INTRODUCTION

Insomnia is commonly defined as the subjective report of difficulty in initially falling asleep, difficulty in maintaining sleep (long or multiple awakenings during the sleep period), or awakening too early with the inability to go back to sleep. In recent years, a diagnosis of insomnia has also included a report of decreased daytime function associated with the poor sleep at night to differentiate a patient with insomnia from an individual who simply requires less sleep. Insomnia may be either an acute or a chronic problem. Acute insomnia, usually defined as poor sleep associated with a specific life event, such as an important examination, resolves when the event passes or within a period of 3 weeks. Chronic insomnia may begin after an acute episode, if conditioning factors are involved, but typically presents as a long-standing complaint despite varied attempts at treatment.

Insomnia is the most common sleep problem. About 30% of respondents from large surveys report at least occasional difficulty with sleep. With the added criterion of associated daytime deficit, about 10% of respondents can still be diagnosed with insomnia. Using the criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn (DSM-IV), which requires persistence of at least 1 month and exclusion of other sleep, mental, or medical disorders as a direct cause, the prevalence of insomnia is about 6%. Reports of chronic insomnia vary with both sex and age. Adult women report insomnia about 50% more often than men. In elderly populations, only about 12% of respondents reported normal sleep. About 57% of older individuals reported some problems with their sleep, and 28% reported chronic insomnia. Insomnia is strongly related to psychiatric disorders and substance abuse. Patients with chronic insomnia were about 40 times more likely to suffer from depression but were also more likely to have anxiety or alcohol abuse compared with normal sleepers.

The most common residual effects from insomnia include subjective dysphoria, fatigue, confusion, and tension/anxiety. These subjective complaints are reflected in significant decrements in quality of life, as measured in both physical and emotional dimensions, and real-world deficits such as increased sick days and health costs, more work errors, and fewer promotions at work.

Insomnia is frequently a chronic problem. Insomnia exists at a prevalence of 2–4% in adolescents, and 50–72% of these adolescents continued to have their sleep problem 2–4 years later. Several studies in adults have found that ≥80% of patients with an insomnia problem continue to report insomnia 2 years later.

Insomnia complaints are frequently trivialized, perhaps because almost everyone has had at least an occasional night of poor sleep. In addition, insomnia is a common symptom of many other medical conditions, so that symptoms that could be related to insomnia may often be attributed to other pathology. However, there is an increased risk of mortality associated with short sleep lengths. In the Alameda County study, the age adjusted mortality rate for males who typically slept <6 hours per night and often had trouble sleeping was 2.5 times the rate for 7–8-hour sleepers with no sleep problem. Several studies have now reported that patients with insomnia are likely to develop a psychiatric disorder, even when patients had no other symptoms of depression at initial interview, and are also at increased risk for developing anxiety, alcohol and drug use disorder, and nicotine dependence.

In older patients, insomnia remains related to depression but is also associated with poor health and decreased activity. Onset of insomnia in old age is related to decreased survival. A recent review of the cardiac consequences of insomnia reported that patients with primary insomnia have elevated heart rate and sympathetic nervous system activation, as determined by spectral analysis of heart rate variability. These patients also have other indicators of increased physiological activation, including increased whole-body and brain metabolic rate, increased cortisol secretion, and increased high-frequency electroencephalographic (EEG) activity. Patients with insomnia have been found to be at increased risk for the development of hypertension. Finally, there are now at least 16 studies that have found significant relationships between difficulty falling asleep or staying asleep and pathological cardiovascular outcomes.
such as myocardial infarction (MI). A meta-analysis of the earliest 10 of these studies reported a combined risk ratio of 1.92 (the 95% confidence interval [CI] was 1.2–2.31). Significant relationships between insomnia and cardiac outcomes remained even when numerous other possible contributing variables, such as age, gender, health status, blood pressure, cholesterol, diabetes, smoking, body mass index (BMI), depression, and snoring, were controlled statistically.

The following sections are designed to aid in the differential diagnosis of insomnia, a requirement in providing appropriate therapies.

**DIFFERENTIAL DIAGNOSIS OF CHRONIC INSOMNIA**

Patients with chronic insomnia frequently present a difficult diagnosis and treatment problem because insomnia is interrelated with numerous medical conditions. Table 8.1 presents a differential diagnosis summary for chronic insomnia. The major categories of concern in diagnosis are (1) medical conditions and medications; (2) psychiatric conditions; (3) other sleep disorders; and (4) primary insomnia. Each of the major categories and subcategories will be described.

An analysis of patients referred to sleep disorder centers revealed that about 25% of the referred patients complained of insomnia. Of the insomnia patients, 35% were identified as having insomnia related to psychiatric disorders; 15% were related to primary insomnia; 12% were insomnias related to the use of drugs and alcohol; and 12% were related to periodic limb movements and restless legs. These numbers should be examined with some skepticism because patients who are actually referred to sleep centers form a specialized subgroup of all patients with insomnia. These patient groups are almost certainly biased towards patients with sleep-associated respiratory disorders and periodic limb movements, whereas patients with insomnia primarily associated with depression, for example, are unlikely to be referred to a sleep center, and, even if referred, are unlikely to be given a definitive all-night sleep test (often because such tests are not reimbursed unless there is clear evidence of sleep apnea).

**Medical conditions and medications**

Many medical disorders produce discomfort, pain, stress, or depression. Any of these can limit the ability to fall asleep or maintain sleep. Common medical conditions which predispose patients to insomnia are now considered.

**Pulmonary disease**

More than 50% of patients with pulmonary disease complain of poor sleep, and several studies have objectively verified the poor sleep. Arterial oxygen saturation falls and arterial carbon dioxide increases during sleep in patients with obstructive pulmonary disease, and these changes are greatest during rapid eye movement (REM) sleep. When a patient with chronic obstructive pulmonary disease (COPD) lies down, his work of breathing is increased, and secretions tend to pool in the airways, causing coughing. Either of these events will cause these patients to have increased awakenings to clear their airway or maintain airflow. Patients may benefit from sleeping on their side or with their head and chest elevated enough to allow movement of secretions and to decrease some of the direct force of gravity. Appropriate treatment of the pulmonary disease will improve sleep unless the medications used also produce poor sleep.

<table>
<thead>
<tr>
<th>Table 8.1</th>
<th>Differential diagnosis of chronic Insomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical conditions and medications</strong></td>
<td></td>
</tr>
<tr>
<td>Pulmonary disease (asthma, COPD)</td>
<td></td>
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<tr>
<td>Musculoskeletal (chronic pain, fibromyalgia)</td>
<td></td>
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<tr>
<td>Cardiovascular (heart failure)</td>
<td></td>
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<tr>
<td>Neurological (Parkinson’s disease, Alzheimer’s disease)</td>
<td></td>
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<tr>
<td>Urinary (nocturia)</td>
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<tr>
<td>Gastrointestinal (gastroesophageal reflux)</td>
<td></td>
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<tr>
<td>Medications</td>
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<tr>
<td>Central nervous system stimulants</td>
<td></td>
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<tr>
<td>Bronchodilators</td>
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<tr>
<td>Antidepressants</td>
<td></td>
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<tr>
<td>Beta-antagonists</td>
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<tr>
<td>Corticosteroids</td>
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<tr>
<td><strong>Psychiatric conditions</strong></td>
<td></td>
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<tr>
<td>Depression</td>
<td></td>
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<tr>
<td>Anxiety</td>
<td></td>
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<tr>
<td>Substance abuse</td>
<td></td>
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<tr>
<td>Post-traumatic stress</td>
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<tr>
<td><strong>Other sleep disorders</strong></td>
<td></td>
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<tr>
<td>Sleep disordered breathing</td>
<td></td>
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<tr>
<td>Restless legs syndrome/ periodic limb movements</td>
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<tr>
<td>Circadian rhythm disorders</td>
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<tr>
<td><strong>Primary insomnia</strong></td>
<td></td>
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<tr>
<td>Primary insomnia</td>
<td></td>
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<tr>
<td>Paradoxical insomnia</td>
<td></td>
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</tbody>
</table>
Asthma patients also have increased wakefulness during the night. Patients with asthma have significant nocturnal bronchoconstriction that results in coughing or wheezing. Treatment with longer-acting bronchodilators may help to resolve this problem.

**Pain**

Pain is a frequent cause of poor sleep. Pain may be secondary to a number of medical problems, including arthritis or rheumatoid arthritis; headache; fibromyalgia; cancer; or after surgery or various injuries. Insomnia related to pain may not be adequately addressed during treatment for the pain condition, and this may cause additional distress, and thus increasingly poor sleep, in patients. Insomnia is reported in 30–50% of patients with cancer and in about 25% of patients with arthritis. A recent study has shown an increase in pain sensitivity secondary to uncomplicated sleep loss, and this has led to the hypothesis that poor sleep secondary to pain could actually increase the pain. One recent study showed that, when both zolpidem and hydrocodone were given following arthroscopic knee surgery, patients used significantly less pain medication and reported decreased fatigue.

**Heart failure**

About 30% of patients with heart failure may have disturbed sleep. Poor sleep in these patients may be secondary to the sleep disturbance from Cheyne–Stokes respiration and related dyspnea. Also, these patients commonly use diuretic medication that can produce frequent awakenings secondary to nocturia.

**Neurological disease**

Parkinson’s disease typically occurs in older individuals. These patients have a common complaint of fragmented sleep and early awakening. It has been estimated that about 30% of patients with Parkinson’s disease have insomnia. It has been reported that there is a progressive decline in sleep parameters – increasing sleep latency, decreasing sleep efficiency, declining REM and slow-wave sleep (SWS) – as Parkinson’s disease worsens. Sleep disturbance may be secondary to neurodegeneration in brainstem areas, movement disorder, medications used for treatment, or depression. These patients may also suffer from REM sleep behavior disorder.

Alzheimer’s disease, which has been estimated to be related to sleep disturbance in about 25% of patients, has several components that produce poor sleep. These patients commonly suffer from nocturnal wandering, agitation, or delirium. They also have increased awakenings and duration of stage 1 sleep that may be an underlying cause of the tendency to get up at night. These patients may also have depression or anxiety that may exacerbate insomnia or independently produce early morning awakening. As patients may already suffer from confusion, the use of sedating medications may not be helpful in such patients, who may respond better to antipsychotic or antidepressant therapy.

**Nocturia**

Numerous medical conditions (and, in some cases, treatments for) congestive heart failure, hypertension, diabetes, and sleep apnea can all produce nocturia. Nocturia has also been found to be related to age and BMI. Finally, normal aging frequently results in prostatic hypertrophy and nocturia. Of interest, effective treatment of sleep apnea reduces nocturia in males, and this implies that treatment of poor sleep might also reduce nocturia in other medical conditions or in normal aging.

**Gastroesophageal reflux**

Sleep-related gastroesophageal reflux has been shown to be associated with insomnia. However, successful treatment of reflux can produce a subjective improvement in sleep.

**Drugs and medications**

Drugs and medications frequently produce acute or chronic insomnia based upon dose, time of administration, tolerance level, and age. It is well-known that caffeine or other stimulants can produce insomnia. In addition, similar caffeine consumption may only start to produce insomnia in some individuals as they age because decreases in metabolic rate with aging increase the effective half-life of caffeine. Ethanol, which is known more as a central nervous system (CNS) depressant, may produce difficulty in maintaining sleep because it increases snoring and sleep apnea and because it suppresses REM sleep and therefore produces increased wakefulness when REM sleep normally occurs. Even the barbiturate sedatives such as secobarbital, which improve sleep during short-term use, produce rapid tolerance that may be perceived as a return of insomnia.

Insomnia holds a prominent position in the side-effect list of many medications. Classes of medications often associated with insomnia include stimulants, anorectics, beta-agonists, calcium channel blockers, corticosteroids, and antidepressants. The role of stimulants such as caffeine in the production of insomnia is clear.
However, respiratory stimulants, such as theophylline when taken in the evening, can also cause insomnia. Most appetite-suppressing medications also have central stimulant properties and therefore can produce insomnia. Beta-adrenergic antagonists such as propranolol, metoprolol, and pindolol may produce sleep-onset insomnia or increased awakenings and dreams.

Many antidepressants have the unique characteristic of having both insomnia and sleepiness as possible side effects. Tricyclic antidepressants are normally considered sedating, but particular tricyclics, such as protriptyline, may also produce insomnia. Monoamine oxidase inhibitors are more frequently associated with insomnia – sleep disturbance is reported in up to 67% of patients in some studies. Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, have been reported to produce insomnia in 5–35% of depressed patients. Selective serotonin and norepinephrine reuptake inhibitors, such as venlafaxine, have been shown to produce insomnia in 4–18% of patients (while producing sleepiness in 12–31% of patients). Norepinephrine and dopamine reuptake inhibitors such as bupropion have been associated with insomnia in 5–19% of patients.

Beta-antagonist antihypertensive agents such as propranolol have been associated with sleep disturbance in only 2–4% of patients, but wide use of these medications may produce more total patients with poor sleep. Effects are related to age and dose, with some decrease in poor sleep over time.

Corticosteroids such as prednisone and cortisol have been shown to produce increased wakefulness during the night. A wide range of patients have reported insomnia associated with corticosteroids, with some estimates as high as 50–71% of patients following the use of prednisone.

**Psychiatric disorders**

Insomnia has a very high association with psychiatric disorders. Historically, it was felt that insomnia was a major secondary symptom of depression, and, for many years, clinicians were admonished to identify and treat depression as a means of improving sleep in patients with identifiable signs of depression. However, this strategy has not been completely successful because many patients continue to report insomnia even when their depression has been treated, and other insomnia patients who are not depressed have been found to progress to depression. Since the initial Johns Hopkins study that showed insomnia in medical students predicting depression as long as 45 years later, at least five other studies have shown insomnia to predict depression with odds ratios between 2 and 10. Patients with a diagnosis of depression reported insomnia as their first symptom (i.e. prior to mood change) 39% of the time, and insomnia was the first symptom to reappear 56% of the time prior to a relapse. Insomnia is reported as a symptom in about 80% of depressed patients, and resolution of insomnia predicts positive treatment response. The strength of these data led the National Institutes of Health (NIH) to conclude that insomnia is actually ‘comorbid’ with, rather than secondary to, major depression and several other conditions, including anxiety, substance abuse, dementia, and a variety of physical problems.

Recent studies have shown that the treatment of both insomnia and depression can produce a better treatment response than treatment of the depression alone. In one study, therapy with fluoxetine and clonazepam for 8 weeks resulted in both improved sleep and greater improvement on the Hamilton Depression Scale than treatment with fluoxetine and placebo. In a second study, 545 patients with insomnia and depression were randomly treated with fluoxetine and eszopiclone or placebo for 8 weeks. Those patients given eszopiclone had better sleep and significantly better Hamilton Depression Scale scores even with sleep items removed from the Hamilton Depression Scale and at lower doses of fluoxetine. These studies suggest that insomnia in an independent contributor in the pathology of depression and that appropriate treatment of the underlying insomnia can improve treatment response. Long-term studies that examine whether treatment of insomnia prior to the appearance of depression can protect against a depressive episode remain to be done.

Although the strongest data in the literature link insomnia and depression, insomnia is also predictive of the development of generalized anxiety disorder, alcoholism, and substance abuse. Treatment of anxiety has traditionally used benzodiazepine agents, and these medications typically have both sedating and anxiolytic properties. Self-treatment for insomnia is often given as one of the initial steps in the development of alcohol abuse and is a cardinal symptom in alcohol withdrawal that can produce relapse. Because of concern with possible development of tolerance to benzodiazepine agents, patients being withdrawn from alcohol or other drugs of abuse frequently receive little treatment for their insomnia. Good studies with medications such as trazodone, used to improve sleep and perhaps to improve withdrawal response, remain to be done.
Other sleep disorders

Sleep apnea

Many patients are referred to sleep centers secondary to reported snoring or sleep apnea. A majority of these patients report problems with inability to remain awake during the day, but it is not uncommon for these patients to complain also of poor sleep at night. In sleep apnea, patients frequently arouse to resume respiration. It is common, however, for these patients to also complain of frequent awakenings or nocturia. Two studies have reported insomnia symptoms in 50–55% of patients undergoing evaluation for sleep apnea.24 One study of patients referred to sleep centers with a simple insomnia complaint reported that about 6% of these patients were found to have sleep apnea.20 A more recent study that performed sleep studies in a group of older individuals selected from their insomnia complaint found that 29% of these patients had sleep apnea.36

Periodic limb movements

Periodic limb movements and restless legs are both common and likely to result in reports of difficulty falling asleep, frequent awakenings, and residual fatigue during the next day. Restless legs probably exist in 5–15% of the population.37 Studies have suggested that 12% of patients with insomnia referred to sleep disorder centers have periodic limb movements or restless legs.20 Population studies have suggested that symptomatic periodic limb movements is rare in young individuals but that the incidence is 29% in individuals between 50 and 65 years of age and 44% in individuals over the age of 65.37 Patients may be asymptomatic if the limb movements do not actually disturb sleep, but as the number or violence of the movements increase, patients may report difficulty maintaining sleep in addition to restlessness.

Circadian rhythm disorders

Circadian rhythm disorders occur when there is a mismatch between the underlying biological rhythm of alertness and the choice of time to sleep. For example, when individuals attempt to go to sleep earlier than expected by their circadian controller, their body is still at a high level of arousal and they have difficulty falling asleep. If this is a consistent clinical problem, it is called delayed sleep phase syndrome. On the other hand, if individuals remain awake after their circadian controller has already decreased physiological function in anticipation of sleep onset, they will become increasingly sleepy, but, after they finally do go to bed and fall asleep, may find that they awaken sooner than they would like. If this is a consistent problem, it is called advanced sleep phase syndrome.

Young adults usually have a circadian rhythm which is slightly longer than 24 hours, and this may predispose them to want to stay up later each night if allowed. Unfortunately, staying up later on Friday and Saturday evening, for example, allows the circadian rhythm to shift so that an attempt to go to bed at a more normal time on Sunday night (an example of delayed sleep phase syndrome) produces difficulty in falling asleep.

Many individuals, including shift workers, retired persons, chronically ill individuals, and students may have irregular sleep patterns. For example, when individuals retire from work, they may no longer have a standard time to arise each morning and their levels of activity during the day may decrease. They may also have a tendency to start to nap during the day. It has been shown that elderly individuals have a flattened 24-hour temperature curve; i.e. their body temperature is lower during the day and higher during the night than that seen in young adults. Such changes in physiological function may be secondary to decreased activity and sleep during the day and more irregular sleep at night. Treatment for an irregular sleep–wake pattern involves establishing standard bed times and wake times, eliminating naps during the period of wakefulness, and increasing levels of activity and bright light exposure during the period of waking.

Circadian rhythms are normally maintained by activity, exposure to bright light, and social cues. Therefore, shifting of rhythms is facilitated by increasing activity, bright light exposure, and social interaction during the new waking period which is being established. Melatonin is a hormone that helps synchronize circadian rhythms and has been used to shift sleep to a new time after third shift work or time zone changes. However, melatonin is less useful in patients who usually go to bed at the same time, because they already secrete melatonin at their usual bedtime. Melatonin is also less useful in rotating shift workers, because, by the time melatonin has helped shift rhythms to a new sleep period, the shift worker has already switched to a different shift time.

Patients with a presumption of primary insomnia

In about 15% of insomnia patients referred to sleep disorders centers, all of the preceding factors can be ruled out as a cause of the reported chronic insomnia,20 and
a diagnosis of primary insomnia is considered. Some of these patients can be differentiated by an apparent short sleep requirement, and others may suffer from long-seated inappropriate behavioral conditioning rather than true primary insomnia.

Short sleepers

One group of patients who may report chronic difficulty falling asleep or a problem with awakening too early in the morning may simply have a short sleep requirement. Such patients may report poor sleep because they actually spend too much time in bed for their sleep requirement and therefore spend excessive time awake in bed. Daily sleep requirement changes rapidly in childhood, but some reduction in daily sleep requirement may continue in later years, so that some older individuals may require ≥6 hours of sleep per 24 hours. In addition, aging is accompanied by lighter sleep, increased awakenings, and a tendency to awaken early in the morning. If these changes have occurred without the development of daytime consequences, they may be a function of normal aging. In such patients, spending less time in bed along with some reassurance that sleep requirements differ from individual to individual usually resolves the problem. These patients can be differentiated from other insomnia patients by the lack of a complaint of daytime compromise secondary to their short sleep.

Inappropriate conditioning

Some patients who have normal psychological status during the day find that they become tense only when they try to fall asleep. Difficulty falling asleep is disturbing, and these patients then begin to worry about whether they will be able to fall asleep and the consequences of not falling asleep. Such thoughts may produce a vicious cycle in which increasing arousal limits the ability to fall asleep and these result in increasing arousal. Eventually, just going to bed can initiate the cycle of worry/arousal. Other patients may begin to plan their next day or think about problems when they go to bed. Eventually, the bedroom sleep setting becomes associated as the place to plan or worry rather than the place to sleep. Inappropriate conditioning as a cause of insomnia is particularly amenable to treatment with behavioral therapy (see Treatment section).

Primary insomnia

Patients with primary insomnia complain of poor sleep and significant daytime symptoms, including subjective fatigue and increased stress, anxiety, or depression. Despite poor sleep at night that should produce partial sleep deprivation and daytime sleepiness, these patients also have difficulty falling asleep when given the Multiple Sleep Latency Test (MSLT). Primary insomnia patients do not have depression or anxiety diagnoses, by definition, but do present with elevated scores consistent with psychopathology, as measured by the Minnesota Multiphasic Personality Inventory (MMPI). Additionally, numerous studies have documented that patients with primary insomnia have increased physiological activation compared with normal controls across numerous dimensions, including increased whole-body and brain metabolic rate; increased heart rate, sympathetic nervous system activation, and decreased parasympathetic nervous system activation, as assessed by heart rate variability; increased high-frequency EEG (beta) activity; and abnormal hormone secretion (increased cortisol and norepinephrine and decreased melatonin).

Primary insomnia patients typically display both mood alteration and evidence of physiological arousal, and this has made identification of underlying causal factors difficult. However, one study examined the effects of increasing physiological arousal in the production of insomnia through the administration of caffeine 400 mg three times per day for a week in normal sleepers. Caffeine use increased physiological arousal, as measured by whole-body metabolic rate, and sleep efficiency declined significantly. During the initial days of caffeine use, subjects had elevated MSLT (i.e. took longer to fall asleep) and reported increased subjective vigor. However, by the end of the week of caffeine use, subjects reported significantly increased daytime fatigue despite an MSLT that remained significantly elevated as compared to baseline. Also, anxiety, as measured by the anxiety scale of the MMPI, moved significantly toward psychopathology by the end of the week. The finding that chronically elevated physiological arousal would paradoxically lead to increased fatigue even while patients were less sleepy on the MSLT was an indication that physiological activation by itself could be responsible for the same paradoxical reports in patients with insomnia. The increase on the anxiety scale of the MMPI, a non-transparent trait measure of personality, offered evidence that cognitive and personality components frequently seen in patients with insomnia could be significantly influenced by a chronically increased level of central arousal.

Other studies have examined the relationship between poor sleep and reports of insomnia in both normal sleepers and insomnia patients to understand
the extent to which the insomnia patient’s complaints of poor sleep and daytime dysphoria are related to their sleep parameters. In one study, normal sleepers were given the same sleep pattern as a matched insomnia patient (a technician awakened or aroused normal sleepers whenever the insomnia patient aroused or awoke) for a week to determine if the poor sleep pattern per se would produce the daytime symptoms that insomnia patients report.\(^4\)\(^3\) The results of the study indicated that normal sleepers given this ‘insomnia’ suffered from mild sleep deprivation but did not develop changes in mood, personality, or physiological activation typically seen in insomnia patients.

In a similar study,\(^4\)\(^2\) it was hypothesized that if nocturnal sleep parameters produced the daytime dysphoria reported by patients with insomnia, then sleep maintenance insomnia patients who were kept awake even longer than usual during the night should have increased dysphoria during the following day. To test this hypothesis, patients with sleep maintenance insomnia were allowed only 80% of their already reduced total sleep each night for seven consecutive nights. This sleep reduction was accomplished by waking patients at the end of each quarter of the night if they accumulated more than 80% of their baseline sleep for that quarter of the night (while holding time in bed for the entire night at the baseline level). This paradigm produced very poor sleep (total sleep of 4.2 hours on each night for the week). The reduction of total sleep time by experimental awakenings resulted in a significant decrease in daytime MSLT values from 15.6 to 11.1 minutes. However, the 11.1-minute value is still considered ‘normal’ for the MSLT and compares well to the 11.06-minute value. The results of the study indicated that normal sleepers given this ‘insomnia’ suffered from mild sleep deprivation but did not develop changes in mood, personality, or physiological activation typically seen in insomnia patients.

Another approach in understanding the antecedents of primary insomnia is to look at normal sleepers prior to the development of a chronic insomnia problem to determine what predispositions may exist. When a large group of normal sleepers were invited to participate in a sleep study, it was found that some slept well and some had a poor night of sleep on their first night in the laboratory.\(^4\)\(^5\) Those subjects who had a poor night of sleep on the first laboratory night were also found to (1) have longer sleep latency on their MSLT; (2) have significantly more difficulty sleeping after two phase advance conditions and after the administration of caffeine; and (3) have a higher heart rate and sympathetic nervous system activation than subjects who had slept well on their first night in the sleep laboratory. However, the groups did not differ in personality or mood dimensions. Such data suggest that there is an underlying dimension of physiological activation, or, perhaps, a pre-insomnia condition, that makes some individuals more reactive to stress and that could evolve into a chronic insomnia pattern over time.

**Paradoxical insomnia**

Another group of patients who would be classified as having primary insomnia based upon their history actually have normal sleep when polysomnographic recordings are made. Despite a normal night of sleep based upon polysomnography, these patients continue to report that they have difficulty falling asleep or remaining asleep. These patients are currently given the diagnosis of paradoxical insomnia. One study showed that these patients, even while having a normal night of sleep in terms of EEG parameters, also had an elevated whole-body metabolic rate throughout the night and day as compared to matched controls.\(^4\)\(^6\) It is therefore possible that these patients actually suffer from a disorder of hyperarousal and that the hyperarousal is responsible for the insomnia symptoms that they report.

**TREATMENT**

Reviews of specific medications and treatment options are provided in several other chapters. This section will therefore only briefly summarize insomnia treatment guidelines that have been updated and revised with the publication of the NIH State-of-the-Science Conference Statement on chronic insomnia in 2005.\(^1\) Treatments for insomnia can be divided into behavioral treatments and pharmacological treatments.
Behavioral therapies

Behavioral therapies, which include relaxation training, stimulus control, and sleep restriction and cognitive therapies such as cognitive restructuring, have been studied for many years. When combined, as cognitive behavioral therapy (CBT), the approach has demonstrated efficacy in insomnia treatment based upon numerous experiments over the past 30 years. CBT, which typically involves a number of visits with a trained practitioner, seeks to identify inappropriate behavior that has begun to interfere with the ability to fall asleep or stay asleep. Once disruptive behaviors – such as becoming tense or worrying when lying down to fall asleep or remaining in bed for long periods even when unable to sleep – are identified, specific behavioral change is recommended and patients track their progress with sleep diaries. Initial progress with CBT may be slower than with pharmacotherapy, but CBT results were otherwise generally comparable with pharmacology. There was some evidence that CBT-related improvement in sleep continued well beyond the end of active treatment. No evidence of side effects related to the treatment has been presented, but there is little actual study of possible side effects of CBT.

The primary limitations of CBT therapy include the fact that there really is no single standardized CBT therapy, there are no real data to indicate how many therapy sessions are necessary for an optimal response, and there are relatively few well-trained practitioners. In addition, there is little availability of this therapy for primary care physicians, who are most likely to identify and treat patients with chronic insomnia.

Pharmacological therapies

In contrast with CBT, prescription medications for use in insomnia have been designed only to relieve the symptoms while the medication is being used so that there is little research on the persistence of symptoms when the medication is discontinued. However, there are currently 10 prescription medications approved as efficacious by the Food and Drug Administration (FDA) available with the indication for the treatment of insomnia. These medications are summarized in Table 8.2. The first five, older medications – estazolam, flurazepam, quazepam, temazepam, and triazolam – are traditional benzodiazepines that are best differentiated by widely varying half-life. The newer agents, which have a non-benzodiazepine structure and have a more targeted action at the γ-aminobutyric acid (GABA) type A receptor, include zolpidem, zaleplon, eszopiclone, and zolpidem extended release. The final, relatively recently approved medication is ramelteon, which is a melatonin agonist.

Adverse effects associated with these medications include hangover sedation that can be related to poor coordination, decreased psychomotor performance, and sleepiness. Hangover effects are most common in the medications with long half-lives and appear to be less with the newer agents (that all have half-lives of ≤7 hours). Some of the compounds may have a risk of dependence or rebound insomnia, and side effects, in general, are worse in the elderly.

Numerous prescription drugs not approved for use in insomnia are commonly used for the treatment of chronic insomnia. Trazodone is currently the most

### Table 8.2 FDA-approved medications for insomnia

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Brand name</th>
<th>Half-life (hours)</th>
<th>Dose (mg) elderly/adult</th>
<th>Drug class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flurazepam</td>
<td>Dalmane</td>
<td>48–120</td>
<td>15/30</td>
<td>BZD</td>
</tr>
<tr>
<td>Temazepam</td>
<td>Restoril</td>
<td>8–20</td>
<td>15/30</td>
<td>BZD</td>
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<td>Triazolam</td>
<td>Halcion</td>
<td>2–6</td>
<td>0.125/0.25</td>
<td>BZD</td>
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<td>Prosom</td>
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<td>1/2</td>
<td>BZD</td>
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<td>Doral</td>
<td>48–120</td>
<td>7.5–15</td>
<td>BZD</td>
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<td>Zolpidem</td>
<td>Ambien</td>
<td>1.5–2.4</td>
<td>5/10</td>
<td>Non-BZD</td>
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<tr>
<td>Zaleplon</td>
<td>Sonata</td>
<td>1</td>
<td>5/10</td>
<td>Non-BZD</td>
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<tr>
<td>Eszopiclone</td>
<td>Lunesta</td>
<td>5–7</td>
<td>1–2/2–3</td>
<td>Non-BZD</td>
</tr>
<tr>
<td>Zolpidem extended release</td>
<td>Ambien CR</td>
<td>1.5–2.4&lt;sup&gt;*&lt;/sup&gt;</td>
<td>6.25/12.5</td>
<td>Non-BZD</td>
</tr>
<tr>
<td>Ramelteon</td>
<td>Rozerem</td>
<td>1.5–5</td>
<td>8/8</td>
<td>Melatonin agonist</td>
</tr>
</tbody>
</table>

BZD, Benzodiazepine; Non-BZD = non-benzodiazepine chemical structure. <sup>*</sup> Time release formulation increases active life about one additional hour from the half-life stated.
commonly used prescription treatment for insomnia. However, there are few studies of trazodone as a treatment for primary insomnia and no studies showing efficacy continuing beyond 2 weeks. In addition, the antidepressants have potentially significant adverse effects that must be considered. Other prescription medications, including barbiturates and antipsychotics, can have significant risks and were not recommended by the NIH. Several non-prescription medications are commonly used to treat insomnia. Antihistamines may be the most common treatment for insomnia, but there is no strong evidence for efficacy, and antihistamines do have risks for adverse effects such as residual sedation, blurred vision, urinary retention, or constipation. The NIH summary concluded that, due to limited or missing evidence for efficacy and/or significant side effects, alcohol, melatonin, valerian, and L-tryptophan were not recommended as treatments for insomnia.

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REFERENCES

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