haloperidol, olanzapine, tacrine, theophylline, TCAs, and warfarin. Inhibition of 3A4 enzymes slows metabolism of benzodiaze- pines (alprazolam, midazolam, triazolam), calcium channel blockers (diltiazem, nifedipine, verapamil), cyclosporine, erythromycin, protease inhibitors (anti- acquired immunodeficiency syndrome (AIDS) drugs, indinavir, ritonavir, saquinavir), steroids, tamoxifen, warfarin, and zolpidem.
- Fluoxetine, paroxetine, and sertraline inhibit 2D6 enzymes and slow metabolism of bupropion, codeine, desipramine, dextromethorphan, flecainide, metoprolol, nortriptyline, phenothiazines, propranolol, risperi- done, and timolol.
- TCAs are metabolized by 2D6 enzymes and may inhibit the metabolism of other drugs metabolized by the 2D6 group (other antidepressants, phenothiazines, carba- mazepine, flecainide, propafenone). Lower-than-usual doses of both the TCA and the other drug may be needed.
- Mirtazapine and venlafaxine are not thought to have clinically significant effects on cytochrome P450 enzymes, but few studies have been done and effects are unknown.

### Antidepressants and Suicide

In 2004, the FDA issued a public health advisory regarding worsening depression and suicidality in pediatric and adult clients taking antidepressant medications. The drugs that are the focus of this warning are the SSRIs citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), and sertraline (Zoloft), and the other antidepressants bupropion (Wellbutrin), mirtazapine (Remeron), and venlafaxine (Effexor). Although the FDA has not presently concluded that these antidepressants worsen depression or cause suicidality, a warning statement recommending observation of adult and pediatric clients treated with these agents for worsening depression or the emergence of suicidality (especially at the onset of drug therapy, or when dosages are increased or decreased) has been added to product labeling. Health care providers should be aware that worsening symptoms could be a result of underlying disease or drug therapy. Symptoms of concern include anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania. The presence of these symptoms, especially if new (ie, not part of the client’s presenting symptoms), severe, or abrupt in onset should prompt evaluation of drug therapy and possible discontinuation of medications. If the decision is made to discontinue antidepressant therapy, it is important that medications be tapered rather than abruptly discontinued.

The FDA plans to continue to review data from clinical trials on antidepressant medications, data from drug manu- facturers, and recommendations from groups such as the Psychopharmacological Drugs Advisory Committee and the Pediatric Subcommittee of the Anti-Infective Drugs Advi- sory Committee to try to determine whether there is significant evidence that some or all antidepressants increase the risk of suicidality.

### Toxicity: Recognition and Management

Some antidepressant drugs are highly toxic and potentially lethal when taken in large doses. Toxicity is most likely to occur in depressed clients who intentionally ingest large amounts of drug in suicide attempts and in young children who accidentally gain access to medication containers. Mea- sures to prevent acute poisoning from drug overdose include dispensing only a few days’ supply (ie, 5 to 7 days) to clients with suicidal tendencies and storing the drugs in places inaccessible to young children. General measures to treat acute poisoning include early detection of signs and symptoms, stopping the drug, and instituting treatment if indicated. Spe- cific symptoms and signs of overdose and treatment measures include the following:

- **SSRIs:** Symptoms include nausea, vomiting, agitation, restlessness, hypomania, and other signs of CNS stimu- lation. Management includes symptomatic and support- tive treatment, such as maintaining an adequate airway and ventilation and administering activated charcoal.

- **TCAs:** Symptoms occur 1 to 4 hours after drug in- gestion and consist primarily of CNS depression and cardiovascular effects (eg, nystagmus, tremor, rest- lessness, seizures, hypotension, dysrhythmias, myocardial depression). Death usually results from cardiac, respiratory, and circulatory failure. Management of TCA toxicity consists of performing gastric lavage and giving activated charcoal to reduce drug absorption; establishing and maintaining a patent airway; performing continuous ECG monitoring of comatose clients or those with respiratory insufficiency or wide QRS intervals; giving intravenous fluids and vasopres- sors for severe hypotension; and giving intravenous phenytoin (Dilantin) or fosphenytoin (Cerebyx), or a parenteral benzodiazepine (eg, lorazepam) if seizures occur.

- **MAO inhibitors:** Symptoms occur 12 hours or more after drug ingestion and consist primarily of adrenergic effects (eg, tachycardia, increased rate of respiration, agitation, tremors, convulsive seizures, sweating, heart block, hypotension, delirium, coma). Management con- sists of diuresis, acidification of urine, or hemodialysis to remove the drug from the body.
Bupropion: Symptoms include agitation and other mental status changes, nausea and vomiting, and seizures. General treatment measures include hospitalization, decreasing absorption (eg, giving activated charcoal to conscious clients), and supporting vital functions. If seizures occur, an intravenous benzodiazepine (eg, lorazepam) is the drug of first choice.

Venlafaxine: Symptoms include increased incidence or severity of adverse effects, with nausea, vomiting, and drowsiness most often reported. Seizures and diastolic hypertension may also occur. There are no specific antidotes; treatment is symptomatic and supportive.

Lithium: Toxic manifestations occur at serum lithium levels greater than 2.5 mEq/L and include nystagmus, tremors, oliguria, confusion, impaired consciousness, visual or tactile hallucinations, choreiform movements, convulsions, coma, and death. Treatment involves supportive care to maintain vital functions, including correction of fluid and electrolyte imbalances. With severe overdoses, hemodialysis is preferred because it removes lithium from the body.

Antidepressant Withdrawal: Prevention and Management

Withdrawal symptoms have been reported with sudden discontinuation of most antidepressant drugs. In general, symptoms occur more rapidly and may be more intense with drugs that have a short half-life. As with other psychotropic drugs, these antidepressant drugs should be tapered in dosage and discontinued gradually unless severe drug toxicity, anaphylactic reactions, or other life-threatening conditions are present. Most antidepressants may be tapered and discontinued over approximately 1 week without serious withdrawal symptoms. For a client on maintenance drug therapy, the occurrence of withdrawal symptoms may indicate that the client has omitted doses or stopped taking the drug.

The most clearly defined withdrawal syndromes are associated with SSRIs and TCAs. With SSRIs, withdrawal symptoms include dizziness, nausea, and headache and last from several days to several weeks. More serious symptoms may include aggression, hypomania, mood disturbances, and suicidal tendencies. Fluoxetine has a long half-life and has not been associated with withdrawal symptoms. Other SSRIs have short half-lives and may cause withdrawal reactions if stopped abruptly. Paroxetine, which has a half-life of approximately 24 hours and does not produce active metabolites, may be associated with relatively severe withdrawal symptoms even when discontinued gradually, over 7 to 10 days. Symptoms may include a flu-like syndrome with nausea, vomiting, fatigue, muscle aches, dizziness, headache, and insomnia. The short-acting SSRIs should be tapered in dosage and gradually discontinued to prevent or minimize withdrawal reactions.

With TCAs, the main concern is strong anticholinergic effects. When stopped abruptly, especially with high doses, these drugs can cause symptoms of excessive cholinergic activity (ie, hypersalivation, diarrhea, urinary urgency, abdominal cramping, and sweating). A recommended rate for tapering TCAs is approximately 25 to 50 milligrams every 2 to 3 days.

Perioperative Use

Antidepressants must be used very cautiously, if at all, perioperatively because of the risk of serious adverse effects and adverse interactions with anesthetics and other commonly used drugs. It is usually recommended that antidepressants be tapered in dosage and gradually discontinued. MAO inhibitors are contraindicated and should be discontinued at least 10 days before elective surgery. TCAs should be discontinued several days before elective surgery and resumed several days after surgery. SSRIs and other antidepressants have not been studied in relation to perioperative use; however, it seems reasonable to discontinue the drugs when feasible because of potential adverse effects, especially on the cardiovascular system and CNS.

Lithium should be stopped 1 to 2 days before surgery and resumed when full oral intake of food and fluids is allowed. Lithium may prolong the effects of anesthetics and neuromuscular blocking drugs.

Use in Special Populations

Use in Various Ethnic Groups

Antidepressant drug therapy for nonwhite populations in the United States is based primarily on dosage recommendations, pharmacokinetic data, and adverse effects derived from white recipients. However, several studies document differences in drug effects in nonwhite populations. The differences are mainly attributed to genetic or ethnic variations in drug-metabolizing enzymes in the liver. Although all ethnic groups are genetically heterogeneous and individual members may respond differently, health care providers must consider potential differences in responses to drug therapy.

African Americans tend to have higher plasma drug levels for a given dose, respond more rapidly, experience a higher incidence of adverse effects, and metabolize TCAs more slowly than whites. To decrease adverse effects, initial doses may need to be lower than those given to whites, and later doses should be titrated according to clinical response and serum drug levels. In addition, baseline and periodic ECGs are recommended to detect adverse drug effects on the heart. Studies have not been done with newer antidepressants. With lithium, African Americans report more adverse reactions than whites and may need smaller doses.

Asians tend to metabolize antidepressant drugs slowly and therefore have higher plasma drug levels for a given dose than whites. Most studies have been done with TCAs and a limited
number of Asian subgroups. Thus, it cannot be assumed that all antidepressant drugs and all people of Asian heritage respond the same. To avoid drug toxicity, initial doses should be approximately half the usual doses given to whites, and later doses should be titrated according to clinical response and serum drug levels. This recommendation is supported by a survey from several Asian countries that reported the use of much smaller doses of TCAs than in the United States. In addition, baseline and periodic ECGs are also recommended for Asian clients to detect adverse drug effects on the heart. Studies have not been done with newer antidepressants. With lithium, there are no apparent differences between effects in Asians and whites.

Hispanics’ reactions to antidepressant drugs is largely unknown. Few studies have been performed; some report a need for lower doses of TCAs and greater susceptibility to anticholinergic effects, whereas others report no differences between Hispanics and whites.

Use in Children

Antidepressant drugs are widely prescribed in children and adolescents, in whom depression commonly occurs. However, only a few drugs are actually approved for use in the pediatric population. There is growing concern about a possibility that some antidepressant medications may worsen depression and suicidality in the pediatric population (see “Antidepressants and Suicidality”). These concerns are currently under investigation by the FDA. Overall, there are few reliable data or guidelines for the use of antidepressants in children and adolescents. Clinical trials are currently underway to address these concerns.

For most children and adolescents, it is probably best to reserve drug therapy for those who do not respond to nonpharmacologic treatment and those whose depression is persistent or severe enough to impair function in usual activities of daily living. The long-term effects of antidepressant drugs on the developing brain are unknown. FDA-approved SSRIs are considered first-line antidepressants and safer than TCAs and MAO inhibitors for children with depression. Fluoxetine is approved for treatment of pediatric major depression. (In addition, fluoxetine, sertraline, and fluvoxamine are approved for treatment of obsessive-compulsive disorder in children.) Common adverse effects include sedation and activation; it is often difficult to distinguish therapeutic effects (improvement of mood, increased energy and motivation) from the adverse effects of behavioral activation (agitation, hypomania, restlessness).

Safety and effectiveness have not been established for amoxapine and MAO inhibitors in children younger than 16 years of age or for bupropion, mirtazapine, and venlafaxine in children younger than 18 years of age.

TCAs are not recommended for use in children younger than 12 years of age except for short-term treatment of enuresis in children older than 6 years of age. Amitriptyline, desipramine, imipramine, and nortriptyline are the TCAs most commonly prescribed to treat depression in children older than 12 years of age. Because of potentially serious adverse effects, blood pressure, ECGs, and plasma drug levels should be monitored. There is evidence that children metabolize TCAs faster than adults, and withdrawal symptoms (eg, increased GI motility, malaise, headache) are more common in children than in adults. Several TCAs are approved for treatment of depression in adolescents. (Clomipramine is approved for treatment of obsessive-compulsive disorder in children, and imipramine is also approved for treating childhood enuresis in children older than 6 years of age.)

Divided doses may be better tolerated and minimize withdrawal symptoms. When a TCA is used for enuresis, effectiveness may decrease over time, and no residual benefits continue after the drug is stopped. Common adverse effects include sedation, fatigue, nervousness, and sleep disorders. A TCA probably is not a drug of first choice for adolescents because TCAs are more toxic in overdose than other antidepressants, and suicide is a leading cause of death in adolescents.

For adolescents, it may be important to discuss sexual effects because the SSRIs and venlafaxine cause a high incidence of sexual dysfunction (eg, anorgasmia, decreased libido, erectile dysfunction). Bupropion and mirtazapine are unlikely to cause sexual dysfunction.

Lithium is not approved for use in children younger than 12 years of age, but it has been used to treat bipolar disorder and aggressiveness. Children normally excrete lithium more rapidly than adults. As with adults, initial doses should be relatively low and gradually increased according to regular measurements of serum drug levels.

Use in Older Adults

SSRIs are the drugs of choice in older adults as in younger ones because they produce fewer sedative, anticholinergic, cardiotoxic, and psychomotor adverse effects than the TCAs and related antidepressants. These drugs produce similar adverse effects in older adults as in younger adults. Although their effects in older adults are not well delineated, SSRIs may be eliminated more slowly, and smaller or less frequent doses may be prudent. The weight loss often associated with SSRIs may be undesirable in older adults. Venlafaxine may also be used in older adults, with smaller initial doses and increments recommended.

TCAs may cause or aggravate conditions that are common in older adults (eg, cardiac conduction abnormalities, urinary retention, narrow-angle glaucoma). In addition, impaired compensatory mechanisms make older adults more likely to experience anticholinergic effects, confusion, hypotension, and sedation. If a TCA is chosen for an older adult, nortriptyline or desipramine is preferred. In addition, any TCA should be given in small doses initially and gradually increased over several weeks, if necessary, to achieve therapeutic effects. Initial and maintenance doses should be small because the
drugs are metabolized and excreted more slowly than in younger adults. Initial dosage should be decreased by 30% to 50% to avoid serious adverse reactions; increments should be small. Vital signs, serum drug levels, and ECGs should be monitored regularly.

MAO inhibitors may be more likely to cause hypertensive crises in older adults because cardiovascular, renal, and hepatic functions are often diminished.

With lithium, initial doses should be low and increased gradually, according to regular measurements of serum drug levels.

Use in Clients With Renal Impairment

Antidepressants should be used cautiously in the presence of severe renal impairment. Mild or moderate impairment contributes to few adverse effects, but severe impairment may increase plasma drug levels and adverse effects of virtually all antidepressants. Thus, small initial doses, slow increases, and less frequent dosing are indicated.

Lithium is eliminated only by the kidneys and it has a very narrow therapeutic range. If given to a client with renal impairment or unstable renal function, the dose must be markedly reduced and plasma lithium levels must be closely monitored.

Use in Clients With Hepatic Impairment

Hepatic impairment leads to reduced first-pass metabolism of most antidepressant drugs, resulting in higher plasma levels. The drugs should be used cautiously in clients with severe liver impairment. Cautious use means lower doses, longer intervals between doses, and slower dose increases than usual.

Fluoxetine and sertraline are less readily metabolized to their active metabolites in clients with hepatic impairment. For example, in clients with cirrhosis, the average half-life of fluoxetine may increase from 2 to 3 days to more than 7 days and that of norfluoxetine, the active metabolite, from 7 to 9 days to 12 days. Clearance of sertraline is also decreased in clients with cirrhosis. Paroxetine has a short half-life and no active metabolites, but increased plasma levels can occur with severe hepatic impairment.

TCAs are also less readily metabolized in people with severe hepatic impairment (eg, severe cirrhosis). This increases the risk of adverse effects such as sedation and hypotension.

Use in Clients With Critical Illness

Critically ill clients may be receiving an antidepressant when the critical illness develops or may need a drug to combat the depression that often develops with major illness. The decision to continue or start an antidepressant should be based on a thorough assessment of the client’s condition, other drugs being given, potential adverse drug effects, and other factors. If an antidepressant is given, its use must be cautious and slow and the client’s responses carefully monitored because critically ill clients are often frail and unstable, with multiple organ dysfunctions.

Use in Home Care

Whatever the primary problem for which a home care nurse is visiting a client, he or she must be vigilant for signs and symptoms of major depression. Depression often accompanies any serious physical illness and may occur in many other circumstances as well. The main role of the nurse may be recognizing depressive states and referring clients for treatment.

If an antidepressant medication was recently started, the nurse may need to remind the client that it usually takes 2 to 4 weeks to take effect. The nurse should encourage the client to continue taking the medication. In addition, the nurse should observe the client’s response and assess for suicidal thoughts or plans, especially at the beginning of therapy or when dosages are increased or decreased. The family should be taught to report any change in the client’s behavior, especially anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania. A client who has one or more of these symptoms may be at greater risk for worsening depression or suicidality.

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**Nursing Actions**

**Antidepressants**

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<th>Nursing Actions</th>
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<tr>
<td>a. Give most selective serotonin reuptake inhibitors (SSRIs) once daily in the morning; citalopram, escitalopram, and sertraline may be given morning or evening.</td>
<td>To prevent insomnia</td>
</tr>
<tr>
<td>b. Mix sertraline oral concentrate (20 mg/mL) in 4 oz of water, ginger ale, lemon/lime soda, lemonade, or orange juice only; give immediately after mixing.</td>
<td>Manufacturer’s recommendations</td>
</tr>
</tbody>
</table>
### Nursing Actions

| c. | Give tricyclic antidepressants (TCAs) and mirtazapine at bedtime. | To aid sleep and decrease daytime sedation |
| d. | Give venlafaxine and lithium with food. | To decrease gastrointestinal (GI) effects (eg, nausea and vomiting) |

#### 2. Observe for therapeutic effects

- a. With antidepressants for depression, observe for statements of feeling better or less depressed; increased appetite, physical activity, and interest in surroundings; improved sleep patterns; improved appearance; decreased anxiety; decreased somatic complaints.
- b. With antidepressants for anxiety disorders, observe for decreased symptoms of the disorders (see Chap. 8).
- c. With lithium, observe for decreases in manic behavior and mood swings.

#### 3. Observe for adverse effects

- a. With SSRIs and venlafaxine, observe for dizziness, headache, nervousness, insomnia, nausea, diarrhea, dizziness, dry mouth, sedation, skin rash, sexual dysfunction.
- b. With TCAs, observe for:
  1. Central nervous system (CNS) effects—drowsiness, dizziness, confusion, poor memory
  2. GI effects—nausea, dry mouth, constipation
  3. Cardiovascular effects—cardiac dysrhythmias, tachycardia, orthostatic hypotension
  4. Other effects—blurred vision, urinary retention, sexual dysfunction, weight gain or loss
- c. With monoamine oxidase (MAO) inhibitors, observe for blurred vision, constipation, dizziness, dry mouth, hypotension, urinary retention, hypoglycemia.
- d. With bupropion, observe for seizure activity, CNS stimulation (agitation, insomnia, hyperactivity, hallucinations, delusions), headache, nausea and vomiting, weight loss.
- e. With mirtazapine, observe for sedation, confusion, dry mouth, constipation, nausea and vomiting, hypotension, tachycardia, urinary retention, photophobia, skin rash, weight gain.
- f. With lithium, observe for:
  1. Metallic taste, hand tremors, nausea, polyuria, polydipsia, diarrhea, muscular weakness, fatigue, edema, weight gain
  2. More severe nausea and diarrhea, vomiting, ataxia, incoordination, dizziness, slurred speech, blurred vision, tinnitus, muscle twitching and tremors, increased muscle tone
  3. Leukocytosis

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(continued)
NURSING ACTIONS | RATIONALE/EXPLANATION
---|---
4. Observe for drug interactions
   a. Drugs that increase effects of SSRIs:
      1. Cimetidine
      2. MAO inhibitors
      3. Linezolid
      4. Sumatriptan
      5. Nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, warfarin
   b. Drugs that decrease effects of SSRIs:
      1. Carbamazepine, phenytoin, rifampin
      2. Cyproheptadine
   c. Drugs that increase effects of mirtazapine and venlafaxine:
      1. MAO inhibitors
   d. Drugs that increase effects of TCAs:
      1. Antidysrhythmics (eg, quinidine, disopyramide, procainamide)
      2. Antihistamines, atropine, and other drugs with anticholinergic effects
      3. Antihypertensives
      4. Cimetidine
      5. CNS depressants (eg, alcohol, benzodiazepine antianxiety and hypnotic agents, opioid analgesics)
      6. MAO inhibitors
      7. SSRIs
   e. Drugs that decrease effects of TCAs:
      1. Carbamazepine, phenytoin, rifampin, nicotine (cigarette smoking)

Drug interactions with the SSRIs vary with individual drugs. May increase serum drug levels of SSRIs by slowing their metabolism. SSRIs and MAO inhibitors should not be given concurrently or close together because serious and fatal reactions have occurred. The reaction, attributed to excess serotonin and called the serotonin syndrome, may cause hyperthermia, muscle spasm, agitation, delirium, and coma. To avoid this reaction, an SSRI should not be started for at least 2 weeks after an MAO inhibitor is discontinued, and an MAO inhibitor should not be started for at least 2 weeks after an SSRI has been discontinued (5 weeks with fluoxetine, because of its long half-life).

The antibiotic linezolid is a reversible nonselective MAO inhibitor (see above).

Postmarketing studies report concomitant use of SSRIs and sumatriptan may result in weakness, hyperreflexia, and incoordination.

Serotonin release by platelets plays a role in hemostasis, and SSRIs may interfere with this release, resulting in an increased incidence of GI bleeding. Concomitant use of NSAIDs, aspirin, or warfarin potentiates this risk.

These drugs induce liver enzymes that accelerate the metabolism of the SSRIs.

This is an antihistamine with antiserotonin effects.

See SSRIs, above. These drugs and MAO inhibitors should not be given concurrently or close together because serious and fatal reactions have occurred. Mirtazapine should be stopped at least 14 days and venlafaxine at least 7 days before starting an MAO inhibitor, and an MAO inhibitor should be stopped at least 14 days before starting mirtazapine or venlafaxine.

Additive effects on cardiac conduction, increasing risk of heart block

Additive anticholinergic effects (eg, dry mouth, blurred vision, urinary retention, constipation)

Additive hypotension

Increases risks of toxicity by decreasing hepatic metabolism and increasing blood levels of TCAs

Additive sedation and CNS depression

TCAs should not be given with MAO inhibitors or within 2 weeks after an MAO inhibitor drug; hyperpyrexia, convulsions, and death have occurred with concurrent use.

Inhibit metabolism of TCAs

These drugs induce drug-metabolizing enzymes in the liver, which increases the rate of TCA metabolism and elimination from the body.
NURSING ACTIONS

f. Drugs that increase effects of MAO inhibitors:
   1. Anticholinergic drugs (eg, atropine, antipsychotic agents, TCAs)
   2. Adrenergic agents (eg, epinephrine, phenylephrine), alcohol (some beers and wines), levodopa, meperidine

   RATIONALE/EXPLANATION
   - Increase neurotoxicity and cardiotoxicity of lithium by increasing excretion of sodium and potassium and thereby decreasing excretion of lithium.
   - Decrease renal clearance of lithium and thus increase serum lithium levels and risks of toxicity.
   - Additive anticholinergic effects
   - Hypertensive crisis and stroke may occur.

  
g. Drugs that increase effects of lithium:
   1. Angiotensin-converting enzyme inhibitors (eg, captopril)
   2. Diuretics (eg, furosemide, hydrochlorothiazide)
   3. NSAIDs
   4. Phenothiazines
   5. TCAs

   RATIONALE/EXPLANATION
   - Decrease renal clearance of lithium and thus increase serum levels and risks of lithium toxicity.
   - Increased risk of hyperglycemia
   - May increase effects of lithium and are sometimes combined with lithium for this purpose. These drugs also may precipitate a manic episode and increase risks of hypothyroidism.
   - Decrease renal clearance of lithium and thus increase serum lithium levels and risks of toxicity.

  
h. Drugs that decrease effects of lithium:
   1. Acetazolamide, sodium chloride (in excessive amounts), drugs with a high sodium content (eg, ticarcillin), theophylline

   RATIONALE/EXPLANATION
   - Increase excretion of lithium

APPLYING YOUR KNOWLEDGE: ANSWERS

10-1 The nurse should never leave an antidepressant at the bedside. Charting the medication as given when it has not yet been taken by the client is not truthful, and the client may forget to take the medication or may hold the medication for a later time and save up multiple doses. This is especially problematic with a client suffering from depression because he or she may have suicidal ideations.

10-2 Some antidepressant medications, such as sertraline, are in the class of selective serotonin reuptake inhibitors (SSRIs), which may not reach a therapeutic effect for up to 2 to 4 weeks. Provide appropriate teaching for both the client and his wife regarding therapeutic effect. Check to make sure that Mr. Mehring is taking the right dosage. Encourage him to continue taking the medication.

10-3 Check with the physician to see if Mr. Mehring’s dose can be taken once a day in the morning. If this is not possible, then check to see if a different SSRI can be given that has once-a-day dosing. Taking the dose in the morning may solve Mr. Mehring’s sleeping difficulty if the problem is due to the drug and not due to the depression.

Review and Application Exercises

Short Answer Exercises

1. During the initial assessment of any client, what kinds of appearances or behaviors may indicate depression?

2. Is antidepressant drug therapy indicated for most episodes of temporary sadness? Why or why not?

3. What are the major groups of antidepressant drugs?

4. How do the drugs act to relieve depression?

5. When a client begins antidepressant drug therapy, why is it important to explain that relief of depression may not occur for a few weeks?

6. What are common adverse effects of TCAs, and how may they be minimized?

7. What is the advantage of giving a TCA at bedtime rather than in the morning?

8. For a client taking an MAO inhibitor, what information would you provide for preventing a hypertensive crisis?
9. How do the SSRIs differ from TCAs?
10. How do the newer drugs, including mirtazapine and venlafaxine, compare with the SSRIs in terms of adverse effects and adverse drug–drug interactions?
11. List the main elements of treatment of antidepressant overdoses.
12. What are common adverse effects of lithium, and how may they be minimized?
13. What is the nurse’s role in assessing and managing depression in special populations? In the home setting?

NCLEX-Style Questions

14. A nurse is teaching the importance of proper diet to a client taking tranylcypromine (Parnate) for depression. Which of the following food selections by the client indicates that further teaching is needed?
   a. a tossed salad and a bowl of vegetable soup
   b. a sandwich with salami and Swiss cheese
   c. a hamburger and french fries
   d. a cold plate with cottage cheese, chicken salad, and grapes

15. A client taking lithium is having problems with coordination and unstable gait. The client’s lithium level is 2.3 mEq/L. The nurse should do which of the following?
   a. Continue to administer the lithium three times per day.
   b. Skip a dose of lithium and then resume the regular medication schedule.
   c. Administer an extra dose of lithium.
   d. Withhold the lithium and notify the physician of the lithium level.

16. Today your client begins a new drug regimen of escitalopram (Lexapro) for depression. Before administering this medication, you should assess for which of the following?
   a. prior recent use of monoamine oxidase inhibitor antidepressants (MAO inhibitors)
   b. prior diet high in tyramine-containing foods
   c. history of cigarette use
   d. history of seizure disorders

17. Your client has been taking imipramine (Tofranil) for 1 week for depression. He tells you he is going to stop taking this medication because it isn’t working. Your best response is which of the following?
   a. “Contact your physician about taking a different antidepressant medication.”
   b. “It may take up to 4 weeks before this medication makes you feel better.”
   c. “You should slowly taper rather than suddenly discontinue this medication.”
   d. “You should take an extra dose today to build up your blood level and get faster results.”

Selected References


