Anxiety disorders are prevalent (the estimated lifetime prevalence is 29% in the general population) and a frequent precipitant of visits to the nonpsychiatric physician. Evaluation and management can be challenging because patients present with feelings of distress and concern about disease in the absence of objective evidence. Suffering no less from the subjective nature of their ailment, they fear something is amiss with their bodies and persistently seek an acceptable explanation and relief. The autonomic arousal accompanying anxiety may affect many organ systems and imitate physical disease. Moreover, anxiety and anxiety-like symptoms may be consequent to a variety of medical ailments and their treatments. Anxiety is a normal human emotion. Distinguishing normal anxiety from pathologic anxiety and anxiety disorders often requires systematic evaluation and a thorough understanding of the individual patient's physical and psychological status. Underrecognized and undertreated, anxiety disorders increase the cost of medical care and render patients vulnerable to further morbidity, including depression, hypochondriasis, demoralization, and varying degrees of disability. A comprehensive and empathic assessment of the anxious patient by the primary care physician permits a reasoned and often therapeutically effective approach to the difficult problems presented.

**Neurotransmitter Mechanisms**

Several monoamine and neuropeptide neurotransmitters are implicated in the neurobiology of anxiety. Norepinephrine plays a prominent role in mediating anxiety states centrally. The locus caeruleus of thepons serves as the chief noradrenergic nucleus. Abnormal firing patterns in the locus caeruleus have been implicated in the pathophysiology of some anxiety conditions, such as panic disorder. In contrast, the inhibitory neurotransmitter γ-aminobutyric acid, which is ubiquitous in the brain, is implicated as serving an anxiolytic function within the limbic system. The resulting somatic manifestations of anxiety are principally mediated by the sympathetic nervous system.

**Classification and Basic Components of the Clinical Presentation**

The classification of anxiety disorders is largely based on clinical features (Table 226-1). In both its normal and pathologic forms, anxiety's manifestations consist of affective, cognitive, behavioral, and somatic components. The affective component is characterized by the experience of dread, foreboding, or panic. In its normal form, the affective component is countered by cognitions that make sense of or seek to neutralize the distress. In the pathologic form, other components of the clinical presentation may be exacerbated by cognitions, such as catastrophizing. A variety of behaviors, such as avoidance or hypervigilance, reflect the anxious state or evolve in response to it. Typical psychological presentations might include complaints of apprehension, motor tension or agitation (restlessness, edginess, jitteriness), and heightened arousal (including hypervigilance, distractibility, impaired concentration, and insomnia). The somatic complaints are mostly those of autonomic hyperactivity and include systemic, cardiopulmonary, gastrointestinal, urinary, and neurologic symptoms (Table 226-2).

**Adjustment Disorder with Anxious Mood**

Most presentations of anxiety within the medical setting are normal reactions to anxiety-provoking situations. For a limited time period, a patient may suffer symptoms similar to those of a generalized anxiety disorder (GAD) (see later discussion). When a patient's capacity for coping is overwhelmed, excessive anxiety may transiently emerge until the patient is able to adjust. This state is termed adjustment disorder with anxious mood and typically resolves in less than 6 months. Adjustment disorders also may be heralded by other manifestations, including depressed mood and misconduct.

**Generalized Anxiety Disorder**

This common condition is characterized by anxiety lasting longer than 6 months and worry extending beyond a specific subject. Typically, the patient ruminates with worries over a variety of concerns and may have been doing this for several...
years with a waxing and waning course. GAD also includes an array of physical concomitants, including restlessness, fatigability, poor concentration, irritability, muscle tension, and insomnia. In addition to the persistent anxious state, the patient may describe more-discrete episodes of acute anxiety.

When sudden spells of extreme anxiety occur with prominent symptoms of sympathetic activation, they may be accompanied by feelings of impending doom, fear of dying, the sensation of panic, and the impulse to flee. Such symptoms characterize panic attacks, which may occasionally be experienced by patients with GAD, although they are a more prominent feature in panic disorder.

### Panic Disorder

Panic disorder is characterized by recurrent unexpected panic attacks, with at least one attack followed by no less than 1 month of persistent concern about having additional attacks, worry about the implications of the attack or its consequences (e.g., losing control, having a heart attack), or a significant change in behavior related to the attacks. Panic disorder is more common in women and in those with a positive family history of panic. Emergence of anxiety symptoms early in life, including a history of separation difficulties during childhood, also represents risk factors for panic disorder.

Many patients become disabled by anticipatory fear of subsequent panic attacks and by phobic avoidant behavior patterns. They avoid places with restricted escape (e.g., crowds, theaters, tunnels, elevators), fearful of being trapped during an attack. In its most extreme form, agoraphobia (literally, “fear of the market place”), avoidant behavior may reach a point at which a patient is afraid to leave the safety of the home or to be left alone. In rare situations, agoraphobia has also been reported to occur in the absence of panic disorder. (More commonly, the patient whose family describes him or her as “never leaving the house” has depression with loss of interest in doing activities as a prominent symptom.)

The course of panic disorder includes times of frequent panic attacks interspersed with periods of less frequent episodes, complicated by phobic avoidance and anticipatory anxiety. The paroxysmal nature of panic attacks and the prominence of autonomic symptoms may mimic cardiac or neurologic disease, causing some patients to become hypervigilant, convinced of a serious underlying medical disorder, and “doctor shoppers” in search of such a diagnosis. Such persons may become demoralized, depressed, and debilitated. Suicide risk appears to be markedly increased in panic disorder, especially in patients with concurrent depression.

### Phobias

A phobia is an irrational fear related to a specific stimulus. On exposure to that stimulus, the individual reliably manifests an anxiety response. A patient may suffer from a specific phobia of any specific stimulus. Although specific phobias commonly generate circumscribed symptoms, they may interfere with some aspect of a patient’s functioning due to avoidance of the phobic stimulus or perseverance in the face of great discomfort (e.g., fear of flying leading to difficulty with travel).

#### Social Anxiety Disorder (Social Phobia)

Patients with social anxiety disorder develop anxiety in situations in which they are the focus of attention or might be scrutinized publicly. The individual fears that he or she will act in a way (or show anxiety symptoms) that will be humiliating or embarrassing. Such patients may experience performance anxiety or “stage fright” but also exhibit distress in more ordinary social settings. In the generalized type of social anxiety disorder, the fear includes most social situations (participating in small groups, dating, initiating or maintaining conversations, speaking to authority figures, attending parties, etc.). Social anxiety disorder needs to be distinguished from the more limited form of normal performance anxiety, which occurs in universally acknowledged anxiety-provoking situational settings (e.g., performing in front of a very large audience or as part of a very important event).

### Obsessive–Compulsive Disorder

More common than previously recognized, obsessive–compulsive disorder (OCD) affects up to 3% of the population. It is characterized by obsessions and/or compulsions that are sufficiently severe to cause patients substantial distress or impair their ability to function.

**Obsessions** are unwanted intrusive thoughts of a bizarre, senseless, or extreme nature. The subject of obsessions typically includes sexual or violent themes, concerns about contamination, and preoccupations with organization or symmetry, which are very distressing to patients and may lead them to fear that they are “going crazy.” The recurrent and persistent thoughts, impulses, or images themselves become a source of anxiety.

**Compulsions** refer to repetitive behaviors that are performed in a stereotypical or ritualized fashion, usually in response to obsessions, sometimes in an effort to neutralize them.
Resisting the drive to perform compulsions causes escalating anxiety, whereas succumbing and performing them is accompanied by feelings of transient relief, followed by feelings of shame. Characteristic compulsions include hand washing (to neutralize contamination obsessions), checking behaviors (e.g., checking door locks and stove burners to counteract obsessions of uncertainty), and counting (to neutralize anxiety associated with other obsessions).

The relationship between the compulsions and obsessions may also be nonsensical or irrational. Usually, patients retain insight regarding the nonsensical or extreme nature of their thoughts and behaviors, which distinguishes them from psychotic persons.

Because of the shame associated with the symptoms of OCD, it is not uncommon for patients to hide the disorder from friends, family, and doctors. OCD may come to the attention of primary care physicians when a patient’s obsessions involve preoccupations with his or her bodily functions (e.g., urinary or bowel obsessions) or susceptibility to disease (e.g., obsessions with contamination or fear of AIDS). Rarely, the compulsions may be performed to such an extreme as to pose medical risk or sequelae (e.g., dermatologic complications of hand washing).

The age of onset of OCD is variable, with a bimodal distribution: a male-dominated peak in the preteen years and a female-dominated peak in the third decade of life. The clinical course is similarly variable; symptoms may arise at any age, wax and wane, and become exacerbated in times of stress.

The etiology and underlying pathophysiology of OCD are poorly understood. It has been related genetically to Tourette disorder and commonly occurs with depression. Associated disorders include body dysmorphic disorder (i.e., preoccupation with a defective body image) and trichotillomania (compulsive hair pulling).

**Posttraumatic Stress Disorder**

Several weeks after surviving exposure to an emotionally traumatic event or events (e.g., combat experience, natural disaster, physical assault, rape), the patient with posttraumatic stress disorder (PTSD) reports persistent reexperiencing of the traumatic event, via intrusive thoughts, vivid dreams, or “flashbacks.” Other characteristics requisite for the diagnosis include avoidance of stimuli associated with the trauma, hyperarousal (e.g., increased startle response), and persistence of symptoms for more than 1 month. In many cases, the symptoms may continue for years. Rarely, the syndrome emerges more than 6 months after the traumatic exposure and in such cases is designated PTSD with delayed onset.

Patients may present for medical assistance with primary complaints of anxiety or with concerns and questions regarding the neurologic underpinnings of their symptoms. Alternatively, PTSD may develop as a consequence of medical illness or procedures (e.g., amputation or cardiac defibrillation), which by their nature represent profound trauma. Medical settings may serve to trigger reexperiencing phenomena. It is important to be aware of the entity and sensitive to the needs of its sufferers.

**Substance Abuse**

Anxiety is often poorly tolerated, leading some patients to seek relief through the use or abuse of anxiolytic substances. A patient’s reliance on alcohol, benzodiazepines (BZDs), or any other sedating medication may reflect an unrecognized underlying anxiety disorder. Chronic use of sedating substances can lead to neural irritability and can cause or exacerbate anxiety after withdrawal. It often becomes difficult to differentiate the cause-and-effect relationship between substance abuse and anxiety. Patients with anxiety disorders are 50% more likely to be alcoholic, and, similarly, the prevalence of anxiety disorders is 50% higher in persons who suffer from alcohol abuse or dependence.

### TABLE 226–3 Medical Causes of Anxiety

<table>
<thead>
<tr>
<th>Type of Cause</th>
<th>Specific Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Angina pectoris, arrhythmias, congestive heart failure, hypertension, hypovolemia, myocardial infarction, syncope (of multiple causes), valvular disease, vascular collapse (shock)</td>
</tr>
<tr>
<td>Dietary</td>
<td>Caffeinism, monosodium glutamate (“Chinese restaurant syndrome”), vitamin-deficiency diseases</td>
</tr>
<tr>
<td>Drug Related</td>
<td>Akathisia (secondary to antipsychotic drugs), anticholinergic toxicity, digitalis toxicity, hallucinogens, hypotensive agents, stimulants (amphetamine, cocaine, and related drugs), withdrawal syndromes (alcohol or sedative-hypnotics)</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Anemia</td>
</tr>
<tr>
<td>Immunologic</td>
<td>Anaphylaxis, systemic lupus erythematosus</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Hyperadrenalism (Cushing disease), hyperkalemia, hyperthermia, hyperthyroidism, hypocalcemia, hypoglycemia, hypotension, hyperthyroidism, menopause, porphyria (acute intermittent)</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Encephalopathies (infectious, metabolic, and toxic), essential tremor, intracranial mass lesions, postconcussion syndrome, seizure disorders (especially of the temporal lobe), vertigo</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Asthma, chronic obstructive pulmonary disease, pneumonia, pneumothorax, pulmonary edema, pulmonary embolism</td>
</tr>
<tr>
<td>Secreting</td>
<td>Carcinoid, insulinoma, pheochromocytoma</td>
</tr>
<tr>
<td>Tumors</td>
<td>Carcinoid, insulinoma, pheochromocytoma</td>
</tr>
</tbody>
</table>

### DIFFERENTIAL DIAGNOSIS (1,6–8,11,12)

The medical differential diagnosis of the symptoms and signs associated with anxiety includes many conditions in which there is stimulation of the sympathetic nervous system (Table 226-3). Some reports suggest that undiagnosed medical ailments are responsible for a significant number of psychiatric referrals for “anxiety.” Unrecognized arrhythmias, endocrinopathies, and medication reactions may mimic anxiety disorders and vice versa.

Among the psychiatric disorders to be considered in the differential diagnosis of anxiety are the depressive disorders. They are among the most critical to recognize because they are common, treatable, carry a high risk of morbidity and mortality when untreated, and frequently coexist with symptoms of anxiety (see Chapter 227). Other psychiatric conditions presenting with anxiety as a prominent component include psychosis, dementias, and drug-related disorders.

### WORKUP (1,4–11,13)

The primary care physician’s evaluation of anxiety needs to include an assessment for medical causes and psychiatric diagnoses.

### Assessment for Medical Causes

The list of possible medical causes is much too extensive to enable a workup that includes every possibility. A reasonable alternative is to focus on any medical conditions for which the patient is already under treatment. This includes a review
of the patient’s concerns, fears, and ongoing therapies. In addition, attention is directed toward the most important disorders commonly linked with anxiety, such as dysrhythmias (see Chapter 25), hyperthyroidism (see Chapter 103), and drug reactions or withdrawal (see Chapters 229 and 235). If the patient has a single prominent symptom or constellation of symptoms that implicate a single organ system, it is worthwhile medically to evaluate that focus in detail.

The presence of multiple physical symptoms (six or more), high patient rating of symptom severity, low patient rating of health status, physician perception of the patient encounter as difficult, and age less than 30 years are important clues for an underlying anxiety or depressive disorder. Such easily identified clinical features have been shown to be independent predictors of underlying psychopathology in patients presenting to primary physicians with bodily symptoms. Because there are effective treatments for anxiety disorders, a diagnostic trial of an anxiolytic medication might help to resolve a difficult diagnostic situation. The physician must of course bear in mind that the suppression of anxiety symptoms does not rule out a medical disorder and may even worsen it (e.g., use of BZDs for anxiety accompanying a severe asthma attack).

Assessment for Psychiatric Disorders

The physician should recall that anxiety symptoms are typically conceptualized in three dimensions: psychological, somatic, and behavioral.

Psychological

Patients suffering from an anxiety disorder may complain of somatic manifestations of anxiety but may omit history pertaining to the psychological experience. Therefore, it is important to inquire specifically about psychic manifestations such as fear, panic, the sensation of impending doom, or the impulse to flee. Reviewing the features of the various anxiety disorders sometimes helps the patient to construct a clearer clinical picture, but care must be taken not to prejudice the patient’s responses or appear too eager to make a psychiatric diagnosis.

Somatic

One also needs to determine the onset, quality, intensity, and duration of symptoms, being certain to include a compassionate inquiry into recent life events and situational stressors present at the time that the symptoms emerged.

Behavioral

Identifiable stimuli or exacerbating factors should be noted, as well as settings that create apprehension. Development of avoidant behaviors should be ascertained. If a particular precipitant is identified, it is helpful to inquire into its origin (e.g., a phobia of dogs arising from a remote history of a dog bite or avoidance of elevators as a consequence of having had a panic attack in one). Often, symptoms may have arisen spontaneously, contributing to the sense that they are autonomous (as in panic disorder or OCD).

Also useful is inquiry into strategies used to alleviate the symptoms. This may uncover additional history about substance use, avoidance, or compulsive behaviors. Family history is reviewed for similar symptoms, known anxiety disorders, and related disorders such as depression or substance abuse. History of childhood school phobia or early patterns of timidity may be informative. Finally, a thorough physical examination is essential, checking for undisclosed sequelae of repetitive behaviors (as in OCD).

PRINCIPLES OF MANAGEMENT (4,5,9–30)

The treatment strategies for anxiety include psychotherapeutic and pharmacologic interventions; a combined approach yields the best results.

Psychotherapy

Psychotherapeutic treatments for anxiety help to alleviate symptoms through insight, education, support, and the reconditioning of behavioral patterns. Supportive, insight-oriented, and behavioral psychotherapies may be used individually or jointly. Data from the National Ambulatory Medical Care Survey of primary care practices show a trend toward the substitution of medication for psychotherapy, a trend that raises concern about the underutilization of psychotherapy. Recognition and utilization of the contributions of psychotherapy to treatment of anxiety are important.

Supportive Psychotherapy

The hallmark of this approach is empathic listening, education, reassurance, encouragement, and guidance. The primary care practitioner frequently performs these functions, whether or not the intervention is labeled as supportive psychotherapy. In the case of anxiety, empathic listening helps patients to feel that another human being can appreciate their suffering and, as important, not judge them harshly because of their condition. Patients with anxiety often feel ashamed, characterizing themselves as “weak” or “silly” because of their fears and behaviors. Empathy helps to cut through the shame and loneliness. Listening and encouraging patients to relate their histories can have a cathartic effect. Many patients with anxiety disorders have hidden some or all of their suffering for years.

In addition to empathic listening, patient education is crucial. It begins by informing the patient of the diagnosis and explaining its origins, prognosis, and treatment plan. Increased knowledge and understanding is empowering because it promotes a sense of command and confidence while reducing feelings of uncertainty, helplessness, and isolation. Such changes themselves are anxiolytic. Fears of serious somatic illness, “going crazy,” and incurable disease are alleviated. Reassurance serves to heal only when it addresses what is wrong and what can be done to relieve the anxiety. It must be offered in concert with true empathy and education. Reassurance in the form of “there is nothing serious,” even if given in a sympathetic, nonpatronizing manner, will be demoralizing and disappointing if offered perfunctorily. Although a negative medical workup may be reassuring to some patients, the patient with an anxiety disorder is often not relieved, because he or she is still experiencing distinctive, intrusive, and distressing symptoms. Once a strategy has been developed to manage the patient’s anxiety, guidance and encouragement are helpful to the patient in negotiating treatment trials and supervening situational stresses.

Insight-Oriented Psychotherapy

The objective with this form of therapy is to guide the patient to an understanding of the associations among circumstances, emotions, and symptoms. By exploring feelings, relationships, and actions (both past and present), the patient may develop new insights into his or her emotional makeup. This can help to reduce the symptoms of anxiety and reframe the meaning of anxiety symptoms when they do occur. Insight therapy typically requires frequent and lengthy sessions for optimal results and the skill of a good psychotherapist.
Cognitive–Behavioral Therapy
Cognitive–behavioral therapy (CBT) is especially effective for anxiety patients. It entails reconditioning or modifying patients’ behaviors or the association between a stimulus and response. Techniques include general relaxation-response training (for tolerating anxiety symptoms—see Appendix 226–1), in vivo exposure and desensitization (for phobias and avoidant behaviors), cognitive therapy (for panic and obsessions), and exposure-response prevention (for OCD). The effectiveness of each of these behavioral techniques is augmented if the patient’s anxiety can be held in check. For this reason, the cognitive and behavioral therapies may be particularly well suited for combination with pharmacotherapies. As with insight-oriented psychotherapy, CBT is best conducted by professionals specially trained in this approach.

Relaxation Techniques
Relaxation techniques are of benefit to almost anyone who suffers from anxiety. Deep muscle relaxation, autogenic exercises, and diaphragmatic breathing are taught and can be complemented by exercise training and regular exercise (see Appendix 226–1). Together, these techniques help to minimize the escalating anxiety that results from autonomic dyscontrol. Their use allows patients to better tolerate moderate anxiety states, abort panic episodes, and use more-aggressive behavioral techniques.

Exposure and Desensitization
Exposure and desensitization entail gradual reconditioning of patients by exposing them to feared stimuli in controlled settings that minimize and allow habituation to their anxiety response. In this way, the feared stimuli become better tolerated, and avoidant behaviors are eradicated as the association with the anxiety response is weakened. Similarly, the exposure-response prevention technique is used in treating OCD patients. After being exposed to a provocative stimulus, they are helped to resist the urge to perform their compulsions in response to that stimulus. Although tolerating the anxiety, they may use sanctioned relaxation techniques. Gradually, the compulsions are reduced.

Pharmacotherapy
Treatment outcomes for psychotherapy are often enhanced when pharmacotherapy is incorporated into the program. The primary goal of drug therapy is sufficient diminution of symptoms to enable performance of tasks previously impaired by anxiety, including an enhanced ability to benefit from CBT. Patients should be informed that treatment will be of limited duration and will reduce their symptoms but not eradicate them. BZDs are still the most widely used of anxiolytics. Antidepressants, anticonvulsants, and neuroleptics are also used.

Benzodiazepines
For rapid specific relief of anxiety symptoms, the BZDs offer substantial or complete relief of anxiety symptoms. There is wide individual variation in pharmacokinetic properties. For some patients, BZDs offer substantial or complete relief of anxiety symptoms. For others, they attenuate severe anxiety pending response to other anxiolytic therapies. There is wide individual variation in clinical response, plasma levels, and dosage requirements.

Ensuring Proper Use. Overuse and drug seeking from multiple sources occur in a small percentage of patients, although rarely with the intensity and risks associated with opiates, barbiturates, and other sedatives. Nevertheless, the physician should know the patient well before prescribing BZDs and be alert for signs of concurrent alcohol or drug dependence (see Chapters 228 and 233). The efficacy of treatment should be evaluated regularly by follow-up visits, with special attention to proper use. The physician should avoid prescribing by phone, calculate exact quantities required, and remain wary of “lost prescriptions” or other signs of medication misuse. To justify continued treatment, the patient should demonstrate a decrement in anxiety, with enhanced performance or decreased avoidant behavior. Requiring the patient to be seen in person for an appointment at least every 3 months is a good guideline, as is stopping the prescription of the BZD if there is a problem with compliance (e.g., attendance at appointments). BZD overuse is uncommon in the absence of a past history of alcohol or drug abuse but can be a serious problem, at times a consequence of careless prescribing practices and inadequate patient education about proper drug use. If dose requirements escalate, especially if accompanied by addictive behaviors, referral is advised to a specialist experienced in treating this problem.

Side Effects, Tolerance, and Dependence. Side effects include sedation (especially in combination with alcohol or other sedative agents), impaired memory acquisition (including amnesia reported with single-dose triazolam use), and, rarely, disinhibition characterized by increased hostility or aggression. Alcohol and cimetidine slow hepatic BZD metabolism and increase the risk of toxicity.

Daily use of BZDs over time leads to receptor adaptation (tolerance) and the development of physical dependence. Psychological dependence does not; however, imply misuse, abuse, or even loss of benefit. Rather, dependence denotes that a discontinuation syndrome will follow abrupt cessation of therapy. Withdrawal is usually accompanied by only mild symptoms but may include rebound anxiety, involuntary movements, insomnia, psychomotor restlessness, and perceptual changes.

Severe withdrawal symptoms are unlikely unless high doses or a high-potency preparation (especially a short-acting one) has been used daily for a prolonged time period and then halted abruptly. In such cases, a delirium tremens–like syndrome may develop. Seizures have been reported after sudden discontinuation of alprazolam after as short a time as 1 to 2 months of maintenance therapy. For less potent or long-acting BZDs, the risk of a severe abstinence syndrome is less. Chronic daily treatment is best discontinued by tapering doses over several weeks.

Selection of Agent. The available BZDs appear to be equally effective for the management of generalized anxiety symptoms when equipotent doses are used. In the future, one may see new BZDs with greater treatment specificity because heterogeneity of brain BZD receptors has been demonstrated. For now, the essential differences among BZDs are in potency and pharmacokinetics (Table 226–4). These factors determine suitability for single-dose and maintenance use and the risk of physical dependence and withdrawal.

For single-dose use, the desirable pharmacokinetic properties are rapid rate of onset and offset. Speed of absorption from the gastrointestinal tract is the most important factor determining onset. Capacity to traverse the blood–brain barrier is also a factor; the more lipophilic it is, the more quickly the drug enters the central nervous system. Lipophilicity also governs the rate of clinical offset by determining how rapidly the drug is redistributed into lipid stores after a single dose. Serum half-life is not relevant to the duration of action of single-dose use. Diazepam is rapidly absorbed and very lipid soluble, giving rapid onset and offset when used in single-dose fashion. Relatively rapid onset is usually desirable in situations in which single-dose use is prescribed.

For maintenance use, a drug’s serum half-life is the pertinent parameter, affected by liver function and whether hepatic metabolites are active or inactive. Drugs with a short half-life are simply converted to water-soluble glucuronides and rapidly cleared by the kidneys. Their disadvantage is the potential for anxiety and even mild withdrawal symptoms between doses. The longer–half-life agents are more likely to accumulate. However, because of
the development of drug tolerance, there is little additional risk of clinically important central nervous system suppression among most users of long-acting agents. The exceptions are the elderly and those with hepatocellular disease, in whom the use of long-acting agents can lead to overwhelming drug accumulation that causes excessive sedation, drowsiness, and psychomotor impairment.

**Determination of Dose.** Dose must ultimately be determined empirically on a case-by-case basis. It is most prudent to begin with low doses and titrate up as necessary. Most patients suffering from anxiety of lesser intensity than panic will not benefit from doses greater than 8 mg/d of lorazepam or its equivalent. Starting doses should typically not exceed the equivalent of 4 mg/d of lorazepam in young, otherwise healthy adults who are BZD naive. In the elderly, starting and maximum doses should be approximately halved (see later discussion). Steady state takes longer to achieve using drugs with a long half-life, an important consideration when deciding how often to adjust dose. A clinically useful rule of thumb is that steady state is 90% achieved after five drug half-lives.

**Antidepressants**

Since the 1990s the **serotonin selective reuptake inhibitors (SSRIs)** and serotonin norepinephrine reuptake inhibitors (SNRIs) have become first-line agents for treatment of anxiety, although initially approved for treatment of depression. They are among the most effective treatments for *panic disorder*, **social anxiety disorder**, generalized anxiety disorder, PTSD, and OCD. As in depression, their beneficial effects are usually delayed for several weeks (see Chapter 227). While several of the SSRIs and SNRIs have received specific U.S. Food and Drug Administration (FDA) approval for such anxiety disorders, most experts regard all SSRIs and SNRIs as having equivalent efficacy for use in this context. Several of the newer antidepressants (e.g., **desvenlafaxine**, milnacipran, and viltadizone) are also being tested for application in specific anxiety disorders. **Tricyclic antidepressants (TCAs)** and the **monoamine oxidase inhibitors (MAOIs)** are generally reserved for patients with refractory anxiety disorders.

**Initiation of Therapy.** Although the antidepressants are “first line” in terms of their efficacy, therapy is often initiated with BZDs to offer some immediate relief. Concurrently, or after anxiety symptoms are attenuated, antidepressant medication may be added. Once the antidepressant agent has become effective, some patients become entirely asymptomatic. In such instances, the BZD may be tapered down and even discontinued. In anxiety disorders, antidepressants are initiated with low doses (e.g., imipramine, 10 mg/d; fluoxetine, 10 mg/d) because brief symptom exacerbation may occur in some patients. Full antidepressant doses, if tolerated, are usually necessary. The recommended dose, for example, of paroxetine in the treatment of panic disorder is 40 mg/d.

**Use in Specific Conditions.** For **panic disorder**, several SSRIs (sertraline, fluoxetine, paroxetine, paroxetine controlled release, and venlafaxine extended release) have received FDA indications for the treatment of *panic disorder*. There is much evidence supporting the use of the other SSRIs and SNRIs as well. TCAs and MAOIs have a long history of effectiveness in panic disorder. SSRIs and SNRIs may also be of utility in the treatment of GAD. Extended-release venlafaxine has demonstrated both short-term and long-term efficacy in persons with GAD and panic disorder.

*Posttraumatic stress disorder* responds best to the initial use of antidepressants, with continuation based on treatment response and the constellation of symptoms. OCD patients respond especially well to SSRIs, though treatment often requires higher doses and needs to be maintained for several years. There is some suggestion that the obsessions respond preferentially, whereas compulsions are best addressed through behavioral interventions combined with medications.

Like the other anxiety disorders, **social anxiety disorder** has been shown to be effectively treated by most of the SSRIs, with sertraline, venlafaxine extended release, paroxetine, and paroxetine controlled release gaining FDA approval. Again, MAOIs have a long history of being particularly effective for social anxiety disorder, although their safety and side effect profile restrict their use to treatment-refractory cases.

**Side Effects.** See Chapter 227.

**Buspirone**

Buspirone is a non-BZD anxiolytic that acts as a partial serotonergic agonist and has mild anxiolytic and antidepressant effects. Because of its benign side effect profile (nonaddicting and no withdrawal), buspirone is a reasonable alternative to BZDs in cases in which chronic anxiolysis is required, especially when substance abuse or noncompliance is a concern. Risk from overdose is low, and the drug is well tolerated. Its anxiolytic effects are modest compared with those of the BZDs, and the onset of action may take weeks, rendering the drug ineffective for single-dose use and of little help to patients with severe symptoms. Some efficacy has been reported in OCD. As a mild anxiolytic that may be taken frequently and safely, it may benefit patients with mild generalized anxiety or adjustment disorders. Treatment is initiated at doses of 5 mg three times a day and adjusted weekly in dose increments of 5 mg/d. In patients requiring more than 20 mg three times a day, referral to a specialist is recommended.

**Beta-Blockers**

β-Adrenergic blocking agents blunt the peripheral catecholamine-mediated manifestations of anxiety. As such, they are very useful on a short-term, as-needed basis for performance anxiety and stage fright (e.g., propranolol 10 to 20 mg as needed). In the case of a special performance, it is suggested that the patient try a test dose a few days earlier to determine both efficacy and side effects. Large doses may blunt psychomotor responses. For generally anxious patients with prominent somatic manifestations of adrenergic excess (e.g., tremor, palpitations), longer-acting

**TABLE 226–4 Pharmacokinetic Properties of Commonly Used Benzodiazepines**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approximate Dose Equivalence (mg)</th>
<th>Relative Rapidity of Effect</th>
<th>Half-Life (hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam (Xanax)</td>
<td>0.5</td>
<td>Fast/intermediate</td>
<td>11</td>
</tr>
<tr>
<td>Alprazolam XR (Xanax XR)</td>
<td>0.5</td>
<td>Intermediate</td>
<td>13</td>
</tr>
<tr>
<td>Alprazolam orally disintegrating tablets (Niravam)</td>
<td>0.5</td>
<td>Fast</td>
<td>2–6</td>
</tr>
<tr>
<td>Clonazepam (Librium)</td>
<td>10</td>
<td>Intermediate</td>
<td>5–30</td>
</tr>
<tr>
<td>Clonazepam (Klonopin)</td>
<td>0.25</td>
<td>Fast/intermediate</td>
<td>15–50</td>
</tr>
<tr>
<td>Lorazepam (Tranxene)</td>
<td>7.5</td>
<td>Fast</td>
<td>30–200</td>
</tr>
<tr>
<td>Diazepam (Valium)</td>
<td>5</td>
<td>Fastest</td>
<td>20–100</td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>1</td>
<td>Intermediate</td>
<td>10–20</td>
</tr>
<tr>
<td>Oxazepam (Serax)</td>
<td>15</td>
<td>Slower</td>
<td>5–15</td>
</tr>
</tbody>
</table>
AGING IS PREFERRED. Lorazepam and oxazepam fulfill these short-acting agent that has no active metabolites and in benzodiazepines.

Because drug metabolism is slowed in the elderly, excessive sedation may cause a fall with serious injury—the risk of hip fracture rises markedly with the use of long-acting BZDs in the elderly. Initial doses should be small (e.g., the equivalent of 2 to 5 mg/d of diazepam) and increased slowly and cautiously. It may take up to 2 weeks to achieve steady-state levels after a change in dose.

Antipsychotics. In the elderly, anxiety accompanied by agitation or specific psychic manifestations may require short-term antipsychotic therapy. The atypical antipsychotics have become first-line agents for this indication. A small dose of a high-potency typical antipsychotic such as haloperidol (Haldol) or fluphenazine (Prolixin) is another option. Lower-potency agents (e.g., chlorpromazine, thioridazine, perphenazine) necessitate the use of higher doses and increase the risk of hypotensive, cardiovascular, and anticholinergic side effects.

Antidepressants. Of the antidepressants, SSRIs are the best tolerated (see Chapter 227). Of the TCAs with antidepressant activity, those with low anticholinergic and antiadrenergic side effects (e.g., nor-triptyline) are preferred. Because antidepressant metabolism slows with age, one should start with half the usual dose and titrate up slowly. Importantly, the time to response can be twice as long in the elderly as compared to younger populations. An adequate trial requires 12 weeks of treatment at a therapeutic dose.

**β-Blockers.** β-Blocker use requires particular caution, given the prevalence of congestive heart failure, heart block, and obstructive lung disease in the elderly and their susceptibility to such side effects as cognitive blunting, nightmares, and depression.

### TABLE 226–5 Anticonvulsants and Atypical Antipsychotics Used for Anxiety

<table>
<thead>
<tr>
<th>Anticonvulsants</th>
<th>Atypical Antipsychotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine (Tegretol)</td>
<td>Aripiprazole (Abilify)</td>
</tr>
<tr>
<td>Gabapentin (Neurontin)</td>
<td>Asenapine (Saphris)</td>
</tr>
<tr>
<td>Lamotrigine (Lamictal)</td>
<td>Clozapine (Clozaril)</td>
</tr>
<tr>
<td>Levetiracetam (Keppra)</td>
<td>Iloperidone (Fanapt)</td>
</tr>
<tr>
<td>Oxcarbazepine (Trileptal)</td>
<td>Lurasidone (Latuda)</td>
</tr>
<tr>
<td>Pregabalin (Lyrica)</td>
<td>Olanzapine (Zyprexa)</td>
</tr>
<tr>
<td>Tiagabine (Gabitril)</td>
<td>Paliperidone (Invega)</td>
</tr>
<tr>
<td>Topiramate (Topamax)</td>
<td>Quetiapine (Seroquel, XR)</td>
</tr>
<tr>
<td>Valproate (Depakote, Depakene)</td>
<td>Risperdone (Risperdal)</td>
</tr>
<tr>
<td>Zonisamide (Zonegran)</td>
<td>Ziprasidone (Geodon)</td>
</tr>
</tbody>
</table>

**Neuroleptics**

Notwithstanding first-line interventions as described in the foregoing, approximately 40% to 70% of patients fail to reach responder status after acute treatment, with an even greater proportion remaining at least somewhat symptomatic. The rapid antianxiety and anti-irritability effects of the atypical antipsychotics have made them relatively popular among clinicians in the treatment of refractory anxiety patients. Furthermore, in anxiety disorders, atypical antipsychotics can be effective at a fraction of the doses necessary to manage psychotic disorders. This drastically reduces such side effects as tardive dyskinesia that conventional neuroleptics pose at higher doses. Nevertheless, patients should be closely monitored for some potentially serious side effects such as prolactin elevation, weight gain, and metabolic syndromes.

Available atypical agents differ markedly in their receptor profiles; choosing among them is based mainly on their side effects, avoiding the most unpleasant side effect for that particular patient (see Chapter 173). Currently, these agents, used either as monotherapy or in combination with traditional agents, cannot be considered first-line treatment, but they do have a place for patients who remain symptomatic or fail to respond to conventional agents and/or are considered treatment refractory or intolerant. Given the notorious sensitivity to side effects of anxious patients, clinicians should favor low doses on treatment initiation and slow titration while dosing these agents.

### Anxiety Pharmacotherapy in the Elderly

Because drug metabolism is slowed in the elderly, excessive sedation is a risk with anxiolytic therapy, especially with the use of long-acting agents.

**Benzodiazepines.** In most instances, nighttime use of a short-acting agent that has no active metabolites and in patients whose metabolism is relatively unaffected by aging is preferred. Lorazepam and oxazepam fulfill these requirements. Their elimination by hepatic conjugation to a water-soluble glucuronide for renal excretion changes little with age. Lorazepam is the faster in onset; oxazepam’s onset is gradual. Their disadvantages include the need for frequent dosing if continuous anxiolysis is desired and rebound anxiety and insomnia if they are discontinued abruptly after prolonged use. Initial oxazepam dose is 10 mg; for lorazepam, it is 0.5 mg. Both are usually given before bed. Intake should be limited to short (5- to 10-day) courses or occasional as-needed use.

For more sustained anxiolysis, a BZD with a longer effective half-life may be required (Table 226–4). However, elimination of active drug metabolites lengthens with age, markedly prolonging drug half-life (e.g., from 20 to 90 hours for diazepam). Accumulation of active metabolites can cause diminished alertness and impair memory acquisition, mimicking dementia. Excessive sedation may cause a fall with serious injury—the risk of hip fracture rises markedly with the use of long-acting BZDs in the elderly. Initial doses should be small (e.g., the equivalent of 2 to 5 mg/d of diazepam) and increased slowly and cautiously. It may take up to 2 weeks to achieve steady-state levels after a change in dose.

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### Therapeutic Recommendations and Indications for Referral (1,31–33)

#### General Guidelines

- Begin with supportive psychotherapy that includes explanation, empathic listening, meaningful reassurance, and encouragement.
- Teach relaxation techniques for the patient willing to use them (see Appendix 226-1).
- Consider referral for psychotherapy when there is emotional upheaval or disabling symptoms. CBT is perhaps the most effective of the psychotherapies for ameliorating pathologic anxiety.
- Supplement psychotherapeutic measures with anxiolytic drug therapy to improve the patient’s ability to perform daily activities previously impaired by anxiety. In most instances, use only in an adjunctive role for a limited duration. If BZD therapy is used, advise the patient of the risk of physical dependence. Inform the patient that drug treatment is likely to reduce symptoms but not eradicate them.
- Refer if there is evidence of substance abuse, either as an etiologic factor or as a mode of self-treatment.
Situational Anxiety and Adjustment Disorder

- Initiate supportive psychotherapy, including the identification of specific provocative stressors and their association with the onset of symptoms.
- If distress from anxiety impairs daily functioning, begin a short course (up to 5 days) of BZD therapy (e.g., clonazepam, 0.5 mg twice daily).
- If the distress represents one of many such episodes in a pattern of emotional upheaval, refer for insight-oriented therapy. Also refer if symptoms continue beyond the stressful period or worsen despite treatment.

Generalized Anxiety Disorder

- Initiate supportive psychotherapy and consider insight-oriented therapy to help diminish the role of psychosocial stressors.
- Consider a short course of BZD therapy for periods of exacerbation (e.g., alprazolam, 0.5 mg three times a day for up to 5 days).
- Prescribe an SSRI if there is a history of associated panic attacks or depression, e.g., begin with venlafaxine extended release (Effexor-XR), 37.5 mg twice daily, and advance the dose as tolerated to 150 mg twice daily; alternatively, paroxetine at a target dose of 40 mg daily can be used.
- Avoid chronic BZD therapy due to risk of dependence. If the patient is coming off long-term therapy, taper over several weeks according to the patient's ability to tolerate decreases. Monitor for any withdrawal symptoms (e.g., tinnitus, perceptual changes, involuntary movements).
- Consider a trial of buspirone if chronic anxiolytic therapy is desired. Begin with 5 mg three times a day and gradually advance to a maximum of 60 mg/d. Risks of physiologic dependence and withdrawal are nil, but potency is low, and it may take weeks to notice any effect.
- Refer patients with disabling chronic anxiety for psychiatric care.

Panic Disorder

- Refer patients with prominent phobic behavior and those with suicidal ideation.
- Screen for suicidality (see Chapter 227), especially if the patient is despondent; refer urgently if there is concern.
- Use pharmacologic therapy to achieve control and minimize phobic avoidance and depression. Begin therapy with a low dose of a serotonin reuptake inhibitor (e.g., escitalopram, 10 mg daily, or paroxetine, 10 mg daily). If agitation is not increased, proceed gradually to full antidepressant doses (e.g., escitalopram, 20 mg/d, or paroxetine, 40 mg/d).
- In situations in which the cost benefits of a generic TCA override the better tolerability of an SSRI, start with a small “test” dose (e.g., imipramine, 10 mg at bedtime, and proceed gradually as tolerated to 100 to 200 mg at bedtime). The added costs of cardiac monitoring and taking blood levels of the TCAs must be factored into the cost–benefit equation.
- Alternatively, an MAOI antidepressant may be prescribed, but dietary restriction and expertise in its use are required (see Chapter 227).
- If rapid relief is sought due to the presence of disabling phobic behavior, start with a potent BZD (e.g., alprazolam, 0.25 to 0.5 mg four times a day, or clonazepam, 0.5 mg at bedtime or twice daily), pending the onset of benefit from antidepressant therapy.
- After a period of well-being, taper BZD medication to the lowest possible maintenance dose or proceed to discontinuation.
- Weigh continued BZD use against the risk of dependence. The use of potent BZDs poses risks of dependence and severe withdrawal. Taper slowly over several weeks when discontinuing therapy that has been continuous for more than 6 weeks.
- For patients requiring longer-term maintenance therapy, it is important to continue the antidepressant medication at its full acute-phase dose.

Social Anxiety Disorder

- Refer for cognitive–behavioral therapy.
- Prescribe a BZD on an as-needed, single-dose basis to help attenuate anxiety, decrease avoidance, and facilitate daily functioning and behavioral therapy.
- Prescribe a low-dose SSRI (e.g., sertraline, 25 mg in the morning, or paroxetine controlled release, 12.5 mg in the morning), and proceed gradually to full antidepressant doses (e.g., sertraline, 150 mg in the morning, or paroxetine controlled release, 50 mg in the morning).
- For patients whose performances are compromised by ordinary “stage fright,” consider a trial of a β-blocker (e.g., propranolol, 10 mg, up to 20 mg four times a day) on an as-needed basis. Give a preperformance trial dose to be sure performance is not compromised by the medication.

Specific Phobias

- Refer for cognitive–behavioral therapy.
- Consider rapidly acting single-dose BZD therapy (e.g., alprazolam, 0.25 to 0.5 mg, or diazepam, 10 mg) on an as-needed basis to provide symptomatic control in anxiety-provoking situations and to facilitate behavioral therapy.

Obsessive–Compulsive Disorder

- Refer for cognitive–behavioral therapy.
- Initiate pharmacologic therapy with an SSRI.
- Refer to an experienced psychopharmacologist for further management of the drug treatment program.

Posttraumatic Stress Disorder

- Refer to a psychiatrist specializing in the treatment of such patients. Most programs begin with an SSRI. Mood stabilizers may be helpful for prominent irritability or anger. BZDs may sometimes be helpful in the short term but must be used with caution because of the risk of substance abuse in this vulnerable population of patients.
- Refer to an experienced psychotherapist. Three psychotherapy techniques—exposure therapy, cognitive therapy, and anxiety management—are considered to be the most useful in the treatment of PTSD. Expert therapists make distinctions among the techniques, depending on which specific type of symptom presentation is most prominent. Insight-oriented psychotherapy helps to overcome emotional memories of the traumatic event; behavioral techniques may also be of benefit.

Treatment of the Elderly

- Initiate supportive psychotherapy: Consider referral to an experienced psychotherapist to assess other options, including CBT.
- Reduce starting doses of medications by one half of the usual adult dose.
- When using BZDs for short-term anxiolysis, prescribe lorazepam or oxazepam.
- For chronic anxiolysis, use longer-half-life agents with caution and at reduced doses and dose intervals.
If agitation, “sundowning,” or psychotic features accompany procedures. Relaxation training is by far the most effective of the program, the primary care physician may choose to train with stress or anxiety. As part of a comprehensive treatment patient to condition his or her body to cope more adaptively come a variety of stress-reducing techniques derived from Stress is not harmful when managed effectively. With the •

ANNOTATED BIBLIOGRAPHY


14. Weissman MM, Klerman GL, Markowitz JS, et al. Suicidal ideation and suicide attempt was 2.8.)


31. National Collaborating Centre for Mental Health, National Collaborating Centre for Primary Care. Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults. Management in primary, secondary and community care. London, UK: National Institute for Health and Clinical Excellence (NICE), 2011. (Clinical guideline; no. 113.) (Evidence-based British clinical guideline that has received wide international adoption.)


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Progressive deep muscle relaxation, autogenic training, and diaphragmatic breathing represent the major techniques practical for use in the primary care setting.

PROGRESSIVE DEEP MUSCLE RELAXATION

Progressive deep muscle relaxation is probably the most extensively used and most effective relaxation technique for the treatment of anxiety- and stress-related problems. A brief modified version can be taught to the patient in one session. The rationale for the technique is the view that anxiety and relaxation are mutually exclusive, that is, anxiety cannot be experienced when the muscles are relaxed.

Before proceeding to train the patient in relaxation as a self-control procedure, the physician should advise reduction or elimination of caffeine from the patient’s diet because relaxation training is aimed at lowering the patient’s autonomic arousal level and caffeine augments arousal.
Autogenic training is a relaxation technique composed of a set of exercises that are intended to induce heaviness and warmth in the muscles through mental imagery.

Autogenic training typically involves the patient sitting comfortably in an armchair in a quiet room with the eyes closed. Verbal formulas are introduced (e.g., “my arm is heavy”), and the patient is instructed to visualize and feel the relaxation of the muscle being focused on while silently repeating and passively concentrating on that formula. The formulas, which consist of verbal somatic suggestions, are intended to facilitate concentration and “mental contact” with the parts of the body indicated by the formula.

Training consists of six psychophysiological exercises, which are practiced several times a day. The training begins with the theme of heaviness (e.g., “my arm feels heavy and relaxed”). The second group of formulas involve warmth (e.g., “my arm feels warm and relaxed”). After warmth training, the patient continues with passive concentration on cardiac activity (e.g., “my heartbeat feels calm and regular”). The fourth exercise focuses on breathing and respiration. In the next exercise, the patient focuses on warmth in the chest and abdomen, and in the last exercise, the focus is passive concentration on cooling of the forehead.

In modern practice, the time and the six standard exercises have been condensed so that a whole round can be practiced in a very brief period of between 5 and 10 minutes. In this condensed version, the autogenic training phrases are focused primarily on the physiologic aspect used in the training, interspersed with general suggestions for relaxation. Each phrase is said slowly, allowing time for the patient to begin to feel some awareness of the effect of the suggestion (Table 226–7).

### TABLE 226–6 Progressive Deep Muscle Relaxation Instructions to Patients

Practice is to be done while sitting in a chair with your back straight, head on a line with your back, both feet on the floor, and hands resting on your lap. Each muscle is to be tightened, held in tightened position for 15–20 s, and then slowly let go while you study the difference between tension and relaxation.

**Forehead.** Wrinkle up your forehead by arching your eyebrows and creasing your forehead, hold the tension, and then slowly let go of the tension.

**Eyes.** Squeeze your eyes together tightly, hold the tension, and then slowly let go of the tension.

**Nose.** Wrinkle up your nose and spread your nostrils, hold the tension, and then slowly let go of the tension.

**Face.** Put a forced smile on your face, and spread your face; hold the tension; and then slowly let go of the tension.

**Tongue.** Push your tongue hard against the roof of your mouth, hold the tension, and then slowly let go of the tension.

**Jaws.** Clench your jaws together tightly, hold the tension, and then slowly let go of the tension.

**Lips.** Pucker up your lips and spread them, hold the tension, and then slowly let go of the tension.

**Neck.** Tighten the muscles of your neck by pulling your chin in and shrugging up your shoulders, hold the tension, and then slowly let go of the tension.

**Right Arm.** Tense your right arm and hand by stretching them out in front of you and clenching your fist tightly, hold the tension, and then slowly let go of the tension.

**Left Arm.** Tense your left arm and hand by stretching them out in front of you, and then slowly let go of the tension.

**Right Leg.** Extend your right leg in front of you (at the height of the chair seat), tense your thigh and leg by pointing your toes inward toward your face, hold the tension, and then slowly let go of the tension.

**Left Leg.** Extend your left leg in front of you, tense your thigh and leg by pointing your toes inward toward your face, hold the tension, and then slowly let go of the tension.

**Upper Back.** Tense your back muscles by sitting slightly forward in the chair and bending your elbows and trying to get them to touch each other behind your back, hold the tension, and then slowly let go of the tension.

**Chest.** Tense your chest muscles by pulling your stomach in and thrusting your chest outward and forward, hold the tension, and then slowly let go of the tension.

**Stomach.** Tense your stomach muscles, making them hard by pushing your stomach out, hold the tension, and then slowly let go of the tension.

**Buttocks and Thighs.** Tense your buttocks and thighs by placing your feet squarely on the floor, pointing your toes into the floor, and forcing your heels to remain on the floor while pushing forward; hold the tension; and then slowly let go of the tension.

Practice should be engaged in twice daily for a period of 12–15 min. Mastery of the technique should be achieved after 2–4 wk of twice-daily practice.

### TABLE 226–7 Autogenic Training Instructions to Patients

Practice is to be done while sitting in a soft, comfortable chair with your eyes closed. As attention is called to specific groups of muscles, try to visualize and feel the relaxation of those muscles. Try to let happen what is being suggested. Repeat each formula two or three times.

- My forehead and scalp feel heavy, limp, loose, and relaxed.
- My eyes and nose feel heavy, limp, loose, and relaxed.
- My face and jaws feel heavy, limp, loose, and relaxed.
- My neck, shoulders, and back feel heavy, limp, loose, and relaxed.
- My arms and hands feel heavy, limp, loose, and relaxed.
- My chest, solar plexus, and the central part of my body feel quiet, calm, comfortable, and relaxed.
- My stomach feels heavy, limp, loose, and relaxed.
- My buttocks, thighs, calves, ankles, and toes feel quiet, heavy, limp, loose, and relaxed.

Practice should be engaged in twice daily for a period of 6–8 min. Mastery of the technique should be achieved after 1–3 wk of twice-daily practice.
CHAPTER 227  Approach to the Patient with Depression

John J. Worthington III  Scott L. Rauch

Depression is not only a very common condition—estimated prevalence 5.8% in men, 9.5% in women, and a lifetime incidence of 16%—but an important cause of disability and a major risk factor for stroke and death from coronary heart disease. Being a treatable, yet potentially fatal disease, it requires early detection and implementation of an effective management program. Most patients with depression present to primary care physicians rather than psychiatrists, often complaining of somatic symptoms such as fatigue or disturbed sleep. The frequency, treatability, and potentially serious consequences of depression make its diagnosis and management high priorities for the primary care physician. Unfortunately, the diagnosis is often not made. Sometimes, it is not evident because the symptoms may masquerade as a variety of psychiatric or somatic conditions. Moreover, the stigma of psychiatric diagnosis can impede recognition of depressive illness by both patients and physicians. All members of the primary care team need to be vigilant in watching for manifestations of depression. The primary care physician should be prepared to initiate further evaluation and basic treatment when symptoms or signs are encountered. A collaborative care approach to management that engages other members of the primary care team can help improve outcomes.

DIAGNOSIS AND MANAGEMENT

An approach to the patient with depression should be systematic and collaborative. The primary care physician should be prepared to initiate further evaluation and basic treatment when symptoms or signs are encountered. A collaborative care approach to management that engages other members of the primary care team can help improve outcomes.

EXERCISE AND EXERCISE TRAINING

In addition to the specific relaxation methods just described, exercise and exercise training have been explored as a means of treating anxiety in both otherwise healthy persons and those with chronic illnesses, ranging from fibromyalgia to coronary heart disease. In many instances, the exercise program is prescribed to help with the underlying medical condition but subsequently found to help with the anxiety that accompanies it. Meta-analyses of randomized trials find significant anxiety-reducing effects for both acute and chronic exercise (see Chapter 18) as well as with implementation of specific exercise training programs (usually of 3 to 12 weeks' duration). Exercise tailored to the patient’s physical capacity, preferences, and perspectives can be a safe and very useful complement to other modes of treatment for anxiety.

PATHOPHYSIOLOGY AND CLINICAL PRESENTATION (1–17)

Mechanisms

The purported mechanisms of depression include psychodynamic, cognitive, genetic, neuroendocrine, and neurotransmitter determinants. Depression most likely represents a complex combination of these elements. Genetic factors and/or early childhood experiences may render persons more susceptible to depression. Neurotransmitter and neurohumoral elements probably serve as important effector pathways for the development of symptoms.

Psychodynamic origins are believed to involve difficulties with formation and maintenance of self-esteem, which may occur from having hypercritical parents or being abused. In addition, growing up in an emotionally unresponsive environment may compromise learning ways effectively to cope with situational stresses. Suffering loss or failure as an adult is likely to be difficult, poorly responded to, and capable of reawakening prior painful feelings of inadequacy and worthlessness that lead...
to depression. Rigid dysfunctional defenses may be erected in an attempt to minimize the chances of loss or failure. 

The cognitive perspective views depression as the consequence rather than as the origin of negative or distorted thinking. Subscribing to inflexible rules of conduct and unattainable goals can be a setup for failure and loss of self-esteem. Setbacks are viewed as a reflection of one’s unworthiness and inadequacy.

Genetic determinants have been discovered from studies of twins, chromosomes, and pedigrees. In some pedigrees, there appears to be a dominant gene with incomplete penetrance that confers risk. A family history of affective disease is commonly elicited. Major depression is up to three times more common among first-degree relatives of people with the disorder than in the general population.

Neurotransmitter theories of depression began with the finding that reserpine could induce depression and monoamine oxidase inhibitors (MAOIs) could reverse it. This led to the identification of altered neurotransmitter metabolism as an important biochemical concomitant of depression and to the discovery of new antidepressant drugs, each increasing the availability of a major central neurotransmitter (e.g., norepinephrine, serotonin, or acetylcholine), usually by selective inhibition of reuptake. On a neurotransmitter basis, norepinephrine appears to affect energy levels and level of alertness, while serotonin’s sphere of influence is on mood.

Neuroendocrine hypotheses derive from the observation that most neurovegetative manifestations of depression (changes in appetite, libido, diurnal rhythms) involve hypothalamic functions. In addition, links between neurotransmitter release and neuroendocrine activity have been identified. Corticotropic-releasing hormone is believed to play an important role, resulting in hypercortisolism. Early-morning awakening, reflecting an abnormal advance in circadian rhythm, may be one consequence.

### Psychological and Somatic Manifestations

Depression’s clinical presentation includes a host of psychological and bodily complaints.

#### Psychological Manifestations

Sadness is a very common symptom. Irritability, discouragement, loss of interest, worry, frustration, and decreased libido are the major dysphoric manifestations and may occur in the absence of overt sadness (Table 227-1). Some patients become preoccupied with physical complaints, such as pain or bowel dysfunction. Others exhibit changes in memory, concentration, or self-image. Diurnal mood variation is characteristic, with symptoms often worse in the morning and improving as the day progresses.

Depressed affect can be subtle, and at times, the patient’s sadness only becomes evident on talking with the physician. As depression worsens, psychomotor abnormalities may appear. Although psychomotor retardation, with slowed speech and a long latency before the patient answers questions, has been thought of as the classic presentation of depression, anxiety is the much more common symptom. Nearly three fourths of patients with a depressive disorder have worry, psychic anxiety, or somatic anxiety as one of their presenting symptoms.

#### Somatic Manifestations

Distinctive neurovegetative symptoms include disturbed sleep (most commonly early-morning awakening), lack of energy, and decreased appetite. Neurovegetative symptoms are predictive of responsiveness to psychopharmacologic intervention. In what is termed an atypical depression, patients may exhibit increased sleep and increased appetite (hypersomnolence and hyperphagia).

### Diagnostic Classification

Although no single classification system is universally accepted, the current standard of diagnosis in the United States is the American Psychiatric Association’s *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) (Table 227-2).

### Major Depression (Major Depressive Disorder, Unipolar Depression)

This is the DSM-IV term for serious depression that is accompanied by neurovegetative symptoms. The lifetime risk of developing a major depression is estimated to be 1 in 4 for women and 1 in 8 for men. Dysphoric mood typically dominates the clinical picture and is persistent. Four or more of the major neurovegetative symptoms dominate the clinical picture and are present for a minimum of 2 weeks, including appetite disturbance, sleep disturbance, psychomotor retardation or agitation, anhedonia, loss of energy, feelings of worthlessness or guilt, decreased concentration, and suicidal thoughts.

Onset is variable. Symptoms usually develop over weeks to months, but they may develop suddenly. Situational factors surrounding the onset of the illness have no bearing on the diagnosis. Historically, distinctions were made between *endogenous* and *reactive depression*, but an identifiable precipitant is no longer considered pertinent with respect to diagnosis; the frequency of episodes appears to increase with age. At least half of patients have recurrent episodes. A family history of a major affective disorder (major depression or bipolar disorder) is common. The relationship between alcoholism and depression is controversial. Traumatic brain injury is associated with a high frequency of posttraumatic major depression as well as anxiety.

### Major Depression with Psychotic Features

A subclassification of major depression, this disorder has the additional features of delusions, hallucinations, bizarre behavior, or disorganized thinking.
Major Affective Disorders

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major depression (unipolar depression)</td>
<td>Severe and episodic with prominent neurovegetative and cognitive symptoms. May be accompanied by psychotic features. Treatment: antidepressant plus psychotherapy.</td>
</tr>
<tr>
<td>Bipolar disorder (manic–depressive illness)</td>
<td>Severe and episodic with a history of a manic episode. Treatment: mood-stabilizing agent in the depressed phase plus psychotherapy.</td>
</tr>
<tr>
<td>Cyclothymic disorder</td>
<td>Severe and episodic, with a history of a manic episode. Tends to occur in individuals older than 50 years.</td>
</tr>
<tr>
<td>Organic Brain Syndrome</td>
<td>Severe and episodic with prominent neurovegetative signs and symptoms. Depression appears as an integral part of the patient's personality or character (hence the older term characterologic depression).</td>
</tr>
<tr>
<td>Dysthymic disorder</td>
<td>Less severe, chronic mood swings. Treatment: mood-stabilizing agent plus psychotherapy.</td>
</tr>
<tr>
<td>Adjustment disorder with depressed mood</td>
<td>Time limited, in response to identifiable precipitant, without neurovegetative symptoms sufficient for major depression. Treatment: psychotherapy plus a trial of antidepressant if necessary.</td>
</tr>
</tbody>
</table>

Chronic Affective Disorders

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<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysthymic disorder</td>
<td>Chronic and less severe, with fewer neurovegetative symptoms. Treatment: psychotherapy plus a trial of antidepressant if neurovegetative symptoms are distressing.</td>
</tr>
<tr>
<td>Organic affective disorder</td>
<td>Depressed or manic due to an organic cause. Treatment: manage underlying medical problem; a trial of antidepressant if necessary.</td>
</tr>
<tr>
<td>Other Conditions</td>
<td>Adjustment disorder with depressed mood. Time limited, in response to identifiable precipitant, without neurovegetative symptoms sufficient for major depression. Treatment: psychotherapy plus a trial of antidepressant if neurovegetative symptoms are distressing.</td>
</tr>
</tbody>
</table>

Major Depression in the Elderly

In the elderly, depression can mimic dementia. The patient may appear withdrawn, unkempt, inattentive, or even confused. The condition may be due to depression alone or to a combination of depression and dementia. Conversely, a clinical presentation consistent with depression is much more likely to be secondary to a medical condition (infarct, brain tumor, etc.) in individuals older than 50 years.

Bipolar Disorder: Depressed Phase

Depression may be a manifestation of bipolar (manic–depressive) illness. The presentation of a depressive episode in a bipolar patient is identical to that of major depression, except that there is a history of a prior manic or hypomanic episode. Mania is manifested by an episode of elation or expansive mood, increased energy, decreased need for sleep, inflated self-esteem, and overinvolved in activities, accompanied by a decreased concern for the consequences. Its diagnosis requires adequate severity substantially to impair level of functioning. Hypomania refers to the hallmark symptoms of mania in the absence of impaired functioning. Bipolar I disorder involves at least one episode of mania; bipolar II disorder involves at least one episode of hypomania. Prevalence is considerable, with estimates as high as 5% of the adult population (1% for bipolar I disease and 4% for bipolar II). Distinguishing between the depressions of unipolar and bipolar disorders is important because initial treatments differ substantially (see later discussion).

Dysthymic Disorder

This category denotes a chronic low-grade depression, characterized by pervasive dysphoric mood for at least 2 years. Some patients complain of lifelong feelings of depression. Symptoms are less severe than are those of major depression, and neurovegetative symptoms are fewer. Depression appears as an integral part of the patient's personality or character (hence the older term characterologic depression). Such patients can be frustrating to treat because of chronic dysphoria, self-pity, and development of irrational patterns of negative thinking (e.g., "Things always go wrong for me"). The physician typically develops feelings of helplessness and may unconsciously communicate a wish that the patient would go away. Typically, onset is in adolescence or early adult life and is accompanied by other symptoms of a personality disorder, such as a history of difficulty with interpersonal relationships, manipulativeness, feelings of emptiness, and lack of an identity. A subgroup of dysthymic patients seems to have an attenuated chronic form of major depression with onset later in life after a period of good functioning. Neurovegetative symptoms may be more prominent.

Dysthymia and major depression can coexist in a given patient (so-called double depression) when a major depressive episode evolves in the context of preexisting dysthymia. However, incomplete recovery from a major depression should be described as major depression in partial remission rather than dysthymia.

Cyclothymic Disorder

This state resembles bipolar illness, but the mood swings are less severe. These patients have a chronic mood disturbance characterized by periods of depression alternating with periods of elevated mood. Neither is of sufficient severity or duration to meet the criteria for major depressive or manic episodes. Interspersed may be periods of normal mood lasting as long as several months.

Seasonal Affective Disorder

This depressive variant is distinguished by its seasonal pattern, characteristically beginning in the fall and ending about 5 months later. It has been linked to a lack of light exposure and is more common in northern latitudes. Alterations in serotonin activity have also been noted. As in other forms of depression, sadness is the dominant affect, and fatigue and decreased libido are common. Atypical features include tendencies to overeat and oversleep. In the United States, women are more commonly affected than are men (ratio, 3:1). The age of onset is typically in the 20s.

Adjustment Disorder with Depressed Mood

This occurs after a significant life stress. Patients usually present with depressed mood associated with feelings of hopelessness, helplessness, worthlessness, and anxiety. Their thoughts are often dominated by the problems that precipitated the episode. Sleep and appetite disturbances are common but are less severe and less persistent than in major depression. The condition is usually self-limited, lasting less than 6 months and improving when the stress is removed or the individual evolves a more adaptive coping mechanism. It is important to note that any patient with symptoms severe enough to meet the criteria for major depression (see prior discussion) should receive that diagnosis regardless of the history of a precipitant. The message that the primary care physician should gather from this chapter is that evaluating the depressive symptoms, regardless of a suspected precipitant, is crucial, and possibly lifesaving, in initiating antidepressant treatment.

Postpartum Depression

Postpartum depression affects more than 10% of new mothers, perhaps as a consequence in susceptible persons of the rapid decline in reproductive hormone levels that occur with childbirth. Those with a prior history of depression, especially postpartum depression, are at greatest risk. Other risk factors
include situational stress but not mode of delivery, gender of the child, breast-feeding, or whether the pregnancy was unwanted. Clinically, symptoms of major depression appear within 4 weeks of delivery and persist for more than 2 weeks (which constitutes the formal definition of the condition); in some instances, onset may be delayed for up to 3 months postpartum. Manifestations are those of major depression, but the consequences to the newborn can be particularly serious, with disruption of normal childhood development leading to cognitive and behavioral problems.

**TABLE 227–3 Organic Etiologies of Depression**

<table>
<thead>
<tr>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug induced: α-methyldopa, antiarrhythmics, benzodiazepines, barbiturates and other CNS depressants, β-blockers, cholinergic drugs, corticosteroids, digoxin, H blockers, and reserpine</td>
</tr>
<tr>
<td>Toxic-metabolic disorders: hypothyroidism or hyperthyroidism (especially in the elderly), Cushing syndrome, hypercalcemia, hypotension, and diabetes mellitus</td>
</tr>
<tr>
<td>Neurologic disorders: stroke, subdural hematoma, multiple sclerosis, brain tumor, Parkinson disease, Huntington disease, epilepsy, and dementia</td>
</tr>
<tr>
<td>Infectious disorders: viral infections (especially mononucleosis and influenza), HIV with or without AIDS, and syphilis</td>
</tr>
<tr>
<td>Nutritional disorders: vitamin B12 deficiency and pellagra</td>
</tr>
<tr>
<td>Other: carcinomas (especially pancreatic carcinoma) and postoperatively (especially cardiac surgery)</td>
</tr>
</tbody>
</table>

**Personality Disorders**

These patients frequently complain of depressive symptoms, with periods of severe dysphoria, but their affective symptoms often fluctuate markedly with environmental changes (especially with changes in interpersonal relationships). Poor impulse control, histories of unstable relationships, and a striking quality of manipulativeness or entitlement are other clues to primarily charactologic pathology.

**WORKUP (2.4–7,10–25)**

The possibility of depression should always be considered in patients who present with fatigue, poor sleep, appetite disturbances, multiple bodily complaints, or expressed feelings of hopelessness or poor self-esteem. Screening in the primary care setting is also important and can be accomplished by asking a pair of simple questions about mood and interest during an annual checkup: “In the prior 2 weeks, have you felt down, depressed, or hopeless?” and “Have you noted a lack of interest or pleasure?”

The onset of depressive symptoms and signs in patients with chronic debilitating disorders or chronic pain can be slow and subtle and should not be overlooked. When depression is suspected, specific inquiry into its manifestations is needed. However, before proceeding with the inquiry, it is useful to complete a detailed medical history for “organic” etiologies (including elicitations of specific patient concerns) and to follow later with a detailed physical examination, especially in patients who present complaining of somatic symptomatology. Not to do so risks alienating the patient, who wants his or her medical complaints taken seriously. Also useful are a few words to explain the rationale for considering depression (e.g., “It’s a serious, treatable condition and is listed as one of the important causes of the symptoms bothering you”). These few simple measures facilitate patient understanding and impart a sense of seriousness and thoroughness to the workup. In addition, they help to reduce the stigma of considering a psychiatric diagnosis.

**History**

The dimensions to explore include neurovegetative symptoms, multiple bodily complaints, psychosocial history, and past psychiatric history of patient and family. It is helpful and often less threatening to ask first about neurovegetative symptoms such as those relating to sleep, appetite, and energy. If the responses suggest depression, one can proceed to inquire about mood and any loss of interest in sex, family, job, and other sources of interest or pleasure. In addition, the patient should be queried about self-opinion and any self-critical feelings. With every depressed patient, it is critical to ask about suicidal thoughts and intentions (see later discussion). Also useful in the exploration of multiple bodily complaints is consideration of systemic illness that might mimic depression.

**Checking for Neurovegetative Symptoms**

Checking for characteristic neurovegetative symptoms can help in diagnosis and is also useful in screening (see later discussion). Specific inquiry into these characteristic symptoms is facilitated by the validated mnemonic SIG E CAPS (“prescribe an energy capsule”).

S—Is your sleep disturbed?
I—Have you noted a loss of libido or interest in your usual activities?
G—Are you feeling guilty or having self-deprecatary thoughts?
E—Have you noticed a decrease in your energy level?

**Uncomplicated Bereavement**

Symptoms of normal grief may initially be identical to those of depression. The question of a superimposed depression should be raised if mourning continues for more than 6 months, if neuvegetative symptoms are particularly severe, if there is severe impairment in the patient’s ability to function, or if psychiatric symptoms emerge.

**Alcoholism and Drug Dependence**

Many alcoholic patients appear depressed. It is not possible to delineate which symptoms are due to alcohol and which, if any, might be due to a primary affective disorder until the patient has been fully detoxified. Other substance abuse disorders may mimic depression, especially abuse of sedative-hypnotics or withdrawal from psychostimulants.
Checking for Multiple Bodily Complaints and Ruling Out Organicity

Patients with low energy, dysphoria, and multiple bodily complaints out of proportion to physical findings are likely to have depression, but, as noted earlier, they still require careful consideration of conditions that may present in similar fashion, such as chronic fatigue syndrome, Lyme disease, fibromyalgia, rheumatoid disease, vasculitis, and endocrinopathies (see Chapter 8 for details of workup). In addition, depression or multiple bodily complaints may be the clinical presentation of domestic violence. Screening for this condition can be as straightforward as asking, “At any time, has a partner ever hit you, kicked you, or otherwise physically hurt you?” Confusion and alterations in level of consciousness strongly suggest organicity, although they are not always present. When they are, drug-induced etiologies are important to consider. Onset is usually temporally related to medication use and should be sought. Worth noting is any use of antiarrhythmics, antihypertensives, sedative–hypnotics, and corticosteroids, as well as over-the-counter agents and substances of abuse. The relation of β-blockers to depression remains inconclusive, but risk appears to be greatest for those that are lipophilic and readily cross the blood–brain barrier. The elderly are particularly susceptible to adverse central nervous system (CNS) effects from drugs that cross the blood–brain barrier.

Primary neuropathology should be sought when depression is accompanied by an alteration of neurologic function. Left frontal lobe involvement by a mass lesion or stroke may trigger a depressive syndrome. Inquiry into focal signs and symptoms helps to differentiate a structural lesion from a functional affective disorder. In some medical illnesses, depression may dominate the early clinical picture. Pancreatic cancer is the archetypal example. Important associated findings should be sought, including profound weight loss, vague upper abdominal discomfort, and onset of painless jaundice (see Chapter 58). HIV infection and emergence of AIDS are frequently associated with depression. In such cases, the diagnosis may be obscured by comorbid medical illness (see Chapter 13). In addition, depressive features may mistakenly be conceptualized as normal grief in response to the medical diagnosis and surrounding tragedy.

Psychosocial History

This should focus on the patient’s current home environment and means of financial and emotional support. Does the patient live alone? If the patient does not, is the family environment accepting or, conversely, contributing to the patient’s discomfort? The availability of responsible family members to observe and supervise the patient might mean the difference between outpatient treatment and hospitalization if the patient is very depressed or debilitated. What are the patient’s daily responsibilities, and what secondary stressors arise if the patient cannot meet these obligations?

Psychiatric History of the Patient and Family

Once the issue of medical etiologies has been put to rest, one should return to eliciting a past psychiatric history. Given depression’s tendency to recur, the patient should always be asked about similar episodes in the past. If there is a history of depressivesyndrome or manic disease, it is important to obtain the details of treatment and treatment response; a positive family history of manic symptoms or bipolar disease should raise suspicion for bipolar disorder in the patient. A history of prior psychosis or suicidality is also important to elicit because of their risks for recurrence. Family history can be difficult to elicit because of shame about any mental illness in the family. It helps to explain that depression is believed to run in families because of hereditary biochemical factors, not defects in character. A family history of major depression, bipolar disorder, or suicide supports a diagnosis of depression in the patient. The genetic predispositions for unipolar depression and bipolar illness are distinct. A family history of other psychiatric diagnoses must be interpreted in the context of changing nomenclature and diagnostic criteria. In the past, mania was frequently misdiagnosed as schizophrenia. “Nervous breakdown” and “going insane” were common nonspecific terms. If family psychiatric history is present, it is worth reviewing symptoms and attempting a tentative retrospective diagnosis.

Physical Examination

The importance of a careful and detailed physical examination cannot be overemphasized, especially because most depressed patients presenting to primary physicians harbor concerns about medical illness. Specific patient concerns elicited during the history should be explicitly checked during the physical examination to facilitate the provision of meaningful reassurance (see Chapter 8 for description of the pertinent physical examination).

Mental Status Examination

Much of the mental status examination can be performed by taking note of the patient’s appearance, affect, behavior, and responses during the history. Has the patient’s condition interfered with grooming and self-care? Is there sadness, tearfulness, despondency, apathy, irritability, anxiety, or anger? Is there psychomotor retardation or agitation? Does the patient offer anything spontaneously, or is there a long period of hesitation before answering (i.e., speech latency)? Is the speech slow? Is normal inflection present? The patient should also be asked explicitly to describe his or her mood. Thought is assessed for form and content. Is the patient’s thought pattern clear and coherent or is it tangential, circumstantial, or nonsensical? Are there ideas of worthlessness, hopelessness, guilt, suicidal thought, or homicidality? Is the patient able to maintain attention? Distractibility may occur in depression, delirium, dementia, or severe anxiety and will interfere with the patient’s overall cognitive performance. Any inattention is worth documenting by testing the ability to recall a series of random numbers (digit span). Patients should be able to repeat a series of at least five to seven numbers without error. “I don’t know” answers are reflective of apathy or lack of energy associated with depression. Tests of memory, calculation, abstractions, and other higher cortical functions should be performed.

Although psychotic depression is uncommon in primary care settings, it is important not to miss this very serious condition. It should be noted whether the patient appears guarded or expresses paranoid thoughts or delusions. Inquiry into any unusual experiences, such as hearing voices or seeing things that other people do not see, provides further evidence of a thought disorder. However, unusual smells, tastes, and tactile experiences suggest an organic brain syndrome.

Evaluation for Suicidality

Depression is a potentially fatal illness. Assessment of suicide risk is an integral part of the workup of every depressed patient. About 15% of patients with major affective disorders take their lives; diagnosing and treating depression can be a lifesaving medical intervention by the primary care physician.
With proper intervention, most suicides can be prevented. Concurrent conditions that increase the risk of suicide include chronic alcoholism, personality disorders, and both functional and drug-induced psychoses; delusional beliefs or hallucinations may lead to self-destruction. Predicting a suicide attempt is difficult, even among patients who complain of suicidal thoughts. Assessment of risk is facilitated by specific inquiry.

**Technique.** Assessing risk of suicide requires attention to the patient's thoughts (ideas, wishes, motives), intent (the degree to which the patient intends to act on the thoughts), and plans. Inquiry necessitates a calm, empathic approach that allows expression of feelings and is free of any implied criticism. On any expression of hopelessness, helplessness, or suffering, one might begin with a rather indirect query (e.g., “Are you feeling so bad that sometimes you would prefer not to go on living?”). A positive response is followed by more direct questions about self-destructive thoughts and plans. A well-worked-out, realistic, and potentially lethal plan suggests great risk, as does the act of putting one's affairs in order.

Asking patients about suicide does not put the idea into their heads. Pitfalls include failure to ask specifically about suicidal thoughts and feelings and premature interruption of the patient who mentions suicide. Any mention of suicide must be taken seriously, and every depressed patient must be asked about suicide. It is an error to avoid the subject for fear of doing so. Truly suicidal patients usually are relieved to be asked about it.

Mental status, especially the patient's ability to resist suicidal thoughts, is important to consider. An extremely impulsive, psychotic, or intoxicated patient has no meaningful internal controls and requires hospitalization.

**Assessment of Risk.** There is no simple formula for precisely assessing suicide risk. Attention to thoughts, intent, and plans is essential, facilitated by consideration of mental status and pertinent psychosocial and demographic predictors (Table 227–4). Patients expressing suicidal thoughts, especially if accompanied by intent and plans, or who lack reliable internal controls to resist suicidal impulses require emergency psychiatric consultation. Such patients should be closely supervised and not allowed to transport themselves. Patients with severe or worsening depression who have thought about suicide but steadfastly deny intent or plans should be given a prompt confirmed appointment with a psychiatrist. Depressed patients with no suicidal thoughts, intent, or plans; a normal mental status examination; and external social supports can be treated by the primary care physician, as long as frequent visits can be arranged and the depression responds to treatment. Patients with suicide potential should never be given more than 1 g or 1 week's supply of a tricyclic antidepressant (TCA) (see later discussion).

**Laboratory Studies and Use of Diagnostic Instruments**

There are no laboratory tests for depression. For a time, there was interest in urinary catecholamine metabolites and the overnight dexamethasone suppression test, but shortcomings in sensitivity and specificity compromised clinical utility. Depression remains a clinical diagnosis. Nonetheless, medical causes of depressed mood and neurovegetative symptoms must be ruled out (see Chapter 8). Of note, multiple sclerosis is the most common neurologic cause of depression discovered by brain magnetic resonance imaging (MRI). MRI should be considered in the workup of new-onset depression with any of the following: (a) psychotic symptoms, (b) new focal neurologic deficit, or (c) onset temporally related to head trauma.

**Written Diagnostic Instruments for In-Office Evaluation**

Validated diagnostic instruments are sometimes useful both for case finding and as supplements to the clinical evaluation. The **Beck Depression Inventory** and the **Hamilton Depression Scale (HAM-D)** help to assess severity and can be used to follow response to therapy and clinical course. The Beck Depression Inventory is a 21-item, self-administered questionnaire. The Hamilton Depression Scale is a 21-item instrument that must be clinician administered. Both take approximately 15 minutes to complete and score. The higher the score, the more severe is the distress. Other available instruments include the Symptom-Driven Diagnostic System for Primary Care, the Medical Outcomes Study depression measure, the Quick Diagnostic Interview Schedule, and PRIME-MD. These involve 2 to 28 questions and take less than 2 to 10 minutes to administer. Test sensitivities are comparable (90% to 95%), as are test specificities (50% to 70%) for the diagnosis of major depression.

**Screening for Depression**

Routine screening for depression by primary care practitioners is important, given the high prevalence of depression among patients seen in office practice (up to 10%), the availability of sensitive screening tests, effective means of treatment, and the potentially serious consequences of untreated disease. The U.S. Preventive Services Task Force found the evidence for diagnosis and treatment in primary care settings sufficient to recommend screening in primary care practice. The best results are obtained when screening results are incorporated into an effective system of follow-up and treatment.

Techniques for screening include the clinical interview (e.g., the SIG E CAPS check for neurovegetative symptoms) and use of the written case-finding instruments described earlier. Of comparable sensitivity and specificity (96% and 57%, respectively) is the two-question approach noted earlier that asks about depressed mood and anhedonia: “Over the last 2 weeks, have you felt down, depressed, or hopeless?” and “Over the last 2 weeks, have you felt little interest or pleasure in doing things?”

Because the positive predictive value of a positive screening test is relatively low (about 25% to 40% if pretest probability is 5% to 10%), positive responses to screening efforts necessitate further evaluation, as noted earlier. False-positive responses are often due to the presence of other important psychopathology, including dysthymia, other depressive syndromes, generalized anxiety disorder, panic disorder, posttraumatic stress, substance abuse, and grief reactions.

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**TABLE 227–4 Risk Factors for Suicide**

<table>
<thead>
<tr>
<th>History of prior attempts</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychotic features present (especially command hallucinations)</td>
<td>Psychotic symptoms</td>
</tr>
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It is important to note that the ultimate effectiveness of screening depends on having a system of response in place to ensure follow-up and treatment. Persons at particularly high risk and especially good candidates for screening are those with high utilization rates of primary care services; the prevalence of mood disorders among this group can be as high as 30%.

Some also argue for including screening for bipolar disorder in primary care practice because of its high prevalence (up to 5%), treatability, and potential for misdiagnosis (confusing it with major depression; see later discussion).

**PRINCIPLES OF MANAGEMENT (2,4–7,10,11,13–17,20,22–24,26–57)**

**Overall Strategy**

Depression is a potentially life-threatening yet treatable condition. Most depressed patients (particularly those with major depression) can be treated as outpatients by their primary care physician in conjunction with supportive efforts by other members of the primary care team, including a nurse care manager and health care assistants. Such collaborative approaches to care have been shown to improve outcomes (see insert). Antidepressants and psychotherapy represent the basic treatment modalities, adapted to the specific type of depressive disorder encountered. Psychiatric referral should be considered in severe cases and in patients whose depression has psychotic, bipolar, or characterologic qualities.

Major depression is managed with antidepressant medication in conjunction with psychotherapy, which plays a very important adjunctive role. Bipolar disease requires psychiatric referral; it responds well to a combination of a mood-stabilizing agent and antidepressant therapy. Psychotic depression is also an indication for psychiatric consultation; antipsychotics are utilized. If there is an organic cause (secondary depression), one treats the causative medical illness and discontinues potentially offending medications. Only if the medical condition responds slowly or is intractable are trials of an antidepressant or supportive psychotherapy indicated.

Persons with a characterologic depression/dysthymic disorder respond best to psychotherapy, but when neurovegetative symptoms are prominent, a trial of antidepressants is helpful because dysthymia responds to selective serotonin reuptake inhibitors (SSRIs). A patient with untreated dysthymia is five times more likely subsequently to develop an episode of major depression. Adjustment disorder with depressed mood can be treated by the primary care physician with supportive psychotherapy. If moderate sleep and appetite disturbances are present (as they commonly are), an antidepressant can provide symptomatic relief.

Management of major depression has two facets, psychotherapeutic and medical. The primary care physician needs to become skilled in providing supportive psychotherapy and using first-line antidepressants.

**Psychotherapy**

Treatment begins with establishing a strong patient–physician relationship (see Chapter 1, Part 1) and providing psychological support. More intensive psychotherapy may also be beneficial. The addition of antidepressant medication improves prognosis. Psychotherapy and medication are often synergistic.

**Psychological Management (Supportive Psychotherapy)**

Patients with major depression benefit from supportive psychotherapy, much of which can be provided by the primary care physician. A clear, empathic, hopeful manner helps to forge a therapeutic alliance and facilitates treatment. A detailed explanation of the diagnosis combined with reassurance that depression is eminently treatable does much to calm a fearful patient and family. When patients feel hopeless or undeserving, it is useful to point out that these are the characteristic symptoms of depression and they will gradually improve.

While conveying hope and optimism, the physician must take care not to dismiss as insignificant the patient’s fears, pains, and negative feelings. Many feel overwhelmed by life stresses. It is important to identify these stresses. Empathic listening and thoughtful comment can help the patient to devise strategies for coping. At the outset of treatment, one should see the patient every 1 to 2 weeks for about half an hour. Appointments can then be spaced out according to the patient’s needs. If a patient becomes severely depressed, agitated, or psychotic, emergency psychiatric referral should be made.

**Cognitive–Behavioral Therapy**

This form of psychotherapy focuses on a patient’s thinking and emotional functioning, helping to motivate change by examining the consequences of one’s behavior. Social problem-solving and relationship skills are emphasized. When performed by a skilled practitioner, the method is of proven efficacy in treating chronic depression; results under study conditions are comparable to pharmacotherapy, although they take a few weeks longer to achieve. When combined with pharmacotherapy, the benefits are additive, and outcomes are significantly better than with either alone. Persons with depression accompanying medical problems also benefit, manifesting improved control of their underlying medical condition through improved compliance.

**Social and Environmental Interventions**

A caring family willing to monitor the severely depressed patient can make the difference between outpatient management and hospitalization. Members can ensure medication compliance and follow-up appointments and minimize social isolation. Also helpful is identifying stressful elements in the patient’s environment so that they might be modified. Worries about the consequences of taking time off from work and issues of confidentiality must be addressed. Helping the patient deal with these important concerns is essential and greatly appreciated.

**Psychopharmacologic Therapy**

The SSRIs serve as first-line antidepressants. TCAs can be effective in patients who do not respond to initial trials of SSRIs. The MAOIs and lithium are reserved for special situations.

**Selective Serotonin Reuptake Inhibitors**

As their name implies, the SSRIs (e.g., fluoxetine [Prozac, Prozac Weekly, Sarafem], sertraline [Zoloft], paroxetine [Paxil], paroxetine controlled release [Paxil CR], fluvoxamine [Luvox], citalopram [Celexa], escitalopram [Lexapro], and vilazodone [Viibryd]) affect CNS serotonin metabolism. As noted, serotonin’s sphere of influence is on mood and thus the application of these agents for depression.

**Efficacy.** For mild to moderate depression, all of these SSRIs appear to be equal in efficacy and comparable in efficacy to the TCAs but safer and better tolerated. For severe depression, there has been controversy as to whether the SSRIs are as effective as the TCAs. Unlike the TCAs, many of which are sedating, many SSRIs have energizing or “activating” side effects, a factor favoring their selection in patients suffering anergy, apathy, and psychomotor retardation. The SSRIs have become
the antidepressant of first choice, especially in circumstances in which the avoidance of tricyclic side effects is desired. Randomized, controlled trials have found the major SSRIs to be similar in efficacy, safety, and side effects. However, a period of trial and error is often necessary to determine the optimal agent and best dose for a particular patient.

**Preparations and Cost.** Generic equivalents of several of SSRIs are becoming increasingly available (e.g., *fluoxetine, sertraline, paroxetine, citalopram*), providing opportunity for major cost savings. Not coincidentally, several of the brand name SSRIs have come to market in various slow-release formulations. Theoretically, they should have fewer side effects, and, since patient compliance is the biggest limiting factor in response to a trial of an antidepressant, they may be considered for patients who have demonstrated sensitivity to adverse events from prior medications. For antidepressant-naïve patients, however, their first trial can begin with one of the SSRI generic equivalents.

**Side Effects.** These activating agents can exacerbate agitation, anxiety, and insomnia, making them problematic for depressed patients already troubled by such symptoms. The motor restlessness (including tremor), initial anxiety, and agitation with insomnia can be the most distressing side effects of SSRIs. Concerns about exacerbation of suicidality with SSRI use in adults proved to be unfounded after detailed investigation. Nonetheless, it is always crucial to remain vigilant and inquire specifically about suicidal thoughts, even as patients, especially those under 25 years old, begin to show improvement (see later discussion).

Paradoxically, up to 20% of patients experience some sedation. Unlike the TCAS, with their associated anticholinergic and α-blocking activity, there is little risk of orthostatic hypotension, tachycardia, heart block, blurred vision, or dry mouth. Sexual dysfunction has been reported, including impotence in men and decreased lubrication in women. Decreased libido and anorgasmia may occur in both men and women. These effects are reversible, but they are a common cause of discontinuation of therapy (see later discussion). Some weight gain from appetite stimulation may occur, but not to the extent associated with TCAs. Headache, nausea, and diarrhea have also been reported. All SSRIs can cause a life-threatening reaction if taken concurrently with an MAOI. At least 2 weeks should pass before starting an MAOI after SSRI use and 5 weeks after fluoxetine use. Some SSRIs (fluoxetine, paroxetine, and fluvoxamine) inhibit liver cytochrome P-450 enzymes, slowing hepatic drug metabolism and prolonging the effects of warfarin, phenytoin, and other drugs that are hepatically metabolized. Although SSRI use in pregnancy does not increase the risk of birth defects or retard the development of intelligence, there is a slight increase in the risk of perinatal complications when treatment is continued during the third trimester (see later discussion).

In many instances, sudden cessation of SSRI therapy can result in a withdrawal syndrome, characterized by dizziness,paresthesias, tremor, anxiety, nausea, and palpitations. The risk is about 25% and is much higher with the use of paroxetine as well as paroxetine controlled release. In most instances, withdrawal symptoms are mild, but in rare instances, they can be severe.

**Use and Dose.** All SSRIs require 3 to 4 weeks of continuous use before clinical improvement becomes evident. *Fluoxetine* is available in 10-, 20- and 40-mg strengths. Some patients with prominent anxiety symptoms do better to start with the lower dose. A liquid form enables even smaller starting doses. In nonelderly patients, fluoxetine can be initiated at 20 mg daily. The dose may be advanced by 10 to 20 mg/d every 4 weeks to the typical target dose of 40 mg/d. The *Physicians’ Desk Reference* maximum dose is 80 mg/d, although higher doses are used to treat obsessive–compulsive disorder (see Chapter 226). Because of the drug’s long serum half-life (2 to 3 days), less frequent dosing is possible for elderly persons needing less than 20 mg daily (e.g., 20 mg eraly 2 to 4 days).

*Sertraline* is started at 50 mg/d and gradually increased to therapeutic doses in the range of 100 to 250 mg/d. *Fluvoxamine* is also started at 50 mg/d and gradually increased to therapeutic doses in the range of 100 to 200 mg/d. *Citalopram* and *paroxetine* are administered in doses comparable with those of fluoxetine. All other SSRIs have shorter half-lives than does fluoxetine, but dosing is still once daily. Paroxetine, fluvoxamine, sertraline, citalopram, and escitalopram are also available in a liquid form.

**Serotonin–Norepinephrine Reuptake Inhibitors**

Serotonin–norepinephrine reuptake inhibitors (SNRIs) act upon and increase the levels of two important cerebral neurotransmitters (serotonin and norepinephrine), which affect mood and energy. These agents stand in contrast to the more widely used SSRIs, which only affect serotonin metabolism. As noted earlier, on a neurotransmitter basis, norepinephrine affects energy levels and level of alertness, while serotonin’s sphere of influence is principally on mood. SNRIs’ dual action and potential to affect depression through a combination of neurotransmitter pathways is thought to account for a perceived therapeutic advantage seen in some patients. Unfortunately, predicting which patients will respond best to an SNRI remains difficult.

**Use.** Currently, the SNRIs serve as second-line agents, mainly due to their high cost compared to generic SSRIs. Available SNRIs FDA approved for use in depression include duloxetine (Cymbalta), venlafaxine XR (Effexor XR), and desvenlafaxine (Pristiq). Milnacipran (Savella), approved in the United States only for treatment fibromyalgia, is used by some clinicians to treat depression. Because use of these agents differs, they are best considered individually.

**Venlafaxine and Venlafaxine Extended Release (Generic and Effexor).**Venlafaxine, which was the first of these agents and available generically, is typically prescribed in long-acting form due to its short half-life. Even with availability of the extended-release form, it requires twice-daily administration, starting at 37.5 mg twice daily and gradually increasing to therapeutic doses in the range of 75 to 150 mg twice daily. At the higher doses, it has more effect on norepinephrine uptake inhibition and possibly achieves a higher remission rate than do other antidepressants.

**Desvenlafaxine Extended Release (Pristiq).**Desvenlafaxine extended release (Pristiq) is a derivative of venlafaxine extended release, delivering the same active metabolite but less likely to engage in drug–drug interactions, being metabolized differently. In clinical use, it has found a place in the patient who has a good therapeutic response to venlafaxine extended release but bothered by side effects of nausea, somnolence, insomnia, dry mouth, and dizziness. It is typically started at 25 mg per day and increased to the usual target dose of 50 mg per day. Some patients need 100 mg per day to get a full response.

**Duloxetine (Cymbalta).**Duloxetine is typically started at 30 mg at bedtime and gradually increased to its therapeutic dose of 60 mg before bed. In addition to treatment of depression, it has been approved for the treatment of painful diabetic peripheral neuropathy, making it a particularly useful agent in depressed patients suffering from this condition (see Chapter 167). The drug is well absorbed, is hepatically metabolized, and requires dosing two to three times per day. Adverse effects include dizziness, nausea, somnolence, and constipation. The drug should not be used in persons with narrow-angled glaucoma; safety in pregnancy is not established. Minor transaminase elevations may be noted. Expense is high compared to that of generic formulations of SSRIs and TCAs.
norepinephrine to serotonin, its common side effects include
twice per day. As might be expected from its 3 to 1 effect on
and increasing within a week to its usual target dose of 50 mg
depression, but its starting dose is usually 12.5 mg twice daily
multiple somatic complaints, though not approved to treat
in fibromyalgia and also has some clinical use in patients with
mentioned purposes in treatment-refractory patients.
Much more commonly,
have no place in the treatment of depression.
except for the depressed patient with psychotic symptoms,
out administering too much of the other compound. Moreover,
make it difficult to achieve therapeutic levels of the tricyclic with-
age among tricyclics of causing the least postural hypotension.
nortriptyline [Aventyl or Pamelor]). Nortriptyline has the advan-
mild anticholinergic activity (e.g.,
triptophy do best with a nonsedating tricyclic that has relatively
low doses suffice. The elderly and those with prostatic hyper-
are best treated with a nonsedating, slightly activating TCA (e.g.,
(Adapin or Sinequan) given at bedtime.
Patients with severe 
insomnia might do best with a strongly sedating
drug, such as doxepin (Adapin or Sinequan) given at bedtime.
The very sedating drug amitriptyline (Elavil) has long been popular
with physicians, but because of its strong anticholinergic side
effects, it is probably not an optimal first-choice agent unless
low doses suffice. The elderly and those with prostatic hyper-
trophy do best with a nonsedating tricyclic that has relatively
mild anticholinergic activity (e.g., desipramine [Norpramin] or
nortriptyline [Aventyl or Pamelor]). Nortriptyline has the advantage
among tricyclics of causing the least postural hypotension.
Persons bothered by anergy and psychomotor retardation are
best treated with a nonsedating, slightly activating TCA (e.g.,
protriptyline) or an SSRI (as per earlier discussion).

The prescribing of a fixed-combination preparation containing a
tricyclic plus a neuroleptic (e.g., Triavil) or a benzodiazepine (e.g.,
Limbitrol) is irrational and should be avoided. Combinations
make it difficult to achieve therapeutic levels of the tricyclic with-
out administering too much of the other compound. Moreover,
except for the depressed patient with psychotic symptoms, typi-
cal antidepressants have no place in the treatment of depression.
Much more commonly, atypical antidepressants are used for aug-
mentation purposes in treatment-refractory patients.

Adverse Effects. Tricyclics can have lethal cardiovascular toxicity
when taken in overdose due to severe cumulative anticholinergic and
α-blocking effects. One should never write a prescription that
dispenses more than 1 g of a tricyclic to a potentially suicidal
patient or to a patient one does not know well. At therapeutic
doses, postural hypotension can occur, especially in the elderly,

**TABLE 227—5 Antidepressants**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Customary Initial Dose</th>
<th>Titrated Dose Up To</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selective Serotonin Reuptake Inhibitors (SSRIs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>Celexa</td>
<td>20 mg/d</td>
<td>20–40 mg/d</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Lexapro</td>
<td>10 mg/d</td>
<td>10–20 mg/d</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Prozac</td>
<td>20 mg/d</td>
<td>20–40 mg/d</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Luvox</td>
<td>50 mg/d</td>
<td>100–250 mg/d</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Paxil</td>
<td>20 mg/d</td>
<td>20–60 mg/d</td>
</tr>
<tr>
<td>Paroxetine (controlled release)</td>
<td>Paxil CR</td>
<td>25 mg/d</td>
<td>50–62.5 mg/d</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Zolofit</td>
<td>50 mg/d</td>
<td>100–250 mg/d</td>
</tr>
<tr>
<td>Vilazodone</td>
<td>Viibryd</td>
<td>10 mg/d</td>
<td>40 mg/d</td>
</tr>
<tr>
<td><strong>Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Cymbalta</td>
<td>30 mg/d</td>
<td>60 mg/d</td>
</tr>
<tr>
<td>Venlafaxine (extended release)</td>
<td>Effexor XR</td>
<td>37.5 mg XR bid</td>
<td>75–150 mg bid</td>
</tr>
<tr>
<td>Desvenlafaxine (extended release)</td>
<td>Pristiq</td>
<td>25 mg/d</td>
<td>50 mg/d</td>
</tr>
<tr>
<td>Milnacipran</td>
<td>Savella</td>
<td>12.5 mg bid</td>
<td>50 mg bid</td>
</tr>
<tr>
<td><strong>Atypical Antidepressants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion (sustained release)</td>
<td>Wellbutrin SR</td>
<td>150 mg SR qam</td>
<td>150–200 mg bid</td>
</tr>
<tr>
<td>Bupropion (extended release)</td>
<td>Wellbutrin XL</td>
<td>150 mg SR qam</td>
<td>300–450 mg qam</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Remeron</td>
<td>15 mg qhs</td>
<td>30–45 mg qhs</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>Serzone</td>
<td>50 mg bid</td>
<td>150–300 mg bid</td>
</tr>
<tr>
<td>Trazodone</td>
<td>Desyrel</td>
<td>50–100 mg qhs</td>
<td>200–600 mg/</td>
</tr>
<tr>
<td><strong>Tricyclic Antidepressants (TCAs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Elavil</td>
<td>25 mg qhs</td>
<td>150–300 mg qhs</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Anafranil</td>
<td>25 mg qhs</td>
<td>150–200 mg qhs</td>
</tr>
<tr>
<td>Desipramine</td>
<td>Norpramin</td>
<td>25 mg qam</td>
<td>150–300 mg qam</td>
</tr>
<tr>
<td>Doxepin</td>
<td>Adamin</td>
<td>25 mg qhs</td>
<td>150–300 mg qhs</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Tofrinal</td>
<td>25 mg qhs</td>
<td>150–300 mg qhs</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Pamelor</td>
<td>10 mg qhs</td>
<td>50–150 mg qhs</td>
</tr>
<tr>
<td>Protriptyline</td>
<td>Vivactil</td>
<td>10 mg qam</td>
<td>30–60 mg qam</td>
</tr>
<tr>
<td>Trimipramine</td>
<td>Sarmonil</td>
<td>25 mg qhs</td>
<td>150–250 mg qhs</td>
</tr>
<tr>
<td><strong>Monoamine Oxidase Inhibitors (MAOs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenelzine</td>
<td>Nardil</td>
<td>15 mg bid</td>
<td>45–90 mg/d</td>
</tr>
<tr>
<td>Tranylcypromine</td>
<td>Parnate</td>
<td>10 mg bid</td>
<td>40–80 mg/d</td>
</tr>
<tr>
<td>Selegiline transdermal</td>
<td>Emsam patch</td>
<td>6 mg per 24 h</td>
<td>6 to 12 mg per 24 h</td>
</tr>
</tbody>
</table>

bid, twice daily; qam, in the morning; qhs, at bedtime.

**Milnacipran (Savella).** This SNRI is FDA approved for use
in fibromyalgia and also has some clinical use in patients with
multiple somatic complaints, though not approved to treat
depression, but its starting dose is usually 12.5 mg twice daily
and increasing within a week to its usual target dose of 50 mg
twice per day. As might be expected from its 3 to 1 effect on
norepinephrine to serotonin, its common side effects include
nausea, constipation, and excessive sweating.

**Tricyclic Antidepressants**
The TCAs are a reasonable choice for antidepressant therapy in
selected persons who fail SSRI treatment. The low cost per tab-
let of the generic formulations weighs in their favor (although brand formulations are very expensive) (Table 227-5). When
used in properly selected patients, TCA therapy can reduce the
cost of therapy by an order of magnitude, but only when used in
persons who can readily tolerate the side effects. Primary care
physicians should become comfortable with using at least one
sedating and one nonsedating TCA compound. These agents
appear to act predominantly on norepinephrine metabolism, inhibiting reuptake at CNS synapses. Some TCAs also affect
serotonin and, to a lesser extent, dopamine metabolism. A large
number of tricyclics are available. All are equally effective. The
major differences are in the degree of anticholinergic and sedative
side effects. All require 3 to 4 weeks of continuous use before
clinical improvement becomes evident. Drug choice for a given
patient is determined by attention to the side effects of available
agents (Table 227-5). Patient comfort and compliance are facili-
tated by avoiding drugs with marked anticholinergic activity.
**Choice of Tricyclic.** In general, the TCAs tend to be sedating.
Patients with severe 
insomnia might do best with a strongly sedating
drug, such as doxepin (Adapin or Sinequan) given at bedtime.
The very sedating drug amitriptyline (Elavil) has long been popular
with physicians, but because of its strong anticholinergic side
effects, it is probably not an optimal first-choice agent unless
low doses suffice. The elderly and those with prostatic hyper-
trophy do best with a nonsedating tricyclic that has relatively
mild anticholinergic activity (e.g., desipramine [Norpramin] or
nortriptyline [Aventyl or Pamelor]). Nortriptyline has the advantage
among tricyclics of causing the least postural hypotension.
Persons bothered by anergy and psychomotor retardation are
best treated with a nonsedating, slightly activating TCA (e.g.,
protriptyline) or an SSRI (as per earlier discussion).

The prescribing of a fixed-combination preparation containing a
tricyclic plus a neuroleptic (e.g., Triavil) or a benzodiazepine (e.g.,
Limbitrol) is irrational and should be avoided. Combinations
make it difficult to achieve therapeutic levels of the tricyclic with-
out administering too much of the other compound. Moreover,
except for the depressed patient with psychotic symptoms, typi-
cal antidepressants have no place in the treatment of depression.
Much more commonly, atypical antidepressants are used for aug-
mentation purposes in treatment-refractory patients.

**Adverse Effects.** Tricyclics can have lethal cardiovascular toxicity
when taken in overdose due to severe cumulative anticholinergic and
α-blocking effects. One should never write a prescription that
dispenses more than 1 g of a tricyclic to a potentially suicidal
patient or to a patient one does not know well. At therapeutic
doses, postural hypotension can occur, especially in the elderly,
leading to falls, fractures, and head injury. If postural hypotension is a problem, triazolam, or an SSRI should be used. Postural hypotension is always worse in the morning, it may be useful to give the nortriptyline in three divided doses. Patients should be instructed to be careful when rising from recumbency or sitting.

Before benefit is noted, patients may want to stop TCA therapy because of dry mouth, lassitude, constipation, or mental clouding. Such symptoms are common with the use of TCAs but may also result from depression. They often pass or abate with continued therapy, a reassuring fact that helps patients to continue TCA treatment. Weight gain is another complaint. It results from TCA-associated stimulation of appetite.

Rarely, more severe dose-related anticholinergic symptoms occur, especially in the elderly. These include ileus, urinary retention, and dyskinesias. In all patients older than 40 years, it is good practice to obtain a baseline electrocardiogram before starting a tricyclic. At therapeutic levels, tricyclics exert anticholinergic effects on the heart, which could cause a rise in heart rate and conduction delay. In patients with bundle-branch block, atrioventricular block, or sinus node disease, there is an increased risk of higher degrees of heart block. In patients without underlying conduction system disease, tricyclics rarely cause conduction problems.

Very rarely, a full anticholinergic syndrome develops in patients taking TCAs, characterized by agitation, delirium, and fever. The most common precipitant is simultaneous use of more than one anticholinergic drug. Most often implicated is concurrent use of thexiouidine (Mellaril), anticholinergic anti Parkinsonian drugs, antihistamines, antispasmodics, and over-the-counter sleep medications containing antihistamines. The number of anticholinergic compounds should be closely monitored, especially in the elderly.

Withdrawal syndrome symptoms (e.g., dizziness, paresthesias, tremor, anxiety, nausea, and palpitations) occur more frequently with abrupt cessation of TCAs than with SSRIs. Their frequency is reported to be as high as 30% to 60%, but they can be avoided by tapering before discontinuation.

Dose. Tricyclics are started at a low dose with gradual increases until the therapeutic dose range is achieved (Table 227–5). After that, trial and error is often required. Drug serum levels can be used to determine compliance and achievement of therapeutic serum concentrations in nonresponders. Blood levels vary widely among patients for any given oral dose due to individual differences in drug absorption and metabolism. Therapeutic serum levels have been established for imipramine, desipramine, amitriptyline, and nortriptyline (Table 227–5). For other TCAs, serum levels are useful only to ascertain compliance. Many clinical laboratories are unreliable in measuring these compounds. One should seek an experienced laboratory.

The most common cause of treatment failure is inadequate dose. In healthy nonelderly adults, a typical starting dose is the equivalent of 50 mg of desipramine. (Nortriptyline has twice the milligram potency of most tricyclics; thus, its starting dose is 25 mg.) The daily dose is best taken at bedtime to facilitate compliance and minimize side effects. Dose can be increased by 50 mg every 3 to 4 days to a dose of 150 to 200 mg at bedtime. Doses are reduced by 50% in the elderly (see later discussion). The final dose chosen is one that provides a therapeutic response without intolerable side effects. The usual maximum dose is 300 mg of desipramine or the equivalent (150 mg for nortriptyline). This is easier said than done. In recent reviews, less than 10% of patients whose depression was diagnosed received a therapeutic dose of a TCA.

Atypical Antidepressants

This class includes bupropion, trazodone, nefazodone, and mirtazapine. These agents have slightly different mechanisms of action than those of the first-line SSRIs and TCAs, providing potential benefits in selected circumstances where SSRIs, SNRIs, and TCAs do not suffice. While mostly the province of the psychiatrist and not considered first-line agents for use by primary care physicians unless familiar with them, these atypical antidepressants and their characteristics should be understood by members of the primary care team since they may be encountered in the course of caring for depressed patients.

Bupropion (Generic and Wellbutrin). Bupropion (available in sustained-release [SR] and extended-release preparations) appears to work by down-regulating postsynaptic β noradrenergic receptors. Unlike the SSRIs, there are no adverse effects on sexual function, making it helpful in depressed persons bothered by such side effects and in patients who do not respond to the SSRIs. Moreover, there is little weight gain, a side effect common with SSRIs. As such, it is a popular drug among psychiatrists, being also used “off-label” for attention deficit disorder, cocaine craving, and chronic fatigue syndrome. In patients with bipolar disorder, it has a lower “switch rate” into a manic episode than first-line antidepressants.

Use. Bupropion is usually started at 150 mg SR/XL in the morning and gradually increased to achieve therapeutic levels with doses in the range of 150 to 200 mg SR/XL twice daily. Use of both the SR and extended-release preparations has markedly increased since the publication of the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study, which found some of the highest success rates associated with bupropion when used as an augmentation agent in patients partially responsive to an SSRI or when prescribed as a monotherapy switch in patients who had been unresponsive.

Adverse Effects. Use of non–SR preparations was associated with an increased risk of seizure activity, but availability in SR preparations reduces the risk of seizure to that of other antidepressants. However, even the SR form is still contraindicated in patients with a known seizure disorder or eating disorder.

Trazodone (Generic and Oleptro). Trazodone was an early nontricyclic second-generation antidepressant with efficacy similar to that of TCAs but better tolerated, not having the latter’s affinity for the mACH receptors, which cause anticholinergic side effects. Its antidepressant and anxiolytic effects are due predominantly to action as a 5-HT 2A receptor antagonist. Being a relatively weak serotonin reuptake and 5-HT 1A receptor inhibitor, it does not stimulate appetite and cause weight gain, unlike SSRIs and 5-HT 2A antagonists like mirtazapine.

Use. Since the drug is sedating, it is particularly helpful for insomnia, even at doses below those associated with antidepressant action (<200 mg/d). Trazodone is usually started at 50 to 100 mg at bedtime as a sleep inducer. For use as an antidepressant, dosing needs to gradually increase to 300 to 600 mg at bedtime.

Side Effects. Postural hypotension due to its alpha-adrenergic blocking effect can be a problem in the elderly. Other common side effects include indigestion, nausea, and headaches. Sexual side effects are fewer than for TCAs, but prazepam, a painful medical emergency, has been reported. Males prescribed trazodone must be warned that a sustained painful erection requires immediate medical attention. Excessive sedation can result from concurrent use with benzodiazepines or alcohol, which should be avoided.

Nefazodone (Generic and Serzone). Nefazodone inhibits serotonin reuptake and uniquely blocks 5-HT 2 receptors and mediates 5-HT 1A transmission. Results achieved with nefazodone are similar to those for SSRIs. The drug is usually started at 50 mg twice daily and gradually tapered up to therapeutic doses in the range of 150 to 300 mg twice daily. After an initial burst of enthusiastic use spurred by publication of an 85% response rate when used in combination with a form of cognitive/behavioral therapy, nefazodone’s clinical use has been greatly lessened after the FDA issued a black box warning because of reports of rare but life-threatening liver failure necessitating liver transplantation (one case per 300,000 patient-years). Periodic liver function
testing has been used, believing that early detection of injury along with immediate withdrawal of the drug enhances the likelihood of recovery. Despite its black box warning, nefazodone is considered an important alternative in the treatment of depression because of little adverse effect on sexual function.

Mirtazapine (Generic and Remeron). Mirtazapine is associated with an increased release of both serotonin and norepinephrine. Mediation of 5-HT1A transmission and blocking of 5-HT, and 5-HT2, receptors may account for its antidepressant and anxiolytic effects. Its onset of action is faster than that for SSRIs. It is usually started at 15 mg at bedtime and gradually tapered up to therapeutic doses in the range of 30 to 45 mg at bedtime. Its side effects of increased appetite and somnolence make it useful for hospitalized patients, but excretion is renal necessitating caution with renal impairment. Due to its sedative effects, use with other sedatives and alcohol can be problematic.

Monoamine Oxidase Inhibitors
MAOIs are quite useful in treating the elderly (see later discussion), being well tolerated by virtue of their lack of anticholinergic side effects. However, they do have other side effects that bear noting.

Side Effects. These drugs can be used safely, but considerable patient education on proper use and precautions is essential. The primary adverse effects are hypotension and insomnia. Hypotension is unrelated to dose and may occur up to a month after starting the drug. It rarely necessitates stopping the drug. Insomnia can be minimized by giving the last daily dose no later than 4 pm. Hypertensive crisis is the most serious adverse effect, caused by ingesting a large amount of tyramine. Dietary and drug precautions must be given to the patient. A low-tyramine diet is required, necessitating avoidance of foods such as fermented cheese, large amounts of yogurt, excessive caffeine, and chocolate, beer, and red wine. Patients can drink white wine, vodka, gin, and whiskey. A blanket warning to avoid all alcohol is not only unwarranted but may also compromise compliance. Sympathomimetics should be avoided, with special warning to watch for unintentional intake in many over-the-counter medications, including combination cold tablets, nasal decongestants, and appetite suppressants. Amphetamines are also not permitted. Treatment of a hypertensive crisis involves prompt cessation of MAOI use and the initiation of antihypertensive therapy with an α-blocker or a direct vasodilator (phenolamine, 5 mg given slowly intravenously, is recommended). Fever is managed by means of external cooling. Severe life-threatening reactions can also occur as a consequence of interactions between MAOIs and SSRIs or narcotic analgesics. A several-week period between cessation of SSRI therapy and initiation of MAOI use is required, as is psychiatric consultation before starting the MAOI.

Choice of MAOI Agent. Tranylcypromine (Parnate) is the preferred MAOI in the elderly because its effects last no more than 24 hours. The starting dose is 10 mg once or twice daily, and the dose is gradually increased as needed over a few weeks. Usually, 20 to 30 mg daily suffices, but occasional patients require as much as 80 mg/d.

Phenelzine (Nardil) is the other available nonselective and irreversible MAOI. Its use is generally limited to treatment refractory patients, particularly those with “atypical” symptomatology including hypersomnia and hyperphagia. The starting dose is 5 mg three times daily, and the dose is gradually increased as needed over a few weeks to its usual target dose of 20 mg three times daily.

Selegiline transdermal (Emsam) is the newest available MAOI. While selegiline is an irreversible MAOI, it is relatively selective for MAO-B. Delivered via a patch, it bypasses the hepatic “first-pass” metabolism and does not require dietary restriction at the clinically effective dose of 6 mg per 24 hours. However, at higher doses of EMSAM (i.e., 9 mg per 24 hours or more), dietary restriction of tyramine intake is recommended.

Other Agents
A host of agents have been used, ranging from anxiolytics to St. John’s wort.

Anxiolytics. The benzodiazepine alprazolam (Xanax) has excellent antianxiety effects and mild antidepressant action. However, prolonged use is associated with significant risk of dependence (see Chapter 226). Buspirone (BuSpar) is similarly purported to have combined anxiolytic and mild antidepressant effects and has the advantage of a more benign side effect profile, without risk of physiologic dependence (see Chapter 226). These agents are reasonable in cases of adjustment disorders with depressive and anxiety features, but they are not indicated for the treatment of major depression.

St. John’s Wort. Fear about the use of pharmacologic agents for depression has stimulated lay interest in the use of “natural” substances for treatment (see also Chapter 238). The use of St. John’s wort is reportedly widespread, but there are few large-scale, randomized, placebo-controlled trials of this herbal preparation. Those that have been completed in persons with major depression of moderate severity failed to demonstrate any benefit over placebo. Of note, the placebo effect in depression can be substantial and might account for the efficacy reported in early studies of St. John’s wort that did not use placebo control. Whether the herbal preparation might be beneficial in persons with mild disease remains to be determined. Pending more data, St. John’s wort should not be used in place of standard treatment for depression, which is of proven efficacy.

Selection of Antidepressant for Major Depression
Studies of efficacy find little difference among SSRIs/SNRIs and between them and atypical antidepressants bupropion, nefazodone, and mirtazapine. Response rates in severe depression may be higher with TCAs, but these drugs are the least well tolerated, especially in the elderly (see below).

Choice of agent should be based on the prior history of response (a good predictor), patient preference, cost, and expected side effects. Also important is taking into account disease severity, patient age, degree of psychomotor retardation, presence of sleep disturbance, and ability to tolerate anticholinergic, cardiac, and postural side effects. Costs are a key consideration because these drugs are likely to be used for prolonged periods of time. The generic SSRI formulations are available at a fraction of the cost of brand name SSRIs/SNRIs and the brand name TCAs (Table 227-5). Although the generic TCAs are less costly on a pill-per-pill basis, their requirements of cardiac monitoring, blood levels, and possibly more frequent office visits to manage their side effects can all contribute to a higher total cost in patients especially vulnerable to their side effects.

In the elderly and others with cardiac disease, prostatic hypertrophy, postural hypotension, or glaucoma, the SSRIs may be better tolerated. When sedation without anticholinergic activity is desired, trazodone is a reasonable choice, particularly in the elderly. For anergic, hypersomnic, or motor-retarded patients, an activating agent is best (e.g., an SSRI or bupropion SR or desipramine). For patients with a mixture of neurovegetative symptoms, nortriptyline is reasonable, being well tolerated and free of excessive sedating, activating, anticholinergic, or antiadrenergic effects.

Monitoring and Duration of Therapy: Failure to Respond
Monitoring response to therapy can be readily accomplished by carefully reviewing symptoms and activity level. The questionnaire instruments used for the assessment of disease severity (see prior discussion) can also be used. If a patient shows little or no response to antidepressant therapy after 6 weeks at full dose...
(which may be 10 weeks from initiation of therapy), then the drug trial should be considered a failure and the patient considered to have treatment-resistant depression. If there is doubt as to the adequacy of a dose or compliance, a serum drug level can be obtained. Initial failure to respond is an indication for a trial of switching to another antidepressant. Options include trying another SSRI/ SNRI and switching to another class of antidepressant. In a major study of patients failing to respond to or intolerant of initial SSRI therapy with citalopram, approximately one in four achieved remission of their depression by switching to another SSRI (e.g., sertraline) or to a non-SSRI antidepressant (e.g., bupropion). Persistent failure to respond is an indication for psychopharmacologic consultation to explore whether augmentation therapy (i.e., adding a second agent, usually from a different class) or switching to yet another agent is the best approach. Sometimes, augmentation can be the more rapid approach to achieving control, but consultation is advised. The addition of psychotherapy may also be helpful as part of the augmentation strategy.

It is important to reassess the patient's use of alcohol. It has long been known that patients who meet criteria for alcohol abuse or dependence are less likely to respond to antidepressant treatment. Even more modest alcohol intake (e.g., an average of 1 oz of alcohol per day) is associated with a lower rate of response. Thus, patients should be encouraged to either abstain from drinking alcohol while on their antidepressant or limiting their alcohol use as much as possible.

If the response to initial therapy was promising but limited by intolerance to drug side effects, then switching to another agent in the same class with a more favorable side effect profile might suffice (e.g., switching from amitriptyline to nortriptyline for postural hypotension).

If depression successfully remits, antidepressant medication is maintained for at least 6 to 9 months. It should be used longer among patients who have experienced moderate to severe depression and who are judged to face a high risk of recurrence, perhaps because of a history of previous episodes. Continuation-phase medication should be maintained at the same dose as was used in the acute-phase treatment. It has been shown to reduce the risk of recurrence by 70% for as long as 36 months after the acute episode. When it is time to discontinue treatment, the dose can be slowly tapered off over a period of 4 weeks while watching for the reemergence of depressive symptoms. Should symptoms recur, the dose is returned to its prior level and maintained for at least another 6 to 9 months.

Major depression is a medical illness with a high rate of recurrence. After a single episode, 50% of patients subsequently have a second episode. After two episodes, the chance of having a third recurrences. After a single episode, 50% of patients subsequently have remission for at least another 6 to 9 months. It should be used longer, possibly for as long as 36 months after the acute episode. When it is time to discontinue treatment, the dose is slowly tapered off over a period of 4 weeks while watching for the reemergence of depressive symptoms. Should symptoms recur, the dose is returned to its prior level and maintained for at least another 6 to 9 months.

Discontinuation of Therapy due to Drug-Associated Sexual Dysfunction

An important and commonly cited cause of discontinuation of antidepressant therapy is antidepressant-associated sexual dysfunction. Manifestations include decreased libido, erectile dysfunction, and delayed orgasm. It is estimated that 30% to 70% of patients taking SSRIs/SNRIs antidepressants experience this side effect. The finding is prevalent even among patients who achieve remission of their depression with SSRI therapy. The problem typically occurs early in treatment and tends to persist, although it may wax and wane. Among the treatment approaches studied is addition of sildenafil (Viagra) or tadalafil (Levitra) or vardenafil (Cialis). Monotherapy treatment with bupropion shows the least impairment of sexual function of the antidepressants. Dose reduction and dose holiday are other options. Evidence of efficacy is strongest for the addition of sildenafil in persons who achieve remission of their depression with SSRI therapy. More than 50% of male participants in one randomized, placebo-controlled trial achieved significant improvement in most dimensions of sexual function with the use of a 50-mg dose taken 1 hour before sexual activity. Libido is the least responsive to sildenafil therapy. Because data are available only from short-term studies in men, results in women and long-term safety and efficacy remain to be established. Bupropion shows the least impairment of sexual function in controlled trials and might be considered as initial therapy where sexual dysfunction is a major concern.

Prevention of Suicide

The best prevention is proper screening for suicidality and prompt referral at the time of initial evaluation. However, some patients are at greatest risk for suicide at the time when they are initially responding to antidepressant medication. Dysphoria may persist as energy lifts, perhaps giving the patient with suicidal thoughts adequate energy to formulate a plan and follow it through. Continuous vigilance is required, as well as care in the choice and amount of antidepressant prescribed. If there is a question of suicide risk, either a nontricyclic should be selected or no more than 1 g of a tricyclic dispensed at a time.

Treatment of Depression in the Elderly

Depression is the most common psychiatric disorder of the elderly, affecting close to 1 million older Americans. Primary treatment modalities include antidepressants and, for severely affected patients, electroconvulsive therapy (ECT). Age-related changes in drug metabolism and susceptibility to drug side effects must be taken into account in the design of the treatment program (see Appendix 173.1).

Choice of Antidepressant

When anergy and psychomotor retardation predominate, the activating effects of SSRIs/SNRIs make them attractive. Similarly, SSRIs are an excellent first choice if there is heart block, dysrhythmia, or postural hypotension. Of the SSRIs, sertraline, citalopram, and escitalopram are the least likely to interfere with hepatic drug metabolism and are preferred in patients taking drugs that are metabolized by the liver (e.g., digoxin, warfarin, phenytoin). The sedating, anticholinergic, cardiac, and postural side effects of many TCAs make their use in the elderly especially problematic. Before starting therapy, postural signs and an electrocardiogram should be performed and particular note taken of the patient's somatic symptoms and degree of psychomotor retardation. Amitriptyline and imipramine are among the most difficult to use; nortriptyline and desipramine are better tolerated. If sedation is desired, trazodone is a reasonable choice, being free of anticholinergic activity. When loss of sex drive results from SSRI/SNRI therapy or is an initial concern, bupropion is a reasonable choice, having the lowest rate of sexual side effects.

Initiating and Monitoring Therapy

One starts with a very low dose of medication (e.g., 10 mg of fluoxetine, 25 mg of desipramine, 10 mg of nortriptyline, or 50 mg of trazodone). The dose can be raised slowly every 5 to 7 days while monitoring subjective response and heart rate and watching for anticholinergic, cardiovascular, and CNS side effects. One slows the increase in dose if tachycardia, excessive sedation, agitation, or orthostatic hypotension develops.

Often, the patient is the last to recognize improvement, and family members commonly report that the patient is sleeping and eating better before the dysphoria resolves. An adequate
trial may take twice as long in the elderly as in younger patients. Several studies have demonstrated patients older than 55 years not showing their response until 12 weeks.

**Treating Failure to Respond**

If there is little improvement after a reasonable trial at therapeutic doses, consultation is warranted to consider the use of an alternative antidepressant (e.g., MAOI) or ECT.

**Use of a Monoamine Oxidase Inhibitor.** MAOIs have been used sparingly in the elderly because of concern for adverse reactions. Actually, MAOIs have no anticholinergic activity and are relatively well tolerated. Many older patients who do not respond to other antidepressants improve with MAOIs. MAOI therapy should be selected and started by a psychopharmacologic consultant, but management can then shift to the primary care physician, who needs to be familiar with drug actions and side effects (see prior discussion).

**Use of Electroconvulsive Therapy.** Elderly patients who are psychotically depressed, severely incapacitated, refractory to or unable to take drug therapy, or in need of a rapid response should be referred for consideration of ECT. The best predictors of response are psychomotor retardation and delusions. Efficacy and safety have been well documented. Attainment of generalized seizure activity is required to achieve benefit. Customizing electrical dose to the patient’s seizure threshold may help to maximize efficacy and minimize adverse effects. Electrode placement appears to be more important than is electrical dose as regards amnesia, with unilateral electrode placement associated with a lower risk. Amnesia occurs for events just before and up to a few weeks after treatment. Long-term cognitive functioning is no different than that for patients treated with antidepressants. Relapses occur with high frequency, making ECT an acute treatment. Maintenance ECT is common these days, usually once or twice per month on an outpatient basis. Quite often, an SSRI/SNRI or a TCA is prescribed for lifelong maintenance treatment in an elderly patient.

**Pretreatment Medical Evaluation and Management.** While there are no absolute medical contraindications to ECT, preexisting cardiopulmonary diseases confer additional risk for complications such as prolonged blood pressure elevation, asystole, and myocardial ischemia. In general, the cardiovascular risk of ECT is similar to that for low-risk noncardiac surgery. Of particular importance are pretreatment identification, evaluation, and management of hypertension, coronary artery disease, congestive heart failure, aortic stenosis, implanted pacemaker or defibrillator, atrial fibrillation, asthma, COPD, and diabetes. In almost all instances, the treatment program should be continued and optimized before the procedure. Drugs taken to achieve control should be continued at established best doses the day of the procedure, except for those with diabetes, who should have the dose of any long-acting insulin reduced by half the morning of the procedure and any oral agents held, and those with asthma or COPD taking a theophylline preparation, which also should be held. There is no evidence supporting use of prophylactic beta-blockade in persons not already requiring a beta-blocker. Cardiac consultation is indicated in persons with unstable angina, severe aortic stenosis, or an implantable cardiac device.

**Treatment of Seasonal Affective Disorder**

*Light therapy* is the first line of treatment. Exposure to 10,000 lux of ordinary white fluorescent light for 30 to 45 minutes at a time once or twice a day is effective. Improvement often occurs within the 1st week or two of therapy. Patients typically sit about 50 cm from a light box and read for the period of treatment, with the light coming in at a 45-degree angle. Improvement has been noted both with morning and nighttime treatments, although the latter may cause insomnia. Elaborate forms of lighting that more closely simulate the spectrum of sunlight are no more effective than is light from a standard white fluorescent source. The intensity of light appears to be the key determinant of efficacy. SSRIs/SNRIs are probably as effective as light therapy. Some clinicians use both. The efficacy of prophylactic therapy early in the winter is often helpful; starting it the weekend when the “clocks change” seems to lessen the chances of a “winter depression.”

**Treatment of Depression in Pregnancy and Postpartum**

Depression in pregnancy or in the postpartum period can be a serious problem, with adverse consequences for both mother and newborn. Inadequate weight gain, frank weight loss, and even malnutrition may ensue, leading to low birth weight. Suicidality is a major concern, as are failure to come for prenatal and obstetric care and difficulty caring for other children. Other consequences include the need for long-term hospitalization, marital discord, divorce, and loss of employment.

**Pregnancy**

The prevalence of depression in pregnancy approaches 10%. Women with depression during pregnancy are at increased risk for intrauterine growth retardation, preterm labor, placental abruption, and altered neonatal behavior. Some of these adverse effects are believed to be related to depression-induced weight loss and abnormal stimulation of the hypothalamic–pituitary–adrenal axis. Although data are incomplete, there is no evidence that SSRI or TCA therapy during pregnancy is associated with increased risk of fetal death, growth impairment, or behavioral defects. As a class, SSRIs/SNRIs do not increase the overall risk of birth defects, but first-trimester use of some SSRI agents has been associated with particular birth defects. Case–control epidemiologic studies suggest the following associations: between paroxetine and right ventricular outflow tract obstruction, between sertraline and omphalocele and sepal defects of the heart, and between paroxetine or citalopram and anencephaly, craniosynososis, and omphalocele. Of note, although the relative increases in risk are statistically significant, the absolute increases and overall risk remain extremely small and for most patients well below the risk of untreated depression. No associations have been found between birth defects and the use of TCIs or other SSRIs/SNRIs. The risk for neonatal withdrawal syndrome is increased with antidepressant use during the third trimester.

On balance, pharmacologic treatment of depression during pregnancy is preferred over withholding or discontinuing antidepressant therapy. Dose requirements change over the course of pregnancy. Increased hepatic metabolism and an increased circulating blood volume necessitate an increase in dose to about 1.6 times that prior to pregnancy. After pregnancy, dose should be reduced by 30% to 50%. Tapering several weeks before delivery can reduce the risk of a neonatal withdrawal syndrome but may compromise the control of symptoms.

**Postpartum Depression**

After childbirth, all women should be asked about depressed mood and anhedonia. Those who answer affirmatively should be evaluated further (see prior discussion); women with evidence of major depression should undergo specific inquiry into any intention to harm themselves or their child. Treatment options include antidepressant therapy and interpersonal psychotherapy; the former is more rapid in onset, but both are equally effective. There is no additive benefit to combining the two. SSRI/SNRI pharmacotherapy is preferred over tricyclic use (much lower risk...
Psychiatric hospitalization is indicated for high suicide risk, lack of reliable social supports (if the depression is severe), history of previously poor response to treatment, or symptoms that are so severe that the patient requires constant observation or nursing care.

PATIENT EDUCATION

Detailed patient education is a central component of supportive psychotherapy (see prior discussion). Patients who come from backgrounds that stigmatize mental illness or oppose psychotropic medication are comforted by learning of depression’s “organic” pathophysiology, which helps them to comply with treatment. Compliance with antidepressant therapy is often compromised by side effects or mistaken attributions. Some patients stop their medication after only a few days if they do not notice an immediate improvement or use it only “as needed.” Before initiating therapy, it is critical to review likely side effects and delayed onset of improvement. The importance of prolonged regular use must be emphasized. If the patient already has a tendency toward constipation, the prescription of a stool softener may make a tricyclic more tolerable. Patients should be instructed to report side effects rather than stopping the medication on their own and to call promptly if suicidal thoughts develop or if depression markedly worsens.

The educational process should include family and other household members. Enlisting their help in decreasing stress at home is helpful. With elderly or severely depressed patients, the family should be taught about the proper use of antidepressants and asked to monitor compliance.

THERAPEUTIC RECOMMENDATIONS (58–60)

- Screen for depression by asking two questions: “Over the last 2 weeks, have you felt down, depressed, or hopeless?” and “Over the last 2 weeks, have you felt little interest or pleasure in doing things?”
- If the patient answers affirmatively, proceed with full evaluation that begins with screening for somatic symptoms; use the SIG E CAPS questions; screen for suicidality by asking about it directly. Also check for bipolar disease by inquiring into past manic symptoms and family history.
- If the patient appears to be at risk for suicide, has psychotic symptoms, has severe depression with no social supports, or is unable to care for himself or herself, arrange prompt psychiatric consultation with a view to possible hospitalization.
- Consider brain MRI scan in the setting of new-onset depression associated with psychotic symptoms, focal neurologic deficits, or onset temporally related to head trauma.
- For patients who are deemed safe to manage on an outpatient basis, arrange for supportive psychotherapy and make any social and environmental interventions that may help; involve the family in the treatment, especially with elderly or severely depressed patients.
- For patients with major depression (or patients with other subtypes who have neurovegetative symptoms), begin antidepressant pharmacotherapy unless there is evidence of bipolar disease, in which case a mood stabilizer should be the first line of treatment along with consideration of psychiatric consultation (see later discussion).
- Consider SSRI drugs as first-line pharmacotherapy; base the choice of agent on cost when minor differences in side effect profiles are not clinically important; prescribe generically to limit cost (e.g., fluoxetine, 20 mg daily).

Bipolar Disorder

Unlike major depression, bipolar disorder requires starting treatment with a mood stabilizer (e.g., lithium, valproate, carbamazepine), not with an antidepressant, which can trigger mania.

Lithium is the best studied of available drugs for bipolar disorder and an appropriate choice for starting treatment in the primary care setting. Effective for bipolar depression, mania, reduction in risk of suicide, and prophylaxis, the drug is inexpensive and generally safe, but with a narrow therapeutic index (the target range for serum concentration is 0.8 to 1.1 mEq/L). An extended-release preparation allows twice-daily dosing and reduced variation in serum concentration. Most adverse effects are related to serum level: rare and mild at less than 1.5 mEq/L, mild to moderate at levels from 1.5 to 2.5 mEq/L, and moderate to severe at levels greater than 2.5 mEq/L. Fine tremor, mild thirst, mild nausea, frequent urination, and generalized malaise may come with the onset of therapy and usually resolve with its continuation, but diarrhea, vomiting, drowsiness, muscular weakness, worsening polyuria, and poor coordination suggest incipient lithium toxicity. Weight gain, coordination difficulties, and mental clouding often cause patients to discontinue therapy. Hypothyroidism, renal tubular injury, and cardiac rhythm disturbances may ensue, especially at toxic doses. Regular monitoring of serum concentration and renal function (blood urea nitrogen, creatinine) is required (the drug is renally excreted). Concurrent use of thiazide therapy may increase serum level due to its enhancement of distal tubular reabsorption; nonsteroidal anti-inflammatory drugs and angiotensin-converting enzyme inhibitors increase the risk of lithium toxicity.

Antidepressant therapy is often a consideration because depression is the principal cause of disability in bipolar disease. Many bipolar patients receive an antidepressant in addition to a mood stabilizer, despite limited evidence in support of this common practice. In a major study comparing mood stabilizer therapy alone versus the addition of an antidepressant (SSRI or enzyme inhibitors increase the risk of lithium toxicity.

INDICATIONS FOR REFERRAL AND ADMISSION (58)

Patients who should be referred for psychiatric consultation include those with refractory or disabling major depression, bipolar illness, psychosis, or substantial risk for suicide. Patients who fail to respond after 3 months of appropriate antidepressant treatment should have a psychiatric consultation. Many of these patients can be referred back to their primary care physician for follow-up after one or two psychiatric appointments.

Psychiatric and Behavioral Problems
Evidence-Based Team Interventions That Work

Depression

Collaborative care incorporating mental health and team-based care into routine primary care improves clinical outcomes in the management of depression. Team-based interventions for treating depression also lead to improved outcomes in diabetes, hypertension, urinary incontinence, dementia, heart failure, and falls. Increased depression-free days and increased quality-adjusted lifestyle measurements also result from team-based treatment of depression.

Initially, costs may increase, but economic outcomes include increased productivity and decreased absenteeism. Such successful depression management requires easily applied treatment guidelines, information exchange between the primary care team and mental health specialists, regular monitoring of depression symptoms, attention to treatment adherence and satisfaction, and treatment consistent with patient preferences.

Interventions that work include the following:

- Medication education and management
- Use of a patient navigator
- Patient-centered focus on increased self-management and patient preference
- Early recognition and care coordination

Team members: Registered nurse, pharmacist, nurse practitioner, mental health specialist, and primary care physician

Annotated Bibliography

Bower A, Gilbody S, Lovell K, et al. Collaborative care for depression and anxiety problems. Cochrane Database Syst Rev 2012;10:CD006825. (Review of 79 RCTs indicates that collaborative care is more effective than usual care at 6, 12, and 24 months and results in increased rate of antidepressant use and increased mental health quality of life.)


Lin E, Korff M, Ciechanowski P, et al. Treatment adjustment and medication adherence for complex patients with diabetes, heart disease, and depression: a randomized controlled trial. Ann Fam Med 2012;10:1. (Working with patients and primary care physicians, nurse care managers identified patient-centered self-care goals to develop individualized plans; the resultant team care resulted in improvement in glycosylated hemoglobin, blood pressure, LDL, and depression.)

Kantor W, Russo J, Lin E, et al. Cost-effectiveness of multicondition collaborative care intervention: a randomized controlled trial. Arch Gen Psychiatry 2012;69:506. (An intervention program by nurse care managers, which focused on improving depression scores and HbA1C and LDL-C levels resulted in improved outcomes with little additional cost.)


http://www.pcpcc.net/content/benefits-integration (Patient-centered primary care collaborative Web site provides additional support for clinical management of depression in primary care setting)

- Consider for psychopharmacologic/psychiatric referral patients who fail 4- to 6-week trials of two different SSRIs at full therapeutic doses.
- Use SNRI or TCAs as second-line pharmacotherapy, but consider whether the patient has responded well to one in the past, the patient has rather severe depression, or SSRI therapy is not proving fully effective. Use with caution in elderly patients and those with suspected cardiac disease; obtain a baseline electrocardiogram to rule out conduction system abnormalities, and check for postural hypotension prior to initiation of treatment.
- For elderly patients, initiate pharmacotherapy at one half to one third of the standard starting doses; similarly, reduce starting doses by one half in women with postpartum depression.
- If the patient responds to the antidepressant, it should be continued for at least 6 to 9 months or longer if depression was moderate to severe and there is appreciable risk of recurrence, and then slowly tapered.
- Never prescribe more than 1 week’s supply or a total of 1 g of a tricyclic if there is suicidal risk.
- Explain to patients that antidepressants must be taken regularly, that they may take 4 weeks to work, and that there may be mild side effects that do not warrant discontinuation of the drug.
- Prescribe a generic formulation whenever possible to minimize cost.
- For depression during pregnancy, strongly consider pharmacologic therapy, even during the first trimester. Review with the patient the important benefits from drug treatment and the very small increase in risk of a birth defect associated with use of some SSRIs. TCA treatment might be considered if there is concern about birth defects with some SSRIs.
- If bipolar disease is diagnosed, start treatment with a mood stabilizer (e.g., lithium carbonate, 300 mg, three times daily) rather than an antidepressant (which may exacerbate mood swings); increase the lithium dose over several days to achieve a target serum level between 0.8 and 1.1 mEq/L (obtained before the first dose of the day). If during lithium therapy severe major depression is problematic, obtain prompt psychiatric consultation before adding an antidepressant medication.

ANOTATED BIBLIOGRAPHY


3. Bombardier CH, Fann JR, Temkin NR et al. Rates of major depressive disorder and clinical outcomes following traumatic brain injury. JAMA 2010;10:1938. (Cohort study, over half met criteria during first year after injury; risk greatest for patients with prior history, independent predictor of impaired quality of life.)


7. Hays RD, Wells KB, Sherbourne CD, et al. Functioning and well-being outcomes of patients with depression compared with chronic general medical illnesses. Arch Gen Psychiatry 1999;52:11. (Patients with depressive symptoms tended to function worse than did those with other chronic medical conditions.)


12. Scholle SH, Rost KM, Goldberg MJ. Physical abuse among depressed women. J Gen Intern Med 1998;13:607. (A very high incidence was found; almost all patients presented to their primary physicians rather than to mental health professionals.)


38. Kupfer DJ, Frank E, Perel JM, et al. Five-year outcome for maintenance therapies in recurrent depression. Arch Gen Psychiatry 2005;62:1050. (A randomized controlled trial; both switch and try another SSRI achieved remission in one fourth of patients who failed initial treatment with either class.)


32. Geddes JR, Carney SM, Davies C, et al. Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. N Engl J Med 2007;356:2684. (A large epidemiologic case-control study; no overall risk was found, but it did find small increases in the risk for certain birth defects associated with a few individual agents.)


30. Fava M, Rush J, Thase ME, et al. 15 years of clinical experience with bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. N Engl J Med 2006;354:1211. (A randomized, controlled trial; both switching classes and trying another SSRI achieved remission in one fourth of patients who failed initial treatment with either class.)


27. Cleve Clin J Med 2010;77:859. (Updated look at an old class of antidepressant drugs.)


25. Carney SM, Davies C, et al. Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. N Engl J Med 2007;356:2684. (A large epidemiologic case-control study; no overall risk was found, but it did find small increases in the risk for certain birth defects associated with a few individual agents.)


Alcohol abuse is a national problem. Surveys reveal that 5% of US adults meet criteria for alcohol abuse; up to 20% of adults attending primary care clinics have alcohol abuse or dependence. The rates of abuse and dependence in persons 18 to 29 years of age are twice those for the nation as a whole. The overall estimated societal costs of alcohol-related health problems, lost productivity, crime, accidental deaths, and fires are staggering (>185 billion). The estimated direct cost of treatment for alcohol problems and medical consequences approaches $26 billion, with more than $18 billion for medical care alone. Promoting healthy behaviors is basic to primary care, so too is understanding every patient's drinking behavior. Although the detection of plainly unhealthy levels of intake and dramatically negative health consequences of drinking is straightforward, problem drinking or specific risk may be subtler. Persons whose drinking falls into the otherwise “low-risk” range may still require attention because of comorbid conditions. Unhealthy drinking (above low-risk quantities) prior to the development of any resultant complications needs to be identified and modified. Timely recognition, coupled with appropriate intervention, is critical. While the suffering by individuals and their families may be greater with alcohol dependence, the societal burden due to unhealthy drinking of less severity is huge, in large part related to involuntary trauma under the influence. The primary care physician and team are uniquely positioned to identify and address harmful patterns of alcohol use and a host of related medical and social problems.

DEFINITIONS (1–3)

Definitions

Alcoholism is an inexact but popular term, encompassing two conditions: alcohol abuse and alcohol dependence. Alcohol use in excess of low-risk cutoffs is epidemiologically associated with excess morbidity and mortality. Unhealthy drinking is anything above these cutoffs, with or without problems due to drinking of any severity.

Low-Risk Drinking

The behavioral hallmark of low-risk drinking is that it does not exceed epidemiologically determined cutoffs and is under voluntary control. With the caveat that a given dose of alcohol affects different people differently, low-risk drinking may be defined quantitatively as on average two or fewer drinks per day for men and one or fewer for women and the elderly. Furthermore, for drinking to be low risk, no single episode of drinking should exceed four drinks for men or three drinks for women, where a standard drink contains roughly 12 g, 15 mL, or 0.5 oz of alcohol (which is the approximate content of 12 oz of beer, 5 oz of wine, or 1.5 oz of liquor, respectively) (Fig. 228-1).

Unhealthy Drinking

Unhealthy drinking is defined as any drinking above the low-risk cutoffs and is associated epidemiologically with excess morbidity and mortality. It encompasses at-risk drinking and problematic drinking.

At-risk drinking is defined as drinking above cutoffs but without evident adverse medical or psychosocial consequences.

Problematic drinking is defined as drinking above cutoffs with consequences but not of a severity to meet formal (DSM-IV) diagnoses.

Alcohol Abuse

Currently, abuse is formally defined in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) as a maladaptive pattern of use leading to impairment in one of several sociobehavioral domains for a 1-year period (Table 228-1).

Alcohol Dependence

Alcohol dependence is defined in DSM-IV as a maladaptive pattern of use, resulting in substantial distress or dysfunction, characterized by at least three of seven symptoms that include tolerance, withdrawal, unsuccessful attempts at cutting down, and preoccupation with and recurrent use of alcohol despite adverse consequences in important areas of life. Patients drink more than they intend and may give up important activities because of drinking. In the upcoming DSM-V, alcohol abuse and dependence are likely to be redefined as a continuum of a single disorder rather than as discrete conditions.

PATHOPHYSIOLOGY, CLINICAL PRESENTATION, AND COURSE (4–27)

Causes and Risk Factors

The causes of alcohol abuse and dependence are incompletely understood, but the etiology is clearly multifactorial. Biogenetic, sociocultural, psychological, and behavioral influences have been identified. Understanding several typical paths to alcohol disorders improves the ability to take a relevant history and to arrive at salient therapeutic recommendations. Therapeutic plans ought to address specific vulnerabilities and comorbidities, understanding that there is considerable variability as to the natural history of alcohol dependence among and within individuals.

Biogenetic and Epigenetic Factors

Alcohol abuse clearly involves genetic determinants. Genetic factors appear to influence the metabolism of alcohol and the effects of alcohol on neurotransmitters, receptors, and cell membranes. More than 100 alcohol-responsive genes and numerous genetic risk factors have been characterized, including the genes for alcohol dehydrogenase, aldehyde dehydrogenase (ALDH), monoamine oxidase, and catechol-O-methyltransferase; more are likely to be identified. The odds ratio of developing alcohol abuse or dependence is about 10 for monozygotic twins versus about 5 for dizygotic twins. Offspring of parents with alcohol dependence frequently have an altered biologic response to alcohol, and young adult offspring with such a response are more likely to develop an alcohol diagnosis within a decade.

Evidence is accumulating that nongenetic material, such as histones, may be altered by alcohol exposure and affect transcription relevant to reward perception and drinking over the long term.
Psychiatric and Behavioral Problems

Sociocultural Factors

Poverty, socialization patterns, and cultural variables affect the probability of development of disease. Parental and peer values, attitudes, and behaviors all contribute. This helps to explain the increasing use of alcohol among women and youth and use patterns of ethnic minorities, despite an overall national decline in consumption. Price variation and local availability of alcohol (reflected by, for instance, the density of liquor stores in a neighborhood) affect the amount of drinking and, in turn, the probability of developing an alcohol diagnosis. The so-called behavioral economics also help define the types of reinforcement or punishment that might affect problematic drinking—a relevant construct in all but the most involuntary drinkers.

Psychological–Psychodynamic Factors

Underlying psychopathology and traits (e.g., dependence conflict, excessive need for power or sensation seeking, gender identification problems) contribute to predisposing a person to drink excessively, either to mask or to solve a psychological problem (the so-called self-medication). Drinking in this context is viewed primarily as a symptom of the underlying psychopathology or trait. These traits may be heritable (for instance, enhanced need to seek sensations or intolerance of negative affective states). A trauma history, by influencing levels of anxiety (even in the absence of full-blown posttraumatic stress disorder), may predispose to development of alcohol addiction.

Behavioral Factors

From the behavioral perspective, alcoholism is viewed as a learned behavior that is reversible, time limited, on a continuum with normal drinking behavior, and established by a series of learning and reinforcement experiences. The strength and pace of acquiring the habit vary with the intensity and rapidity of reinforcement. Social interactions, emotional stress, guilty or negative thoughts, and the need for sleep or pain relief precipitate and sustain drinking. Any of these precipitants coupled with learned expectations about the reinforcing, pleasurable effects of alcohol may initiate and maintain the drinking behavior. The neurobiology of adaptation and tolerance affects the learning process. In the presence of reinforcing neurochemistry, environmental cues acquire greater salience, and learning is more likely to occur as the brain forges strong associations among behavior, environment, and reward, thus increasing the likelihood of repeating behavior that will lead to the reward. There are many candidates for the neuroanatomic substrate of such enhanced learning (e.g., dopamine in the nucleus accumbens), and they may not be specific for one reinforcing drug or another.

### Table 228–1 Criteria for Substance Abuse and Dependence According to DSM-IV

<table>
<thead>
<tr>
<th>Substance Abuse</th>
<th>Substance Dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by at least one of the following occurring within the same 12-mo period:</td>
<td>A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by at least three of the following occurring in the same 12-mo time period:</td>
</tr>
<tr>
<td>Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home</td>
<td>Tolerance, as defined by either of the following:</td>
</tr>
<tr>
<td>Recurrent substance use in situations in which it is physically hazardous</td>
<td>A need for markedly increased amounts of the substance to achieve intoxication or desired effect</td>
</tr>
<tr>
<td>Recurrent substance-related legal problems</td>
<td>Markedly diminished effect with continued use of the same amount of the substance</td>
</tr>
<tr>
<td>Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance</td>
<td>Withdrawal as manifested by either of the following:</td>
</tr>
<tr>
<td>The symptoms have never met the criteria for Substance Dependence for this class of drugs.</td>
<td>The characteristic withdrawal syndrome for the substance</td>
</tr>
</tbody>
</table>

Specify if

- With physiologic dependence if either tolerance or withdrawal is present
- Without physiologic dependence if neither is present


### Figure 228–1 The standard drink. (From U.S. Department of Health and Human Services. Helping patients who drink too much: a clinician’s guide. Rockville, MD: Author, 2005.)
Epidemiologic Patterns
Alcohol use varies by age, gender, and socioeconomic group.

Young People. Alcohol use and abuse among young people is high. Two thirds of high school seniors have used alcohol in the past year, and nearly one half report being intoxicated in that time span. Over 40% of young adults have had five or more drinks on an occasion in the last month. Adults who began smoking or drinking regularly in their early teens suffer the most serious alcohol, drug, and psychiatric problems.

Women. As a result of social change, women are consulting alcohol abuse clinics at double the former rates, and the gap between men and women in terms of alcohol consumption and problems continues to narrow.

The Elderly. Older patients may begin to use alcohol excessively for stress, especially in reaction to the loss of a loved one, loss of physical function or role, or other stressful transitions or because of sleep difficulties. The use of alcohol along with the multiple medications that are prescribed to the elderly can be especially problematic.

Ethnic Minorities. Certain ethnic groups are relatively protected from alcohol dependence. Some subgroups of Asians have a form of ALDH that metabolizes acetaldehyde slowly, therefore yielding higher concentrations of this chemical, which is perceived as unpleasant. People with more of this isoform of ALDH enjoy drinking less than those with proportionally less and have a lower likelihood of developing dependence.

Clinical Presentation and Course
There is a wide spectrum of drinking behaviors, from low-risk drinking to frank alcohol abuse, dependence, and deterioration.

Low-Risk Drinking
Low-risk drinking is characterized by varying consumption and beverage according to internal cues and external circumstances. The hallmarks of such moderate drinking are that it is under voluntary control and does not exceed recommended maxima. Otherwise, low-risk quantities of drinking may be considered either risky or problematic in a patient with signs or symptoms made worse by alcohol or with strong family histories. Such patients should be informed about the increased risk.

At-Risk Drinking
Persons drinking more than the recommended maxima but without negative consequences and who do not meet criteria for abuse or dependence can be classified as “at-risk drinkers.” Patients must drink greater more than the recommended maxima or in risky situations to fit into this category, but if there are problems stemming from drinking, then it is more useful to classify them as problem drinkers.

Problem Drinking
Such persons experience negative consequences of drinking, which might be minor and of distress only to the drinker or may cause significant problems for family, friends, or colleagues. Thus, problematic drinking may range from preclinical to severe and obvious.

Alcohol Abuse
This person meets the criteria for heavy social drinking, gets drunk on occasion, and also exhibits the negative medical, legal, social, or psychological consequences of excessive alcohol consumption. He or she makes or thinks of making attempts at cutting down or quitting. Functioning may vary from seemingly intact behavior to difficulty coping. The person may deny a drinking problem and blame external events or persons; denial is common even among those with multiple arrests for drunk driving. By definition, patients with alcohol abuse have not reached a severity sufficient for them to be diagnosed with dependence.

Alcohol Dependence
The dependent patient’s consumption of alcohol may be independent of usual precipitants or social situations, that is, the internal drive to drink is paramount and usually overwhelming. External circumstances might constrain drinking for a time, yielding a “binge pattern” syndrome. Most continue to work, some even in high positions. Alcohol is usually given high priority (e.g., one goes to a party to drink, not to socialize). Tolerance to alcohol develops, and withdrawal symptoms (mood disturbance, tremor, nausea, sweats) may be noted during the day when the blood alcohol level drops. Drinking periodically during the day is often needed to ward off or relieve withdrawal symptoms. The patient is aware of the compulsion to drink but may have rationalized it and turn a blind eye to the experience of harm. Recognizing and overcoming such denial may require the help of family, friends, or others affected by the drinking.

Severe Deterioration
Such individuals maintain a near-constant state of intoxication, having no care for their person or surroundings, and undergo periodic hospitalizations for detoxification and for medical care necessary after alcohol-related trauma or organ damage.

Clinical Course
There is considerable individual variation. Onset ranges from an initial phase of nonproblematic drinking to immediate heavy drinking. Early onset of drinking is associated with an increased risk of alcohol abuse, but the association is not necessarily causative. The course of alcohol dependence may be punctuated by periods of spontaneous remission. The prognosis remains relatively favorable until drinking reaches the severity that is obvious clinically. Once the addiction becomes more severe, it can be difficult to break in the absence of treatment, and the clinical course is often progressive. Twenty to fifty percent of those who meet criteria for dependence may spontaneously remit, but this lucky group may cluster at the less severe end of the dependence spectrum. The early detection of at-risk or unhealthy alcohol use is important before the patient becomes alcohol dependent. At the point of addiction, continued drinking may be punctuated by periods of abstinence or controlled drinking followed by relapse and progression, especially if there is no expert intervention. Controversy continues regarding whether total abstinence is required to prevent relapse to dependent drinking.

Medical Complications
The risk of organ damage is related in part to the dose and duration of alcohol exposure, with some conditions (e.g., alcoholic cardiomyopathy, fatty liver, alcoholic hepatitis, or anemia) manifesting reversibility with abstinence and others (e.g., cirrhosis or neuropathy) seeming to progress inexorably once organ damage has occurred. Predicting the risk of irreversible organ damage is imperfect; occasionally, resilience is afforded by abstinence and good nutrition. Risk appears to be a function of genetic predisposition, alcohol dose, and chronicity of exposure.

Cardiovascular Complications. Although moderate alcohol consumption (up to two drinks a day in men, one in women) is associated with reductions in coronary events and coronary mortality, the consumption of more than three drinks a day...
is associated with an increased risk for hypertension and overall mortality. High levels of alcohol consumption place the patient at risk for atrial fibrillation (see Chapter 28) and more chronically for alcoholic cardiomyopathy (see Chapter 32).

**Gynecologic and Reproductive Complications.** Increase in the risk of osteoporosis is associated with drinking on average more than two standard drinks daily. Invasive breast cancer risk has been found to increase with as little as one half drink per day: There may be no safe level of drinking with regard to breast cancer risk. Fetal alcohol syndrome occurs in infants born to mothers who drink heavily during pregnancy. Features include permanently stunted growth, mental retardation, musculoskeletal abnormalities, poor coordination, and cardiac malformations. Incidence approaches 33% among pregnant women who drink more than 150 g (>10 standard drinks) of alcohol per day. Another one third of children born to such women have mental retardation or severe behavior disorders. Intellectual impairment in offspring is associated with as few as one to two drinks per day during pregnancy. Controversy exists about a safe or low-risk cut point, with international guidelines varying considerably.

In men, persistent impotence and loss of libido reflect impaired gonadotropin release and accelerated testosterone metabolism that occur as consequences of chronic alcohol excess; they predate end-stage liver disease.

**Gastrointestinal Complications.** Alcoholic hepatitis, pancreatitis, and gastritis may follow binge drinking. Fatty liver and esophagitis ensue from chronic use. Late-stage complications include cirrhosis and oral and colorectal cancers.

**Neurologic Complications.** Cerebellar degenerative disease, peripheral neuropathy, Wernicke encephalopathy, and Korsakoff dementia are among the serious neurologic consequences of alcohol excess (see Chapters 166, 176, and 173). Thiamine supplementation can prevent the latter two conditions and should be broadly recommended.

**DIAGNOSIS (1–3)**

The fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) specifies the most widely used criteria for the formal diagnoses of alcohol abuse and alcohol dependence (see Table 228–1). These criteria are undergoing revision for DSM-V; as noted, it is likely that the diagnostic distinction between abuse and dependence will be converted into a single disorder of alcohol use with different levels of severity varying with number of criteria met. All of the DSM-IV criteria are likely to be retained in the new model. Diagnosis of late-stage disease poses little difficulty. The challenge is the early detection in daily primary care practice.

**WORKUP (1,3,11,26,28–30)**

**Overall Strategy**

Formal diagnosis involves the identification of excessive quantity and duration of consumption, physiologic manifestations of ethanol addiction, loss of control over drinking, and chronic damage to physical health and social functioning. The tenor and words used to discuss alcohol use should be nonjudgmental and empathic. There is no great separation between the diagnostic interview and therapeutic counseling.

If problem drinking is identified, one helps the patient to understand and acknowledge the problem, its potential consequences, and the need for change. The objective then shifts to negotiating and carrying out an acceptable plan of care, one that is personalized and multifaceted. These elements may be encompassed in a brief intervention and include referral for specialized care for more complex problems.

**Screening**

The high prevalence of unhealthy drinking, including alcohol abuse, its serious consequences, and good response to intervention, argues for routinely screening all adolescents and adults who come for primary care. The U.S. Preventive Services Task Force recommends universal screening and brief intervention to reduce alcohol misuse. Screening coupled with brief intervention for unhealthy alcohol use is among the handful of most cost-effective and highest-impact preventive services in primary care.

Drinking is addressed as would any health-related behavior, such as exercise or seat belt use. A high index of suspicion for alcoholism is indicated for the patient who presents with a family history positive for alcoholism, anxiety, insomnia, recurrent infection, a potentially alcohol-related illness, child abuse, domestic violence, multiple psychosomatic problems, suicidality, depression, or interpersonal, occupational, financial, or legal problems. Recently, tobacco smoking has emerged as a marker for alcohol abuse and dependence.

The two dimensions of the screening evaluation are quantity of and problems related to the use of alcohol.

**Screening for Quantity/Frequency**

A simple set of questions designed to elicit quantity consumed is the first step in assessing whether a patient drinks less or greater than the recommended levels. Because beer and wine may not be recognized as “alcohol” by many patients, those who say that they do not drink should be questioned about these beverages. For abstainers, clarifying why they do not drink may be important: The patient may be abstaining due to prior problems. The task then becomes assisting in relapse prevention and maintaining the healthy change. For patients who drink any alcohol at all, the following questions may be useful, either in a written, on line, or verbal exchange:

**How many times in the past year have you had 5 or more drinks in a day (for men) or 4 or more drinks in a day (for women)?**

If the answer is one or more occasions, then the patient has screened positive for unhealthy drinking, and further questioning may be warranted. If not, support and advice about low-risk drinking cutoffs should be offered. For those screening positive, ask:

**On average, how many days per week do you have an alcoholic drink?**

and

**On a typical drinking day, how many drinks do you have?**

The answers to these questions permit a weekly consumption calculation.

**Assessing Behaviors and Consequences**

For the patient who consumes alcohol, a number of validated approaches to assess problems are available. These include the CAGE questions (see next paragraph) and self-administered questionnaires.

**The CAGE Questions (Table 228–2).** This validated tool for behavioral screening is widely used in primary care settings. A score of 2 (the standard cutoff) has a sensitivity for alcohol abuse or dependence that ranges from 70% to 85% and specificity of 85% to 91%. In the elderly, in whom the clinical presentation may be harder to ascertain, sensitivity falls to 50%, whereas specificity remains greater than 90%. Including questions on
the quantity and frequency of drinking improves detection in the elderly. The CAGE questions focus on consequences of drinking and provide a natural entry into discussions about the patient’s perception of negative consequences. For example, if a patient endorses being annoyed by others’ comments about his or her drinking, then exploring what aspects are annoying and what the patient thinks of them is a natural next step.

Other Tests. Alcohol Use Disorders Identification Test (AUDIT, Table 228–3) is a 10-item questionnaire keyed to a World Health Organization hierarchy of alcohol problems. It focuses on “harmful drinking,” which indicates drinking in harmful situations. A shorter questionnaire consisting of the three consumption questions of the AUDIT (the so-called AUDIT-C) performs well in detecting unhealthy drinking and DSM-IV alcohol diagnoses and is a clinical and research standard due to its efficiency and performance. Each of the 10 items can be scored 0 to 4 for all patients; a cutoff of 4 is a sensitive if not specific indication of harmful alcohol use.

Clinical Assessment

The acutely intoxicated patient represents a small proportion of the alcohol problem presenting to most outpatient primary care practices and poses little diagnostic challenge. For others, a detailed drinking history is in order for all patients suspected of having an alcohol problem on the basis of any of the following:

- A positive response to the NIAAA single question screener, CAGE, AUDIT, or AUDIT-C
- A family complaint or a history of alcoholism in the family
- A pattern of near-daily drinking accompanied by complaints that might be related to drinking (e.g., frequent nonspecific illness, accidents, gastroesophageal reflux disease, insomnia)

### TABLE 228–2 The CAGE Test

<table>
<thead>
<tr>
<th>Question</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you ever felt the need to Cut down on drinking?</td>
<td></td>
</tr>
<tr>
<td>Have you ever felt Annoyed by criticism of drinking?</td>
<td></td>
</tr>
<tr>
<td>Have you ever had Guilty feelings about drinking?</td>
<td></td>
</tr>
<tr>
<td>Have you ever taken a morning Eye opener?</td>
<td></td>
</tr>
</tbody>
</table>


### TABLE 228–3 The Alcohol Use Disorders Identification Test

**PATIENT:** Because alcohol use can affect your health and can interfere with certain medications and treatments, it is important that we ask some questions about your use of alcohol. Your answers will remain confidential, so please be honest.

Place an X in one box that best describes your answer to each question.

<table>
<thead>
<tr>
<th>Questions</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How often do you have a drink containing alcohol?</td>
<td>Never</td>
<td>Monthly or less</td>
<td>2 to 4 times a month</td>
<td>2 to 3 times a week</td>
<td>4 or more times a week</td>
</tr>
<tr>
<td>2. How many drinks containing alcohol do you have on a typical day when you are drinking?</td>
<td>1 or 2</td>
<td>3 or 4</td>
<td>5 or 6</td>
<td>7 to 9</td>
<td>10 or more</td>
</tr>
<tr>
<td>3. How often do you have 5 or more drinks on one occasion?</td>
<td>Never</td>
<td>Less than monthly</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily or almost daily</td>
</tr>
<tr>
<td>4. How often during the last year have you found that you were not able to stop drinking once you had started?</td>
<td>Never</td>
<td>Less than monthly</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily or almost daily</td>
</tr>
<tr>
<td>5. How often during the last year have you failed to do what was normally expected of you because of drinking?</td>
<td>Never</td>
<td>Less than monthly</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily or almost daily</td>
</tr>
<tr>
<td>6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?</td>
<td>Never</td>
<td>Less than monthly</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily or almost daily</td>
</tr>
<tr>
<td>7. How often during the last year have you had a feeling of guilt or remorse after drinking?</td>
<td>Never</td>
<td>Less than monthly</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily or almost daily</td>
</tr>
<tr>
<td>8. How often during the last year have you been unable to remember what happened the night before because of your drinking?</td>
<td>Never</td>
<td>Less than monthly</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily or almost daily</td>
</tr>
<tr>
<td>9. Have you or someone else been injured because of your drinking?</td>
<td>No</td>
<td>Yes, but not in the last year</td>
<td>Yes, during the last year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down?</td>
<td>No</td>
<td>Yes, but not in the last year</td>
<td>Yes, during the last year</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total**

Notes: This questionnaire (the AUDIT) is reprinted with permission from the World Health Organization. To reflect standard drink sizes in the United States, the number of drinks in question 3 was changed from 6 to 5. A free AUDIT manual with guidelines for use in primary care settings is available online at www.who.org.

quickly, require less alcohol to achieve these levels.

Other activities related to drinking, including other drug use
Perceived negative consequences
Pressures (internal or external) to drink
Consumption: quantity, frequency, and rate of consumption
Setting: time, place, and occasion for drinking
Abnormal liver function tests; macrocytic anemia
Suggestive manifestations on physical examination, such as
A lifestyle that may promote prolonged drinking, including
tobacco or drug use
Intrapsychic or interpersonal problems or stressful changes
in life events
Suggestive manifestations on physical examination, such as
alcohol on the breath, spider angioma, hepatomegaly, ple-
thetic facies, tremor, ecchymoses, peripheral neuropathy,
resistant hypertension, or tachycardia
Abnormal liver function tests; macrocytic anemia

Taking a Drinking History
Patients may not volunteer drinking problems and request help. To the extent that a patient has protected and main-
tained the drinking despite significant consequences, denial is
likely to be strong. Consequently, one has to use an interview
technique that is kind and supportive yet firm and clear when
there are serious concerns for well-being or for risk, such as
driving under the influence or putting others at risk due to
occupational impairment. Where indicated, family members,
friends, and even the employer may facilitate both history tak-
ing and therapy.

The Drinking Profile. To understand the impact and dimensions
of drinking, a drinking profile that goes beyond issues of quan-
tity and frequency will prove useful and should include atten-
tion to the following:
• Setting: time, place, and occasion for drinking
• Social network: the people involved with the drinking and
their relationship to the patient
• Consumption: quantity, frequency, and rate of consumption
as it relates to that of others in the drinking context and as it
relates to the patient’s expected consumption
• Pressures (internal or external) to drink
• Perceived benefits of drinking—what the patient “gets out of” it
• Perceived negative consequences
• Other activities related to drinking, including other drug use

The profile is an effective tool for understanding the context
and consequences of drinking. It may assist in gaining insight
into the resistant patient, treating a willing patient, and educat-
ing a person with a potential problem. It also permits one to
personalize treatment.

Sources of Diagnostic Error
Missing the diagnosis may be due to subtlety of presentation,
not considering the diagnosis so long as he or she is performing
daily activities, societal acceptance of dangerous levels of alcohol
intake, and general expectations of excess alcohol consumption
at some social occasions. There may be unintentional collusion
with the patient in denying the problem, especially if the patient
is of similar or higher social status, has similar habits and lifestyle,
or is attractive, verbal, and intelligent. Worry about a resistant
patient’s response or overidentification may lead the practitioner
to avoid exploring the subject of alcohol problems fully, if at all.

MANAGEMENT (11,19,25,26,29–48)

Prevention of Alcohol Abuse
Prevention involves more than warning people of the health haz-
ards of alcohol abuse. It requires screening for the early detection
of alcohol abuse (see prior discussion) and providing patient-
specific information. By screening or otherwise inquiring about
drinking at the time of the yearly checkup, the primary physi-
cian can educate the patient and provide suitable guidelines for
drinking behavior, just as one does for exercise and diet. Such
very brief physician interventions or trials of advice can be easily
included in an annual health maintenance visit.

People who do drink need to know how alcohol can affect
them, how to behave responsibly when drinking (especially
with regard to driving), and how to drink in a way that prevents
drunkenness (Tables 228–4 and 228–5). Individuals should
know that their attitudes and behaviors will affect how their
children/spouses drink. All patients should be cautioned that
drinking is a risky way to deal with insomnia and emotional
problems. Waiting room literature and hospital and commu-
nity health education programs can complement instruction.
National campaigns focus on alcohol-related accidents, crime,
concomitants of abuse, and birth defects.

Overall Approach to Management
After uncovering unhealthy, at-risk, or problematic drinking
determining whether there is alcohol abuse or dependence,
the task shifts to designing a successful management program,
which requires a multifaceted, personalized, long-term strategy and, in the case of alcohol dependence, is usually conducted in collaboration with an alcohol specialty team. Therapies can be classified as pharmacologic, psychological/behavioral, and sociocultural. Selection is best done on an individualized basis to meet the patient’s specific needs, adjusted for stage of illness.

The acutely intoxicated patient in the outpatient setting is assessed quickly as to safety (i.e., level of risk of harm to self or others). If no imminent risk is perceived, another appointment should be made with advice to return in the sober state. If unsafe, then one would recommend management in a supervised setting, if not an emergency room, until safety can be assured. Whether to recommend acute cessation of all alcohol intake is a more complex question (see Detoxification below).

Determinants of Successful Treatment

**Early detection and prompt initiation** of treatment are essential to success, with success rates of 50% to 90% attained in patients abusing alcohol but without physical or social impairment. In general, the more intact the matrix of the patient’s life (employment, family, social relations), the better prognosis. For persons with dependence, success rates depend on the length of time a person stays in treatment, patient involvement in goal setting and treatment planning, and continued attachment to family or an integrated social network. Involving family members or significant others supports the lifestyle changes that must be made and promotes remaining in treatment.

Other determinants of successful treatment include the use of a personalized multifaceted plan, an active role for the patient, and continuous review. A goal of total abstinence is associated with the most stable outcomes. Cessation is necessary to halt or reverse many of the medical complications, such as injury to the liver, myocardium, and nervous system. A small but significant percentage of people having met criteria for alcohol dependence may sustain low-risk drinking (15% or less). Currently, there is no means of confidently determining who with the diagnosis of alcohol dependence may drink in moderation safely.

Role for the Primary Care Physician and Team

Preventing morbidity and facilitating behavioral change are essential roles for the primary care physician and team. 

**Preventing Morbidity.** Patients with alcohol problems or drinking at high-risk levels should be vaccinated with the polypotent *pneumococcal vaccine* and should take B vitamin supplements (especially thiamine). Attention to and awareness of the heightened risk for hepatitis, hypertension, breast cancer, osteoporosis, pharyngeal and GI cancers, depression, peripheral neuropathy, and trauma should be stressed in this high-risk population. The riskiness of driving and assuring the availability of sober drivers should be highlighted. Psychoactive medications may pose specific risks, as may common prescribed and over-the-counter medications.

**Facilitating Behavioral Change.** The doctor–patient relationship—the core of the primary care experience—provides a powerful means of effecting behavioral change. When used over the course of years, the relationship permits the identification and anticipation of problems, support during difficult periods, and prevention of relapse. Long-term management by the primary care physician, supported by the primary care team, requires a willingness to be continuously available and to shoulder a substantial care burden. Whether one intends to provide sole care for the alcohol-dependent patient or to involve the specialist, the primary physician has the important initial task of assisting the patient in acknowledging the drinking problem and developing a plan to deal with any comorbid psychopathology. Referral and collaboration with addiction specialists, counselors, and psychiatrists can be particularly useful in helping the patient to identify and restructure destructive patterns of drinking, learn new coping skills, and deal with any comorbid psychopathology. Referral and collaboration may help to relieve the burden on the primary physician while allowing continuation of the patient–doctor relationship.

Management of the Nondependent Drinker

**The Brief Intervention.**

For outpatients drinking more than recommended levels who do not have dependence, a program of brief (<20 minutes), clear, and empathic discussions about changing drinking behavior has been demonstrated to reduce alcohol consumption and complications. The key components of the brief intervention are as follows:

- Making the link between the patient’s drinking and potential or actual harms (psychosocial or physical)
- Giving feedback to the patient about normative drinking, such as using normative tables (Table 228–6), which is especially useful when patients have inaccurate beliefs about what is typical for their cohort
- Reviewing the benefits of recommended change, referring predominantly to the patient’s statements, beliefs, and goals but also to objective medical findings
- Giving clear instructions and agreeing about the modification of behavior—for example, when and how to cut down to a specific level or to abstain completely
- Instructing the patient not yet ready to change behavior to track drinking and consequences in a structured way (e.g., keeping a journal)
- Agreeing clearly about follow-up

Follow-up is critical and cost-effective. Studies find that improved drinking persists for at least 1 year after two brief physician discussions coupled with two nurse follow-up phone calls.
Management of Alcohol Dependence

Remission from dependent drinking depends on both neurologic recovery of more normal reward pathways in the brain (requiring abstinence) and learning how to live without recourse to drinking (requiring the development of new behaviors and adaptations). With the advent of effective pharmacologic therapies for dependence, care of the alcohol-dependent patient is migrating to the primary care setting, but specialty referral remains an important option for treatment, especially for addressing major barriers to care (e.g., denial and resistance) and affecting durable behavioral change. Patients meeting the diagnostic criteria for alcohol dependence should be advised of the role for expert assistance in abstaining from alcohol, but a long-term perspective of primary care makes ongoing primary care essential. Recommending change without treatment compromises the work of recovery entails learning to deal with dependence's challenges, such resistance is waning in the face of experience.

Physicians should offer medication to appropriate patients and discuss the role of the individual benefits and risks. These are typically not sufficient for sobriety, so should not be over-sold. Medications are among many effective treatments. Many patients are wary, fearing the substitution of one dependence for another. The regular use of potentially addicting agents, such as benzodiazepines (BZDs), should be avoided. Medication should be prescribed with strict directions for use so that patients do not replicate escaping from a negative internal state by dint of a self-administered drug. A core goal of recovery remains the development of intra- and interpersonal, nondrug strategies. Frequent evaluation is needed.

Pharmacologic agents can be classified functionally as those that reduce the urge to drink, blunt withdrawal symptoms, or treat underlying psychiatric problems.

**Pharmacologic Therapy**

Advances in understanding the neurobiology of alcohol dependence are spurring pharmacologic approaches to the treatment of dependent persons. Pharmacologic interventions work by decreasing the craving and physical rewards of drinking and by relieving the dysphoria and distress of abstinence. Such treatment increases the likelihood of abstinence or significant decrease in drinking, enabling the patient to engage in comprehensive, durable psychosocial treatment. Although some object to this approach on the grounds that the cognitive and emotional work of recovery entails learning to deal with dependence's challenges, such resistance is waning in the face of experience.

**Naltrexone.** This U.S. Food and Drug Administration-approved, pure mu-opioid antagonist appears to blunt both the craving for and the pleasurable effects of alcohol by impairing the release of dopamine in the nucleus accumbens (a neurochemical event believed to be important to reinforcement, euphoria, craving, and addiction). In theory, if a patient drinks while using the medication, the experience of intoxication is less rewarding.

In clinical trials, the drug has demonstrated efficacy, reducing the rate of relapse to heavy drinking by 50% when paired with comprehensive services, especially coping skills therapy.
Results appear to be best in persons who describe intense cravings (COMBINE). It also decreases the intensity, duration, and frequency of slips or relapses. Doses of 50 mg daily are prescribed for at least 6 months in alcohol-dependent patients. An intramuscular preparation administered monthly offers the advantages of improved compliance and potentially fewer hepatic side effects, given the lack of first-pass metabolism, but comparisons with the oral formulation have not been conducted.

Adverse effects are mostly minor, with self-limited nausea and headache being the common side effects. However, high doses may cause hepatocellular injury, necessitating the monitoring of liver enzymes with such use. Clinically, liver enzyme tests usually show improvement associated with decreased drinking rather than the reverse.

Contraindications include opiate use and hepatoxic disease. Patients need to understand that the drug renders the therapeutic use of opioids problematic; the drug should be held for at least 10 days prior to surgery. There is also potential opiate toxicity if naltrexone is withdrawn or stopped while opiates are administered, which is a common scenario after trauma. The high doses of agonists needed for analgesia may become toxic as the naltrexone blockade washes out over time.

Acamprosate (Calcium Acetylhomotaurinate). This synthetic analogue of calcium acetylhomotaurinate (a natural analogue of GABA) is approved for the treatment of alcohol dependence. It enhances GABA activity without being a direct agonist at the GABA receptor (the site of BDZ activity). There is also some effect at other receptors (e.g., N-methyl-D-aspartate), but little if any effect on mood, memory, or cognition and no abuse or dependence potential.

Acamprosate increases the mean duration of sobriety by 40% and the time before full-blown resumption of heavy drinking. Benefit occurs as early as 1 month into treatment, lasts during a full year of active treatment, and persists for 1 year after treatment is discontinued. The drug is typically prescribed for 1 year in conjunction with supportive counseling services; treatment is continued irrespective of drinking episodes during that time.

The addition of acamprosate to a program of naltrexone and behavioral therapy appears to offer little additional benefit. Compared with naltrexone in a randomized trial of intensive counseling plus naltrexone, acamprosate, combined therapy, or placebo (COMBINE), only naltrexone appeared to offer additional improvement over placebo. However, other trials have supported the efficacy of acamprosate, counteracting the results of the COMBINE study, which was thought to have an unusually robust counseling component, which might have obscured the benefit of acamprosate.

Pharmacokinetics includes unmetabolized renal elimination and crossing of the blood–brain barrier. The drug should be used at reduced dose in moderate renal insufficiency and avoided in renal failure (creatinine clearance <30 mL/min). The dose is 666 mg three times daily for patients who weigh 60 kg or greater and 666 mg in the morning followed by two doses of 333 mg for patients whose weight less than 60 kg. Adverse effects include dose-related diarrhea that is relatively minor and resolves with dose reduction or cessation.

Disulfiram (Antabuse). This aversive therapy agent was the first drug approved for the treatment of alcohol dependence. The drug sensitizes the patient to the effects of alcohol by inhibiting hepatic ALDH, which results in an accumulation of acetaldehyde. Within minutes of taking as little as 1 oz of alcohol in the presence of disulfiram, the patient experiences an increase in serum acetaldehyde concentration that leads to palpitations, flushing, diaphoresis, tachypnea, tachycardia, and shortness of breath. Nausea, vomiting, and headache develop if a greater amount of alcohol is taken. Symptoms last for about 90 minutes and usually are self-limited. The goal of using this drug is that either the patient will be motivated to avoid the worsened consequences of drinking or the experience of aversion will decrease use.

Use. Candidates require careful medical before initiating therapy, and a written agreement or informed consent is appropriate, given the risks entailed. Although on balance there is a lack of good placebo-controlled trials supporting its use, there may be a role for disulfiram in specific situations. For reliable patients with a sober and helpful partner, it may be effective when the patient contracts to use the drug under scheduled supervision. The partner (significant other) in this case may witness administration by initialing a log. The drug may be used for stable patients entering a high-risk situation (e.g., a stressful period of transition such as divorce or job change) or events where drinking is common, such as weddings or reunions. The standard dose is 250 mg at bedtime. Duration of therapy is individualized. Treatment should be terminated if the patient fails to keep appointments, resumes drinking, becomes pregnant or depressed, or develops abnormalities in liver function tests or cardiovascular status. Part of the informed consent process should be a contingency plan for relapse to drinking.

Side Effects. The most prominent are drowsiness and lethargy, countered by administering the drug before bedtime. Important drug–drug interactions occur with antihypertensive agents (e.g., potentiation of the hypotensive effect of alcohol), BDZs (e.g., reduced intensity of the disulfiram reaction), tricyclic antidepressants (TCAs) and phenothiazines (e.g., potentiation of central nervous system effects), and drugs metabolized by hepatic microsomes (e.g., prolongation of their half-lives). Occasionally, marked hypotension or a cardiac arrhythmia may occur. Fatalities from myocardial infarction and stroke have been reported. Higher doses have resulted in death. The agent can worsen depression and schizophrenia.

Investigational Agents (Topiramate and Ondansetron). Topiramate is a GABA-receptor facilitator that inhibits the limbic glutamnergic pathways involved in alcohol dependence. In a small number of well-conducted trials, it reduces the urge to drink and facilitates abstinence. When taken over a period of 14 weeks, study patients experience a 50% reduction in days of heavy drinking, a fivefold increase in rate of reaching 28 or more days of continuous abstinence. Confirmation of these encouraging findings in primary care practice and FDA approval could make the drug a practical first-line treatment for alcohol dependence and facilitate management by the primary physician. Side effects include paresthesias, taste perversion, anorexia, and difficulty with concentration. It may be started even in patients continuing to drink.

Ondansetron, a serotonin receptor antagonist, was found in a randomized, controlled trial of high-risk patients with early-onset alcoholism (persons who manifest increased serotonergic activity) to significantly reduce alcohol intake. Confirmatory evidence is awaited.

Counseling

Several approaches to counseling patients with unhealthy drinking have been validated. Members of the primary care team can provide potentially helpful input and perspective with every interaction. While some forms of counseling may seem time intensive, others are efficient and easily part of routine visits. Consideration should also be given to incorporating behavioral health counselors into the primary care team if the physician is unable to deliver counseling. Some modes of counseling focus on medication compliance and adherence to abstinence. Others concentrate on an empathic biopsychosocial understanding of the context of the patient’s drinking, directing advice in accordance with the patient’s priorities and perspectives while providing regular, ongoing feedback.

Medical Management Counseling. This nuts-and-bolts counseling is adapted for primary care and was tested in a large randomized trial of several medications and counseling conditions.
Psychotherapy and Cognitive–Behavioral Therapy

Both psychotherapy and cognitive–behavioral therapy go beyond counseling.

Psychotherapy. More likely to be provided by the specialist than the primary care provider, psychotherapy places emphasis on psychiatric restructuring and lessening of maladaptive internal processes (such as emotional or cognitive responses to stress). Such treatment is indicated for those whose interpersonal or psychological problems are significant. If there is significant psychopathology, specialist referral may be indicated. The best candidates are patients who demonstrate some insight, are intellectually curious, and eager to be involved in the process. Alcoholism is associated with special needs that require the therapist to take a much more active role than is typical in insight-oriented psychotherapy. Therapists should provide structure, guidance, support, nurturance, and instruction in helping the patient to control drinking while working on the underlying conflicts and dysfunctional defense mechanisms. Behavioral–cognitive and sociocultural approaches are also used.

Cognitive–Behavioral Therapies. These are based on the notion that alcoholism is a learned behavior that can be extinguished and reshaped. Cognitive–behavioral therapy focuses on the observables of the drinking behavior (frequency, duration, quantity, time, place, activity, age, gender, and role-appropriate drinking behaviors). It attempts to identify the precipitants of drinking and the factors that perpetuate it. Behavioral components are helpful in dealing with problems involving role changes and behaviors in specific situations. In Project MATCH, this was no more effective than 12-step facilitation therapy.

Sociocultural Treatment. This approach emphasizes altering external factors. It may include residential care, halfway houses, and direct social manipulation, such as finding jobs, helping with shelter and money, and removing a person from his or her family. This is a treatment appropriate for homeless, jobless, unstable persons whose social functioning is impaired; for patients who have experienced repeated treatment failures; for young people; and for others with severely complex problems. Any of these approaches and the community services that follow can be used as adjuncts to other treatments wherever necessary.

Settings for Care

Inpatient care may be necessary for detoxification and treatment of withdrawal. For achieving long-term abstinence, randomized studies show no overall advantage for residential over nonresidential treatment programs. As a result, expensive long-term inpatient care is no longer the standard for treatment of alcoholism. Only one methodologically sound randomized trial demonstrated an advantage for inpatient care, and this was part of an employee assistance program (EAP), which is itself a well-recognized determinant of success.

The net result is the current emphasis on outpatient care, except for the treatment of severe acute withdrawal syndrome. Inpatient care remains an option for people who have failed all other forms of treatment and who will not deal with the problems so long as they are in environments that maintain destructive drinking. It is a costly approach. For most patients, an outpatient program that combines psychotherapy and behavioral–cognitive approaches can be offered in primary care practices by the physician and/or staff after some training.

Community Services

AA and other programs derived from the AA model provide critical elements of sober social support, caring, and structure, which are essential to many patients. The desire to abstain from alcohol and drugs is the only qualification to be welcome. *Anyone who wants to spend a day sober should be encouraged to go to meetings.* Research establishing and explicating the relationship between involvement in AA and good outcomes is robust and growing. AA is free and convenient, and the tenor and composition of meetings are so varied that finding a good fit is usually achievable. Patients should “shop around” and keep a journal, listening for personal stories that resonate and making note of desirable styles of sobriety. The AA program has a quasireligious orientation, making it particularly useful to the religious person. Relatively superficial involvement (e.g., two to four meetings per month) is a useful adjunct to other forms of treatment; deeper immersion into the program correlates with more robust sobriety. Information and local meetings are easily obtained electronically. *Al-Anon and Alateen* assist family members of the alcoholic. Other popular self-help groups are *Women for Sobriety*, which stresses individual responsibility to boost self-esteem, and *SMART Recovery*, which stresses using reason rather than spirituality.

EAP can be useful because motivation to keep a job is often high. Most large companies offer such programs, and their counselors can work in tandem with physicians. EAPs may also offer family, marital, and financial help, as may programs available through social service agencies, community guidance centers, and even state or federal agencies. Patients should obtain assurance from their company’s EAP that confidentiality is guarded and ascertain what the company’s policies are with respect to protecting employment if treatment is obtained. *Clergy and church organizations* can be a natural resource for religious persons.

Dealing with Barriers to Treatment

Denial and resistance to treatment represent commonly encountered, major barriers to successful management.

Denial

One should expect ambivalence about being diagnosed with alcohol abuse and changing one’s behavior. There appears to be a relationship between the condition’s severity and the likelihood of denial, which can be elicited by listening carefully and empathetically to how the patient explains the findings. Suggesting a journal or a weekly log of drinking events can help to establish links between drinking and particular...
environmental, interpersonal, or psychological precipitants and determine without direct confrontation exactly how much the patient drinks. Creating an alliance with the patient in the pursuit of salient goals, and against impediments (e.g., drinking) to their achievement, is a key route to changing recalcitrant habits.

For the patient in denial, one can review the evidence on how alcohol directly affects the patient’s health or stands in the way of the patient’s pursuit of salient personal goals. Using screening instruments and presenting the findings in terms of a specific diagnosis or negative consequence sometimes help to objectify the problem. If the patient continues to resist, then one can bring in family, friends, or employer to present the patient with their evidence of how destructive the drinking is. Again, these sessions should be factual, nonjudgmental discussions of the relationship of alcohol to the patient’s health and behavior and its effect on those important to him or her.

Resistance to Treatment

Patients who acknowledge their drinking problem yet continue to refuse to relinquish alcohol or accept help should be handled respectfully and empathically but also firmly. Disputatious confrontation is not effective, but exploring the patient’s fears and resistance can be more productive. The hostile or belligerent patient should be dealt with clearly and unemotionally, in a manner that enhances ability to control anger. Remember that the patient’s behavior is sick and his or her anger will often be directed at the primary physician or therapist, either covertly or overtly. The ultimate goal is to help the patient gain self-control, regulation, and a sense of effective agency and success.

Often those who resist treatment must first fear the loss of something very important (e.g., spouse, job) before seeking help; this must outweigh the fear of loss of alcohol. It may fall on the primary physician to assist family, friends, and coworkers. One way is to develop a contingency contract with the patient, for example, agreeing that failure to seek and comply with treatment will result in the family’s refusing the patient access to living quarters until or unless help is sought. This so-called tough love approach, in which loss is seriously threatened or carried out unless the patient goes for treatment, must be embraced by all in the patient’s social circle and sustained indefinitely because relapse is frequent once the danger of losing a loved one or job passes. Empty threats mean that the contingency contract is artificial and does not speak to the needs or understanding of those in the patient’s life. If one is dealing with an “enabling” family or social context, it is better to present the options available, continue exploring the issue, and provide health education while treating the patient’s medical problems and awaiting willingness to undergo treatment. Should the patient agree to seek treatment, it is important to keep the waiting period brief and remind the patient a day or two ahead of the appointment.

Clearly, this is a time-consuming exercise and may be feasible only in the hands of an addictions expert; this underscores the importance of developing a network of referrals and support for alcohol problems in primary care.

Pharmacologic Therapies for Concurrent Psychiatric Conditions

Comorbid psychiatric disorders are common among patients with alcohol abuse and may require specific treatment. The diagnosis of comorbid psychiatric disease is complex in the setting of alcohol dependence. Depression, anxiety, and insomnia are prevalent problems. Some resolve with abstinence alone. Some patients recognize symptoms of these conditions as part of the addiction syndrome and can talk themselves through rough patches; others cannot.

Medications should be prescribed with awareness of the potential risks, especially when considering the use of anxiolytics and hypnotics, with their own risk of inducing dependence. Prescribing such agents should be strictly time limited and only when both prescriber and patient understanding the ramifications. Psychoactive medications for patients in early recovery should not be prescribed on an as-needed basis. Such as-needed dosing reinforces the message that the patient cannot tolerate negative symptoms without recourse to drugs. It also may direct the patient’s attention to subjective states when objective recovery activities and behaviors should be taking center stage.

Depression

Depressive symptoms may be secondary to drinking and improve with abstinence. Diagnosis of a depression independent of drinking requires careful history taking (see Chapter 227), with attention to symptoms that were present during periods of stable, prolonged abstinence in the past; such a diagnosis often cannot be made with confidence until a period of sobriety permits observation. Treating patients with provisional diagnoses of depression is often effective, even if the disorder turns out to be secondary to drinking. Insomnia and anxiety might form part of a syndrome that resembles depression and would meet diagnostic criteria but for the presence of substance use.

Although depression improves without antidepressant medication in many cases of alcohol dependence, pharmacologic treatment is indicated when symptoms are severe. For patients scoring high on depression symptom scales, TCAs such as propranolol or doxepin is a reasonable consideration. The sedating antidepressant nefazodone has demonstrated some advantage in restoring sleep architecture. In all cases of suspected secondary (that is substance-related) depression, time-limited trials are preferred, with the medication tapered several months after sobriety is achieved.

Anxiety

Decisions to abstain and change drinking behavior often go against decades of habitual dependence: Courage is required; trepidation is common. The wise admonition of AA to take it “1 day at a time” might help to ease the sense of permanent loss conferred by giving up a trusted, if maladaptive, resource. Anxiety about maintaining abstinence is nevertheless common. Patients anxious about relapse and used to self-medicating their symptoms may feel helpless to withstand distress without pharmacologic help. Their requests for drug therapy may take on a sense of compelling urgency. Particularly anxious patients have a high probability of relapse to heavy drinking over the 1st year of treatment.

If anxiety is prominent, especially if it is severe or marked by panic episodes, an SSRI is an appropriate first-line agent. Because of the high prevalence of comorbid psychiatric diagnoses, including bipolar disorder, inquiring about episodes of mania when sober is critical, as SSRIs may precipitate them. Before a BZD is prescribed, consultation with an addiction psychiatrist is warranted.

Insomnia

If insomnia (common in the 1st months of recovery from alcohol) is prominent, reassurance and sleep hygiene should be the first consideration. If treatment is warranted (e.g., because of persistence or severity), a sedating antidepressant such as trazodone or doxepin is a reasonable consideration. The sedating atypical antipsychotic quetiapine in low doses (25 or 50 mg) at bedtime usually produces improved sleep. Although the BZD-like sedatives zolpidem and eszopiclone are touted as being nonaddicting and helpful for sleep, caution is advised with these agents in alcohol-dependent persons because of cross-tolerance.
between BZDs and alcohol, which can subject patients to physiologic dependence.

**Treatment of Alcohol Withdrawal**

**Overall Approach**

The acute withdrawal syndrome (tachycardia, elevation in blood pressure, tremor, hyperreflexia, increased irritability) in the setting of precipitous decrease in drinking and its severest manifestations and complications (seizures, hallucinations, and delirium tremens) are best prevented and treated by the use of BZDs. Although it is not possible to predict with certainty which patients will experience significant withdrawal syndromes, the intensity and duration of alcohol use and the abruptness of alcohol reduction are important risk factors.

**Determining Severity, Site of Care, and Need for Pharmacologic Therapy**

The determinants of treatment for withdrawal include the severity of symptoms, the past history of withdrawal, and any comorbid medical conditions. The *Clinical Institute Withdrawal Assessment—Alcohol, revised* (CIWA-Ar), is the best-validated instrument for the objective assessment of withdrawal severity and risk (Table 228–5). Its use is common in inpatient settings but may also be helpful in the office. In its absence, a rough clinical estimate of severity must suffice. Decision making is based largely on severity of symptoms:

- **Mild symptoms** (e.g., CIWA-Ar score <8)—no pharmacologic treatment necessary, only continued monitoring unless there is a history of severe withdrawal or comorbid disease, in which pharmacologic therapy is needed
- **Moderate symptoms** (e.g., CIWA-Ar score 8 to 15)—pharmacologic therapy may be of benefit symptomatically.
- **Severe symptoms** (CIWA scores >15)—requires pharmacologic therapy; risk of seizures high

An exception to this general rule is the patient who exhibits any withdrawal despite intoxicating levels of alcohol: This demonstrates significant tolerance and is an indication for close observation in an inpatient setting if drinking will not resume imminently.

Most patients with long-standing alcohol dependence should be offered a structured setting for withdrawal; achieving a slow, safe tapering of alcohol intake as an outpatient remains problematic but is likely to improve with the advent of improved pharmacologic measures. Consider *outpatient* management if the patient is reliable, can provide informed consent, has only mild symptoms, has no critical underlying medical illnesses that would make withdrawal particularly risky, has no prior history of severe withdrawal, and has a supportive family that can provide supervision.

**Pharmacologic Therapy of Withdrawal (Table 228–7)**

Expert consensus guidelines favor BZDs over alcohol itself, barbiturates, anticonvulsants, or investigational agents (such as ondansetron).

**Benzodiazepines.** BZDs with prolonged activity (e.g., diazepam, chlordiazepoxide) appear to be more effective in preventing withdrawal seizures and in achieving a smoother withdrawal with fewer rebound symptoms than the short-acting agents; however, they are also more likely to cause excessive sedation, particularly in the elderly and patients with liver disease. The non–hepatically metabolized BZDs (lorazepam, oxazepam) are indicated for use in persons with hepatocellular disease, but because they are shorter acting, close monitoring of the patient is needed.

**Table 228–7 Treatment Regimens for Alcohol Withdrawal**

<table>
<thead>
<tr>
<th>Severity of Withdrawal Syndrome</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (CIWA-Ar score &lt;8)</td>
<td>Monitor every 4–8 h until no worsening for 24 h; treat as for moderate or severe disease if there is a prior history of severe withdrawal or if there is serious concurrent illness.</td>
</tr>
<tr>
<td>Moderate (CIWA-Ar score 8–15)</td>
<td>Begin diazepam 10 mg q6h for 4 doses and then 5 mg q6h for 8 doses or chlordiazepoxide 30 mg q6h for 4 dose and then 25 mg q6h for 8 doses; then halt and allow drug metabolism to achieve tapering. For persons with concurrent liver disease, begin lorazepam 2 mg q6h for 4 doses and then 1 mg q6h for 8 doses. Provide additional medication as needed when symptoms are not controlled.</td>
</tr>
<tr>
<td>Severe (CIWA-Ar score &gt;15)</td>
<td>Admit to inpatient facility, and begin symptom-triggered regimen with hourly administration of diazepam 10–20 mg, chlordiazepoxide 50–100 mg, or lorazepam 2–4 mg, and reassess hourly, repeating the dose if CIWA score &gt;8–10.</td>
</tr>
</tbody>
</table>

CIWA-Ar, Clinical Institute Withdrawal Assessment—Alcohol, revised; q6h, every 6 h.


Several BZD regimens have been developed and are effective when used as intended. *Fixed-dose regimen* are the standard approach to treatment, using a long-acting agent (e.g., diazepam) and a *loading-dose regimen* at the outset (see Therapeutic Recommendations). The loading dose is given at the outset and repeated until the patient is sedated (thus the call for a sober companion to assist in observation). Normal drug metabolism results in tapering. Alternatively, *symptom-triggered* therapy using a shorter-acting agent (e.g., chlordiazepoxide) has been shown to decrease the mean duration of therapy and amount of drug required compared with fixed-dose treatment, but it requires close monitoring of the patient, which is usually feasible only in the inpatient setting.

**Beta-Blockers.** Beta-blockers such as atenolol (e.g., 50 to 100 mg/d) can help to control adrenergic symptoms and reduce BZD requirements, but they are not sufficient as monotherapy because they do not prevent seizures, hallucinations, or delirium tremens.

**Approach to Alcohol Hangover**

Known formally as *veitalgia*, the alcohol hangover usually ensues after the consumption of 1.5 g/kg (five to six drinks in men and three to five drinks in women not tolerant to alcohol). The syndrome is characterized by headache, anorexia, nausea, fatigue, diarrhea, and tremulousness. Visuospatial skills, cognitive function, and job performance are impaired despite the clearing of alcohol from the bloodstream and can lead to accidents. Many metabolic abnormalities may be at play, including dehydration and excess acetaldehyde. There are many purported preventive measures and cures; none are supported by evidence. The best treatment is prevention through patient education and counseling. All patients should be warned that psychomotor and cognitive impairment can be substantial and appropriate caution is warranted.
INDICATIONS FOR ADMISSION AND REFERRAL (29,30)

Admission

The patient who has medically decompensated because of a complication of alcohol use (e.g., heart failure, pancreatitis, gastrointestinal bleeding, and hepatitis) requires prompt care and admission as appropriate. Other candidates include persons with evidence of severe withdrawal (tremor, agitation, hallucinations, seizures) and those unable to tolerate a severe withdrawal syndrome (prior history of severe withdrawal, concurrent medical or psychiatric illness, chronic and severe alcohol-related illness). A free-standing detoxification center may suffice for the patient who is otherwise low risk.

Referral

Patients with major psychopathology, poor ties to the physician, or a disintegrated social network have serious drawbacks to successful treatment by even the most willing primary care physician. Such patients should be referred for coordinated specialized care by the primary care physician, ensuring continuity and a personalized treatment. The primary physician can often provide much of the care appropriate for alcohol dependence, including medication, counseling, care of medical consequences, and harm reduction. It is helpful to support patients in recovery and to prevent relapse long term. Understanding the available specialized referral resources in the community and matching them to the patient's needs when appropriate is critically important and makes the primary care physician an essential component of coordinated care even for the most severely affected.

RECOMMENDATIONS (1,29,30)

- Screen all patients, starting with adolescents, for alcohol use and abuse; check for drinking at unhealthy levels and for problems and consequences of use. Congratulate patients who are drinking below unhealthy levels.
- Approach patients with alcohol abuse optimistically, sharing the knowledge that brief interventions work for nondependent drinkers and counseling and/or medications work for dependent drinkers.
- Provide brief, clear, patient-oriented guidance for behavior change (the brief intervention) for patients not meeting criteria for dependence.
- Establish rapport by being accepting, understanding, and respectful.
- Ally with the patient in pursuit of his or her goals and against the behavior that stands in the way, in this case drinking alcohol. Support motivation by recalling these goals, and frustrations due to alcohol, at regular intervals during the process of change.
- Offer instruction and explanation as treatment proceeds, always engaging the patient in establishing realistic goals and not pushing beyond limits.
- Think of treatment as a series of short-term programs (combining to be a long-term strategy) for developing and increasing the patient's sense of mastery.
- Make sure your practice has developed a list of specialty and community resources with whom you can collaborate as appropriate. Have a low threshold for referral and/or collaborative care with an alcohol specialty team, and use community resources such as AA.
- For all patients, set an achievable, mutually desired goal; clear drinking objectives; and put the plans in writing for future reference.
- If serious problems indicate that abstinence is best, address the issue through a supportive educational advice session; if there is resistance to abstinence, it may still be negotiated and accomplished in the context of harm reduction.
- If the program fails the patient (or less accurately, the patient fails the program) and objectives are not met, then negotiate more support and treatment (e.g., medications, counseling, more frequent visits, or family member involvement). Inability to cut down or quit is a criterion for the diagnosis of dependence, so the patient may have a more severe diagnosis than initially thought.
- Engage family members early; if the patient resists, seek conditional agreement from the patient to involve them in the future, for instance, if drinking persists beyond a deadline.
- If a patient comes to a visit drunk but otherwise stable, explain that it is better to work together in the sober state, and reschedule the visit. If this behavior continues, renegotiate the treatment agreement to include rules about coming intoxicated.
- Encourage self-monitoring of drinking behavior via logs; teach the patient to detect causes, consequences, and maintaining factors; and help to acquire alternate ways of coping with the people, places, situations, and feelings associated with heavy drinking.
- Provide information, practice, feedback, and homework as the patient learns to handle feelings and develops new skills for assessing and modifying behavior related to drinking.
- For patients with significant psychiatric comorbidities, consider the use of the appropriate psychoactive drug treatment while dealing with the alcohol problem:
  - For anxiety, consider an SSRI (see Chapter 226).
  - For depression, consider a tricyclic or SSRI (see Chapter 227).
- For patients with alcohol dependence, offer pharmacologic therapy:
  - Naltrexone (50 mg/d orally or 380 mg once-monthly intramuscular administration) especially for those reporting craving: Concurrent opioid use is a contraindication.
  - Acamprosate (666 mg tid for weight >60 kg); few precautions
  - Disulfiram, 250 mg/d, for patients strongly motivated to attain total abstinence. Begin 250 mg at bedtime, and renew on a monthly basis. Obtain written informed consent involving a sober companion and the patient.
- Reevaluate the need for continued drug therapy after 6 months while working on psychosocial interventions that will sustain long-term abstinence.
- Select those components of available specialized treatment programs that match the patient's needs, wants, and ability to cope.
- Refer to a community social service agency for coordinated care and assistance for patients who are homeless, are jobless, or have other serious social problems.
- For patients who have failed outpatient treatments or who need to be taken out of their environment to cease drinking, consider an inpatient or residential alcohol program.
- For treatment of withdrawal (Table 228–7):
  - Consider outpatient management if the patient is reliable, has no or only mild symptoms, has no critical underlying medical illnesses that would make withdrawal particularly risky, has no prior history of severe withdrawal, and has a supportive family that can provide supervision; otherwise, arrange inpatient care.
  - Prescribe a long-acting BZD (one option is a fixed schedule of diazepam 10 mg every 6 hours for four doses, then 5 mg every 6 hours for eight doses); achieve tapering by normal drug metabolism (Table 228–7).
  - Promptly admit unstable patients and those with other medical conditions or with symptoms suggesting potentially severe withdrawal (e.g., tachycardia, tremor, hallucinations, increased irritability).
RESOURCE MATERIALS

- The National Institute on Alcohol Abuse and Alcoholism Web site http://www.niaaa.nih.gov (An excellent resource for every possible professional need; it offers ongoing publication of the latest findings and policy positions plus resource materials for medical education and health education. The site also is oriented for patients and provides information on the disease and treatments.)
- The National Institute on Drug Abuse Web site http://www.nida.nih.gov (Gives information on drugs in addition to alcohol.)
- The U.S. Department of Health and Human Services Substances Abuse and Mental Health Services Administration’s National Drug and Treatment Referral Routing Service 1-800-662-HELP (4357)
- AA, Al-Anon, Alateen, Narcotics Anonymous, and Smart Recovery (Important self-help groups with Web-based directories and schedules of local meetings)
- Books recommended for patients and their families:
  - Sober for Good by Anne M. Fletcher (New York: Houghton Mifflin) 2001 (A commonsense approach to assessing drinking and deciding when and how to change; treatment relevant for the patient who is resistant to considering abstinence.)
  - Get Your Loved One Sober. Robert J. Meyers and Brenda L Wolfe (Center City MI: Hazelden) 2004 (This book helps the “significant other” maintain quality of life in a way that also moves the drinker toward recovery, helping to soften the sense of crisis and seemingly inescapable interdependence.)

ANNOTATED BIBLIOGRAPHY

3. Morse RM, Flavin DK. Joint Committee of the National Council on Alcoholism and Drug Dependence and the American Society of Addiction Medicine to Study the Definition and Criteria for the diagnosis of alcoholism. JAMA 1992;268:1012. (Consensus definition and criteria.)
7. Chen WJ, Rosner B, Hankinson SE, et al. Moderate alcohol consumption in during adult life, drinking patterns, and breast cancer risk. JAMA 2011;306:1894. (Nurse’s Health Study, as little as 5 grams of alcohol [one half drink] per day associated with increased risk of invasive breast cancer, as was higher lifetime drinking, in a dose-response relationship.)
12. Grant BF, Stinson FS, Dawson DA, et al. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders. Results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch Gen Psychiatry 2004;61:807. (Finds that the approach increases the likelihood of detecting emotional problems.)
13. Grant BF, Stinson FS, Dawson DA, et al. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders. Results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch Gen Psychiatry 2004;61:807. (Finds that the approach increases the likelihood of detecting emotional problems.)
15. Hanna EZ, Grant BF. Parallels to early onset alcohol use in the relationship of early onset smoking with drug use and DSM-IV drug and depressive disorder findings from the National Longitudinal Epidemiologic Survey. Alcohol Clin Exp Res 1999;23:513. (Covers the issues of youth, comorbidity, severity of illness, and familial transmission.)
28. Bradley KA, DeBenedetti AF, Volk RJ, et al. AUDIT-C as a brief screen for alcohol misuse in primary care. Arch Intern Med 2007;113:1208. (Finds that three questions from the Alcohol Use Disorders Identification Test provide a useful and valid screening tool.)
29. United States Preventive Services Taskforce. Screening and behavioral counseling intervention in primary care to reduce alcohol misuse: recommenda-
tion statement. Ann Intern Med 2004;140:554. (Strongly recommends screening and brief intervention for all adults in primary care.)
33. Brown RL, Saunders LA Bobula JA, et al. Randomized-controlled trial of a telephone and mail intervention for alcohol use disorders: three-month drinking outcomes. Alcohol Clin Exp Res 2007;31:1172. (Find that the approach extends the usefulness of brief interventions, both to patients with alcohol dependence and to methods other than face-to-face discussions.)


40. Kristol JH, Cramer JA, Keol WE, et al. Naltrexone in the treatment of alcohol dependence. N Engl J Med 2001;345:1734. (RCT, finding that the treatment was no better than placebo in this study of older men, in which the emphasis was on abstinence.)


42. Nunes EV, Levin FR. Treatment of depression in patients with alcohol or other drug dependence: a meta-analysis. JAMA 2004;291:1887. (A rigorous meta-analysis, finding that outcomes depend on efficacy in treating depression.)


There is an important relationship between one’s sexual life and emotional and physical well-being. With the advent of orally effective medication for treating erectile dysfunction and the increased interest in pharmacologic agents for treating female sexual disorders, the frequency of sexual dysfunction complaints in primary care practice has risen to nearly 15% to 20% of visits. However, the incidence of sexual problems in any medical practice is a function of the frequency with which physicians take a sexual history. Approximately 43% of women and 31% of men report some specific sexual dysfunction when questioned. Therefore, the primary care physician needs to know how to take a sexual history, perform an appropriate medical evaluation (see Chapters 115 and 132), and carry out basic types of sexual counseling and supportive therapy. More than 80% of sexual complaints can be treated successfully in the primary care setting.

DEFINITIONS (1–5)

The consensus psychiatric definitions of sexual disorders are those specified in the Diagnostic and Statistical Manual of Mental Disorders (DSM), with a fifth edition pending. They are classified as primary when there has never been a period of satisfactory functioning and secondary when the difficulty occurs after adequate functioning had been obtained.

Male Disorders

Erectile dysfunction (impotence) is defined as the inability of a male to maintain an erection sufficient to engage in intercourse and is considered a problem if it occurs in more than 25% of attempts.

Premature Ejaculation

This condition is defined as recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it (most often <2 minutes after penetration or on <10 thrusts).

Male Orgasmic Disorder

This disorder (“retarded ejaculation”) is defined as persistent delay or absence of orgasm following normal sexual excitement. It is often restricted to failure to reach orgasm in the vagina during intercourse. Orgasm can usually occur with masturbation and/or from a partner’s manual or oral stimulation. There is a persistent failure to ejaculate in the presence of a satisfactory erection. This condition must be differentiated from retrograde ejaculation.

Retrograde Ejaculation

Retrograde ejaculation is a physical impairment of internal vesicle sphincter activity. The bladder neck does not close off properly during orgasm, causing semen to spurt backward into the bladder.

Female Disorders

Frigidity is a term applied to a wide variety of conditions in the woman, from complete lack of any sexual response to various inadequacies in orgasmic response. Because it is nonspecific and has a derogatory connotation, the term has been eliminated from most recent classifications.
Female Sexual Arousal Disorder
This disorder is defined as the inability to respond to sexual stimulation with lubrication and genital vasocongestion.

Female Orgasmic Disorder
This disorder (“orgasmic dysfunction”) is defined as a recurrent delay in, or absence of, orgasm following a normal sexual excitement phase, despite the ability to enjoy sexual intercourse and have normal sexual desire. Some women who can have orgasm with direct clitoral stimulation find it impossible to reach orgasm during intercourse. This is a normal variant of sensitivity requiring the pairing of direct clitoral contact with intercourse.

Vaginismus
Vaginismus is an involuntary spasm of the musculature of the outer third of the vagina, making penile penetration impossible.

Both Sexes
Dyspareunia
Dyspareunia is a condition defined as painful intercourse leading to avoidance of sexual contact.

Hypoactive Sexual Desire Disorder
This disorder ("low libido") is defined as a deficit or absence of sexual fantasies and lack of desire to engage in sexual activity.

Sexual Aversion Disorder
This disorder is defined as an active avoidance of genital sexual contact with a sexual partner.

Hypersexual/Sexual-Addiction Disorder
Although not listed in the DSM-IV but likely to be included in the DSM-V, this is viewed as an addiction, which can be a primary problem or a coping mechanism. There is excessive and/or compulsive sexual activity that affects the patient's sexual and nonsexual functioning.

PATHOPHYSIOLOGY AND CLINICAL PRESENTATION (1–12)

Pathophysiology
Organic conditions are responsible for between 50% and 85% of sexual problems in both sexes. This figure represents a dramatic shift in the understanding of the causes of sexual disorders that were once thought to be primarily of psychogenic origin. Neurogenic, hormonal, vascular, and drug-induced mechanisms are prominent (see Chapters 115 and 132). For example, diabetes mellitus is a particularly important cause of erectile dysfunction (see Chapter 102); selective serotonin reuptake inhibitor (SSRI) antidepressant use is associated with reduced libido. Recent research emphasizes increasing links between general and sexual health. Obesity, metabolic syndrome, and other cardiovascular risk factors are associated with erectile dysfunction as well as female sexual dysfunction. When the coexisting medical illness is treated or lifestyle factors addressed, sexual function will often concurrently improve.

Organically based sexual dysfunctions are usually compounded by psychological issues. There is a strong bidirectional association between depression and sexual dysfunction in both men and women. Although there are no rigid correlations between developmental factors and dysfunctional syndromes, sexual disorders can be related to prior experiences. Early sexual attitudes may be negatively shaped by parental communication that sex is bad, dirty, or sinful; by inadequate information about sex; or by myths and misconceptions such as the ever-ready penis or mutual climax. Other negative experiences range from unpleasant sexual encounters to childhood sexual abuse to rape. Intrapsychic conflicts extend from fear of sexual failure, to concerns about sexual identity, to profound depression.

Interpersonal issues of a sexual and nonsexual nature sometimes interfere with sexual functioning, especially in the setting of inadequate communication and lack of cooperation between partners. Sexual problems may develop from such nonsexual factors as situational stress and financial pressures. Finally, sexual difficulty may occur in the context of the anxiety generated by an organic illness, such as a post–heart attack fear of death.

Once a sexual problem ensues, regardless of the cause, a vicious cycle of fear of failure, anxiety, and guilt is likely to ensue and be self-perpetuating.

Clinical Presentation
Sexual dysfunction may present as the chief complaint or be an underlying or concurrent problem. Clinical presentations can be quite complex. For example, patients with sexual dysfunction may present with somatic complaints with no apparent medical cause (e.g., headache, low back pain, urinary symptoms, genitalized pelvic pain, vulvar pruritus).

Male Erectile Disorder
Most normal men experience occasional erectile failure due to fatigue, too much alcohol, or any number of transient unfavorable circumstances. In the United States, it is estimated that up to 30 million men have erectile dysfunction, accounting for more than 500,000 ambulatory visits to health care professionals annually. Primary (lifelong) erectile dysfunction occurs in 1% of men younger than age 35 years. Secondary (acquired) erectile dysfunction occurs in 40% of men older than 60 years; this figure increases to 73% of men older than age 80 years. Erectile dysfunction may be the first symptom of vascular disease and should prompt further investigation. Primary impotence and long-standing secondary impotence are much more likely to be associated with medical disorders or more serious psychological issues, such as fears of intimacy, feelings of intense hostility toward women, and gender identity questions.

Premature Ejaculation
Premature ejaculation is the most common male sexual disorder, occurring in 30% to 40% of adult men. The lifetime prevalence of premature ejaculation is 15%. The psychological causes of the disorder range from early conditioning to ambivalence and hostility toward women. Its increasing frequency has been associated with women wanting more sexual satisfaction, particularly orgasm. Once premature ejaculation occurs, it can easily be reinforced by the negative attitudes expressed by the partner. In addition, prolonged periods of no sexual activity seem to make the problem worse. If premature ejaculation occurs over a long period of time and remains untreated, secondary impotence may result. It is often easily treated in the context of a good relationship.

Male Orgasmic Disorder
Retarded ejaculation occurs most often in younger, less sexually experienced men (usually younger than age 35 years). The lifetime prevalence is 2%. Its milder form is often related to
The lifetime prevalence of this condition is 40% for women and 5% of men. Patients often seek medical treatment, but the condition probably accounts for less than 10% of female sexual complaints and occurs more often during the early years of sexual activity. The disorder has a lifetime prevalence of 35%. Among affected women, 30% to 40% report clitoral stimulation during intercourse to achieve orgasm; 5% to 8% present with total anorgasmia. The capacity for orgasm appears to increase with sexual experience, and that includes the aging woman. Claims that stimulation of the Gräfenberg spot, or G spot, in a region in the anterior wall of the vagina will cause orgasm and female ejaculation have never been substantiated. Premature ejaculation in the male may contribute to female orgasmic dysfunction. Again, the psychological factors involved are variable, and the prognosis for the condition is a function of which factors are responsible. These range from fears of loss of control and unrealistic expectations about sexual performance to poor partner communication. Depression must not be overlooked.

**Vaginismus**

Vaginismus is associated with a high incidence of pelvic pathology (see Chapter 115). The frequency of vaginismus is unknown, but the condition probably accounts for less than 10% of female sexual disorders. Lifelong vaginismus has an abrupt onset, at the first attempt at penetration, and has a chronic course. Acquired vaginismus may occur suddenly, following a sexual trauma or medical condition. A careful gynecologic examination is always warranted and, in fact, is the only definitive way to make a diagnosis. Vaginismus is one cause of dyspareunia. When related to psychological factors, vaginismus can be considered a conditioned response and treated behaviorally. There is often confusion about sexual anatomy and physiology, leading to fears of penetration and concerns about femininity. If the condition is long-standing, partners of these women can become seriously affected, developing secondary impotence. This disorder has been at the center of many cases of unconsummated marriages of long duration.

**Dyspareunia**

The overall prevalence for this condition is 20% (15% of women and 5% of men). Patients often seek medical treatment, but the physical exam is often unremarkable, with no genital abnormalities. The condition is usually chronic and results in avoidance of sex.

**Hyposexual/Sexual-Addiction Disorder**

The ready availability of Internet pornography and “cybersex” activities has dramatically increased the opportunity for potentially adverse sexual behaviors. Sexual “addiction” is an emerging source of distress among patients and may be a primary problem or a coping mechanism. Excessive and/or compulsive sexual activities may affect the patient’s sexual and nonsexual functioning.

**WORKUP (1,3–5,7)**

**Sexual History**

The sexual history should be an integral part of every medical evaluation, given the importance of sexual function to overall health, the central role that sexual dysfunction might play in somatic complaints and quality of life, and the need to review safer sexual practices. The history is most easily obtained in conjunction with performing the gynecologic and menstrual review of systems in women and the genitourinary review in men. In this way, sexual practices and concerns can be comfortably elicited in the context of routine history taking, especially if the physician displays an open, nonjudgmental, unembarrassed, and accepting attitude. One needs to take into account differences in social values, class, and age. Clinicians should be aware that sexual problems such as erectile dysfunction may be the presenting complaint in patients suffering from or at risk for numerous medical conditions including obesity and cardiovascular disease. In addition, careful inquiry about medication use, including herbal agents, may reveal potential side effects contributing to sexual problems (see also Chapters 115 and 132).

Helpful screening questions include “Does your present sexual functioning meet your expectations?” “Has there been a change in your sexual functioning?” “Would you like to change anything about your sexual functioning?” Additional routine questions to ask are “Have you been sexually active (or involved) with a partner in the last 6 months? (with women, men, or both?)” “Do you practice safe(s) sex?” Failure to ask HIV screening questions may result in criticism of inadequate treatment or even lead to a malpractice suit.

If a sexual problem is uncovered, the chief complaint should be explored in detail. Ask patients to describe the problem in their own words, noting its duration, circumstances, possible precipitating and alleviating factors, and severity. Avoid using “why” questions, which tend to make patients uncomfortable; use “what” questions instead. A thorough description sometimes helps to distinguish an organic from a functional etiology (see Chapters 115 and 132). For example, in the impotent male, preservation of erectile function on awakening suggests a psychological cause, as does erection with attempts at masturbation.
Also try to elicit what type of treatment the patient views as potentially helpful, be it medical, information, or support. Clarify the patient’s expectations and goals, for example, to save a marriage or to use the problem as an excuse for an extramarital affair or divorce.

The sexual history taker should gain comfort in and routinely inquire about the role of the Internet in the patient’s sexual and nonsexual functioning and the possibility of excessive and/or compulsive sexual activities.

**Physical Examination and Laboratory Studies**

With improved understanding of the pathophysiology of sexual function and more sophisticated diagnostic testing, many sexual problems once believed to be purely psychogenic have been found to have an organic component as well. Take special note of sexual dysfunction as a common side effect of SSRIs, which occurs in more than 30% of patients taking the medication. Even when psychological or interpersonal problems are believed to be the principal cause of sexual dysfunction, a careful medical evaluation that includes a detailed physical examination in conjunction with a few pertinent laboratory studies is always indicated (see Chapters 115 and 132).

**PRINCIPLES OF TREATMENT (3–5, 12–35)**

The primary care physician is often the first person consulted by a patient with a sexual problem. Even the physician without formal training in sex therapy can help many patients to deal effectively with their sexual difficulties. When the problem stems from guilt and misinformation, the physician can use his or her position as an authority figure to give permission and reassurance, relabeling as “neutral” or “positive” sexual activities that the patient might fear are “bad” or “sinful,” while reinforcing the normal range of sexual activities.

Educating patients and correcting misinformation is a function that should not be overlooked or underestimated. Giving permission or providing information may be all that is necessary to help many patients. An essential part of modern sexual counseling is the teaching of safer sexual practices and review of risk factors for HIV infection (see Chapters 7, 13, and 119). Explaining the relationship between a healthy lifestyle and a healthy sex life may help motivate the patient to address both issues, for example, losing weight to improve erectile dysfunction.

**Behavioral Methods**

If the problem persists, a trial of behavioral methods (see later discussion) with specific suggestions to patient and partner can be helpful and is an appropriate next step. The objectives are to increase communication between partners, encourage experimentation, change the goal of sexual activity toward feeling good and away from emphasis on erection or orgasm, and relieve anxiety associated with pressure to perform at each sexual encounter. A trial of such therapy is reasonable when there is no evidence of organic illness or significant underlying psychopathology.

**Pharmacologic Approaches**

Medication can be prescribed for specific sexual complaints of various etiologies instead of or in conjunction with behavioral techniques. This may lead to improved sexual function without the need for referral to specialists (see also Chapters 115 and 132). Review of patients’ current medications may reveal opportunities to minimize sexual side effects. For example, while many medications for hypertension inhibit sexual function, the angiotensin II receptor blockers (e.g., losartan) and α-blockers (e.g., doxazosin), also useful for benign prostate hypertrophy (BPH), may actually lead to improvement. Optimizing medical management, for example, for cardiovascular disease, may also alleviate sexual dysfunction, for example, erectile dysfunction.

**Male Erectile Disorder: Phosphodiesterase Inhibitors (e.g., Sildenafil, Vardenafil, Tadalafil)**

Selective inhibitors of phosphodiesterase type 5 (PDE5) facilitate erections by increasing the amount of available cyclic guanosine monophosphate (needed for vascular relaxation and erection) (see Chapter 132). Drugs in this class, which include sildenafil (Viagra), vardenafil (Levitra), and tadalafil (Cialis), have revolutionized the treatment of erectile dysfunction, being effective in persons with both organic and mixed psychogenic and organic impotence. Efficacy ranges from about 50% to 75% in terms of ability to obtain and sustain erection sufficient to engage in intercourse and may be improved by statins. The PDE5 inhibitors have little effect on libido and thus may be of limited use when poor libido is the principal problem; however, in depressed men with sexual dysfunction, treatment with sildenafil is associated with a significant improvement in erectile function and sex drive, and 75% of responders have more than a 50% reduction in measures of depression. The PDE5 inhibitors are also effective in the treatment of antidepressant-induced erectile dysfunction. Avanafil, a new PDE5 inhibitor under review by the U.S. Food and Drug Administration (FDA), promises a faster onset of action than its competitors. Other PDE5 inhibitors in development include mirodenafil, udenafil (Zycla), udenafil (Helleva), and SLx-2101, not yet FDA approved.

**Adverse Effects.** Key recognized adverse effects of approved PDE5 inhibitors include the potential for severe hypotension with concurrent nitrate use (absolute contraindication) and visual disturbance, generally mild and transient. PDE5 inhibitors should also be used with caution in patients taking α-blockers, for example, for BPH and/or hypertension due to the risk of symptomatic hypotension. Case series have suggested a link between PDE5 inhibitors and nonarteritic anterior ischemic optic neuropathy (NAION), although a review of available clinical trials could not confirm a causal relationship. Emerging research also warns of an association between PDE5 inhibitors and new-onset hearing loss.

**Other Drugs for Erectile Dysfunction**

Yohimbine (Yocon) is approved for the treatment of male erectile disorder, but its efficacy is uncertain. Other second- and third-line orally administered agents include L-arginine (ArginMax), phenylamine (Vasomax), and sublingual apomorphine (Uprima), none of which is approved by the FDA (see Chapter 132). Dopaminergic agents such as cabergoline (Dostinex) have been used off-label to treat PDE5 inadequate responders, demonstrating moderate benefit even in patients with normal prolactin levels. Small studies suggest a potential role for methylenedioxymethamphetamine, an opioid antagonist. Centrally acting melanocortin receptor agonists such as bremendimeth (PT-141), in development as an intranasal preparation, appear effective, but side effects may limit utility. Clavulanic acid (Zoraxel) appears to enhance sexual function through serotonin/dopamine modulation and is currently in development stages. Topical impotence medications, including alprostadil cream (Topiglan), minoxidil solution, and nitroglycerine ointment, are under investigation. Transdermal testosterone helps to restore libido and erectile function in truly hypogonadal men (see Chapter 132) but is not recommended for men with normal levels of bioavailable testosterone. Clomiphene
Citrate (Clomid), a gonadotropin-releasing hormone (GnRH) agonist, may also benefit this patient population. Numerous herbal agents for erectile dysfunction have been tried with limited success, the most promising being Panax ginseng, Butea superba, and Lepidium meyenii (maca root).

Premature Ejaculation: Antidepressants and Topical Anesthetics

There remain no specific FDA-approved treatments for premature ejaculation, but some are under study and others are used off-label for the problem. When premature ejaculation is secondary to male erectile disorder, the PDE5 inhibitors should be used first to treat the erectile dysfunction.

Both tricyclics and selective serotonin reuptake inhibitors appear to be helpful. The tricyclic domperidone (Anafrilan) can be prescribed as needed 6 hours before planned intercourse, as can a daily SSRI. Dapoxetine (Priligy), an SSRI with a rapid onset and short half-life, is being studied for premature ejaculation as a specific indication and use as an on-demand treatment. Another potential on-demand treatment is tramadol, although there is a risk of dependency in the long term due to the drug's opioid properties.

Topical anesthetics (such as lidocaine derivatives), the most popular of which is EMLA Cream, can be used to slow ejaculation without the systemic side effects of antidepressants. However, these agents may cause penile numbness, resulting in erectile problems. TEMPE (Topical Eutectic-Like Mixture for Premature Ejaculation), a topical lidocaine and prilocaine spray, appears promising in delaying ejaculation with less frequent side effects. No topical agent is FDA approved for premature ejaculation.

Low Libido and Orgasmic Dysfunction: Transdermal Testosterone, Bupropion, and Sildenafil (PDE5 Inhibitors)

Much sexual dysfunction is a consequence of reduced libido and orgasmic dysfunction, which has triggered considerable interest in pharmacologic approaches to management.

In Women. The gradual decrease in testosterone levels that occurs with menopause has stimulated studies of hormone replacement therapy (HRT) as a means of treating decreased libido in menopausal women. However, results from the Women's Health Initiative (WHI) studies linking HRT to increased risks of cardiovascular disease, thromboembolism, and breast cancer have raised concerns about the safety of this approach (see Chapter 118). Testosterone use requires relatively high doses, which may result in acne, hirsutism, alopecia, reduction in high density lipoprotein cholesterol, and hepatic toxicity. There are no data on the safety of long-term testosterone use in women.

Testosterone supplementation (often as a transdermal patch and usually in combination with estrogen) has been shown to improve libido, sexual arousal, and the frequency of sexual fantasies in menopausal women. The commercially available patches are intended for men and release considerably greater doses of testosterone. A newer testosterone patch, LibiGel, specifically designed to treat hypoactive sexual desire disorder in postmenopausal women, is undergoing study. A similar agent, Intrinsa, was rejected by the FDA due to safety concerns.

Estrogen has been shown to improve sexual function in postmenopausal women with vasomotor symptoms. Dehydroepiandrosterone (DHEA), available as a nutritional supplement, may be beneficial in treating female sexual dysfunction in women with adrenal insufficiency. Topical prostaglandin E1 (alprostadil), specifically targeting clitoral engorgement and vaginal vasocongestion, has shown no clear benefit.

Antidepressants such as bupropion (Wellbutrin) may increase arousability and sexual response, especially in women with an underlying depression. Side effects include nervousness, insomnia, and risk of seizure. Other dopaminergic agonists used in men have also been tried in women based on limited anecdotal evidence. The SSRI antidepressants may actually reduce libido, causing some to consider switching to bupropion (or adding a phosphodiesterase inhibitor—see next section) for the treatment of the underlying condition or using it as an adjunct off-label (see Chapter 227). Non-SSRI antidepressants mirtazapine (Remeron) and possibly duloxetine (Cymbalta) have also been associated with fewer sexual problems compared to SSRIs.

Phosphodiesterase-5 inhibitors (e.g., sildenafil [Viagra]) in general fail to demonstrate effectiveness in women with orgasmic dysfunction and arousal disorder, but may be of some benefit to women who exhibit greatly diminished vasocongestion. However, in an important randomized controlled trial, sildenafil was shown to reduce adverse sexual effects in women taking SSRIs. The prostaglandin alprostadil applied topically to the genitalia as a cream before intercourse to improve arousal has shown mixed results and may cause transient local burning. Other medications used to treat male sexual dysfunction, including yohimbine, apomorphine, melancortin agonists, and l-arginine, are being investigated in women. While herbal agents have had variable success, small studies support use of maca root for antidepressant-induced female sexual dysfunction. EROS-CTD, a clitoral therapy suction device, is the only FDA-approved medical–surgical intervention for the treatment of female sexual dysfunction; it can improve sexual arousal and orgasm.

In Men. Both hormone replacement and use of PDE5 inhibitors have been the subject of study and application.

Testosterone replacement (via a transdermal patch or gel) represents an effective approach in men with poor libido and sexual dysfunction due to true hypogonadism (documented low levels of bioavailable serum testosterone). Routine use in aging men with sexual dysfunction in the absence of documented low bioavailable testosterone is not routinely recommended due to a host of potential medical risks, ranging from polycythemia and stroke to stimulation of a preclinical prostate cancer (see Chapter 132). Limited evidence suggests a potential role for oxytocin in facilitating sexual arousal.

Sildenafil has been prescribed for those with low libido and/ or erectile dysfunction associated with mild to moderate depression, resulting in significant improvement not only in sex drive and sexual function but also in measures of depression, suggesting that some of the interplay between depression and sexual dysfunction may be amenable to the specific treatment of the sexual dysfunction. Results in other patients with diminished libido have been more variable.

THERAPEUTIC RECOMMENDATIONS (SEE ALSO CHAPTERS 115 AND 132)

Emphasis on behavioral methods, since as noted earlier, much potentially useful pharmacologic intervention is still being studied and not yet FDA approved.

Erectile Dysfunction

● First, educate the patient about his ability to satisfy his partner without having penile–vaginal intercourse.

● Then, begin to outline “sensate focus” exercises, which start with nongenital massage and progress to genital massage. There should be a prohibition against intercourse, even if erections occur.

● After erection is obtained by genital massage, advise the patient to progress to attempting intercourse. In the woman–superior position (woman on top of man), the woman may...
manually stimulate the penis, and, if erection is obtained, she may insert it into her vagina in a slow, non-demanding fashion, relieving the man of any responsibility for insertion. This may also be done with a partial erection. Gradual movement is begun. There is an emphasis on the pleasures of vaginal containment.

- Consider supplementing behavioral therapy with PDE5 inhibitor therapy (e.g., sildenafil—see Chapter 132). Do not prescribe if nitrates are being used concurrently (risk of severe hypotension); use with caution and provide a thorough patient education in men with underlying coronary heart disease. Avoid or use with caution in men taking α-blockers (often prescribed for benign prostatic hypertrophy).
- Consider an external vacuum constriction device.

**Premature Ejaculation**

- Educate the patient that his condition has little to do with the sensitivity of the penis but is usually the result of previous conditioning and anxiety.
- Suggest an increase in the frequency of sexual activity.
- Teach the “squeeze” technique. In this technique, the woman manually stimulates the penis. When ejaculation is approaching the point of inevitability, as indicated by the man, the woman squeezes the penis with her thumb on the frenulum, her index finger placed above, and her middle finger below the corona]  

**Orgasmic Dysfunction**

- Change the goal of sexual activity away from orgasm toward enjoyment of the experience.
- Give permission to the woman to express sexual feelings.
- Outline “sensate focus” exercises, which start with non-genital massage and progress to genital massage. Suggest the use of the back-protected position (the man in a seated position with the woman between his legs with her back against his chest) with the woman in control to alleviate self-consciousness.
- Instruct the man in stimulative techniques: He should not force responsivity but rather seek to accommodate desires; he should not approach the clitoris directly because of sensitivity.
- After success in manual genital stimulation, controlled intercourse in the man-superior position with the man making no demands comes next. This is followed by a lateral position that allows for mutual freedom of pelvic movement.
- For women who have never experienced orgasm, suggestions regarding self-stimulation are appropriate. The use of fantasy material is most helpful.
- For women who do have orgasms with masturbation but not intercourse, the “bridge technique” may be useful. After insertion of the penis, the man can stimulate the woman (clitorally) manually or with a vibrator. This pairing can be helpful in achieving orgasm, and often after the woman experiences orgasm in this way, the need for supplementary stimulation disappears.
- Consider use of estrogen/testosterone in the postmenopausal woman who experiences orgasmic dysfunction or low libido, but only after taking into account cardiac, vascular, and malignancy risks associated with long-term hormone replacement use.
- Consider use of bupropion in women with concurrent depression and sildenafil in women taking SSRIs for depression.
- Consider EROS-CTD, a clitoral therapy suction device.

**Vaginismus**

- Explain to the patient and her partner that this condition is involuntary and not willfully caused. Physical demonstration of the involuntary vaginal spasm may be done by inserting a gloved finger into the vaginal entrance.
- Ask the couple to refrain from intercourse during the early treatment.
- Encourage the woman to accept larger and larger objects into the vagina in a stepwise gradual fashion. This may be accomplished with the use of graduated Hegar dilators to be used in the office and at home, or the woman may begin by using her fingers, first one and then several approximately the size of the penis. She may use her partner’s fingers. Syringe containers of different sizes make good dilators.
- Suggest that the woman should gradually insert the penis while she is in the woman-superior position.

**Hypoactive Sexual Desire Disorder**

- Consider transdermal testosterone for men with documented hypogonadism (low bioavailable testosterone level) and for women with surgically induced menopause (in combination with estrogen). Testosterone use in men without hypogonadism and in women with physiologic menopause or other causes of low libido has not been validated.
Lack of knowledge regarding safer sex practices is a major contributor to the spread of HIV infection. Concerns about HIV infection can also interfere with the enjoyment of sexual activity. Detailed review of safer sex practices is essential (see Chapters 7, 13, and 119). Condom use is critical for those with multiple sexual partners and for monogamous partners in whom HIV status is unknown. With prudent precautions and a little creativity (e.g., making condom application an early part of foreplay), a safe and enjoyable sexual life can still be attained.

### ANNOTATED BIBLIOGRAPHY

2. Kafka MP. Hypersexual disorder: a proposed diagnosis for DSM-V. Arch Sex Behav 2010;39:377. (Highlights clinical importance of hypersexuality, proposed as a new psychiatric disorder.)
Broadly speaking, these patients are referred to as “somatizers,” with particular subgroups specified when necessary.

Explanatory Models

Somatizing has been understood from a variety of perspectives, including as a biologic disorder, a cognitive and perceptual process, a form of interpersonal communication, and an unconscious psychological process.

The biologic model of somatization, the newest of the explanatory models, is rooted in a growing body of research suggesting that genetic, neurobiologic, endocrine, and immune system factors can lead to abnormal processing of somatic stimuli. Abnormalities in biomarkers for autonomic, hypothalamic-pituitary–adrenal, and cytokine (particularly IL-1 and IL-6) function have all been associated with somatization. In addition, abnormalities in serotonin levels, related genes, and brain structures involved in the perception of pain and the physiologic state of the body have supported the notion that somatizers may have abnormalities in the central processing of bodily sensations.

The Cognitive/Perceptual Model

In this model, somatization is viewed as a self-validating and self-perpetuating disorder of symptom amplification, an error in nociception, the perception of bodily sensations. Somatizers are unusually sensitive to visceral and bodily sensation and are therefore bothered by normal physiologic sensations and minor discomforts that nonsomatizers ignore, dismiss, or have completely out of their awareness. As these bodily sensations seem so intense, noxious, and disturbing, somatizers with high levels of anxiety, often referred to as hypochondriacal, will readily misattribute them to serious disease.

Once the individual believes himself or herself to be sick, this belief alters subsequent somatic perceptions, and a process of symptom amplification begins. The belief that one is sick makes preexisting symptoms seem more intense because they are now subject to closer scrutiny. The patient’s apparent worsening condition even more firmly convinces the patient that he or she is sick. These patients become hypervigilant for other symptoms that confirm their suspicions and ignore contradictory...
information indicating that they are not in fact sick. For example, an individual may notice breathlessness after climbing a flight of stairs and wonder whether this signifies the onset of heart or lung disease. With this suspicion in mind, the patient now thinks that his face looks unusually pale in the mirror when he next shaves. This too seems to provide further evidence of disease progression. Thus, a self-validating and self-perpetuating cycle of cognitive and perceptual amplification has been set in motion.

The Psychodynamic Model

This model suggests that the patient’s mind and body produce physical symptoms as a way of trying to solve problems in the patient’s life or as a way of protecting the patient from intolerable emotions. This model considers that the symptoms, and their associated behaviors, serve a protective function, but a maladaptive one that can cause its own problems. Some somatizing patients have unconsciously learned that illness behaviors can be used to negotiate stressful circumstances, secure support, and solicit care. The following are some, but by no means all, examples of how physical symptoms and illness behaviors can be produced to serve a protective function.

For some patients, physical symptoms can provide an acceptable problem for which to ask for help. The patient may perceive some insurmountable life problem with which he or she is unable to cope; either because of past experiences or current interpersonal context, he or she is not able to allow the desperation he or she feels into full awareness or to verbalize it to others and ask for help. Instead, the body produces physical symptoms, for which the patient asks to take “time out” and with which he or she shows others “I am in a desperate situation and so I need special care and attention, unusual assistance, and support at this time.”

Other somatizing patients may struggle with feelings of loneliness, and difficulty obtaining loving attention from others, or trouble treating themselves in a forgiving way. Their minds and bodies may produce symptoms to help them gratify yearnings for contact, comfort, and support. Still other patients may have feelings of anger or aggression that they are unable to acknowledge. For these patients, physical symptoms may be an unconscious way of exacting retribution from people in their lives by whom they feel wronged or a way of showing someone in their life that they are not meeting needs.

For patients who struggle with feelings of helplessness around various life problems, physical symptoms, which elicit predictable reactions for others, may be a way of regaining a sense of control. For other patients, physical symptoms may be a way of protecting against underlying feelings of worthlessness. These patients may be able to attribute failures, disappointments, or rejections to a physical incapacity, which can be less painful than focusing on a belief that there is something fundamentally wrong with them. Other patients may be part of a family that functions best when one of its members is ill, and their symptoms optimize the functioning of a challenged family. It is important to emphasize, once again, that these patients are not consciously or intentionally producing their symptoms.

Severe Health Anxiety and Hypochondriasis

Some degree of health anxiety is normative and adaptive, in that it can motivate one to seek medical attention when a symptom develops. However, when health anxiety becomes persistent and preoccupying, the body’s normal, physiologic “background noise” becomes a nusus for catastrophizing about having a serious disease. This can lead to significant suffering, impaired social and occupational functioning, and overutilization of health care services. Severe health anxiety is classified as “hypochondriasis” when the disease fear persists despite appropriate medical evaluation and reassurance.

Hypochondriacal symptoms shift and fluctuate over time, are often nonspecific and ambiguous, and frequently are similar to the transient benign bodily discomforts experienced by healthy individuals. When interviewed, patients with hypochondriasis talk mainly about their illnesses and medical care and little about family, work, or hobbies. They often seem as concerned with establishing the authenticity of their complaints as with obtaining symptom relief. Some adamantly deny any emotional contribution to their symptoms. This stands in sharp contrast to many patients with serious physical disease who are willing to consider the possibility that anxiety and depression make their symptoms worse. However, other patients with hypochondriasis are aware of their tendency to obsess over symptoms and catastrophize about diseases and are quite distressed by this pattern.

Multiple Medically Unexplained Physical Symptoms

At least a third of symptoms in primary care are medically unexplained. Patients with multiple MUPS are said to have somatization disorder if they meet a specific symptom count (at least four different sites of pain on the body: at least two gastrointestinal problems, one sexual dysfunction, and one pseudoneurologic symptom), and undifferentiated somatiform disorder if they fall short of this specific number. There is also a disorder characterized by one or more pain symptoms that are either without medical explanation, or seemingly out of proportion to any known organic cause (see Chapter 235). For the sake of simplicity, we refer to this varied group of patients as having MUPS. In fact, research supports the notion that making the specific psychiatric diagnosis of somatization disorder is less important than counting the number of MUPS, which is linearly predictive of degree of functional impairment and of anxiety and depression. Thus, screening for these underlying conditions is very important in patients with MUPS. Unlike in hypochondriasis, patients with MUPS often present their symptoms in a matter-of-fact manner, are not overtly anxious, and do not have a specific disease conviction tied to their symptoms. They often have particular difficulty talking about their feelings or connecting the stressors of their lives with their symptoms. For many such patients, difficulties in processing emotions and experiencing their body accurately are related to a history of childhood trauma.

Conversion Reactions

Conversion reactions are sensory or motor dysfunctions suggestive of a neurologic disorder, but are actually expressions of an unconscious psychological need or conflict. The emotional distress is thought of as being “converted” into, or expressed as, physical distress. The process is entirely unconscious, so these patients are not malingerers. Symptoms are either sensory or neuromuscular (e.g., weakness, paralysis, ataxia, blindness, aphasia, deafness, anesthesia, paresthesias, or seizures) and usually of short duration. Other features include a prior history of similar symptoms, major emotional stress before onset, and apparent symbolic meaning of the symptom (e.g., paralysis after losing control and striking someone or blindness after viewing a horrifying event). Approximately, half of these patients have a history of childhood abuse or neglect, and over two thirds have an anxiety disorder, such as posttraumatic stress disorder (PTSD). Greater than three quarters of conversion disorder patients have a depressive disorder.
Anxiety

A number of anxiety disorders can produce somatic or health-related symptoms. Patients with generalized anxiety are in a chronic state of tension and hypervigilance. They often suffer from multiple somatic manifestations of this constant stress, including restlessness, difficulty concentrating, dry mouth, cold and clammy hands, and gastrointestinal disturbances. Panic anxiety has somatic manifestations that include palpitations, chest pain, tachycardia, dyspnea, choking sensations, diarrhea, sweating, tingling in hands and feet, and fainting. Such signs and symptoms may easily be misinterpreted as evidence of serious illness, such as heart attack. Patients with obsessive–compulsive disorder (OCD) also commonly have fears and obsessions related to germs and disease and typically have a variety of other obsessions and compulsive rituals (e.g., excessive hand washing, checking, counting).

Depression

Depression’s neurovegetative symptoms may overshadow the characteristic affective, cognitive, and behavioral changes that are part of the depressive syndrome (see Chapter 227). The chief complaint may be headache, constipation, weakness, fatigue, abdominal pain, insomnia, anorexia, or weight loss. At least one half of somatizing ambulatory medical patients are significantly depressed. These patients worry about and focus attention on their bodies. A positive review of systems, chronic pain, or complaints involving multiple organ systems typify the clinical presentation, and symptoms may recur with the periodicity characteristic of depressions. In most non-Western cultures, somatization is the typical presentation for depression.

Differential Diagnosis (2,3,7,9,12)

Somatizing patients, of course, have the same vulnerability for medical illness as their nonsomatizing counterparts, if not more so. Even in patients with a somatization disorder as well those without it, consideration of medical conditions that may present as vague multisystem complaints is always in order. Potentially mimicking conditions deserving consideration include connective tissue disorders such as systemic lupus and vasculitis; systemic infectious diseases such as HIV, TB, syphilis, Lyme disease, and subacute bacterial endocarditis; endocrine conditions such as hypothyroidism and hyperparathyroidism; occult malignancy, particularly in the setting of paraneoplastic syndrome; and neurologic conditions such as multiple sclerosis. Domestic violence may present with multiple, perplexing bodily complaints that may superficially resemble those of a somatization disorder (see Appendix 236-1). The psychiatric differential diagnosis of somatization includes anxiety (including OCD and PTSD), depression, somatic delusions, body dysmorphic disorder (BDD), malingering, and factitious disorder.

Somatic Delusions

Schizophrenia, severe affective disorders, and organic brain syndromes are common sources of somatic delusions. These are false fixed ideas that are often vivid, bizarre, or highly personalized. Unlike hypochondriacal concerns, they tend not to fluctuate. The individual may believe that some extraordinary change has occurred in his or her body, for example, that organs are shriveling up, body parts are deformed or missing, or foreign objects are inside an orifice or organ.

Body Dysmorphic Disorder

Patients with BDD have a relatively unshakable, circumscribed belief that they are physically deformed, although their appearance is actually unremarkable. A facial feature is often the focus. This rare condition is chronic and extremely disabling and causes profound social withdrawal. Patients with BDD often seek referrals to dermatologists and plastic surgeons, but are typically unsatisfied with attempts to correct their perceived deformity. Such patients should be frequently screened for depression and anxiety and warrant a referral to psychiatry as they have a relatively high suicide rate.

Malingering and Factitious Disorder

Malingering differs from all of the aforementioned conditions in that the malingerer does not actually experience the symptoms reported and is consciously feigning disease. Malingering occurs in situations in which illness confers a secondary gain, beyond the sick role itself. Examples include a prisoner feigning chest pain in order to spend time in a hospital rather than prison, or a substance abuser feigning abdominal pain in order to obtain opiates. Symptoms are exaggerated, and the patient’s description of them may vary with each interview. When unaware of being observed, the patient may relax the simulation and thus betray himself. Antisocial personality disorder and substance abuse are often comorbid with malingering.

While malingers feign symptoms to achieve secondary gains, patients with factitious disorder (also known as Munchausen syndrome) consciously produce actual symptoms in order to obtain the primary gain of the sick role itself. The concept of primary gain refers to a process in which assumption of the sick role facilitates the resolution of an unconscious internal conflict. For these patients, being sick confers such psychological benefits that they can cause themselves serious injury in order to produce symptoms. For example, some patients with factitious disorder have been known to inject insulin in order to produce a syncopal episode from hypoglycemia. Testing for C-peptide differentiates these patients from those with a true insulinoma. Patients with factitious disorder tend to be female and are often employed in medical fields such as nursing.

Workup (2,3,5,7,9)

History—Step 1: Differentiating Somatization from “Organic” Disease

The task is not always easy, but the quality, timing, and precipitants of symptoms, as well as the patient’s response to illness, attitude, and choice of words, can be of considerable help, while keeping in mind that a host of important medical conditions may present as poorly explained multiple bodily complaints (e.g., depression—see Chapter 227; generalized anxiety disorder—see Chapter 226; chronic fatigue syndrome—see Chapter 8; connective tissue disease—see Chapter 146; systemic infectious diseases [e.g., HIV, Lyme, syphilis, TB, subacute bacterial endocarditis]—see Chapters 7, 160, 38, 11, respectively; endocrinopathies such as hyperparathyroidism and thyroid disease—see Chapters 96, 103, and 104; paraneoplastic syndromes—see chapter 92; and neurologic conditions such as multiple sclerosis—see Chapter 172). Similarly, domestic violence may present in this fashion, necessitating a few screening questions when suspected (see Appendix 236-1).

In addition to careful consideration of medical conditions, attention to predisposing factors, symptom quality, timing, and attitude toward symptoms helps identify somatizing and differentiate it from “organic” causes of bodily complaints.
Predisposing Factors
Details of previous medical care experiences can be revealing: A history of prior medically unexplained symptoms, of consulting multiple physicians for the same complaint, or of the immediate replacement of a treated symptom with a new one helps in the diagnosis of psychogenic illness. A thorough history should also include screening for childhood trauma, or current or past anxiety or depression.

Quality of Symptoms
A complaint that is inconsistent with known pathophysiology is likely to be psychogenic in origin. Psychogenic sensory complaints often involve combinations of sensory modalities that are neurologically impossible (e.g., a patient reporting loss of position and vibratory sense can nonetheless walk normally; see Chapter 167). Conversion seizures, otherwise known as nonepileptic events, may not involve stereotyped movements, incontinence, tongue biting, or changes in prolactin level. The patient with conversion blindness exhibits a withdrawal or staring reflex when a hand is flashed before the face. With conversion paralysis of the upper extremity, the patient’s arm avoids striking the face when being held above it and released. In conversion paralysis of a lower extremity, a patient’s attempt to lift the afflicted leg while supine will fail to invoke involuntary contractions in the contralateral leg, as is the case in neurologic disease (Hoover sign).

Psychogenic symptoms are more likely to resemble symptoms that have afflicted someone important to the patient (a so-called figure of identity) or to be excessively vague or overly detailed. Inconsistent complaints and vivid, elaborate, highly personalized, or idiosyncratic descriptions are suggestive. Psychological factors may be revealed in the choice of words (e.g., “pain in the neck” or “not having a leg to stand on”).

Timing
Psychogenic symptoms are typically unaffected by activity or by the passage of time. Although any physical symptoms can be precipitated by stress, the onset of psychogenic complaints is often closely associated with significant emotional stress, such as the loss of a loved one or the onset of a major interpersonal conflict or sexual problem. Functional complaints are also prone to occur on the anniversary of a psychologically meaningful event.

Attitude Toward Symptoms
When the patient is unconcerned, inappropriately calm, or more invested in establishing authenticity than obtaining relief, one should suspect an emotional component. (However, this finding lacks specificity, as stoic and stolid patients may also appear unemotional when afflicted with serious organic disease.) In addition, as noted above, patients with psychogenic complaints who unconsciously derive considerable gain from their illness are often reluctant to consider an emotional cause for their symptoms.

History—Step 2: Defining the Underlying Psychological Mechanism
Once a psychogenic etiology is suspected on the basis of the clinical presentation, evaluation should proceed to possible psychological and interpersonal underpinnings (please see section above describing Explanatory Models). Might this patient be hypersensitive to sensations in his or her body and be caught in a symptom amplification cycle? Are there significant unresolved conflicts in this patient’s life, and is this symptom helping the patient to temporarily cope, solve a problem, or avoid focusing on difficult emotions? What would this patient’s life look like without this symptom; what might change in the patient’s life, and what might the patient have to face or deal with? Is there some conflict or feeling that the patient is experiencing that seems quite clear to you, but of which the patient seems blissfully unaware?

Physical Examination and Laboratory Studies
Thorough physical and mental status examinations are essential. Not only may unexpected evidence of organic illness turn up, but a normal examination is a prerequisite for effective reassurance and the avoidance of unnecessary laboratory testing. Checking for manifestations of conditions that can cause multiple bodily complaints (see Differential Diagnosis) is essential.

Obtaining a few simple laboratory tests (e.g., sedimentation rate, serum calcium) may be in order, but only if there is some suggestive evidence from the history or physical examination. Absent clinical evidence of organic disease, there is little role for extensive testing, and invasive studies should be avoided. Performing a test simply for the purpose of reassurance is often futile because patients who are highly anxious about their health to begin with frequently find some other source of concern when the result is negative. In addition, the likelihood of a false-positive result is higher than the likelihood of a true-positive result when the pretest probability of organic disease is low (see Chapter 2). For example, obtaining a sensitive but nonspecific test such as an antinuclear antibody level in the absence of clinical criteria for lupus is likely to generate a disturbing false-positive result, given that the test can be positive in up to 25% of healthy people (see Chapter 146).

PRINCIPLES OF MANAGEMENT (3,4,7,8,13–15)
Overall Approach
Management must be directed at the underlying psychological causes and at the presenting bodily complaints. A combination of (i) putting the complaints in perspective, (ii) emphasizing reassurance and support, and (iii) attending to any maladaptive patterns of interpersonal behavior comprise the basic approach to management. It is also important to employ medications when appropriate. Conversion disorder and disorders that can masquerade as somatization require some unique management techniques.

Putting the Complaint in Perspective
The first step is to put the complaint in perspective while still recognizing that the patient has come because of physical symptoms. When the results of the workup are presented, the reality of the symptoms should not be denied, nor should it be implied that they are imaginary or “all in your head.” The patient can be told that serious, damaging organic disease has been ruled out and that stress can amplify real bodily sensations and disrupt normal function. It is important to avoid saying “there is nothing wrong” because this contradicts the patient’s experience and triggers feelings of shame or anger.

Cognitive–behavioral therapy can be very helpful in this task. Such treatment can help to target cognitive and perceptual mechanisms of illness, including overattention to bodily sensation, beliefs about symptom etiology, interpersonal context in which somatization occurs, sick role behaviors, and mood. Controlled studies find that cognitive–behavioral therapy is able to achieve significant reductions in fears of illness and unnecessary medical visits.
Providing Support

Whatever their source, the symptoms are an indication of considerable distress, which the patient should be encouraged to discuss. The patient needs to know that the relationship with his or her physician will not be terminated because the medical workup is “negative,” and should be reassured that, although no serious medical disease has been found, the physician will continue to monitor symptoms for the emergence of serious disease in the future. Follow-up visits should be scheduled on a regular basis to provide further time to discuss personal and situational problems. By offering the patient a long-term relationship that is not contingent on the necessity of having ongoing somatic symptoms, one may remove a major stimulus for their development. Patients may also benefit from a referral to a psychotherapist for further emotional support if they are willing.

Managing the Somatizing Patient with Underlying Maladaptive Patterns of Behavior or Personality Disorder

Most patients with somatization in the setting of long-standing maladaptive behavioral patterns or frank personality disorder can be managed by the primary physician. As with other somatizing patients, medical intervention should be minimized when possible. Major diagnostic workups for equivocal or questionable findings should be avoided as long as medically responsible to do so, as should pain medication and tranquilizers. Even though medication is often requested, these patients generally do not respond to it and are especially prone to developing troublesome side effects.

For patients with a long-standing pattern of interpersonal conflict, somatic symptoms and decisions about their treatment can become tools in struggles around chronic themes. For example, a patient who feels helpless and wronged and is afraid of abandonment may return for follow-up expressing anger about symptoms intractable to treatments, which can cause the physician to feel helpless, wronged, and concerned that the patient may “fire” him. To avoid struggles and optimize care, the physician should be involved as much as possible in therapeutic and diagnostic decisions. The physician needs to make it clear that his or her role is to help the patient tolerate discomfort rather than to eliminate it. The goal of medical management is improved functioning and diminished role impairment rather than outright cure. Therapeutic suggestions should be made with the caveat that, although they may be helpful, they will probably not completely eliminate the problem.

In patients for whom maintaining the sick role is important to their sense of identity, the situational or psychological need to remain distressed and symptomatic must be recognized. For these patients, acknowledging the strength to endure suffering, tolerate discomfort, and survive misfortune can be helpful to the patient’s self-esteem, as the patient may value these qualities in himself.

Role of Drug Therapy

The role of medication in somatization is still unclear. All too often, patients are told that their symptoms are due to their “nerves” and sent away with a prescription for a minor tranquilizer. Such an intervention frequently alienates the patient, who perceives it as a “brush off” and an inadequate substitute for the physician’s personal, ongoing interest and attention.

That said, it is especially important to be on the lookout for depression because of its high prevalence, subtle manifestations, and treatability. Similarly, anxiety disorders, including panic disorder and generalized anxiety disorder, may often be ameliorated with antidepressants, benzodiazepines, or β-blockers, often in conjunction with cognitive and behavioral interventions (see Chapter 226). In addition, antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, have been associated with symptom improvement in patients with MUPS and in hypochondriasis. However, overall, these patients report more side effects than other types of patients, and some studies have had high dropout rates; therefore, cognitive–behavioral therapy is typically recommended as a first-line treatment when available.

Approach to Conversion Reactions

There are two aspects to the treatment of conversion reactions: (i) symptom remission and (ii) management of the precipitating stress, internal conflict, or secondary gain in order to avoid recurrence or chronicity. The first is done through education, reassurance, and positive suggestion to reduce anxiety (these patients are often exceptionally suggestible). The patient should be assured that the disorder is known to be self-limited and that the symptoms will therefore gradually improve and finally vanish. Conversion symptoms may recur, however, unless psychotherapy is arranged to neutralize the psychological forces at work.

Approach to Malingering and Factitious Disorder

Once firmly established as diagnoses, malingering or factitious disorder may be dealt with by gently confronting the patient with the physician’s conclusions. Frequently, such patients will deny the behavioral diagnosis and pursue medical care elsewhere. For those few patients who do remain in treatment, diagnostic and therapeutic procedures should be avoided when possible because they reinforce the patient’s behavior. Any abnormal laboratory tests or physical findings must be considered suspect. In the case of factitious disorder, referrals to psychotherapy and family therapy may be of utility in helping both the patient and the members of their support system to better understand the psychological distress that precipitates illness behaviors.

INDICATIONS FOR REFERRAL

Most somatizing patients can be managed by the primary care physician and team. Referral for psychotherapy should be considered (along with primary care management) in patients for whom anxiety, psychological conflict, or interpersonal problems are contributing to their symptoms; when a conversion reaction, psychosis, or serious anxiety/depressive disorder is present; or when the primary physician has such strong feelings toward the patient with a personality disorder that he or she cannot serve that patient well without additional support.

TREATMENT RECOMMENDATIONS

- Explain the results of the medical workup without denying or being unsympathetic to the reality of the patient’s discomfort.
- Get to know the patient as a person. Inquire, for instance, how the patient spends his or her days, about psychosocial stressors, and about social supports.
- Uncouple as much as is possible medical attention from symptom flares.
- Set up appointments at regular intervals, and make it apparent to the patient that physical symptoms need not be present to have access to the doctor.
• Avoid as-needed appointments when possible.
• Identify and treat any medication-responsive condition such as depression or anxiety disorder (see Chapters 226 and 227). Consider SSRIs (e.g., fluoxetine) for MUPS or hypochondriasis.
• Avoid use of tranquilizers for suppression of nonspecific symptoms.
• In patients with maladaptive behavioral patterns and personality disorders, do not attempt to remove or cure symptoms; acknowledge the suffering and offer support; avoid the use of medication and extensive workup of vague symptoms; make improved coping and improved adaptation to chronic discomfort the goal of care.
• For persons willing to explore and deal with their fears and illness concerns, consider a referral for psychotherapy. Cognitive–behavioral therapy has the strongest evidence base for this population.

ANNOTATED BIBLIOGRAPHY


CHAPTER 231
Approach to Difficult Patient Interactions
Fremont Meyer Ilana Braun

Although the frequency of difficult patient encounters specifically in primary care practices is unknown, up to 30% of patients in the general hospital setting exhibit difficult behavior at one time or another. Difficult behaviors can take many forms: late arrivals to appointments or no-shows, intense questioning of the clinician, rejection of treatment recommendations, demand of unnecessary tests or medications, frequent e-mails or ill-timed pages, and abusive behavior toward staff. Patients may exhibit such behaviors in response to suffering caused by illness, perceived medical error, adverse life events, or simply as a result of the psychological threat posed by being a patient. Cultural differences, psychiatric disorders including personality disorders, life circumstances, and relational styles can also manifest themselves as difficult behavior. Exogenous factors, including physician attributes and the challenges of negotiating the health care system, may contribute to patients' difficult behaviors in the health care setting.

PSYCHOLOGICAL MECHANISMS, INTERPERSONAL FACTORS, AND CLINICAL PRESENTATIONS (1–4)

Psychological Mechanisms
Difficult interactions often derive from feelings of threat, being from illness, loss of independence, conflicts in other parts of life, or perceived physician error. Preexisting personality disorder is another potential source.

Threat from Illness
People often become angry when their wishes and aims are frustrated by disease. Illness can provoke difficult behavior when it brings with it the prospect of disfigurement, pain, and emasculation; lost effectiveness, opportunity, or autonomy; abandonment; or even death. Some patients are particularly sensitive to and react against the helplessness, lack of control, and enforced passivity that illness confers. Others resent that the vagaries of chance seem to have unfairly singled them out for misfortune.

Threat of Dependence and of the Doctor–Patient Relationship
Some people have difficulty tolerating the role of patient. For them, participation in the doctor–patient relationship represents the threat of dependence, infantilization, and emasculation—of allowing someone powerful to take control of and responsibility
for them. Their anger functions to keep the physician at a distance. It is a defense against any closeness or attachment to the doctor that might develop.

By contrast, other patients crave such intimacy. These persons may become difficult if they sense that their doctors are treating them dismissively, not taking them seriously, or not caring about their case as much as they would like.

**Threats or Conflicts Elsewhere in Life**

Sometimes, anger directed toward a physician is displaced. Patients commonly besiege or reproach their clinicians in response to stresses that they are encountering elsewhere in their lives. Often in such instances, the animosity and hostility seem inappropriate to the situation and disproportionate to any provocation the doctor can identify. Usually, this displaced anger develops when a patient is in conflict with important people in his or her life, including employers and close family, to whom the patient cannot properly express his or her emotion. In a process referred to as transference, the patient can also displace onto the current doctor the dissatisfaction and disillusionment that have actually been aroused by previous physicians.

**Threat of Physician Fallibility**

Many patients respond to illness by investing enormous faith in their physicians. Medical error, whether as a result of action or omission, can shake a patient’s sense of emotional security as much as it can lead to physical suffering. Anger in this context grows not only from a belief of having been wronged but also out of a frightening realization that the medical system, which has been entrusted with the patient’s care, is fallible.

**Character Pathology: Borderline Personality**

This form of character pathology commonly contributes to difficult behavior. It constitutes the common underlying factor for a variety of personality disorders, including narcissistic, antisocial, and histrionic varieties. Patients with these personality disorders tend to reveal their underlying borderline personality organization when under stress, such as that induced by illness. They often have difficult childhood histories entailing emotionally distant or neglectful caregivers and sexual and physical abuse; they are at high risk for domestic violence in their intimate relationships. Adverse life events and genetic factors appear to interact as risk factors. A serious medical illness often leads to intensified feelings of vulnerability, which exacerbates underlying fears of neglect and abandonment, and may lead to behavioral regression and further illumination of maladaptive personality traits. Primitive defense mechanisms are resorted to, including splitting and denial, and suicidal ideation is not uncommon.

**Splitting.** In medical settings, these patients are prone to utilize primitive defenses such as splitting and denial. In splitting, the patient rigidly separates medical caregivers into “good ones” and “bad ones” and often cooperates with those perceived as good while rejecting the advice of those perceived as bad. As a result, different medical staff members experience the patient differently, which may result in inconsistent patient care and discord among the team. There may be disagreements on the patient’s level of pain, veracity of reported physical symptoms, and need for psychotropic medication. Patients often shift their alliances for unclear reasons, resulting in behavioral instability.

**Denial.** Such patients may also engage in pathologic denial, leading them to reject the details or even knowledge of their illness, decide suddenly that they are cured, or flee from medical treatment. The opportunities often afforded by the medical setting to switch providers, get second opinions at other institutions, and ultimately even divide care across several institutions can further fuel denial or splitting behaviors.

**Suicidal Ideation.** In addition to posing management and interpersonal challenges, patients with personality disorders are at risk for suicidal ideation and attempts; in particular, 75% of patients with borderline personality disorder attempt suicide at least once, and approximately 10% eventually complete suicide, with prior attempts, hopelessness, impulsivity, and substance abuse increasing the risk of completed suicide. For this reason, clinicians must assess for the presence of suicidal ideation, intent, or plan and act decisively to assure the patient’s safety.

**Personal, Physician, and Patient–Doctor Factors**

All physician–patient relationships are influenced by dynamics within the patient, the physician, their interaction, the patient’s illness, and the hospital and larger psychosocial systems. When a difficult relationship develops, optimal care requires open-minded examination of all these areas.

**Patient Factors.** Although personality disorders are often implicated in difficult behavior, other psychiatric diagnoses such as depression, anxiety, somatization, substance abuse, delirium, dementia, and psychosis may also result in difficulty. For example, patients with anxiety disorders may be problematic when their high anxiety prevents them from obtaining information about treatment options; they may then ask questions that suggest that they were not listening.

**Physician Factors.** Difficult patients tend to provoke strong emotions in clinicians, a phenomenon known as countertransference. On occasion, a difficult patient will remind a physician of one of their own problematic family members, only intensifying the countertransference. When unrecognized, these reactions can prompt a variety of maladaptive clinician responses: distancing (in some cases, to the point of inappropriate termination of care) or the opposite, overinvolvement and failure to set appropriate limits on patient behavior. Cycles of poor patient–physician interaction can develop. Difficulty tolerating a patient’s tearfulness, anger, or anxiety may lead the physician to ignore these emotions, thereby eliciting amplification of the patient’s emotional expression with the goal of engaging the physician. A physician’s lack of awareness of his or her own negative emotions, such as anger or resentment, may contribute to his or her being curt or distant. Clinicians who are particularly attached to the ideal of physicians as inexhaustible caregivers may be uncomfortable setting limits on patients’ unreasonable demands. Finally, physicians who have less interest in, or less time to address, psychosocial concerns may be prone to perceiving encounters as difficult.

**Physician–Patient Relationship Issues.** In recent years, the patient-as-consumer metaphor has led some patients to demand “fair value,” with attention to rights and preferences, engendering potential conflicts about the boundaries of a treatment relationship. Patients, encouraged by the popular press to advocate for themselves, may question the physician about additional treatment options they have researched on the Internet, causing physicians to feel demeaned and to perceive that their expertise is in question. Conversely, those patients who have a more traditional view of the doctor–patient relationship, or who are emotionally regressed due to their illness, may experience difficulty with a physician who presents the risks and benefits of various treatments and then expects the patient to make a decision.

**Differential Diagnosis (5)**

A thoughtful diagnostic approach to difficult patient interactions involves consideration of the multiplicity of psychological, personal, and interpersonal factors previously noted (see Table 231-1).
TABLE 231–1 Important Causes of Difficult Patient Interactions

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<thead>
<tr>
<th>Psychological Mechanisms</th>
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<td>Threat from illness</td>
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<td>Threat of relationship with illness</td>
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<td>Character pathology—borderline personality</td>
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<th>Other Personal, Physician, and Patient–Doctor Factors</th>
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<tr>
<td>Patient factors—underlying depression, anxiety, somatization, substance abuse, delirium, dementia, psychosis</td>
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<tr>
<td>Physician factors—countertransference issues leading to distancing or overinvolvement</td>
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<tr>
<td>Physician–patient relationship issues—patient-as-consumer metaphor; overdependence</td>
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WORKUP (1,3,4,6,7)

Recognition of underlying psychopathology, such as the borderline personality, is particularly important, but so is self-awareness of one’s feelings and responses and picking up on verbal and nonverbal clues.

Verbal and Nonverbal Clues

Frowns, tightened fists, clenched jaws, refusal to make eye contact, abrupt and jerky gestures, and slamming of doors may be obvious nonverbal signifiers of disgruntlement. Verbal clues include statements of demand, annoyance, resentment, cynicism, sarcasm, and negativism. Passive-aggressive acts such as long silences and self-destructive behaviors such as failing to adhere to a medical regimen, keep appointments, or give up habits that are harmful to one’s health may be more oblique expressions of anger.

Emotional Response to Patient

It is important for the interviewer to pay as close attention to his or her subjective emotional responses during an interview as to objective data; reactions to the patient may provide important diagnostic clues. Feelings of anxiety, irritation, defensive ness, and guilt may develop in a physician who feels blamed and attacked. Alternatively, a sense of boredom during an examination may represent an unconscious response to anger and hostility on the part of the patient.

Indicators Suggesting a Personality Disorder

Clues to a personality disorder diagnosis include multiple lifetime changes in jobs, relationships, personal goals, and personal histories including substance abuse, physical and sexual abuse, or childhood neglect. Poor responses to usual treatment for anxiety and depression, frequent reports of suicidal ideation, and frequent unusual side effects and patient misunderstandings are other potential indicators.

PRINCIPLES OF MANAGEMENT (1,3,4,6,7)

The fundamental keys to managing the difficult patient include reflecting on one’s emotional reactions to the patient, acknowledging the patient’s feelings, setting limits, exploring causes, and responding appropriately without retaliating.

Acknowledging the Patient’s Feelings

Having recognized that a difficult patient is angry, a physician can calmly and without judgment acknowledge this emotion and the tension in the room. “You seem to be upset with me. Kindly tell me why.” The doctor need not agree that the anger is justified, but simply sympathetically note in conversation its existence. This intervention introduces a quality of openness, frankness, and sensitivity into the therapeutic relationship and helps to bring about a more open give-and-take discussion. The physician should convey neither fear nor rejection of the patient’s feelings, but rather try to understand them and be helpful. One should practice active listening by asking open-ended questions, reflecting back, and summarizing the patient’s chief concerns. In this way, the physician demonstrates an often reassuring ability to tolerate negative emotion and conveys to the patient that anger will not destroy the therapeutic relationship.

Setting Limits

When interacting with a globally difficult patient, one need not be bullied. It is possible and indeed necessary to set limits on the patient’s behavior while at the same time making clear that there will be no counterattack in retribution. If the patient’s hostility interferes with communication, the therapeutic regimen, or coping with illness, this should be pointed out without condemnation. The physician needs to indicate that although the patient’s anger is understandable under the circumstances, it nonetheless prevents the patient from receiving the excellent care that he or she deserves.

Exploring the Causes and Responding Appropriately

It is important not only to recognize that the patient is difficult but also to learn what prompts this behavior. During the interview, the physician should note the subject matter that provokes irritation, annoyance, or hostility. If the source of the patient’s frustration remains obscure, the physician may explicitly comment that the patient seems angry and ask him or her to tell the physician more about it.

Having identified the frustrations and threats the patient is facing, the physician should be able to approach the patient more effectively. For the patient who is anxious about being ill, a detailed exploration of exact fears and sources of despair is helpful. Even the act of ventilating his or her anxiety may help to relieve it. For the person who is angry about being thrust into the patient role, a physician might consider structuring the relationship so as to minimize those aspects that threaten the patient most. For example, if the patient most fears dependence, the physician should assume a somewhat cool, reserved, and businesslike stance while still conveying support and sympathy. If the anger seems to be displaced on the physician from another situation or relationship, this may be pointed out without encouraging the patient to vent the hostility on its actual source. Finally, if the patient is frightened because of perceived harm as a result of either medical care or omission of medical care, the claim should be evaluated respectfully. If true harm has been sustained or an error has been made, a direct yet sensitive explanation should be given along with a sincere apology if appropriate. There is mounting evidence to suggest that, in the face of medical errors or bad outcomes, thorough explanations, transparency, and sincere expression of regret significantly boost patient satisfaction.

Avoiding Retaliation

The physician should take care to not react defensively or with hostility and subtly retaliate against the difficult and
indications for referral (1,3,4,6,7)

When a patient is suspected of having a personality disorder, a mental health clinician should be consulted even if the patient refuses to be seen by the consultant. The consultant can help clarify the dynamics and diagnosis of the patient, help medical clinicians tailor their approach to the patient’s particular personality style, set appropriate limits and boundaries with the patient, guide team meetings to reduce conflict among staff, and provide education and emotional support to the team.

When an on-site clinician is unavailable, physicians should obtain the patient’s written consent to collaborate with any existing mental health professionals. Convening the team to discuss the care of the patient can help clinicians stay on the same page, reduce staff conflict, contain dysfunctional patient behavior, and support the treatment team in a way that allows them to help the patient through treatment.

in the United States, with medications accounting for more than $2 billion/year. An estimated $63 billion is wasted each year in the United States because of insomnia-driven workplace difficulties. Given the extent and significance of the problem, it is essential that the primary care physician be skilled in the assessment and basic treatment of insomnia.

definition, pathophysiology, and clinical presentation (1–9)

Definition

Insomnia is defined as persistent global dissatisfaction with sleep, occurring despite an adequate opportunity for sleep, that produces clinically significant impairment of social, occupational, or other daytime function. Persistence can be defined as sleep disturbance occurring at least three nights a week for at least 3 months. Note that insomnia actually persists for greater than 1 year in 70% of patients, with greater than 3 years in 50%. Global dissatisfaction with sleep can be defined as complaints of difficulty initiating or maintaining sleep (e.g., frequent or prolonged awakenings with difficulty returning to sleep), early-morning awakening, and/or of sleep that is nonrestorative.

clinical presentations

Insomnia-associated daytime manifestations include fatigue, low energy, cognitive impairment (disturbance of attention, concentration, and/or memory), daytime sleepiness, and mood disturbance (dysphoria, irritability). In children, sleep dissatisfaction may present as resistance going to bed; daytime manifestations include behavioral problems such as hyperactivity, aggression, and impulsivity.

annotated bibliography

3. Oldham JM. A 44-year-old woman with borderline personality disorder. JAMA 2002;287:1029. (A useful case-based review of this important character disorder, which may present as anger; 53 references.)
4. Vincent C. Understanding and responding to adverse events. N Engl J Med 2003;348:1051. (Includes useful suggestions on how to respond to complaints that have been harmed by medical treatment.)
Sleep Physiology and Pathophysiology

Sleep physiology can be examined by polysomnography, continuous all-night recording of respiration, electroencephalogram (EEG), electrocardiogram, and the monitoring of eye movements, muscle tone, and blood oxygen saturation. It helps to differentiate normal from disturbed sleep.

Normal Sleep

Normal sleep has two basic phases: rapid eye movement (REM) sleep and non-REM (NREM) sleep.

REM Sleep. REM sleep is a state of mental and physical activation. Pulse and respiration are increased, but muscle tone is diminished; little body movement occurs. The brain is active, and the EEG shows a pattern similar to that seen during waking. Most dreaming occurs during REM sleep.

Non-REM Sleep. In contrast, this is a time of deep rest. Pulse, respiration, and EEG all slow, and the patient goes from light sleep, called stages 1 and 2, to deep or delta sleep, called stages 3 and 4. REM sleep and NREM sleep normally cycle in a reciprocal pattern, giving a typical “architecture” to the polysomnogram. The entire cycle lasts about 90 minutes and is repeated smoothly four or five times during the night. The ventrolateral preoptic area (VLPO), located in the anterior hypothalamus, appears to be a key “sleep center.” Reciprocal inhibition between the VLPO and “wake and alertness” centers such as the tuberomammillary nucleus (TMN) in the posterior hypothalamus and other areas in the forebrain and brainstem produces alternating periods of sleep and waking.

The alteration of sleep and wake, that is, the sleep cycle, may be regulated by a “biologic clock”—the suprachiasmatic nucleus (SCN)—located in the hypothalamus. The absence of light appears to be one of the signals that prompts the SCN to stimulate the pineal gland to secrete melatonin, which may inhibit the stimulation of wake centers by the SCN, allowing the VLPO to promote sleep. Information is emerging regarding subtypes of melatonin receptors (MT1 and 2), stimulation of which may have different aspects of sleep and awakening.

VLPO neurons express inhibitory neurotransmitters such as γ-aminobutyric acid (GABA) and galanin (most available insomnia medications stimulate GABA receptors). TMN neurons secrete histamine, which, along with the serotonin, noradrenaline, and acetylcholine secreted by the brainstem and other centers, may stimulate the cortex and thalamus to promote alertness and wakefulness. Medications such as antihistamines, antidepressants, and stimulants may produce insomnia or sedation by affecting these neurotransmitters. Adenosine accumulates in the brain during waking. Increasing concentrations of adenosine may inhibit wake and alertness centers; caffeine may promote wake and may produce insomnia because it is a potent adenosine receptor antagonist.

Not all persons who sleep less than the average amount each night have insomnia. Natural short sleepers are persons who regularly have less than 7 hours of well-maintained sleep yet suffer no problems in daytime function. Normal aging is associated with reductions in total sleep time, sleep continuity, and slow-wave sleep but does not produce insomnia or other formal sleep disorders. Anxiety and discomfort related to these normal changes may respond to counseling but not to medication or other treatment, so it is important to distinguish normal sleep changes from the specific symptoms of insomnia.

Insomnia

Insomnia has no single or pathognomonic polysomnographic pattern. Some insomniacs have sleep times that are slightly shorter than normal, some have less stage delta sleep, and some have repeated arousals. However, the degree of gross polysomnographic change is often not concordant with the degree of subjective distress.

At present, the precise etiology and underlying pathophysiology of insomnia remains obscure. Patients with at risk for insomnia may have high levels of physiologic arousal, perhaps driven by the overactivity in brain alertness and wake centers during both sleep and waking observed in functional imaging research studies. Such patients may, when stressed, develop maladaptive psychological responses to this arousal. The response and the arousal itself may persist, leading to chronic insomnia.

Classification: Types of Insomnia

Definitions and classifications of insomnia are found in the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders, fifth edition, (DSM-V); the American Academy of Sleep Medicine’s International Classification of Sleep Disorders, second edition (ICSD-2); and the World Health Organization’s International Statistical Classification of Diseases and Related Health Problems, tenth revision.

The insomnia section of DSM-V incorporates recent data and provides a new, perhaps more useful approach to classification. It drops the etiologic assumptions, such as “primary insomnia” and “insomnia due to a general medical condition,” and drops various insomnia subtypes used in ICSD and earlier versions of the DSM (e.g., psychophysologic, paradoxical insomnia), creating instead a single “insomnia disorder.” These changes highlight insomnia as a problem independent of, albeit often coexisting with, psychiatric and medical disorders and reinforce a bidirectional interaction between insomnia and depression, substance abuse, and anxiety, as well as between insomnia and comorbid medical problems. This may help clinicians focus clinical attention on insomnia itself. The result is movement from thinking about causes to considering comorbidities (see Tables 232-1 and 232-2).

Differential Diagnosis (1,3,4,6)

Psychiatric disorders, substance abuse, and medical conditions may present with insomnia as a major complaint.

Situational and Psychiatric Disorders

At least 50% of patients with insomnia disorder have comorbid psychiatric problems. Patients experiencing severe acute psychotic or situational stress are subject to severe short-term insomnia, having difficulty falling asleep. More sustained difficulty occurs in patients with anxiety and obsessive disorders, who report chronic difficulty falling asleep because they lie in bed and ruminate. Patients with character disorders such as narcissistic or borderline character disorders may feel angry about not being able to get the sleep they feel they are entitled to. The anger at failed efforts to sleep may produce arousal and make it increasingly difficult for them to fall asleep. Active psychosis of any type (e.g., schizophrenia) produces disturbed sleep and accounts for the other 10% of psychiatric insomnia. Hallucinations, delusions, and other signs and symptoms of psychotic illness present with the insomnia, facilitating recognition.

Patients with major depression complain of either difficulty falling asleep or of waking in the early morning and being unable to return to sleep. Diurnal variation of mood is often noted. Severe depression with agitation may lead to markedly diminished total sleep and overall exhaustion (see Chapter 227). It is important to recognize that insomnia may be the presenting symptom of major depression, and patients with insomnia...
are at risk for developing depression. Insomnia may also persist after other symptoms of depression resolve.

Patients with dysthyemic disorder (a variant of depression) often complain of feeling tired and irritable, have difficulty falling asleep, and report that they cannot get enough sleep to feel rested. Sometimes, they deny feeling sad or depressed and focus only on their physical complaints. Patients in the manic phase of a bipolar affective disorder may report difficulty falling asleep or staying asleep, but they do not report feeling tired during waking times.

It is important to recognize the significant bidirectional relationship between insomnia and depression. Patients with insomnia but without current depression are much more likely to develop future depression than are those without insomnia. Successful treatment of insomnia in depressed patients predicts better outcomes for the depression and lower rates of depression relapse.

**Drugs and Substance Abuse (See Also Chapter 235)**

Drugs and alcohol are present in about 10% to 15% of all patients with insomnia and may be its cause. Alcohol induces sedation, but the resulting sleep is often shallow, fragmented, and not restorative. Alcoholics can have prematurely “aged” sleep (i.e., shallow and short) during and for months after the cessation of drinking. Sedative, especially barbiturates, when used on a regular long-term basis lead to shallow, fragmented sleep. Rebound insomnia and rebound anxiety prompt severe, and tolerance leads to dose escalation, and so patients get caught in a vicious cycle. Sedatives and alcohol depress respiratory function, which can lead to sleep of very poor quality in patients with sleep apnea.

Stimulant drugs, such as amphetamines, activating antidepressants, and the phenylpropanolamine found in many over-the-counter decongestants, can induce significant difficulty in falling asleep. The caffeine and other stimulant xanthines found in tea, coffee, cola drinks, and chocolate are well recognized and often used for their ability to keep one awake. Sedatives and alcohol depress respiratory function, which can lead to sleep of very poor quality in patients with sleep apnea.

**Medical Problems**

Approximately 10% of patients with insomnia disorder have comorbid medical problems. Chronic pain is a leading, although often overlooked, factor (e.g., that experienced by elderly persons with degenerative joint disease). Delirium is another important cause in the elderly, resulting from unrecognized infection or medication toxicity (as from anticholinergic agents used in over-the-counter sleep remedies). Cardiopulmonary dysfunction may contribute by causing orthopnea, paroxysmal nocturnal dyspnea, or nocturnal angina. Urinary frequency due to infection, prostatism, diabetes, or poor timing of diuretic use is another important disrupter of sleep. Often, it is the nocturia and disturbed sleep that causes the patient with prostatism finally to seek definitive therapy. Nocturia has also been noted to be a consequence of sleep apnea.

**Primary Sleep Disorders**

Circadian rhythm disorders may present with insomnia. In the delayed sleep phase syndrome subtype, the patient falls asleep later than the usual bedtime, sleeps well, and gets up later than is socially acceptable. This common disturbance often presents in adolescents. Shift-work disorder or jet travel across time zones (jet lag), in which the inability to rapidly reset one’s diurnal rhythm to local time, may produce insomnia. For travel westward across time zones, the typical experience is awakening in the middle of the night local time (morning at home) and being unable to fall back to sleep despite feeling tired. Restful sleep is not achieved. Moreover, there is marked afternoon or early-evening sleepiness (bedtime at home). The inability to attain restful sleep culminates in exhaustion, and the patient requests help for insomnia. Endogenous disruptions of the brain’s internal circadian rhythm locker can produce a similar picture.

Restless legs syndrome is another motor disturbance associated with insomnia. Characteristic features include involuntary
leg movements when awake and periodic leg movements when asleep (see Appendix 232–1).

Sleep apnea is a disorder characterized by repeated apneic periods due to soft tissue upper airway obstruction followed by disruption of sleep. In severe cases, behavioral changes, pulmonary hypertension, cardiac arrhythmias, and death can occur. Up to 50% of patients with sleep apnea complain of insomnia as well as of daytime sleepiness (see Chapter 46).

WORKUP (1,3,4,6)

Since the goal of management is improving daytime functioning and ameliorating global sleep dissatisfaction, the initial workup should focus on discovery of predisposing, precipitating, and perpetuating factors (the “3 Ps”).

History

In addition to getting a good description of the sleep problem, it is important to elucidate any predisposing factors such as prior episodes of stress-related insomnia and a family history of insomnia; precipitating factors such as medical, psychosocial, or environmental problems; and any perpetuating factors such as feelings of frustration, anger, anxiety, or despair related to difficulty sleeping. A full description of the problem may be facilitated by having the patient keep a sleep log or diary, which includes time in bed, estimate of time asleep, any awakenings, time of morning arousal, estimate of sleep quality, and comments on unusual events and any associated symptoms (e.g., orthopnea, urinary frequency, pain, palpitations). Entries are recorded by the patient directly on getting up each morning. Close attention must also be given to use of sedatives, hypnotics (including over-the-counter preparations), and stimulants (see Table 232–2). Screening for abuse of alcohol and other substances is essential (see Chapters 228 and 235). It is most important to listen carefully for and inquire directly about symptoms of depression, bipolar disease, anxiety disorder, and psychosis (see Chapters 226 and 227). Occupational and travel patterns should be noted. Whenever possible, interviewing the spouse, bed partner, or family member is of great value, particularly for symptoms suggestive of sleep apnea (e.g., excessive snoring, apneic episodes, disturbed sleep). Family members may also bring to light covert substance use or abuse that patients may minimize or deny. Past and family medical and psychiatric histories are sometimes revealing. Perimenopausal women should be asked about hot flashes.

Physical Examination

The pertinent physical examination is a function of the history. One checks for upper airway soft tissue obstruction in the patient with suspected sleep apnea; for jugular venous distention, rales, wheezes, heaves, and gallops when there is concern about a cardiopulmonary etiology; for moist skin, tachycardia, proptosis, goiter, and tremor when hyperthyroidism is under consideration; and for prostatic enlargement in the elderly male. Testing should be limited, selective, and based on evidence from laboratory testing and clinical setting.

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Cognitive–Behavioral Measures (Table 232–3)

Formal cognitive–behavioral therapy for insomnia (CBTi) is a well-developed, structured approach that brings together education about sleep and sleep hygiene coupled with various behavioral techniques such as stimulus control techniques, sleep restriction therapy, cognitive therapy, and relaxation. CBTi has an efficacy at least equal to hypnotic medication and may be especially well suited as a first line of therapy for patients with chronic insomnia, for patients with current or past histories of substance abuse, and for many patients with anxiety and character disorders. CBTi may be used with medication, concurrently or, in some cases, after medication has produced acute improvement. There is some evidence that CBTi continued after medication has been stopped has better long-term outcomes than does either CBTi or medication alone.

CBTi is typically provided by specially trained psychologists, access to whom may be limited. In most primary care settings, elements of CBTi can be implemented with good results. These include patient education about sleep hygiene and recommendations for simple behavioral exercises.

Patient Education. Patient education regarding good sleep hygiene plays an essential role in the primary care cognitive–behavioral program. Key elements of advice address the range of sleep disturbances that the patient may experience (Table 232–3).

PRINCIPLES OF MANAGEMENT (8–30)

Overall Approach

Treatment for insomnia disorder is directed at improving daytime functioning, improving the subjective quality of sleep, and relieving distress related to sleep. There are two basic treatment approaches: cognitive–behavioral measures and hypnotic medications. Cognitive–behavioral measures include various behavioral techniques and self-help strategies (such as improvements in sleep hygiene). Successful treatment often requires both pharmacologic and behavioral approaches, especially in persons with chronic insomnia. Treatment of transient insomnia may involve little more than explanation of the impact of stress and supportive counseling to reduce anxiety and secondary perpetuation. Short courses of hypnotic medication can also be helpful and appropriate. Chronic insomnia presents a greater therapeutic challenge, with dual modality therapy even more important.

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TABLE 232–3 Behavioral Approaches to Insomnia

| Cognitive–behavioral therapy—to identify and change maladaptive beliefs, behaviors, and affects around sleep |
| Progressive muscle relaxation—to reduce excess stimulation |
| Stimulus control therapy—to break the association between bed and sleeplessness and its associated frustrations |
| Sleep restriction therapy—to limit the time spent in bed to the time actually sleeping |
| Sleep hygiene—to wind down, find a suitable sleep environment, get reasonable amounts of well-timed exercise, and avoid substances, such as caffeine, that may interfere with sleep |
of normative patterns, timing, exercise, napping, preparation for sleep, dietary factors, and substance use. Herbal and other nonprescription remedies that patients are likely to try on their own should be reviewed from an evidence-based perspective.

**Relaxation.** Progressive muscle relaxation, guided imagery, and related attention-focusing techniques can help to reduce excessive arousal and anxiety and may be useful for most patients with insomnia.

**Stimulus Control.** This approach has shown best results in patients with learned or psychophysiological insomnia because it identifies and breaks the associations between anxiety, frustration, and related behaviors connected to sleep-onset–related problems. Stimulus control is related to education about the rules of good “sleep hygiene” (Table 232–3).

**Sleep Restriction**

Patients are taught how to limit time in bed to time actually asleep; this has been shown to reduce sleep latency, improve sleep continuity and quality, and reduce insomnia symptoms.

**Pharmacotherapy (Table 232–4)**

When behavioral methods do not suffice for chronic insomnia and/or when the goal is short-term reduction of sleep-related dissatisfaction, pharmacologic therapy is a reasonable approach while staying mindful of the potential for adverse effects.

**Precautions Regarding Adverse Effects**

Adverse psychomotor side effects require attention since they are frequent and their consequences potentially serious.

**Abnormal Behaviors, Cognitive Impairment, and Compromised Ability to Drive.** Short-acting benzodiazepines and nonbenzodiazepine hypnotics have been associated with abnormal nocturnal behaviors, such as driving and eating, especially when used in larger than recommended doses or in combination with alcohol or other psychoactive agents. All sedative–hypnotics can produce cognitive and psychomotor impairment (compromising the ability to drive safely), especially during time of peak serum levels. Therefore, when sedative–hypnotics are considered, patients should be warned about their adverse potential

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**TABLE 232–4  Effective Drugs for Insomnia**

<table>
<thead>
<tr>
<th>Agent (Brand Name)</th>
<th>Onset</th>
<th>Duration</th>
<th>Dose (mg)</th>
<th>Relative Cost (Brand)</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Benzodiazepine receptor agonists
| Zaleplon (Sonata) | Rapid | Short | 5–10 | $ ($$$$) | May impair AM performance; anterograde amnesia; modest potential for abuse, withdrawal, dependence; drug–drug effects |
| Zolpidem (Ambien) | Rapid | Short–intermediate | 5–10 | $ ($$$$) | May be used for awakenings at night; possible interaction with inducers of CYP 3A4 |
| Zolpidem (Intermezzo) (sublingual) | Rapid | Very short | 1.75–3.5 | $$ | Sublingual, for middle-of-night awakening |
| Zolpidem (Zolpimist) (oral spray) | Rapid | Short | 10 | $$ | Faster onset of action; ease of use might lead to excess dosing |
| Eszopiclone (Lunesta) | Rapid | Short–intermediate | 1–3 | $$ $$ | Bad taste, potential interactions with ketonozole, nefazodone, and inducers of CYP 3A4 |

Benzodiazepines

| Triazolam (Halcion) | Rapid | Short | 0.124–0.25 | $ ($) | May impair AM performance; anterograde amnesia; modest potential for abuse, withdrawal, dependence; drug–drug effects |
| Diazepam (Valium) | Rapid | Long | 2–3 | $ ($) | May be used for awakenings at night; possible interaction with inducers of CYP 3A4 |
| Estazolam | Rapid–Intermediate | Intermediate | 1–2 | $ ($) | Sublingual, for middle-of-night awakening |
| Flurazepam (Dalmane) | Intermediate | Long | 1–3 | $ ($) | Faster onset of action; ease of use might lead to excess dosing |
| Lorazepam (Ativan) | Intermediate | Intermediate | 15 | $ ($) | No potential for abuse |
| Clonazepam (Klonopin) | Intermediate | Long | 0.5–1.0 | $ ($) | No potential for abuse |
| Oxazepam (Serax) | Intermediate–slow | Short–intermediate | 10–15 | $ ($) | No potential for abuse |
| Temazepam (Restoril) | Intermediate–slow | Intermediate | 15 | $ ($) | No potential for abuse |

Melatonin Receptor Agonists

| Ramelteon (Rozerem) | Rapid | Short | 8 | $$ | Very-low-dose preparation may be helpful in elderly with chronic insomnia. |

Antidepressants

| Doxepin (Silenor) | Rapid | Long | 3–6 | $$$ | Antidepressant amnesia |

*C*Generic formulation available at lower cost.

CYP, cytochrome P450.
and educated to avoid concomitant alcohol or drug use, avoid driving or operating machinery after medication ingestion, and report unusual behavior or cognitive disturbance.

**Full Risk.** Sedative–hypnotic medications, including benzodiazepine receptor agonists, antidepressants, and antipsychotic agents, increase nighttime fall risk, especially in the elderly. Subsequent fractures are a serious and potentially life-threatening concern, especially for frail elderly patients (see Chapter 239). Increased fall risk may extend to the day after hypnotic use. Use of a short-acting sedative hypnotic, a selective serotonin reuptake inhibitor (SSRI), or an atypical antipsychotic does not substantially reduce fall risk. Use of anticholinergics and even nonsteroidal anti-inflammatory drugs may contribute as well. Controversy continues regarding the relative contributions to fall risk of sedative–hypnotics and insomnia itself. Therefore, multimodal treatment designed to reduce severity of insomnia disorder symptoms is especially important in the elderly and others at risk for falls (e.g., patients with balance or gait disturbance, lower limb neurologic problems, or hypotension). Alternatives to hypnotic agents should be used wherever possible.

**Approach to Use.** Hypnotics should be used with caution and in the lowest effective dose; their use should be reevaluated frequently, and attempts to wean should be made. Older patients, their families, and caregivers (e.g., nurses and aids in nursing homes) should be warned of the risks and fall precautions used. Trends in recent years in hypnotic use include the replacement of the benzodiazepines with nonbenzodiazepine agents active at the benzodiazepine receptor.

*Patients who engage in substance use and/or abuse need to achieve abstinence from alcohol and “recreational” stimulants, including caffeine and tobacco as a first step, before hypnotic and related agents are used (see Chapters 54, 228, and 235). Patients with current or past histories of abuse of alcohol or other drugs or substances should generally not receive a benzodiazepine or related agent due to their increased risk of drug dependency (although most authorities now agree that patients without a personal or family history of current or past substance abuse are at low risk for addiction to hypnotics when these agents are appropriately prescribed and their use is carefully monitored).*

**Benzodiazepine Receptor Agonists**

These nonbenzodiazepine drugs (e.g., zolpidem [Ambien], zaleplon [Sonata], and eszopiclone [Lunesta]) act at the benzodiazepine receptor complex, producing a clinical hypnotic effect similar to that of benzodiazepines but without many of the undesirable side effects such as disturbance of sleep architecture, daytime sedation, rebound insomnia, or marked habituation potential (although still listed by the Drug Enforcement Administration as class IV drugs due to their slight risk of inducing mild euphoria). The onset of action is rapid, reducing sleep latency (time to onset of sleep). The use of high doses can cause next-day somnolence and cognitive impairment, but less so than with benzodiazepines. Zaleplon is the shorter acting (2 to 3 hours), making it useful for difficulty limited to falling asleep or if the patient awakens in the middle of the night; it is less likely to cause residual sedation but may not prevent premature awakening. A sublingual zolpidem preparation is also approved for middle-of-the-night awakening. The cost for these agents is high—up to five times that of generic benzodiazepines and much more for branded sustained-release formulations (which also may increase risk of daytime sedation). Anterograde amnesia, sleep walking, sleep-related eating disorder, and sleep-driving without conscious awareness have all been reported with use of these agents. Use in frail elderly nursing home residents is associated with increased risk of hip fracture.

**Benzodiazepines (Table 232–4)**

Many preparations are marketed for insomnia; none has proven to be substantially superior to any other. Most are safe and effective at low doses when used for very short periods, but all have problems associated with chronic use, including habituation, dependency, and withdrawal syndrome. Unlike the benzodiazepine-like drugs, they tend to disrupt normal sleep architecture by prolonging the first two stages of sleep and shortening deep and REM stages. Daytime drowsiness, impairment of cognitive function, and psychomotor retardation are well-described adverse effects, especially with higher doses and use of longer-acting preparations. Rebound insomnia and anxiety can occur with continuous use, necessitating the shortest possible duration of therapy and tapering to the lowest possible dose. Drug interactions are common, since metabolism for most is via cytochrome enzymes (e.g., CYP 3A4)—the following are exceptions: lorazepam, oxazepam, and temazepam. Choice of agent can be based on cost and desired onset, duration of action, and route of metabolism (see also Chapter 226).

The short-acting drugs are best prescribed for those whose primary problem is falling asleep. The intermediate-acting agents may be useful for those patients who complain of problems with staying asleep (sleep continuity). Long-acting agents are considered when daytime anxiety compounds the discomfort.

**Melatonin Receptor Agonists**

Ramelteon, a specific agonist of melatonin receptors in the SCN, is FDA approved for patients who have problems with sleep initiation but not sleep maintenance. Most studies indicate that 7.5 mg is the optimal dose. Ramelteon does not seem to produce rebound and may be used several times a week for more than 3 months for patients with a positive response. Being free of potential for abuse, it is not a controlled substance.

Melatonin preparations are widely available, sold without prescription, and very popular for insomnia. The substance is variably absorbed and distributed in the brain. Onset of action is slow, necessitating intake 3 to 5 hours before bedtime; use at bedtime is ineffective. There is no scientifically established dose, and scientific evidence of efficacy is limited. There are some data suggesting benefit in persons with delayed sleep phase disorder and in elderly patients; however, given the absence of dose and purity standards, melatonin use cannot be recommended. Ramelteon appears at present to be the better option for melatonin receptor agonist therapy for persons with difficulty with sleep initiation.

**Antidepressants and Antipsychotics**

Evidence supporting the use of antidepressants for primary sleep disorders is very limited, yet these agents are widely used in practice (e.g., trazodone, 25 to 50 mg at bedtime; nortriptyline, 10 to 25 mg at bedtime). Low-dose doxepin (3 to 6 mg) is the only FDA-approved antidepressant for primary insomnia. At these very low doses, it appears free of adverse anticholinergic side effects (which would otherwise make this tricyclic agent ill advised for use, especially in the elderly). These agents can be of particular value for patients in whom typical hypnotics are contraindicated, such as those with substance abuse.

Second-generation antipsychotic agents can relieve insomnia associated with agitation due to psychosis or delirium, but they should not be considered first-line treatment for insomnia, given their potentially serious adverse effects (see Chapter 173 and its Appendix).

**Traditional Hypnotics: Antihistamines, Choral Hydrate, and Barbiturates**

Use of these older hypnotics continues despite evidence to the contrary of their safety and efficacy. Some clinicians still resort to antihistamines (e.g., diphenhydramine, 25 to 50 mg at
Approaches, might welcome referral, if available, to a specifically trained therapist for formal cognitive–behavioral therapy.

THERAPEUTIC RECOMMENDATIONS

For All Patients

- Teach the basic elements of sleep hygiene, which should include the following advice:
  - Establish regular bed and wake times.
  - Avoid any and all naps.
  - Get regular exercise (although not at night).
  - Use the bed only for sleeping or lovemaking (rather than reading or watching television).
  - Get into bed only when ready for sleep (leaving the bed if sleep is not forthcoming).
  - Avoid caffeinated beverages, stimulants, cigarettes, and alcohol.
- Teach basic behavioral and relaxation measures (Table 232–3). Consider offering these first, in lieu of medication, or, if needed be, supplemented by a limited course of hypnotic medication (Table 232–4).
- Elicit and address any concurrent psychosocial or situational stresses that may be compromising sleep.
- Reassure patients about normal sleep patterns, particularly elderly patients who have normal daytime function but are upset by changes in sleep pattern associated with normal aging.

For Insomnia Alone

- If due to sleep apnea or restless legs syndrome, treat specifically (see Chapter 46 and Appendix 232–1).
- For short-term insomnia, stress sleep hygiene measures and, if need be, supplement with either a benzodiazepine receptor agonist (e.g., generic zolpidem, 5 to 10 mg at bedtime) or a short-acting benzodiazepine (e.g., lorazepam, 1 mg at bedtime).
- For difficulty predominantly with sleep initiation, consider a rapidly acting benzodiazepine receptor agonist such as zolpidem, zaleplon, or the melatonin receptor agonist ramelteon (7.5 mg at bedtime); the latter appears to be safe for prolonged use.
- For sleep maintenance, consider a long-acting benzodiazepine receptor agonist (e.g., eszopiclone or zolpidem CR) or the more traditional treatment with an intermediate-acting benzodiazepine such as temazepam. If there is awakening in the middle of the night, the shorter-acting zaleplon or sublingual zolpidem can be used.
- Inform patients that the absorption of benzodiazepine receptor agonists is slowed by a heavy, fatty meal, which may delay onset of action and falling asleep.
- Advise against use of alcohol, over-the-counter antihistamine-containing sleep preparations, and unproven “natural” or herbal preparations (e.g., melatonin, kava, 5–L-tryptophan, chamomile tea, passion flower).
- For chronic insomnia, review sleep hygiene advice and consider cognitive–behavioral measures (see Table 232–3). If necessary, add a course of pharmacologic therapy (as noted above); if refractory, consider referral for formal cognitive–behavioral therapy.
- Continue cognitive–behavioral measures and attempt to stop hypnotics by 4 weeks; note that the continued use of medication may impair nonpharmacologic measures.
- If longer-term pharmacotherapy appears necessary, consider a benzodiazepine receptor agonist, but be aware that data are limited on safety and efficacy beyond 6 months of use, and chronic use may limit the long-term benefits of cognitive–behavioral therapy.

PATIENT EDUCATION

As noted earlier, instructing patients in key behavioral elements of good sleep hygiene represents an important component of patient education. Other elements of the educational effort include advice to avoid trying too hard to fall asleep and reassurance that one does not need to have 8 hours of sleep every night to have effective rest, an especially important point for elderly persons without daytime tiredness who experience normal aging-related changes in sleep pattern. Informing patients that much of the time they spend in bed believing they are “only drowsy” is time actually spent in the lighter stages of sleep can help ameliorate frustration. Advising the elderly about the normal changes in sleep pattern can be very reassuring.

INDICATIONS FOR REFERRAL

Referral is indicated for persons with comorbid psychopathology unresponsive to basic treatment measures, including those with substance abuse problems, which preclude use of many hypnotic agents. Those inadequately responsive to basic educational and behavioral measures, yet eager to focus on nonpharmacologic approaches, might welcome referral, if available, to a specifically trained therapist for formal cognitive–behavioral therapy.
For chronic primary insomnia in the elderly, consider a trial of very-low-dose doxepin (3 to 6 mg at bedtime) to monitor for cardiac arrhythmias, QTc interval changes, and anticho- linerergic side effects (unusual at these low doses); avoid use of most other antidepressants for treatment unless there is underlying depression (see below).

Monitor carefully for efficacy, side effects (especially in the elderly), and the development of tolerance (particularly with benzodiazepine use).

In the absence of clear-cut benefit or if there are concerns for patient safety, halt pharmacologic therapy and substitute a comprehensive program of environmental and behavioral measures.

For Patients with Comorbid Conditions

- **Depression.** For patients with depression who experience depression-induced early-morning awakening or other insomnia symptoms:
  - Begin an SSRI, such as paroxetine 20 mg or citalopram 20 mg, taken 1 hour before bedtime every night for 2 weeks; see the patient frequently until symptoms resolve and increase the dose as needed to fully treat the depression (see Chapter 227).
  - Monitor electrocardiographic QTc interval in patients greater than 65 years of age or with evidence of cardiac conduction system dysfunction. If QTc interval prolongation is a concern, consider sertraline an alternative SSRI (starting dose 25 to 50 mg/d).
  - Note that insomnia may persist even after mood symptoms resolve. Ensure that insomnia does resolve, as doing so greatly improves outcomes for depression and reduces the rate of relapse and recurrence.

- **Anxiety Disorder.** Begin treatment with a hypnotic:
  - If the insomnia is related to an anxiety disorder, use a benzodiazepine receptor agonist (e.g., zolpidem [Ambien, 5 to 10 mg at bedtime] or eszopiclone [Lunesta, 1 mg at bedtime]) or a short-acting benzodiazepine (e.g., lorazepam, 1 mg at bedtime).
  - If the patient has a chronic anxiety disorder or is bothered by persistent anxiety, clonazepam (0.5 mg) at bedtime may be helpful (see Chapter 226).

- **Pain and Other Underlying Medical Problems**
  - If insomnia is due to pain, menopausal hot flashes, or an underlying medical problem, treat specifically (e.g., see Chapters 237, 118), especially if interfering with quality of life.
  - Supplement treatment if necessary with a short course of a benzodiazepine receptor agonist or a benzodiazepine agent to help reestablish a normal sleep pattern.

- **Substance Abuse**
  - Obtain a complete history of alcohol and substance use in every patient, checking also for tobacco use, caffeine intake, nonprescription drugs, and stimulants.
  - Do not prescribe a benzodiazepine in patients with current or past alcohol or drug use problems.
  - Consider referral for cognitive–behavioral therapy or begin in the primary care practice a combination of patient education and simple behavioral measures; supplemented if necessary by a nonbenzodiazepine agent such as trazodone, nortriptyline, buspirone, or ramelteon. Attend to the underlying substance abuse problem (see Chapters 228 and 235).

## ANNOTATED BIBLIOGRAPHY

2. Brzozinski A. Melatonin in humans. N Engl J Med 1997;336:186. (A comprehensive review; includes a basic science review of melatonin’s contribution to sleep and the pharmacology of oral use.)
7. Ohayon MM. Severe hot flashes are associated with chronic insomnia. Arch Intern Med 2006;166:1262. (A cohort study; the prevalence of insomnia increased markedly with the presence of hot flashes.)
9. Thase ME. Correlates and consequences of chronic insomnia. Gen Hosp Psychiatry 2005;27:100. (Finds that the treatment of insomnia can have a beneficial effect on the outcome of concurrent illness.)
12. Berry SD, Lee Y, Cai S, et al. Nonbenzodiazepine sleep medication use and hip fractures in nursing home residents. JAMA Intern Med 2011;171:754. (Gait-modifying study, significant increase in fall and fracture risk in this frail elderly population.)
22. Lack LC, Wright HR. Clinical management of delayed sleep phase disorder. Behav Sleep Med 2007;5:57. (Evidence of modest efficacy.)
PATHOPHYSIOLOGY AND CLINICAL PRESENTATION (1,2)

The pathogenesis of the condition is unknown. Both hereditary and seemingly acquired forms exist, with the hereditary form manifesting onset typically before the age of 40 years, whereas those without a family history are more likely to begin experiencing symptoms after age 50 years. Purported etiologic factors include small-fiber neuropathy, dialysis, iron and folate deficiencies, and pregnancy; cigarette smoking, obesity, and sedentary lifestyle have also been implicated. Working hypotheses regarding pathophysiologic processes may include abnormalities in the subcortical brain regarding iron, dopaminergic transmission, and circadian rhythms. Thus, with resultant loss of cortical and spinal inhibition of motor activity that occurs mostly at night. The clinical presentation is likely to be dominated by complaints of difficulty sleeping, with symptoms of restless leg being reported in the context of an inquiry into causes. The principal clinical manifestations of restless legs syndrome are encompassed by its definition (see prior discussion). Getting up and walking about can provide sustained relief, but with resumption of inactivity, symptoms may recur. With progression, the uncomfortable leg sensations develop earlier in the day and become increasingly severe at night. Involuntary jerking movements may be reported by the patient, and spouse or family members may note quasirhythmic limb movements during sleep (so-called periodic limb movements).

DIFFERENTIAL DIAGNOSIS AND WORKUP (2,4)

Restless legs syndrome needs to be distinguished from nocturnal leg cramps, which cause frank calf pain and a knot in the muscle, relieved by stretching. Paresthesias from prolonged sitting and akathisia in persons with peripheral neuropathy may worsen with sitting and mimic restless legs syndrome; however, symptoms occur only with prolonged sitting, and there are no symptoms on lying down. In persons with periodic leg movements with sleep, other etiologies need to be considered, including sleep apnea, use of neuroleptics and antidepressants, spinal cord lesions, stroke, narcolepsy, and neurodegenerative disease. Because patients often present complaining of difficulty sleeping and not symptoms of restless legs syndrome, it is important to inquire about the condition as part of the workup for insomnia (see prior discussion). Diagnosis is clinical, based on a careful history addressing the four cardinal features that define the condition. The drug history should be reviewed for medications that may affect dopaminergic transmission (e.g., antidepressants, neuroleptics, some calcium channel blockers). There are no diagnostic physical findings. A suggestive electromyogram pattern exists, but such testing is rarely necessary. Checking serum chemistries for purported contributing factors (e.g., creatinine, ferritin, folate) is reasonable.

TREATMENT (2–4)

In many instances, symptoms are mild and sufficiently self-limited to require no treatment, but if sleep and quality of life are significantly compromised, then treatment is indicated. In those instances where a purported etiologic factor is identified (e.g., iron deficiency), treatment should be directed at correcting it (see Chapter 82); however, nonspecific administration of iron does not appear to be helpful.

Nonpharmacologic Measures

A host of nonpharmacologic measures can be helpful and include the following:

- Reducing or eliminating stimulants and depressants (nicotine, alcohol, caffeine)
- Curtailing as much as possible potentially contributing medications, especially antihistamines, dopamine blockers (e.g., neuroleptics, anxiolytics, metoclopramide), and antidepressants (both SSRIs and tricyclic antidepressants)
- Encouraging good sleep hygiene measures (regular hours, avoiding perturbing activities before bed)
- Advising regular moderate exercise, including a trial of a brief walk before bed
- Messaging of limbs and hot bath or shower

Pharmacologic Measures

Pharmacologic therapy should only be considered when non-drug measures prove insufficient and symptoms are disruptive of sleep and impairing quality of life. Pharmacologic approaches are tailored to whether the patient experiences disruptive symptoms only occasionally (in which case a short-acting, rapid-onset agent is preferred) or has daily difficulties, necessitating longer-acting therapy. When symptoms are clearly related to a precipitant, treatment may be anticipatory if the precipitant cannot be avoided. Available agents include dopaminergic drugs, mild-to-moderate-strength opioids, benzodiazepines, and benzodiazepine receptor agonists. Optimal therapy is yet to be devised.
Dopaminergic Agents

These are among the best studied for use in persons with nightly, disrupting symptoms. Efficacy is high (approaching 90% to 100%) for both restless leg and period movement. The nonergot dopaminergic agents are preferred because they have none of the heart valve and fibrotic concerns of ergot-derived dopamine ago-

nist. The two FDA-approved medications for restless legs syn-
drome in this class are pramipexole (Mirapex, starting at 0.125 mg, 2 to 3 hours before bed), the best studied, and ropinirole (Requip, starting at 0.25 mg, 1 to 2 hours before bed). (Levodopa had been used, but is shorter acting and associated with a high frequency of a paradoxical worsening of symptoms.) Although effective, these agents have a high rate of discontinuation (up to 25%) not only for inadequate response or bothersome side effects (e.g., nausea, dizziness, fatigue, hypersonnia, or insomnia) but also because of augmentation and impulse control disorders.

Augmentation of Symptoms. This adverse effect was first noted with continued use of levodopa (in up to 80%). It is charac-
terized by onset of symptoms earlier in the day, greater severity, spread to upper extremities and trunk, and reduced response to taking the medication. The risk of augmentation increases with duration of therapy, reported in 20% of persons taking pramipexole after 1 year and in 30% after 2 years; milder degrees are seen in up to 50%. Similar rates are found with ropinirole use. Treatment of this complication involves use earlier in the day, splitting the dose, or adding a second dose. Failure to respond to such measures requires termination of treatment. Of note, an acute withdrawal syndrome (severe leg restlessness for a few days) is associated with sudden cessation of treatment.

Impulse Control Disorders. Compulsive shopping, gambling, eating, and hypersexuality have been reported in 7% to 17% of persons taking these dopaminergic agents for restless legs syn-
drome. These adverse effects can be severe enough to be socially destructive. Risk factors include higher doses, younger age, and perhaps genetic factors, but such effects have been seen even at low doses. The mechanism is believed to involve excessive dopaminergic stimulation of the ventral striatum of the brain.

Opiates, Anticonvulsants, Benzodiazepines, and Benzodiazepine Receptor Agonists

Opiates (e.g., oxycodone, 5 mg at bedtime) are sometimes used as second-line agents in persons with incapacitating disease who fail dopamine agonist therapy, but dependence is a concern, and the evidence for efficacy is based mostly on clinical experience rather than controlled studies. One advantage over dopaminergic therapies is the absence of augmentation. Anticonvulsants (e.g., gabapentin, 300 mg at bedtime) represent another alternative; gabapentin was found in controlled trials to be equivalent to ropinirole in efficacy, but only for a subset of patients. Side effects limit use and include hypersomnia, daytime fatigue, dizziness, and gait instability. Pregabalin shows similar results when studied for restless legs syndrome. There is no augmentation with anticonvulsant use.

Benzodiazepines are helpful for occasional use, probably because of their ability to induce sleep. Clonazepam is the best studied, but morning sedation can be problematic. Long-term benzodiazepine use can lead to tolerance and dependency (see Chapter 226), though not to augmentation. Shorter-acting benzodiazepine receptor agonist preparations (e.g., zolpidem, 5 mg at bedtime) may be better tolerated, but amnestic reactions and other adverse effects associated with persistent use (see earlier discussion) also limit applicability as long-term therapy.

A.H.G.

ANNOTATED BIBLIOGRAPHY

1. Allen RP. Controversies and challenges in defining the etiology and patho-


3. Earley CJ, Silber MH. Restless legs syndrome: understanding its conse-

quences and the need for better treatment. Sleep Med 2011;11:807. (A state-
of-the-art review; finds current therapies lacking; 96 references.)


mary and review; source of many of the recommendations in this appendix; 44 references.)

Management of Obesity

Carolyn Crimmins Hintlian  W. Scott Butsch

Obesity has been a major health problem in industrialized soci-
eties and is becoming a global epidemic. In the United States, more than 69% of the population is overweight (body mass index [BMI] 25 to 29.9 kg/m²), 35% obese (BMI ≥30 kg/m²), and more than 6% severely obese (BMI ≥40 kg/m²). The health risk increases when weight gain results in moderate to severe obesity. Mortality rates (all-cause, cardiovascular, and cancer related) closely parallel increases in the BMI once levels of obe-
sity are reached.

Although often viewed as largely a behavioral problem, obesity is becoming better understood as a chronic heterogeneous disease with a more complex pathophysiology than previously appreci-
ated. Often resistant to treatment, the condition results from a failure of normal weight and energy regulatory mechanisms, necessitating a multifaceted approach to management. Weight loss is not a cure, but a goal. The degree of weight loss necessary to achieve many of its associated health benefits can be surpris-
ingly modest, putting the goal within the reach of most persons. Patient requests for advice and medication are best responded to with a comprehensive assessment (see Chapter 10) and an indivi-
dualized program that takes into account the patient's overall health status, as well as precipitants, preferences, and lifestyle.

The effective management of obesity starts with a careful workup of the medical and psychosocial dimensions of the problem (see Chapter 10), including a determination of cardio-

vascular risk (e.g., see Chapter 18). Treating etiologically and attending to concurrent obesity-related medical condi-
tions (e.g., hypertension, hypercholesterolemia, sleep apnea, diabetes, osteoarthritis) are essential (see Chapters 26, 27, 46, 102, and 157).

The goal is to achieve the best weight possible in the context of overall health. With product and procedure claims constantly bombarding persons with weight problems, patients appreciate an evidence-based approach to weight loss that is tailored to
their needs. Knowing the rationale, safety, and effectiveness of available treatment modalities (including popular diets, pharmacotherapy, dietary supplements, endoluminal devices, and surgical approaches) is essential to the design of a safe and effective program. In addition, knowledge of available community resources is helpful in guiding patients to additional sources of support, education, and treatment.

PRINCIPLES OF MANAGEMENT

Goals, Strategy, and Patient Selection (1–12)

Goals

Although modest from the patient’s perspective, a 5% to 10% reduction in weight is often sufficient to achieve many of the health-related benefits of weight loss (e.g., reduction in blood pressure, cholesterol, glucose intolerance, osteoarthritis complaints). This medically meaningful goal can be used as an initial target while recognizing that the request for help in losing weight may be part of a complex decision to make significant interpersonal, environmental, and lifestyle changes (see also “Patient Selection”).

Strategy

Because it is a chronic disease driven by a complex set of powerful and often incompletely understood etiologic factors, obesity management requires a comprehensive, multidimensional approach and continuous effort that includes a lifelong commitment to lifestyle and behavioral changes. Addressing barriers to weight loss and designing a program that matches the complexity of the patient’s weight problem constitute key strategic elements.

Addressing Adaption to Weight Loss. Powerful counterregulatory systems defend against body weight loss, making the process of weight loss and maintenance at a lower weight difficult. Not only is there a disproportionate reduction in energy expenditure with weight loss (metabolic adaptation), there is also hormonal compensation. Levels of leptin and anorexigenic hormones (e.g., peptide YY, amylin, and cholecystokinin) decrease, and the levels of the orexigenic hormone ghrelin increase (see Chapter 10). These hormonal changes are associated with an increased urge to eat and overall hunger. Given this physiologic response, it is not surprising that no single measure or particular approach is effective for all persons. There are few predictors of how well a particular intervention may work; however, treatment plans should match the complexity of the individual’s obesity.

Matching Treatment with the Complexity of the Patient’s Obesity. Despite the variability in response to specific interventions, a few recommendations emerge from consensus panels regarding overall strategy:

1. For those not ready to lose weight, the best approach is to educate them about health risks, address other cardiovascular risk factors, and encourage the maintenance of their current weight through healthy lifestyle changes. Weight status does not necessarily reflect health status.

2. For motivated persons, be they overweight (BMI 25 to 29.9 kg/m²) and having at least one obesity-related medical condition, or obese (BMI ≥30 kg/m²), a stepwise approach to weight loss, including more intense lifestyle interventions, can be initiated. The aggressiveness of therapy can be determined by the extent and severity of the weight-related comorbidities, psychosocial and functional limitations, and overall quality of life. Time limits, for example, 6 months, may be set to reach 5% to 10% body weight loss with the understanding of patient–patient variation. Special attention should be given to specific factors contributing to increased body weight, for example, diet, exercise, sleep, and stress. A more targeted approach may center only in one area, for example, poor sleep behaviors if there is a particular strong contribution to increased body weight. Depending on the area of lifestyle modification addressed, referrals to a diettian, psychologist, social worker, exercise trainer, or sleep specialist, for example, may be necessary. If there is no response to the above lifestyle intervention and a continued weight plateau, one can consider adding pharmacologic therapy (see later discussion).

3. For persons with severe obesity who are at greatest risk (BMI ≥35 kg/m² with two or more obesity-related medical conditions or BMI ≥40 kg/m²), a more aggressive approach, including management of comorbidities and consideration of both pharmacologic and surgical weight-loss options, should be considered. A surgical approach may be entertained if repeated attempts using the foregoing measures have been unsuccessful.

One proposed method of assessing obesity-related risks and guiding treatment is the Edmonton obesity staging system. It predicts mortality independent of BMI, focusing on weight-related comorbidities rather than BMI alone. For example, if an individual with obesity does not have weight-related comorbidities and no psychopathology and functional limitations, prevention of further weight gain, and not weight loss, is encouraged. Further validation and refinement are needed before use in clinical care.

Patient Selection

In most instances, self-selection will determine who undergoes a comprehensive weight-loss program because behavioral change is required. Nonetheless, physician input can play an important motivating role in the question of who should be encouraged most to undergo an intensive program of weight reduction.

One should understand that obesity does not present uniformly across populations and therefore should be treated on an individual basis. Physicians should first assess motivation and individual risks. One suggested approach is to identify persons at greatest health risk, namely, those with signs and symptoms of insulin resistance and the metabolic syndrome. Such persons are at particularly high risk for adverse cardiovascular events, but prognosis, as noted earlier, can be greatly improved through modest weight reduction (on the order of 5% to 10%).

Cardiovascular risk stratification helps identify such persons and is best carried out using a validated risk assessment tool such as the Framingham Score (see Chapter 18), which utilizes independent risk factors such as blood pressure, fasting lipid profile, presence of diabetes, and smoking to determine cardiovascular risk. Complementing this determination is waist circumference, a measure of abdominal fat content. A waist circumference of greater than 35 inches in women and 40 inches in men raises cardiovascular risk.

Other determinants of overall risk include weight-related complications such as obstructive sleep apnea, fatty liver disease, and severe gastroesophageal reflux increase overall risk and help determine treatment options. Not to be overlooked are quality-of-life complications such as osteoarthritis of weight-bearing joints, marked venous insufficiency, and psychosocial dysfunction.

Dietary Approaches (10–34)

“Going on a diet” is the typical first step in weight reduction, but the word “diet” implies that one is making only a temporary change in one’s eating habits and patterns. Patients need to understand that the most effective diet is not a “diet” at all but rather an individualized weight management program that
focuses on the implementation of gradual, permanent lifestyle change. The emphasis is on more modular approaches focusing not only eating habits but also exercise, sleep duration, and stress reduction techniques that can be followed for a lifetime. The plethora of available and often contradictory diets heavily promoted for their supposed special advantages are only as good in the long run as their degree of caloric restriction and palatability encouraging adherence. The approach to the patient with obesity needs to be a stepwise care plan with lifestyle modification. Durable weight loss is difficult, and its maintenance requires a strong support system and a program of regular exercise. Some of the most firmly held beliefs promoted in the popular media about weight loss are actually myths and unproven assumptions. For example, the belief that slow gradual weight loss is best for long-term success is contradicted by evidence that very-low-calorie diets result in greater, more durable weight loss. Another myth is that small changes in food intake and/or exercise will produce substantial, continuous weight changes. While small changes may help initially, energy requirements change as body mass changes over time, so, as weight is lost, it takes more exercise and reduced intake to perpetuate the loss.

**Determining Daily Caloric Intake**

It is easy to gain weight from a very small imbalance in the number of calories consumed over calories used. The desired daily caloric intake needs to be determined. The traditional rule of thumb—reducing dietary caloric intake by 500 to 1,000 kcal/d can produce a loss of about 1 lb/wk—has been superseded by a more realistic model of caloric intake and expenditure, where a reduction of 250 kcal/d can lead to a weight loss of about 25 lb over 3 years, with half occurring the 1st year. Individuals with obesity burn their calories less efficiently and likely have to cut more than 500 kcal/d to lose weight.

Predictive equations are used in clinical practice to estimate energy needs. Web-based programs are available (see Table 233–1). The Mifflin-St. Jeor equation provides the best estimate of resting metabolic rate to within 10% of that measured.

**Dietary Composition.** All weight reduction programs should be nutritionally adequate—for example, and include a balanced diet. Most fad diets are neither nutritionally sound nor based on proven scientific evidence. Extravagant claims that a particular food or class of foods dramatically alters weight, appetite, or calorigenesis are unfounded.

The cornerstones of efficacy and safety are a reduction in calories and nutritional balance. Nutrient content and the timing and number of meals and snacks are important determinants for short-term and long-term appetite control. Limiting calories is critical to decreasing body fat and maintaining weight loss.

When following a hypocaloric dietary regimen, the patient must realize that initial rapid weight loss may occur because of a negative fluid balance. After 2 to 3 weeks, the rate of weight loss slows down. Most subsequent loss reflects the catabolism of fat. Loss of fat is directly proportional to the size and duration of the energy deficit. Patients often become discouraged when they enter the slower phase. Most adjust to caloric restriction by unknowingly diminishing their expenditure of energy, one reason an exercise program is such an important adjunct (see later discussion).

**Counseling and Medical Nutrition Therapy by the Dietitian**

Customizing the weight-loss program to the individual needs of the patient and arranging for follow-up are important to sustaining behavioral change. *Nutrition counseling* is an essential step in the educational process. It begins with the physician's endorsement (an essential component that is often overlooked). Patients need to recognize their lifestyle patterns and achieve a basic understanding of the caloric and nutritional contents of foods to be able to choose intelligently. Successful weight loss goes beyond diet choice. Factors like eating behavior, support, and exercise are critical to long-term success. The patient also must also be presented with an approach that focuses on the connections relating body, brain, and appetite. Factors that control appetite include emotionally satisfying food, stress, and exercise.

An essential component of comprehensive management is to have registered dietitians (RDs) provide intensive behavioral counseling for obesity through medical nutrition therapy (MNT). An MNT intervention includes counseling on behavioral and lifestyle changes required to impact caloric eating habits and health. The services of an RD can be beneficial because such persons are specifically trained in assessing nutritional requirements and counseling food selection and preparation. The nutritionist can also review appetite-influencing factors such as exercise and the use of food for emotional satisfaction and stress management. Helping to assess and change attitudes and behaviors toward food and eating are important objectives.

The assessment integrates medical concerns with the patient's individual and family lifestyle, economic status, learning ability, and psychological needs. An individualized weight control plan is constructed to address specific needs and food preferences. Dietary changes must be gradually implemented to ensure lifelong positive eating habits. Nutrition counseling is likely to increase patient adherence to a dietary regimen and improve outcome.

Beneficiaries who receive such nutrition counseling and interventions exhibit significant improvements in weight and restructured behaviors that impact long-term weight management. Studies show MNT provided by an RD to overweight and obese adults for less than 6 months yields significant weight losses of approximately 1 to 2 lb/wk. MNT provided from 6 to 12 months yields significant mean weight losses of up to 10% of body weight with maintenance of this weight beyond 1 year.

Participation in weight-loss programs with good adherence is the strongest predictor of weight loss. This includes enhanced lifestyle counseling techniques such as the frequency of meetings (can be in person or remote), food records, the inclusion of exercise, diabetes, and calorie recommendations.

**Self-Directed and Commercial Weight-Loss Programs**

Many commercial and self-directed weight-loss programs are available (see Table 233–1); weight-loss books are constant best sellers reflecting the demand for weight loss. Some commercial and self-directed programs provide menus and a line of foods or supplements to buy; others include individual or group support. Advances in technology have introduced many enhanced lifestyle counseling interventions by telephone, Internet, and e-mail. The use of mobile technologies to deliver behavioral weight-loss treatment appears to be promising. Regarding Internet-based diet programs, interventions appear to be more effective when they include interaction with a health professional (e.g., via e-mail) rather than being limited to Web sites at which patients access information.

Integrated approaches provided over the long term with frequent health care professional contacts and a program that includes moderate diet modification, an exercise program, and a behavioral approach are more effective, especially for mildly to moderately overweight persons. Noncommercial, community-based programs offer a low-cost alternative for those who seek the assistance of group support; however, in many instances, little professional guidance is provided. Group therapy has been shown to produce greater weight loss than individual therapy, even among clients who prefer individual therapy. Compliance remains a key determinant of success, and attendance at group meetings is critical to compliance.
TABLE 233–1 Selected Online Weight Management Programs

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<tr>
<th>Program</th>
<th>Web Site</th>
<th>Program Features</th>
<th>Cost</th>
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<tbody>
<tr>
<td>Online Food and Activity Tools</td>
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<tr>
<td>Calories Count</td>
<td><a href="http://www.caloriescount.com">www.caloriescount.com</a></td>
<td>■ Associated with the Calorie Control Council</td>
<td>Free</td>
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<tr>
<td>Lose It!</td>
<td><a href="http://www.loseit.com">www.loseit.com</a></td>
<td>■ Meal plans, fitness plans, recipes, community boards available</td>
<td>Free</td>
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<td>■ Smartphone app with Web site sync</td>
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<td>■ Provides calorie tracking with comprehensive database of foods and activities</td>
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<td></td>
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<td>■ Peer support</td>
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<td></td>
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<td>■ Bar code scanner</td>
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<tr>
<td>MyFitnessPal</td>
<td><a href="http://www.fitnesspal.com">www.fitnesspal.com</a></td>
<td>■ Smartphone app and Web site sync</td>
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<td></td>
<td></td>
<td>■ Tracks calories and exercise</td>
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<td></td>
<td></td>
<td>■ Bar code scanner and the ability to retrieve meals and dishes that are frequently eaten</td>
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<tr>
<td>SuperTracker</td>
<td><a href="http://www.choosemyplate.gov">www.choosemyplate.gov</a></td>
<td>■ Online tool available at the USDA's ChooseMyPlate.gov</td>
<td>Free</td>
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<td></td>
<td></td>
<td>■ Can help plan, analyze, and track diet and physical activity</td>
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<td>■ Provides personalized features such as goal setting, virtual coaching, and writing daily journals.</td>
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<td>Dietary intake compared to USDA dietary guidelines</td>
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<tr>
<td>FitDay</td>
<td><a href="http://www.fitday.com">www.fitday.com</a></td>
<td>■ Daily recording of intake and provides long-term analysis of how individual's diet is progressing</td>
<td>Free for tracking</td>
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<tr>
<td></td>
<td></td>
<td>■ FitDay dietitian: provides nutrition counseling via e-mail from an RD</td>
<td>$60/mo</td>
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<tr>
<td>Online Weight-Loss Programs</td>
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<tr>
<td>Diet.com</td>
<td><a href="http://www.diet.com">www.diet.com</a></td>
<td>■ Extensive introductory questionnaire to determine type of menu recommendations and content</td>
<td>Free to join</td>
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<td></td>
<td></td>
<td>■ Active online community</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Easy access to staff doctor</td>
<td></td>
</tr>
<tr>
<td>Retrofit</td>
<td><a href="http://www.retrofitme.com">www.retrofitme.com</a></td>
<td>■ Personalized weekly online appointments with health experts</td>
<td>Starts at $238/mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Including an RD, exercise physiologist, and behavior coach</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>■ Utilizes technology—wireless activity tracker</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Automatic data collection and reporting</td>
<td></td>
</tr>
<tr>
<td>SparkPeople</td>
<td><a href="http://www.sparkpeople.com">www.sparkpeople.com</a></td>
<td>■ Targeted e-mails to engage member through changes</td>
<td>Free</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Very customizable meal plans</td>
<td></td>
</tr>
<tr>
<td>Weight Watchers</td>
<td><a href="http://www.weightwatchers.com">www.weightwatchers.com</a></td>
<td>■ Active online community</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Oldest national weight-loss program</td>
<td>$30 sign up fee</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Online support provided</td>
<td>$13–15/wk</td>
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<tr>
<td></td>
<td></td>
<td>■ Group meetings provide emotional support.</td>
<td>Online – $19/mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Combination of using online tools with the benefit of attending dietitian-led meetings</td>
<td></td>
</tr>
<tr>
<td>Commercial Programs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medically Supervised VLCD Programs</td>
<td><a href="http://www.hmrprogram.com">www.hmrprogram.com</a></td>
<td>■ HMR prepackaged meal replacements (full low-calorie meals, oatmeal, soups, shakes, bars)</td>
<td>$25/weekly class</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Intensive lifestyle education, personalized attention and follow-up, and a strong emphasis on long-term health and weight maintenance</td>
<td>$77–$100/wk for product depending on plan</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Medical supervision through affiliated physicians</td>
<td></td>
</tr>
<tr>
<td>Medifast</td>
<td><a href="http://www.medifast1.com">www.medifast1.com</a></td>
<td>■ Structured meal plans suggested—5 Medifast meals/day</td>
<td>No sign up fee</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Allows one home-cooked meal per day</td>
<td>$78/wk for product</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Online support provided</td>
<td></td>
</tr>
<tr>
<td>Optifast</td>
<td><a href="http://www.optifast.com">www.optifast.com</a></td>
<td>■ Optifast prepackaged products (bars, shakes, or soups)</td>
<td>$125–210/wk for product</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Has full liquid or partial liquid diet plan</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>■ Medical monitoring required</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Distributed through weight-loss clinics</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Often suggested prior to bariatric surgery</td>
<td></td>
</tr>
<tr>
<td>Diet Programs with Meal Items</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slimfast</td>
<td><a href="http://www.slimfast.com">www.slimfast.com</a></td>
<td>■ Option to use as meal replacement</td>
<td>Purchase online or available in stores.</td>
</tr>
<tr>
<td>Jenny Craig</td>
<td><a href="http://www.jennycraig.com">www.jennycraig.com</a></td>
<td>■ Meal-delivery service of prepacked food</td>
<td>$30/mo plus weekly food costs $90–170</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ E-tools enhance face-to-face and phone consults with in-house trained counselors</td>
<td></td>
</tr>
<tr>
<td>Nutrisystem</td>
<td><a href="http://www.nutrisystem.com">www.nutrisystem.com</a></td>
<td>■ Meal-delivery service of prepacked food</td>
<td>$239.99–$289.99/mo plus shipping</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Support is available through phone counseling, weekly e-classes with a dietitian, and tracking tools.</td>
<td></td>
</tr>
</tbody>
</table>

*VLCD, very-low-calorie diet.
Dietary Approaches for Weight Management

As noted, there are a host of dietary approaches, differing in composition but sharing the common denominator of a reduction in total calories, the essential determinant of weight loss.

Low-Fat Diet. A low-fat reduced energy diet is a well-studied weight-loss dietary strategy. It derives from early dietary programs for hypercholesterolemia to reduce coronary heart disease risk. These programs limit total fat, saturated fat, partially hydrogenated unsaturated fatty acids, and dietary cholesterol. They are based on the observation that saturated fat and partially hydrogenated unsaturated fatty acids are major contributors to the production of low-density-lipoprotein cholesterol, with a lesser contribution from dietary cholesterol. Advances in understanding the cardiovascularly beneficial effects of essential poly- and monounsaturates have led to a better appreciation for the importance of fat composition rather than just total fat content of the diet (see Chapter 27).

Low-Carbohydrate Diet. Taking a truly low-carbohydrate diet high in protein (total daily carbohydrate intake as low as 20 g/d) leads to increased ketone production, which was hypothesized decades ago by Atkins to decrease hunger and increase satiety, the rationale he invoked for his popular diets. More recently, the atherogenic potential and caloric pitfalls of diets rich in the so-called “low-fat” foods and excess carbohydrate intake have rekindled interest in low-carbohydrate diets. As glycogen stores are depleted in response to low carbohydrate intake, the resultant diuresis produces an initial dramatic weight loss. Having patients focus on reducing carbohydrates rather than reducing calories may be a successful short-term strategy for some individuals. Markedly reducing carbohydrate intake (<35% of calories from carbohydrates) certainly results in reduced energy intake, the sine qua non requirement of weight reduction. Low-carbohydrate diets can lead to slightly more short-term weight loss than just cutting fat and calories; however, such diets are very hard to sustain. Benefit wanes after 6 months, and most people regain lost weight after time. Concern about the high-fat content of some iterations of this diet has led to examinations of its effects on coronary risk factors (see Chapter 27).

Meal Replacements. For people who have difficulty with self-selection and/or portion control, meal replacements (e.g., liquid meals, meal bars, or calorie-controlled packaged meals) may be used as part of the diet component of a comprehensive weight management program. Substituting one or two daily meals or snacks with meal replacements has been shown to be a successful weight-loss and weight maintenance strategy. They work simply because they limit the number of calories eaten at a meal. Meal replacements also add structure to a person’s eating habits. Structure seems to help some people to stick with a weight management plan. In addition, less time is spent thinking about preparing and eating food.

Very-Low-Calorie Diets. Very-low-calorie diets are considered for use in persons with a BMI greater than 30 kg/m^2 who require major weight loss. These medically supervised diets severely limit calories to between 500 and 800 per day. They consist of 1.5 g of protein/kg of body weight per day and are generally offered as a liquid or partial liquid diet as part of a commercial program (see Table 233–1). Protein-sparing modified fasts, consisting of a protein in the form of lean meat, fish, or fowl, are less commonly prescribed. Very-low-calorie diets achieve rapid weight reduction with preservation of lean body mass. Patients can achieve 15% to 25% weight loss within 3 to 4 months and then, if reinitiated as solid foods with a higher calorie content. Weight regain, up to 40% to 50% of the lost weight after 1 to 2 years, may occur, especially in absence of close supervision.

The very-low-calorie diet is not recommended for children, adolescents, pregnant or lactating women, or the elderly. It should be avoided in individuals who are overweight and those with type 1 diabetes, pancreatitis, severe renal or hepatic impairment, active cancer, or a severe psychological disturbance. Cetion should be used in those with cardiovascular disease, especially congestive heart failure, and those who require chronic steroids. High dropout rates and poor long-term maintenance are discouraging aspects of this form of treatment.

Diets for Maintenance of Weight Loss

Once weight loss is achieved, attention needs to focus on maintenance of weight loss. A combination of diet and exercise appears to be most effective. Among dietary measures, randomized controlled study finds a dietary program of modest increase in protein content and a modest reduction in glycemic index achieves the best results with regard to compliance and weight, when compared with a low-protein/low-glycemic diet, a low-protein/high-glycemic diet, a high-protein/high-glycemic diet, or a control diet.

Behavioral Treatment (29–35)

The aim of the behavioral approach is to develop alternative eating behaviors that are practical and lead to a decreased caloric intake and increase physical activity. Strong evidence exists to support the use of a combination of behavioral theory and cognitive–behavioral theory in facilitating modification of habits.

Key features of behavioral therapy and cognitive–behavioral therapy programs include the following:

- **Describing the behavior to be controlled (self-monitoring).** Patients are instructed to keep detailed records of all eating behaviors, including specific portion sizes, time and place of eating, stimuli preceding eating that the patient is aware of, and a description of surroundings. Patients are encouraged to weigh themselves weekly.
- **Modifying and controlling stimuli.** Behavioral change around food choices and food preparation, in addition to visual cues, is addressed. Meal-replacement and partial–meal-replacement programs and structured meal plans have been studied and found to be effective as a form of stimulus control.
- **Mindful eating.** Studies have shown increasing awareness and having structured eating habits is helpful in losing weight. Examples include smaller portions, slower-paced eating, and structured meal plans.
- **Promptly reinforcing behaviors that delay and control eating.** Patients are advised to eat only in one room (cue elimination), have company while eating (cue supervision), develop methods of making diet food attractive (cue strengthening), arrange for positive feedback if they comply with exercise and diet programs. The patient is educated to focus on setting realistic goals for nutrition, weight, and physical activity. These goals are time limited, realistic, and moderately challenging.
- **Cognitive restructuring.** The patient is encouraged to transform negative, self-defeating thoughts into positive, beneficial thoughts that can help toward weight-loss success.
- **Motivational interviewing.** This patient-centered strategy is designed to elicit behavior change by assisting patients to explore and resolve ambivalence to change. Open-ended questions, reflective listening, affirmations, and summarization are used to help patient explore and resolve ambivalence and barriers to change. In addition, distracting activities such as watching television or reading while eating are discouraged. Eating behavior is made to be associated with highly specific stimuli.

Both individual and group behavioral programs are available; the average length of treatment is 18 weeks. The longer the duration of the program, the larger the effect, and the better the outcome.
Exercise (9,36–40—see also Chapter 18)

An exercise component should be part of every weight-loss program, not only for its effect on weight but also for its contribution to fitness. Fitness level strongly correlates with cardiovascular and all-cause mortality. While very beneficial, exercise alone without decreased caloric intake achieves only modest weight reduction; the combination enhances weight loss and preserves lean body mass. Exercise is essential to maintenance of weight loss as total energy expenditure and basal metabolic rate decrease with reduction in weight. Because the energy cost of most exercise is proportional to body weight, obese persons use more energy and burn more body fat for the same amount of activity than do persons of normal weight. Exercise may also benefit the dieter by increasing feelings of self-control, reducing stress, improving appearance, and alleviating depression. Regular physical activity appears to be one of the best predictors of successful weight maintenance.

The Exercise Prescription

The amount of exercise needed to decrease body fat is related to its type, duration, intensity, and frequency. For general health, at least 150 minutes a week of moderate-intensity physical activity or 75 minutes a week of vigorous activity is recommended. For weight loss and maintenance, 150 to 250 minutes a week of moderate-intensity physical activity serves as a good foundation for a weight-loss program, with more than 250 min/wk needed for continued weight loss. Incorporating informal exercise (e.g., parking farther away, taking the stairs, exercising while watching TV, taking activity breaks during work) can be beneficial. However, as seen with caloric reduction, there is great heterogeneity in weight change of individuals in response to exercise. Differences may be explained by the amount of dietary compensation with exercise-induced weight loss, particularly in lean phenotypes. A specific exercise prescription is essential. Both aerobic and anaerobic exercise can be prescribed. The physician’s role in the design and encouragement of the exercise prescription is essential. To ensure compliance, the program has to be physically realistic, medically safe, and capable of being incorporated into the patient’s daily routine (see Chapter 18 for details of the exercise prescription).

Pharmacologic Treatment (41–47) (Table 233–2)

Pharmacologic treatment of obesity has been plagued by an adverse safety profile, especially with prolonged use. The search for agents that are both safe and effective continues, and new agents are emerging as the pathophysiology of the condition becomes better understood. Pharmacotherapy deserves consideration for adults with a BMI greater than or equal to 27 kg/m² plus two or more obesity-related medical conditions or with a BMI greater than or equal to 30 kg/m² and an insufficient response to lifestyle and behavioral modifications. Before pharmacotherapy is initiated, weight stabilization should be achieved.

Choice of agent is based on efficacy, safety, and impact on both weight and other health consequences, the so-called double benefit. For example, the antidepressant bupropion may be chosen in a patient with obesity who is also depressed or is a smoker. Advances in understanding mechanisms of appetite control, energy expenditure, and nutrient sensing promise a host of new, more effective agents, but at the present the options are limited (see Table 233–2). Effectiveness of each agent is based on ability to achieve 3% to 5% weight loss after 3 months. A proposed guideline suggests using the “4 x rule”—losing four [4] lb per month for the first three [3] months, or 12 lb. Continuation of the agent is recommended only in those individuals who respond within the first 3 months; if this short-term goal is not met, discontinuation of the medication should be entertained. Long-term use is necessary for sustained effect in obesity; cessation of a drug is almost always met with weight regain. It is important to understand the heterogeneity among individuals seeking weight loss and that responses to pharmacologic agents vary. Although average weight loss with available agents is modest for the general population, there are a small number of high responders. These individuals are important to identify; persons who achieve short-term weight loss (at 3 months) are more likely to maintain weight loss at 1 year.

Adverse effects from these medications require consideration, especially when contemplating long-term use, as is often necessary. The decision to use weight-loss medication should be based on an assessment that benefit exceeds risk. Close monitoring is essential.

Sympathomimetics

Phentermine (Ionamin, Adipex-P) is one of several approved sympathomimetics, including diethylpropion (Tenuate), phendimetrazine (Bontril), and benzphetamine (Didrex), which are Food and Drug Administration (FDA) approved for short-term use and act to increase the levels of norepinephrine in the central nervous system. Phentermine is the most widely prescribed weight-loss medication. Only short-term (3-month) use is FDA approved, based on early clinical trials constructed on the past belief that obesity could be cured. Despite the approval only for short-term use, clinical experts often continue treatment in those who have an early therapeutic response. Although effective in suppressing appetite and achieving modest weight reduction, adrenergic stimulants can cause adverse cardiovascular side effects. Many agents in this class (e.g., ephedrine, phenylpropanolamine, and amphetamines) used for appetite suppression have been removed from the market because of either hypertensive crisis, arrhythmias, stroke, and sudden death or addiction potential. Phentermine was a component of the infamous “fen–phen” combination but was never implicated as a cause of cardiac valvular injury (see later discussion). Careful prescribing and monitoring are essential. Elevations in blood pressure and heart rate make these agents relatively contraindicated in persons with hypertension, coronary heart disease, and tachyarrhythmias (see Table 233–2). Persons with insomnia may experience worsening. Other bothersome side effects include dry mouth, nervousness, and constipation.

Selective Serotonin Agonist Therapy: Lorcaserin. After more than a decade since withdrawal from the market of the serotonin agonist fenfluramine due to its adverse effect on heart valves, the FDA approved the more selective serotonin agonist, lorcaserin (Belviq). This agent has a high affinity for serotonin 2c receptors found only in the central nervous system compared with 5-HT2B receptors affected by fenfluramine. Three placebo-controlled clinical trials have not reported an increased risk of valvulopathy or other adverse cardiovascular events. The drug was initially rejected due to concerns over an increase in mammary tumors in animals: however, this was associated with toxic 5-HT2B receptors found only in the central nervous system compared with both phentermine and orlistat. Caution should be used in patients with congestive heart failure and depression, in particular, those taking selective serotonin reuptake inhibitors, as there may be a small but significant risk of serotonin syndrome.

Inhibition of Fat Absorption: Orlistat. Orlistat (Xenical, Alli), FDA approved for use in obesity, binds to and blocks the topical activity of pancreatic and gastric lipases, inhibiting about 30% of intestinal dietary fat absorption. A randomized, double-blinded, placebo-controlled study lasting 3 years demonstrated modest weight loss (a 2.75-kg reduction in weight) along with...
<table>
<thead>
<tr>
<th>Generic Drug Name (Brand Name)</th>
<th>Example of Usual Doses</th>
<th>Interactions/Issues*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lorcaserin (Belviq)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective serotonin 2c receptor agonist</td>
<td>10 mg bid</td>
<td>10 mg bid</td>
<td>AE: HA, nasopharyngitis, URI, dizziness, fatigue, dry mouth</td>
</tr>
<tr>
<td><strong>Orlistat (Xenical, Alli)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipase inhibitor</td>
<td>120 mg qd</td>
<td>120 mg qd–120 mg tid</td>
<td>CAUTION in CHE, on SSRI</td>
</tr>
<tr>
<td><strong>Phentermine (Adipex-P, Ionamin)</strong></td>
<td>15 mg qd</td>
<td>15–30 mg qd</td>
<td>AE: tachycardia, HTN, dry mouth, insomnia</td>
</tr>
<tr>
<td>Sympathomimetic amine, increases NE, DA activity</td>
<td></td>
<td></td>
<td>Monitor fat-soluble vitamins (A, D, E, K).</td>
</tr>
<tr>
<td><strong>Phentermine + topiramate XR (Qsymia)</strong></td>
<td>3.75/23 mg qd</td>
<td>3.75/23–15/92 mg qd</td>
<td>AE: same as phentermine and topiramate</td>
</tr>
<tr>
<td>Sympathomimetic amine and GABA enhancer</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Bupropion (Wellbutrin)</strong></td>
<td></td>
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</tr>
<tr>
<td>Weak DA and NE reuptake inhibitor</td>
<td>150 mg qd</td>
<td>150–400 mg qd</td>
<td>AE: insomnia, anxiety, HA, diarrhea, dry mouth</td>
</tr>
<tr>
<td><strong>Exenatide (Byetta)</strong></td>
<td>5 µg bid</td>
<td>5–10 µg bid</td>
<td>AE: nausea, hypoglycemia pancreatitis</td>
</tr>
<tr>
<td><strong>Exenatide XR (Bydureon)</strong></td>
<td>2 mg/wk with exenatide XR</td>
<td></td>
<td>Injectable medications</td>
</tr>
<tr>
<td>Synthetic GLP1 analogues</td>
<td>0.6 mg qd</td>
<td>0.6–1.8 mg qd</td>
<td>Injectable medication</td>
</tr>
<tr>
<td><strong>Liraglutide (Victoza)</strong></td>
<td>500 mg qd</td>
<td>500–2,000 mg qd</td>
<td>Monitor serum insulin.</td>
</tr>
<tr>
<td>Acylated human GLP1 receptor agonist</td>
<td></td>
<td></td>
<td>Use in insulin resistance.</td>
</tr>
<tr>
<td><strong>Metformin (Glucophage, Glumetza)</strong></td>
<td>12.5 mg qd</td>
<td>12.5–50 mg qd</td>
<td>May be combined with bupropion</td>
</tr>
<tr>
<td>Insulin sensitizer, reduces hepatic glucose production</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Naltrexone (Revia)</strong></td>
<td>120 mg qd</td>
<td>120 mg qd–120 mg tid</td>
<td>AE: hypoglycemia, nausea, vomiting, HA</td>
</tr>
<tr>
<td>Opioid receptor antagonist</td>
<td>25 mg qd</td>
<td>25–200 mg qd</td>
<td>Take before meals.</td>
</tr>
<tr>
<td><strong>Pramlintide (Symlin)</strong></td>
<td>25 mg qd</td>
<td>25–200 mg qd</td>
<td>Monitor serum bicarbonate.</td>
</tr>
<tr>
<td>Synthetic amylin analogue</td>
<td>100 mg qd</td>
<td>100–400 mg qd</td>
<td>Synergistic combination with phentermine</td>
</tr>
<tr>
<td><strong>Topiramate (Topamax)</strong></td>
<td></td>
<td></td>
<td>Use in antipsychotic-induced weight gain.</td>
</tr>
<tr>
<td>Antiepileptic drug, enhances GABA receptor activity</td>
<td></td>
<td></td>
<td>Use in binge eating disorder.</td>
</tr>
<tr>
<td><strong>Zonisamide (Zonegran)</strong></td>
<td></td>
<td></td>
<td>Pregnancy category D</td>
</tr>
<tr>
<td>Antiepileptic drug, enhances 5-HT and DA activity</td>
<td></td>
<td></td>
<td>Monitor serum creatinine and bicarbonate.</td>
</tr>
</tbody>
</table>

*This is an incomplete list of all the AE (adverse effects) and CI (contraindications) of the medications.

†Alli is an over-the-counter form of orlistat, available in 60-mg doses.

Adipex-P is a tablet form available in 37.5 mg.

CV, cardiovascular; NE, norepinephrine; DA, dopamine; 5-HT, serotonin; GABA γ-amino butyric acid; GLP1, glucagonlike peptide-1; SSRI, selective serotonin reuptake inhibitors; HA, headache; URI, upper respiratory infection; MEN, multiple endocrine neoplasia; PCOS, polycystic ovarian syndrome; XR, extended release.
some improvements in lipid profile and insulin levels. However, about 80% of patients experience some adverse gastrointestinal effects from the ensuing malabsorption and maldigestion that takes place (e.g., abdominal cramping, bloating, oily and greasy stools, diarrhea). In addition, its high cost and malabsorption of both healthy fats (monounsaturated and polyunsaturated fats) and fat-soluble vitamins adds to its inferiority. As a result, fat-soluble supplementation may be necessary and should be taken 2 hours before or after orlistat.

Other Single-Agent Pharmacotherapy. Several medications approved for other indications have been shown in clinical trials to produce weight loss, making the potential for “double benefit” a consideration in its selection for use in obesity. Agents include anticonvulsants (topiramate and zonisamide), antidepressants (bupropion), antidiabetics (exenatide, liraglutide, pramlintide, and metformin), and an opioid receptor antagonist (naloxone).

Topiramate and zonisamide have been used effectively in patients with seizures and bipolar disorder, and topiramate has been helpful in treatment of migraines and binge eating disorder. Both metformin and topiramate can counter the weight gain associated with use of atypical antipsychotics; metformin appears to block the histamine H1 receptor-mediated appetite-stimulating effects. Bupropion may be chosen in a patient with obesity who is depressed or is a smoker. The double benefit of naltrexone monotherapy is less clear, but the agent has been used in patients already taking bupropion. Concern about effect on weight sometimes influences choice of an agent such as metformin, liraglutide, exenatide, or pramlintide (see Chapter 102).

Combination Preparations

Given the redundant physiologic pathways of energy regulation, it should not be surprising that single-agent pharmacotherapy for obesity is of only modest benefit and that combination pharmacotherapies with synergistic effects have been sought. The aims of combination therapy are to enhance effectiveness while limiting toxicity (through dose reduction). The addition of a second agent is often considered when monotherapy is met with weight stabilization.

Phentermine/Topiramate. Among currently approved obesity medications, the combination of phentermine and topiramate extended release (Qsymia, FDA approved for long-term use) has produced the best weight-loss effect in clinical trials. Subjects with an average BMI greater than 35 kg/m² demonstrate greater than 10% weight loss at 1 year with continued greater than 10% weight loss after 2 years. Contraindications (both relative and absolute) include unstable cardiac or cerebrovascular disease, seizures, arrhythmias, anxiety, hyperthryoidism, and glaucoma. Women who are pregnant should not be treated with this combination because of the risk of orofacial clefts in the fetus, and all women of childbearing should be cautioned to stop this medication well before becoming pregnant (see Table 233–2).

Others. Clinical trials combining bupropion–naltrexone and bupropion–zonisamide are ongoing, and results are awaited with interest.

Attention to Medications That Cause Weight Gain (Table 233–3)

The potential for some medications to cause weight gain should not be lost sight of in design of a comprehensive weight-loss program. Their identification and consideration of alternatives are important elements of program design.

Complementary/Alternative Medicine Therapies (48–53)

Complementary alternative medicine (CAM) therapies range from dietary supplements to mind–body approaches (meditation, hypnosis, yoga) and “energy medicine” techniques (acupuncture).

Dietary Supplements

Numerous dietary supplements have been promoted for use in weight loss; however, none have consistently demonstrated significant benefit over placebo. Common supplements can be grouped by purported mechanisms: increased energy expenditure

### TABLE 233–3 Common Medications That Cause Weight Gain

<table>
<thead>
<tr>
<th>Category and Drug</th>
<th>Alternative Drug Weight Neutral or Cause Less Weight Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticoagulant Agents</strong></td>
<td>Topiramate, zonisamide</td>
</tr>
<tr>
<td><strong>Valproic acid, vigabatrin, carbamazepine</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Antidepressant Agents</strong></td>
<td>Bupropion (substitute for SSRI)</td>
</tr>
<tr>
<td><strong>SSRIs: paroxetine, citalopram, fluoxetine, sertraline</strong></td>
<td>Desipramine (substitute for TCA)</td>
</tr>
<tr>
<td><strong>TCAs: amitriptyline, nortriptyline</strong></td>
<td>Translycypromine (substitute for MAOIs)</td>
</tr>
<tr>
<td><strong>MAOIs: phenelzine</strong></td>
<td>Nefazodone</td>
</tr>
<tr>
<td><strong>Other: mirtazapine, trazodone</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Antidiabetic Agents</strong></td>
<td>Metformin, exenatide, liraglutide, pramlintide, acarbose, sitagliptin, saxagliptin</td>
</tr>
<tr>
<td><strong>Sulfonylureas: glyburide, glipizide, glimepiride</strong></td>
<td></td>
</tr>
<tr>
<td><strong>TZDs: rosiglitazone, pioglitazone</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Insulin</strong></td>
<td>Loratadine</td>
</tr>
<tr>
<td><strong>Antihyperensive Agents</strong></td>
<td>ACE inhibitors, ARBs, calcium channel blockers</td>
</tr>
<tr>
<td><strong>β-Adrenergic blockers: propranolol, metoprolol</strong></td>
<td>Doxazosin</td>
</tr>
<tr>
<td><strong>α-Adrenergic blockers: clonidine, prazosin</strong></td>
<td>Ziprasidone</td>
</tr>
<tr>
<td><strong>Antipsychotic Agents</strong></td>
<td></td>
</tr>
<tr>
<td><strong>AAP: clozapine, olanzapine, quetiapine, risperidone, haloperidol, aripiprazole</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Migraine Prophylaxis Agents</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Propranolol, metoprolol</strong></td>
<td>Topiramate, verapamil</td>
</tr>
<tr>
<td><strong>Mood Stabilizing Agents</strong></td>
<td>Topiramate, lamotrigine</td>
</tr>
<tr>
<td><strong>Lithium</strong></td>
<td>Topiramate</td>
</tr>
<tr>
<td><strong>Pain Medications</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Gabapentin, pregabalin</strong></td>
<td>Naproxen, ibuprofen, acetaminophen</td>
</tr>
<tr>
<td><strong>Steroids</strong></td>
<td>Naproxen, ibuprofen, acetaminophen</td>
</tr>
<tr>
<td><strong>Prednisone, hydrocortisone, dexamethasone</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Depot medroxyprogesterone acetate</strong></td>
<td>Oral progestrone, intrauterine device</td>
</tr>
</tbody>
</table>

*Arranged in order from greatest to least weight gain. Bold italicized drugs have the greatest degree of weight gain. AAP, atypical antipsychotics; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; MAOI, monoamine oxidase inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; TZD, thiazolidinediones.*
(bitter orange, guarana), modulation of carbohydrate metabolism (chromium, ginseng), increased satiety (garlic, psyllium), inhibition of fat absorption (chitosan), and increased fat oxidation (green tea, 1-carnitine, hydroxycitric acid, conjugated linoleic acid).

Hydroxycitric acid is derived from the tamarind tropic fruit (Garcinia cambogia), native to India. It inhibits a citrate cleavage enzyme believed to play a role in lipogenesis and is claimed to lower body weight and reduce fat in humans. Although small randomized, placebo-controlled studies have shown modest weight loss, there has not been clear consistent evidence of significant weight loss or fat mobilization. These and other dietary supplements are widely used for weight loss; yet few, if any, have favorable risk/benefit profiles or evidence of efficacy. Nonetheless, they remain popular and attractive, being perceived as an easier approach to weight loss than lifestyle change and presumed safe because they are “natural.” Use is heavily promoted, and there are no requirements for the demonstration of efficacy, safety, uniformity, purity, or labeling. Moreover, no consistent listing of ingredients or standardization of preparations is available.

Other Alternative Medicine Measures

Mind–body medicine measures include meditation, hypnosis, and yoga. In addition, acupuncture is used as a means of altering “energy.” These CAM therapies have been subjected to more carefully designed studies, though small in scale and of short duration. They have shown little to no benefit when applied as monotherapy.

Surgical Treatment and Endoscopic Techniques (54–69) (Table 233–4)

Bariatric Surgical Treatment

There is strong evidence supporting bariatric surgery as the most effective and most durable therapy for moderate to severe obesity. In addition to a significant benefit in cardiovascular and total mortality, longitudinal studies report an average 18% weight loss 20 years after surgery, resulting in the improvement or complete resolution of obesity-related comorbidities like diabetes and cancer.

Mechanisms of Action. Bariatric surgery was initially thought to cause weight loss by mechanical restriction of caloric intake and malabsorption of ingested calories. However, more recent studies have led to acceptance of a physiologic basis to bariatric surgery, particularly in the Roux-en-Y gastric bypass (RYGB) and the vertical sleeve gastrectomy (VSG). Several biochemical and microbiologic alterations have been identified as possible explanations for the profound and durable weight-loss effects of surgery. These alterations include changes in regulatory gut hormones (e.g., GLP1, ghrelin), bile acids, and gut microbiota. The ability of the operation to alter the physiologic networks that control energy balance and metabolic function (e.g., decrease in ghrelin and increase in anorexigenic hormones such as glucagon-like peptide-1) appears to be at least as important as the obvious mechanical effects of surgery. In addition, observations highlighting the weight-independent effects of surgery on diabetes have challenged the historical belief that the treatment of obesity

<table>
<thead>
<tr>
<th>Procedure (type)</th>
<th>Benefits</th>
<th>Complications*</th>
<th>Contraindication</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjustable gastric band (gastric)</td>
<td>No anastomosis, Potentially reversible, No nutritional deficiencies</td>
<td>Stomal obstruction, Band slippage, Band erosion, Band infection, Esophageal dilation, Port infections, GERD/esophagitis</td>
<td>Dysmotility, Failure to lose weight, ↑Reoperation rate</td>
<td>Previous weight-loss surgery, Portal hypertension with varices, Chronic steroid use</td>
</tr>
<tr>
<td>VSG (gastric)</td>
<td>Weight-independent effects on glucose regulation, Enables endoscopic surveillance, Reduced risk of nutritional deficiencies</td>
<td>Intraoperative bleeding, Gastric leaks, Severe recurrent GERD</td>
<td>Vitamin B₁₂ deficiency, Weight regain</td>
<td>Portal hypertension with varices, Severe GERD</td>
</tr>
<tr>
<td>RYGB (gastric + intestinal)</td>
<td>Rapid improvement of glucose regulation, Weight-independent effects, Effective control of GERD</td>
<td>Internal hernia, Anastomotic leak, Anastomotic ulcer, G–G and GJ stenosis, Gastric remnant distention, Internal hernia, Anastomotic leak, Anastomotic ulcer, G–G stenosis, GJ stenosis</td>
<td>Gallstones, Micronutrient deficiencies, Hyperinsulinemic hypoglycemia, Ventral hernia, Weight regain, Nephrolithiasis, Renal failure, Micro- and macronutrient deficiencies, Fat malabsorption, Osteoporosis, Hypoglycemia</td>
<td>Portal hypertension with varices, Class C cirrhosis</td>
</tr>
<tr>
<td>Biliopancreatic diversion ± duodenal switch (gastric + intestinal)</td>
<td>Rapid improvement of glucose regulation, Weight-independent effects on glucose regulation are the greatest.</td>
<td>Internal hernia, Anastomotic leak, Anastomotic ulcer, G–G stenosis, GJ stenosis</td>
<td>Portal hypertension with varices, Class C cirrhosis, Need for surveillance endoscopy</td>
<td>Weight-independent effects on glucose regulation, Higher-risk procedure (higher rates of complications), Less commonly performed Used in higher BMI</td>
</tr>
</tbody>
</table>

*All surgical procedures may have perioperative complications (i.e., myocardial infarction or other cardiac events, deep venous thrombosis, bleeding, wound infections).

DM, diabetes mellitus; GERD, gastroesophageal reflux disease; G–G, gastro–gastrointestinal; GJ, gastrojejunal; BMI, body mass index in kg/m².
depends solely on caloric reduction. Despite an incomplete understanding of how surgery works, research has begun to demonstrate that the complex physiologic systems involved in energy regulation can be manipulated by bariatric surgical interventions.

**Candidacy.** Surgical treatment has traditionally been offered to persons with

- BMI greater than or equal to 35 kg/m² who have at least one obesity-related comorbidity
- BMI greater than or equal to 40 kg/m², plus
- Past history of weight-loss attempts, the absence of underlying endocrine disease, and psychological fitness (e.g., having an understanding of the operation and the behavioral changes needed)

Recent recommendations have been offered to expand candidacy for the adjustable gastric banding (AGB) to those with a BMI between 30 and 35 kg/m² who have poorly controlled diabetes. Despite the complexity of the obesity, a surgical referral may be considered in persons with physical disabilities (neurologic, musculoskeletal, etc.) and insulin-dependent diabetes and those who have an overall poor quality of life due to their obesity. However, not all candidates are suitable to proceed to surgery; risks as well as benefits need to be clearly understood (see next section).

**Contraindications** range from serious concomitant medical illness (e.g., cardiovascular or hepatic problems precluding general anesthesia) to psychiatric disease (particularly substance or drug abuse and eating disorders such as bulimia) and plans for pregnancy. Data are not clear regarding advanced age (>65 years) as a risk factor.

**Surgical Options and Selection Considerations.** Most, if not all, of the four surgical options for obesity (Roux-en-Y gastric bypass (RYGB), vertical sleeve gastrectomy (VSG), adjustable gastric banding (AGB), and bilipancreatic diversion (BPD) with or without duodenal switch (BPD and BPD/DS)) are laparoscopic operations. Each approach has particular benefits, risks, and contraindications (Table 233–4), necessitating a careful matching of operation and patient. Currently, there are not enough predictive data to inform selection of one surgical option over another for an individual with severe obesity. There remains great individual variation in response to the surgery regardless of the type of operation. Long-term observational studies have shown the operations that involve both a gastric and intestinal component, that is, RYGB and BPD, achieve the greatest degree of long-term weight loss (25% reduction in weight vs. 15% reduction with gastric banding after 20 years) but entail more perioperative risk compared with VSG and AGB. Recent studies have shown both RYGB and VSG can result in diabetes remission that is superior to medical management. These operations, in addition to BPD/DS, influence the significant early improvement in glucose regulation that differs from a more gradual effect seen with the adjustable gastric band or diet-induced weight loss. Overall, gastric bypass remains the most commonly performed bariatric surgery and appears to be more effective in promoting weight loss and long-term weight maintenance than are other operations.

**Benefits.** Benefits include, but are not limited to, significant improvement if not complete resolution of glucose intolerance, hypertension, obstructive sleep apnea, gastroesophageal reflux, and dyslipidemia. Most improvements persist with time. Medical costs and quality-of-life measures improve after surgery. Psychosocial benefits depend on the degree of weight loss and are independent of side effects and complications. Patients who lose significant amounts of weight become more employable and more physically active, show improvement in their sex life and self-esteem, and acquire a more gregarious outlook on life.

**Risks and Costs.** The risks and complications of surgery are substantial and require serious consideration (see Table 233–4). Overall, there is continued improvement in postoperative mortality and perioperative rates; these rates vary by surgical approach, setting, and patient characteristics. The 30-day mortality rate for RYGB and AGB is 0.3%, and complication rates (e.g., deep vein thrombophlebitis, pulmonary embolization, leaks about the anastomosis, wound infection) range from 4 to 14%. Risk of a major adverse outcome short term was 4.3%. Cost per quality-adjusted life-year has been estimated at $40,000, comparable to other services deemed cost-effective.

**Postoperative Behavioral and Dietary Requirements.** Before and after surgery, patients must be educated on the expected changes in eating behaviors. Studies show changes in food preferences and decreased reward-based eating behaviors after certain surgical procedures. Regardless, patients may have difficulty adapting to their postoperative anatomy and need to be instructed how to eat slower and more carefully and reassured early intolerances may be temporary. Patients are required to take a daily vitamin and mineral supplement for life. Requirements depend on the operation.

**Decision Making.** Surgical candidacy and choice of operation are a collaborative effort involving a thoroughly informed patient and family, the consulting surgeon, primary care physician, and other professionals involved in the care of the patient. Considerations include local surgical morbidity and mortality rates (lowest in centers with greatest experience), the amount of weight loss desired, the underlying medical and psychological states of the patient, and the risks for short- and long-term complications. Those individuals who have untreated mental illness, inadequate understanding of risks and benefits of weight-loss surgery, and active substance abuse should prompt a psychiatric consult prior to surgery. Furthermore, poor compliance should be addressed prior to initiation of any weight-loss treatment.

**Endoscopic Techniques**

Newer nonsurgical techniques have been developed including implantable gastric stimulation devices, intragastric balloons, and endoluminal synthetic liners; the latter two can be endoscopically placed into the stomach and duodenum, respectively. Large randomized trials are under way in the United States, but international trails have shown a mean weight loss of 10% to 20% body weight loss and 20% complication rate. Although these minimally invasive techniques give promise to the treatment of obesity, the exact function they will serve in treatment (e.g., as a primary therapy, a bridge to a second procedure or to enhance prediction of outcomes after a surgical procedure) remains to be elucidated.

**Suction Lumpectomy (Liposuction)**

This popular cosmetic procedure, often performed in ambulatory settings, removes localized fat accumulations; no clear benefit has been established in terms of durable weight loss. The limited outcome data reveal considerable psychological satisfaction but, unlike other weight-loss efforts, fail to show improvement in the metabolic derangements associated with obesity. Safety has been an issue when performed in settings lacking adequate patient-safety precautions.

**PATIENT EDUCATION**

Patients need to know that obesity is a complex disease caused by genetic, biologic, environmental, and psychosocial determinants and that weight loss is a typically long and demanding process. As noted earlier, knowledge must be provided about the basic principles of nutrition and physical activity, such as the caloric value of foods and health benefits of exercise. In addition, practical methods for changing eating habits should be discussed (e.g., mindful eating, meal planning, improving sleep duration, relaxation techniques to reduce stress).
While physician support and encouragement are essential, inputs from all members of the medical home team are important in supporting and educating the patient. Of particular benefit are the efforts of the RD, either on-site or by referral (see Indications for Referral). Chronic care management by the nurse practitioner can enhance compliance and results (see insert).

A few principles are worth noting for discussions with patients. Physician language should be nonpejorative, avoiding terms like obesity and fat that can undermine the patient–doctor relationship. Physician acknowledgment of weight status increases patient prioritization and desire to lose weight as well as weight-loss attempts. Managing patient expectations is critical, as they may be far beyond the efficacy of most current treatments options. Lifestyle modification remains the mainstay of treatment, despite long-term efficacy of less than 5% body weight loss. Heterogeneity of individual responsiveness is substantial; reduction to average body weight is not a realistic goal. Men generally lose weight faster than do women due to increased lean muscle mass and higher energy expenditure, and older individuals lose weight more slowly than do their younger counterparts, given a lower metabolic rate. Interestingly, setting realistic goals for weight loss does not necessarily lead to better weight-loss outcomes; for some patients, it may be more effective to be ambitious.

Although rapid–weight-loss programs are popular, patients need to be informed about their inadequacies for achieving long-term weight loss. Providing information about appropriate and reliable resources of commercial or nonprofit programs (see Table 233–1) can be helpful. Those being considered for pharmacotherapy need to understand that prescribed weight-loss medications are not “diet pills,” absorbing need for lifestyle modification. Patient education should stress that prescribed medication is intended for sustained use as part of a comprehensive approach to weight loss and should be taken only as prescribed in conjunction with close monitoring to ensure safety. Use of nonprescription diet aids and supplements needs to be discussed, since self-treatment is heavily promoted and frequent. Evidence-based information regarding dietary supplements, commercial diet plans, and herbal and other complements, commercial diet plans, and herbal and other complements should be provided and discussed to enable patients to make informed decisions about their use.

Those considering bariatric surgery require an intensive and customized educational effort that should also include family. Informed, shared decision making is essential. Although mortality risk is low (0.3%), perioperative risk leading to a major adverse outcome is greater and needs to be addressed and taken into account.

### INDICATIONS FOR REFERRAL

Although the interest, involvement, and encouragement of the primary physician and medical home team are critical, the medical complexity of the obesity often dictates the referral process. The severity of the obesity, presence of weight-related medical comorbidities, and general interest in losing weight are key factors for selecting treatment choices. Referral to an RD/nutritionist (if not already embedded in the primary care medical home) can be essential to achieving improved outcomes. Other helpful professionals include the exercise trainer, sleep specialist, and psychologist, who may aid in specific areas of lifestyle modification. The psychologist may be helpful with counseling on specific eating behaviors (e.g., emotional, binge or night-eating disorders), lack of motivation, stress reduction sleep dysfunction, and adherence. Dietitians are useful consultants for assistance with patient barriers to healthy eating (e.g., cultural and ethnic food preferences, personalizing meal plans, and education after weight-loss surgery). To sustain lifestyle modification, a randomized trial finds high-frequency dietitian telephone contact to be as effective as face-to-face visits. Familiarity with community and commercial resources and their level of professional supervision is helpful when a patient requests a group approach.

When weight-loss pharmacotherapy and surgical intervention are being considered due to inadequate results with repeated attempts at lifestyle modification or medically complex obesity, referral to a multidisciplinary weight-loss center or specialist in Obesity Medicine may be helpful. Such referral may also be indicated if weight loss is desired prior to an upcoming elective surgery (e.g., hip or knee replacement or hernia repair). Subspecialty board certification in Obesity Medicine is now available, helping to inform referral. Multidisciplinary centers can offer comprehensive evaluation and intensive treatment options, including surgery, despite the complexity of the obesity. Rates of serious complications from bariatric surgery are inversely related to hospital and surgeon volume of these procedures. As noted, even persons with physical disabilities (neurologic, musculoskeletal, etc.) and insulin-dependent diabetes and those who have an overall poor quality of life due to their obesity can be considered, if indicated. Those individuals who have untreated mental illness, inadequate understanding of risks and benefits of weight-loss surgery, and active substance abuse should prompt a psychiatric consult prior to considering surgical referral.

### MANAGEMENT RECOMMENDATIONS

(17,43,70–74)

- Identify and specifically treat etiologic factors (see Chapter 10).
- Seek to engage rather than blame; establish an interactive, respectful relationship.
- Tailor choice of treatment by taking into account factors in addition to the BMI.
- Understand an individual’s biopsychosocial limits, and be realistic about what treatments can and cannot do, but do not limit expectations or aspirations unnecessarily.
- Implement measures sequentially, starting with basic behavioral changes in diet and exercise.
- Avoid and discourage fad diets, supplements, herbal products, and online appetite suppressants not proven to be safe and effective. Warn against diets based on unsubstantiated medical claims, which may have popular appeal but are ineffective for long-term weight control.
- Recruit and engage all members of the primary care/medical home team in the patient’s weight-loss effort.
- In engaging patient participation in self-care, consider the use of technologic devices for monitoring caloric intake (see Table 233–1), physical activity (e.g., wristbands, clip-on devices like Fitbit), and sleep habits.
- Because diets of equal calorie intake are equally effective in achieving modest weight-loss results, tailor the dietary prescription to the individual.
- Individualize changes in eating and exercise patterns, but recognize and address other contributing factors, such as sleep and stress.
- Encourage modest weight loss, but also focus on desirable nonweight outcomes, such as improvements in metabolic profile, waist circumference, and overall well-being.
- Recommend a weight-loss group program to those interested in group support; commercial programs that include a group program and professional supervision can be beneficial; advise against programs that offer only food products or supplements.
- Advise a referral to an RD for assistance with cultural and ethnic foods, fad diets, or more structure in their eating habits and meal plan.
- Restrict the use of very-low-calorie diets to patients who require short-term weight loss; require medical supervision.
Evidence-Based Team Interventions That Work

In Obesity

Available Evidence: Obesity in adults is often associated with multiple comorbidities such as diabetes, hypertension, and lipid disorders. As specifically regards weight reduction, most evidence focuses on nutrition and lifestyle counseling, exercise, and medications.

Interventions That Work

- Behavioral strategies: food and activity diary, problem-solving skills, modification of eating strategies
- Lifestyle counseling
- Dietary counseling
- Incorporating cognitive–behavioral therapies
- Cognitive strategies: correcting negative thoughts

Team Members: primary care physician, dietitian, nurse-educator, and cognitive–behavioral therapist

Level of Evidence: Limited for weight loss specifically but good when incorporating management of diabetes, hypertension, and lipids—see Chapters 26, 27, and 102

Annotated Bibliography


Feigenbaum A, Pasternak S, Zusk E, et al. Influence of intense multidisciplinary follow-up and orlistat on weight reduction in a primary care setting. BMC Fam Pract 2006;6:S5. (Frequent counseling by family physician and dietitian coupled with orlistat therapy leads to greater weight loss than does orlistat-only intervention.)

Avoid or minimize, if possible, drugs that commonly cause weight gain; consider medications that are weight neutral or cause less weight gain.

Consider pharmacotherapy in people who have indications by BMI for treatment and remain at too high a weight despite continued lifestyle modification.

When selecting a weight-loss medication, consider the safety, efficacy, and potential for “double effect” (benefitting weight loss and an additional underlying condition—e.g., metformin for weight gain associated with atypical antipsychotics, or buproprion in persons with depression or smoking).

Monitor patients closely while on a medication, and evaluate efficacy over 3 months (4 × 3 rule—4 lb/mo × 3 months); discontinue medication if there is no response.

Address compliance potential and capacity to understand treatment options in persons being considered for intensive or invasive weight-loss therapies.

Consider referral to a weight center for multidisciplinary evaluation and consideration of intensive therapy, including bariatric surgery, if there is no response to other measures, medical complications are present, or the patient is at high risk for such complications.

Coordinate efforts with the bariatric surgeon for perioperative medical care and postsurgical long-term management.

ANNOTATED BIBLIOGRAPHY

1. Adams KF, Catkin A, Harris TB, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 70 years old. N Engl J Med 2006;355:763. (Presents major epidemiologic data, extending the data on the risk of excess weight to include persons who are overweight but not obese.)


8. Reaven GM. Importance of identifying the overweight person who will benefit the most by losing weight. Ann Intern Med 2001;138:420. (Suggests that the best candidates are those with the metabolic syndrome.)


11. Wadden TA, Berkowitz RI, Womble LG, et al. Randomized trial of lifestyle, medication and pharmacotherapy for obesity. N Engl J Med 2005;353:2111. (Finds that combination therapy was better than was either alone.)


15. Dansinger ML, Gleason JA, Griffith JL, et al. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease reduction. JAMA 2005;299:41. (Benefit was related to adherence, not to the particular type of diet.)


20. National Task Force on the Prevention and Treatment of Obesity. Very-low-calorie diets. JAMA 1993;270:967. (Finds that those diets were effective and safe for short-term use under close medical supervision anddiscuss means of improving outcome; 124 references.)


Q22
39. Lee D, Sui X, Artero EG, et al. Long-term effects of changes in cardiorespiratory fitness. (Significant association to face-to-face contact in supporting lifestyle modification.)


43. McCaware MT, Wing RR, Klein ML, et al. Behavioral strategies of individuals who have maintained long-term weight losses. Obes Res 1999;7:334. (One ingredient was a continued exercise program.)


47. Goossens G, De Leenheer AL, De Aey JF. Efficacy of diet and physical activity interventions on weight loss and cardiometabolic risk factors in severely obese adults: a randomized trial. JAMA 2010;104:1795. (A thorough review of medications used for weight loss.)

48. Jakicie JM, Marcus BH, Gallagher K. Exercise effect of exercise duration and intensity on weight loss in overweight and sedentary women: a randomized trial. JAMA 2003;290:1323. (Long-term weight loss increased with an increase in exercise, but even modest exercise achieved significant weight loss when combined with diet.)


51. Chanoine J-P, Hamps L, Jensen C, et al. Effect of orlistat on weight and body composition in obese adolescents: a randomized controlled trial. JAMA 2005;293:2873. (A 1-year trial, finding that the treatment was beneficial when used in conjunction with a program of diet and exercise.)

52. Saper RB, Eisenberg DM, Phillips RS. Common dietary supplements for obesity/e_txtbk/index.htm. (A summary of the evidence and recommendations regarding cardiac complications and the need for the evaluation of fenfluramine users.)

53. Saper RB, Eisenberg DM, Phillips RS. Common dietary supplements for obesity. (Compares the use of less traditional methods of behavior modification, such as Internet interventions, meal replacements, and telephone interventions.)


56. Flum DR, Salem L, Elrod JA. Early mortality among Medicare beneficiaries undergoing bariatric surgical procedure. JAMA 2005;294:1903. (Documents the risk in older patients.)


60. Mechanick JI, Youdim A, Jones DB, et al.; for the Clinical practice guidelines for the perioperative nutritional, metabolic, and non-surgical support of the patient with bariatric surgery. (Presents the use of less traditional methods of behavior modification, such as Internet interventions, meal replacements, and telephone interventions.)


62. O’Brien PE, Dixon JB, Laurie C, et al. Treatment of mild to moderate obesity with laparoscopic adjustable gastric banding or an intensive medical program. Ann Intern Med 2006;144:625. (RCT finding that surgery was better than was medical therapy in this group with a BMI of 30 to 35.)


65. Schauer PR, Kushner RH, Wolski K, et al. Bariatric Surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med 2012;366:1567. (Higher percentage of patients after gastric bypass or sleeve gastrectomy achieved the primary endpoint, a glycated hemoglobin level of 6% or less compared with the intensive medical therapy group.)


Anorexia nervosa, bulimia nervosa (the binge–purge syndrome), and eating disorder not otherwise specified (i.e., eating disorder that does not meet criteria for anorexia nervosa or bulimia nervosa) are the three DSM-IV eating disorder diagnoses of adolescents and adults. Of the eating disorders not otherwise specified, binge eating disorder has received the most research attention. The lifetime prevalence estimates of anorexia nervosa, bulimia nervosa, and binge eating disorder in the United States are approximately 0.9%, 1.5%, and 3.5%, respectively, among women, and 0.3%, 0.5%, and 2.0%, respectively, among men.

These illnesses are psychiatric disorders that can have serious medical consequences and are associated with a high rate of comorbid anxiety, mood, and substance abuse disorders. They extend beyond racial and socioeconomic boundaries. Because patients with these conditions often hide the problem, a high index of suspicion is required for diagnosis. Primary care physicians need to be able to recognize these disorders, evaluate and treat their medical complications, arrange and coordinate a comprehensive multidisciplinary treatment program, assist in ambulatory monitoring, and determine when a patient requires hospitalization.

**Pathophysiology, Clinical Presentation, and Course (1–10)**

### Anorexia Nervosa

Anorexia nervosa is a syndrome characterized by severe weight loss (e.g., body weight <85% of expected or body mass index <17.5 kg/m²) resulting from inadequate food intake by persons with no medical reason to lose weight. A distorted body image and an intense fear of weight gain lead to the relentless pursuit of an unreasonable and unhealthy thinness. Weight is lost in two ways. Patients with restrictive anorexia nervosa starve themselves. In contrast, other patients have symptoms of bulimia nervosa and lose weight by purging after eating, usually by vomiting or taking laxatives. Those with bulimic symptoms may have a gravier prognosis and more medical problems as complications of low weight are compounded by purging. Originally more prevalent among persons more medical problems as complications of low weight are com-

### Pathogenesis

The pathogenesis of anorexia nervosa is unknown but appears to be multifactorial. There is a genetic vulnerability to development of anorexia nervosa, though the specific genes involved have not been clearly identified. Neurochemical, psychological, and sociocultural factors have all been suggested as contributing factors. Neuroendocrine abnormalities are well documented (see later discussion). Although many of these hormonal alterations are a consequence of chronic starvation, there is increasing evidence to suggest that some may contribute to symptoms of anorexia nervosa.

Onset frequently coincides with a patient’s time of separation from home or the loss of a loved one. Others attribute anorexia nervosa to problems in emotional development and disturbed family interactions, although these may also be sequelae rather than causes of the eating disorder. Psychological studies find these patients to be bright, compulsive perfectionists who perform well at school and work. The prevalences of comorbid psychiatric disorders, including anxiety, depression, and obsessive–compulsive disorder, are increased among patients with anorexia nervosa. Sociocultural pressure to be thin also contributes to the problem.

### Cardiovascular Consequences

Cardiac muscle atrophy is associated with a reduction in left ventricular wall thickness and cardiac output, but, typically, congestive failure does not occur. Sinus bradycardia and hypotension are common. Electrocardiographic changes, primarily low-voltage ST-segment depression, T-wave flattening, and prolonged QT intervals, have been reported. Sudden death, which occurs in anorexia nervosa, is presumably due to ventricular arrhythmias. QT-interval prolongation, which is reversible with refeeding, may herald increased risk of this outcome. Autopsies of some patients performed after sudden death have shown a degeneration of myocardial cells, which may predispose to arrhythmias.

### Endocrine and Metabolic Consequences

Extreme weight loss produces a number of adverse endocrine and metabolic changes. Thyroid hormone metabolism is altered (“ick euthyroid” syndrome), with thyroxine preferentially converted to the inactive reverse 3,5,3′-triiodothyronine (T3) instead of active T3. A compensatory rise in thyrotropin (thyroid-stimulating hormone) does not occur, suggesting dysfunction of the hypothalamic–pituitary axis. Treatment with thyroid hormone replacement is not indicated, and these thyroid function abnormalities normalize with weight recovery. Starvation also produces reversible hypothalamic–pituitary dysfunction that can lead to hypothyroidism, amenorrhea, infertility, estrogen deficiency, low levels of testosterone and osteopenia (see Chapter 112).

Besides weight loss, other factors, such as hypercortisolemia and hypeoleptinemia, may contribute to suppression of the hypothalamic–pituitary–reproductive axis as menstruation ceases in up to 25% of female patients with anorexia nervosa before weight loss becomes significant, and amenorrhea may persist after weight is regained. Many patients with anorexia nervosa demonstrate excessive secretion of cortisol. Although these patients do not appear cushingoid, with weight gain, they tend to accumulate fat in a central distribution. In addition, hypercortisolemia may contribute to clinical sequelae, such as bone loss and depressive symptoms. Finally, resistance to pituitary growth hormone leads to low levels of IGF-I and contributes to the profound bone loss associated with this disorder.

Posterior pituitary function is also disrupted. Excessive or reduced vasopressin secretion can lead to either hypotension (syndrome of inappropriate antidiuretic hormone) or central diabetes insipidus, respectively. Abnormal secretion of oxytocin has also been reported, though the clinical significance of this is unclear. In addition to pituitary consequences, hypothalamic dysfunction in anorexia nervosa can lead to failure to defend core body temperature and resultant hypothermia.

Recent evidence suggests that secretion of hormones implicated in regulation of appetite are abnormal in anorexia nervosa, even after weight recovery. Levels of hormones involved in food...
motivation pathways, such as cortisol, oxytocin, and peptide YY, have been found to correlate with severity of disordered eating psychopathology in women. This raises the question of whether endocrine dysfunction may underlie disordered eating behaviors in some patients with anorexia nervosa.

Acquired defects in lipoprotein metabolism may alter serum cholesterol (predominantly increased HDL and total cholesterol) and raise carotene levels. Blood levels of glucose, protein, amino acids, and insulin are normal or mildly reduced. Severe hypoglycemia and coma have been reported when starvation is very advanced. Electrolyte abnormalities, including hypokalemia, hypophosphatemia, hypomagnesemia, and hyper- or hypopituitarism, can occur, particularly in the purging subtype of anorexia nervosa.

**Clinical Course**

The disease may occur as a single episode, as repeated episodes separated by remissions, or as a chronic condition. More than half of patients relapse after an initial hospital stay for weight gain. Approximately 50% of patients have a complete recovery (i.e., regain weight and menses), 30% have partial recovery, and 10% to 20% develop a chronic illness. Bulimic symptoms, lower weight, and older age at presentation are associated with poor outcome. Even after weight is restored, the patient with anorexia nervosa may have persistent weight preoccupation, disordered eating patterns, and psychosocial problems. Up to 50% of patients with anorexia nervosa develop bulimia nervosa.

The mortality rate is 12 times that of age-matched unaffected persons. Most deaths are sudden, apparently caused by cardiac arrhythmias. Fatal hypoglycemic coma has also been reported.

**Bulimia Nervosa**

This eating disorder is driven by excessive concern about body weight or shape and is characterized by repeated episodes of binge eating (at least two times per week for 3 months), during which large amounts of high-calorie foods are consumed, usually in secrecy. The binge is followed by self-deprecating thoughts and purging, excessive exercise, or fasting (at least two times per week for 3 months) to prevent weight gain. Most bulimic patients purge by inducing vomiting or using laxatives, but some use diuretics or exercise excessively. They fear losing control of their eating behavior and are ashamed when it happens. Binges may be repeated several times daily. At other times, people with bulimia nervosa may diet rigorously or take diet pills. Some patients may have no regular eating pattern, fasting, or restricting eating severely outside of binging episodes. The result of this behavior is frequent weight fluctuations but not severe weight loss.

In contrast to persons with anorexia nervosa, those with bulimia nervosa are aware that their behavior is abnormal but often conceal the illness because of embarrassment. The bulimic patient’s typically normal weight permits the illness to be hidden. Detection of surreptitious vomiting or laxative abuse can be a challenge (see later discussion).

**Pathogenesis**

The high prevalence of alcohol and drug abuse among patients with bulimia nervosa has led some to postulate that bulimia nervosa is part of an impulse control disorder. Depression has also been proposed as a precipitant. Changes in neurotransmitter metabolism and a response to antidepressant medication suggest a biochemical component to the condition. Cultural pressure to be thin probably contributes. Patients commonly report that a diet preceded their disease. The bingeing sometimes observed when experimentally starved normal persons resume eating has led to speculation that strict dieting contributes to the onset of bulimia nervosa. Bulimia nervosa is more prevalent in individuals with type 1 diabetes, who can purge by withholding insulin after overeating. Diabetic patients with bulimia nervosa generally have worse glucose control, have poorer quality of life, and may be at greater risk of diabetic complications.

**Pathophysiology**

The medical consequences of bulimia nervosa usually depend on the specific behaviors present, but menstrual irregularities are common regardless of the purging method.
Bingeing. Bingeing has few complications, although abdominal pain from distention is common. Acute gastric dilation is rare but has been reported.

Chronic Induced Emesis. Repeated regurgitation of stomach contents produces volume depletion and a hypochloremic metabolic alkalosis. Dizziness, syncope, thirst, orthostatic changes in vital signs, and an elevated blood urea nitrogen occur in the volume-depleted patient. Renal compensation for the alkalosis and volume depletion causes potassium depletion and hypokalemia, which may predispose to cardiac arrhythmias, muscle cramps and weakness, paresthesias, polyuria, and constipation. T-wave flattening and U waves are seen on the electrocardiogram. Serum and urine chloride levels are low.

Reversible, painless parotid swelling can develop with chronic vomiting and is often accompanied by hyperamylasemia. Irreversible dental problems also occur. Repeated exposure of the teeth to stomach acid causes enamel decalcification and erosion. Teeth diminish in size and become discolored and sensitive to temperature changes. Many vomiters have symptoms of reflux esophagitis, but hematemesis due to a Mallory-Weiss tear is unusual, and esophageal rupture is rare. Some patients use emetine (ipecac) to induce vomiting. Prolonged use may cause a reversible proximal myopathy and a potentially fatal cardiomyopathy.

Laxative Abuse. Laxative abuse is a common and potentially dangerous form of purging. It may begin as a response to constipation and continue because of the temporary weight loss induced through volume depletion. Stimulant laxatives are used most often. The resultant increase in colonic motility produces abdominal cramps, and electrolytes are lost in a watery diarrhea. Volume depletion, hyponatremia, hypokalemia, and either metabolic acidosis or metabolic alkalosis may result. Calcium and magnesium depletion has also been reported. The irritation of intestinal mucosa or development of hemorrhoids as a result of rapid fecal transit may cause rectal bleeding, and rectal prolapse can occur. When laxative abuse stops, transient fluid retention, edema, and constipation are common.

Diuretic Abuse. Patients use diuretics more often to prevent fluid retention than to induce weight loss. Use contributes to a hypochloremic metabolic alkalosis, hypokalemia, and volume depletion. Dilutional hyponatremia may also occur. In contrast to vomiters and laxative abusers, patients who use diuretics do not have low urinary levels of sodium and chloride. Fluid retention transiently develops when diuretics are stopped.

Clinical Presentation and Course

Bingeing and purging may be concealed, and no physical signs are characteristic. The clinical presentation is often dominated by one of its medical complications, such as abdominal pain, diarrhea, heartburn, hypokalemia, volume depletion, hyponatremia, or parotid swelling. Findings related to vomiting may also include abrasions and calluses on the back of the hand, cheilosis at the angles of the mouth, and discoloration of teeth.

Patients with concomitant depression, substance use disorders, impulsivity, and personality disorders may have worse prognoses for recovery. Mortality is lower than in anorexia nervosa but higher than in an age-matched control population.

Binge Eating Disorder

This condition is characterized by recurrent binge eating (at least 2 days weekly for 6 months) accompanied by marked distress and lack of control over eating and associated with eating alone, too rapidly, when not hungry, or until uncomfortably full. The patient has feelings of guilt or disgust after a binge but does not purge, exercise excessively, or fast. Of the several eating disorders, this is the most common among male patients and is more prevalent among the obese.

Night-Eating Syndrome

See Appendix 234-1.

Differential Diagnosis (1)

The differential diagnosis spans the array of conditions that may cause unexplained weight loss (see Chapter 9), secondary amenorrhea (see Chapter 112), electrolyte disturbances with volume depletion (see Chapters 59 and 64), and osteoporosis (see Chapter 164). Among them are malignancy, chronic infection, intestinal disorders (malabsorption, inflammatory bowel disease, or hepatitis), and endocrinopathies (e.g., hyperthyroidism, panhypopituitarism, adrenal insufficiency, diabetes mellitus). Tumors of the central nervous system mimick anorexia nervosa in rare cases. Psychiatric illnesses that can be confused with anorexia nervosa include depression, schizophrenia, and obsessive-compulsive neurosis (see Chapters 226, 227, and 230). Binge eating may be a manifestation of depression and, rarely, of an organic brain syndrome.

Workup (1,11)

The diagnoses of anorexia nervosa and bulimia nervosa are based exclusively on clinical findings (Table 234-1). Laboratory studies help in the detection of complications (see later discussion) and in excluding other causes of weight loss (see Chapter 9).

Anorexia Nervosa

History

The diagnosis should be suspected in patients with unexplained weight loss. The history should explore the patient’s attitudes toward weight loss, desired weight, and eating habits. A 24-hour dietary recall is more revealing than are the answers to general questions about diet. Detailed weight and menstrual histories should be obtained, including the dates and circumstances at the onset of weight loss, minimum and maximum weights, recent weight changes, and last normal menstrual period. One needs to ask all patients about bingeing, vomiting, and the use of laxatives, diuretics, diet pills, and emetics and to quantify daily exercise (excessive exercise is a common contributor to the weight loss).

It is also important to ask about symptoms of malnutrition (fatigue, skin or hair changes), dehydration (light-headedness, syncope, thirst), hypokalemia (cramps, weakness, paresthesias, polyuria, palpitations), and other problems common to purgers (e.g., heartburn, abdominal pain, rectal bleeding). Because the risk for suicide is increased in patients with an eating disorder, one must screen for suicidality during the initial visit (see Chapter 227). Likewise, because of the increased prevalence of depression, anxiety, and personality disorders among these patients, the history should be reviewed for suggestive symptoms (see Chapters 226, 227, and 230). Exploring the psychosocial history can provide information important not only to diagnosis but also to planning initial management.

Physical Examination

Important objectives are to assess the severity of malnutrition and dehydration and check for the development of complications.
One should specifically take note of the general state of nutrition and hydration and follow with measurement of the height and weight (without street clothing). The blood pressure and pulse are checked for significant postural changes and the temperature noted for hypothermia. The skin is examined for pallor and the hair for changes of lanugo or acrocyanosis. In addition to these measures, a detailed physical examination is essential to rule out other causes of weight loss (see Chapter 9).

**Laboratory Studies**

Because serious volume, electrolyte, and cardiac rhythm disturbances may complicate anorexia nervosa, especially if the patient is also bulimic, one needs to obtain a full set of serum electrolytes including phosphorus plus blood urea nitrogen, creatinine, and an electrocardiogram with rhythm strip. The finding of hyponatremia suggests excess water intake, purging behaviors, or inappropriate antidiuretic hormone secretion. Determination of the serum calcium (plus albumin) and magnesium is needed if a dysrhythmia is noted or laxative abuse is suspected. A complete blood cell count and measurement of glucose, liver function, and gonadotropins (see Chapter 112) may help in the initial assessment of complications of starvation, such as cytopenias, hypoglycemia, fatty liver, and hypothalamic amenorrhea. If a patient has been low weight for 6 months or more, one should obtain a bone mineral density measurement to check for resultant osteopenia or osteoporosis (see Chapters 144 and 164). Unexplained weight loss may necessitate additional laboratory and imaging studies (see Chapter 9).

**Bulimia Nervosa**

**History**

The diagnosis of bulimia nervosa requires a high index of suspicion because binging and purging may be concealed and no physical signs are characteristic. Four screening questions are helpful:

- Do you ever eat in secret?
- Does your weight affect the way you feel about yourself?
- Have any members of your family ever suffered with an eating disorder?
- Do you currently suffer with or have you ever suffered with an eating disorder?

Clues to the presence of bulimia nervosa include a preoccupation with weight and food, a history of frequent weight fluctuations, and problems common to patients who purge and become dehydrated (dizziness, thirst, syncope) or hypokalemic (muscle cramps or weakness, paresthesias, polyuria). In addition, vomiters may describe heartburn, and laxative abusers may complain of constipation and fluid retention. When the diagnosis is suspected, the physician should ask directly about binging and purging and should order a determination of serum electrolytes. A direct inquiry may elicit the history from a patient seeking help but ashamed to volunteer the information.

**Physical Examination**

Physical examination should include a check of postural signs for evidence of volume depletion. Salivary gland enlargement or scars on the dorsum of the hand, suggestive of chronic self-induced vomiting, may be noted. The teeth should be examined for enamel erosion and discoloration.

**Laboratory Studies**

Most useful are the serum and urine electrolytes, blood urea nitrogen, and creatinine and the electrocardiogram. Calcium and magnesium should be measured in laxative abusers. The pattern of serum and urine electrolytes helps to determine the mode of purging. Hypokalemic alkalosis suggests frequent vomiting or diuretic use. A non-union gap acidosis suggests laxative abuse. Some patients who vomit deny that it is voluntary. Organic causes of chronic vomiting should be excluded in these cases (see Chapter 59).

**Binge Eating Disorder**

The workup focuses on the history because physical examination and laboratory findings are almost always normal, except in obese patients (see Chapter 10). It is most important to explore the patient’s experiences with eating because distress characterizes the syndrome, as do feelings of disgust and guilt after a binge.

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**TABLE 234–1 American Psychiatric Association Diagnostic Criteria for Eating Disorders**

<table>
<thead>
<tr>
<th>Anorexia Nervosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refusal to maintain minimally normal weight (e.g., 85% of ideal)</td>
</tr>
<tr>
<td>Intense fear of weight gain or becoming fat</td>
</tr>
<tr>
<td>Inaccurate perception of body weight or shape, undue influence of weight or shape on self-perception, or denial of seriousness of low weight</td>
</tr>
<tr>
<td>Amenorrhea (if female)</td>
</tr>
<tr>
<td>■ Restricting type: no current binging or purging activity</td>
</tr>
<tr>
<td>■ Binge-eating/purging type: regular binge–purge activity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bulimia Nervosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent binge eating (at least twice weekly for 3 mo)</td>
</tr>
<tr>
<td>Recurrent inappropriate compensatory behavior to prevent weight gain (e.g., vomiting, medication misuse, fasting, or excessive exercise) at least twice weekly for 3 mo</td>
</tr>
<tr>
<td>Excessive concern about body shape and weight</td>
</tr>
<tr>
<td>Absence of anorexia nervosa</td>
</tr>
<tr>
<td>■ Purgung type: regular self-induced vomiting or misuse of laxatives, diuretics, or enemas</td>
</tr>
<tr>
<td>■ Nonpurgung type: no regular purging during current episode of bulimia nervosa</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Eating Disorder Not Otherwise Specified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disorder of eating that does not meet criteria for any specific eating disorder (e.g., binge eating disorder)</td>
</tr>
<tr>
<td>Recurrent binge eating (at least twice weekly for 6 mo)</td>
</tr>
<tr>
<td>Eating an amount of food larger than most people would eat in a discrete period of time, accompanied by a sense of lack of control over eating</td>
</tr>
<tr>
<td>Associated with at least three of the following:</td>
</tr>
<tr>
<td>Eating rapidly</td>
</tr>
<tr>
<td>Eating until uncomfortably full</td>
</tr>
<tr>
<td>Eating when not hungry</td>
</tr>
<tr>
<td>Eating alone due to embarrassment about how much one is eating</td>
</tr>
<tr>
<td>Feeling disgusted with oneself, depressed, or guilty after overeating</td>
</tr>
<tr>
<td>Marked distress regarding binge eating</td>
</tr>
<tr>
<td>No regular purging, excessive exercise, or fasting</td>
</tr>
<tr>
<td>Absence of anorexia nervosa</td>
</tr>
</tbody>
</table>


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**PRINCIPLES OF MANAGEMENT AND PATIENT EDUCATION**

**Goals, Site, and Scope of Treatment**

The goals of treatment are to stop the abnormal eating behaviors, restore body weight, and prevent relapse by addressing the psychological problems that are part of the illness. Weight
restoration, the immediate goal in anorexia nervosa, may require hospitalization, ideally in a psychiatric unit experienced in treating the disorder. Patients who do not meet medical criteria for hospitalization (e.g., suicidality or major electrolyte or cardiovascular disturbance; see later discussion), who are highly motivated for change, and who have a supportive environment can gain weight in an outpatient setting, but they require close monitoring. Several therapies produce short-term weight gain in patients with anorexia nervosa, but relapse is common, so that a comprehensive, multidimensional approach is necessary. For bulimia nervosa, outpatient treatment is usually sufficient. Once it has been determined that hospitalization is not required, the design of the outpatient management program can proceed. The multidimensional nature of eating disorders necessitates a multidisciplinary approach that may combine medical, nutritional, psychological, and pharmacologic measures. A team approach is helpful. It can be coordinated by either the primary physician or a medical specialist experienced in treating eating disorders. Close coordination and communication are essential. A set of overall treatment goals should be collectively developed, agreed on, and consistently communicated to the patient. Teamwork also helps ease the burden of treating these patients, who can be difficult when they deny the seriousness of their illness or exhibit deceptive, manipulative, angry, or distrusting behavior.

The immediate management tasks for the primary care physician are to identify and correct any potentially dangerous metabolic disturbances, set a few basic agreed-on goals, initiate some simple behavioral measures, and arrange timely referral to persons expert in the management of eating disorders. Given the potentially life-threatening nature of some eating disorders, one should proceed with referral as quickly as possible.

Outpatient Monitoring and Treatment of Metabolic Disturbances

One monitors the weight and vital signs regularly. In patients who purge, it is especially important to check postural signs, cardiac rhythm, and serum electrolytes at each visit. If the QT interval was prolonged on the electrocardiogram at the time of the first visit, then a repeated electrocardiogram is warranted, especially before medications with potential cardiac or metabolic effects are prescribed.

The hypokalemic patient requires supplemental potassium, which must be given as potassium chloride to correct the metabolic alkalosis that maintains the hypokalemia. Patients should be instructed to take the supplement at a time when purging will not occur; often, this is at bedtime. Maintaining normal electrolyte levels should be a condition of continued outpatient treatment. Patients not able to maintain a normal potassium level with supplements require hospitalization.

Setting Goals and Implementing a Dietary Plan

Setting goals is an important component of care for patients with eating disorders. Several goals are optimally specified by the primary physician. The first goal is to halt the use of diuretics and laxatives as quickly as possible. Sometimes, gradual tapering of laxatives is necessary because of the onset of severe constipation. For patients with anorexia nervosa, a weight goal and a minimum acceptable weight below which hospitalization will be required should be specified. The minimum weight is usually set at 75% of ideal body weight. The weight goal is more difficult to determine and is often a point of disagreement between physician and patient. An estimate of desirable weight for height can be derived from standard tables (see Chapter 10). The weight goal should be at least 85% of the chart weight and, for female patients, a weight at which the patient has menstruated.

Unless the patient was originally obese, it is usually close to the patient’s premorbid weight. The patient and all caregivers should know of and agree to these weight guidelines. A dietitian can be very helpful in formulating and implementing an eating plan. Weight should be regained slowly, at a rate of 1 to 2 lb weekly, to avoid precipitating refeeding syndrome and congestive heart failure. Nutritional supplements should be added if the patient is unable to gain weight at an acceptable rate.

Treating the Complications of Refeeding and Rehydration

During a reequilibration period of several weeks, temporary fluid retention and weight gain may occur. Patients with pedal edema can be aided by support stockings, leg elevation, mild salt restriction, and reassurance that the condition is temporary. Diuretics in the setting of volume depletion should be avoided even if edema is present because they may exacerbate the underlying metabolic and volume disturbances. To prevent constipation, patients should increase dietary fiber and may benefit from fiber supplements or stool softeners. Irritant laxative preparations are to be avoided at all costs.

Osteopenia usually improves with an increase in weight and, independently, resumption of menstrual cycles. Periods return within 12 months in about 70% of those who reach 90% of their ideal weight. Oral estrogen replacement therapy has not shown benefit for reversing osteopenia in those who remain amenorrheic. However, transdermal estradiol/progesterin is effective at improving, but not normalizing bone mineral density in adolescent girls. Other studies have shown benefit with oral estrogen/progesterin in combination with IGF-I, and oral bisphosphonates alone. However, further data on safety and efficacy of these therapies are needed before their use becomes standard practice.

Priority should be given to restoring normal weight and good nutrition, including an adequate intake of calcium and vitamin D. Encouragement of other bone-protective lifestyle factors, such as avoidance of tobacco and excessive alcohol use, is important. While weight-bearing exercise is beneficial to bone in healthy individuals, overexercise in anorexia nervosa can perpetuate the low weight and amenorrhea that leads to bone loss, and high-impact exercise can lead to fractures.

Psychotherapy

Because of the complex nature of eating disorders and the increased probability of serious underlying psychopathology (not to mention suicide risk), psychiatric referral for specialized multimodality care is best. Individual or group psychotherapy, cognitive-behavioral therapy (CBT), and family-based treatment are all used. Adolescents with anorexia nervosa appear to respond well to family-based treatment. Patients with bulimia nervosa respond well to CBT provided in an individual or group setting (and perhaps supplemented by psychopharmacologic treatment; see later discussion); so do patients with binge eating disorder. For bulimia nervosa, CBT reduces symptoms (e.g., frequency of purging) and appears to be more effective than is insight-oriented psychotherapy.

Psychopharmacologic Therapy

Eating disorders are best treated with psychopharmacologic therapy by physicians skilled and experienced in their management. Even if not prescribing these medications, primary care physicians need to be familiar with their use and associated risks. This is particularly important given the increased risk for concurrent drug and alcohol abuse and potential for prolonged QT intervals, electrolyte abnormalities, and cardiac arrhythmias.
in some patients with eating disorders. Psychopharmacologic treatment is customized to the underlying psychopathology.

**Bulimia Nervosa**

Psychopharmacologic intervention is helpful in patients with bulimia nervosa. Antidepressants reduce the frequency of bingeing episodes, even in the patients without coexistent depression, but they are most effective when used in conjunction with psychotherapy. A combination of antidepressants and CBT may be particularly effective.

A broad range of antidepressant agents may be useful; these include selective serotonin reuptake inhibitors (SSRIs; e.g., fluoxetine, 60 mg/d), tricyclics (e.g., amitriptyline, desipramine, and imipramine, up to 300 mg/d), monoamine oxidase inhibitors (e.g., phenelzine and isocarboxazid), and others (e.g., trazodone). Tricyclics and monoamine oxidase inhibitors must be prescribed with caution given potential for dangerous side effects. Bupropion is contraindicated due to increased risk of seizures. SSRIs are generally considered first-line agents due to efficacy and tolerability; evidence of efficacy is best for fluoxetine. In addition to improving eating disorder symptoms, antidepressants may be used to treat comorbid anxiety and depression. These medications may also be useful in preventing relapse.

**Anorexia Nervosa**

In contrast, antidepressant medications have not been demonstrated to reduce symptoms or produce weight gain in anorexia nervosa. Even after weight was regained, fluoxetine (at 60 mg/d) did not sustain recovery better than did placebo in a randomized controlled trial. The antipsychotic olanzapine may assist in weight gain, but data are limited, and some studies have shown no improvement. Caution must be used given potential for QT prolongation and other side effects. Psychotropic medications do not appear to be effective in treating depression or anxiety in low-weight patients with anorexia nervosa.

**Binge Eating Disorder**

In binge eating disorder, SSRIs and topiramate have shown promise.

### PATIENT EDUCATION

The physician needs to inform the patient of the seriousness of his or her illness and its complications. The connection between the eating disorder, symptoms, and laboratory abnormalities as well as bone density results should be explained in detail. For patients with anorexia nervosa, the consequences of starvation and the necessity of weight gain must be emphasized. Patients who purge need to understand the potential consequences of their behavior (e.g., irreversible erosion of tooth enamel, cardiac arrhythmias) and the ineffectiveness of laxative or diuretic use for achieving real weight loss. Patients who have been starving themselves or abusing laxatives or diuretics should be instructed in the likelihood of transient discomfort (e.g., edema, constipation, bloating) as they stop purging and begin to eat.

### INDICATIONS FOR ADMISSION AND REFERRAL

As noted earlier, anorexia nervosa is a potentially life-threatening condition. Medical criteria for hospitalization in adults with anorexia nervosa may include the following: (a) extremely low weight (e.g., <75% of ideal body weight) or rapid progression of weight loss, (b) intractable purging, (c) presence of cardiac arrhythmias, (d) persistent hypokalemia unresponsive to outpatient treatment, (e) symptoms of inadequate cerebral perfusion or mentation (syncope, severe dizziness, listlessness), (f) symptomatic hypoglycemia, (g) markedly abnormal vital signs (i.e., bradycardia, tachycardia, hypotension, or hypothermia), (h) acute complication of eating disorder or refeeding, or (i) lack of response to outpatient management. The patient should understand that anorexia nervosa is a life-threatening illness and that the first priority is to protect life. Psychiatric hospitalization may be required for behavior beyond the patient’s control or for incapacitating depression and suicidality.

When outpatient management is deemed appropriate for a patient, referrals for psychiatric care and nutritional counseling are essential. It is best to select persons with expertise in the care of patients with eating disorders because treatment can be difficult. For patients with tooth enamel erosion caused by chronic emesis, a dental consultation should be obtained.

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**TREATMENT RECOMMENDATIONS (1,7,8,14,17,26)**

Effective treatment is a multidisciplinary effort, likely to require a coordinated team approach that includes care by mental health and nutritional professionals. The guidelines that follow pertain to the role of the primary physician:

- At the time of the first visit, assess the degree of malnutrition, dehydration, and electrolyte disturbance, and decide whether care should proceed on an inpatient or outpatient basis.
- Be sure that other causes of weight loss and its complications have been ruled out (see Chapters 9, 25, 59, 103, and 112).
- Obtain expert psychiatric and nutritional consultations; organize and coordinate a multidisciplinary team approach to management.
- Educate the patient about the medical complications of the illness.
- Set medical guidelines for outpatient management:
  - Minimum acceptable weight
  - Weight goal
  - Weight gain of 1 to 2 lb per week for underweight patients
  - Recommendations regarding acceptable exercise regimen
  - Maintenance of normal electrolytes
  - Compliance with concomitant psychiatric or psychological treatment
- Monitor weight, postural signs, cardiac rhythm, and electrolytes.
- Treat any hypokalemia with potassium chloride.
- Consider antidepressants to control symptoms in bulimic patients.
- Monitor bone mineral density, and counsel regarding measures to protect bone.
- Anticipate and treat complications of refeeding and rehydration (edema, constipation).
- Hospitalize the patient under any of the following circumstances:
  - Weight is extremely low, weight loss is rapidly progressive, and/or patient is unresponsive to outpatient treatment.
  - Purging behaviors are intractable.
  - Cardiac arrhythmias develop (urgent).
  - Persistent hypokalemia is present and unresponsive to outpatient treatment.
  - Syncope, severe dizziness, or listlessness develops (urgent).
  - Symptomatic hypoglycemia is present.
  - Vital signs are markedly abnormal.
  - Acute complication of eating disorder or refeeding develops.
  - Severe depression develops (urgent if patient becomes suicidal).
ANOTATED BIBLIOGRAPHY


8. Miller KK. Endocrine dysregulation in anorexia nervosa update. J Clin Endocrinol Metab 2011;96(10):2939–2949. (Comprehensive review of endocrine dysregulation and consequences in anorexia nervosa, including section on bone loss.)

9. Roche F, Barthelemy JC, Maynad N, et al. Refeeding normalizes the QT rate dependence of female anorexic patients. Am J Cardiol 2005;95:277. (Prolonged QT intervals on the electrocardiogram, which may increase the risk of sudden death, are reversible with refeeding.)


16. Bacalchik J, Hay P. Antidepressants versus placebo for people with bulimia nervosa. Cochrane Database Syst Rev 2003;4:CD003191. (A meta-analysis of 19 trials found that a number of antidepressants were better than placebo at reducing bingeing episodes in patients with bulimia nervosa, no one antidepressant was clearly superior to others.)


24. Walsh BT, Kaplan AS, Etta E, et al. Fluoxetine after weight restoration in anorexia nervosa: a randomized controlled trial. JAMA 2006;295:2605. (Fluoxetine was no better than placebo in maintaining weight gain after initial treatment for anorexia nervosa.)


APPENDIX 234-1

Night-Eating Syndrome

Night-eating syndrome is a little studied but potentially important form of disturbed eating and sleeping. As originally described, it is characterized by morning anorexia, evening hyperphagia, and insomnia. Prevalence estimates range from 1.5% of the general population to as much as 25% among very obese persons, although the condition can also occur in non-obese individuals. The condition can be a source of both disturbed sleep and obesity.

PATHOPHYSIOLOGY AND CLINICAL PRESENTATION

The cause of the syndrome remains unknown, but a distinctive circadian pattern was noted, which included nighttime awakening with consumption of food and concordant reductions in the usual nighttime surges of melanotin and leptin and loss of normal daily cycling of plasma cortisol levels. The interplay of these hormones and cortisol-releasing hormone provides potential clues to the underlying pathophysiology and the relationship of the condition to situational stress. Dietary composition is high in carbohydrate, which increases serum serotonin and the bioavailability of tryptophan for transport into the brain (helping to restore sleep).

The condition differs from bulimia nervosa and binge eating not only in its predominantly nocturnal timing but also in the amount of calories consumed, which are substantially fewer than for bulimics and binge eaters. It differs from the eating behaviors associated with sleep walking and related conditions. Clinical course is unknown.

DIAGNOSIS

At present, diagnosis remains clinical, possibly supported by observing the characteristic pattern of reductions in nocturnal melanotin and leptin and increase in cortisol (recognizing these may be nonspecific). Differentiation from other eating disorders (see above) and sleep disorders (see Chapter 232) can be difficult, and these disorders may be concurrent. The condition needs to be differentiated from night walking and associated night eating, where alertness is impaired and there is amnesia of the event.
MANAGEMENT

Since psychosocial stress appears to be a precipitant, attention to it appears to be a reasonable first line of treatment. Similarly, identification and treatment of any concurrent sleep or eating disorders (e.g., restless leg syndrome, sleep apnea) are likely to be helpful. The observed dietary and hormonal abnormalities have led to suggestions about use of SSRI agents to increase serotonin or possible benefit from exogenous melatonin or measures that might nocturnally raise leptin and reduce cortisol (e.g., a CRH receptor antagonist). Much more work is needed before such measures can be recommended for use in primary care practice. Referral is indicated when the problem appears to be compromising quality of life.

A.H.G.

ANNOTATED BIBLIOGRAPHY


DEFINITIONS (4)

Consensus psychiatric definitions, as expressed in the Diagnostic and Statistical Manual of Mental Disorders 4th edition, (DSM-IV-TR), define substance abuse as illegal, maladaptive, or dangerous use of a substance, whereas substance dependence is defined as compulsive, out of control, and persistent drug-seeking and drug-taking behavior despite serious medical, psychological, and social consequences (see Table 235–1). The upcoming major revision of the DSM (DSM-V) may alter these definitions by considering them to be different manifestations of a single condition.

Addiction is a term that is used interchangeably with substance dependence. Physical dependence is the development of physical tolerance and a physical withdrawal and does not necessarily mean addiction or substance dependence. Example: A patient taking prescribed narcotic pain relievers for a medical condition develops tolerance and shows signs and symptoms of withdrawal if the pain medication is abruptly stopped.
SECTION XV  Psychiatric and Behavioral Problems

PATHOPHYSIOLOGY AND CLINICAL PRESENTATION (5–17)

Drug use disorders are complex disorders caused by biopsychosocial factors. Addiction affects the brain reward and inhibitory control centers that normally ensure the survival of species. With prolonged drug exposure in vulnerable persons, neurons in key circuits undergo molecular adaptations. The mesolimbic dopamine system provides powerful reinforcement behaviors with important survival value (e.g., sexual activity) by producing a sense of euphoria on stimulation. The most addictive of drugs (e.g., cocaine, amphetamines, opiates, alcohol, and nicotine) are believed to tap into the “brain reward” system by mimicking or enhancing the action of endogenous neurotransmitters such as dopamine or endorphins. It has been hypothesized that the drugs that produce these adaptive responses in the mesolimbic dopamine system cause the core symptoms of substance use disorders.

A subset of these responses also produces adaptive changes in other neurons that lead to physical dependence. When the drug is stopped, the person feels that the world is intolerable without it. In this model, the pathologic behaviors (e.g., denial, manipulations) of the person with a substance use disorder become more understandable. The key motivational system in the person’s brain has been usurped by drugs. Without the drug, the person experiences strong negative emotions, an inability to feel pleasure, and an intense craving for the drug. In addition, drugs dysregulate the brain inhibitory control systems such that despite serious consequences, individuals show diminished inhibitory control over drug use–related decision making. Overtime with repeated drug use, people with addictions stop experiencing any pleasure from what most people would find pleasure in and lose control over intense urges to use.

Figure 235–1  Past month use of selected illicit drugs among persons aged 12 or older: 2002–2011. Findings from National Survey on Drug Use and Health, SAMHSA.

Figure 235–2  Past year initiates of specific illicit drugs among persons aged 12 or older: 2011. Findings from National Survey on Drug Use and Health, SAMHSA.
Why some people become addicted during the course of drug use and others do not and why some people recover and some do not are not fully understood. Individual vulnerability appears in part genetic, such as the linkage of the dopamine receptor gene to multiple substance dependences. Developmental experiences, chronic pain, current levels of distress, and complex social factors, including family and peer relationships and the availability of valued behavioral alternatives, are all contributors to individual vulnerability. Psychiatric disorders are a significant risk factor in substance use disorders and complicate diagnosis and treatment (Table 235–2).

**Cocaine, Amphetamines, and Other Central Nervous System Stimulants**

These agents show their effect mainly by increasing synaptic dopamine in the mesocorticlimbic system (dopamine neurons in the ventral tegmental area and its projections in the nucleus accumbens and prefrontal cortex). Animal studies show that natural rewards such as food, sex, and success increase levels of the brain dopamine, thereby increasing neural activity in the nucleus accumbens. Increase in dopamine levels yields to feelings of euphoria and high. The enhancement of the effects of serotonin and norepinephrine by these drugs likely contributes to their sympathomimetic effects. Cocaine specifically binds to dopamine transporter and inhibits the reuptake of dopamine in the synapse causing in accumulation of dopamine in the synapse and also blocks the reuptake of norepinephrine and serotonin. Amphetamine acts predominantly by promoting dopamine release; it also decreases dopamine reuptake, resulting in increased dopamine in the synapse.

The repeated use of stimulants causes neuronal changes that lead to compulsive use as well as to tolerance and withdrawal symptoms when the drug use is stopped abruptly. Chronic abuse is associated with low D2-receptor availability.

**Cocaine**

Cocaine is derived from coca leaves. It can be snorted, injected, or smoked. Street names for cocaine include “coke,” “snow,” “flake,” and “blow.” Crack is cocaine hydrochloride powder that has been processed to form a rock crystal that is then usually smoked. Faster absorption results in shorter duration of action. High from snorting may last 15 to 30 minutes, and smoking may cause a more intense and rapid high lasting from 5 to 10 minutes. Due to short duration of action, addicted persons develop binge use patterns, meaning they use in large amounts and repeatedly in a short period of time to maintain the high feeling.

It is estimated that in the United States, there are 1.0 million persons with cocaine dependence or abuse. In the 1980s and 1990s, the drug was very popular and was extensively abused. The rate and the number of those with cocaine use disorders declined between 2002 and 2009 from 0.6% (1.5 million) to 0.4% (1.0 million), respectively.

**Stimulants (Amphetamines, Methamphetamine, Methylphenidate)**

These agents are commonly abused, but some are also prescribed therapeutically (e.g., to treat attention deficit disorder).
When abused, these medications are taken orally, crushed, and snorted or used intravenously.

**Methamphetamine** is another very addictive stimulant that is closely related to amphetamine. It is a white, odorless, bitter-tasting powder taken orally or by snorting or injecting or a rock “crystal” that is heated and smoked. Other street names are speed, meth, chalk, ice, crystal, and glass. Methamphetamine has a longer duration of action than does cocaine and causes toxicity at the dopamine nerve terminals in the central nervous system (CNS).

The number of current methamphetamine users decreased between 2006 and 2010, from 731,000 (0.3%) to 353,000 (0.1%), but due to its potent addiction liability and destructive health and social consequences, it is still considered one of the most dangerous drugs of abuse.

**Clinical Effects and Patterns of Abuse.** CNS stimulants are highly addictive substances that affect many organ systems. Cocaine's effects appear almost immediately after a single dose and disappear within a few minutes to an hour. Cocaine initially constricts blood vessels, dilates pupils, and causes tachycardia, hypertension, fever, and tremor and produces euphoria, increased energy, and confidence followed by restlessness, anxiety, hostility, hypersexuality, and paranoia.

Prescription stimulants are abused to enhance performance and to get “high.” They can also be abused as a weight loss agent, to increase wakefulness, and to increase focus and attention. When abused, these medications are usually crushed and then snorted or injected. At low doses, it increases wakefulness and physical activity and causes euphoria and hypersexuality. At higher doses, it can cause anxiety, irritability, insomnia, and paranoia.

Due to longer duration of action, the clinical side effects of methamphetamine are related to its toxic effects on nerve terminals. Specifically chronic users of crystal meth develop psychotic symptoms, including paranoia, visual and auditory hallucinations, and delusions, sometimes irreversible changes in brain function and structure, memory loss, aggressive or violent behavior, and severe dental problems (“meth mouth”).

With chronic use resulting in dependence, patients with cocaine and stimulant use exhibit irritability, loss of appetite, weight loss, depression, a lack of energy, and malnourishment. Repeatedly snorting cocaine can cause loss of sense of smell, nosebleeds, swallowing problems, hoarseness, and irritation of the nasal septum.

Intravenous cocaine users are subject to developing infections, abscesses, and sepsis. They present with “track marks,” and IV users of cocaine are at increased risk for contracting infectious diseases such as human immunodeficiency virus (HIV) and viral hepatitis. This risk stems not only from sharing contaminated needles and drug paraphernalia but also from engaging in risky sexual behaviors as a result of intoxication.

Persons with stimulant dependence are at high risk for the development of a paranoid psychosis. **Withdrawal** from cocaine is called “crash.” It is characterized by severe dysphoria, depression, anhedonia, fatigue, hypersonnia, and a craving for cocaine. Crystal meth and prescription stimulant withdrawal present similarly, and the long-term withdrawal symptoms can be significant and quite disabling. Patients present with anhedonia, hypersonnia, lack of energy and motivation, and inability to deal with demands of daily life routines.

**Overdosing** with cocaine or amphetamine produces tachyarhythmias, perspiration or chills, nausea or vomiting, hypertension, high fever, seizures, delirium, paranoia, psychosis, coma, and cardiovascular collapse. Stroke and myocardial infarction have been reported with crack use. Cocaine-related deaths are often a result of cardiac arrest or seizures followed by respiratory arrest.

**Opioids**

The term “opiod” encompasses the opiates (natural alkaloids and semisynthetic opioids derived from the resin of the opium poppy) and the nonopiate opioids (wholly synthetic agents originally developed to provide opiate-like analgesic effect without some of the adverse effects). Most opioid abuse in the United States involves prescription opioids. Leading examples include morphine, hydrocodone, and oxycodone. The synthetic opioids such as methadone, fentanyl, and meperidine are also widely used (see Chapter 236) and may be abused. The opiates bind to endogenous opiate receptors, producing analgesia and sense
Neurons in the locus caeruleus appear to adapt to prolonged opiate exposure and fire at abnormally high rates when opiates are abruptly withdrawn, thereby triggering much of the physical withdrawal syndrome. Heroin derives from the seed of poppy plants, appearing as a white or brown powder or as a black, sticky substance. It is injected, snorted, or smoked. Street names for heroin include “smack,” “H,” “ska,” and “junk.” In 2010, it was estimated that 359,000 persons had heroin dependence or abuse in the United States.

Hydrocodone and oxycodone are examples of prescription opiates taken for nonmedical purposes, often in the form of popularly prescribed combination preparations with acetaminophen (e.g., Vicodin) or as a slow-release preparation (e.g., OxyContin). Their use is a serious public health problem. National Institute on Drug Abuse’s (NIDA) Monitoring the Future (MTF) survey found that about 1 in 12 high school seniors reported past year nonmedical use of the prescription pain reliever Vicodin in 2010 and 1 in 20 reported abusing OxyContin—making these medications among the most commonly abused drugs by adolescents.

**Opioid Use Among Patients with Chronic Noncancerous Pain.** Chronic noncancer is a risk factor to develop opioid abuse/dependence. Addictive disorders develop in up to 32% of patients with chronic noncancer pain. Patients who misuse or abuse their prescribed medications and lose control over their use can become addicted and present with behaviors that raise concern. Such aberrant drug-related behaviors (ADRB) include more interest in immediate-release and brand-name opioids than in other medications or in any other aspect of treatment. It encompasses taking excessive doses and increasing dosage without consulting the clinician, insisting that higher doses are needed. Making multiple phone calls about prescriptions and attempting unscheduled visits (typically after office hours or when the clinician is unavailable) are also characteristic, as is appearing sedated or obtaining medications illegally (e.g., from multiple clinicians, street dealers, family members, the Internet, forged prescriptions).

Contributing factors include poor response to opioid pain relievers (medication failure), development of tolerance, and withdrawal. Other reasons for nonadherence and escalating behavior to obtain prescription pain medications are diversion of medications and untreated mental illness such as depression, anxiety, and insomnia.

Prescription opioid abuse is considered to be an epidemic problem in the United States. Unintentional overdose deaths involving opioid pain relievers have quadrupled since 1999 and by 2007, outnumbered those involving heroin and cocaine. The perception of prescription drugs as less harmful than illicit drugs is another likely contributor to the problem. In 2010, an estimated number of 1.9 million persons had pain reliever dependence or abuse. According to 2009 Drug Abuse Warning Network (DAWN), which monitors emergency department (ED) visits, roughly 343,000 ED visits involved prescription opioid pain relievers, a rate more than double that of 5 years prior.

There is significant increase in use of methadone for chronic noncancer pain in recent years as well as methadone-linked death reports (Fig. 235–6). Data show most of these deaths are linked to methadone prescribed for pain management.

**Clinical Effects and Patterns of Abuse**

Prescribed pain relievers when abused can be taken orally, crushed, snorted, or used intravenously. Especially controlled-release oxycodone HCl, when crushed, becomes a rapid-release drug with the same abuse potential. Opiates produce an initial sense of euphoria (a “rush”), especially after IV injection, smoking, or crushing, which is followed by a sense of tranquility and then sleepiness and mental clouding. Respiratory depression, sedation, and loss of motor control occur when large amounts are abused. When tolerance and dependence develop with repeated consumption, increasing doses are required.
to achieve the desired euphoria. Tolerance to the respiratory depressant effects of opiates develops approximately in parallel. Tolerance to opiate-induced pupillary constriction does not develop.

Unlike alcohol, opiates do not directly produce serious organ pathology. Constipation is the major side effect and may represent a significant problem. Other effects of opioids are sensation of urinary urgency, miosis, hypotension, and infertility.

**Dependence.** As opiates produce high levels of physiologic dependence, repeated use of the drug is needed to prevent withdrawal symptoms. IV injection of the drug is a widely used method of administration and commonly involves sharing needles. This results in hepatitis C, HIV infection, endocarditis, infection of the local injection site, and other complications of unsterile self-injection. Heroin dependence increases mortality and morbidity risks. A recent study followed 581 men with heroin addiction from 1962 to 1997. By 1997, 282 of the men had died, at an average age of 47. Heroin overdose and chronic liver disease, which is associated with hepatitis B, hepatitis C, and alcohol abuse, caused 17% and 15% of deaths, respectively.

**Withdrawal.** In general, clinically significant withdrawal symptoms do not occur with less than 2 weeks of opioid use, unless the person has a previous opioid dependence. Withdrawal from opiates is quite uncomfortable, both physically and psychologically, but not lethal. Various factors influence the severity of withdrawal symptoms, such as specific drug used (long acting vs. short acting), total daily amount used, duration and regularity of use, and psychological and individual factors.

Withdrawal from heroin may begin 6 to 12 hours after the last dose in dependent persons and is manifested by tearing, rhinorrhea, yawning, sweating followed by sleep disturbance, dilated pupils, drug craving, loss of appetite, piloeruction (“goose flesh” or “cold turkey”), irritability, tachycardia, hypertension, tremor, nausea, vomiting diarrhea, chills, fever, agitation, and severe muscle cramps.

The hyperactivity of noradrenergic neurons in the locus caeruleus is responsible for an increase in blood pressure, heart rate, respiration, sweating, and diarrhea, whereas increases in cyclic adenosine monophosphate in opioid receptors and changes in the dopamine neurons of the ventral tegmental area seem to be responsible for dysphoria, craving, and relapse.

**Overdosing.** Overdoses of opiates may be lethal because of respiratory depression. Overdosing is most frequent when the heroin dose is purer than what the addicted person is accustomed to, when tolerance levels are miscalculated after detoxification, when the user is inexperienced, or when opiates are mixed with other CNS depressants.

**Sedative–Hypnotics**

The sedative–hypnotics include the benzodiazepines, barbiturates, and barbiturate-like drugs (e.g., glutethimide, ethchlorvynol). These agents enhance the inhibitory effects of γ-aminobutyric acid (GABA) receptors in the brain. Because ethyl alcohol similarly affects these receptors, marked sedation is associated with concurrent use.

**Benzodiazepines**

Benzodiazepines are most commonly prescribed for the short-term treatment of insomnia and for anxiety disorders (see Chapters 226 and 232). They can cause dependence with long-term use, and so they must be slowly tapered after a course of treatment. The likelihood of dependence is greater with high-potency, short-acting compounds (e.g., alprazolam, triazolam) than with low-potency, long-acting compounds (e.g., diazepam, chlor Diazepoxide). Flunitrazepam is fast-acting benzodiazepine that is abused in club settings and associated with date rape. Commonly referred to as “rophies,” the “date rape pill,” or the “forget-me pill,” when combined with alcohol, it induces sedation and antegrade amnesia. Victims may have the tasteless, colorless agent added to their drink, rendering them susceptible to sexual exploitation. Although abuse and addiction may occur, it is relatively uncommon for the benzodiazepines to produce addictive behaviors (compulsive nonmedical use) except in patients with a prior history of drug abuse. Prolonged benzodiazepine use, carefully monitored, may be necessary for patients with disabling anxiety disorders (see Chapter 226).

**Barbiturates**

The barbiturates, in comparison to the benzodiazepines and similarly acting compounds, have a greater potential for abuse, overdose, and drug–drug interactions (by inducing hepatic microsomal enzymes). The barbiturates are usually used as anticonvulsants and for headaches; phenobarbital has value in treating benzodiazepine withdrawal.

**Clinical Effects and Patterns of Abuse**

When abused, the sedative–hypnotics produce disinhibition, which appears very similar to alcohol intoxication, often followed by slurred speech, incoordination, unsteady gait, nystagmus, and impairment in attention or memory. This can be followed by heavy sedation, stupor, and coma when used in high quantities.
**Oxidizing** with barbiturates produces respiratory depression and coma and may cause death. Benzodiazepines are not likely to be lethal when taken alone in overdose, but when combined with alcohol, they can cause death from respiratory depression.

**Withdrawal** from sedative–hypnotic drugs produces tachycardia, hypertension, fever, tremulousness, hyperreflexia, anxiety, restlessness, insomnia, and anorexia. Seizures and delirium may occur and may be severe. Unlike opiate withdrawal, sedative–hypnotic withdrawal may be fatal.

**Marijuana**

Marijuana is produced from the dried leaves and flowers of the hemp plant, *Cannabis sativa*. The active ingredient, *Δ*-9-tetrahydrocannabinol (THC), acts by binding to an endogenous THC receptor in the brain, the normal function of which is unknown. During the last decade, the clonal selection of hemp plants for high THC content has markedly increased the potency of marijuana sold on the street.

Marijuana is generally smoked, although it is occasionally taken orally, and produces a feeling of relaxation, mild euphoria, and increased sociability. Physical symptoms and signs include mild tachycardia, dry mouth, and conjunctival injection. 4.5 million Americans suffered from marijuana or hashish dependence or abuse in 2010. Despite the common perception of harmless effects and potential usefulness in selected medical situations, marijuana is now the most widely used illicit drug by adolescents in the United States, and may be a risk factor for later drug abuse. Young people are typically motivated to use marijuana to achieve altered feelings of relaxation, altered perception, and increased sociability. Physical symptoms and signs include mild tachycardia, dry mouth, and conjunctival injection. 4.5 million Americans suffered from marijuana or hashish dependence or abuse in 2010. Despite the common perception of harmless-ness and potential usefulness in selected medical situations, marijuana use is associated with a high rate of dependence and abuse.

**Clinical Effects and Patterns of Abuse**

The most common immediate adverse effect of hallucinogen use is a panic reaction or a “bad trip.” Extreme agitation or delirium occurs rarely, although it occurs often as a result of exposure to additional drugs or adulterants, particularly phencyclidine. In such circumstances, a toxic screen should be obtained. Patients in whom psychotic episodes develop after hallucinogen use are difficult to sort out. Generally, the history of psychiatric disturbance precedes the use of the hallucinogen. Flashbacks, which consist of a brief, recurrent visual illusions or hallucinations, may occur for months or, rarely, for several years after hallucinogen use.

**Hallucinogens**

The hallucinogens, or psychedelic compounds, are a group of structurally diverse compounds that appear to act by mimicking the actions of serotonin at certain of its receptor subtypes. The most widely used hallucinogens are the indolealkylamine compounds, including o-dyseric acid diethylamide (LSD), PCP (phencyclidine), psilocybin (which is the active ingredient in magic mushrooms), and mescaline.

**Clinical Effects and Patterns of Abuse**

LSD produces both sympathomimetic and perceptual effects. The sympathomimetic effects, such as increased pulse rate, blood pressure, and mydriasis, generally precede the perceptual changes, which include visual illusions, hallucinations, confusion among sensory modalities (synesthesias), depersonalization, and altered time perception. Most LSD “trips” last 8 to 12 hours. The predominant effects of psilocybin and mescaline are similar to those of LSD.

The most common immediate adverse effect of hallucinogen use is a panic reaction or “bad trip.” Extreme agitation or delirium occurs rarely, although it occurs often as a result of exposure to additional drugs or adulterants, particularly phencyclidine. In such circumstances, a toxic screen should be obtained. Patients in whom psychotic episodes develop after hallucinogen use are difficult to sort out. Generally, the history of psychiatric disturbance precedes the use of the hallucinogen. Flashbacks, which consist of a brief, recurrent visual illusions or hallucinations, may occur for months or, rarely, for several years after hallucinogen use.

**Club Drugs**

A host of drugs with psychoactive and stimulant effects are commonly used by participants at dance clubs and all-night dance parties to “enhance” their experience.

**Ecstasy (MDMA)**

Ecstasy is a synthetic drug with psychoactive and stimulant properties. It is absorbed orally; immediate effects last 3 to 6 hours; and residual effects (anxiety, cognitive impairment, paranoia) may persist for weeks. In the club setting, persons use MDMA for its disinhibitory effects, which may induce feelings of euphoria and hallucinations. The substance has a reputation as an aphrodisiac. MDMA also produces muscle twitching and bruxism. Use during all-night dance parties (raves) has led to deaths caused by the combination of the drug plus many hours of intense exertion, lack of hydration, hyperthermia, and rhabdomyolysis.

**Ketamine**

Ketamine (“vitamin K,” “special K”) is a popular club drug that has sedative, hallucinogenic, and euphoric properties—hence, its attractiveness for recreational use. It resembles phencyclidine, but its duration of action is shorter. At high doses, it produces tachycardia, hypertension, amnesia, delirium, and motor difficulties; abusers may present with chest pain and rhabdomyolysis. Flashbacks may occur, and memory may be impaired for several days.
**GHB (1,4-Butanediol/γ-Hydroxybutyrate)**

Butanediol is an anesthetic agent converted on ingestion to γ-hydroxybutyrate (GHB), which is an active metabolite of the inhibitory neurotransmitter GABA. It has anesthetic qualities and induces a sense of euphoria and sexual disinhibition, making it a popular club drug, referred to as “GHB,” “grievous bodily harm,” “G,” “liquid ecstasy,” and “Georgia home boy.” Outside the United States, the drug is used as an anesthetic. Sources from inside the United States include γ-butyrolactone (GBL), which has been sold as a supplement in health food stores and over the Internet; it is converted to GHB on ingestion. GHB can also be produced by mixing of GBL with sodium hydroxide. Toxic effects include vomiting, respiratory depression, seizures, short-duration coma, and death. Addiction and withdrawal have also been reported.

**Alcohol and Tobacco**

See Chapters 54 and 228.

**WORKUP (18–22)**

**Screening for Substance Abuse**

Given its prevalence, harmful health consequences, and potential treatability, substance abuse should be screened for as part of the routine prevention and health maintenance examination for adults. Particular attention needs to be paid to persons who present with suggestive history or physical findings (Table 235–3). The effectiveness of screening has been extensively demonstrated and proven to be superior to routine medical advice or nonspecific alcohol or drug counseling. When combined with referral and treatment, it can decrease the frequency and severity of drug and alcohol use, reduce the risk of trauma, and increase the percentage of patients who enter specialized substance abuse treatment.

**Screening Instruments**

Screening instruments can be useful for substance abuse identification. The Drug Abuse Screening Test (DAST-20) and the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST; see http://www.sbirt.samhsa.gov) are the most commonly used tools with proven research validity and clinical utility. In 2010, National Institute on Drug Abuse introduced the NIDA-Modified Clinician’s Alcohol, Tobacco, and Drug Use Screening Tool in General Medical Settings (Fig. 235–7):

**Step 1.** The screening starts with a simple single question for each group of abuse, that is, alcohol, tobacco, and drugs.

**Step 2.** If the patient reports past year prescription drug use for nonmedical reasons or illicit drug use, clinicians should proceed to ask lifetime drug use (Fig. 235–8).

**Step 3.** Risk stratification is performed. Depending on the total score, patients will be identified as low, moderate, or high risk (Fig. 235–10).

Patients who score moderate or high should be provided with scientific information related to medical and psychiatric consequences of the specific drug use in a nonjudgmental, neutral way. The clinicians should leave time to answer patient’s questions and also assess patient’s reaction to determine the patient’s readiness to change. Information on drugs, their effects, and treatment options are available to the public and clinicians at expert-authored evidence-based government Web sites (e.g., http://www.drugabuse.gov/publications/hb6/drugs-abuse); information from these sites can be downloaded and handed to patients during the visit. Depending on the level of readiness, clinician should be ready to provide help and assistance. This may vary from meeting information for self-help groups to more traditional substance abuse treatment options. Patients, who show interest in learning more about how to “get clean,” should be given information about detoxification from a particular drug and available outpatient care providers.

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**TABLE 235–3**  **Historical and Physical Findings Suggestive of Substance Abuse**

<table>
<thead>
<tr>
<th>Substance</th>
<th>History</th>
<th>Physical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opiates</td>
<td>Fever</td>
<td>Needle tracks, petechiae, murrur</td>
</tr>
<tr>
<td>HIV infection</td>
<td>Lymphadenopathy, rash</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Jaundice, hepatomegaly/tenderness</td>
<td></td>
</tr>
<tr>
<td>Pneumonia, tuberculosis</td>
<td>Pulmonary consolidation</td>
<td></td>
</tr>
<tr>
<td>Sedatives</td>
<td>Depression</td>
<td>Psychomotor retardation, sadness</td>
</tr>
<tr>
<td>Seizures</td>
<td>Observed convulsion</td>
<td></td>
</tr>
<tr>
<td>Lethargy, amnesia</td>
<td>Cognitive impairment, slurred speech</td>
<td></td>
</tr>
<tr>
<td>Stimulants</td>
<td>Agitation</td>
<td>Delirium</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>Perforated septum; mucosal edema</td>
<td></td>
</tr>
<tr>
<td>Stroke, focal deficits</td>
<td>New neurologic deficits</td>
<td></td>
</tr>
<tr>
<td>Chest pain, infarction</td>
<td>New S4 gallop, single S2</td>
<td></td>
</tr>
<tr>
<td>Syncope, palpitations</td>
<td>Atrhythmia, enlarged heart, S3</td>
<td></td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>Psychosis, hallucinations</td>
<td>Disordered thinking</td>
</tr>
<tr>
<td>Enlarged breasts</td>
<td></td>
<td>Gynecomastia</td>
</tr>
<tr>
<td>Alcohol</td>
<td>See Chapter 228</td>
<td></td>
</tr>
<tr>
<td>Any substance</td>
<td>Withdrawal syndrome</td>
<td>Tremor, tachycardia, agitation, fever</td>
</tr>
</tbody>
</table>


---

**Figure 235–7**  NIDA quick screen: clinician’s screening tool for drug use in general medical setting—Step 1 http://www.drugabuse.gov/sites/default/files/pdf/screening_qr.pdf.
or inpatient facility information. This information is readily available at 1-800-662-HELP or findtreatment.samhsa.gov.

For those patients who are defensive about their drug use and clearly not ready to approach the subject, it is important for the clinician to acknowledge the difficulty and make a point to follow up on this issue in the upcoming visits (Fig. 235–10).

**Diagnosis**

A careful medical workup entailing history, physical examination, and laboratory testing is essential.

**History (Table 235–3)**

Asking questions about drug use is usually an emotionally charged issue. The best way of obtaining history starts with screening every patient for alcohol, tobacco, and illicit drug use in primary care setting. The screening should take place as part of the routine visit and should be applied to everyone regardless of age and gender differences.

The importance of a nonjudgmental approach to getting an accurate history and forming a therapeutic relationship cannot be overemphasized (see http://www.niaaa.nih.gov).

In addition to the information obtained during screening, there may be other behavioral, psychological, or social changes or problems that may point to the possibility of substance use such as recent marriage or relationship difficulties, unexplained absences at work, loss of employment, decline in school performance, debt, legal problems, family services involvement, anxiety, oppositional, irritable behavior, multiple ED visits, drug-seeking behavior, doctor shopping, apparent cognitive impairment, and driving under the influence. History taking should include obtaining information about any past or current prescribed medications with abuse potential and ADRB. Information from State Prescription Monitoring Programs should be included in the assessment.

When a drug use is identified, specific inquiry is directed toward obtaining more information, including age of first use; last use; route of use; frequency; symptoms of tolerance; withdrawal; difficulty cutting down; time spent obtaining and taking the drugs; effects on social, medical, and mental functioning; and continued use despite recognized adverse consequences.

**Figure 235–8** NIDA quick screen: clinician’s screening tool for drug use in general medical setting—Step 2.

**STEP 2**

Ask the patient about lifetime drug use.

Q1. Which one of the following substances have you ever used in your lifetime?

<table>
<thead>
<tr>
<th>Substance</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Cannabis</td>
<td>(marijuana, pot, grass, hash, etc.)</td>
</tr>
<tr>
<td>b. Cocaine</td>
<td>(coke, crack, etc.)</td>
</tr>
<tr>
<td>c. Prescription stimulants*</td>
<td>(Ritalin, Concerta, Dexedrine, Adderall, diet pills, etc.)</td>
</tr>
<tr>
<td>d. Methamphetamine</td>
<td>(speed, ice, etc.)</td>
</tr>
<tr>
<td>e. Inhalants</td>
<td>(nitrous, glue, gas, paint thinner, etc.)</td>
</tr>
<tr>
<td>f. Sedatives or sleeping pills*</td>
<td>(Valium, Serepax, Xanax, etc.)</td>
</tr>
<tr>
<td>g. Hallucinogens</td>
<td>(LSD, acid, mushrooms, PCP, Special K, ecstasy, etc.)</td>
</tr>
<tr>
<td>h. Street opioids</td>
<td>(heroin, opium, etc.)</td>
</tr>
<tr>
<td>i. Prescription opioids*</td>
<td>(fentanyl, oxycodone, hydrocodone, methadone, buprenorphine, etc.)</td>
</tr>
<tr>
<td>j. Other—Specify</td>
<td></td>
</tr>
</tbody>
</table>

- Please report nonmedical use only: Do not record medications that are used as prescribed by a doctor.

**Figure 235–9** NIDA quick screen: clinician’s screening tool for drug use in general medical setting—Step 2.

**Patient reports lifetime use of one or more substance:**

Ask the following questions for each drug mentioned (scores will be tallied at the end)

Q2. In the past 3 months, how often have you used each of the substances you mentioned [first drug, second drug, etc.]?

<table>
<thead>
<tr>
<th>Frequency</th>
<th>0</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monthly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily or Almost Daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If the answer to Question 2 is “never,” skip to Question 6. Otherwise, continue: In the past three months...

Q3. How often have you had a strong desire or urge to use?  

<table>
<thead>
<tr>
<th>Frequency</th>
<th>0</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily or Almost Daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Q4. How often has your use of [first drug, second drug, etc.] led to health, social, legal, or financial problems?

<table>
<thead>
<tr>
<th>Frequency</th>
<th>0</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monthly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily or Almost Daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Q5. How often have you failed to do what was normally expected of you because of your use of [first drug, second drug, etc.]?

<table>
<thead>
<tr>
<th>Frequency</th>
<th>0</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monthly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily or Almost Daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For each substance ever used (i.e., those mentioned in the “lifetime” question):

<table>
<thead>
<tr>
<th>Substance</th>
<th>No</th>
<th>YES, but not in the past three months</th>
<th>YES, in the past three months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q6. Has a friend or relative or anyone else ever expressed concern about your use of [first drug, second drug, etc.]?</td>
<td>0</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Q7. Have you ever tried and failed to control, cut down, or stop using [first drug, second drug, etc.]?</td>
<td>0</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Q8. Have you ever used any drug by injection? (nonmedical use only)</td>
<td>Recommend HIV/hepatitis B &amp; C testing</td>
<td>Ask about pattern of injecting. Recommend HIV/hepatitis B &amp; C testing</td>
<td></td>
</tr>
</tbody>
</table>
Past treatment history, periods of abstinence, longest abstinence in the past, how abstinence was achieved, and relapses provide information on the progression and severity of the drug use problem.

**Physical Examination (Table 235–3)**

Physical examination should include a check for manifestations of IV drug abuse (e.g., fever, tachycardia, icterus, needle puncture marks and “tracks,” hand edema, heart murmur, thrombophlebitis, abscesses). Other signs to check for include hypertension, papillary constriction, ulceration and perforation of the nasal septum, mucosal congestion, gynecomastia, lymphadenopathy, liver enlargement, tremor, and cognitive impairment. Less specific but more common clues include poor hygiene or unkempt appearance, poor nutrition, and a change in alertness or pattern of speech (Table 235–3).

**Laboratory (Table 235–4)**

When substance abuse is suspected, a *toxicology screen* with urine and blood testing may be helpful. For patients suspected of abusing alcohol, it is best to check the blood or use a breathalyzer. For suspected opioid-abusing patients, in addition to checking for opioids, it is important to check for methadone and buprenorphine separately because these do not produce opioid-positive results in routine urine tests.

The standard urine toxicology tests are mostly not sensitive to semisynthetic opioids such as oxycodone and hydrocodone, which are the most commonly abused prescription pain relievers. Further specific testing methods may be needed to detect these substances in the urine (Table 235–4).

Also part of the workup are complete blood count and differential, blood chemistry profile, hepatitis panel, syphilis serology, pregnancy test for females, tuberculin skin test, chest x-ray, and electrocardiogram in patients older than 40 years of age. HIV testing (see Chapter 13) should be done with the patient’s consent.

### TABLE 235–4 Urine Drug Testing

<table>
<thead>
<tr>
<th>Substance</th>
<th>Time Window for Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>12 h</td>
</tr>
<tr>
<td>Cocaine</td>
<td>24–72 h</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>24–72 h</td>
</tr>
<tr>
<td>Heroin</td>
<td>24 h</td>
</tr>
<tr>
<td>Methadone</td>
<td>72 h</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>72 h</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>48 h</td>
</tr>
<tr>
<td>Marijuana</td>
<td>3–30 d</td>
</tr>
<tr>
<td>Phencyclidine</td>
<td>3–10 d</td>
</tr>
</tbody>
</table>

### PRINCIPLES OF MANAGEMENT (1,6,22–37)

#### Overall Approach

Substance use disorders are best understood as chronic, relapsing, progressive diseases. Even after successful episodic treatment (e.g., inpatient detoxification), patients remain at high risk for relapse. Relapses should be seen not as failures of treatment but as recurrence of the disease and as occasions to reinstate abstinence and subsequently to redouble efforts to maintain abstinence.

Establishing mutual trust is a critical task for effective management. Mutual mistrust has been well documented in studies of the interactions of physicians providing primary medical care to opiate-addicted patients. Proactive but nonconfrontational approaches that are well matched to a patient’s stage of motivation can help to build mutual trust.
Getting the Patient into Care: Matching Approach with Motivation

The best chance of successful intervention, even with severe dependence and high levels of denial, is to match the patient's motivational state with treatment approach. This can be done by using the standard stage-of-change construct for achieving behavioral change.

In the precontemplation stage, the patient does not recognize a problem, and a labeling, coercive approach will fail. The best strategy is to be empathic in demonstrating to the patient the problems (such as liver disease or loss of employment) that can result from substance abuse. Even in the face of patient resistance, an empathic, nonjudgmental approach will often lead to more-open discussion.

In the contemplation stage, the patient recognizes a problem but is ambivalent about stopping, and the treatment strategy is to use the ambivalence to demonstrate the downside of the substance use. Similarly, with the planning stage, the treatment should be designed to help the patient and family to plan concrete steps to implement to change. Then, in the action stage with support (Alcoholic Anonymous is a good example), the patient carries out behavioral changes that result in abstinence.

In the maintenance stage, the focus is relapse prevention: High-risk behavior is examined and changed before a return to precontemplation. It is important to honor confidentiality, but it is useful to include the family in matching the treatment with the stage of change. Forceful confrontation will almost always result in increased resistance and withdrawal from treatment. Keeping information about referral resources close at hand helps to take advantage of the patient's motivation. Although an intoxicated patient has impaired judgment and insight, he or she often remembers an empathic, nonjudgmental clinician and seeks help later.

Implementing Evidence-Based Management (Table 235–5)

The National Quality Forum (NQF) has endorsed a set of evidence-based practices for the management of patients with substance use disorders (Table 235–5). These practices encompass screening and diagnosis (see Screening and Diagnosis), initiation of treatment, and continued engagement in such treatment. Supplementing these practices are additional psychosocial interventions and pharmacotherapies aimed at helping to achieve cessation or significant reduction of substance use and improve psychosocial functioning. Many of these evidence-based practices are developed for use in primary care settings.

Care should be offered long term and include coordinated management of substance use illness and any coexisting conditions. Approaches that increase retention in treatment include case management, structured self-help referral, adherence to pharmacotherapy, active outreach, treatment contracts, continuity of treatment provider, low-level incentives, social reinforcements, and assistance with obtaining adequate housing.

Role of Primary Care in Management

The primary care physician and medical home team can play a major role in addressing substance abuse problems. The primary care setting has been shown to be effective for screening and brief intervention. In addition, the chronic disease model, which forms the basis of the primary care medical home (see Chapter 1), supports a longitudinal multidisciplinary approach that benefits this patient population. The primary care physician and team can provide education and counseling in a supportive environment that increases patient engagement and motivation. Individuals with drug abuse are more likely to keep an appointment at a primary care office than at a substance abuse specialty clinic. By familiarizing themselves with the current treatment approaches, the primary care team can make a substantial contribution not only by screening but also by promoting engagement; facilitating referral to specialty, self-help, and family groups; and supporting compliance with pharmacologic treatment. Advances in pharmacotherapy also make possible management largely centered in the primary care setting for practices structured and willing to take on responsibility for comprehensive care of such patients. While some treatment programs require specialized clinical settings (e.g., methadone maintenance), others might well be carried out in the primary care setting, especially with advances in pharmacologic maintenance therapy (see later discussion).

Role of Pharmacologic Therapy

Advances noted earlier in understanding the pathophysiology of substance abuse have led to new avenues of pharmacologic intervention. They provide the opportunity to expand treatment to more patients and improve adherence by making possible treatment in the primary care setting. Combination with counseling appears to enhance outcomes.

Role of Abstinence

Although most substance abuse treatment programs stress the importance of abstinence, the value of harm reduction approach should not be undervalued for some patients, especially for those with serious medical or psychiatric comorbidities and severe forms of drug dependence.

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**TABLE 235–5 National Quality Forum Endorsed Approach to Management**

1. **Identification of Substance Use Conditions**
   - Use of validated screening tools:
     - Screening, Brief Intervention, Referral and Treatment (SBIRT) for alcohol use disorders
     - NIDA quick screen: clinician’s screening tool for drug use in general medical setting
   - Diagnosis and assessment according to criteria of DSM-IV-TR for substance use disorders

2. **Initiation and Engagement in Treatment**
   - Brief intervention using SBIRT, NIDA quick screen
   - Promoting engagement in treatment
     - Motivational interviewing
     - Self-help groups
     - Family-based support groups
     - Withdrawal management (detoxification)

3. **Therapeutic Interventions to Treat Substance Use Illness**
   - Psychosocial interventions
     - Outpatient group therapies
     - Individual substance abuse counseling
     - Family therapies
     - Residential, rehabilitation programs
   - Pharmacotherapy
     - Opioid agonist therapies such as buprenorphine/naloxone or methadone maintenance
     - Naltrexone, acamprosate, disulfiram, topiramate, naltrexone injection

4. **Continuing Care Management of Substance Use Illness**
   - Case management at primary care setting or substance abuse specialty clinics

Management of Opioid Dependence

Opioid agonist therapy is the primary approach to preventing withdrawals and craving and blocking the euphoric effects of heroin and other illicit opioid drugs. It is also indicated for persons addicted to opioid prescription drugs taken for pain relief. Practitioners are faced with the challenge of treating pain safely with opioid pain relievers, given the potential for abuse and diversion (see Chapter 236).

Methadone Maintenance Therapy

Methadone is an orally active opioid agonist and analogue of morphine that acts on many of the same opioid μ receptors as morphine, but without inducing euphoria when used in proper doses. It has served as the mainstay of therapy for opioid abuse. Use is restricted to outpatient treatment programs and regulated under federal and state laws.

Use. The dose needed for successful maintenance varies between 80 and 120 mg daily. The medication is long acting, reaching its plasma peak levels in about 4 hours. Because of its extensive bioavailability and longer half-life than that of many other opioids, an adequate single oral dose of methadone taken once daily suppresses withdrawal and drug craving for 24 to 36 hours in most patients who are opioid addicted.

Administration is restricted to specially licensed treatment centers where patients must come to have their dose administered and taken under direct observation. At these programs, in addition to methadone treatment, patients are provided with weekly individual and group therapies. Patient treatment with other involved health care professionals is coordinated to ensure optimal care. Patients are required to provide random samples for urine toxicology. Compliant patients can earn “take home” privileges up to 6 to 13 doses at a time. The need to expand treatment beyond methadone clinics has been a stimulus to the development of alternative approaches to pharmacotherapy (see later discussion).

Providing medical treatment to individuals on methadone maintenance treatment can pose some challenges, particularly ongoing illicit drug use (including IV use) despite being on methadone maintenance. Such use poses risks of developing infectious diseases, mental impairment, and overdosing, leading some states to implement intranasal Narcan overdose prevention programs. Practitioners caring for methadone-prescribed patients are advised to educate them and household members of potential adverse effects of mixing illicit drugs with methadone. The intranasal Narcan can be provided or prescribed to such high-risk individuals as well as to household members.

Side Effects and Drug–Drug Interactions. Clinicians need to be familiar with side effects of methadone, most commonly constipation, sweating, insomnia, and decreased libido. Methadone has a potential to prolong QT interval, especially at high doses (see Chapter 29) and in the context of drug–drug interactions that impede methadone metabolism.

Being metabolized by cytochrome enzymes—mainly by CYP3A4 and CYP2B2 enzyme systems and to a smaller extent by CYP2D6—methadone is associated with a number of drug–drug interactions that might enhance activity and risk of side effects. Included in the list of potential agents associated with drug–drug interactions are antibiotics, anticonvulsants, antivirals, antidepressants, and certain benzodiazepines that affect cytochrome enzyme activity. Methadone also can have more pronounced side effects in individuals with decreased renal or hepatic function or preexisting cardiovascular or respiratory illness.

Efficacy. Methadone maintenance therapy is of proven efficacy in retaining persons in treatment and reducing illicit drug use. It helps opioid-dependent patients to stabilize their lives and avoid the dangers of IV drug abuse. Methadone maintenance therapy is the treatment of choice for pregnant women who are addicted to opioids.

Buprenorphine/Naloxone Maintenance Therapy

Buprenorphine is a partial opioid agonist with an intrinsic activity of 40% at the μ receptor and is the first U.S. Food and Drug Administration (FDA)–approved medication for the office-based treatment of opioid addiction. The drug’s high affinity at the μ receptor, weak opioid effects, and slow dissociation rate make it well suited for maintenance therapy.

Use. The drug is classified as a Schedule III drug by the FDA and is available for outpatient use as a combination sublingual tablet (Suboxone) containing the opioid antagonist naloxone in a 1:4 ratio with buprenorphine. Physicians desiring to treat patients with opioid dependence in the office setting must obtain a waiver in order to prescribe buprenorphine/naloxone combination for opioid addiction. The recommended dose for opioid dependence is between 8 and 16 mg daily. Naloxone is not absorbed sublingually, but its presence limits IV abuse potential of the sublingual tablet. Naloxone becomes active when injected and can precipitate withdrawal symptoms.

Use in pregnancy has been the subject of active research. Although methadone remains the treatment of choice for opioid-addicted women during pregnancy, ongoing study suggests better results with buprenorphine compared to methadone in reducing neonatal abstinence syndrome (NAS) symptoms. Newborns born to mothers maintained on buprenorphine had lower severity of NAS symptoms, thus requiring less medication and spent less time in the hospital compared to methadone.

Efficacy. In randomized, controlled trials, about 50% of patients treated in the outpatient setting with the combination show no evidence of opioid use in urine testing at 4 weeks and adverse effects no greater than those of placebo. In the largest such study involving persons abusing prescription opiates, 49% of participants treated with buprenorphine/naloxone significantly reduced prescription opiate abuse during extended (at least 12 week) treatment; however, the success rate dropped to 8.6% once treatment was discontinued. Reductions in prescription painkiller abuse were seen regardless of presence of chronic pain or participation in intensive addiction counseling.

Naltrexone Treatment

Naltrexone is a synthetic opioid antagonist that tightly binds to μ opioid receptors and blocks opioid effect. Due to its higher affinity, it displaces opioid agonists such as heroin, morphine, or methadone when given to patients who are actively abusing opioids and precipitates withdrawal. Having no agonist effect, it does not have abuse potential and does not cause withdrawal symptoms when stopped.

Use. It is preferred medication for individuals with high motivation to stay clean such as health care professionals. The patient should be opioid free for 7 to 10 days before the administration of this medication. The recommended dose is 50 mg daily to effectively block the effects of opioids. Naltrexone is available in oral and intramuscular form. Despite its advantages, oral form has not been effective in treating opioid dependence due to poor patient compliance. On the other hand, the intramuscular form (Vivitrol) appears to be more promising, administered every 4 weeks intramuscularly.

Side Effects. The major side effects of naltrexone are gastrointestinal (e.g., nausea and vomiting) and neuromuscular (e.g., anxiety, depression, nervousness, insomnia, headache, joint or muscle pain); some patients experience tiredness. The injectable form may cause an injection site reaction.
Opioid-Addicted Patients with Chronic Noncancer Pain

Patients with chronic noncancer pain and coexisting opioid addiction benefit from a multidisciplinary team approach that incorporates primary care and specialty addiction consultation. If such patients present with active ongoing addiction, they need to be referred for consideration of inpatient detoxification to stop use. After detoxification, patients should be referred to a methadone maintenance treatment program where an integrated approach to both addiction and pain control can be implemented. Specific management protocols have been developed. Patient failure to follow up with a comprehensive program of opioid agonist maintenance therapy is likely to result in relapse.

Cocaine Dependence

Presently, there are no FDA-approved medications to treat cocaine addiction. Several medications marketed for other diseases (e.g., vigabatrin, modafinil, tiagabine, disulfiram, and topiramate) show promise and have been reported to reduce cocaine use in controlled clinical trials. Among these, disulfiram (used to treat alcoholism) has produced the most consistent reductions in cocaine abuse.

A cocaine vaccine that prevents entry of cocaine into the brain holds great promise for reducing the risk of relapse. Behavioral treatments (e.g., contingency management, motivational incentives) have proven to be effective in both residential and outpatient settings. Motivational incentives may be particularly useful for helping patients achieve initial abstinence from cocaine and for helping patients stay in treatment. Cognitive–behavioral therapy (CBT) is an effective approach for preventing relapse. CBT is focused on helping cocaine-addicted individuals abstain—and remain abstinent—from cocaine and other substances.

Community-based recovery groups—such as Cocaine Anonymous—use a 12-step program that can be helpful to people trying to sustain abstinence. Participants may benefit from the supportive fellowship and from sharing with those experiencing common problems and issues.

Treatment of Acute Overdoses and Toxic Reactions

An overdose or toxic reaction should be treated in the ED setting. The details of such treatment are beyond the scope of this book, but some highlights are included here to aid in decision making and triage:

- **Cocaine**—no specific cocaine antagonist; treatment is aimed at relieving symptoms and providing cardiovascular support.
- **Opiates**—cardiovascular and airway supportive care; naloxone (Narcan), an opiate antagonist, is administered intravenously; the usual dose is 0.01 mg/kg; an average dose is approximately two ampules (0.8 mg); and its half-life is shorter than the half-life of heroin, so continuous observation and possibly repeated dosing are necessary.
- **Sedative–hypnotics**—airway and cardiovascular support; the benzodiazepine antagonist flumazenil is available, but clinical experience is limited.
- **Marijuana**—for panic reaction, offering reassurance that the feeling will pass, and ensuring that the patient is in a safe environment.
- **Hallucinogens**—for a “bad trip,” reassurance and maintenance of a safe environment; rarely, 1 to 2 mg of lorazepam orally (or its equivalent) for agitation; for extreme agitation or delirium, 2 mg of lorazepam every 2 hours (or the equivalent) as needed. Physical restraint is often more provoking than beneficial and is particularly dangerous with the extreme agitation and muscle injury that accompany phencyclidine use. It is essential to obtain a toxic screen to search for adulterants and additional drugs. For flashbacks, reassurance is best.

ANNOTATED BIBLIOGRAPHY


Q33

1. Lynskey MT, Heath AD, Bochol K, et al. Escalation of drug use in early-onset cannabis users vs. co-twin controls. JAMA 2003;289:427. (A cross-sectional twin study, showing that the effect of peers and the social context of use were powerful determinants.)


34. Sees KL, Delucchi KL, Masson C, et al. Methadone maintenance vs. 180-day psychosocially enriched detoxification for treatment of opioid dependence: a randomized controlled trial. JAMA 2000;283:1303. (Methadone maintenance was the more effective treatment in terms of reducing heroin use and high-risk behaviors.)


Queries

[1] Note that the table citation 226-65 has been changed to Table 226-6. Please check.
[2] Please check the cross reference “see insert”.
[3] Please provide comment for reference “49.”
[4] Please check whether the edit made to the sentence beginning “Therapeutic plans ought to address ...” is okay.
[5] Please check if edit to sentence starting “Patients meeting the diagnostic...” is okay.
[6] Please check whether the edit made to the sentence beginning “Another potential on-demand treatment ...” is okay.
[7] Please check if edit to sentence starting “Do not prescribe if...” is okay.
[8] Please note that the references have been renumbered for the sequential order.
[9] Note that the reference (36) is not cited in the text. Please provide the citation for the reference or delete from the list.
[10] Please check whether the edits made to the sentence beginning “Patients with multiple MUPS ...” retain intended meaning.
[11] Note that the term “PDD” has been changed to “BDD”. Please check if okay.
[12] Please note that the references have been renumbered for the sequential order.
[13] Note that the references (8–10) are not cited in the text. Please provide the citation for the references or delete from the reference list.
[14] Please provide the expansion of “PLMS” if appropriate.
[15] Please note that the word “table” has been added before the number 232-3. Please check if okay.
[16] Please provide the citation for reference (31).
[17] Please check whether the edits made to the sentence beginning “The condition is defined ...” are okay.
[18] Please check if edit to sentence starting “Opiates (e.g., oxycodone, 5 mg at bedtime)...” is okay.
[19] Please check “?” for significance in Table 232-4.
[20] Please check the cross reference “see insert”.
[21] Please check if edit to sentence starting “Other helpful professionals...” is okay.
[22] Please check if edit to sentence starting “Consider referral to a weight...” is okay.
[23] Please provide the expansion for “IGF”.
[24] Please provide the expansion for “HDL” if appropriate
[25] Please check sentence starting “If fluid retention is...” for completeness.
[26] Please provide the expansion of “CRH” if appropriate.
[27] Please check whether the edit made to the sentence beginning “The perception of prescription drugs ...” is okay.
[28] Note that the “Table 235-4” has been changed to Table 235-3. Please check.
[29] Note that the table footnote citation “A Consensus Report from National Quality Report, 2007” has been deleted in Table caption 235-2. Please check.
[30] Please clarify whether the source line “*Findings from ....” in the Figure 235-3 caption signifies to “no. 1” in the artwork of the same.
[31] Note that the asterisk (*) has been deleted in figure caption 235-5.
[32] Note that the figure caption 235-6 is not matching with the figure. Please check.
[33] Please provide comment for Ref (2).