be intentional. To qualify for a diagnosis of enuresis, the voiding of urine must occur at least twice a week for at least 3 consecutive months or must cause clinically significant distress or impairment in social, academic (occupational), or other important areas of functioning (Criterion B). The individual must have reached an age at which continence is expected (i.e., a chronological age of at least 5 years or, for children with developmental delays, a mental age of at least 5 years) (Criterion C). The urinary incontinence is not attributable to the physiological effects of a substance (e.g., a diuretic, an antipsychotic medication) or another medical condition (e.g., diabetes, spina bifida, a seizure disorder) (Criterion D).

Associated Features Supporting Diagnosis

During nocturnal enuresis, occasionally the voiding takes place during rapid eye movement (REM) sleep, and the child may recall a dream that involved the act of urinating. During daytime (diurnal) enuresis, the child defers voiding until incontinence occurs, sometimes because of a reluctance to use the toilet as a result of social anxiety or a preoccupation with school or play activity. The enuretic event most commonly occurs in the early afternoon on school days and may be associated with symptoms of disruptive behavior. The enuresis commonly persists after appropriate treatment of an associated infection.

Prevalence

The prevalence of enuresis is 5%–10% among 5-year-olds, 3%–5% among 10-year-olds, and around 1% among individuals 15 years or older.

Development and Course

Two types of course of enuresis have been described: a "primary" type, in which the individual has never established urinary continence, and a "secondary" type, in which the disturbance develops after a period of established urinary continence. There are no differences in prevalence of comorbid mental disorders between the two types. By definition, primary enuresis begins at age 5 years. The most common time for the onset of secondary enuresis is between ages 5 and 8 years, but it may occur at any time. After age 5 years, the rate of spontaneous remission is 5%–10% per year. Most children with the disorder become continent by adolescence, but in approximately 1% of cases the disorder continues into adulthood. Diurnal enuresis is uncommon after age 9 years. While occasional diurnal incontinence is not uncommon in middle childhood, it is substantially more common in those who also have persistent nocturnal enuresis. When enuresis persists into late childhood or adolescence, the frequency of incontinence may increase, whereas continence in early childhood is usually associated with a declining frequency of wet nights.

Risk and Prognostic Factors

Environmental. A number of predisposing factors for enuresis have been suggested, including delayed or lax toilet training and psychosocial stress.

Genetic and physiological. Enuresis has been associated with delays in the development of normal circadian rhythms of urine production, with resulting nocturnal polyuria or abnormalities of central vasopressin receptor sensitivity, and reduced functional bladder capacities with bladder hyperreactivity (unstable bladder syndrome). Nocturnal enuresis is a genetically heterogeneous disorder. Heritability has been shown in family, twin, and segregation analyses. Risk for childhood nocturnal enuresis is approximately 3.6 times higher in offspring of enuretic mothers and 10.1 times higher in the presence of paternal urinary incontinence. The risk magnitudes for nocturnal enuresis and diurnal incontinence are similar.

Culture-Related Diagnostic Issues

Enuresis has been reported in a variety of European, African, and Asian countries as well as in the United States. At a national level, prevalence rates are remarkably similar, and there is great similarity in the developmental trajectories found in different countries. There are very high rates of enuresis in orphanages and other residential institutions, likely related to the mode and environment in which toilet training occurs.

Gender-Related Diagnostic Issues

Nocturnal enuresis is more common in males. Diurnal incontinence is more common in females. The relative risk of having a child who develops enuresis is greater for previously enuretic fathers than for previously enuretic mothers.

Functional Consequences of Enuresis

The amount of impairment associated with enuresis is a function of the limitation on the child's social activities (e.g., ineligibility for sleep-away camp) or its effect on the child's self-esteem, the degree of social ostracism by peers, and the anger, punishment, and rejection on the part of caregivers.

Differential Diagnosis

Neurogenic bladder or another medical condition. The diagnosis of enuresis is not made in the presence of a neurogenic bladder or another medical condition that causes polyuria or urgency (e.g., untreated diabetes mellitus or diabetes insipidus) or during an acute urinary tract infection. However, a diagnosis is compatible with such conditions if urinary incontinence was regularly present prior to the development of another medical condition or if it persists after the institution of appropriate treatment of the medical condition.

Medication side effects. Enuresis may occur during treatment with antipsychotic medications, diuretics, or other medications that may induce incontinence. In this case, the diagnosis should not be made in isolation but may be noted as a medication side effect. However, a diagnosis of enuresis may be made if urinary incontinence was regularly present prior to treatment with the medication.

Comorbidity

Although most children with enuresis do not have a comorbid mental disorder, the prevalence of comorbid behavioral symptoms is higher in children with enuresis than in children without enuresis. Developmental delays, including speech, language, learning, and motor skills delays, are also present in a portion of children with enuresis. Encopresis, sleepwalking, and sleep terror disorder may be present. Urinary tract infections are more common in children with enuresis, especially the diurnal subtype, than in those who are continent.

Encopresis

Diagnostic Criteria **307.7 (F98.1)**

A. Repeated passage of feces into inappropriate places (e.g., clothing, floor), whether involuntary or intentional.
B. At least one such event occurs each month for at least 3 months.
C. Chronological age is at least 4 years (or equivalent developmental level).
D. The behavior is not attributable to the physiological effects of a substance (e.g., laxatives) or another medical condition except through a mechanism involving constipation.

Specify whether:

With constipation and overflow incontinence: There is evidence of constipation on physical examination or by history.

Without constipation and overflow incontinence: There is no evidence of constipation on physical examination or by history.

Subtypes

Feces in the with constipation and overflow incontinence subtype are characteristically (but not invariably) poorly formed, and leakage can be infrequent to continuous, occurring mostly during the day and rarely during sleep. Only part of the feces is passed during toileting, and the incontinence resolves after treatment of the constipation.

In the without constipation and overflow incontinence subtype, feces are likely to be of normal form and consistency, and soiling is intermittent. Feces may be deposited in a prominent location. This is usually associated with the presence of oppositional defiant disorder or conduct disorder or may be the consequence of anal masturbation. Soiling without constipation appears to be less common than soiling with constipation.

Diagnostic Features

The essential feature of encopresis is repeated passage of feces into inappropriate places (e.g., clothing or floor) (Criterion A). Most often the passage is involuntary but occasionally may be intentional. The event must occur at least once a month for at least 3 months (Criterion B), and the chronological age of the child must be at least 4 years (or for children with developmental delays, the mental age must be at least 4 years) (Criterion C). The fecal incontinence must not be exclusively attributable to the physiological effects of a substance (e.g., laxatives) or another medical condition except through a mechanism involving constipation (Criterion D).

When the passage of feces is involuntary rather than intentional, it is often related to constipation, impaction, and retention with subsequent overflow. The constipation may develop for psychological reasons (e.g., anxiety about defecating in a particular place, a more general pattern of anxious or oppositional behavior), leading to avoidance of defecation. Physiological predispositions to constipation include ineffectual straining or paradoxical defecation dynamics, with contraction rather than relaxation of the external sphincter or pelvic floor during straining for defecation. Dehydration associated with a febrile illness, hypothyroidism, or a medication side effect can also induce constipation. Once constipation has developed, it may be complicated by an anal fissure, painful defecation, and further fecal retention. The consistency of the stool may vary. In some individuals the stool may be of normal or near-normal consistency. In other individuals—such as those with overflow incontinence secondary to fecal retention—it may be liquid.

Associated Features Supporting Diagnosis

The child with encopresis often feels ashamed and may wish to avoid situations (e.g., camp, school) that might lead to embarrassment. The amount of impairment is a function of the effect on the child's self-esteem, the degree of social ostracism by peers, and the anger, punishment, and rejection on the part of caregivers. Smearing feces may be deliberate or accidental, resulting from the child's attempt to clean or hide feces that were passed involuntarily. When the incontinence is clearly deliberate, features of oppositional defiant disorder or conduct disorder may also be present. Many children with encopresis and chronic constipation also have enuresis symptoms and may have associated urinary reflux in the bladder or ureters that may lead to chronic urinary infections, the symptoms of which may remit with treatment of the constipation.

Prevalence

It is estimated that approximately 1% of 5-year-olds have encopresis, and the disorder is more common in males than in females.

Development and Course

Encopresis is not diagnosed until a child has reached a chronological age of at least 4 years (or for children with developmental delays, a mental age of at least 4 years). Inadequate, inconsistent toilet training and psychosocial stress (e.g., entering school, the birth of a sibling) may be predisposing factors. Two types of course have been described: a "primary" type, in which the individual has never established fecal continence, and a "secondary" type, in which the disturbance develops after a period of established fecal continence. Encopresis can persist, with intermittent exacerbations, for years.

Risk and Prognostic Factors

Genetic and physiological. Painful defecation can lead to constipation and a cycle of withholding behaviors that make encopresis more likely. Use of some medications (e.g., anticonvulsants, cough suppressants) may increase constipation and make encopresis more likely.

Diagnostic Markers

In addition to physical examination, gastrointestinal imaging (e.g., abdominal radiograph) may be informative to assess retained stool and gas in the colon. Additional tests, such as barium enema and anorectal manography, may be used to help exclude other medical conditions, such as Hirschsprung's disease.

Differential Diagnosis

A diagnosis of encopresis in the presence of another medical condition is appropriate only if the mechanism involves constipation that cannot be explained by other medical conditions. Fecal incontinence related to other medical conditions (e.g., chronic diarrhea, spina bifida, anal stenosis) would not warrant a DSM-5 diagnosis of encopresis.

Comorbidity

Urinary tract infections can be comorbid with encopresis and are more common in females.

Other Specified Elimination Disorder

This category applies to presentations in which symptoms characteristic of an elimination disorder that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for any of the disorders in the elimination disorders diagnostic class. The other specified elimination disorder category is used in situations in which the clinician chooses to communicate the specific reason that the presentation does not meet the criteria for any specific elimination disorder. This is done by recording "other specified elimination disorder" followed by the specific reason (e.g., "low-frequency enuresis").

Coding note: Code **788.39 (N39.498)** for other specified elimination disorder with urinary symptoms; **787.60 (R15.9)** for other specified elimination disorder with fecal symptoms.

Unspecified Elimination Disorder

This category applies to presentations in which symptoms characteristic of an elimination disorder that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for any of the disorders in the elimination disorders diagnostic class. The unspecified elimination disorder category is used in situations in which the clinician chooses *not* to specify the reason that the criteria are not met for a specific elimination disorder, and includes presentations in which there is insufficient information to make a more specific diagnosis (e.g., in emergency room settings).

Coding note: Code **788.30 (R32)** for unspecified elimination disorder with urinary symptoms; **787.60 (R15.9)** for unspecified elimination disorder with fecal symptoms.

Sleep-Wake Disorders

The DSM-5 classification of sleep-wake disorders is intended for use by general mental health and medical clinicians (those caring for adult, geriatric, and pediatric patients). Sleep-wake disorders encompass 10 disorders or disorder groups: insomnia disorder, hypersomnolence disorder, narcolepsy, breathing-related sleep disorders, circadian rhythm sleep-wake disorders, non–rapid eye movement (NREM) sleep arousal disorders, nightmare disorder, rapid eye movement (REM) sleep behavior disorder, restless legs syndrome, and substance/medication-induced sleep disorder. Individuals with these disorders typically present with sleep-wake complaints of dissatisfaction regarding the quality, timing, and amount of sleep. Resulting daytime distress and impairment are core features shared by all of these sleep-wake disorders.

The organization of this chapter is designed to facilitate differential diagnosis of sleep-wake complaints and to clarify when referral to a sleep specialist is appropriate for further assessment and treatment planning. The DSM-5 sleep disorders nosology uses a simple, clinically useful approach, while also reflecting scientific advances in epidemiology, genetics, pathophysiology, assessment, and interventions research since DSM-IV. In some cases (e.g., insomnia disorder), a "lumping" approach has been adopted, whereas in others (e.g., narcolepsy), a "splitting" approach has been taken, reflecting the availability of validators derived from epidemiological, neurobiological, and interventions research.

Sleep disorders are often accompanied by depression, anxiety, and cognitive changes that must be addressed in treatment planning and management. Furthermore, persistent sleep disturbances (both insomnia and excessive sleepiness) are established risk factors for the subsequent development of mental illnesses and substance use disorders. They may also represent a prodromal expression of an episode of mental illness, allowing the possibility of early intervention to preempt or to attenuate a full-blown episode.

The differential diagnosis of sleep-wake complaints necessitates a multidimensional approach, with consideration of possibly coexisting medical and neurological conditions. Coexisting clinical conditions are the rule, not the exception. Sleep disturbances furnish a clinically useful indicator of medical and neurological conditions that often coexist with depression and other common mental disorders. Prominent among these comorbidities are breathing-related sleep disorders, disorders of the heart and lungs (e.g., congestive heart failure, chronic obstructive pulmonary disease), neurodegenerative disorders (e.g., Alzheimer's disease), and disorders of the musculoskeletal system (e.g., osteoarthritis). These disorders not only may disturb sleep but also may themselves be worsened during sleep (e.g., prolonged apneas or electrocardiographic arrhythmias during REM sleep; confusional arousals in patients with dementing illness; seizures in persons with complex partial seizures). REM sleep behavior disorder is often an early indicator of neurodegenerative disorders (alpha synucleinopathies) like Parkinson's disease. For all of these reasons—related to differential diagnosis, clinical comorbidity, and facilitation of treatment planning—sleep disorders are included in DSM-5.

The approach taken to the classification of sleep-wake disorders in DSM-5 can be understood within the context of "lumping versus splitting." DSM-IV represented an effort to simplify sleep-wake disorders classification and thus aggregated diagnoses under broader, less differentiated labels. At the other pole, the *International Classification of Sleep Disorders,*

2nd Edition (ICSD-2) elaborated numerous diagnostic subtypes. DSM-IV was prepared for use by mental health and general medical clinicians who are not experts in sleep medicine. ICSD-2 reflected the science and opinions of the sleep specialist community and was prepared for use by specialists.

The weight of available evidence supports the superior performance characteristics (interrater reliability, as well as convergent, discriminant, and face validity) of simpler, less-differentiated approaches to diagnosis of sleep-wake disorders. The text accompanying each set of diagnostic criteria provides linkages to the corresponding disorders included in ICSD-2. The DSM-5 sleep-wake disorders classification also specifies corresponding non-psychiatric listings (e.g., neurology codes) from the *International Classification of Diseases* (ICD).

The field of sleep disorders medicine has progressed in this direction since the publication of DSM-IV. The use of biological validators is now embodied in the DSM-5 classification of sleep-wake disorders, particularly for disorders of excessive sleepiness, such as narcolepsy; for breathing-related sleep disorders, for which formal sleep studies (i.e., polysomnography) are indicated; and for restless legs syndrome, which can often coexist with periodic limb movements during sleep, detectable via polysomnography.

Insomnia Disorder

Diagnostic Criteria **307.42 (F51.01)**

A. A predominant complaint of dissatisfaction with sleep quantity or quality, associated with one (or more) of the following symptoms:
   1. Difficulty initiating sleep. (In children, this may manifest as difficulty initiating sleep without caregiver intervention.)
   2. Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings. (In children, this may manifest as difficulty returning to sleep without caregiver intervention.)
   3. Early-morning awakening with inability to return to sleep.

B. The sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning.

C. The sleep difficulty occurs at least 3 nights per week.

D. The sleep difficulty is present for at least 3 months.

E. The sleep difficulty occurs despite adequate opportunity for sleep.

F. The insomnia is not better explained by and does not occur exclusively during the course of another sleep-wake disorder (e.g., narcolepsy, a breathing-related sleep disorder, a circadian rhythm sleep-wake disorder, a parasomnia).

G. The insomnia is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication).

H. Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia.

Specify if:

With non–sleep disorder mental comorbidity, including substance use disorders

With other medical comorbidity

With other sleep disorder

Coding note: The code 307.42 (F51.01) applies to all three specifiers. Code also the relevant associated mental disorder, medical condition, or other sleep disorder immediately after the code for insomnia disorder in order to indicate the association.

Specify if:

Episodic: Symptoms last at least 1 month but less than 3 months.

Persistent: Symptoms last 3 months or longer.

Recurrent: Two (or more) episodes within the space of 1 year.

Note: Acute and short-term insomnia (i.e., symptoms lasting less than 3 months but otherwise meeting all criteria with regard to frequency, intensity, distress, and/or impairment) should be coded as an other specified insomnia disorder.

Note. The diagnosis of insomnia disorder is given whether it occurs as an independent condition or is comorbid with another mental disorder (e.g., major depressive disorder), medical condition (e.g., pain), or another sleep disorder (e.g., a breathing-related sleep disorder). For instance, insomnia may develop its own course with some anxiety and depressive features but in the absence of criteria being met for any one mental disorder. Insomnia may also manifest as a clinical feature of a more predominant mental disorder. Persistent insomnia may even be a risk factor for depression and is a common residual symptom after treatment for this condition. With comorbid insomnia and a mental disorder, treatment may also need to target both conditions. Given these different courses, it is often impossible to establish the precise nature of the relationship between these clinical entities, and this relationship may change over time. Therefore, in the presence of insomnia and a comorbid disorder, it is not necessary to make a causal attribution between the two conditions. Rather, the diagnosis of insomnia disorder is made with concurrent specification of the clinically comorbid conditions. A concurrent insomnia diagnosis should only be considered when the insomnia is sufficiently severe to warrant independent clinical attention; otherwise, no separate diagnosis is necessary.

Diagnostic Features

The essential feature of insomnia disorder is dissatisfaction with sleep quantity or quality with complaints of difficulty initiating or maintaining sleep. The sleep complaints are accompanied by clinically significant distress or impairment in social, occupational, or other important areas of functioning. The sleep disturbance may occur during the course of another mental disorder or medical condition, or it may occur independently.

Different manifestations of insomnia can occur at different times of the sleep period. *Sleep-onset insomnia* (or *initial insomnia*) involves difficulty initiating sleep at bedtime. *Sleep maintenance insomnia* (or *middle insomnia*) involves frequent or prolonged awakenings throughout the night. *Late insomnia* involves early-morning awakening with an inability to return to sleep. Difficulty maintaining sleep is the most common single symptom of insomnia, followed by difficulty falling asleep, while a combination of these symptoms is the most common presentation overall. The specific type of sleep complaint often varies over time. Individuals who complain of difficulty falling asleep at one time may later complain of difficulty maintaining sleep, and vice versa. Symptoms of difficulty falling asleep and difficulty maintaining sleep can be quantified by the individual's retrospective self-report, sleep diaries, or other methods, such as actigraphy or polysomnography, but the diagnosis of insomnia disorder is based on the individual's subjective perception of sleep or a caretaker's report.

Nonrestorative sleep, a complaint of poor sleep quality that does not leave the individual rested upon awakening despite adequate duration, is a common sleep complaint usually occurring in association with difficulty initiating or maintaining sleep, or less frequently in isolation. This complaint can also be reported in association with other sleep disorders (e.g., breathing-related sleep disorder). When a complaint of nonrestorative sleep occurs in isolation (i.e., in the absence of difficulty initiating and/or maintaining sleep) but all diagnostic criteria with regard to frequency, duration, and daytime distress and impairments are otherwise met, a diagnosis of other specified insomnia disorder or unspecified insomnia disorder is made.

Aside from the frequency and duration criteria required to make the diagnosis, additional criteria are useful to quantify insomnia severity. These quantitative criteria, while arbitrary, are provided for illustrative purpose only. For instance, difficulty initiating sleep is defined by a subjective sleep latency greater than 20–30 minutes, and difficulty maintaining sleep is defined by a subjective time awake after sleep onset greater than 20–30 minutes. Although there is no standard definition of early-morning awakening, this symptom involves awakening at least 30 minutes before the scheduled time and before total sleep time reaches 6½ hours. It is essential to take into account not only the final awakening time but also the bedtime on the previous evening. Awakening at 4:00 A.M. does not have the same clinical significance in those who go to bed at 9:00 P.M. as in those who go to bed at 11:00 P.M. Such a symptom may also reflect an age-dependent decrease in the ability to sustain sleep or an age-dependent shift in the timing of the main sleep period.

Insomnia disorder involves daytime impairments as well as nighttime sleep difficulties. These include fatigue or, less commonly, daytime sleepiness; the latter is more common among older individuals and when insomnia is comorbid with another medical condition (e.g., chronic pain) or sleep disorder (e.g., sleep apnea). Impairment in cognitive performance may include difficulties with attention, concentration and memory, and even with performing simple manual skills. Associated mood disturbances are typically described as irritability or mood lability and less commonly as depressive or anxiety symptoms. Not all individuals with nighttime sleep disturbances are distressed or have functional impairment. For example, sleep continuity is often interrupted in healthy older adults who nevertheless identify themselves as good sleepers. A diagnosis of insomnia disorder should be reserved for those individuals with significant daytime distress or impairment related to their nighttime sleep difficulties.

Associated Features Supporting Diagnosis

Insomnia is often associated with physiological and cognitive arousal and conditioning factors that interfere with sleep. A preoccupation with sleep and distress due to the inability to sleep may lead to a vicious cycle: the more the individual strives to sleep, the more frustration builds and further impairs sleep. Thus, excessive attention and efforts to sleep, which override normal sleep-onset mechanisms, may contribute to the development of insomnia. Individuals with persistent insomnia may also acquire maladaptive sleep habits (e.g., spending excessive time in bed; following an erratic sleep schedule; napping) and cognitions (e.g., fear of sleeplessness; apprehensions of daytime impairments; clock monitoring) during the course of the disorder. Engaging in such activities in an environment in which the individual has frequently spent sleepless nights may further compound the conditioned arousal and perpetuate sleep difficulties. Conversely, the individual may fall asleep more easily when not trying to do so. Some individuals also report better sleep when away from their own bedrooms and their usual routines.

Insomnia may be accompanied by a variety of daytime complaints and symptoms, including fatigue, decreased energy, and mood disturbances. Symptoms of anxiety or depression that do not meet criteria for a specific mental disorder may be present, as well as an excessive focus on the perceived effects of sleep loss on daytime functioning.

Individuals with insomnia may have elevated scores on self-report psychological or personality inventories with profiles indicating mild depression and anxiety, a worrisome cognitive style, an emotion-focused and internalizing style of conflict resolution, and a somatic focus. Patterns of neurocognitive impairment among individuals with insomnia disorder are inconsistent, although there may be impairments in performing tasks of higher complexity and those requiring frequent changes in performance strategy. Individuals with insomnia often require more effort to maintain cognitive performance.

Prevalence

Population-based estimates indicate that about one-third of adults report insomnia symptoms, 10%–15% experience associated daytime impairments, and 6%–10% have symptoms

that meet criteria for insomnia disorder. Insomnia disorder is the most prevalent of all sleep disorders. In primary care settings, approximately 10%–20% of individuals complain of significant insomnia symptoms. Insomnia is a more prevalent complaint among females than among males, with a gender ratio of about 1.44:1. Although insomnia can be a symptom or an independent disorder, it is most frequently observed as a comorbid condition with another medical condition or mental disorder. For instance, 40%–50% of individuals with insomnia also present with a comorbid mental disorder.

Development and Course

The onset of insomnia symptoms can occur at any time during life, but the first episode is more common in young adulthood. Less frequently, insomnia begins in childhood or adolescence. In women, new-onset insomnia may occur during menopause and persist even after other symptoms (e.g., hot flashes) have resolved. Insomnia may have a late-life onset, which is often associated with the onset of other health-related conditions.

Insomnia can be situational, persistent, or recurrent. Situational or acute insomnia usually lasts a few days or a few weeks and is often associated with life events or rapid changes in sleep schedules or environment. It usually resolves once the initial precipitating event subsides. For some individuals, perhaps those more vulnerable to sleep disturbances, insomnia may persist long after the initial triggering event, possibly because of conditioning factors and heightened arousal. The factors that precipitate insomnia may differ from those that perpetuate it. For example, an individual who is bedridden with a painful injury and has difficulty sleeping may then develop negative associations for sleep. Conditioned arousal may then persist and lead to persistent insomnia. A similar course may develop in the context of an acute psychological stress or a mental disorder. For instance, insomnia that occurs during an episode of major depressive disorder can become a focus of attention, with consequent negative conditioning, and persist even after resolution of the depressive episode. In some cases, insomnia may also have an insidious onset without any identifiable precipitating factor.

The course of insomnia may also be episodic, with recurrent episodes of sleep difficulties associated with the occurrence of stressful events. Chronicity rates range from 45% to 75% for follow-ups of 1–7 years. Even when the course of the insomnia has become chronic, there is night-to-night variability in sleep patterns, with an occasional restful night's sleep interspersed with several nights of poor sleep. The characteristics of insomnia may also change over time. Many individuals with insomnia have a history of "light" or easily disturbed sleep prior to onset of more persistent sleep problems.

Insomnia complaints are more prevalent among middle-age and older adults. The type of insomnia symptom changes as a function of age, with difficulties initiating sleep being more common among young adults and problems maintaining sleep occurring more frequently among middle-age and older individuals.

Difficulties initiating and maintaining sleep can also occur in children and adolescents, but there are more limited data on prevalence, risk factors, and comorbidity during these developmental phases of the lifespan. Sleep difficulties in childhood can result from conditioning factors (e.g., a child who does not learn to fall asleep or return to sleep without the presence of a parent) or from the absence of consistent sleep schedules and bedtime routines. Insomnia in adolescence is often triggered or exacerbated by irregular sleep schedules (e.g., phase delay). In both children and adolescents, psychological and medical factors can contribute to insomnia.

The increased prevalence of insomnia in older adults is partly explained by the higher incidence of physical health problems with aging. Changes in sleep patterns associated with the normal developmental process must be differentiated from those exceeding age-related changes. Although polysomnography is of limited value in the routine evaluation of insomnia, it may be more useful in the differential diagnosis among older adults because the etiologies of insomnia (e.g., sleep apnea) are more often identifiable in older individuals.

Risk and Prognostic Factors

While the risk and prognostic factors discussed in this section increase vulnerability to insomnia, sleep disturbances are more likely to occur when predisposed individuals are exposed to precipitating events, such as major life events (e.g., illness, separation) or less severe but more chronic daily stress. Most individuals resume normal sleep patterns after the initial triggering event has disappeared, but others—perhaps those more vulnerable to insomnia—continue experiencing persistent sleep difficulties. Perpetuating factors such as poor sleep habits, irregular sleep scheduling, and the fear of not sleeping feed into the insomnia problem and may contribute to a vicious cycle that may induce persistent insomnia.

Temperamental. Anxiety or worry-prone personality or cognitive styles, increased arousal predisposition, and tendency to repress emotions can increase vulnerability to insomnia.

Environmental. Noise, light, uncomfortably high or low temperature, and high altitude may also increase vulnerability to insomnia.

Genetic and physiological. Female gender and advancing age are associated with increased vulnerability to insomnia. Disrupted sleep and insomnia display a familial disposition. The prevalence of insomnia is higher among monozygotic twins relative to dizygotic twins; it is also higher in first-degree family members compared with the general population. The extent to which this link is inherited through a genetic predisposition, learned by observations of parental models, or established as a by-product of another psychopathology remains undetermined.

Course modifiers. Deleterious course modifiers include poor sleep hygiene practices (e.g., excessive caffeine use, irregular sleep schedules).

Gender-Related Diagnostic Issues

Insomnia is a more prevalent complaint among females than among males, with first onset often associated with the birth of a new child or with menopause. Despite higher prevalence among older females, polysomnographic studies suggest better preservation of sleep continuity and slow-wave sleep in older females than in older males.

Diagnostic Markers

Polysomnography usually shows impairments of sleep continuity (e.g., increased sleep latency and time awake after sleep onset and decreased sleep efficiency [percentage of time in bed asleep] and may show increased stage 1 sleep and decreased stages 3 and 4 sleep. The severity of these sleep impairments does not always match the individual's clinical presentation or subjective complaint of poor sleep, as individuals with insomnia often underestimate sleep duration and overestimate wakefulness relative to polysomnography. Quantitative electroencephalographic analyses may indicate that individuals with insomnia have greater high-frequency electroencephalography power relative to good sleepers both around the sleep onset period and during non–rapid eye movement sleep, a feature suggestive of increased cortical arousal. Individuals with insomnia disorder may have a lower sleep propensity and typically do not show increased daytime sleepiness on objective sleep laboratory measures compared with individuals without sleep disorders.

Other laboratory measures show evidence, although not consistently, of increased arousal and a generalized activation of the hypothalamic-pituitary-adrenal axis (e.g., increased cortisol levels, heart rate variability, reactivity to stress, metabolic rate). In general, findings are consistent with the hypothesis that increased physiological and cognitive arousal plays a significant role in insomnia disorder.

Individuals with insomnia disorder may appear either fatigued or haggard or, conversely, overaroused and "wired." However, there are no consistent or characteristic abnormalities on physical examination. There may be an increased incidence of stress-

related psychophysiological symptoms (e.g., tension headache, muscle tension or pain, gastrointestinal symptoms).

Functional Consequences of Insomnia Disorder

Interpersonal, social, and occupational problems may develop as a result of insomnia or excessive concern with sleep, increased daytime irritability, and poor concentration. Decreased attention and concentration are common and may be related to higher rates of accidents observed in insomnia. Persistent insomnia is also associated with long-term consequences, including increased risks of major depressive disorder, hypertension, and myocardial infarction; increased absenteeism and reduced productivity at work; reduced quality of life; and increased economic burden.

Differential Diagnosis

Normal sleep variations. Normal sleep duration varies considerably across individuals. Some individuals who require little sleep ("short sleepers") may be concerned about their sleep duration. Short sleepers differ from individuals with insomnia disorder by the lack of difficulty falling or staying asleep and by the absence of characteristic daytime symptoms (e.g., fatigue, concentration problems, irritability). However, some short sleepers may desire or attempt to sleep for a longer period of time and, by prolonging time in bed, may create an insomnia-like sleep pattern. Clinical insomnia also should be distinguished from normal, age-related sleep changes. Insomnia must also be distinguished from sleep deprivation due to inadequate opportunity or circumstance for sleep resulting, for example, from an emergency or from professional or family obligations forcing the individual to stay awake.

Situational/acute insomnia. *Situational/acute insomnia* is a condition lasting a few days to a few weeks, often associated with life events or with changes in sleep schedules. These acute or short-term insomnia symptoms may also produce significant distress and interfere with social, personal, and occupational functioning. When such symptoms are frequent enough and meet all other criteria except for the 3-month duration, a diagnosis of other specified insomnia disorder or unspecified insomnia disorder is made.

Delayed sleep phase and shift work types of circadian rhythm sleep-wake disorder. Individuals with the delayed sleep phase type of circadian rhythm sleep-wake disorder report sleep-onset insomnia only when they try to sleep at socially normal times, but they do not report difficulty falling asleep or staying asleep when their bed and rising times are delayed and coincide with their endogenous circadian rhythm. Shift work type differs from insomnia disorder by the history of recent shift work.

Restless legs syndrome. Restless legs syndrome often produces difficulties initiating and maintaining sleep. However, an urge to move the legs and any accompanying unpleasant leg sensations are features that differentiate this disorder from insomnia disorder.

Breathing-related sleep disorders. Most individuals with a breathing-related sleep disorder have a history of loud snoring, breathing pauses during sleep, and excessive daytime sleepiness. Nonetheless, as many as 50% of individuals with sleep apnea may also report insomnia symptoms, a feature that is more common among females and older adults.

Narcolepsy. Narcolepsy may cause insomnia complaints but is distinguished from insomnia disorder by the predominance of symptoms of excessive daytime sleepiness, cataplexy, sleep paralysis, and sleep-related hallucinations.

Parasomnias. Parasomnias are characterized by a complaint of unusual behavior or events during sleep that may lead to intermittent awakenings and difficulty resuming sleep. However, it is these behavioral events, rather than the insomnia per se, that dominate the clinical picture.

Substance/medication-induced sleep disorder, insomnia type. Substance/medication-induced sleep disorder, insomnia type, is distinguished from insomnia disorder by the fact that a substance (i.e., a drug of abuse, a medication, or exposure to a toxin) is judged to be etiologically related to the insomnia (see "Substance/Medication-Induced Sleep Disorder" later in this chapter). For example, insomnia occurring only in the context of heavy coffee consumption would be diagnosed as caffeine-induced sleep disorder, insomnia type, with onset during intoxication.

Comorbidity

Insomnia is a common comorbidity of many medical conditions, including diabetes, coronary heart disease, chronic obstructive pulmonary disease, arthritis, fibromyalgia, and other chronic pain conditions. The risk relationship appears to be bidirectional: insomnia increases the risk of medical conditions, and medical problems increase the risk of insomnia. The direction of the relationship is not always clear and may change over time; for this reason, comorbid insomnia is the preferred terminology in the presence of coexisting insomnia with another medical condition (or mental disorder).

Individuals with insomnia disorder frequently have a comorbid mental disorder, particularly bipolar, depressive, and anxiety disorders. Persistent insomnia represents a risk factor or an early symptom of subsequent bipolar, depressive, anxiety, and substance use disorders. Individuals with insomnia may misuse medications or alcohol to help with nighttime sleep, anxiolytics to combat tension or anxiety, and caffeine or other stimulants to combat excessive fatigue. In addition to worsening the insomnia, this type of substance use may in some cases progress to a substance use disorder.

Relationship to International Classification of Sleep Disorders

There are several distinct insomnia phenotypes relating to the perceived source of the insomnia that are recognized by the *International Classification of Sleep Disorders,* 2nd Edition (ICSD-2). These include *psychophysiological insomnia, idiopathic insomnia, sleep-state misperception,* and *inadequate sleep hygiene.* Despite their clinical appeal and heuristic value, there is limited evidence to support these distinct phenotypes.

Hypersomnolence Disorder

Diagnostic Criteria **307.44 (F51.11)**

A. Self-reported excessive sleepiness (hypersomnolence) despite a main sleep period lasting at least 7 hours, with at least one of the following symptoms:
   1. Recurrent periods of sleep or lapses into sleep within the same day.
   2. A prolonged main sleep episode of more than 9 hours per day that is nonrestorative (i.e., unrefreshing).
   3. Difficulty being fully awake after abrupt awakening.

B. The hypersomnolence occurs at least three times per week, for at least 3 months.

C. The hypersomnolence is accompanied by significant distress or impairment in cognitive, social, occupational, or other important areas of functioning.

D. The hypersomnolence is not better explained by and does not occur exclusively during the course of another sleep disorder (e.g., narcolepsy, breathing-related sleep disorder, circadian rhythm sleep-wake disorder, or a parasomnia).

E. The hypersomnolence is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication).

F. Coexisting mental and medical disorders do not adequately explain the predominant complaint of hypersomnolence.

Specify if:

With mental disorder, including substance use disorders

With medical condition

With another sleep disorder

Coding note: The code 307.44 (F51.11) applies to all three specifiers. Code also the relevant associated mental disorder, medical condition, or other sleep disorder immediately after the code for hypersomnolence disorder in order to indicate the association.

Specify if:

Acute: Duration of less than 1 month.

Subacute: Duration of 1–3 months.

Persistent: Duration of more than 3 months.

Specify current severity:

Specify severity based on degree of difficulty maintaining daytime alertness as manifested by the occurrence of multiple attacks of irresistible sleepiness within any given day occurring, for example, while sedentary, driving, visiting with friends, or working.

Mild: Difficulty maintaining daytime alertness 1–2 days/week.

Moderate: Difficulty maintaining daytime alertness 3–4 days/week.

Severe: Difficulty maintaining daytime alertness 5–7 days/week.

Diagnostic Features

Hypersomnolence is a broad diagnostic term and includes symptoms of excessive quantity of sleep (e.g., extended nocturnal sleep or involuntary daytime sleep), deteriorated quality of wakefulness (i.e., sleep propensity during wakefulness as shown by difficulty awakening or inability to remain awake when required), and sleep inertia (i.e., a period of impaired performance and reduced vigilance following awakening from the regular sleep episode or from a nap) (Criterion A). Individuals with this disorder fall asleep quickly and have a good sleep efficiency (>90%). They may have difficulty waking up in the morning, sometimes appearing confused, combative, or ataxic. This prolonged impairment of alertness at the sleep-wake transition is often referred to as *sleep inertia* (i.e., sleep drunkenness). It can also occur upon awakening from a daytime nap. During that period, the individual appears awake, but there is a decline in motor dexterity, behavior may be very inappropriate, and memory deficits, disorientation in time and space, and feelings of grogginess may occur. This period may last some minutes to hours.

The persistent need for sleep can lead to automatic behavior (usually of a very routine, low-complexity type) that the individual carries out with little or no subsequent recall. For example, individuals may find themselves having driven several miles from where they thought they were, unaware of the "automatic" driving they did in the preceding minutes. For some individuals with hypersomnolence disorder, the major sleep episode (for most individuals, nocturnal sleep) has a duration of 9 hours or more. However, the sleep is often nonrestorative and is followed by difficulty awakening in the morning. For other individuals with hypersomnolence disorder, the major sleep episode is of normal nocturnal sleep duration (6–9 hours). In these cases, the excessive sleepiness is characterized by several unintentional daytime naps. These daytime naps tend to be relatively long (often lasting 1 hour or more), are experienced as nonrestorative (i.e., unrefreshing), and do not lead to improved alertness. Individuals with hypersomnolence have daytime naps nearly everyday regardless of the nocturnal sleep duration. Subjective sleep quality may or may not be reported as good. Individuals typically feel sleepiness developing over a period of time, rather than

experiencing a sudden sleep "attack." Unintentional sleep episodes typically occur in low-stimulation and low-activity situations (e.g., while attending lectures, reading, watching television, or driving long distances), but in more severe cases they can manifest in high-attention situations such as at work, in meetings, or at social gatherings.

Associated Features Supporting Diagnosis

Nonrestorative sleep, automatic behavior, difficulties awakening in the morning, and sleep inertia, although common in hypersomnolence disorder, may also be seen in a variety of conditions, including narcolepsy. Approximately 80% of individuals with hypersomnolence report that their sleep is nonrestorative, and as many have difficulties awakening in the morning. Sleep inertia, though less common (i.e., observed in 36%–50% of individuals with hypersomnolence disorder), is highly specific to hypersomnolence. Short naps (i.e., duration of less than 30 minutes) are often unrefreshing. Individuals with hypersomnolence often appear sleepy and may even fall asleep in the clinician's waiting area.

A subset of individuals with hypersomnolence disorder have a family history of hypersomnolence and also have symptoms of autonomic nervous system dysfunction, including recurrent vascular-type headaches, reactivity of the peripheral vascular system (Raynaud's phenomenon), and fainting.

Prevalence

Approximately 5%–10% of individuals who consult in sleep disorders clinics with complaints of daytime sleepiness are diagnosed as having hypersomnolence disorder. It is estimated that about 1% of the European and U.S. general population has episodes of sleep inertia. Hypersomnolence occurs with relatively equal frequency in males and females.

Development and Course

Hypersomnolence disorder has a persistent course, with a progressive evolution in the severity of symptoms. In most extreme cases, sleep episodes can last up to 20 hours. However, the average nighttime sleep duration is around 9½ hours. While many individuals with hypersomnolence are able to reduce their sleep time during working days, weekend and holiday sleep is greatly increased (by up to 3 hours). Awakenings are very difficult and accompanied by sleep inertia episodes in nearly 40% of cases. Hypersomnolence fully manifests in most cases in late adolescence or early adulthood, with a mean age at onset of 17–24 years. Individuals with hypersomnolence disorder are diagnosed, on average, 10–15 years after the appearance of the first symptoms. Pediatric cases are rare.

Hypersomnolence has a progressive onset, with symptoms beginning between ages 15 and 25 years, with a gradual progression over weeks to months. For most individuals, the course is then persistent and stable, unless treatment is initiated. The development of other sleep disorders (e.g., breathing-related sleep disorder) may worsen the degree of sleepiness. Although hyperactivity may be one of the presenting signs of daytime sleepiness in children, voluntary napping increases with age. This normal phenomenon is distinct from hypersomnolence.

Risk and Prognostic Factors

Environmental. Hypersomnolence can be increased temporarily by psychological stress and alcohol use, but they have not been documented as environmental precipitating factors. Viral infections have been reported to have preceded or accompanied hypersomnolence in about 10% of cases. Viral infections, such as HIV pneumonia, infectious mononucleosis, and Guillain-Barré syndrome, can also evolve into hypersomnolence within

months after the infection. Hypersomnolence can also appear within 6–18 months following a head trauma.

Genetic and physiological. Hypersomnolence may be familial, with an autosomal-dominant mode of inheritance.

Diagnostic Markers

Nocturnal polysomnography demonstrates a normal to prolonged sleep duration, short sleep latency, and normal to increased sleep continuity. The distribution of rapid eye movement (REM) sleep is also normal. Sleep efficiency is mostly greater than 90%. Some individuals with hypersomnolence disorder have increased amounts of slow-wave sleep. The multiple sleep latency test documents sleep tendency, typically indicated by mean sleep latency values of less than 8 minutes. In hypersomnolence disorder, the mean sleep latency is typically less than 10 minutes and frequently 8 minutes or less. Sleep-onset REM periods (SOREMPs; i.e., the occurrence of REM sleep within 20 minutes of sleep onset) may be present but occur less than two times in four to five nap opportunities.

Functional Consequences of Hypersomnolence Disorder

The low level of alertness that occurs while an individual fights the need for sleep can lead to reduced efficiency, diminished concentration, and poor memory during daytime activities. Hypersomnolence can lead to significant distress and dysfunction in work and social relationships. Prolonged nocturnal sleep and difficulty awakening can result in difficulty in meeting morning obligations, such as arriving at work on time. Unintentional daytime sleep episodes can be embarrassing and even dangerous, if, for instance, the individual is driving or operating machinery when the episode occurs.

Differential Diagnosis

Normative variation in sleep. "Normal" sleep duration varies considerably in the general population. "Long sleepers" (i.e., individuals who require a greater than average amount of sleep) do not have excessive sleepiness, sleep inertia, or automatic behavior when they obtain their required amount of nocturnal sleep. Sleep is reported to be refreshing. If social or occupational demands lead to shorter nocturnal sleep, daytime symptoms may appear. In hypersomnolence disorder, by contrast, symptoms of excessive sleepiness occur regardless of nocturnal sleep duration. An inadequate amount of nocturnal sleep, or *behaviorally induced insufficient sleep syndrome,* can produce symptoms of daytime sleepiness very similar to those of hypersomnolence. An average sleep duration of fewer than 7 hours per night strongly suggests inadequate nocturnal sleep, and an average of more than 9–10 hours of sleep per 24-hour period suggests hypersomnolence. Individuals with inadequate nocturnal sleep typically "catch up" with longer sleep durations on days when they are free from social or occupational demands or on vacations. Unlike hypersomnolence, insufficient nocturnal sleep is unlikely to persist unabated for decades. A diagnosis of hypersomnolence disorder should not be made if there is a question regarding the adequacy of nocturnal sleep duration. A diagnostic and therapeutic trial of sleep extension for 10–14 days can often clarify the diagnosis.

Poor sleep quality and fatigue. Hypersomnolence disorder should be distinguished from excessive sleepiness related to insufficient sleep quantity or quality and fatigue (i.e., tiredness not necessarily relieved by increased sleep and unrelated to sleep quantity or quality). Excessive sleepiness and fatigue are difficult to differentiate and may overlap considerably.

Breathing-related sleep disorders. Individuals with hypersomnolence and breathing-related sleep disorders may have similar patterns of excessive sleepiness. Breathing-

related sleep disorders are suggested by a history of loud snoring, pauses in breathing during sleep, brain injury, or cardiovascular disease and by the presence of obesity, oropharyngeal anatomical abnormalities, hypertension, or heart failure on physical examination. Polysomnographic studies can confirm the presence of apneic events in breathing-related sleep disorder (and their absence in hypersomnolence disorder).

Circadian rhythm sleep-wake disorders. Circadian rhythm sleep-wake disorders are often characterized by daytime sleepiness. A history of an abnormal sleep-wake schedule (with shifted or irregular hours) is present in individuals with a circadian rhythm sleep-wake disorder.

Parasomnias. Parasomnias rarely produce the prolonged, undisturbed nocturnal sleep or daytime sleepiness characteristic of hypersomnolence disorder.

Other mental disorders. Hypersomnolence disorder must be distinguished from mental disorders that include hypersomnolence as an essential or associated feature. In particular, complaints of daytime sleepiness may occur in a major depressive episode, with atypical features, and in the depressed phase of bipolar disorder. Assessment for other mental disorders is essential before a diagnosis of hypersomnolence disorder is considered. A diagnosis of hypersomnolence disorder can be made in the presence of another current or past mental disorder.

Comorbidity

Hypersomnolence can be associated with depressive disorders, bipolar disorders (during a depressive episode), and major depressive disorder, with seasonal pattern. Many individuals with hypersomnolence disorder have symptoms of depression that may meet criteria for a depressive disorder. This presentation may be related to the psychosocial consequences of persistent increased sleep need. Individuals with hypersomnolence disorder are also at risk for substance-related disorders, particularly related to self-medication with stimulants. This general lack of specificity may contribute to very heterogeneous profiles among individuals whose symptoms meet the same diagnostic criteria for hypersomnolence disorder. Neurodegenerative conditions, such as Alzheimer's disease, Parkinson's disease, and multiple system atrophy, may also be associated with hypersomnolence.

Relationship to International Classification of Sleep Disorders

The *International Classification of Sleep Disorders,* 2nd Edition (ICSD-2), differentiates nine subtypes of "hypersomnias of central origin," including recurrent hypersomnia (Kleine-Levin syndrome).

Narcolepsy

Diagnostic Criteria

A. Recurrent periods of an irrepressible need to sleep, lapsing into sleep, or napping occurring within the same day. These must have been occurring at least three times per week over the past 3 months.

B. The presence of at least one of the following:

   1. Episodes of cataplexy, defined as either (a) or (b), occurring at least a few times per month:

      a. In individuals with long-standing disease, brief (seconds to minutes) episodes of sudden bilateral loss of muscle tone with maintained consciousness that are precipitated by laughter or joking.

b. In children or in individuals within 6 months of onset, spontaneous grimaces or jaw-opening episodes with tongue thrusting or a global hypotonia, without any obvious emotional triggers.

2. Hypocretin deficiency, as measured using cerebrospinal fluid (CSF) hypocretin-1 immunoreactivity values (less than or equal to one-third of values obtained in healthy subjects tested using the same assay, or less than or equal to 110 pg/mL). Low CSF levels of hypocretin-1 must not be observed in the context of acute brain injury, inflammation, or infection.
3. Nocturnal sleep polysomnography showing rapid eye movement (REM) sleep latency less than or equal to 15 minutes, or a multiple sleep latency test showing a mean sleep latency less than or equal to 8 minutes and two or more sleep-onset REM periods.

Specify whether:

347.00 (G47.419) Narcolepsy without cataplexy but with hypocretin deficiency: Criterion B requirements of low CSF hypocretin-1 levels and positive polysomnography/multiple sleep latency test are met, but no cataplexy is present (Criterion B1 not met).

347.01 (G47.411) Narcolepsy with cataplexy but without hypocretin deficiency: In this rare subtype (less than 5% of narcolepsy cases), Criterion B requirements of cataplexy and positive polysomnography/multiple sleep latency test are met, but CSF hypocretin-1 levels are normal (Criterion B2 not met).

347.00 (G47.419) Autosomal dominant cerebellar ataxia, deafness, and narcolepsy: This subtype is caused by exon 21 DNA (cytosine-5)-methyltransferase-1 mutations and is characterized by late-onset (age 30–40 years) narcolepsy (with low or intermediate CSF hypocretin-1 levels), deafness, cerebellar ataxia, and eventually dementia.

347.00 (G47.419) Autosomal dominant narcolepsy, obesity, and type 2 diabetes: Narcolepsy, obesity, and type 2 diabetes and low CSF hypocretin-1 levels have been described in rare cases and are associated with a mutation in the myelin oligodendrocyte glycoprotein gene.

347.10 (G47.429) Narcolepsy secondary to another medical condition: This subtype is for narcolepsy that develops secondary to medical conditions that cause infectious (e.g., Whipple's disease, sarcoidosis), traumatic, or tumoral destruction of hypocretin neurons.

Coding note (for ICD-9-CM code 347.10 only): Code first the underlying medical condition (e.g., 040.2 Whipple's disease; 347.10 narcolepsy secondary to Whipple's disease).

Specify current severity:

Mild: Infrequent cataplexy (less than once per week), need for naps only once or twice per day, and less disturbed nocturnal sleep.

Moderate: Cataplexy once daily or every few days, disturbed nocturnal sleep, and need for multiple naps daily.

Severe: Drug-resistant cataplexy with multiple attacks daily, nearly constant sleepiness, and disturbed nocturnal sleep (i.e., movements, insomnia, and vivid dreaming).

Subtypes

In narcolepsy without cataplexy but with hypocretin deficiency, unclear "cataplexy-like" symptoms may be reported (e.g., the symptoms are not triggered by emotions and are unusually long lasting). In extremely rare cases, cerebrospinal fluid (CSF) levels of hypocretin-1 are low, and polysomnographic/multiple sleep latency test (MSLT) results are negative: repeating the test is advised before establishing the subtype diagnosis. In narco-

lepsy with cataplexy but without hypocretin deficiency, test results for human leukocyte antigen (HLA) DQB1*06:02 may be negative. Seizures, falls of other origin, and conversion disorder (functional neurological symptom disorder) should be excluded. In narcolepsy secondary to infectious (e.g., Whipple's disease, sarcoidosis), traumatic, or tumoral destruction of hypocretin neurons, test results for HLA DQB1*06:02 may be positive and may result from the insult triggering the autoimmune process. In other cases, the destruction of hypocretin neurons may be secondary to trauma or hypothalamic surgery. Head trauma or infections of the central nervous system can, however, produce transitory decreases in CSF hypocretin-1 levels without hypocretin cell loss, complicating the diagnosis.

Diagnostic Features

The essential features of sleepiness in narcolepsy are recurrent daytime naps or lapses into sleep. Sleepiness typically occurs daily but must occur at a minimum three times a week for at least 3 months (Criterion A). Narcolepsy generally produces cataplexy, which most commonly presents as brief episodes (seconds to minutes) of sudden, bilateral loss of muscle tone precipitated by emotions, typically laughing and joking. Muscles affected may include those of the neck, jaw, arms, legs, or whole body, resulting in head bobbing, jaw dropping, or complete falls. Individuals are awake and aware during cataplexy. To meet Criterion B1(a), cataplexy must be triggered by laughter or joking and must occur at least a few times per month when the condition is untreated or in the past.

Cataplexy should not be confused with "weakness" occurring in the context of athletic activities (physiological) or exclusively after unusual emotional triggers such as stress or anxiety (suggesting possible psychopathology). Episodes lasting hours or days, or those not triggered by emotions, are unlikely to be cataplexy, nor is rolling on the floor while laughing hysterically.

In children close to onset, genuine cataplexy can be atypical, affecting primarily the face, causing grimaces or jaw opening with tongue thrusting ("cataplectic faces"). Alternatively, cataplexy may present as low-grade continuous hypotonia, yielding a wobbling walk. In these cases, Criterion B1(b) can be met in children or in individuals within 6 months of a rapid onset.

Narcolepsy-cataplexy nearly always results from the loss of hypothalamic hypocretin (orexin)–producing cells, causing hypocretin deficiency (less than or equal to one-third of control values, or 110 pg/mL in most laboratories). Cell loss is likely autoimmune, and approximately 99% of affected individuals carry HLA-DQB1*06:02 (vs. 12%–38% of control subjects). Thus, checking for the presence of DQB1*06:02 prior to a lumbar puncture for evaluation of CSF hypocretin-1 immunoreactivity may be useful. Rarely, low CSF levels of hypocretin-1 occur without cataplexy, notably in youths who may develop cataplexy later. CSF hypocretin-1 measurement represents the gold standard, excepting associated severe conditions (neurological, inflammatory, infectious, trauma) that can interfere with the assay.

A nocturnal polysomnographic sleep study followed by an MSLT can also be used to confirm the diagnosis (Criterion B3). These tests must be performed after the individual has stopped all psychotropic medications, following 2 weeks of adequate sleep time (as documented with sleep diaries, actigraphy). Short rapid eye movement (REM) latency (sleep-onset REM period, REM latency less than or equal to 15 minutes) during polysomnography is sufficient to confirm the diagnosis and meets Criterion B3. Alternatively, the MSLT result must be positive, showing a mean sleep latency of less than or equal to 8 minutes and two or more sleep-onset REM periods in four to five naps.

Associated Features Supporting Diagnosis

When sleepiness is severe, automatic behaviors may occur, with the individual continuing his or her activities in a semi-automatic, hazelike fashion without memory or consciousness. Approximately 20%–60% of individuals experience vivid hypnagogic hallucinations

before or upon falling asleep or hypnopompic hallucinations just after awakening. These hallucinations are distinct from the less vivid, nonhallucinatory dreamlike mentation at sleep onset that occurs in normal sleepers. Nightmares and vivid dreaming are also frequent in narcolepsy, as is REM sleep behavior disorder. Approximately 20%–60% of individuals experience sleep paralysis upon falling asleep or awakening, leaving them awake but unable to move or speak. However, many normal sleepers also report sleep paralysis, especially with stress or sleep deprivation. Nocturnal eating may occur. Obesity is common. Nocturnal sleep disruption with frequent long or short awakenings is common and can be disabling.

Individuals may appear sleepy or fall asleep in the waiting area or during clinical examination. During cataplexy, individuals may slump in a chair and have slurred speech or drooping eyelids. If the clinician has time to check reflexes during cataplexy (most attacks are less than 10 seconds), reflexes are abolished—an important finding distinguishing genuine cataplexy from conversion disorder.

Prevalence

Narcolepsy-cataplexy affects 0.02%–0.04% of the general population in most countries. Narcolepsy affects both genders, with possibly a slight male preponderance.

Development and Course

Onset is typically in children and adolescents/young adults but rarely in older adults. Two peaks of onset are suggested, at ages 15–25 years and ages 30–35 years. Onset can be abrupt or progressive (over years). Severity is highest when onset is abrupt in children, and then decreases with age or with treatment, so that symptoms such as cataplexy can occasionally disappear. Abrupt onset in young, prepubescent children can be associated with obesity and premature puberty, a phenotype more frequently observed since 2009. In adolescents, onset is more difficult to pinpoint. Onset in adults is often unclear, with some individuals reporting having had excessive sleepiness since birth. Once the disorder has manifested, the course is persistent and lifelong.

In 90% of cases, the first symptom to manifest is sleepiness or increased sleep, followed by cataplexy (within 1 year in 50% of cases, within 3 years in 85%). Sleepiness, hypnagogic hallucinations, vivid dreaming, and REM sleep behavior disorder (excessive movements during REM sleep) are early symptoms. Excessive sleep rapidly progresses to an inability to stay awake during the day, and to maintain good sleep at night, without a clear increase in total 24-hour sleep needs. In the first months, cataplexy may be atypical, especially in children. Sleep paralysis usually develops around puberty in children with prepubertal onset. Exacerbations of symptoms suggest lack of compliance with medications or development of a concurrent sleep disorder, notably sleep apnea.

Young children and adolescents with narcolepsy often develop aggression or behavioral problems secondary to sleepiness and/or nighttime sleep disruption. Workload and social pressure increase through high school and college, reducing available sleep time at night. Pregnancy does not seem to modify symptoms consistently. After retirement, individuals typically have more opportunity for napping, reducing the need for stimulants. Maintaining a regular schedule benefits individuals at all ages.

Risk and Prognostic Factors

Temperamental. Parasomnias, such as sleepwalking, bruxism, REM sleep behavior disorder, and enuresis, may be more common in individuals who develop narcolepsy. Individuals commonly report that they need more sleep than other family members.

Environmental. Group A streptococcal throat infection, influenza (notably pandemic H1N1 2009), or other winter infections are likely triggers of the autoimmune process, pro-

ducing narcolepsy a few months later. Head trauma and abrupt changes in sleep-wake patterns (e.g., job changes, stress) may be additional triggers.

Genetic and physiological. Monozygotic twins are 25%–32% concordant for narcolepsy. The prevalence of narcolepsy is 1%–2% in first-degree relatives (a 10- to 40-fold increase overall). Narcolepsy is strongly associated with DQB1*06:02 (99% vs. 12%–38% in control subjects of various ethnic groups; 25% in the general U.S. population). DQB1*03:01 increases, while DQB1*05:01, DQB1*06:01, and DQB1*06:03 reduce risk in the presence of DQB1*06:02, but the effect is small. Polymorphisms within the T-cell receptor alpha gene and other immune modulating genes also modulate risk slightly.

Culture-Related Diagnostic Issues

Narcolepsy has been described in all ethnic groups and in many cultures. Among African Americans, more cases present without cataplexy or with atypical cataplexy, complicating diagnosis, especially in the presence of obesity and obstructive sleep apnea.

Diagnostic Markers

Functional imaging suggests impaired hypothalamic responses to humorous stimuli. Nocturnal polysomnography followed by an MSLT is used to confirm the diagnosis of narcolepsy, especially when the disorder is first being diagnosed and before treatment has begun, and if hypocretin deficiency has not been documented biochemically. The polysomnography/MSLT should be performed after the individual is no longer taking any psychotropic drugs and after regular sleep-wake patterns, without shift work or sleep deprivation, have been documented.

A sleep-onset REM period during the polysomnography (REM sleep latency less than or equal to 15 minutes) is highly specific (approximately 1% positive in control subjects) but moderately sensitive (approximately 50%). A positive MSLT result displays an average sleep latency of less than or equal to 8 minutes, and sleep-onset REM periods in two or more naps on a four- or five-nap test. The MSLT result is positive in 90%–95% of individuals with narcolepsy versus 2%–4% of control subjects or individuals with other sleep disorders. Additional polysomnographic findings often include frequent arousals, decreased sleep efficiency, and increased stage 1 sleep. Periodic limb movements (found in about 40% of individuals with narcolepsy) and sleep apnea are often noted.

Hypocretin deficiency is demonstrated by measuring CSF hypocretin-1 immunoreactivity. The test is particularly useful in individuals with suspected conversion disorder and those without typical cataplexy, or in treatment-refractory cases. The diagnostic value of the test is not affected by medications, sleep deprivation, or circadian time, but the findings are uninterpretable when the individual is severely ill with a concurrent infection or head trauma or is comatose. CSF cytology, protein, and glucose are within normal range even when sampled within weeks of rapid onset. CSF hypocretin-1 in these incipient cases is typically already very diminished or undetectable.

Functional Consequences of Narcolepsy

Driving and working are impaired, and individuals with narcolepsy should avoid jobs that place themselves (e.g., working with machinery) or others (e.g., bus driver, pilot) in danger. Once the narcolepsy is controlled with therapy, patients can usually drive, although rarely long distances alone. Untreated individuals are also at risk for social isolation and accidental injury to themselves or others. Social relations may suffer as these individuals strive to avert cataplexy by exerting control over emotions.

Differential Diagnosis

Other hypersomnias. Hypersomnolence and narcolepsy are similar with respect to the degree of daytime sleepiness, age at onset, and stable course over time but can be distin-

guished based on distinctive clinical and laboratory features. Individuals with hypersomnolence typically have longer and less disrupted nocturnal sleep, greater difficulty awakening, more persistent daytime sleepiness (as opposed to more discrete "sleep attacks" in narcolepsy), longer and less refreshing daytime sleep episodes, and little or no dreaming during daytime naps. By contrast, individuals with narcolepsy have cataplexy and recurrent intrusions of elements of REM sleep into the transition between sleep and wakefulness (e.g., sleep-related hallucinations and sleep paralysis). The MSLT typically demonstrates shorter sleep latencies (i.e., greater physiological sleepiness) as well as the presence of multiple sleep-onset REM periods in individuals with narcolepsy.

Sleep deprivation and insufficient nocturnal sleep. Sleep deprivation and insufficient nocturnal sleep are common in adolescents and shift workers. In adolescents, difficulties falling asleep at night are common, causing sleep deprivation. The MSLT result may be positive if conducted while the individual is sleep deprived or while his or her sleep is phase delayed.

Sleep apnea syndromes. Sleep apneas are especially likely in the presence of obesity. Because obstructive sleep apnea is more frequent than narcolepsy, cataplexy may be overlooked (or absent), and the individual is assumed to have obstructive sleep apnea unresponsive to usual therapies.

Major depressive disorder. Narcolepsy or hypersomnia may be associated or confused with depression. Cataplexy is not present in depression. The MSLT results are most often normal, and there is dissociation between subjective and objective sleepiness, as measured by the mean sleep latency during the MSLT.

Conversion disorder (functional neurological symptom disorder). Atypical features, such as long-lasting cataplexy or unusual triggers, may be present in conversion disorder (functional neurological symptom disorder). Individuals may report sleeping and dreaming, yet the MSLT does not show the characteristic sleep-onset REM period. Full-blown, long-lasting pseudocataplexy may occur during consultation, allowing the examining physician enough time to verify reflexes, which remain intact.

Attention-deficit/hyperactivity disorder or other behavioral problems. In children and adolescents, sleepiness can cause behavioral problems, including aggressiveness and inattention, leading to a misdiagnosis of attention-deficit/hyperactivity disorder.

Seizures. In young children, cataplexy can be misdiagnosed as seizures. Seizures are not commonly triggered by emotions, and when they are, the trigger is not usually laughing or joking. During a seizure, individuals are more likely to hurt themselves when falling. Seizures characterized by isolated atonia are rarely seen in isolation of other seizures, and they also have signatures on the electroencephalogram.

Chorea and movement disorders. In young children, cataplexy can be misdiagnosed as chorea or pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, especially in the context of a strep throat infection and high antistreptolysin O antibody levels. Some children may have an overlapping movement disorder close to onset of the cataplexy.

Schizophrenia. In the presence of florid and vivid hypnagogic hallucinations, individuals may think these experiences are real—a feature that suggests schizophrenia. Similarly, with stimulant treatment, persecutory delusions may develop. If cataplexy is present, the clinician should first assume that these symptoms are secondary to narcolepsy before considering a co-occurring diagnosis of schizophrenia.

Comorbidity

Narcolepsy can co-occur with bipolar, depressive, and anxiety disorders, and in rare cases with schizophrenia. Narcolepsy is also associated with increased body mass index or obe-

sity, especially when the narcolepsy is untreated. Rapid weight gain is common in young children with a sudden disease onset. Comorbid sleep apnea should be considered if there is a sudden aggravation of preexisting narcolepsy.

Relationship to International Classification of Sleep Disorders

The *International Classification of Sleep Disorders,* 2nd Edition (ICSD-2), differentiates five subtypes of narcolepsy.

Breathing-Related Sleep Disorders

The breathing-related sleep disorders category encompasses three relatively distinct disorders: obstructive sleep apnea hypopnea, central sleep apnea, and sleep-related hypoventilation.

Obstructive Sleep Apnea Hypopnea

Diagnostic Criteria **327.23 (G47.33)**

A. Either (1) or (2):

1. Evidence by polysomnography of at least five obstructive apneas or hypopneas per hour of sleep and either of the following sleep symptoms:
   a. Nocturnal breathing disturbances: snoring, snorting/gasping, or breathing pauses during sleep.
   b. Daytime sleepiness, fatigue, or unrefreshing sleep despite sufficient opportunities to sleep that is not better explained by another mental disorder (including a sleep disorder) and is not attributable to another medical condition.
2. Evidence by polysomnography of 15 or more obstructive apneas and/or hypopneas per hour of sleep regardless of accompanying symptoms.

Specify current severity:

Mild: Apnea hypopnea index is less than 15.
Moderate: Apnea hypopnea index is 15–30.
Severe: Apnea hypopnea index is greater than 30.

Specifiers

Disease severity is measured by a count of the number of apneas plus hypopneas per hour of sleep (apnea hypopnea index) using polysomnography or other overnight monitoring. Overall severity is also informed by levels of nocturnal desaturation and sleep fragmentation (measured by brain cortical arousal frequency and sleep stages) and degree of associated symptoms and daytime impairment. However, the exact number and thresholds may vary according to the specific measurement techniques used, and these numbers may change over time. Regardless of the apnea hypopnea index (count) per se, the disorder is considered to be more severe when apneas and hypopneas are accompanied by significant oxygen hemoglobin desaturation (e.g., when more than 10% of the sleep time is spent at desaturation levels of less than 90%) or when sleep is severely fragmented as shown by an

elevated arousal index (arousal index greater than 30) or reduced stages in deep sleep (e.g., percentage stage N3 [slow-wave sleep] less than 5%).

Diagnostic Features

Obstructive sleep apnea hypopnea is the most common breathing-related sleep disorder. It is characterized by repeated episodes of upper (pharyngeal) airway obstruction (apneas and hypopneas) during sleep. *Apnea* refers to the total absence of airflow, and *hypopnea* refers to a reduction in airflow. Each apnea or hypopnea represents a reduction in breathing of at least 10 seconds in duration in adults or two missed breaths in children and is typically associated with drops in oxygen saturation of 3% or greater and/or an electroencephalographic arousal. Both sleep-related (nocturnal) and wake-time symptoms are common. The cardinal symptoms of obstructive sleep apnea hypopnea are snoring and daytime sleepiness.

Obstructive sleep apnea hypopnea in adults is diagnosed on the basis of polysomnographic findings and symptoms. The diagnosis is based on symptoms of 1) nocturnal breathing disturbances (i.e., snoring, snorting/gasping, breathing pauses during sleep), or 2) daytime sleepiness, fatigue, or unrefreshing sleep despite sufficient opportunities to sleep that are not better explained by another mental disorder and not attributable to another medical condition, along with 3) evidence by polysomnography of five or more obstructive apneas or hypopneas per hour of sleep (Criterion A1). Diagnosis can be made in the absence of these symptoms if there is evidence by polysomnography of 15 or more obstructive apneas and/or hypopneas per hour of sleep (Criterion A2).

Specific attention to disturbed sleep occurring in association with snoring or breathing pauses and physical findings that increase risk of obstructive sleep apnea hypopnea (e.g., central obesity, crowded pharyngeal airway, elevated blood pressure) is needed to reduce the chance of misdiagnosing this treatable condition.

Associated Features Supporting Diagnosis

Because of the frequency of nocturnal awakenings that occur with obstructive sleep apnea hypopnea, individuals may report symptoms of insomnia. Other common, though nonspecific, symptoms of obstructive sleep apnea hypopnea are heartburn, nocturia, morning headaches, dry mouth, erectile dysfunction, and reduced libido. Rarely, individuals may complain of difficulty breathing while lying supine or sleeping. Hypertension may occur in more than 60% of individuals with obstructive sleep apnea hypopnea.

Prevalence

Obstructive sleep apnea hypopnea is a very common disorder, affecting at least 1%–2% of children, 2%–15% of middle-age adults, and more than 20% of older individuals. In the general community, prevalence rates of undiagnosed obstructive sleep apnea hypopnea may be very high in elderly individuals. Since the disorder is strongly associated with obesity, increases in obesity rates are likely to be accompanied by an increased prevalence of this disorder. Prevalence may be particularly high among males, older adults, and certain racial/ethnic groups. In adults, the male-to-female ratio of obstructive sleep apnea hypopnea ranges from 2:1 to 4:1. Gender differences decline in older age, possibly because of an increased prevalence in females after menopause. There is no gender difference among prepubertal children.

Development and Course

The age distribution of obstructive sleep apnea hypopnea likely follows a **J**-shaped distribution. There is a peak in children ages 3–8 years when the nasopharynx may be compromised by a relatively large mass of tonsillar tissue compared with the size of the upper

airway. With growth of the airway and regression of lymphoid tissue during later childhood, there is reduction in prevalence. Then, as obesity prevalence increases in midlife and females enter menopause, obstructive sleep apnea hypopnea again increases. The course in older age is unclear; the disorder may level off after age 65 years, but in other individuals, prevalence may increase with aging. Because there is some age dependency of the occurrence of apneas and hypopneas, polysomnographic results must be interpreted in light of other clinical data. In particular, significant clinical symptoms of insomnia or hypersomnia should be investigated regardless of the individual's age.

Obstructive sleep apnea hypopnea usually has an insidious onset, gradual progression, and persistent course. Typically the loud snoring has been present for many years, often since childhood, but an increase in its severity may lead the individual to seek evaluation. Weight gain may precipitate an increase in symptoms. Although obstructive sleep apnea hypopnea can occur at any age, it most commonly manifests among individuals ages 40–60 years. Over 4–5 years, the average apnea hypopnea index increases in adults and older individuals by approximately two apneas/hypopneas per hour. The apnea hypopnea index is increased and incident obstructive sleep apnea hypopnea is greater among individuals who are older, who are male, or who have a higher baseline body mass index (BMI) or increase their BMI over time. Spontaneous resolution of obstructive sleep apnea hypopnea has been reported with weight loss, particularly after bariatric surgery. In children, seasonal variation in obstructive sleep apnea hypopnea has been observed, as has improvement with overall growth.

In young children, the signs and symptoms of obstructive sleep apnea hypopnea may be more subtle than in adults, making diagnosis more difficult to establish. Polysomnography is useful in confirming diagnosis. Evidence of fragmentation of sleep on the polysomnogram may not be as apparent as in studies of older individuals, possibly because of the high homeostatic drive in young individuals. Symptoms such as snoring are usually parent-reported and thus have reduced sensitivity. Agitated arousals and unusual sleep postures, such as sleeping on the hands and knees, may occur. Nocturnal enuresis also may occur and should raise the suspicion of obstructive sleep apnea hypopnea if it recurs in a child who was previously dry at night. Children may also manifest excessive daytime sleepiness, although this is not as common or pronounced as in adults. Daytime mouth breathing, difficulty in swallowing, and poor speech articulation are also common features in children. Children younger than 5 years more often present with nighttime symptoms, such as observed apneas or labored breathing, than with behavioral symptoms (i.e., the nighttime symptoms are more noticeable and more often bring the child to clinical attention). In children older than 5 years, daytime symptoms such as sleepiness and behavioral problems (e.g., impulsivity and hyperactivity), attention-deficit/hyperactivity disorder, learning difficulties, and morning headaches are more often the focus of concern. Children with obstructive sleep apnea hypopnea also may present with failure to thrive and developmental delays. In young children, obesity is a less common risk factor, while delayed growth and "failure to thrive" may be present.

Risk and Prognostic Factors

Genetic and physiological. The major risk factors for obstructive sleep apnea hypopnea are obesity and male gender. Others include maxillary-mandibular retrognathia or micrognathia, positive family history of sleep apnea, genetic syndromes that reduce upper airway patency (e.g., Down's syndrome, Treacher Collin's syndrome), adenotonsillar hypertrophy (especially in young children), menopause (in females), and various endocrine syndromes (e.g., acromegaly). Compared with premenopausal females, males are at increased risk for obstructive sleep apnea hypopnea, possibly reflecting the influences of sex hormones on ventilatory control and body fat distribution, as well as because of gender differences in airway structure. Medications for mental disorders and medical conditions that tend to induce somnolence may worsen the course of apnea symptoms if these medications are not managed carefully.

Obstructive sleep apnea hypopnea has a strong genetic basis, as evidenced by the significant familial aggregation of the apnea hypopnea index. The prevalence of obstructive sleep apnea hypopnea is approximately twice as high among the first-degree relatives of probands with obstructive sleep apnea hypopnea as compared with members of control families. One-third of the variance in the apnea hypopnea index is explained by shared familial factors. Although genetic markers with diagnostic or prognostic value are not yet available for use, eliciting a family history of obstructive sleep apnea hypopnea should increase the clinical suspicion for the disorder.

Culture-Related Diagnostic Issues

There is a potential for sleepiness and fatigue to be reported differently across cultures. In some groups, snoring may be considered a sign of health and thus may not trigger concerns. Individuals of Asian ancestry may be at increased risk for obstructive sleep apnea hypopnea despite relatively low BMI, possibly reflecting the influence of craniofacial risk factors that narrow the nasopharynx.

Gender-Related Issues

Females may more commonly report fatigue rather than sleepiness and may underreport snoring.

Diagnostic Markers

Polysomnography provides quantitative data on frequency of sleep-related respiratory disturbances and associated changes in oxygen saturation and sleep continuity. Polysomnographic findings in children differ from those in adults in that children demonstrate labored breathing, partial obstructive hypoventilation with cyclical desaturations, hypercapnia and paradoxical movements. Apnea hypopnea index levels as low as 2 are used to define thresholds of abnormality in children.

Arterial blood gas measurements while the individual is awake are usually normal, but some individuals can have waking hypoxemia or hypercapnia. This pattern should alert the clinician to the possibility of coexisting lung disease or hypoventilation. Imaging procedures may reveal narrowing of the upper airway. Cardiac testing may show evidence of impaired ventricular function. Individuals with severe nocturnal oxygen desaturation may also have elevated hemoglobin or hematocrit values. Validated sleep measures (e.g., multiple sleep latency test [MSLT], maintenance of wakefulness test) may identify sleepiness.

Functional Consequences of Obstructive Sleep Apnea Hypopnea

More than 50% of individuals with moderate to severe obstructive sleep apnea hypopnea report symptoms of daytime sleepiness. A twofold increased risk of occupational accidents has been reported in association with symptoms of snoring and sleepiness. Motor vehicle crashes also have been reported to be as much as sevenfold higher among individuals with elevated apnea hypopnea index values. Clinicians should be cognizant of state government requirements for reporting this disorder, especially in relationship to commercial drivers. Reduced scores on measures of health-related quality of life are common in individuals with obstructive sleep apnea hypopnea, with the largest decrements observed in the physical and vitality subscales.

Differential Diagnosis

Primary snoring and other sleep disorders. Individuals with obstructive sleep apnea hypopnea must be differentiated from individuals with primary snoring (i.e., otherwise

asymptomatic individuals who snore and do not have abnormalities on overnight polysomnography). Individuals with obstructive sleep apnea hypopnea may additionally report nocturnal gasping and choking. The presence of sleepiness or other daytime symptoms not explained by other etiologies suggests the diagnosis of obstructive sleep apnea hypopnea, but this differentiation requires polysomnography. Definitive differential diagnosis between hypersomnia, central sleep apnea, sleep-related hypoventilation, and obstructive sleep apnea hypopnea also requires polysomnographic studies.

Obstructive sleep apnea hypopnea must be differentiated from other causes of sleepiness, such as narcolepsy, hypersomnia, and circadian rhythm sleep disorders. Obstructive sleep apnea hypopnea can be differentiated from narcolepsy by the absence of cataplexy, sleep-related hallucinations, and sleep paralysis and by the presence of loud snoring, gasping during sleep, or observed apneas in sleep. Daytime sleep episodes in narcolepsy are characteristically shorter, more refreshing, and more often associated with dreaming. Obstructive sleep apnea hypopnea shows characteristic apneas and hypopneas and oxygen desaturation during nocturnal polysomnographic studies. Narcolepsy results in multiple sleep-onset rapid eye movement (REM) periods during the MSLT. Narcolepsy, like obstructive sleep apnea hypopnea, may be associated with obesity, and some individuals have concurrent narcolepsy and obstructive sleep apnea hypopnea. A diagnosis of narcolepsy does not exclude the diagnosis of obstructive sleep apnea hypopnea, as the two conditions may co-occur.

Insomnia disorder. For individuals complaining of difficulty initiating or maintaining sleep or early-morning awakenings, insomnia disorder can be differentiated from obstructive sleep apnea hypopnea by the absence of snoring and the absence of the history, signs, and symptoms characteristic of the latter disorder. However, insomnia and obstructive sleep apnea hypopnea may coexist, and if so, both disorders may need to be addressed concurrently to improve sleep.

Panic attacks. Nocturnal panic attacks may include symptoms of gasping or choking during sleep that may be difficult to distinguish clinically from obstructive sleep apnea hypopnea. However, the lower frequency of episodes, intense autonomic arousal, and lack of excessive sleepiness differentiate nocturnal panic attacks from obstructive sleep apnea hypopnea. Polysomnography in individuals with nocturnal panic attacks does not reveal the typical pattern of apneas or oxygen desaturation characteristic of obstructive sleep apnea hypopnea. Individuals with obstructive sleep apnea hypopnea do not provide a history of daytime panic attacks.

Attention-deficit/hyperactivity disorder. Attention-deficit/hyperactivity disorder in children may include symptoms of inattention, academic impairment, hyperactivity, and internalizing behaviors, all of which may also be symptoms of childhood obstructive sleep apnea hypopnea. The presence of other symptoms and signs of childhood obstructive sleep apnea hypopnea (e.g., labored breathing or snoring during sleep and adenotonsillar hypertrophy) would suggest the presence of obstructive sleep apnea hypopnea. Obstructive sleep apnea hypopnea and attention-deficit/hyperactivity disorder may commonly co-occur, and there may be causal links between them; therefore, risk factors such as enlarged tonsils, obesity, or a family history of sleep apnea may help alert the clinician to their co-occurrence.

Substance/medication-induced insomnia or hypersomnia. Substance use and substance withdrawal (including medications) can produce insomnia or hypersomnia. A careful history is usually sufficient to identify the relevant substance/medication, and follow-up shows improvement of the sleep disturbance after discontinuation of the substance/medication. In other cases, the use of a substance/medication (e.g., alcohol, barbiturates, benzodiazepines, tobacco) has been shown to exacerbate obstructive sleep apnea hypopnea. An individual with symptoms and signs consistent with obstructive sleep apnea hypop-

nea should receive that diagnosis, even in the presence of concurrent substance use that is exacerbating the condition.

Comorbidity

Systemic hypertension, coronary artery disease, heart failure, stroke, diabetes, and increased mortality are consistently associated with obstructive sleep apnea hypopnea. Risk estimates vary from 30% to as much as 300% for moderate to severe obstructive sleep apnea hypopnea. Evidence of pulmonary hypertension and right heart failure (e.g., cor pulmonale, ankle edema, hepatic congestion) are rare in obstructive sleep apnea hypopnea and when present indicate either very severe disease or associated hypoventilation or cardiopulmonary comorbidities. Obstructive sleep apnea hypopnea also may occur with increased frequency in association with a number of medical or neurological conditions (e.g., cerebrovascular disease, Parkinson's disease). Physical findings reflect the co-occurrence of these conditions.

As many as one-third of individuals referred for evaluation of obstructive sleep apnea hypopnea report symptoms of depression, with as many of 10% having depression scores consistent with moderate to severe depression. Severity of obstructive sleep apnea hypopnea, as measured by the apnea hypopnea index, has been found to be correlated with severity of symptoms of depression. This association may be stronger in males than in females.

Relationship to International Classification of Sleep Disorders

The *International Classification of Sleep Disorders,* 2nd Edition (ICSD-2), differentiates 11 subtypes of "sleep-related breathing disorders," including primary central sleep apnea, obstructive sleep apnea, and sleep-related hypoventilation.

Central Sleep Apnea

Diagnostic Criteria

A. Evidence by polysomnography of five or more central apneas per hour of sleep.
B. The disorder is not better explained by another current sleep disorder.

Specify whether:

327.21 (G47.31) Idiopathic central sleep apnea: Characterized by repeated episodes of apneas and hypopneas during sleep caused by variability in respiratory effort but without evidence of airway obstruction.

786.04 (R06.3) Cheyne-Stokes breathing: A pattern of periodic crescendo-decrescendo variation in tidal volume that results in central apneas and hypopneas at a frequency of at least five events per hour, accompanied by frequent arousal.

780.57 (G47.37) Central sleep apnea comorbid with opioid use: The pathogenesis of this subtype is attributed to the effects of opioids on the respiratory rhythm generators in the medulla as well as the differential effects on hypoxic versus hypercapnic respiratory drive.

Coding note (for 780.57 [G47.37] code only): When an opioid use disorder is present, first code the opioid use disorder: 305.50 (F11.10) mild opioid use disorder or 304.00 (F11.20) moderate or severe opioid use disorder; then code 780.57 (G47.37) central sleep apnea comorbid with opioid use. When an opioid use disorder is not present (e.g., after a one-time heavy use of the substance), code only 780.57 (G47.37) central sleep apnea comorbid with opioid use.

Note: See the section "Diagnostic Features" in text.

Specify current severity:

Severity of central sleep apnea is graded according to the frequency of the breathing disturbances as well as the extent of associated oxygen desaturation and sleep fragmentation that occur as a consequence of repetitive respiratory disturbances.

Subtypes

Idiopathic central sleep apnea and Cheyne-Stokes breathing are characterized by increased gain of the ventilatory control system, also referred to as *high loop gain,* which leads to instability in ventilation and $PaCO_2$ levels. This instability is termed *periodic breathing* and can be recognized by hyperventilation alternating with hypoventilation. Individuals with these disorders typically have pCO_2 levels while awake that are slightly hypocapneic or normocapneic. Central sleep apnea may also manifest during initiation of treatment of obstructive sleep apnea hypopnea or may occur in association with obstructive sleep apnea hypopnea syndrome (termed *complex sleep apnea*). The occurrence of central sleep apnea in association with obstructive sleep apnea is also considered to be due to high loop gain. In contrast, the pathogenesis of central sleep apnea comorbid with opioid use has been attributed to the effects of opioids on the respiratory rhythm generators in the medulla as well as to its differential effects on hypoxic versus hypercapneic respiratory drive. These individuals may have elevated pCO_2 levels while awake. Individuals receiving chronic methadone maintenance therapy have been noted to have increased somnolence and depression, although the role of breathing disorders associated with opioid medication in causing these problems has not been studied.

Specifiers

An increase in the central apnea index (i.e., number of central apneas per hour of sleep) reflects an increase in severity of central sleep apnea. Sleep continuity and quality may be markedly impaired with reductions in restorative stages of non–rapid eye movement (REM) sleep (i.e., decreased slow-wave sleep [stage N3]). In individuals with severe Cheyne-Stokes breathing, the pattern can also be observed during resting wakefulness, a finding that is thought to be a poor prognostic marker for mortality.

Diagnostic Features

Central sleep apnea disorders are characterized by repeated episodes of apneas and hypopneas during sleep caused by variability in respiratory effort. These are disorders of ventilatory control in which respiratory events occur in a periodic or intermittent pattern. *Idiopathic central sleep apnea* is characterized by sleepiness, insomnia, and awakenings due to dyspnea in association with five or more central apneas per hour of sleep. Central sleep apnea occurring in individuals with heart failure, stroke, or renal failure typically have a breathing pattern called *Cheyne-Stokes breathing,* which is characterized by a pattern of periodic crescendo-decrescendo variation in tidal volume that results in central apneas and hypopneas occurring at a frequency of at least five events per hour that are accompanied by frequent arousals. Central and obstructive sleep apneas may coexist; the ratio of central to obstructive apneas/hypopneas may be used to identify which condition is predominant.

Alterations in neuromuscular control of breathing can occur in association with medications or substances used in individuals with mental health conditions, which can cause or exacerbate impairments of respiratory rhythm and ventilation. Individuals taking these medications have a sleep-related breathing disorder that could contribute to sleep disturbances and symptoms such as sleepiness, confusion, and depression. Specifically, *chronic*

use of long-acting opioid medications is often associated with impairment of respiratory control leading to central sleep apnea.

Associated Features Supporting Diagnosis

Individuals with central sleep apnea hypopneas can manifest with sleepiness or insomnia. There can be complaints of sleep fragmentation, including awakening with dyspnea. Some individuals are asymptomatic. Obstructive sleep apnea hypopnea can coexist with Cheyne-Stokes breathing, and thus snoring and abruptly terminating apneas may be observed during sleep.

Prevalence

The prevalence of idiopathic central sleep apnea is unknown but thought to be rare. The prevalence of Cheyne-Stokes breathing is high in individuals with depressed cardiac ventricular ejection fraction. In individuals with an ejection fraction of less than 45%, the prevalence has been reported to be 20% or higher. The male-to-female ratio for prevalence is even more highly skewed toward males than for obstructive sleep apnea hypopnea. Prevalence increases with age, and most patients are older than 60 years. Cheyne-Stokes breathing occurs in approximately 20% of individuals with acute stroke. Central sleep apnea comorbid with opioid use occurs in approximately 30% of individuals taking chronic opioids for nonmalignant pain and similarly in individuals receiving methadone maintenance therapy.

Development and Course

The onset of Cheyne-Stokes breathing appears tied to the development of heart failure. The Cheyne-Stokes breathing pattern is associated with oscillations in heart rate, blood pressure and oxygen desaturation, and elevated sympathetic nervous system activity that can promote progression of heart failure. The clinical significance of Cheyne-Stokes breathing in the setting of stroke is not known, but Cheyne-Stokes breathing may be a transient finding that resolves with time after acute stroke. Central sleep apnea comorbid with opioid use has been documented with chronic use (i.e., several months).

Risk and Prognostic Factors

Genetic and physiological. Cheyne-Stokes breathing is frequently present in individuals with heart failure. The coexistence of atrial fibrillation further increases risk, as do older age and male gender. Cheyne-Stokes breathing is also seen in association with acute stroke and possibly renal failure. The underlying ventilatory instability in the setting of heart failure has been attributed to increased ventilatory chemosensitivity and hyperventilation due to pulmonary vascular congestion and circulatory delay. Central sleep apnea is seen in individuals taking long-acting opioids.

Diagnostic Markers

Physical findings seen in individuals with a Cheyne-Stokes breathing pattern relate to its risk factors. Findings consistent with heart failure, such as jugular venous distension, S_3 heart sound, lung crackles, and lower extremity edema, may be present. Polysomnography is used to characterize the breathing characteristics of each breathing-related sleep disorder subtype. Central sleep apneas are recorded when periods of breathing cessation for longer than 10 seconds occur. Cheyne-Stokes breathing is characterized by a pattern of periodic crescendo-decrescendo variation in tidal volume that results in central apneas and hypopneas occurring at a frequency of at least five events per hour that are accompanied by frequent arousals. The cycle length of Cheyne-Stokes breathing (or time from end of one central apnea to the end of the next apnea) is about 60 seconds.

Functional Consequences of Central Sleep Apnea

Idiopathic central sleep apnea has been reported to cause symptoms of disrupted sleep, including insomnia and sleepiness. Cheyne-Stokes breathing with comorbid heart failure has been associated with excessive sleepiness, fatigue, and insomnia, although many individuals may be asymptomatic. Coexistence of heart failure and Cheyne-Stokes breathing may be associated with increased cardiac arrhythmias and increased mortality or cardiac transplantation. Individuals with central sleep apnea comorbid with opioid use may present with symptoms of sleepiness or insomnia.

Differential Diagnosis

Idiopathic central sleep apnea must be distinguished from other breathing-related sleep disorders, other sleep disorders, and medical conditions and mental disorders that cause sleep fragmentation, sleepiness, and fatigue. This is achieved using polysomnography.

Other breathing-related sleep disorders and sleep disorders. Central sleep apnea can be distinguished from obstructive sleep apnea hypopnea by the presence of at least five central apneas per hour of sleep. These conditions may co-occur, but central sleep apnea is considered to predominate when the ratio of central to obstructive respiratory events exceeds 50%.

Cheyne-Stokes breathing can be distinguished from other mental disorders, including other sleep disorders, and other medical conditions that cause sleep fragmentation, sleepiness, and fatigue based on the presence of a predisposing condition (e.g., heart failure or stroke) and signs and polysomnographic evidence of the characteristic breathing pattern. Polysomnographic respiratory findings can help distinguish Cheyne-Stokes breathing from insomnia due to other medical conditions. High-altitude periodic breathing has a pattern that resembles Cheyne-Stokes breathing but has a shorter cycle time, occurs only at high altitude, and is not associated with heart failure.

Central sleep apnea comorbid with opioid use can be differentiated from other types of breathing-related sleep disorders based on the use of long-acting opioid medications in conjunction with polysomnographic evidence of central apneas and periodic or ataxic breathing. It can be distinguished from insomnia due to drug or substance use based on polysomnographic evidence of central sleep apnea.

Comorbidity

Central sleep apnea disorders are frequently present in users of long-acting opioids, such as methadone. Individuals taking these medications have a sleep-related breathing disorder that could contribute to sleep disturbances and symptoms such as sleepiness, confusion, and depression. While the individual is asleep, breathing patterns such as central apneas, periodic apneas, and ataxic breathing may be observed. Obstructive sleep apnea hypopnea may coexist with central sleep apnea, and features consistent with this condition can also be present (see "Obstructive Sleep Apnea Hypopnea" earlier in this chapter). Cheyne-Stokes breathing is more commonly observed in association with conditions that include heart failure, stroke, and renal failure and is seen more frequently in individuals with atrial fibrillation. Individuals with Cheyne-Stokes breathing are more likely to be older, to be male, and to have lower weight than individuals with obstructive sleep apnea hypopnea.

Sleep-Related Hypoventilation

Diagnostic Criteria

A. Polysomnograpy demonstrates episodes of decreased respiration associated with elevated CO_2 levels. (**Note:** In the absence of objective measurement of CO_2, persistent low levels of hemoglobin oxygen saturation unassociated with apneic/hypopneic events may indicate hypoventilation.)

B. The disturbance is not better explained by another current sleep disorder.

Specify whether:

327.24 (G47.34) Idiopathic hypoventilation: This subtype is not attributable to any readily identified condition.

327.25 (G47.35) Congenital central alveolar hypoventilation: This subtype is a rare congenital disorder in which the individual typically presents in the perinatal period with shallow breathing, or cyanosis and apnea during sleep.

327.26 (G47.36) Comorbid sleep-related hypoventilation: This subtype occurs as a consequence of a medical condition, such as a pulmonary disorder (e.g., interstitial lung disease, chronic obstructive pulmonary disease) or a neuromuscular or chest wall disorder (e.g., muscular dystrophies, postpolio syndrome, cervical spinal cord injury, kyphoscoliosis), or medications (e.g., benzodiazepines, opiates). It also occurs with obesity (obesity hypoventilation disorder), where it reflects a combination of increased work of breathing due to reduced chest wall compliance and ventilation-perfusion mismatch and variably reduced ventilatory drive. Such individuals usually are characterized by body mass index of greater than 30 and hypercapnia during wakefulness (with a pCO_2 of greater than 45), without other evidence of hypoventilation.

Specify current severity:

Severity is graded according to the degree of hypoxemia and hypercarbia present during sleep and evidence of end organ impairment due to these abnormalities (e.g., right-sided heart failure). The presence of blood gas abnormalities during wakefulness is an indicator of greater severity.

Subtypes

Regarding obesity hypoventilation disorder, the prevalence of obesity hypoventilation in the general population is not known but is thought to be increasing in association with the increased prevalence of obesity and extreme obesity.

Diagnostic Features

Sleep-related hypoventilation can occur independently or, more frequently, comorbid with medical or neurological disorders, medication use, or substance use disorder. Although symptoms are not mandatory to make this diagnosis, individuals often report excessive daytime sleepiness, frequent arousals and awakenings during sleep, morning headaches, and insomnia complaints.

Associated Features Supporting Diagnosis

Individuals with sleep-related hypoventilation can present with sleep-related complaints of insomnia or sleepiness. Episodes of orthopnea can occur in individuals with diaphragm weakness. Headaches upon awakening may be present. During sleep, episodes of shallow breathing may be observed, and obstructive sleep apnea hypopnea or central sleep apnea may coexist. Consequences of ventilatory insufficiency, including pulmonary hypertension, cor pulmonale (right heart failure), polycythemia, and neurocognitive dysfunction,

can be present. With progression of ventilatory insufficiency, blood gas abnormalities extend into wakefulness. Features of the medical condition causing sleep-related hypoventilation can also be present. Episodes of hypoventilation may be associated with frequent arousals or bradytachycardia. Individuals may complain of excessive sleepiness and insomnia or morning headaches or may present with findings of neurocognitive dysfunction or depression. Hypoventilation may not be present during wakefulness.

Prevalence

Idiopathic sleep-related hypoventilation in adults is very uncommon. The prevalence of congenital central alveolar hypoventilation is unknown, but the disorder is rare. Comorbid sleep-related hypoventilation (i.e., hypoventilation comorbid with other conditions, such as chronic obstructive pulmonary disease [COPD], neuromuscular disorders, or obesity) is more common.

Development and Course

Idiopathic sleep-related hypoventilation is thought to be a slowly progressive disorder of respiratory impairment. When this disorder occurs comorbidly with other disorders (e.g., COPD, neuromuscular disorders, obesity), disease severity reflects the severity of the underlying condition, and the disorder progresses as the condition worsens. Complications such as pulmonary hypertension, cor pulmonale, cardiac dysrhythmias, polycythemia, neurocognitive dysfunction, and worsening respiratory failure can develop with increasing severity of blood gas abnormalities.

Congenital central alveolar hypoventilation usually manifests at birth with shallow, erratic, or absent breathing. This disorder can also manifest during infancy, childhood, and adulthood because of variable penetrance of the *PHOX2B* mutation. Children with congenital central alveolar hypoventilation are more likely to have disorders of the autonomic nervous system, Hirschsprung's disease, neural crest tumors, and characteristic box-shaped face (i.e., the face is short relative to its width).

Risk and Prognostic Factors

Environmental. Ventilatory drive can be reduced in individuals using central nervous system depressants, including benzodiazepines, opiates, and alcohol.

Genetic and physiological. Idiopathic sleep-related hypoventilation is associated with reduced ventilatory drive due to a blunted chemoresponsiveness to CO_2 (reduced respiratory drive; i.e., "won't breathe"), reflecting underlying neurological deficits in centers governing the control of ventilation. More commonly, sleep-related hypoventilation is comorbid with another medical condition, such as a pulmonary disorder, a neuromuscular or chest wall disorder, or hypothyroidism, or with use of medications (e.g., benzodiazepines, opiates). In these conditions, the hypoventilation may be a consequence of increased work of breathing and/or impairment of respiratory muscle function (i.e., "can't breathe") or reduced respiratory drive (i.e., "won't breathe").

Neuromuscular disorders influence breathing through impairment of respiratory motor innervation or respiratory muscle function. They include conditions such as amyotrophic lateral sclerosis, spinal cord injury, diaphragmatic paralysis, myasthenia gravis, Lambert-Eaton syndrome, toxic or metabolic myopathies, postpolio syndrome, and Charcot-Marie-Tooth syndrome.

Congenital central alveolar hypoventilation is a genetic disorder attributable to mutations of *PHOX2B,* a gene that is crucial for the development of the embryonic autonomic nervous system and neural crest derivatives. Children with congenital central alveolar hypoventilation show blunted ventilatory responses to hypercapnia, especially in non–rapid eye movement sleep.

Gender-Related Diagnostic Issues

Gender distributions for sleep-related hypoventilation occurring in association with comorbid conditions reflect the gender distributions of the comorbid conditions. For example, COPD is more frequently present in males and with increasing age.

Diagnostic Markers

Sleep-related hypoventilation is diagnosed using polysomnography showing sleep-related hypoxemia and hypercapnia that is not better explained by another breathing-related sleep disorder. The documentation of increased arterial pCO_2 levels to greater than 55 mmHg during sleep or a 10 mmHg or greater increase in pCO_2 levels (to a level that also exceeds 50 mmHg) during sleep in comparison to awake supine values, for 10 minutes or longer, is the gold standard for diagnosis. However, obtaining arterial blood gas determinations during sleep is impractical, and non-invasive measures of pCO_2 have not been adequately validated during sleep and are not widely used during polysomnography in adults. Prolonged and sustained decreases in oxygen saturation (oxygen saturation of less than 90% for more than 5 minutes with a nadir of at least 85%, or oxygen saturation of less than 90% for at least 30% of sleep time) in the absence of evidence of upper airway obstruction are often used as an indication of sleep-related hypoventilation; however, this finding is not specific, as there are other potential causes of hypoxemia, such as that due to lung disease.

Functional Consequences of Sleep-Related Hypoventilation

The consequences of sleep-related hypoventilation are related to the effects of chronic exposure to hypercapnia and hypoxemia. These blood gas derangements cause vasoconstriction of the pulmonary vasculature leading to pulmonary hypertension, which, if severe, can result in right-sided heart failure (cor pulmonale). Hypoxemia can lead to dysfunction of organs such as the brain, blood, and heart, leading to outcomes such as cognitive dysfunction, polycythemia, and cardiac arrhythmias. Hypercapnia can depress ventilatory drive, leading to progressive respiratory failure.

Differential Diagnosis

Other medical conditions affecting ventilation. In adults, the idiopathic variety of sleep-related hypoventilation is very uncommon and is determined by excluding the presence of lung diseases, skeletal malformations, neuromuscular disorders, and other medical and neurological disorders or medications that affect ventilation. Sleep-related hypoventilation must be distinguished from other causes of sleep-related hypoxemia, such as that due to lung disease.

Other breathing-related sleep disorders. Sleep-related hypoventilation can be distinguished from obstructive sleep apnea hypopnea and central sleep apnea based on clinical features and findings on polysomnography. Sleep-related hypoventilation typically shows more sustained periods of oxygen desaturation rather that the periodic episodes seen in obstructive sleep apnea hypopnea and central sleep apnea. Obstructive sleep apnea hypopnea and central sleep apnea also show a pattern of discrete episodes of repeated airflow decreases that can be absent in sleep-related hypoventilation.

Comorbidity

Sleep-related hypoventilation often occurs in association with a pulmonary disorder (e.g., interstitial lung disease, COPD), with a neuromuscular or chest wall disorder (e.g., muscular dystrophies, post-polio syndrome, cervical spinal cord injury, obesity, kyphoscoliosis), or,

most relevant to the mental health provider, with medication use (e.g., benzodiazepines, opiates). Congenital central alveolar hypoventilation often occurs in association with autonomic dysfunction and may occur in association with Hirschsprung's disease. COPD, a disorder of lower airway obstruction usually associated with cigarette smoking, can result in sleep-related hypoventilation and hypoxemia. The presence of coexisting obstructive sleep apnea hypopnea is thought to exacerbate hypoxemia and hypercapnia during sleep and wakefulness. The relationship between congenital central alveolar hypoventilation and idiopathic sleep-related hypoventilation is unclear; in some individuals, idiopathic sleep-related hypoventilation may represent cases of late-onset congenital central alveolar hypoventilation.

Relationship to International Classification of Sleep Disorders

The *International Classification of Sleep Disorders,* 2nd Edition (ICSD-2), combines sleep-related hypoventilation and sleep-related hypoxemia under the category of sleep-related hypoventilation/hypoxemic syndromes. This approach to classification reflects the frequent co-occurrence of disorders that lead to hypoventilation and hypoxemia. In contrast, the classification used in DSM-5 reflects evidence that there are distinct sleep-related pathogenetic processes leading to hypoventilation.

Circadian Rhythm Sleep-Wake Disorders

Diagnostic Criteria

A. A persistent or recurrent pattern of sleep disruption that is primarily due to an alteration of the circadian system or to a misalignment between the endogenous circadian rhythm and the sleep–wake schedule required by an individual's physical environment or social or professional schedule.
B. The sleep disruption leads to excessive sleepiness or insomnia, or both.
C. The sleep disturbance causes clinically significant distress or impairment in social, occupational, and other important areas of functioning.

Coding note: For ICD-9-CM, code **307.45** for all subtypes. For ICD-10-CM, code is based on subtype.

Specify whether:

307.45 (G47.21) Delayed sleep phase type: A pattern of delayed sleep onset and awakening times, with an inability to fall asleep and awaken at a desired or conventionally acceptable earlier time.

Specify if:

Familial: A family history of delayed sleep phase is present.

Specify if:

Overlapping with non-24-hour sleep-wake type: Delayed sleep phase type may overlap with another circadian rhythm sleep-wake disorder, non-24-hour sleep-wake type.

307.45 (G47.22) Advanced sleep phase type: A pattern of advanced sleep onset and awakening times, with an inability to remain awake or asleep until the desired or conventionally acceptable later sleep or wake times.

Specify if:

Familial: A family history of advanced sleep phase is present.

307.45 (G47.23) Irregular sleep-wake type: A temporally disorganized sleep-wake pattern, such that the timing of sleep and wake periods is variable throughout the 24-hour period.

307.45 (G47.24) Non-24-hour sleep-wake type: A pattern of sleep-wake cycles that is not synchronized to the 24-hour environment, with a consistent daily drift (usually to later and later times) of sleep onset and wake times.

307.45 (G47.26) Shift work type: Insomnia during the major sleep period and/or excessive sleepiness (including inadvertent sleep) during the major awake period associated with a shift work schedule (i.e., requiring unconventional work hours).

307.45 (G47.20) Unspecified type

Specify if:

Episodic: Symptoms last at least 1 month but less than 3 months.

Persistent: Symptoms last 3 months or longer.

Recurrent: Two or more episodes occur within the space of 1 year.

Delayed Sleep Phase Type

Diagnostic Features

The delayed sleep phase type is based primarily on a history of a delay in the timing of the major sleep period (usually more than 2 hours) in relation to the desired sleep and wake-up time, resulting in symptoms of insomnia and excessive sleepiness. When allowed to set their own schedule, individuals with delayed sleep phase type exhibit normal sleep quality and duration for age. Symptoms of sleep-onset insomnia, difficulty waking in the morning, and excessive early day sleepiness are prominent.

Associated Features Supporting Diagnosis

Common associated features of delayed sleep phase type include a history of mental disorders or a concurrent mental disorder. Extreme and prolonged difficulty awakening with morning confusion is also common. Psychophysiological insomnia may develop as a result of maladaptive behaviors that impair sleep and increase arousal because of repeated attempts to fall asleep at an earlier time.

Prevalence

Prevalence of delayed sleep phase type in the general population is approximately 0.17% but appears to be greater than 7% in adolescents. Although the prevalence of familial delayed sleep phase type has not been established, a family history of delayed sleep phase is present in individuals with delayed sleep phase type.

Development and Course

Course is persistent, lasting longer than 3 months, with intermittent exacerbations throughout adulthood. Although age at onset is variable, symptoms begin typically in adolescence and early adulthood and persist for several months to years before diagnosis is established. Severity may decrease with age. Relapse of symptoms is common.

Clinical expression may vary across the lifespan depending on social, school, and work obligations. Exacerbation is usually triggered by a change in work or school schedule that requires an early rise time. Individuals who can alter their work schedules to accommodate the delayed circadian sleep and wake timing can experience remission of symptoms.

Increased prevalence in adolescence may be a consequence of both physiological and behavioral factors. Hormonal changes may be involved specifically, as delayed sleep phase is associated with the onset of puberty. Thus, delayed sleep phase type in adolescents should be differentiated from the common delay in the timing of circadian rhythms in this age group. In the familial form, the course is persistent and may not improve significantly with age.

Risk and Prognostic Factors

Genetic and physiological. Predisposing factors may include a longer than average circadian period, changes in light sensitivity, and impaired homeostatic sleep drive. Some individuals with delayed sleep phase type may be hypersensitive to evening light, which can serve as a delay signal to the circadian clock, or they may be hyposensitive to morning light such that its phase-advancing effects are reduced. Genetic factors may play a role in the pathogenesis of familial and sporadic forms of delayed sleep phase type, including mutations in circadian genes (e.g., *PER3*, *CKIe*).

Diagnostic Markers

Confirmation of the diagnosis includes a complete history and use of a sleep diary or actigraphy (i.e., a wrist-worn motion detector that monitors motor activity for prolonged periods and can be used as a proxy for sleep-wake patterns for at least 7 days). The period covered should include weekends, when social and occupational obligations are less strict, to ensure that the individual exhibits a consistently delayed sleep-wake pattern. Biomarkers such as salivary dim light melatonin onset should be obtained only when the diagnosis is unclear.

Functional Consequences of Delayed Sleep Phase Type

Excessive early day sleepiness is prominent. Extreme and prolonged difficulty awakening with morning confusion (i.e., sleep inertia) is also common. The severity of insomnia and excessive sleepiness symptoms varies substantially among individuals and largely depends on the occupational and social demands on the individual.

Differential Diagnosis

Normative variations in sleep. Delayed sleep phase type must be distinguished from "normal" sleep patterns in which an individual has a late schedule that does not cause personal, social, or occupational distress (most commonly seen in adolescents and young adults).

Other sleep disorders. Insomnia disorder and other circadian rhythm sleep-wake disorders should be included in the differential. Excessive sleepiness may also be caused by other sleep disturbances, such as breathing-related sleep disorders, insomnias, sleep-related movement disorders, and medical, neurological, and mental disorders. Overnight polysomnography may help in evaluating for other comorbid sleep disorders, such as sleep apnea. The circadian nature of delayed sleep phase type, however, should differentiate it from other disorders with similar complaints.

Comorbidity

Delayed sleep phase type is strongly associated with depression, personality disorder, and somatic symptom disorder or illness anxiety disorder. In addition, comorbid sleep disorders, such as insomnia disorder, restless legs syndrome, and sleep apnea, as well as depressive and bipolar disorders and anxiety disorders, can exacerbate symptoms of insomnia and excessive sleepiness. Delayed sleep phase type may overlap with another circadian rhythm sleep-wake disorder, non-24-hour sleep-wake type. Sighted individuals with non-24-hour sleep-wake type disorder commonly also have a history of delayed circadian sleep phase.

Advanced Sleep Phase Type

Specifiers

Advanced sleep phase type may be documented with the specified "familial." Although the prevalence of familial advanced sleep phase type has not been established, a family history of advanced sleep phase is present in individuals with advanced sleep phase type. In this type, specific mutations demonstrate an autosomal dominant mode of inheritance. In the familial form, onset of symptoms may occur earlier (during childhood and early adulthood), the course is persistent, and the severity of symptoms may increase with age.

Diagnostic Features

Advanced sleep phase type is characterized by sleep-wake times that are several hours earlier than desired or conventional times. Diagnosis is based primarily on a history of an advance in the timing of the major sleep period (usually more than 2 hours) in relation to the desired sleep and wake-up time, with symptoms of early morning insomnia and excessive daytime sleepiness. When allowed to set their schedule, individuals with advanced sleep phase type will exhibit normal sleep quality and duration for age.

Associated Features Supporting Diagnosis

Individuals with advanced sleep phase type are "morning types," having earlier sleep-wake times, with the timing of circadian biomarkers such as melatonin and core body temperature rhythms occurring 2–4 hours earlier than normal. When required to keep a conventional schedule requiring a delay of bedtime, these individuals will continue to have an early rise time, leading to persistent sleep deprivation and daytime sleepiness. Use of hypnotics or alcohol to combat sleep-maintenance insomnia and stimulants to reduce daytime sleepiness may lead to substance abuse in these individuals.

Prevalence

The estimated prevalence of advanced sleep phase type is approximately 1% in middle-age adults. Sleep-wake times and circadian phase advance in older individuals, probably accounting for increased prevalence in this population.

Development and Course

Onset is usually in late adulthood. In the familial form, onset can be earlier. The course is typically persistent, lasting more than 3 months, but the severity may increase depending on work and social schedules. The advanced sleep phase type is more common in older adults.

Clinical expression may vary across the lifespan depending on social, school, and work obligations. Individuals who can alter their work schedules to accommodate the advanced circadian sleep and wake timing can experience remission of symptoms. Increasing age tends to advance the sleep phase, however, it is unclear whether the common age-associated advanced sleep phase type is due solely to a change in circadian timing (as seen in the familial form) or also to age-related changes in the homeostatic regulation of sleep, resulting in earlier awakening. Severity, remission, and relapse of symptoms suggest lack of adherence to behavioral and environmental treatments designed to control sleep and wake structure and light exposure.

Risk and Prognostic Factors

Environmental. Decreased late afternoon/early evening exposure to light and/or exposure to early morning light due to early morning awakening can increase the risk of advanced sleep phase type by advancing circadian rhythms. By going to bed early, these individuals are not exposed to light in the phase delay region of the curve, resulting in perpetuation of advanced phase. In familial advanced sleep phase type, a shortening of the endogenous circadian period can result in an advanced sleep phase, although circadian period does not appear to systematically decrease with age.

Genetic and physiological. Advanced sleep phase type has demonstrated an autosomal dominant mode of inheritance, including a *PER2* gene mutation causing hypophosphorylation of the PER2 protein and a missense mutation in *CKI*.

Culture-Related Diagnostic Issues

African Americans may have a shorter circadian period and larger magnitude phase advances to light than do Caucasians, possibly increasing the risk for development of advanced sleep phase type in this population.

Diagnostic Markers

A sleep diary and actigraphy may be used as diagnostic markers, as described earlier for delayed sleep phase type.

Functional Consequences of Advanced Sleep Phase Type

Excessive sleepiness associated with advanced sleep phase can have a negative effect on cognitive performance, social interaction, and safety. Use of wake-promoting agents to combat sleepiness or sedatives for early morning awakening may increase potential for substance abuse.

Differential Diagnosis

Other sleep disorders. Behavioral factors such as irregular sleep schedules, voluntary early awakening, and exposure to light in the early morning should be considered, particularly in older adults. Careful attention should be paid to rule out other sleep-wake disorders, such as insomnia disorder, and other mental disorders and medical conditions that can cause early morning awakening.

Depressive and bipolar disorders. Because early morning awakening, fatigue, and sleepiness are prominent features of major depressive disorder, depressive and bipolar disorders must also be considered.

Comorbidity

Medical conditions and mental disorders with the symptom of early morning awakening, such as insomnia, can co-occur with the advance sleep phase type.

Irregular Sleep-Wake Type

Diagnostic Features

The diagnosis of irregular sleep-wake type is based primarily on a history of symptoms of insomnia at night (during the usual sleep period) and excessive sleepiness (napping) during the day. Irregular sleep-wake type is characterized by a lack of discernable sleep-wake

circadian rhythm. There is no major sleep period, and sleep is fragmented into at least three periods during the 24-hour day.

Associated Features Supporting Diagnosis

Individuals with irregular sleep-wake type typically present with insomnia or excessive sleepiness, depending on the time of day. Sleep and wake periods across 24 hours are fragmented, although the longest sleep period tends to occur between 2:00 A.M. and 6:00 A.M. and is usually less than 4 hours. A history of isolation or reclusion may occur in association with the disorder and contribute to the symptoms via a lack of external stimuli to help entrain a normal pattern. Individuals or their caregivers report frequent naps throughout the day. Irregular sleep-wake type is most commonly associated with neurodegenerative disorders, such as major neurocognitive disorder, and many neurodevelopmental disorders in children.

Prevalence

Prevalence of irregular sleep-wake type in the general population is unknown.

Development and Course

The course of irregular sleep-wake type is persistent. Age at onset is variable, but the disorder is more common in older adults.

Risk and Prognostic Factors

Temperamental. Neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, and Huntington's disease, and neurodevelopmental disorders in children increase the risk for irregular sleep-wake type.

Environmental. Decreased exposure to environmental light and structured daytime activity can be associated with a low-amplitude circadian rhythm. Hospitalized individuals are especially prone to such weak external entraining stimuli, and even outside the hospital setting, individuals with major neurocognitive disorder (i.e., dementia) are exposed to significantly less bright light.

Diagnostic Markers

A detailed sleep history and a sleep diary (by a caregiver) or actigraphy help confirm the irregular sleep-wake pattern.

Functional Consequences of Irregular Sleep-Wake Type

Lack of a clearly discernible major sleep and wake period in irregular sleep-wake type results in insomnia or excessive sleepiness, depending on the time of day. Disruption of the caregiver's sleep also often occurs and is an important consideration.

Differential Diagnosis

Normative variations in sleep. Irregular sleep-wake type should be distinguished from a voluntary irregular sleep-wake schedule and poor sleep hygiene, which can result in insomnia and excessive sleepiness.

Other medical conditions and mental disorders. Other causes of insomnia and daytime sleepiness, including comorbid medical conditions and mental disorders or medication, should be considered.

Comorbidity

Irregular sleep-wake type is often comorbid with neurodegenerative and neurodevelopmental disorders, such as major neurocognitive disorder, intellectual disability (intellectual developmental disorder), and traumatic brain injury. It is also comorbid with other medical conditions and mental disorders in which there is social isolation and/or lack of light and structured activities.

Non-24-Hour Sleep-Wake Type

Diagnostic Features

The diagnosis of non-24-hour sleep-wake type is based primarily on a history of symptoms of insomnia or excessive sleepiness related to abnormal synchronization between the 24-hour light-dark cycle and the endogenous circadian rhythm. Individuals typically present with periods of insomnia, excessive sleepiness, or both, which alternate with short asymptomatic periods. Starting with the asymptomatic period, when the individual's sleep phase is aligned to the external environment, sleep latency will gradually increase and the individual will complain of sleep-onset insomnia. As the sleep phase continues to drift so that sleep time is now in the daytime, the individual will have trouble staying awake during the day and will complain of sleepiness. Because the circadian period is not aligned to the external 24-hour environment, symptoms will depend on when an individual tries to sleep in relation to the circadian rhythm of sleep propensity.

Associated Features Supporting Diagnosis

Non-24-hour sleep-wake type is most common among blind or visually impaired individuals who have decreased light perception. In sighted individuals, there is often a history of delayed sleep phase and of decreased exposure to light and structured social and physical activity. Sighted individuals with non-24-hour sleep-wake type also demonstrate increased sleep duration.

Prevalence

Prevalence of non-24-hour sleep-wake type in the general population is unclear, but the disorder appears rare in sighted individuals. The prevalence in blind individuals is estimated to be 50%.

Development and Course

Course of non-24-hour sleep-wake type is persistent, with intermittent remission and exacerbations due to changes in work and social schedules throughout the lifespan. Age at onset is variable, depending on the onset of visual impairment. In sighted individuals, because of the overlap with delayed sleep phase type, non-24-hour sleep-wake type may develop in adolescence or early adulthood. Remission and relapse of symptoms in blind and sighted individuals largely depend on adherence to treatments designed to control sleep and wake structure and light exposure.

Clinical expression may vary across the lifespan depending on social, school, and work obligations. In adolescents and adults, irregular sleep-wake schedules and exposure to light or lack of light at critical times of the day can exacerbate the effects of sleep loss and disrupt circadian entrainment. Consequently, symptoms of insomnia, daytime sleepiness, and school, professional, and interpersonal functioning may worsen.

Risk and Prognostic Factors

Environmental. In sighted individuals, decreased exposure or sensitivity to light and social and physical activity cues may contribute to a free-running circadian rhythm. With the

high frequency of mental disorders involving social isolation and cases of non-24-hour sleep-wake type developing after a change in sleep habits (e.g., night shift work, job loss), behavioral factors in combination with physiological tendency may precipitate and perpetuate this disorder in sighted individuals. Hospitalized individuals with neurological and psychiatric disorders can become insensitive to social cues, predisposing them to the development of non-24-hour sleep-wake type.

Genetic and physiological. Blindness is a risk factor for non-24-hour sleep-wake type. Non-24-hour sleep-wake type has been associated with traumatic brain injury.

Diagnostic Markers

Diagnosis is confirmed by history and sleep diary or actigraphy for an extended period. Sequential measurement of phase markers (e.g., melatonin) can help determine circadian phase in both sighted and blind individuals.

Functional Consequences of Non-24-Hour Sleep-Wake Type

Complaints of insomnia (sleep onset and sleep maintenance), excessive sleepiness, or both are prominent. The unpredictability of sleep and wake times (typically a daily delay drift) results in an inability to attend school or maintain a steady job and may increase potential for social isolation.

Differential Diagnosis

Circadian rhythm sleep-wake disorders. In sighted individuals, non-24-hour sleep-wake type should be differentiated from delayed sleep phase type, as individuals with delayed sleep phase type may display a similar progressive delay in sleep period for several days.

Depressive disorders. Depressive symptoms and depressive disorders may result in similar circadian dysregulation and symptoms.

Comorbidity

Blindness is often comorbid with non-24-hour sleep-wake type, as are depressive and bipolar disorders with social isolation.

Shift Work Type

Diagnostic Features

Diagnosis is primarily based on a history of the individual working outside of the normal 8:00 A.M. to 6:00 P.M. daytime window (particularly at night) on a regularly scheduled (i.e., non-overtime) basis. Symptoms of excessive sleepiness at work, and impaired sleep at home, on a persistent basis are prominent. Presence of both sets of symptoms are usually required for a diagnosis of shift work type. Typically, when the individual reverts to a day-work routine, symptoms resolve. Although the etiology is slightly different, individuals who travel across many time zones on a very frequent basis may experience effects similar to those experienced by individuals with shift work type who work rotating shifts.

Prevalence

The prevalence of shift work type is unclear, but the disorder is estimated to affect 5%–10% of the night worker population (16%–20% of the workforce). Prevalence rises with advancement into middle-age and beyond (Drake et al. 2004).

Development and Course

Shift work type can appear in individuals of any age but is more prevalent in individuals older than 50 years and typically worsens with the passage of time if the disruptive work hours persist. Although older adults may show similar rates of circadian phase adjustment to a change in routine as do younger adults, they appear to experience significantly more sleep disruption as a consequence of the circadian phase shift.

Risk and Prognostic Factors

Temperamental. Predisposing factors include a morning-type disposition, a need for long (i.e., more than 8 hours) sleep durations in order to feel well rested, and strong competing social and domestic needs (e.g., parents of young children). Individuals who are able to commit to a nocturnal lifestyle, with few competing day-oriented demands, appear at lower risk for shift work type.

Genetic and physiological. Because shift workers are more likely than day workers to be obese, obstructive sleep apnea may be present and may exacerbate the symptoms.

Diagnostic Markers

A history and sleep diary or actigraphy may be useful in diagnosis, as discussed earlier for delayed sleep phase type.

Functional Consequences of Shift Work Type

Individuals with shift work type not only may perform poorly at work but also appear to be at risk for accidents both at work and on the drive home. They may also be at risk for poor mental health (e.g., alcohol use disorder, substance use disorder, depression) and physical health (e.g., gastrointestinal disorders, cardiovascular disease, diabetes, cancer). Individuals with a history of bipolar disorder are particularly vulnerable to shift work type–related episodes of mania resulting from missed nights of sleep. Shift work type often results in interpersonal problems.

Differential Diagnosis

Normative variations in sleep with shift work. The diagnosis of shift work type, as opposed to the "normal" difficulties of shift work, must depend to some extent on the severity of symptoms and/or level of distress experienced by the individual. Presence of shift work type symptoms even when the individual is able to live on a day-oriented routine for several weeks at a time may suggest the presence of other sleep disorders, such as sleep apnea, insomnia, and narcolepsy, which should be ruled out.

Comorbidity

Shift work type has been associated with increased alcohol use disorder, other substance use disorders, and depression. A variety of physical health disorders (e.g., gastrointestinal disorders, cardiovascular disease, diabetes, cancer) have been found to be associated with prolonged exposure to shift work.

Relationship to International Classification of Sleep Disorders

The *International Classification of Sleep Disorders,* 2nd Edition (ICSD-2), differentiates nine circadian rhythm sleep disorders, including jet lag type.

Parasomnias

Parasomnias are disorders characterized by abnormal behavioral, experiential, or physiological events occurring in association with sleep, specific sleep stages, or sleep-wake transitions. The most common parasomnias—non–rapid eye movement (NREM) sleep arousal disorders and rapid eye movement (REM) sleep behavior disorder—represent admixtures of wakefulness and NREM sleep and wakefulness and REM sleep, respectively. These conditions serve as a reminder that sleep and wakefulness are not mutually exclusive and that sleep is not necessarily a global, whole-brain phenomenon.

Non–Rapid Eye Movement Sleep Arousal Disorders

Diagnostic Criteria

A. Recurrent episodes of incomplete awakening from sleep, usually occurring during the first third of the major sleep episode, accompanied by either one of the following:

   1. **Sleepwalking:** Repeated episodes of rising from bed during sleep and walking about. While sleepwalking, the individual has a blank, staring face; is relatively unresponsive to the efforts of others to communicate with him or her; and can be awakened only with great difficulty.
   2. **Sleep terrors:** Recurrent episodes of abrupt terror arousals from sleep, usually beginning with a panicky scream. There is intense fear and signs of autonomic arousal, such as mydriasis, tachycardia, rapid breathing, and sweating, during each episode. There is relative unresponsiveness to efforts of others to comfort the individual during the episodes.

B. No or little (e.g., only a single visual scene) dream imagery is recalled.

C. Amnesia for the episodes is present.

D. The episodes cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication).

F. Coexisting mental and medical disorders do not explain the episodes of sleepwalking or sleep terrors.

Coding note: For ICD-9-CM, code **307.46** for all subtypes. For ICD-10-CM, code is based on subtype.

Specify whether:

307.46 (F51.3) Sleepwalking type

Specify if:

With sleep-related eating

With sleep-related sexual behavior (sexsomnia)

307.46 (F51.4) Sleep terror type

Diagnostic Features

The essential feature of non–rapid eye movement (NREM) sleep arousal disorders is the repeated occurrence of incomplete arousals, usually beginning during the first third of the major sleep episode (Criterion A), that typically are brief, lasting 1–10 minutes, but may be protracted, lasting up to 1 hour. The maximum duration of an event is unknown. The eyes are typically open during these events. Many individuals exhibit both subtypes of arousals on different occasions, which underscores the unitary underlying pathophysiology. The subtypes reflect varying degrees of simultaneous occurrence of wakefulness and NREM sleep, resulting in complex behaviors arising from sleep with varying degrees of conscious awareness, motor activity, and autonomic activation.

The essential feature of *sleepwalking* is repeated episodes of complex motor behavior initiated during sleep, including rising from bed and walking about (Criterion A1). Sleepwalking episodes begin during any stage of NREM sleep, most commonly during slow-wave sleep and therefore most often occurring during the first third of the night. During episodes, the individual has reduced alertness and responsiveness, a blank stare, and relative unresponsiveness to communication with others or efforts by others to awaken the individual. If awakened during the episode (or on awakening the following morning), the individual has limited recall for the episode. After the episode, there may initially be a brief period of confusion or difficulty orienting, followed by full recovery of cognitive function and appropriate behavior.

The essential feature of *sleep terrors* is the repeated occurrence of precipitous awakenings from sleep, usually beginning with a panicky scream or cry (Criterion A2). Sleep terrors usually begin during the first third of the major sleep episode and last 1–10 minutes, but they may last considerably longer, particularly in children. The episodes are accompanied by impressive autonomic arousal and behavioral manifestations of intense fear. During an episode, the individual is difficult to awaken or comfort. If the individual awakens after the sleep terror, little or none of the dream, or only fragmentary, single images, are recalled. During a typical episode of sleep terrors, the individual abruptly sits up in bed screaming or crying, with a frightened expression and autonomic signs of intense anxiety (e.g., tachycardia, rapid breathing, sweating, dilation of the pupils). The individual may be inconsolable and is usually unresponsive to the efforts of others to awaken or comfort him or her. Sleep terrors are also called "night terrors" or "pavor nocturnus."

Associated Features Supporting Diagnosis

Sleepwalking episodes can include a wide variety of behaviors. Episodes may begin with confusion: the individual may simply sit up in bed, look about, or pick at the blanket or sheet. This behavior then becomes progressively complex. The individual may actually leave the bed and walk into closets, out of the room, and even out of buildings. Individuals may use the bathroom, eat, talk, or engage in more complex behaviors. Running and frantic attempts to escape some apparent threat can also occur. Most behaviors during sleepwalking episodes are routine and of low complexity. However, cases of unlocking doors and even operating machinery (driving an automobile) have been reported. Sleepwalking can also include inappropriate behavior (e.g., commonly, urinating in a closet or wastebasket). Most episodes last for several minutes to a half hour but may be more protracted. Inasmuch as sleep is a state of relative analgesia, painful injuries sustained during sleepwalking may not be appreciated until awakening after the fact.

There are two "specialized" forms of sleepwalking: sleep-related eating behavior and sleep-related sexual behavior (sexsomnia or sleep sex). Individuals with *sleep-related eating* experience unwanted recurrent episodes of eating with varying degrees of amnesia, ranging from no awareness to full awareness without the ability to not eat. During these episodes, inappropriate foods may be ingested. Individuals with sleep-related eating disorder may find evidence of their eating only the next morning. In *sexsomnia,* varying degrees of

sexual activity (e.g., masturbation, fondling, groping, sexual intercourse) occur as complex behaviors arising from sleep without conscious awareness. This condition is more common in males and may result in serious interpersonal relationship problems or medicolegal consequences.

During a typical episode of sleep terrors, there is often a sense of overwhelming dread, with a compulsion to escape. Although fragmentary vivid dream images may occur, a story-like dream sequence (as in nightmares) is not reported. Most commonly, the individual does not awaken fully, but returns to sleep and has amnesia for the episode on awakening the next morning. Usually only one episode will occur on any one night. Occasionally several episodes may occur at intervals throughout the night. These events rarely arise during daytime naps.

Prevalence

Isolated or infrequent NREM sleep arousal disorders are very common in the general population. From 10% to 30% of children have had at least one episode of sleepwalking, and 2%–3% sleepwalk often. The prevalence of sleepwalking disorder, marked by repeated episodes and impairment or distress, is much lower, probably in the range of 1%–5%. The prevalence of sleepwalking episodes (not sleepwalking disorder) is 1.0%–7.0% among adults, with weekly to monthly episodes occurring in 0.5%–0.7%. The lifetime prevalence of sleepwalking in adults is 29.2%, with a past-year prevalence of sleepwalking of 3.6%.

The prevalence of sleep terrors in the general population is unknown. The prevalence of sleep terror episodes (as opposed to sleep terror disorder, in which there is recurrence and distress or impairment) is approximately 36.9% at 18 months of age, 19.7% at 30 months of age, and 2.2% in adults.

Development and Course

NREM sleep arousal disorders occur most commonly in childhood and diminish in frequency with increasing age. The onset of sleepwalking in adults with no prior history of sleepwalking as children should prompt a search for specific etiologies, such as obstructive sleep apnea, nocturnal seizures, or effect of medication.

Risk and Prognostic Factors

Environmental. Sedative use, sleep deprivation, sleep-wake schedule disruptions, fatigue, and physical or emotional stress increase the likelihood of episodes. Fever and sleep deprivation can produce an increased frequency of NREM sleep arousal disorders.

Genetic and physiological. A family history for sleepwalking or sleep terrors may occur in up to 80% of individuals who sleepwalk. The risk for sleepwalking is further increased (to as much as 60% of offspring) when both parents have a history of the disorder.

Individuals with sleep terrors frequently have a positive family history of either sleep terrors or sleepwalking, with as high as a 10-fold increase in the prevalence of the disorder among first-degree biological relatives. Sleep terrors are much more common in monozygotic twins as compared with dizygotic twins. The exact mode of inheritance is unknown.

Gender-Related Diagnostic Issues

Violent or sexual activity during sleepwalking episodes is more likely to occur in adults. Eating during sleepwalking episodes is more commonly seen in females. Sleepwalking occurs more often in females during childhood but more often in males during adulthood.

Older children and adults provide a more detailed recollection of fearful images associated with sleep terrors than do younger children, who are more likely to have complete amnesia or report only a vague sense of fear. Among children, sleep terrors are more common in males than in females. Among adults, the sex ratio is even.

Diagnostic Markers

NREM sleep arousal disorders arise from any stage of NREM sleep but most commonly from deep NREM sleep (slow-wave sleep). They are most likely to appear in the first third of the night and do not commonly occur during daytime naps. During the episode, the polysomnogram may be obscured with movement artifact. In the absence of such artifact, the electroencephalogram typically shows theta or alpha frequency activity during the episode, indicating partial or incomplete arousal.

Polysomnography in conjunction with audiovisual monitoring can be used to document episodes of sleepwalking. In the absence of actually capturing an event during a polysomnographic recording, there are no polysomnographic features that can serve as a marker for sleepwalking. Sleep deprivation may increase the likelihood of capturing an event. As a group, individuals who sleepwalk show instability of deep NREM sleep, but the overlap in findings with individuals who do not sleepwalk is great enough to preclude use of this indicator in establishing a diagnosis. Unlike arousals from REM sleep associated with nightmares, in which there is an increase in heart rate and respiration prior to the arousal, the NREM sleep arousals of sleep terrors begin precipitously from sleep, without anticipatory autonomic changes. The arousals are associated with impressive autonomic activity, with doubling or tripling of the heart rate. The pathophysiology is poorly understood, but there appears to be instability in the deeper stages of NREM sleep. Absent capturing an event during a formal sleep study, there are no reliable polysomnographic indicators of the tendency to experience sleep terrors.

Functional Consequences of Non-REM Sleep Arousal Disorders

For the diagnosis of a NREM sleep arousal disorder to be made, the individual or household members must experience clinically significant distress or impairment, although parasomnia symptoms may occur occasionally in nonclinical populations and would be subthreshold for the diagnosis. Embarrassment concerning the episodes can impair social relationships. Social isolation or occupational difficulties can result. The determination of a "disorder" depends on a number of factors, which may vary on an individual basis and will depend on the frequency of events, potential for violence or injurious behaviors, embarrassment, or disruption/distress of other household members. Severity determination is best made based on the nature or consequence of the behaviors rather than simply on frequency. Uncommonly, NREM sleep arousal disorders may result in serious injury to the individual or to someone trying to console the individual. Injuries to others are confined to those in close proximity; individuals are not "sought out." Typically, sleepwalking in both children and adults is not associated with significant mental disorders. For individuals with sleep-related eating behaviors, unknowingly preparing or eating food during the sleep period may create problems such as poor diabetes control, weight gain, injury (cuts and burns), or consequences of eating dangerous or toxic inedibles. NREM sleep arousal disorders may rarely result in violent or injurious behaviors with forensic implications.

Differential Diagnosis

Nightmare disorder. In contrast to individuals with NREM sleep arousal disorders, individuals with nightmare disorder typically awaken easily and completely, report vivid storylike dreams accompanying the episodes, and tend to have episodes later in the night. NREM sleep arousal disorders occur during NREM sleep, whereas nightmares usually occur during REM sleep. Parents of children with NREM sleep arousal disorders may misinterpret reports of fragmentary imagery as nightmares.

Breathing-related sleep disorders. Breathing disorders during sleep can also produce confusional arousals with subsequent amnesia. However, breathing-related sleep disorders are also characterized by characteristic symptoms of snoring, breathing pauses, and

daytime sleepiness. In some individuals, a breathing-related sleep disorder may precipitate episodes of sleepwalking.

REM sleep behavior disorder. REM sleep behavior disorder may be difficult to distinguish from NREM sleep arousal disorders. REM sleep behavior disorder is characterized by episodes of prominent, complex movements, often involving personal injury arising from sleep. In contrast to NREM sleep arousal disorders, REM sleep behavior disorder occurs during REM sleep. Individuals with REM sleep behavior disorder awaken easily and report more detailed and vivid dream content than do individuals with NREM sleep arousal disorders. They often report that they "act out dreams."

Parasomnia overlap syndrome. Parasomnia overlap syndrome consists of clinical and polysomnographic features of both sleepwalking and REM sleep behavior disorder.

Sleep-related seizures. Some types of seizures can produce episodes of very unusual behaviors that occur predominantly or exclusively during sleep. Nocturnal seizures may closely mimic NREM sleep arousal disorders but tend to be more stereotypic in nature, occur multiple times nightly, and be more likely to occur from daytime naps. The presence of sleep-related seizures does not preclude the presence of NREM sleep arousal disorders. Sleep-related seizures should be classified as a form of epilepsy.

Alcohol-induced blackouts. Alcohol-induced blackouts may be associated with extremely complex behaviors in the absence of other suggestions of intoxication. They do not involve the loss of consciousness but rather reflect an isolated disruption of memory for events during a drinking episode. By history, these behaviors may be indistinguishable from those seen in NREM sleep arousal disorders.

Dissociative amnesia, with dissociative fugue. Dissociative fugue may be extremely difficult to distinguish from sleepwalking. Unlike all other parasomnias, nocturnal dissociative fugue arises from a period of wakefulness during sleep, rather than precipitously from sleep without intervening wakefulness. A history of recurrent childhood physical or sexual abuse is usually present (but may be difficult to obtain).

Malingering or other voluntary behavior occurring during wakefulness. As with dissociative fugue, malingering or other voluntary behavior occurring during wakefulness arises from wakefulness.

Panic disorder. Panic attacks may also cause abrupt awakenings from deep NREM sleep accompanied by fearfulness, but these episodes produce rapid and complete awakening without the confusion, amnesia, or motor activity typical of NREM sleep arousal disorders.

Medication-induced complex behaviors. Behaviors similar to those in NREM sleep arousal disorders can be induced by use of, or withdrawal from, substances or medications (e.g., benzodiazepines, nonbenzodiazepine sedative-hypnotics, opiates, cocaine, nicotine, antipsychotics, tricyclic antidepressants, chloral hydrate). Such behaviors may arise from the sleep period and may be extremely complex. The underlying pathophysiology appears to be a relatively isolated amnesia. In such cases, substance/medication-induced sleep disorder, parasomnia type, should be diagnosed (see "Substance/Medication-Induced Sleep Disorder" later in this chapter).

Night eating syndrome. The sleep-related eating disorder form of sleepwalking is to be differentiated from night eating syndrome, in which there is a delay in the circadian rhythm of food ingestion and an association with insomnia and/or depression.

Comorbidity

In adults, there is an association between sleepwalking and major depressive episodes and obsessive-compulsive disorder. Children or adults with sleep terrors may have elevated scores for depression and anxiety on personality inventories.

Relationship to International Classification of Sleep Disorders

The *International Classification of Sleep Disorders,* 2nd Edition, includes "confusional arousal" as a NREM sleep arousal disorder.

Nightmare Disorder

Diagnostic Criteria **307.47 (F51.5)**

A. Repeated occurrences of extended, extremely dysphoric, and well-remembered dreams that usually involve efforts to avoid threats to survival, security, or physical integrity and that generally occur during the second half of the major sleep episode.
B. On awakening from the dysphoric dreams, the individual rapidly becomes oriented and alert.
C. The sleep disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The nightmare symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication).
E. Coexisting mental and medical disorders do not adequately explain the predominant complaint of dysphoric dreams.

Specify if:

During sleep onset

Specify if:

With associated non–sleep disorder, including substance use disorders
With associated other medical condition
With associated other sleep disorder

Coding note: The code 307.47 (F51.5) applies to all three specifiers. Code also the relevant associated mental disorder, medical condition, or other sleep disorder immediately after the code for nightmare disorder in order to indicate the association.

Specify if:

Acute: Duration of period of nightmares is 1 month or less.
Subacute: Duration of period of nightmares is greater than 1 month but less than 6 months.
Persistent: Duration of period of nightmares is 6 months or greater.

Specify current severity:

Severity can be rated by the frequency with which the nightmares occur:

Mild: Less than one episode per week on average.
Moderate: One or more episodes per week but less than nightly.
Severe: Episodes nightly.

Diagnostic Features

Nightmares are typically lengthy, elaborate, storylike sequences of dream imagery that seem real and that incite anxiety, fear, or other dysphoric emotions. Nightmare content typically focuses on attempts to avoid or cope with imminent danger but may involve themes that evoke other negative emotions. Nightmares occurring after traumatic experiences may replicate the threatening situation ("replicative nightmares"), but most do not. On awakening, nightmares are well remembered and can be described in detail. They arise

almost exclusively during rapid eye movement (REM) sleep and can thus occur throughout sleep but are more likely in the second half of the major sleep episode when dreaming is longer and more intense. Factors that increase early-night REM intensity, such as sleep fragmentation or deprivation, jet lag, and REM-sensitive medications, might facilitate nightmares earlier in the night, including at sleep onset.

Nightmares usually terminate with awakening and rapid return of full alertness. However, the dysphoric emotions may persist into wakefulness and contribute to difficulty returning to sleep and lasting daytime distress. Some nightmares, known as "bad dreams," may not induce awakening and are recalled only later. If nightmares occur during sleep-onset REM periods (*hypnagogic*), the dysphoric emotion is frequently accompanied by a sense of being both awake and unable to move voluntarily (*isolated sleep paralysis*).

Associated Features Supporting Diagnosis

Mild autonomic arousal, including sweating, tachycardia, and tachypnea, may characterize nightmares. Body movements and vocalizations are not characteristic because of REM sleep–related loss of skeletal muscle tone, but such behaviors may occur under situations of emotional stress or sleep fragmentation and in posttraumatic stress disorder (PTSD). When talking or emoting occurs, it is typically a brief event terminating the nightmare.

Individuals with frequent nightmares are at substantially greater risk for suicidal ideation and suicide attempts, even when gender and mental illness are taken into account.

Prevalence

Prevalence of nightmares increases through childhood into adolescence. From 1.3% to 3.9% of parents report that their preschool children have nightmares "often" or "always". Prevalence increases from ages 10 to 13 for both males and females but continues to increase to ages 20–29 for females (while decreasing for males), when it can be twice as high for females as for males. Prevalence decreases steadily with age for both sexes, but the gender difference remains. Among adults, prevalence of nightmares at least monthly is 6%, whereas prevalence for frequent nightmares is 1%–2%. Estimates often combine idiopathic and posttraumatic nightmares indiscriminately.

Development and Course

Nightmares often begin between ages 3 and 6 years but reach a peak prevalence and severity in late adolescence or early adulthood. Nightmares most likely appear in children exposed to acute or chronic psychosocial stressors and thus may not resolve spontaneously. In a minority, frequent nightmares persist into adulthood, becoming virtually a lifelong disturbance. Although specific nightmare content may reflect the individual's age, the essential features of the disorder are the same across age groups.

Risk and Prognostic Factors

Temperamental. Individuals who experience nightmares report more frequent past adverse events, but not necessarily trauma, and often display personality disturbances or psychiatric diagnosis.

Environmental. Sleep deprivation or fragmentation, and irregular sleep-wake schedules that alter the timing, intensity, or quantity of REM sleep, can put individuals at risk for nightmares.

Genetic and physiological. Twin studies have identified genetic effects on the disposition to nightmares and their co-occurrence with other parasomnias (e.g., sleeptalking).

Course modifiers. Adaptive parental bedside behaviors, such as soothing the child following nightmares, may protect against developing chronic nightmares.

Culture-Related Diagnostic Issues

The significance attributed to nightmares may vary by culture, and sensitivity to such beliefs may facilitate disclosure.

Gender-Related Diagnostic Issues

Adult females report having nightmares more frequently than do adult males. Nightmare content differs by sex, with adult females tending to report themes of sexual harassment or of loved ones disappearing/dying, and adult males tending to report themes of physical aggression or war/terror.

Diagnostic Markers

Polysomnographic studies demonstrate abrupt awakenings from REM sleep, usually during the second half of the night, prior to report of a nightmare. Heart, respiratory, and eye movement rates may quicken or increase in variability before awakening. Nightmares following traumatic events may also arise during non-REM (NREM), particularly stage 2, sleep. The typical sleep of individuals with nightmares is mildly impaired (e.g., reduced efficiency, less slow-wave sleep, more awakenings), with more frequent periodic leg movements in sleep and relative sympathetic nervous system activation after REM sleep deprivation.

Functional Consequences of Nightmare Disorder

Nightmares cause more significant subjective distress than demonstrable social or occupational impairment. However, if awakenings are frequent or result in sleep avoidance, individuals may experience excessive daytime sleepiness, poor concentration, depression, anxiety, or irritability. Frequent childhood nightmares (e.g., several per week), may cause significant distress to parents and child.

Differential Diagnosis

Sleep terror disorder. Both nightmare disorder and sleep terror disorder include awakenings or partial awakenings with fearfulness and autonomic activation, but the two disorders are differentiable. Nightmares typically occur later in the night, during REM sleep, and produce vivid, storylike, and clearly recalled dreams; mild autonomic arousal; and complete awakenings. Sleep terrors typically arise in the first third of the night during stage 3 or 4 NREM sleep and produce either no dream recall or images without an elaborate storylike quality. The terrors lead to partial awakenings that leave the individual confused, disoriented, and only partially responsive and with substantial autonomic arousal. There is usually amnesia for the event in the morning.

REM sleep behavior disorder. The presence of complex motor activity during frightening dreams should prompt further evaluation for REM sleep behavior disorder, which occurs more typically among late middle-age males and, unlike nightmare disorder, is associated with often violent dream enactments and a history of nocturnal injuries. The dream disturbance of REM sleep behavior disorder is described by patients as nightmares but is controlled by appropriate medication.

Bereavement. Dysphoric dreams may occur during bereavement but typically involve loss and sadness and are followed by self-reflection and insight, rather than distress, on awakening.

Narcolepsy. Nightmares are a frequent complaint in narcolepsy, but the presence of excessive sleepiness and cataplexy differentiates this condition from nightmare disorder.

Nocturnal seizures. Seizures may rarely manifest as nightmares and should be evaluated with polysomnography and continuous video electroencephalography. Nocturnal seizures usually involve stereotypical motor activity. Associated nightmares, if recalled,

are often repetitive in nature or reflect epileptogenic features such as the content of diurnal auras (e.g., unmotivated dread), phosphenes, or ictal imagery. Disorders of arousal, especially confusional arousals, may also be present.

Breathing-related sleep disorders. Breathing-related sleep disorders can lead to awakenings with autonomic arousal, but these are not usually accompanied by recall of nightmares.

Panic disorder. Attacks arising during sleep can produce abrupt awakenings with autonomic arousal and fearfulness, but nightmares are typically not reported and symptoms are similar to panic attacks arising during wakefulness.

Sleep-related dissociative disorders. Individuals may recall actual physical or emotional trauma as a "dream" during electroencephalography-documented awakenings.

Medication or substance use. Numerous substances/medications can precipitate nightmares, including dopaminergics; beta-adrenergic antagonists and other antihypertensives; amphetamine, cocaine, and other stimulants; antidepressants; smoking cessation aids; and melatonin. Withdrawal of REM sleep–suppressant medications (e.g., antidepressants) and alcohol can produce REM sleep rebound accompanied by nightmares. If nightmares are sufficiently severe to warrant independent clinical attention, a diagnosis of substance/medication-induced sleep disorder should be considered.

Comorbidity

Nightmares may be comorbid with several medical conditions, including coronary heart disease, cancer, parkinsonism, and pain, and can accompany medical treatments, such as hemodialysis, or withdrawal from medications or substances of abuse. Nightmares frequently are comorbid with other mental disorders, including PTSD; insomnia disorder; schizophrenia; psychosis; mood, anxiety, adjustment, and personality disorders; and grief during bereavement. A concurrent nightmare disorder diagnosis should only be considered when independent clinical attention is warranted (i.e., Criteria A–C are met). Otherwise, no separate diagnosis is necessary. These conditions should be listed under the appropriate comorbid category specifier. However, nightmare disorder may be diagnosed as a separate disorder in individuals with PTSD if the nightmares are temporally unrelated to PTSD (i.e., preceding other PTSD symptoms or persisting after other PTSD symptoms have resolved).

Nightmares are normally characteristic of REM sleep behavior disorder, PTSD, and acute stress disorder, but nightmare disorder may be independently coded if nightmares preceded the condition and their frequency or severity necessitates independent clinical attention. The latter may be determined by asking whether nightmares were a problem before onset of the other disorder and whether they continued after other symptoms had remitted.

Relationship to International Classification of Sleep Disorders

The *International Classification of Sleep Disorders,* 2nd Edition (ICSD-2), presents similar diagnostic criteria for nightmare disorder.

Rapid Eye Movement Sleep Behavior Disorder

Diagnostic Criteria **327.42 (G47.52)**

A. Repeated episodes of arousal during sleep associated with vocalization and/or complex motor behaviors.

B. These behaviors arise during rapid eye movement (REM) sleep and therefore usually occur more than 90 minutes after sleep onset, are more frequent during the later portions of the sleep period, and uncommonly occur during daytime naps.

C. Upon awakening from these episodes, the individual is completely awake, alert, and not confused or disoriented.
D. Either of the following:
   1. REM sleep without atonia on polysomnographic recording.
   2. A history suggestive of REM sleep behavior disorder and an established synucleinopathy diagnosis (e.g., Parkinson's disease, multiple system atrophy).
E. The behaviors cause clinically significant distress or impairment in social, occupational, or other important areas of functioning (which may include injury to self or the bed partner).
F. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.
G. Coexisting mental and medical disorders do not explain the episodes.

Diagnostic Features

The essential feature of rapid eye movement (REM) sleep behavior disorder is repeated episodes of arousal, often associated with vocalizations and/or complex motor behaviors arising from REM sleep (Criterion A). These behaviors often reflect motor responses to the content of action-filled or violent dreams of being attacked or trying to escape from a threatening situation, which may be termed *dream enacting behaviors.* The vocalizations are often loud, emotion-filled, and profane. These behaviors may be very bothersome to the individual and the bed partner and may result in significant injury (e.g., falling, jumping, or flying out of bed; running, punching, thrusting, hitting, or kicking). Upon awakening, the individual is immediately awake, alert, and oriented (Criterion C) and is often able to recall dream mentation, which closely correlates with the observed behavior. The eyes typically remain closed during these events. The diagnosis of REM sleep behavior disorder requires clinically significant distress or impairment (Criterion E); this determination will depend on a number of factors, including the frequency of events, the potential for violence or injurious behaviors, embarrassment, and distress in other household members.

Associated Features Supporting Diagnosis

Severity determination is best made based on the nature or consequence of the behavior rather than simply on frequency. Although the behaviors are typically prominent and violent, lesser behaviors may also occur.

Prevalence

The prevalence of REM sleep behavior disorder is approximately 0.38%–0.5% in the general population. Prevalence in patients with psychiatric disorders may be greater, possibly related to medications prescribed for the psychiatric disorder.

Development and Course

The onset of REM sleep behavior disorder may be gradual or rapid, and the course is usually progressive. REM sleep behavior disorder associated with neurodegenerative disorders may improve as the underlying neurodegenerative disorder progresses. Because of the very high association with the later appearance of an underlying neurodegenerative disorder, most notably one of the synucleinopathies (Parkinson's disease, multiple system atrophy, or major or mild neurocognitive disorder with Lewy bodies), the neurological status of individuals with REM sleep behavior disorder should be closely monitored.

REM sleep behavior disorder overwhelmingly affects males older than 50 years, but increasingly this disorder is being identified in females and in younger individuals. Symp-

toms in young individuals, particularly young females, should raise the possibility of narcolepsy or medication-induced REM sleep behavior disorder.

Risk and Prognostic Factors

Genetic and physiological. Many widely prescribed medications, including tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and beta-blockers, may result in polysomnographic evidence of REM sleep without atonia and in frank REM sleep behavior disorder. It is not known whether the medications per se result in REM sleep behavior disorder or they unmask an underlying predisposition.

Diagnostic Markers

Associated laboratory findings from polysomnography indicate increased tonic and/or phasic electromyographic activity during REM sleep that is normally associated with muscle atonia. The increased muscle activity variably affects different muscle groups, mandating more extensive electromyographic monitoring than is employed in conventional sleep studies. For this reason, it is suggested that electromyographic monitoring include the submentalis, bilateral extensor digitorum, and bilateral anterior tibialis muscle groups. Continuous video monitoring is mandatory. Other polysomnographic findings may include very frequent periodic and aperiodic extremity electromyography activity during non-REM (NREM) sleep. This polysomnography observation, termed *REM sleep without atonia,* is present in virtually all cases of REM sleep behavior disorder but may also be an asymptomatic polysomnographic finding. Clinical dream-enacting behaviors coupled with the polysomnographic finding of REM without atonia is necessary for the diagnosis of REM sleep behavior disorder. REM sleep without atonia without a clinical history of dream-enacting behaviors is simply an asymptomatic polysomnographic observation. It is not known whether isolated REM sleep without atonia is a precursor to REM sleep behavior disorder.

Functional Consequences of Rapid Eye Movement Sleep Behavior Disorder

REM sleep behavior disorder may occur in isolated occasions in otherwise unaffected individuals. Embarrassment concerning the episodes can impair social relationships. Individuals may avoid situations in which others might become aware of the disturbance, visiting friends overnight, or sleeping with bed partners. Social isolation or occupational difficulties can result. Uncommonly, REM sleep behavior disorder may result in serious injury to the victim or to the bed partner.

Differential Diagnosis

Other parasomnias. Confusional arousals, sleepwalking, and sleep terrors can easily be confused with REM sleep behavior disorder. In general, these disorders occur in younger individuals. Unlike REM sleep behavior disorder, they arise from deep NREM sleep and therefore tend to occur in the early portion of the sleep period. Awakening from a confusional arousal is associated with confusion, disorientation, and incomplete recall of dream mentation accompanying the behavior. Polysomnographic monitoring in the disorders of arousal reveals normal REM atonia.

Nocturnal seizures. Nocturnal seizures may perfectly mimic REM sleep behavior disorder, but the behaviors are generally more stereotyped. Polysomnographic monitoring employing a full electroencephalographic seizure montage may differentiate the two. REM sleep without atonia is not present on polysomnographic monitoring.

Obstructive sleep apnea. Obstructive sleep apnea may result in behaviors indistinguishable from REM sleep behavior disorder. Polysomnographic monitoring is necessary to differentiate between the two. In this case, the symptoms resolve following effective treatment of the obstructive sleep apnea, and REM sleep without atonia is not present on polysomnography monitoring.

Other specified dissociative disorder (sleep-related psychogenic dissociative disorder). Unlike virtually all other parasomnias, which arise precipitously from NREM or REM sleep, psychogenic dissociative behaviors arise from a period of well-defined wakefulness during the sleep period. Unlike REM sleep behavior disorder, this condition is more prevalent in young females.

Malingering. Many cases of malingering in which the individual reports problematic sleep movements perfectly mimic the clinical features of REM sleep behavior disorder, and polysomnographic documentation is mandatory.

Comorbidity

REM sleep behavior disorder is present concurrently in approximately 30% of patients with narcolepsy. When it occurs in narcolepsy, the demographics reflect the younger age range of narcolepsy, with equal frequency in males and females. Based on findings from individuals presenting to sleep clinics, most individuals (>50%) with initially "idiopathic" REM sleep behavior disorder will eventually develop a neurodegenerative disease—most notably, one of the synucleinopathies (Parkinson's disease, multiple system atrophy, or major or mild neurocognitive disorder with Lewy bodies). REM sleep behavior disorder often predates any other sign of these disorders by many years (often more than a decade).

Relationship to International Classification of Sleep Disorders

REM sleep behavior disorder is virtually identical to REM sleep behavior disorder in the *International Classification of Sleep Disorders,* 2nd Edition (ICSD-2).

Restless Legs Syndrome

Diagnostic Criteria **333.94 (G25.81)**

A. An urge to move the legs, usually accompanied by or in response to uncomfortable and unpleasant sensations in the legs, characterized by all of the following:
   1. The urge to move the legs begins or worsens during periods of rest or inactivity.
   2. The urge to move the legs is partially or totally relieved by movement.
   3. The urge to move the legs is worse in the evening or at night than during the day, or occurs only in the evening or at night.

B. The symptoms in Criterion A occur at least three times per week and have persisted for at least 3 months.

C. The symptoms in Criterion A are accompanied by significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning.

D. The symptoms in Criterion A are not attributable to another mental disorder or medical condition (e.g., arthritis, leg edema, peripheral ischemia, leg cramps) and are not better explained by a behavioral condition (e.g., positional discomfort, habitual foot tapping).

E. The symptoms are not attributable to the physiological effects of a drug of abuse or medication (e.g., akathisia).

Diagnostic Features

Restless legs syndrome (RLS) is a sensorimotor, neurological sleep disorder characterized by a desire to move the legs or arms, usually associated with uncomfortable sensations typically described as creeping, crawling, tingling, burning, or itching (Criterion A). The diagnosis of RLS is based primarily on patient self-report and history. Symptoms are worse when the individual is at rest, and frequent movements of the legs occur in an effort to relieve the uncomfortable sensations. Symptoms are worse in the evening or night, and in some individuals they occur only in the evening or night. Evening worsening occurs independently of any differences in activity. It is important to differentiate RLS from other conditions such as positional discomfort and leg cramps (Criterion D).

The symptoms of RLS can delay sleep onset and awaken the individual from sleep and are associated with significant sleep fragmentation. The relief obtained from moving the legs may no longer be apparent in severe cases. RLS is associated with daytime sleepiness and is frequently accompanied by significant clinical distress or functional impairment.

Associated Features Supporting Diagnosis

Periodic leg movements in sleep (PLMS) can serve as corroborating evidence for RLS, with up to 90% of individuals diagnosed with RLS demonstrating PLMS when recordings are taken over multiple nights. Periodic leg movements during wakefulness are supportive of an RLS diagnosis. Reports of difficulty initiating and maintaining sleep and of excessive daytime sleepiness may also support the diagnosis of RLS. Additional supportive features include a family history of RLS among first-degree relatives and a reduction in symptoms, at least initially, with dopaminergic treatment.

Prevalence

Prevalence rates of RLS vary widely when broad criteria are utilized but range from 2% to 7.2% when more defined criteria are employed. When frequency of symptoms is at least three times per week with moderate or severe distress, the prevalence rate is 1.6%; when frequency of symptoms is a minimum of one time per week, the prevalence rate is 4.5%. Females are 1.5–2 times more likely than males to have RLS. RLS also increases with age. The prevalence of RLS may be lower in Asian populations.

Development and Course

The onset of RLS typically occurs in the second or third decade. Approximately 40% of individuals diagnosed with RLS during adulthood report having experienced symptoms before age 20 years, and 20% report having experienced symptoms before age 10 years. Prevalence rates of RLS increase steadily with age until about age 60 years, with symptoms remaining stable or decreasing slightly in older age groups. Compared with nonfamilial cases, familial RLS usually has a younger age at onset and a slower progressive course. The clinical course of RLS differs by age at onset. When onset occurs before age 45, there is often a slow progression of symptoms. In late-onset RLS, rapid progression is typical, and aggravating factors are common. Symptoms of RLS appear similar across the lifespan, remaining stable or decreasing slightly in older age groups.

Diagnosis of RLS in children can be difficult because of the self-report component. While Criterion A for adults assumes that the description of "urge to move" is by the patient, pediatric diagnosis requires a description in the child's own words rather than by a parent or caretaker. Typically children age 6 years or older are able to provide detailed, adequate descriptors of RLS. However, children rarely use or understand the word "urge," reporting instead that their legs "have to" or "got to" move. Also, potentially related to prolonged periods of sitting during class, two-thirds of children and adolescents report daytime leg sensations. Thus, for diagnostic Criterion A3, it is important to compare equal

duration of sitting or lying down in the day to sitting or lying down in the evening or night. Nocturnal worsening tends to persist even in the context of pediatric RLS. As with RLS in adults, there is a significant negative impact on sleep, mood, cognition, and function. Impairment in children and adolescents is manifested more often in behavioral and educational domains.

Risk and Prognostic Factors

Genetic and physiological. Predisposing factors include female gender, advancing age, genetic risk variants, and family history of RLS. Precipitating factors are often time-limited, such as iron deficiency, with most individuals resuming normal sleep patterns after the initial triggering event has disappeared. Genetic risk variants also play a role in RLS secondary to such disorders as uremia, suggesting that individuals with a genetic susceptibility develop RLS in the presence of further risk factors. RLS has a strong familial component.

There are defined pathophysiological pathways subserving RLS. Genome-wide association studies have found that RLS is significantly associated with common genetic variants in intronic or intergenic regions in *MEIS1*, *BTBD9*, and *MAP2K5* on chromosomes 2p, 6p, and 15q, respectively. The association of these three variants with RLS has been independently replicated. *BTBD9* confers a very large (80%) excessive risk when even a single allele is present. Because of the high frequency of this variant in individuals of European descent, the population attributable risk (PAR) approximates 50%. At-risk alleles associated with *MEIS1* and *BTBD9* are less common in individuals of African or Asian descent, perhaps suggesting lower risk for RLS in these populations.

Pathophysiological mechanisms in RLS also include disturbances in the central dopaminergic system and disturbances in iron metabolism. The endogenous opiate system may also be involved. Treatment effects of dopaminergic drugs (primarily D_2 and D_3 nonergot agonists) provide further support that RLS is grounded in dysfunctional central dopaminergic pathways. While the effective treatment of RLS has also been shown to significantly reduce depressive symptoms, serotonergic antidepressants can induce or aggravate RLS in some individuals.

Gender-Related Diagnostic Issues

Although RLS is more prevalent in females than in males, there are no diagnostic differences according to gender. However, the prevalence of RLS during pregnancy is two to three times greater than in the general population. RLS associated with pregnancy peaks during the third trimester and improves or resolves in most cases soon after delivery. The gender difference in prevalence of RLS is explained at least in part by parity, with nulliparous females being at the same risk of RLS as age-matched males.

Diagnostic Markers

Polysomnography demonstrates significant abnormalities in RLS, commonly increased latency to sleep, and higher arousal index. Polysomnography with a preceding immobilization test may provide an indicator of the motor sign of RLS, periodic limb movements, under standard conditions of sleep and during quiet resting, both of which can provoke RLS symptoms.

Functional Consequences of Restless Legs Syndrome

Forms of RLS severe enough to significantly impair functioning or associated with mental disorders, including depression and anxiety, occur in approximately 2%–3% of the population.

Although the impact of milder symptoms is less well characterized, individuals with RLS complain of disruption in at least one activity of daily living, with up to 50% reporting

a negative impact on mood, and 47.6% reporting a lack of energy. The most common consequences of RLS are sleep disturbance, including reduced sleep time, sleep fragmentation, and overall disturbance; depression, generalized anxiety disorder, panic disorder, and posttraumatic stress disorder; and quality-of-life impairments. RLS can result in daytime sleepiness or fatigue and is frequently accompanied by significant distress or impairment in affective, social, occupational, educational, academic, behavioral, or cognitive functioning.

Differential Diagnosis

The most important conditions in the differential diagnosis of RLS are leg cramps, positional discomfort, arthralgias/arthritis, myalgias, positional ischemia (numbness), leg edema, peripheral neuropathy, radiculopathy, and habitual foot tapping. "Knotting" of the muscle (cramps), relief with a single postural shift, limitation to joints, soreness to palpation (myalgias), and other abnormalities on physical examination are not characteristic of RLS. Unlike RLS, nocturnal leg cramps do not typically present with the desire to move the limbs nor are there frequent limb movements. Less common conditions to be differentiated from RLS include neuroleptic-induced akathisia, myelopathy, symptomatic venous insufficiency, peripheral artery disease, eczema, other orthopedic problems, and anxiety-induced restlessness. Worsening at night and periodic limb movements are more common in RLS than in medication-induced akathisia or peripheral neuropathy.

While is it important that RLS symptoms not be solely accounted for by another medical or behavioral condition, it should also be appreciated that any of these similar conditions can occur in an individual with RLS. This necessitates a separate focus on each possible condition in the diagnostic process and when assessing impact. For cases in which the diagnosis of RLS is not certain, evaluation for the supportive features of RLS, particularly PLMS or a family history of RLS, may be helpful. Clinical features, such as response to a dopaminergic agent and positive family history for RLS, can help with the differential diagnosis.

Comorbidity

Depressive disorders, anxiety disorders, and attentional disorders are commonly comorbid with RLS and are discussed in the section "Functional Consequences of Restless Legs Syndrome." The main medical disorder comorbid with RLS is cardiovascular disease. There may be an association with numerous other medical disorders, including hypertension, narcolepsy, migraine, Parkinson's disease, multiple sclerosis, peripheral neuropathy, obstructive sleep apnea, diabetes mellitus, fibromyalgia, osteoporosis, obesity, thyroid disease, and cancer. Iron deficiency, pregnancy, and chronic renal failure are also comorbid with RLS.

Relationship to International Classification of Sleep Disorders

The *International Classification of Sleep Disorders,* 2nd Edition (ICSD-2), presents similar diagnostic criteria for RLS but does not contain a criterion specifying frequency or duration of symptoms.

Substance/Medication-Induced Sleep Disorder

Diagnostic Criteria

A. A prominent and severe disturbance in sleep.
B. There is evidence from the history, physical examination, or laboratory findings of both (1) and (2):

1. The symptoms in Criterion A developed during or soon after substance intoxication or after withdrawal from or exposure to a medication.
2. The involved substance/medication is capable of producing the symptoms in Criterion A.

C. The disturbance is not better explained by a sleep disorder that is not substance/medication-induced. Such evidence of an independent sleep disorder could include the following:

   The symptoms precede the onset of the substance/medication use; the symptoms persist for a substantial period of time (e.g., about 1 month) after the cessation of acute withdrawal or severe intoxication; or there is other evidence suggesting the existence of an independent non-substance/medication-induced sleep disorder (e.g., a history of recurrent non-substance/medication-related episodes).

D. The disturbance does not occur exclusively during the course of a delirium.

E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Note: This diagnosis should be made instead of a diagnosis of substance intoxication or substance withdrawal only when the symptoms in Criterion A predominate in the clinical picture and when they are sufficiently severe to warrant clinical attention.

Coding note: The ICD-9-CM and ICD-10-CM codes for the [specific substance/medication]-induced sleep disorders are indicated in the table below. Note that the ICD-10-CM code depends on whether or not there is a comorbid substance use disorder present for the same class of substance. If a mild substance use disorder is comorbid with the substance-induced sleep disorder, the 4th position character is "1," and the clinician should record "mild [substance] use disorder" before the substance-induced sleep disorder (e.g., "mild cocaine use disorder with cocaine-induced sleep disorder"). If a moderate or severe substance use disorder is comorbid with the substance-induced sleep disorder, the 4th position character is "2," and the clinician should record "moderate [substance] use disorder" or "severe [substance] use disorder," depending on the severity of the comorbid substance use disorder. If there is no comorbid substance use disorder (e.g., after a one-time heavy use of the substance), then the 4th position character is "9," and the clinician should record only the substance-induced sleep disorder. A moderate or severe tobacco use disorder is required in order to code a tobacco-induced sleep disorder; it is not permissible to code a comorbid mild tobacco use disorder or no tobacco use disorder with a tobacco-induced sleep disorder.

Specify whether:

Insomnia type: Characterized by difficulty falling asleep or maintaining sleep, frequent nocturnal awakenings, or nonrestorative sleep.

Daytime sleepiness type: Characterized by predominant complaint of excessive sleepiness/fatigue during waking hours or, less commonly, a long sleep period.

Parasomnia type: Characterized by abnormal behavioral events during sleep.

Mixed type: Characterized by a substance/medication-induced sleep problem characterized by multiple types of sleep symptoms, but no symptom clearly predominates.

Specify if (see Table 1 in the chapter "Substance-Related and Addictive Disorders" for diagnoses associated with substance class):

With onset during intoxication: This specifier should be used if criteria are met for intoxication with the substance/medication and symptoms developed during the intoxication period.

With onset during discontinuation/withdrawal: This specifier should be used if criteria are met for discontinuation/withdrawal from the substance/medication and symptoms developed during, or shortly after, discontinuation of the substance/medication.

		ICD-10-CM		
	ICD-9-CM	With use disorder, mild	With use disorder, moderate or severe	Without use disorder
Alcohol	291.82	F10.182	F10.282	F10.982
Caffeine	292.85	F15.182	F15.282	F15.982
Cannabis	292.85	F12.188	F12.288	F12.988
Opioid	292.85	F11.182	F11.282	F11.982
Sedative, hypnotic, or anxiolytic	292.85	F13.182	F13.282	F13.982
Amphetamine (or other stimulant)	292.85	F15.182	F15.282	F15.982
Cocaine	292.85	F14.182	F14.282	F14.982
Tobacco	292.85	NA	F17.208	NA
Other (or unknown) substance	292.85	F19.182	F19.282	F19.982

Recording Procedures

ICD-9-CM. The name of the substance/medication-induced sleep disorder begins with the specific substance (e.g., cocaine, bupropion) that is presumed to be causing the sleep disturbance. The diagnostic code is selected from the table included in the criteria set, which is based on the drug class. For substances that do not fit into any of the classes (e.g., bupropion), the code for "other substance" should be used; and in cases in which a substance is judged to be an etiological factor but the specific class of substance is unknown, the category "unknown substance" should be used.

The name of the disorder is followed by the specification of onset (i.e., onset during intoxication, onset during discontinuation/withdrawal), followed by the subtype designation (i.e., insomnia type, daytime sleepiness type, parasomnia type, mixed type). Unlike the recording procedures for ICD-10-CM, which combine the substance-induced disorder and substance use disorder into a single code, for ICD-9-CM a separate diagnostic code is given for the substance use disorder. For example, in the case of insomnia occurring during withdrawal in a man with a severe lorazepam use disorder, the diagnosis is 292.85 lorazepam-induced sleep disorder, with onset during withdrawal, insomnia type. An additional diagnosis of 304.10 severe lorazepam use disorder is also given. When more than one substance is judged to play a significant role in the development of the sleep disturbance, each should be listed separately (e.g., 292.85 alcohol-induced sleep disorder, with onset during intoxication, insomnia type; 292.85 cocaine-induced sleep disorder, with onset during intoxication, insomnia type).

ICD-10-CM. The name of the substance/medication-induced sleep disorder begins with the specific substance (e.g., cocaine, bupropion) that is presumed to be causing the sleep disturbance. The diagnostic code is selected from the table included in the criteria set, which is based on the drug class and presence or absence of a comorbid substance use disorder. For substances that do not fit into any of the classes (e.g., bupropion), the code for "other substance" should be used; and in cases in which a substance is judged to be an etiological factor but the specific class of substance is unknown, the category "unknown substance" should be used.

When recording the name of the disorder, the comorbid substance use disorder (if any) is listed first, followed by the word "with," followed by the name of the substance-induced sleep disorder, followed by the specification of onset (i.e., onset during intoxication, onset

during discontinuation/withdrawal), followed by the subtype designation (i.e., insomnia type, daytime sleepiness type, parasomnia type, mixed type). For example, in the case of insomnia occurring during withdrawal in a man with a severe lorazepam use disorder, the diagnosis is F13.282 severe lorazepam use disorder with lorazepam-induced sleep disorder, with onset during withdrawal, insomnia type. A separate diagnosis of the comorbid severe lorazepam use disorder is not given. If the substance-induced sleep disorder occurs without a comorbid substance use disorder (e.g., with medication use), no accompanying substance use disorder is noted (e.g., F19.982 bupropion-induced sleep disorder, with onset during medication use, insomnia type). When more than one substance is judged to play a significant role in the development of the sleep disturbance, each should be listed separately (e.g., F10.282 severe alcohol use disorder with alcohol-induced sleep disorder, with onset during intoxication, insomnia type; F14.282 severe cocaine use disorder with cocaine-induced sleep disorder, with onset during intoxication, insomnia type).

Diagnostic Features

The essential feature of substance/medication-induced sleep disorder is a prominent sleep disturbance that is sufficiently severe to warrant independent clinical attention (Criterion A) and that is judged to be primarily associated with the pharmacological effects of a substance (i.e., a drug of abuse, a medication, toxin exposure) (Criterion B). Depending on the substance involved, one of four types of sleep disturbances is reported. Insomnia type and daytime sleepiness type are most common, while parasomnia type is seen less often. The mixed type is noted when more than one type of sleep disturbance–related symptom is present and none predominates. The disturbance must not be better explained by another sleep disorder (Criterion C). A substance/medication-induced sleep disorder is distinguished from insomnia disorder or a disorder associated with excessive daytime sleepiness by considering onset and course. For drugs of abuse, there must be evidence of intoxication or withdrawal from the history, physical examination, or laboratory findings. Substance/medication-induced sleep disorder arises only in association with intoxication or discontinuation/withdrawal states, whereas other sleep disorders may precede the onset of substance use or occur during times of sustained abstinence. As discontinuation/withdrawal states for some substances can be protracted, onset of the sleep disturbance can occur 4 weeks after cessation of substance use, and the disturbance may have features atypical of other sleep disorders (e.g., atypical age at onset or course). The diagnosis is not made if the sleep disturbance occurs only during a delirium (Criterion D). The symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning (Criterion E). This diagnosis should be made instead of a diagnosis of substance intoxication or substance withdrawal only when the symptoms in Criterion A predominate in the clinical picture and when the symptoms warrant independent clinical attention.

Associated Features Supporting Diagnosis

During periods of substance/medication use, intoxication, or withdrawal, individuals frequently complain of dysphoric mood, including depression and anxiety, irritability, cognitive impairment, inability to concentrate, and fatigue.

Prominent and severe sleep disturbances can occur in association with intoxication with the following classes of substances: alcohol; caffeine; cannabis; opioids; sedatives, hypnotics, or anxiolytics; stimulants (including cocaine); and other (or unknown) substances. Prominent and severe sleep disturbances can occur in association with withdrawal from the following classes of substances: alcohol; caffeine; cannabis; opioids; sedatives, hypnotics, or anxiolytics; stimulant (including cocaine); tobacco; and other (or unknown) substances. Some medications that invoke sleep disturbances include adrenergic agonists and antagonists, dopamine agonists and antagonists, cholinergic agonists and antagonists, serotonergic agonists and antagonists, antihistamines, and corticosteroids.

Alcohol. Alcohol-induced sleep disorder typically occurs as insomnia type. During acute intoxication, alcohol produces an immediate sedative effect depending on dose, accompanied by increased stages 3 and 4 non–rapid eye movement (NREM) sleep and reduced rapid eye movement (REM) sleep. Following these initial effects, there may be increased wakefulness, restless sleep, and vivid and anxiety-laden dreams for the remaining sleep period. In parallel, stages 3 and 4 sleep are reduced, and wakefulness and REM sleep are increased. Alcohol can aggravate breathing-related sleep disorder. With habitual use, alcohol continues to show a short-lived sedative effect in the first half of the night, followed by sleep continuity disruption in the second half. During alcohol withdrawal, there is extremely disrupted sleep continuity, and an increased amount and intensity of REM sleep, associated frequently with vivid dreaming, which in extreme form, constitutes part of alcohol withdrawal delirium. After acute withdrawal, chronic alcohol users may continue to complain of light, fragmented sleep for weeks to years associated with a persistent deficit in slow-wave sleep.

Caffeine. Caffeine-induced sleep disorder produces insomnia in a dose-dependent manner, with some individuals presenting with daytime sleepiness related to withdrawal.

Cannabis. Acute administration of cannabis may shorten sleep latency, though arousing effects with increments in sleep latency also occur. Cannabis enhances slow-wave sleep and suppresses REM sleep after acute administration. In chronic users, tolerance to the sleep-inducing and slow-wave sleep–enhancing effects develops. Upon withdrawal, sleep difficulties and unpleasant dreams have been reported lasting for several weeks. Polysomnography studies demonstrate reduced slow-wave sleep and increased REM sleep during this phase.

Opioids. Opioids may produce an increase in sleepiness and in subjective depth of sleep, and reduced REM sleep, during acute short-term use. With continued administration, tolerance to the sedative effects of opioids develops and there are complaints of insomnia. Consistent with their respiratory depressant effects, opioids exacerbate sleep apnea.

Sedative, hypnotic, or anxiolytic substances. Sedatives, hypnotics, and anxiolytics (e.g., barbiturates, benzodiazepines receptor agonists, meprobamate, glutethimide, methyprylon) have similar effects as opioids on sleep. During acute intoxication, sedative-hypnotic drugs produce the expected increase in sleepiness and decrease in wakefulness. Chronic use (particularly of barbiturates and the older nonbarbiturate, nonbenzodiazepine drugs) may cause tolerance with subsequent return of insomnia. Daytime sleepiness may occur. Sedative-hypnotic drugs can increase the frequency and severity of obstructive sleep apnea events. Parasomnias are associated with use of benzodiazepine receptor agonists, especially when these medications are taken at higher doses and when they are combined with other sedative drugs. Abrupt discontinuation of chronic sedative, hypnotic, or anxiolytic use can lead to withdrawal but more commonly rebound insomnia, a condition of an exacerbation of insomnia upon drug discontinuation for 1–2 days reported to occur even with short-term use. Sedative, hypnotic, or anxiolytic drugs with short durations of action are most likely to produce complaints of rebound insomnia, whereas those with longer durations of action are more often associated with daytime sleepiness. Any sedative, hypnotic, or anxiolytic drug can potentially cause daytime sedation, withdrawal, or rebound insomnia.

Amphetamines and related substances and other stimulants. Sleep disorders induced by amphetamine and related substances and other stimulants are characterized by insomnia during intoxication and excessive sleepiness during withdrawal. During acute intoxication, stimulants reduce the total amount of sleep, increase sleep latency and sleep continuity disturbances, and decrease REM sleep. Slow-wave sleep tends to be reduced. During withdrawal from chronic stimulant use, there is both prolonged nocturnal sleep duration and excessive daytime sleepiness. Multiple sleep latency tests may show increased daytime sleepiness dur-

ing the withdrawal phase. Drugs like 3,4-methylenedioxymethamphetamine (MDMA; "ecstasy") and related substances lead to restless and disturbed sleep within 48 hours of intake; frequent use of these compounds is associated with persisting symptoms of anxiety, depression, and sleep disturbances, even during longer-term abstinence.

Tobacco. Chronic tobacco consumption is associated primarily with symptoms of insomnia, decreased slow-wave sleep with a reduction of sleep efficiency, and increased daytime sleepiness. Withdrawal from tobacco can lead to impaired sleep. Individuals who smoke heavily may experience regular nocturnal awakenings caused by tobacco craving.

Other or unknown substances/medications. Other substances/medications may produce sleep disturbances, particularly medications that affect the central or autonomic nervous systems (e.g., adrenergic agonists and antagonists, dopamine agonists and antagonists, cholinergic agonists and antagonists, serotonergic agonists and antagonists, antihistamines, corticosteroids).

Development and Course

Insomnia in children can be identified by either a parent or the child. Often the child has a clear sleep disturbance associated with initiation of a medication but may not report symptoms, although parents observe the sleep disturbances. The use of some illicit substances (e.g., cannabis, ecstasy) is prevalent in adolescence and early adulthood. Insomnia or any other sleep disturbance encountered in this age group should prompt careful consideration of whether the sleep disturbance is due to consumption of these substances. Help-seeking behavior for the sleep disturbance in these age groups is limited, and thus corroborative report may be elicited from a parent, caregiver, or teacher. Older individuals take more medications and are at increased risk for developing a substance/medication-induced sleep disorder. They may interpret sleep disturbance as part of normal aging and fail to report symptoms. Individuals with major neurocognitive disorder (e.g., dementia) are at risk for substance/medication-induced sleep disorders but may not report symptoms, making corroborative report from caregiver(s) particularly important.

Risk and Prognostic Factors

Risk and prognostic factors involved in substance abuse/dependence or medication use are normative for certain age groups. They are relevant for, and likely applicable to, the type of sleep disturbance encountered (see the chapter "Substance-Related and Addictive Disorders" for descriptions of respective substance use disorders).

Temperamental. Substance use generally precipitates or accompanies insomnia in vulnerable individuals. Thus, presence of insomnia in response to stress or change in sleep environment or timing can represent a risk for developing substance/medication-induced sleep disorder. A similar risk may be present for individuals with other sleep disorders (e.g., individuals with hypersomnia who use stimulants).

Culture-Related Diagnostic Issues

The consumption of substances, including prescribed medications, may depend in part on cultural background and specific local drug regulations.

Gender-Related Diagnostic Issues

Gender-specific prevalences (i.e., females affected more than males at a ratio of about 2:1) exist for patterns of consumption of some substances (e.g., alcohol). The same amount and duration of consumption of a given substance may lead to highly different sleep-related outcomes in males and females based on, for example, gender-specific differences in hepatic functioning.

Diagnostic Markers

Each of the substance/medication-induced sleep disorders produces electroencephalographic sleep patterns that are associated with, but cannot be considered diagnostic of, other disorders. The electroencephalographic sleep profile for each substance is related to the stage of use, whether intake/intoxication, chronic use, or withdrawal following discontinuation of the substance. All-night polysomnography can help define the severity of insomnia complaints, while the multiple sleep latency test provides information about the severity of daytime sleepiness. Monitoring of nocturnal respiration and periodic limb movements with polysomnography may verify a substance's impact on nocturnal breathing and motor behavior. Sleep diaries for 2 weeks and actigraphy are considered helpful in confirming the presence of substance/medication-induced sleep disorder. Drug screening can be of use when the individual is not aware or unwilling to relate information about substance intake.

Functional Consequences of Substance/Medication-Induced Sleep Disorder

While there are many functional consequences associated with sleep disorders, the only unique consequence for substance/medication-induced sleep disorder is increased risk for relapse. The degree of sleep disturbance during alcohol withdrawal (e.g., REM sleep rebound predicts risk of relapse of drinking). Monitoring of sleep quality and daytime sleepiness during and after withdrawal may provide clinically meaningful information on whether an individual is at increased risk for relapse.

Differential Diagnosis

Substance intoxication or substance withdrawal. Sleep disturbances are commonly encountered in the context of substance intoxication or substance discontinuation/withdrawal. A diagnosis of substance/medication-induced sleep disorder should be made instead of a diagnosis of substance intoxication or substance withdrawal only when the sleep disturbance is predominant in the clinical picture and is sufficiently severe to warrant independent clinical attention.

Delirium. If the substance/medication-induced sleep disturbance occurs exclusively during the course of a delirium, it is not diagnosed separately.

Other sleep disorders. A substance/medication-induced sleep disorder is distinguished from another sleep disorder if a substance/medication is judged to be etiologically related to the symptoms. A substance/medication-induced sleep disorder attributed to a prescribed medication for a mental disorder or medical condition must have its onset while the individual is receiving the medication or during discontinuation, if there is a discontinuation/withdrawal syndrome associated with the medication. Once treatment is discontinued, the sleep disturbance will usually remit within days to several weeks. If symptoms persist beyond 4 weeks, other causes for the sleep disturbance–related symptoms should be considered. Not infrequently, individuals with another sleep disorder use medications or drugs of abuse to self-medicate their symptoms (e.g., alcohol for management of insomnia). If the substance/medication is judged to play a significant role in the exacerbation of the sleep disturbance, an additional diagnosis of a substance/medication-induced sleep disorder may be warranted.

Sleep disorder due to another medical condition. Substance/medication-induced sleep disorder and sleep disorder associated with another medical condition may produce similar symptoms of insomnia, daytime sleepiness, or a parasomnia. Many individuals with other medical conditions that cause sleep disturbance are treated with medications that may also cause sleep disturbances. The chronology of symptoms is the most important factor in distinguishing between these two sources of sleep symptoms. Difficulties with sleep that clearly preceded the use of any medication for treatment of a medical condition would

suggest a diagnosis of sleep disorder associated with another medical condition. Conversely, sleep symptoms that appear only after the initiation of a particular medication/substance suggest a substance/medication-induced sleep disorder. If the disturbance is comorbid with another medical condition and is also exacerbated by substance use, both diagnoses (i.e., sleep disorder associated with another medical condition and substance/medication-induced sleep disorder) are given. When there is insufficient evidence to determine whether the sleep disturbance is attributable to a substance/medication or to another medical condition or is primary (i.e., not due to either a substance/medication or another medical condition), a diagnosis of other specified sleep-wake disorder or unspecified sleep-wake disorder is indicated.

Comorbidity

See the "Comorbidity" sections for other sleep disorders in this chapter, including insomnia, hypersomnolence, central sleep apnea, sleep-related hypoventilation, and circadian rhythm sleep-wake disorders, shift work type.

Relationship to International Classification of Sleep Disorders

The *International Classification of Sleep Disorders,* 2nd Edition (ICSD-2), lists sleep disorders "due to drug or substance" under their respective phenotypes (e.g., insomnia, hypersomnia).

Other Specified Insomnia Disorder

780.52 (G47.09)

This category applies to presentations in which symptoms characteristic of insomnia disorder that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for insomnia disorder or any of the disorders in the sleep-wake disorders diagnostic class. The other specified insomnia disorder category is used in situations in which the clinician chooses to communicate the specific reason that the presentation does not meet the criteria for insomnia disorder or any specific sleep-wake disorder. This is done by recording "other specified insomnia disorder" followed by the specific reason (e.g., "brief insomnia disorder").

Examples of presentations that can be specified using the "other specified" designation include the following:

1. **Brief insomnia disorder:** Duration is less than 3 months.
2. **Restricted to nonrestorative sleep:** Predominant complaint is nonrestorative sleep unaccompanied by other sleep symptoms such as difficulty falling asleep or remaining asleep.

Unspecified Insomnia Disorder

780.52 (G47.00)

This category applies to presentations in which symptoms characteristic of insomnia disorder that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for insomnia disorder or any of the disorders in the sleep-wake disorders diagnostic class. The unspecified

insomnia disorder category is used in situations in which the clinician chooses *not* to specify the reason that the criteria are not met for insomnia disorder or a specific sleep-wake disorder, and includes presentations in which there is insufficient information to make a more specific diagnosis.

Other Specified Hypersomnolence Disorder

780.54 (G47.19)

This category applies to presentations in which symptoms characteristic of hypersomnolence disorder that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for hypersomnolence disorder or any of the disorders in the sleep-wake disorders diagnostic class. The other specified hypersomnolence disorder category is used in situations in which the clinician chooses to communicate the specific reason that the presentation does not meet the criteria for hypersomnolence disorder or any specific sleep-wake disorder. This is done by recording "other specified hypersomnolence disorder" followed by the specific reason (e.g., "brief-duration hypersomnolence," as in Kleine-Levin syndrome).

Unspecified Hypersomnolence Disorder

780.54 (G47.10)

This category applies to presentations in which symptoms characteristic of hypersomnolence disorder that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for hypersomnolence disorder or any of the disorders in the sleep-wake disorders diagnostic class. The unspecified hypersomnolence disorder category is used in situations in which the clinician chooses *not* to specify the reason that the criteria are not met for hypersomnolence disorder or a specific sleep-wake disorder, and includes presentations in which there is insufficient information to make a more specific diagnosis.

Other Specified Sleep-Wake Disorder

780.59 (G47.8)

This category applies to presentations in which symptoms characteristic of a sleep-wake disorder that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for any of the disorders in the sleep-wake disorders diagnostic class and do not qualify for a diagnosis of other specified insomnia disorder or other specified hypersomnolence disorder. The other specified sleep-wake disorder category is used in situations in which the clinician chooses to communicate the specific reason that the presentation does not meet the criteria for any specific sleep-wake disorder. This is done by recording "other specified sleep-wake disorder" followed by the specific reason (e.g., "repeated arousals during rapid eye movement sleep without polysomnography or history of Parkinson's disease or other synucleinopathy").

Unspecified Sleep-Wake Disorder

780.59 (G47.9)

This category applies to presentations in which symptoms characteristic of a sleep-wake disorder that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for any of the disorders in the sleep-wake disorders diagnostic class and do not qualify for a diagnosis of unspecified insomnia disorder or unspecified hypersomnolence disorder. The unspecified sleep-wake disorder category is used in situations in which the clinician chooses *not* to specify the reason that the criteria are not met for a specific sleep-wake disorder, and includes presentations in which there is insufficient information to make a more specific diagnosis.

Sexual Dysfunctions

Sexual dysfunctions include delayed ejaculation, erectile disorder, female orgasmic disorder, female sexual interest/arousal disorder, genito-pelvic pain/penetration disorder, male hypoactive sexual desire disorder, premature (early) ejaculation, substance/medication-induced sexual dysfunction, other specified sexual dysfunction, and unspecified sexual dysfunction. Sexual dysfunctions are a heterogeneous group of disorders that are typically characterized by a clinically significant disturbance in a person's ability to respond sexually or to experience sexual pleasure. An individual may have several sexual dysfunctions at the same time. In such cases, all of the dysfunctions should be diagnosed.

Clinical judgment should be used to determine if the sexual difficulties are the result of inadequate sexual stimulation; in these cases, there may still be a need for care, but a diagnosis of a sexual dysfunction would not be made. These cases may include, but are not limited to, conditions in which lack of knowledge about effective stimulation prevents the experience of arousal or orgasm.

Subtypes are used to designate the onset of the difficulty. In many individuals with sexual dysfunctions, the time of onset may indicate different etiologies and interventions. *Lifelong* refers to a sexual problem that has been present from first sexual experiences, and *acquired* applies to sexual disorders that develop after a period of relatively normal sexual function. *Generalized* refers to sexual difficulties that are not limited to certain types of stimulation, situations, or partners, and *situational* refers to sexual difficulties that only occur with certain types of stimulation, situations, or partners.

In addition to the lifelong/acquired and generalized/situational subtypes, a number of factors must be considered during the assessment of sexual dysfunction, given that they may be relevant to etiology and/or treatment, and that may contribute, to varying degrees, across individuals: 1) partner factors (e.g., partner's sexual problems; partner's health status); 2) relationship factors (e.g., poor communication; discrepancies in desire for sexual activity); 3) individual vulnerability factors (e.g., poor body image; history of sexual or emotional abuse), psychiatric comorbidity (e.g., depression, anxiety), or stressors (e.g., job loss, bereavement); 4) cultural or religious factors (e.g., inhibitions related to prohibitions against sexual activity or pleasure; attitudes toward sexuality); and 5) medical factors relevant to prognosis, course, or treatment.

Clinical judgment about the diagnosis of sexual dysfunction should take into consideration cultural factors that may influence expectations or engender prohibitions about the experience of sexual pleasure. Aging may be associated with a normative decrease in sexual response.

Sexual response has a requisite biological underpinning, yet is usually experienced in an intrapersonal, interpersonal, and cultural context. Thus, sexual function involves a complex interaction among biological, sociocultural, and psychological factors. In many clinical contexts, a precise understanding of the etiology of a sexual problem is unknown. Nonetheless, a sexual dysfunction diagnosis requires ruling out problems that are better explained by a nonsexual mental disorder, by the effects of a substance (e.g., drug or medication), by a medical condition (e.g., due to pelvic nerve damage), or by severe relationship distress, partner violence, or other stressors.

If the sexual dysfunction is mostly explainable by another nonsexual mental disorder (e.g., depressive or bipolar disorder, anxiety disorder, posttraumatic stress disorder, psychotic dis-

order), then only the other mental disorder diagnosis should be made. If the problem is thought to be better explained by the use/misuse or discontinuation of a drug or substance, it should be diagnosed accordingly as a substance/medication-induced sexual dysfunction. If the sexual dysfunction is attributable to another medical condition (e.g., peripheral neuropathy), the individual would not receive a psychiatric diagnosis. If severe relationship distress, partner violence, or significant stressors better explain the sexual difficulties, then a sexual dysfunction diagnosis is not made, but an appropriate V or Z code for the relationship problem or stressor may be listed. In many cases, a precise etiological relationship between another condition (e.g., a medical condition) and a sexual dysfunction cannot be established.

Delayed Ejaculation

Diagnostic Criteria **302.74 (F52.32)**

A. Either of the following symptoms must be experienced on almost all or all occasions (approximately 75%–100%) of partnered sexual activity (in identified situational contexts or, if generalized, in all contexts), and without the individual desiring delay:
   1. Marked delay in ejaculation.
   2. Marked infrequency or absence of ejaculation.

B. The symptoms in Criterion A have persisted for a minimum duration of approximately 6 months.

C. The symptoms in Criterion A cause clinically significant distress in the individual.

D. The sexual dysfunction is not better explained by a nonsexual mental disorder or as a consequence of severe relationship distress or other significant stressors and is not attributable to the effects of a substance/medication or another medical condition.

Specify whether:

Lifelong: The disturbance has been present since the individual became sexually active.

Acquired: The disturbance began after a period of relatively normal sexual function.

Specify whether:

Generalized: Not limited to certain types of stimulation, situations, or partners.

Situational: Only occurs with certain types of stimulation, situations, or partners.

Specify current severity:

Mild: Evidence of mild distress over the symptoms in Criterion A.

Moderate: Evidence of moderate distress over the symptoms in Criterion A.

Severe: Evidence of severe or extreme distress over the symptoms in Criterion A.

Diagnostic Features

The distinguishing feature of delayed ejaculation is a marked delay in or inability to achieve ejaculation (Criterion A). The man reports difficulty or inability to ejaculate despite the presence of adequate sexual stimulation and the desire to ejaculate. The presenting complaint usually involves partnered sexual activity. In most cases, the diagnosis will be made by self-report of the individual. The definition of "delay" does not have precise boundaries, as there is noconsensus as to what constitutes a reasonable time to reach orgasm or what is unacceptably long for most men and their sexual partners.

Associated Features Supporting Diagnosis

The man and his partner may report prolonged thrusting to achieve orgasm to the point of exhaustion or genital discomfort and then ceasing efforts. Some men may report avoiding

sexual activity because of a repetitive pattern of difficulty ejaculating. Some sexual partners may report feeling less sexually attractive because their partner cannot ejaculate easily.

In addition to the subtypes "lifelong/acquired" and "generalized/situational," the following five factors must be considered during assessment and diagnosis of delayed ejaculation, given that they may be relevant to etiology and/or treatment: 1) partner factors (e.g., partner's sexual problems, partner's health status); 2) relationship factors (e.g., poor communication, discrepancies in desire for sexual activity); 3) individual vulnerability factors (e.g., poor body image; history of sexual or emotional abuse), psychiatric comorbidity (e.g., depression, anxiety), or stressors (e.g., job loss, bereavement); 4) cultural/religious factors (e.g., inhibitions related to prohibitions against sexual activity; attitudes toward sexuality); and 5) medical factors relevant to prognosis, course, or treatment. Each of these factors may contribute differently to the presenting symptoms of different men with this disorder.

Prevalence

Prevalence is unclear because of the lack of a precise definition of this syndrome. It is the least common male sexual complaint. Only 75% of men report always ejaculating during sexual activity, and less than 1% of men will complain of problems with reaching ejaculation that last more than 6 months.

Development and Course

Lifelong delayed ejaculation begins with early sexual experiences and continues throughout life. By definition, acquired delayed ejaculation begins after a period of normal sexual function. There is minimal evidence concerning the course of acquired delayed ejaculation. The prevalence of delayed ejaculation appears to remain relatively constant until around age 50 years, when the incidence begins to increase significantly. Men in their 80s report twice as much difficulty ejaculating as men younger than 59 years.

Risk and Prognostic Factors

Genetic and physiological. Age-related loss of the fast-conducting peripheral sensory nerves and age-related decreased sex steroid secretion may be associated with the increase in delayed ejaculation in men older than 50 years.

Culture-Related Diagnostic Issues

Complaints of ejaculatory delay vary across countries and cultures. Such complaints are more common among men in Asian populations than in men living in Europe, Australia, or the United States. This variation may be attributable to cultural or genetic differences between cultures.

Functional Consequences of Delayed Ejaculation

Difficulty with ejaculation may contribute to difficulties in conception. Delayed ejaculation is often associated with considerable psychological distress in one or both partners.

Differential Diagnosis

Another medical condition. The major differential diagnosis is between delayed ejaculation fully explained by another medical illness or injury and delayed ejaculation with a psychogenic, idiopathic, or combined psychological and medical etiology. A situational aspect to the complaint is suggestive of a psychological basis for the problem (e.g., men who can ejaculate during sexual activity with one sex but not the other; men who can ejaculate with one partner but not another of the same sex; men with paraphilic arousal pat-

terns; men who require highly ritualized activity to ejaculate during partnered sexual activity). Another medical illness or injury may produce delays in ejaculation independent of psychological issues. For example, inability to ejaculate can be caused by interruption of the nerve supply to the genitals, such as can occur after traumatic surgical injury to the lumbar sympathetic ganglia, abdominoperitoneal surgery, or lumbar sympathectomy. Ejaculation is thought to be under autonomic nervous system control involving the hypogastric (sympathetic) and pudendal (parasympathetic) nerves. A number of neurodegenerative diseases, such as multiple sclerosis and diabetic and alcoholic neuropathy, can cause inability to ejaculate. Delayed ejaculation should also be differentiated from retrograde ejaculation (i.e., ejaculation into the bladder), which may follow transurethral prostatic resection.

Substance/medication use. A number of pharmacological agents, such as antidepressants, antipsychotics, alpha sympathetic drugs, and opioid drugs, can cause ejaculatory problems.

Dysfunction with orgasm. It is important in the history to ascertain whether the complaint concerns delayed ejaculation or the sensation of orgasm, or both. Ejaculation occurs in the genitals, whereas the experience of orgasm is believed to be primarily subjective. Ejaculation and orgasm usually occur together but not always. For example, a man with a normal ejaculatory pattern may complain of decreased pleasure (i.e., anhedonic ejaculation). Such a complaint would not be coded as delayed ejaculation but could be coded as other specified sexual dysfunction or unspecified sexual dysfunction.

Comorbidity

There is some evidence to suggest that delayed ejaculation may be more common in severe forms of major depressive disorder.

Erectile Disorder

Diagnostic Criteria **302.72 (F52.21)**

A. At least one of the three following symptoms must be experienced on almost all or all (approximately 75%–100%) occasions of sexual activity (in identified situational contexts or, if generalized, in all contexts):
   1. Marked difficulty in obtaining an erection during sexual activity.
   2. Marked difficulty in maintaining an erection until the completion of sexual activity.
   3. Marked decrease in erectile rigidity.

B. The symptoms in Criterion A have persisted for a minimum duration of approximately 6 months.

C. The symptoms in Criterion A cause clinically significant distress in the individual.

D. The sexual dysfunction is not better explained by a nonsexual mental disorder or as a consequence of severe relationship distress or other significant stressors and is not attributable to the effects of a substance/medication or another medical condition.

Specify whether:

Lifelong: The disturbance has been present since the individual became sexually active.

Acquired: The disturbance began after a period of relatively normal sexual function.

Specify whether:

Generalized: Not limited to certain types of stimulation, situations, or partners.

Situational: Only occurs with certain types of stimulation, situations, or partners.

Specify current severity:

Mild: Evidence of mild distress over the symptoms in Criterion A.

Moderate: Evidence of moderate distress over the symptoms in Criterion A.

Severe: Evidence of severe or extreme distress over the symptoms in Criterion A.

Diagnostic Features

The essential feature of erectile disorder is the repeated failure to obtain or maintain erections during partnered sexual activities (Criterion A). A careful sexual history is necessary to ascertain that the problem has been present for a significant duration of time (i.e., at least approximately 6 months) and occurs on the majority of sexual occasions (i.e., at least 75% of the time). Symptoms may occur only in specific situations involving certain types of stimulation or partners, or they may occur in a generalized manner in all types of situations, stimulation, or partners.

Associated Features Supporting Diagnosis

Many men with erectile disorder may have low self-esteem, low self-confidence, and a decreased sense of masculinity, and may experience depressed affect. Fear and/or avoidance of future sexual encounters may occur. Decreased sexual satisfaction and reduced sexual desire in the individual's partner are common.

In addition to the subtypes "lifelong/acquired" and "generalized/situational," the following five factors must be considered during assessment and diagnosis of erectile disorder given that they may be relevant to etiology and/or treatment: 1) partner factors (e.g., partner's sexual problems, partner's health status); 2) relationship factors (e.g., poor communication, discrepancies in desire for sexual activity); 3) individual vulnerability factors (e.g., poor body image, history of sexual or emotional abuse), psychiatric comorbidity (e.g., depression, anxiety), or stressors (e.g., job loss, bereavement); 4) cultural/religious factors (e.g., inhibitions related to prohibitions against sexual activity; attitudes toward sexuality); and 5) medical factors relevant to prognosis, course, or treatment. Each of these factors may contribute differently to the presenting symptoms of different men with this disorder.

Prevalence

The prevalence of lifelong versus acquired erectile disorder is unknown. There is a strong age-related increase in both prevalence and incidence of problems with erection, particularly after age 50 years. Approximately 13%–21% of men ages 40–80 years complain of occasional problems with erections. Approximately 2% of men younger than age 40–50 years complain of frequent problems with erections, whereas 40%–50% of men older than 60–70 years may have significant problems with erections. About 20% of men fear erectile problems on their first sexual experience, whereas approximately 8% experienced erectile problems that hindered penetration during their first sexual experience.

Development and Course

Erectile failure on first sexual attempt has been found to be related to having sex with a previously unknown partner, concomitant use of drugs or alcohol, not wanting to have sex, and peer pressure. There is minimal evidence regarding the persistence of such problems after the first attempt. It is assumed that most of these problems spontaneously remit without professional intervention, but some men may continue to have episodic problems. In contrast, acquired erectile disorder is often associated with biological factors such as diabetes and cardiovascular disease. Acquired erectile disorder is likely to be persistent in most men.

The natural history of lifelong erectile disorder is unknown. Clinical observation supports the association of lifelong erectile disorder with psychological factors that are self-

limiting or responsive to psychological interventions, whereas, as noted above, acquired erectile disorder is more likely to be related to biological factors and to be persistent. The incidence of erectile disorder increases with age. A minority of men diagnosed as having moderate erectile failure may experience spontaneous remission of symptoms without medical intervention. Distress associated with erectile disorder is lower in older men as compared with younger men.

Risk and Prognostic Factors

Temperamental. Neurotic personality traits may be associated with erectile problems in college students, and submissive personality traits may be associated with erectile problems in men age 40 years and older. *Alexithymia* (i.e., deficits in cognitive processing of emotions) is common in men diagnosed with "psychogenic" erectile dysfunction. Erectile problems are common in men diagnosed with depression and posttraumatic stress disorder.

Course modifiers. Risk factors for acquired erectile disorder include age, smoking tobacco, lack of physical exercise, diabetes, and decreased desire.

Culture-Related Diagnostic Issues

Complaints of erectile disorder have been found to vary across countries. It is unclear to what extent these differences represent differences in cultural expectations as opposed to genuine differences in the frequency of erectile failure.

Diagnostic Markers

Nocturnal penile tumescence testing and measured erectile turgidity during sleep can be employed to help differentiate organic from psychogenic erectile problems on the assumption that adequate erections during rapid eye movement sleep indicate a psychological etiology to the problem. A number of other diagnostic procedures may be employed depending on the clinician's assessment of their relevance given the individual's age, comorbid medical problems, and clinical presentation. Doppler ultrasonography and intravascular injection of vasoactive drugs, as well as invasive diagnostic procedures such as dynamic infusion cavernosography, can be used to assess vascular integrity. Pudendal nerve conduction studies, including somatosensory evoked potentials, can be employed when a peripheral neuropathy is suspected. In men also complaining of decreased sexual desire, serum bioavailable or free testosterone is frequently assessed to determine if the difficulty is secondary to endocrinological factors. Thyroid function may also be assessed. Determination of fasting serum glucose is useful to screen for the presence of diabetes mellitus. The assessment of serum lipids is important, as erectile disorder in men 40 years and older is predictive of the future risk of coronary artery disease.

Functional Consequences of Erectile Disorder

Erectile disorder can interfere with fertility and produce both individual and interpersonal distress. Fear and/or avoidance of sexual encounters may interfere with the ability to develop intimate relationships.

Differential Diagnosis

Nonsexual mental disorders. Major depressive disorder and erectile disorder are closely associated, and erectile disorder accompanying severe depressive disorder may occur.

Normal erectile function. The differential should include consideration of normal erectile function in men with excessive expectations.

Substance/medication use. Another major differential diagnosis is whether the erectile problem is secondary to substance/medication use. An onset that coincides with the beginning of substance/medication use and that dissipates with discontinuation of the substance/medication or dose reduction is suggestive of a substance/medication-induced sexual dysfunction.

Another medical condition. The most difficult aspect of the differential diagnosis of erectile disorder is ruling out erectile problems that are fully explained by medical factors. Such cases would not receive a diagnosis of a mental disorder. The distinction between erectile disorder as a mental disorder and erectile dysfunction as the result of another medical condition is usually unclear, and many cases will have complex, interactive biological and psychiatric etiologies. If the individual is older than 40–50 years and/or has concomitant medical problems, the differential diagnosis should include medical etiologies, especially vascular disease. The presence of an organic disease known to cause erectile problems does not confirm a causal relationship. For example, a man with diabetes mellitus can develop erectile disorder in response to psychological stress. In general, erectile dysfunction due to organic factors is generalized and gradual in onset. An exception would be erectile problems after traumatic injury to the nervous innervation of the genital organs (e.g., spinal cord injury). Erectile problems that are situational and inconsistent and that have an acute onset after a stressful life event are most often due to psychological events. An age of less than 40 years is also suggestive of a psychological etiology to the difficulty.

Other sexual dysfunctions. Erectile disorder may coexist with premature (early) ejaculation and male hypoactive sexual desire disorder.

Comorbidity

Erectile disorder can be comorbid with other sexual diagnoses, such as premature (early) ejaculation and male hypoactive sexual desire disorder, as well as with anxiety and depressive disorders. Erectile disorder is common in men with lower urinary tract symptoms related to prostatic hypertrophy. Erectile disorder may be comorbid with dyslipidemia, cardiovascular disease, hypogonadism, multiple sclerosis, diabetes mellitus, and other diseases that interfere with the vascular, neurological, or endocrine function necessary for normal erectile function.

Relationship to International Classification of Diseases

Erectile response is coded as failure of genital response in ICD-10 (F2.2).

Female Orgasmic Disorder

Diagnostic Criteria **302.73 (F52.31)**

A. Presence of either of the following symptoms and experienced on almost all or all (approximately 75%–100%) occasions of sexual activity (in identified situational contexts or, if generalized, in all contexts):
   1. Marked delay in, marked infrequency of, or absence of orgasm.
   2. Markedly reduced intensity of orgasmic sensations.

B. The symptoms in Criterion A have persisted for a minimum duration of approximately 6 months.

C. The symptoms in Criterion A cause clinically significant distress in the individual.

D. The sexual dysfunction is not better explained by a nonsexual mental disorder or as a consequence of severe relationship distress (e.g., partner violence) or other significant

stressors and is not attributable to the effects of a substance/medication or another medical condition.

Specify whether:

Lifelong: The disturbance has been present since the individual became sexually active.

Acquired: The disturbance began after a period of relatively normal sexual function.

Specify whether:

Generalized: Not limited to certain types of stimulation, situations, or partners.

Situational: Only occurs with certain types of stimulation, situations, or partners.

Specify if:

Never experienced an orgasm under any situation.

Specify current severity:

Mild: Evidence of mild distress over the symptoms in Criterion A.

Moderate: Evidence of moderate distress over the symptoms in Criterion A.

Severe: Evidence of severe or extreme distress over the symptoms in Criterion A.

Diagnostic Features

Female orgasmic disorder is characterized by difficulty experiencing orgasm and/or markedly reduced intensity of orgasmic sensations (Criterion A). Women show wide variability in the type or intensity of stimulation that elicits orgasm. Similarly, subjective descriptions of orgasm are extremely varied, suggesting that it is experienced in very different ways, both across women and on different occasions by the same woman. For a diagnosis of female orgasmic disorder, symptoms must be experienced on almost all or all (approximately 75%–100%) occasions of sexual activity (in identified situational contexts or, if generalized, in all contexts) and have a minimum duration of approximately 6 months. The use of the minimum severity and duration criteria is intended to distinguish transient orgasm difficulties from more persistent orgasmic dysfunction. The inclusion of "approximately" in Criterion B allows for clinician judgment in cases in which symptom duration does not meet the recommended 6-month threshold.

For a woman to have a diagnosis of female orgasmic disorder, clinically significant distress must accompany the symptoms (Criterion C). In many cases of orgasm problems, the causes are multifactorial or cannot be determined. If female orgasmic disorder is deemed to be better explained by another mental disorder, the effects of a substance/medication, or a medical condition, then a diagnosis of female orgasmic disorder would not be made. Finally, if interpersonal or significant contextual factors, such as severe relationship distress, intimate partner violence, or other significant stressors, are present, then a diagnosis of female orgasmic disorder would not be made.

Many women require clitoral stimulation to reach orgasm, and a relatively small proportion of women report that they always experience orgasm during penile-vaginal intercourse. Thus, a woman's experiencing orgasm through clitoral stimulation but not during intercourse does not meet criteria for a clinical diagnosis of female orgasmic disorder. It is also important to consider whether orgasmic difficulties are the result of inadequate sexual stimulation; in these cases, there may still be a need for care, but a diagnosis of female orgasmic disorder would not be made.

Associated Features Supporting Diagnosis

Associations between specific patterns of personality traits or psychopathology and orgasmic dysfunction have generally not been supported. Compared with women without the disorder, some women with female orgasmic disorder may have greater difficulty communicating about sexual issues. Overall sexual satisfaction, however, is not strongly correlated with orgasmic experience. Many women report high levels of sexual satisfaction

despite rarely or never experiencing orgasm. Orgasmic difficulties in women often co-occur with problems related to sexual interest and arousal.

In addition to the subtypes "lifelong/acquired" and "generalized/situational," the following five factors must be considered during assessment and diagnosis of female orgasmic disorder given that they may be relevant to etiology and/or treatment: 1) partner factors (e.g., partner's sexual problems, partner's health status); 2) relationship factors (e.g., poor communication, discrepancies in desire for sexual activity); 3) individual vulnerability factors (e.g., poor body image, history of sexual or emotional abuse), psychiatric comorbidity (e.g., depression, anxiety), or stressors (e.g., job loss, bereavement); (4) cultural/religious factors (e.g., inhibitions related to prohibitions against sexual activity; attitudes toward sexuality); and 5) medical factors relevant to prognosis, course, or treatment. Each of these factors may contribute differently to the presenting symptoms of different women with this disorder.

Prevalence

Reported prevalence rates for female orgasmic problems in women vary widely, from 10% to 42%, depending on multiple factors (e.g., age, culture, duration, and severity of symptoms); however, these estimates do not take into account the presence of distress. Only a proportion of women experiencing orgasm difficulties also report associated distress. Variation in how symptoms are assessed (e.g., the duration of symptoms and the recall period) also influence prevalence rates. Approximately 10% of women do not experience orgasm throughout their lifetime.

Development and Course

By definition, lifelong female orgasmic disorder indicates that the orgasmic difficulties have always been present, whereas the acquired subtype would be assigned if the woman's orgasmic difficulties developed after a period of normal orgasmic functioning.

A woman's first experience of orgasm can occur any time from the prepubertal period to well into adulthood. Women show a more variable pattern in age at first orgasm than do men, and women's reports of having experienced orgasm increase with age. Many women learn to experience orgasm as they experience a wide variety of stimulation and acquire more knowledge about their bodies. Women's rates of orgasm consistency (defined as "usually or always" experiencing orgasm) are higher during masturbation than during sexual activity with a partner.

Risk and Prognostic Factors

Temperamental. A wide range of psychological factors, such as anxiety and concerns about pregnancy, can potentially interfere with a woman's ability to experience orgasm.

Environmental. There is a strong association between relationship problems, physical health, and mental health and orgasm difficulties in women. Sociocultural factors (e.g., gender role expectations and religious norms) are also important influences on the experience of orgasmic difficulties.

Genetic and physiological. Many physiological factors may influence a woman's experience of orgasm, including medical conditions and medications. Conditions such as multiple sclerosis, pelvic nerve damage from radical hysterectomy, and spinal cord injury can all influence orgasmic functioning in women. Selective serotonin reuptake inhibitors are known to delay or inhibit orgasm in women. Women with vulvovaginal atrophy (characterized by symptoms such as vaginal dryness, itching, and pain) are significantly more likely to report orgasm difficulties than are women without this condition. Menopausal status is not consistently associated with the likelihood of orgasm difficulties. There may be a significant genetic contribution to variation in female orgasmic function. However,

psychological, sociocultural, and physiological factors likely interact in complex ways to influence women's experience of orgasm and of orgasm difficulties.

Culture-Related Diagnostic Issues

The degree to which lack of orgasm in women is regarded as a problem that requires treatment may vary depending on cultural context. In addition, women differ in how important orgasm is to their sexual satisfaction. There may be marked sociocultural and generational differences in women's orgasmic ability. For example, the prevalence of inability to reach orgasm has ranged from 17.7% (in Northern Europe) to 42.2% (in Southeast Asia).

Diagnostic Markers

Although measurable physiological changes occur during female orgasm, including changes in hormones, pelvic floor musculature, and brain activation, there is significant variability in these indicators of orgasm across women. In clinical situations, the diagnosis of female orgasmic disorder is based on a woman's self-report.

Functional Consequences of Female Orgasmic Disorder

The functional consequences of female orgasmic disorder are unclear. Although there is a strong association between relationship problems and orgasmic difficulties in women, it is unclear whether relationship factors are risk factors for orgasmic difficulties or are consequences of those difficulties.

Differential Diagnosis

Nonsexual mental disorders. Nonsexual mental disorders, such as major depressive disorder, which is characterized by markedly diminished interest or pleasure in all, or almost all, activities, may explain female orgasmic disorder. If the orgasmic difficulties are better explained by another mental disorder, then a diagnosis of female orgasmic disorder would not be made.

Substance/medication-induced sexual dysfunction. Substance/medication use may explain the orgasmic difficulties.

Another medical condition. If the disorder is due to another medical condition (e.g., multiple sclerosis, spinal cord injury), then a diagnosis of female orgasmic disorder would not be made.

Interpersonal factors. If interpersonal or significant contextual factors, such as severe relationship distress, intimate partner violence, or other significant stressors, are associated with the orgasmic difficulties, then a diagnosis of female orgasmic disorder would not be made.

Other sexual dysfunctions. Female orgasmic disorder may occur in association with other sexual dysfunctions (e.g., female sexual interest/arousal disorder). The presence of another sexual dysfunction does not rule out a diagnosis of female orgasmic disorder. Occasional orgasmic difficulties that are short-term or infrequent and are not accompanied by clinically significant distress or impairment are not diagnosed as female orgasmic disorder. A diagnosis is also not appropriate if the problems are the result of inadequate sexual stimulation.

Comorbidity

Women with female orgasmic disorder may have co-occurring sexual interest/arousal difficulties. Women with diagnoses of other nonsexual mental disorders, such as major depressive disorder, may experience lower sexual interest/arousal, and this may indirectly increase the likelihood of orgasmic difficulties.

Female Sexual Interest/Arousal Disorder

Diagnostic Criteria **302.72 (F52.22)**

A. Lack of, or significantly reduced, sexual interest/arousal, as manifested by at least three of the following:
   1. Absent/reduced interest in sexual activity.
   2. Absent/reduced sexual/erotic thoughts or fantasies.
   3. No/reduced initiation of sexual activity, and typically unreceptive to a partner's attempts to initiate.
   4. Absent/reduced sexual excitement/pleasure during sexual activity in almost all or all (approximately 75%–100%) sexual encounters (in identified situational contexts or, if generalized, in all contexts).
   5. Absent/reduced sexual interest/arousal in response to any internal or external sexual/erotic cues (e.g., written, verbal, visual).
   6. Absent/reduced genital or nongenital sensations during sexual activity in almost all or all (approximately 75%–100%) sexual encounters (in identified situational contexts or, if generalized, in all contexts).

B. The symptoms in Criterion A have persisted for a minimum duration of approximately 6 months.

C. The symptoms in Criterion A cause clinically significant distress in the individual.

D. The sexual dysfunction is not better explained by a nonsexual mental disorder or as a consequence of severe relationship distress (e.g., partner violence) or other significant stressors and is not attributable to the effects of a substance/medication or another medical condition.

Specify whether:

Lifelong: The disturbance has been present since the individual became sexually active.

Acquired: The disturbance began after a period of relatively normal sexual function.

Specify whether:

Generalized: Not limited to certain types of stimulation, situations, or partners.

Situational: Only occurs with certain types of stimulation, situations, or partners.

Specify current severity:

Mild: Evidence of mild distress over the symptoms in Criterion A.

Moderate: Evidence of moderate distress over the symptoms in Criterion A.

Severe: Evidence of severe or extreme distress over the symptoms in Criterion A.

Diagnostic Features

In assessing female sexual interest/arousal disorder, interpersonal context must be taken into account. A "desire discrepancy," in which a woman has lower desire for sexual activity than her partner, is not sufficient to diagnose female sexual interest/arousal disorder. In order for the criteria for the disorder to be met, there must be absence or reduced frequency or intensity of at least three of six indicators (Criterion A) for a minimum duration of approximately 6 months (Criterion B). There may be different symptom profiles across women, as well as variability in how sexual interest and arousal are expressed. For example, in one woman, sexual interest/arousal disorder may be expressed as a lack of interest in sexual activity, an absence of erotic or sexual thoughts, and reluctance to initiate sexual activity and respond to a partner's sexual invitations. In another woman, an inability to become sexually excited, to respond to sexual stimuli with sexual desire, and a correspond-

ing lack of signs of physical sexual arousal may be the primary features. Because sexual desire and arousal frequently coexist and are elicited in response to adequate sexual cues, the criteria for female sexual interest/arousal disorder take into account that difficulties in desire and arousal often simultaneously characterize the complaints of women with this disorder. Short-term changes in sexual interest or arousal are common and may be adaptive responses to events in a woman's life and do not represent a sexual dysfunction. Diagnosis of female sexual interest/arousal disorder requires a minimum duration of symptoms of approximately 6 months as a reflection that the symptoms must be a persistent problem. The estimation of persistence may be determined by clinical judgment when a duration of 6 months cannot be ascertained precisely.

There may be absent or reduced frequency or intensity of interest in sexual activity (Criterion A1), which was previously termed *hypoactive sexual desire disorder*. The frequency or intensity of sexual and erotic thoughts or fantasies may be absent or reduced (Criterion A2). The expression of fantasies varies widely across women and may include memories of past sexual experiences. The normative decline in sexual thoughts with age should be taken into account when this criterion is being assessed. Absence or reduced frequency of initiating sexual activity and of receptivity to a partner's sexual invitations (Criterion A3) is a behaviorally focused criterion. A couple's beliefs and preferences for sexual initiation patterns are highly relevant to the assessment of this criterion. There may be absent or reduced sexual excitement or pleasure during sexual activity in almost all or all (approximately 75%–100%) sexual encounters (Criterion A4). Lack of pleasure is a common presenting clinical complaint in women with low desire. Among women who report low sexual desire, there are fewer sexual or erotic cues that elicit sexual interest or arousal (i.e., there is a lack of "responsive desire"). Assessment of the adequacy of sexual stimuli will assist in determining if there is a difficulty with responsive sexual desire (Criterion A5). Frequency or intensity of genital or nongenital sensations during sexual activity may be reduced or absent (Criterion A6). This may include reduced vaginal lubrication/vasocongestion, but because physiological measures of genital sexual response do not differentiate women who report sexual arousal concerns from those who do not, the self-report of reduced or absent genital or nongenital sensations is sufficient.

For a diagnosis of female sexual interest/arousal disorder to be made, clinically significant distress must accompany the symptoms in Criterion A. Distress may be experienced as a result of the lack of sexual interest/arousal or as a result of significant interference in a woman's life and well-being. If a lifelong lack of sexual desire is better explained by one's self-identification as "asexual," then a diagnosis of female sexual interest/arousal disorder would not be made.

Associated Features Supporting Diagnosis

Female sexual interest/arousal disorder is frequently associated with problems in experiencing orgasm, pain experienced during sexual activity, infrequent sexual activity, and couple-level discrepancies in desire. Relationship difficulties and mood disorders are also frequently associated features of female sexual interest/arousal disorder. Unrealistic expectations and norms regarding the "appropriate" level of sexual interest or arousal, along with poor sexual techniques and lack of information about sexuality, may also be evident in women diagnosed with female sexual interest/arousal disorder. The latter, as well as normative beliefs about gender roles, are important factors to consider.

In addition to the subtypes "lifelong/acquired" and "generalized/situational," the following five factors must be considered during assessment and diagnosis of female sexual interest/arousal disorder given that they may be relevant to etiology and/or treatment: 1) partner factors (e.g., partner's sexual problems, partner's health status); 2) relationship factors (e.g., poor communication, discrepancies in desire for sexual activity); 3) individual vulnerability factors (e.g., poor body image, history of sexual or emotional abuse), psychiatric comorbidity (e.g., depression, anxiety), or stressors (e.g., job loss, bereavement); 4) cultural/religious factors (e.g., inhibitions related to prohibitions against sexual activity; attitudes toward sexuality); and

5) medical factors relevant to prognosis, course, or treatment. Note that each of these factors may contribute differently to the presenting symptoms of different women with this disorder.

Prevalence

The prevalence of female sexual interest/arousal disorder, as defined in this manual, is unknown. The prevalence of low sexual desire and of problems with sexual arousal (with and without associated distress), as defined by DSM-IV or ICD-10, may vary markedly in relation to age, cultural setting, duration of symptoms, and presence of distress. Regarding duration of symptoms, there are striking differences in prevalence estimates between short-term and persistent problems related to lack of sexual interest. When distress about sexual functioning is required, prevalence estimates are markedly lower. Some older women report less distress about low sexual desire than younger women, although sexual desire may decrease with age.

Development and Course

By definition, lifelong female sexual interest/arousal disorder suggests that the lack of sexual interest or arousal has been present for the woman's entire sexual life. For Criteria A3, A4, and A6, which assess functioning during sexual activity, a subtype of lifelong would mean presence of symptoms since the individual's first sexual experiences. The acquired subtype would be assigned if the difficulties with sexual interest or arousal developed after a period of nonproblematic sexual functioning. Adaptive and normative changes in sexual functioning may result from partner-related, interpersonal, or personal events and may be transient in nature. However, persistence of symptoms for approximately 6 months or more would constitute a sexual dysfunction.

There are normative changes in sexual interest and arousal across the life span. Furthermore, women in relationships of longer duration are more likely to report engaging in sex despite no obvious feelings of sexual desire at the outset of a sexual encounter compared with women in shorter-duration relationships. Vaginal dryness in older women is related to age and menopausal status.

Risk and Prognostic Factors

Temperamental. Temperamental factors include negative cognitions and attitudes about sexuality and past history of mental disorders. Differences in propensity for sexual excitation and sexual inhibition may also predict the likelihood of developing sexual problems.

Environmental. Environmental factors include relationship difficulties, partner sexual functioning, and developmental history, such as early relationships with caregivers and childhood stressors.

Genetic and physiological. Some medical conditions (e.g., diabetes mellitus, thyroid dysfunction) can be risk factors for female sexual interest/arousal disorder. There appears to be a strong influence of genetic factors on vulnerability to sexual problems in women. Psychophysiological research using vaginal photoplethysmography has not found differences between women with and without perceived lack of genital arousal.

Culture-Related Diagnostic Issues

There is marked variability in prevalence rates of low desire across cultures. Lower rates of sexual desire may be more common among East Asian women compared with Euro-Canadian women. Although the lower levels of sexual desire and arousal found in men and women from East Asian countries compared with Euro-American groups may reflect less interest in sex in those cultures, the possibility remains that such group differences are an artifact of the measures used to quantify desire. A judgment about whether low sexual

desire reported by a woman from a certain ethnocultural group meets criteria for female sexual interest/arousal disorder must take into account the fact that different cultures may pathologize some behaviors and not others.

Gender-Related Diagnostic Issues

By definition, the diagnosis of female sexual interest/arousal disorder is only given to women. Distressing difficulties with sexual desire in men would be considered under male hypoactive sexual desire disorder.

Functional Consequences of Female Sexual Interest/Arousal Disorder

Difficulties in sexual interest/arousal are often associated with decreased relationship satisfaction.

Differential Diagnosis

Nonsexual mental disorders. Nonsexual mental disorders, such as major depressive disorder, in which there is "markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day," may explain the lack of sexual interest/arousal. If the lack of interest or arousal is completely attributable to another mental disorder, then a diagnosis of female sexual interest/arousal disorder would not be made.

Substance/medication use. Substance or medication use may explain the lack of interest/arousal.

Another medical condition. If the sexual symptoms are considered to be almost exclusively associated with the effects of another medical condition (e.g., diabetes mellitus, endothelial disease, thyroid dysfunction, central nervous system disease), then a diagnosis of female sexual interest/arousal disorder would not be made.

Interpersonal factors. If interpersonal or significant contextual factors, such as severe relationship distress, intimate partner violence, or other significant stressors, explain the sexual interest/arousal symptoms, then a diagnosis of female sexual interest/arousal disorder would not be made.

Other sexual dysfunctions. The presence of another sexual dysfunction does not rule out a diagnosis of female sexual interest/arousal disorder. It is common for women to experience more than one sexual dysfunction. For example, the presence of chronic genital pain may lead to a lack of desire for the (painful) sexual activity. Lack of interest and arousal during sexual activity may impair orgasmic ability. For some women, all aspects of the sexual response may be unsatisfying and distressing.

Inadequate or absent sexual stimuli. When differential diagnoses are being considered, it is important to assess the adequacy of sexual stimuli within the woman's sexual experience. In cases where inadequate or absent sexual stimuli are contributing to the clinical picture, there may be evidence for clinical care, but a sexual dysfunction diagnosis would not be made. Similarly, transient and adaptive alterations in sexual functioning that are secondary to a significant life or personal event must be considered in the differential diagnosis.

Comorbidity

Comorbidity between sexual interest/arousal problems and other sexual difficulties is extremely common. Sexual distress and dissatisfaction with sex life are also highly correlated in women with low sexual desire. Distressing low desire is associated with depression, thyroid problems, anxiety, urinary incontinence, and other medical factors. Arthritis and inflammatory or irritable bowel disease are also associated with sexual arousal prob-

lems. Low desire appears to be comorbid with depression, sexual and physical abuse in adulthood, global mental functioning, and use of alcohol.

Genito-Pelvic Pain/Penetration Disorder

Diagnostic Criteria **302.76 (F52.6)**

A. Persistent or recurrent difficulties with one (or more) of the following:
   1. Vaginal penetration during intercourse.
   2. Marked vulvovaginal or pelvic pain during vaginal intercourse or penetration attempts.
   3. Marked fear or anxiety about vulvovaginal or pelvic pain in anticipation of, during, or as a result of vaginal penetration.
   4. Marked tensing or tightening of the pelvic floor muscles during attempted vaginal penetration.

B. The symptoms in Criterion A have persisted for a minimum duration of approximately 6 months.

C. The symptoms in Criterion A cause clinically significant distress in the individual.

D. The sexual dysfunction is not better explained by a nonsexual mental disorder or as a consequence of a severe relationship distress (e.g., partner violence) or other significant stressors and is not attributable to the effects of a substance/medication or another medical condition.

Specify whether:

Lifelong: The disturbance has been present since the individual became sexually active.

Acquired: The disturbance began after a period of relatively normal sexual function.

Specify current severity:

Mild: Evidence of mild distress over the symptoms in Criterion A.

Moderate: Evidence of moderate distress over the symptoms in Criterion A.

Severe: Evidence of severe or extreme distress over the symptoms in Criterion A.

Diagnostic Features

Genito-pelvic pain/penetration disorder refers to four commonly comorbid symptom dimensions: 1) difficulty having intercourse, 2) genito-pelvic pain, 3) fear of pain or vaginal penetration, and 4) tension of the pelvic floor muscles (Criterion A). Because major difficulty in any one of these symptom dimensions is often sufficient to cause clinically significant distress, a diagnosis can be made on the basis of marked difficulty in only one symptom dimension. However, all four symptom dimensions should be assessed even if a diagnosis can be made on the basis of only one symptom dimension.

Marked difficulty having vaginal intercourse/penetration (Criterion A1) can vary from a total inability to experience vaginal penetration in any situation (e.g., intercourse, gynecological examinations, tampon insertion) to the ability to easily experience penetration in one situation and but not in another. Although the most common clinical situation is when a woman is unable to experience intercourse or penetration with a partner, difficulties in undergoing required gynecological examinations may also be present. *Marked vulvovaginal or pelvic pain during vaginal intercourse or penetration attempts* (Criterion A2) refers to pain occurring in different locations in the genito-pelvic area. Location of pain as well as intensity should be assessed. Typically, pain can be characterized as superficial (vulvovaginal or occurring during penetration) or deep (pelvic; i.e., not felt until deeper penetration). The intensity of the pain is often not linearly related to distress or interference with sexual intercourse or other sexual activities. Some genito-pelvic pain only occurs when provoked (i.e., by intercourse or mechanical stim-

ulation); other genito-pelvic pain may be spontaneous as well as provoked. Genito-pelvic pain can also be usefully characterized qualitatively (e.g., "burning," "cutting," "shooting," "throbbing"). The pain may persist for a period after intercourse is completed and may also occur during urination. Typically, the pain experienced during sexual intercourse can be reproduced during a gynecological examination.

Marked fear or anxiety about vulvovaginal or pelvic pain either in anticipation of, or during, or as a result of vaginal penetration (Criterion A3) is commonly reported by women who have regularly experienced pain during sexual intercourse. This "normal" reaction may lead to avoidance of sexual/intimate situations. In other cases, this marked fear does not appear to be closely related to the experience of pain but nonetheless leads to avoidance of intercourse and vaginal penetration situations. Some have described this as similar to a phobic reaction except that the phobic object may be vaginal penetration or the fear of pain.

Marked tensing or tightening of the pelvic floor muscles during attempted vaginal penetration (Criterion A4) can vary from reflexive-like spasm of the pelvic floor in response to attempted vaginal entry to "normal/voluntary" muscle guarding in response to the anticipated or the repeated experience of pain or to fear or anxiety. In the case of "normal/guarding" reactions, penetration may be possible under circumstances of relaxation. The characterization and assessment of pelvic floor dysfunction is often best undertaken by a specialist gynecologist or by a pelvic floor physical therapist.

Associated Features Supporting Diagnosis

Genito-pelvic pain/penetration disorder is frequently associated with other sexual dysfunctions, particularly reduced sexual desire and interest (female sexual interest/arousal disorder). Sometimes desire and interest are preserved in sexual situations that are not painful or do not require penetration. Even when individuals with genito-pelvic pain/penetration disorder report sexual interest/motivation, there is often behavioral avoidance of sexual situations and opportunities. Avoidance of gynecological examinations despite medical recommendations is also frequent. The pattern of avoidance is similar to that seen in phobic disorders. It is common for women who have not succeeded in having sexual intercourse to come for treatment only when they wish to conceive. Many women with genito-pelvic pain/penetration disorder will experience associated relationship/marital problems; they also often report that the symptoms significantly diminish their feelings of femininity.

In addition to the subtype "lifelong/acquired," five factors should be considered during assessment and diagnosis of genito-pelvic pain/penetration disorder because they may be relevant to etiology and/or treatment: 1) partner factors (e.g., partner's sexual problems, partner's health status); 2) relationship factors (e.g., poor communication, discrepancies in desire for sexual activity); 3) individual vulnerability factors (e.g., poor body image, history of sexual or emotional abuse), psychiatric comorbidity (e.g., depression, anxiety), or stressors (e.g., job loss, bereavement); 4) cultural/religious factors (e.g., inhibitions related to prohibitions against sexual activity; attitudes toward sexuality); and 5) medical factors relevant to prognosis, course, or treatment. Each of these factors may contribute differently to the presenting symptoms of different women with this disorder.

There are no valid physiological measures of any of the component symptom dimensions of genito-pelvic pain/penetration disorder. Validated psychometric inventories may be used to formally assess the pain and anxiety components related to genito-pelvic pain/penetration disorder.

Prevalence

The prevalence of genito-pelvic pain/penetration disorder is unknown. However, approximately 15% of women in North America report recurrent pain during intercourse. Difficulties having intercourse appear to be a frequent referral to sexual dysfunction clinics and to specialist clinicians.

Development and Course

The development and course of genito-pelvic pain/penetration disorder is unclear. Because women generally do not seek treatment until they experience problems in sexual functioning, it can, in general, be difficult to characterize genito-pelvic pain/penetration disorder as lifelong (primary) or acquired (secondary). Although women typically come to clinical attention after the initiation of sexual activity, there are often earlier clinical signs. For example, difficulty with or the avoidance of use of tampons is an important predictor of later problems. Difficulties with vaginal penetration (inability or fear or pain) may not be obvious until sexual intercourse is attempted. Even once intercourse is attempted, the frequency of attempts may not be significant or regular. In cases where it is difficult to establish whether symptomatology is lifelong or acquired, it is useful to determine the presence of any consistent period of successful pain-, fear-, and tension-free intercourse. If the experience of such a period can be established, then genito-pelvic pain/penetration disorder can be characterized as acquired. Once symptomatology is well established for a period of approximately 6 months, the probability of spontaneous and significant symptomatic remission appears to diminish.

Complaints related to genito-pelvic pain peak during early adulthood and in the peri- and postmenopausal period. Women with complaints about difficulty having intercourse appear to be primarily premenopausal. There may also be an increase in genito-pelvic pain–related symptoms in the postpartum period.

Risk and Prognostic Factors

Environmental. Sexual and/or physical abuse have often been cited as predictors of the DSM-IV-defined sexual pain disorders dyspareunia and vaginismus. This is a matter of controversy in the current literature.

Genetic and physiological. Women experiencing superficial pain during sexual intercourse often report the onset of the pain after a history of vaginal infections. Even after the infections have resolved and there are no known residual physical findings, the pain persists. Pain during tampon insertion or the inability to insert tampons before any sexual contact has been attempted is an important risk factor for genito-pelvic pain/penetration disorder.

Culture-Related Diagnostic Issues

In the past, inadequate sexual education and religious orthodoxy have often been considered to be culturally related predisposing factors to the DSM-IV diagnosis of vaginismus. This perception appears to be confirmed by recent reports from Turkey, a primarily Muslim country, indicating a strikingly high prevalence for the disorder. However, most available research, although limited in scope, does not support this notion (Lahaie et al. 2010).

Gender-Related Diagnostic Issues

By definition, the diagnosis of genito-pelvic pain/penetration disorder is only given to women. There is relatively new research concerning urological chronic pelvic pain syndrome in men, suggesting that men may experience some similar problems. The research and clinical experience are not sufficiently developed yet to justify the application of this diagnosis to men. Other specified sexual dysfunction or unspecified sexual dysfunction may be diagnosed in men appearing to fit this pattern.

Functional Consequences of Genito-Pelvic Pain/Penetration Disorder

Functional difficulties in genito-pelvic pain/penetration disorder are often associated with interference in relationship satisfaction and sometimes with the ability to conceive via penile/vaginal intercourse.

Differential Diagnosis

Another medical condition. In many instances, women with genito-pelvic pain/penetration disorder will also be diagnosed with another medical condition (e.g., lichen sclerosus, endometriosis, pelvic inflammatory disease, vulvovaginal atrophy). In some cases, treating the medical condition may alleviate the genito-pelvic pain/penetration disorder. Much of the time, this is not the case. There are no reliable tools or diagnostic methods to allow clinicians to know whether the medical condition or genito-pelvic pain/penetration disorder is primary. Often, the associated medical conditions are difficult to diagnose and treat. For example, the increased incidence of postmenopausal pain during intercourse may sometimes be attributable to vaginal dryness or vulvovaginal atrophy associated with declining estrogen levels. The relationship, however, between vulvovaginal atrophy/dryness, estrogen, and pain is not well understood.

Somatic symptom and related disorders. Some women with genito-pelvic pain/penetration disorder may also be diagnosable with somatic symptom disorder. Since both genito-pelvic pain/penetration disorder and the somatic symptom and related disorders are new diagnoses, it is not yet clear whether they can be reliably differentiated. Some women diagnosed with genito-pelvic pain/penetration disorder will also be diagnosed with a specific phobia.

Inadequate sexual stimuli. It is important that the clinician, in considering differential diagnoses, assess the adequacy of sexual stimuli within the woman's sexual experience. Sexual situations in which there is inadequate foreplay or arousal may lead to difficulties in penetration, pain, or avoidance. Erectile dysfunction or premature ejaculation in the male partner may result in difficulties with penetration. These conditions should be carefully assessed. In some situations, a diagnosis of genito-pelvic pain/penetration disorder may not be appropriate.

Comorbidity

Comorbidity between genito-pelvic pain/penetration disorder and other sexual difficulties appears to be common. Comorbidity with relationship distress is also common. This is not surprising, since in Western cultures the inability to have (pain-free) intercourse with a desired partner and the avoidance of sexual opportunities may be either a contributing factor to or the result of other sexual or relationship problems. Because pelvic floor symptoms are implicated in the diagnosis of genito-pelvic pain/penetration disorder, there is likely to be a higher prevalence of other disorders related to the pelvic floor or reproductive organs (e.g., interstitial cystitis, constipation, vaginal infection, endometriosis, irritable bowel syndrome).

Male Hypoactive Sexual Desire Disorder

Diagnostic Criteria **302.71 (F52.0)**

A. Persistently or recurrently deficient (or absent) sexual/erotic thoughts or fantasies and desire for sexual activity. The judgment of deficiency is made by the clinician, taking into account factors that affect sexual functioning, such as age and general and sociocultural contexts of the individual's life.
B. The symptoms in Criterion A have persisted for a minimum duration of approximately 6 months.
C. The symptoms in Criterion A cause clinically significant distress in the individual.
D. The sexual dysfunction is not better explained by a nonsexual mental disorder or as a consequence of severe relationship distress or other significant stressors and is not attributable to thes effects of a substance/medication or another medical condition.

Specify whether:

Lifelong: The disturbance has been present since the individual became sexually active.

Acquired: The disturbance began after a period of relatively normal sexual function.

Specify whether:

Generalized: Not limited to certain types of stimulation, situations, or partners.

Situational: Only occurs with certain types of stimulation, situations, or partners.

Specify current severity:

Mild: Evidence of mild distress over the symptoms in Criterion A.

Moderate: Evidence of moderate distress over the symptoms in Criterion A.

Severe: Evidence of severe or extreme distress over the symptoms in Criterion A.

Diagnostic Features

When an assessment for male hypoactive sexual desire disorder is being made, interpersonal context must be taken into account. A "desire discrepancy," in which a man has lower desire for sexual activity than his partner, is not sufficient to diagnose male hypoactive sexual desire disorder. Both low/absent desire for sex and deficient/absent sexual thoughts or fantasies are required for a diagnosis of the disorder. There may be variation across men in how sexual desire is expressed.

The lack of desire for sex and deficient/absent erotic thoughts or fantasies must be persistent or recurrent and must occur for a minimum duration of approximately 6 months. The inclusion of this duration criterion is meant to safeguard against making a diagnosis in cases in which a man's low sexual desire may represent an adaptive response to adverse life conditions (e.g., concern about a partner's pregnancy when the man is considering terminating the relationship). The introduction of "approximately" in Criterion B allows for clinician judgment in cases in which symptom duration does not meet the recommended 6-month threshold.

Associated Features Supporting Diagnosis

Male hypoactive sexual desire disorder is sometimes associated with erectile and/or ejaculatory concerns. For example, persistent difficulties obtaining an erection may lead a man to lose interest in sexual activity. Men with hypoactive sexual desire disorder often report that they no longer initiate sexual activity and that they are minimally receptive to a partner's attempt to initiate. Sexual activities (e.g., masturbation or partnered sexual activity) may sometimes occur even in the presence of low sexual desire. Relationship-specific preferences regarding patterns of sexual initiation must be taken into account when making a diagnosis of male hypoactive sexual desire disorder. Although men are more likely to initiate sexual activity, and thus low desire may be characterized by a pattern of non-initiation, many men may prefer to have their partner initiate sexual activity. In such situations, the man's lack of receptivity to a partner's initiation should be considered when evaluating low desire.

In addition to the subtypes "lifelong/acquired" and "generalized/situational," the following five factors must be considered during assessment and diagnosis of male hypoactive sexual desire disorder given that they may be relevant to etiology and/or treatment: 1) partner factors (e.g., partner's sexual problems, partner's health status); 2) relationship factors (e.g., poor communication, discrepancies in desire for sexual activity); 3) individual vulnerability factors (e.g., poor body image, history of sexual or emotional abuse), psychiatric comorbidity (e.g., depression, anxiety), or stressors (e.g., job loss, bereavement); 4) cultural/religious factors (e.g., inhibitions related to prohibitions against sexual activity; attitudes toward sexuality); and 5) medical factors relevant to prognosis, course, or treat-

ment. Each of these factors may contribute differently to the presenting symptoms of different men with this disorder.

Prevalence

The prevalence of male hypoactive sexual desire disorder varies depending on country of origin and method of assessment. Approximately 6% of younger men (ages 18–24 years) and 41% of older men (ages 66–74 years) have problems with sexual desire. However, a persistent lack of interest in sex, lasting 6 months or more, affects only a small proportion of men ages 16–44 (1.8%).

Development and Course

By definition, lifelong male hypoactive sexual desire disorder indicates that low or no sexual desire has always been present, whereas the acquired subtype would be assigned if the man's low desire developed after a period of normal sexual desire. There is a requirement that low desire persist for approximately 6 months or more; thus, short-term changes in sexual desire should not be diagnosed as male hypoactive sexual desire disorder.

There is a normative age-related decline in sexual desire. Like women, men identify a variety of triggers for their sexual desire, and they describe a wide range of reasons that they choose to engage in sexual activity. Although erotic visual cues may be more potent elicitors of desire in younger men, the potency of sexual cues may decrease with age and must be considered when evaluating men for hypoactive sexual desire disorder.

Risk and Prognostic Factors

Temperamental. Mood and anxiety symptoms appear to be strong predictors of low desire in men. Up to half of men with a past history of psychiatric symptoms may have moderate or severe loss of desire, compared with only 15% of those without such a history. A man's feelings about himself, his perception of his partner's sexual desire toward him, feelings of being emotionally connected, and contextual variables may all negatively (as well as positively) affect sexual desire.

Environmental. Alcohol use may increase the occurrence of low desire. Among gay men, self-directed homophobia, interpersonal problems, attitudes, lack of adequate sex education, and trauma resulting from early life experiences must be taken into account in explaining the low desire. Social and cultural contextual factors should also be considered.

Genetic and physiological. Endocrine disorders such as hyperprolactinemia significantly affect sexual desire in men. Age is a significant risk factor for low desire in men. It is unclear whether or not men with low desire also have abnormally low levels of testosterone; however, among hypogonadal men, low desire is common. There also may be a critical threshold below which testosterone will affect sexual desire in men and above which there is little effect of testosterone on men's desire.

Culture-Related Diagnostic Issues

There is marked variability in prevalence rates of low desire across cultures, ranging from 12.5% in Northern European men to 28% in Southeast Asian men ages 40–80 years. Just as there are higher rates of low desire among East Asian subgroups of women, men of East Asian ancestry also have higher rates of low desire. Guilt about sex may mediate this association between East Asian ethnicity and sexual desire in men.

Gender-Related Diagnostic Issues

In contrast to the classification of sexual disorders in women, desire and arousal disorders have been retained as separate constructs in men. Despite some similarities in the experi-

ence of desire across men and women, and the fact that desire fluctuates over time and is dependent on contextual factors, men do report a significantly higher intensity and frequency of sexual desire compared with women.

Differential Diagnosis

Nonsexual mental disorders. Nonsexual mental disorders, such as major depressive disorder, which is characterized by "markedly diminished interest or pleasure in all, or almost all, activities," may explain the lack of sexual desire. If the lack of desire is better explained by another mental disorder, then a diagnosis of male hypoactive sexual desire disorder would not be made.

Substance/medication use. Substance/medication use may explain the lack of sexual desire.

Another medical condition. If the low/absent desire and deficient/absent erotic thoughts or fantasies are better explained by the effects of another medical condition (e.g., hypogonadism, diabetes mellitus, thyroid dysfunction, central nervous system disease), then a diagnosis of male hypoactive sexual desire disorder would not be made.

Interpersonal factors. If interpersonal or significant contextual factors, such as severe relationship distress or other significant stressors, are associated with the loss of desire in the man, then a diagnosis of male hypoactive sexual desire disorder would not be made.

Other sexual dysfunctions. The presence of another sexual dysfunction does not rule out a diagnosis of male hypoactive sexual desire disorder; there is some evidence that up to one-half of men with low sexual desire also have erectile difficulties, and slightly fewer may also have early ejaculation difficulties. If the man's low desire is explained by self-identification as an asexual, then a diagnosis of male hypoactive sexual desire disorder is not made.

Comorbidity

Depression and other mental disorders, as well as endocrinological factors, are often comorbid with male hypoactive sexual desire disorder.

Premature (Early) Ejaculation

Diagnostic Criteria **302.75** (F52.4)

A. A persistent or recurrent pattern of ejaculation occurring during partnered sexual activity within approximately 1 minute following vaginal penetration and before the individual wishes it.

   Note: Although the diagnosis of premature (early) ejaculation may be applied to individuals engaged in nonvaginal sexual activities, specific duration criteria have not been established for these activities.

B. The symptom in Criterion A must have been present for at least 6 months and must be experienced on almost all or all (approximately 75%–100%) occasions of sexual activity (in identified situational contexts or, if generalized, in all contexts).

C. The symptom in Criterion A causes clinically significant distress in the individual.

D. The sexual dysfunction is not better explained by a nonsexual mental disorder or as a consequence of severe relationship distress or other significant stressors and is not attributable to the effects of a substance/medication or another medical condition.

Specify whether:

Lifelong: The disturbance has been present since the individual became sexually active.

Acquired: The disturbance began after a period of relatively normal sexual function.

Specify whether:

Generalized: Not limited to certain types of stimulation, situations, or partners.

Situational: Only occurs with certain types of stimulation, situations, or partners.

Specify current severity:

Mild: Ejaculation occurring within approximately 30 seconds to 1 minute of vaginal penetration.

Moderate: Ejaculation occurring within approximately 15–30 seconds of vaginal penetration.

Severe: Ejaculation occurring prior to sexual activity, at the start of sexual activity, or within approximately 15 seconds of vaginal penetration.

Diagnostic Features

Premature (early) ejaculation is manifested by ejaculation that occurs prior to or shortly after vaginal penetration, operationalized by an individual's estimate of ejaculatory latency (i.e., elapsed time before ejaculation) after vaginal penetration. Estimated and measured intravaginal ejaculatory latencies are highly correlated as long as the ejaculatory latency is of short duration; therefore, self-reported estimates of ejaculatory latency are sufficient for diagnostic purposes. A 60-second intravaginal ejaculatory latency time is an appropriate cutoff for the diagnosis of lifelong premature (early) ejaculation in heterosexual men. There are insufficient data to determine if this duration criterion can be applied to acquired premature (early) ejaculation. The durational definition may apply to males of varying sexual orientations, since ejaculatory latencies appear to be similar across men of different sexual orientations and across different sexual activities.

Associated Features Supporting Diagnosis

Many males with premature (early) ejaculation complain of a sense of lack of control over ejaculation and report apprehension about their anticipated inability to delay ejaculation on future sexual encounters.

The following factors may be relevant in the evaluation of any sexual dysfunction: 1) partner factors (e.g., partner's sexual problems, partner's health status); 2) relationship factors (e.g., poor communication, discrepancies in desire for sexual activity); 3) individual vulnerability factors (e.g., poor body image, history of sexual or emotional abuse), psychiatric comorbidity (e.g., depression, anxiety), and stressors (e.g., job loss, bereavement); 4) cultural/religious factors (e.g., inhibitions related to prohibitions against sexual activity; attitudes toward sexuality); and 5) medical factors relevant to prognosis, course, or treatment.

Prevalence

Estimates of the prevalence of premature (early) ejaculation vary widely depending on the definition utilized. Internationally, more than 20%–30% of men ages 18–70 years report concern about how rapidly they ejaculate. With the new definition of premature (early) ejaculation (i.e., ejaculation occurring within approximately 1 minute of vaginal penetration), only 1%–3% of men would be diagnosed with the disorder. Prevalence of premature (early) ejaculation may increase with age.

Development and Course

By definition, lifelong premature (early) ejaculation starts during a male's initial sexual experiences and persists thereafter. Some men may experience premature (early) ejaculation during their initial sexual encounters but gain ejaculatory control over time. It is the persistence of ejaculatory problems for longer than 6 months that determines the diagnosis of premature (early) ejaculation. In contrast, some men develop the disorder after a period of

having a normal ejaculatory latency, known as *acquired premature (early) ejaculation.* There is far less known about acquired premature (early) ejaculation than about lifelong premature (early) ejaculation. The acquired form likely has a later onset, usually appearing during or after the fourth decade of life. Lifelong is relatively stable throughout life. Little is known about the course of acquired premature (early) ejaculation. Reversal of medical conditions such as hyperthyroidism and prostatitis appears to restore ejaculatory latencies to baseline values. Lifelong premature (early) ejaculation begins with early sexual experiences and persists throughout an individual's life. In approximately 20% of men with premature (early) ejaculation, ejaculatory latencies decrease further with age. Age and relationship length have been found to be negatively associated with prevalence of premature (early) ejaculation.

Risk and Prognostic Factors

Temperamental. Premature (early) ejaculation may be more common in men with anxiety disorders, especially social anxiety disorder (social phobia).

Genetic and physiological. There is a moderate genetic contribution to lifelong premature (early) ejaculation. Premature (early) ejaculation may be associated with dopamine transporter gene polymorphism or serotonin transporter gene polymorphism. Thyroid disease, prostatitis, and drug withdrawal are associated with acquired premature (early) ejaculation. Positron emission tomography measures of regional cerebral blood flow during ejaculation have shown primary activation in the mesocephalic transition zone, including the ventral tegmental area.

Culture-Related Diagnostic Issues

Perception of what constitutes a normal ejaculatory latency is different in many cultures. Measured ejaculatory latencies may differ in some countries. Such differences may be explained by cultural or religious factors as well as genetic differences between populations.

Gender-Related Diagnostic Issues

Premature (early) ejaculation is a sexual disorder in males. Males and their sexual partners may differ in their perception of what constitutes an acceptable ejaculatory latency. There may be increasing concerns in females about early ejaculation in their sexual partners, which may be a reflection of changing societal attitudes concerning female sexual activity.

Diagnostic Markers

Ejaculatory latency is usually monitored in research settings by the sexual partner utilizing a timing device (e.g., stopwatch), though this is not ideal in real-life sexual situations. For vaginal intercourse, the time between intravaginal penetration and ejaculation is measured.

Functional Consequences of Premature (Early) Ejaculation

A pattern of premature (early) ejaculation may be associated with decreased self-esteem, a sense of lack of control, and adverse consequences for partner relationships. It may also cause personal distress in the sexual partner and decreased sexual satisfaction in the sexual partner. Ejaculation prior to penetration may be associated with difficulties in conception.

Differential Diagnosis

Substance/medication-induced sexual dysfunction. When problems with premature ejaculation are due exclusively to substance use, intoxication, or withdrawal, substance/medication-induced sexual dysfunction should be diagnosed.

Ejaculatory concerns that do not meet diagnostic criteria. It is necessary to identify males with normal ejaculatory latencies who desire longer ejaculatory latencies and males who have episodic premature (early) ejaculation (e.g., during the first sexual encounter with a new partner when a short ejaculatory latency may be common or normative). Neither of these situations would lead to a diagnosis of premature (early) ejaculation, even though these situations may be distressing to some males.

Comorbidity

Premature (early) ejaculation may be associated with erectile problems. In many cases, it may be difficult to determine which difficulty preceded the other. Lifelong premature (early) ejaculation may be associated with certain anxiety disorders. Acquired premature (early) ejaculation may be associated with prostatitis, thyroid disease, or drug withdrawal (e.g., during opioid withdrawal).

Substance/Medication-Induced Sexual Dysfunction

Diagnostic Criteria

A. A clinically significant disturbance in sexual function is predominant in the clinical picture.
B. There is evidence from the history, physical examination, or laboratory findings of both (1) and (2):
   1. The symptoms in Criterion A developed during or soon after substance intoxication or withdrawal or after exposure to a medication.
   2. The involved substance/medication is capable of producing the symptoms in Criterion A.
C. The disturbance is not better explained by a sexual dysfunction that is not substance/medication-induced. Such evidence of an independent sexual dysfunction could include the following:

   The symptoms precede the onset of the substance/medication use; the symptoms persist for a substantial period of time (e.g., about 1 month) after the cessation of acute withdrawal or severe intoxication; or there is other evidence suggesting the existence of an independent non-substance/medication-induced sexual dysfunction (e.g., a history of recurrent non-substance/medication-related episodes).
D. The disturbance does not occur exclusively during the course of a delirium.
E. The disturbance causes clinically significant distress in the individual.

Note: This diagnosis should be made instead of a diagnosis of substance intoxication or substance withdrawal only when the symptoms in Criterion A predominate in the clinical picture and are sufficiently severe to warrant clinical attention.

Coding note: The ICD-9-CM and ICD-10-CM codes for the [specific substance/medication]-induced sexual dysfunctions are indicated in the table below. Note that the ICD-10-CM code depends on whether or not there is a comorbid substance use disorder present for the same class of substance. If a mild substance use disorder is comorbid with the substance-induced sexual dysfunction, the 4th position character is "1," and the clinician should record "mild [substance] use disorder" before the substance-induced sexual dysfunction (e.g., "mild cocaine use disorder with cocaine-induced sexual dysfunction"). If a moderate or severe substance use disorder is comorbid with the substance-induced sexual dysfunction, the 4th position character is "2," and the clinician should record "moderate [substance] use disorder" or "severe [substance] use disorder," depending on the severity of the comorbid substance

use disorder. If there is no comorbid substance use disorder (e.g., after a one-time heavy use of the substance), then the 4th position character is "9," and the clinician should record only the substance-induced sexual dysfunction.

		ICD-10-CM		
	ICD-9-CM	With use disorder, mild	With use disorder, moderate or severe	Without use disorder
Alcohol	291.89	F10.181	F10.281	F10.981
Opioid	292.89	F11.181	F11.281	F11.981
Sedative, hypnotic, or anxiolytic	292.89	F13.181	F13.281	F13.981
Amphetamine (or other stimulant)	292.89	F15.181	F15.281	F15.981
Cocaine	292.89	F14.181	F14.281	F14.981
Other (or unknown) substance	292.89	F19.181	F19.281	F19.981

Specify if (see Table 1 in the chapter "Substance-Related and Addictive Disorders" for diagnoses associated with substance class):

With onset during intoxication: If the criteria are met for intoxication with the substance and the symptoms develop during intoxication.

With onset during withdrawal: If criteria are met for withdrawal from the substance and the symptoms develop during, or shortly after, withdrawal.

With onset after medication use: Symptoms may appear either at initiation of medication or after a modification or change in use.

Specify current severity:

Mild: Occurs on 25%–50% of occasions of sexual activity.

Moderate: Occurs on 50%–75% of occasions of sexual activity.

Severe: Occurs on 75% or more of occasions of sexual activity.

Recording Procedures

ICD-9-CM. The name of the substance/medication-induced sexual dysfunction begins with the specific substance (e.g., alcohol, fluoxetine) that is presumed to be causing the sexual dysfunction. The diagnostic code is selected from the table included in the criteria set, which is based on the drug class. For substances that do not fit into any of the classes (e.g., fluoxetine), the code for "other substance" should be used; and in cases in which a substance is judged to be an etiological factor but the specific class of substance is unknown, the category "unknown substance" should be used.

The name of the disorder is followed by the specification of onset (i.e., onset during intoxication, onset during withdrawal, with onset after medication use), followed by the severity specifier (e.g., mild, moderate, severe). Unlike the recording procedures for ICD-10-CM, which combine the substance-induced disorder and substance use disorder into a single code, for ICD-9-CM a separate diagnostic code is given for the substance use disorder. For example, in the case of erectile dysfunction occurring during intoxication in a man with a severe alcohol use disorder, the diagnosis is 291.89 alcohol-induced sexual dysfunction, with onset during intoxication, moderate. An additional diagnosis of 303.90 severe alcohol use disorder is also given. When more than one substance is judged to play a sig-

nificant role in the development of the sexual dysfunction, each should be listed separately (e.g., 292.89 cocaine-induced sexual dysfunction with onset during intoxication, moderate; 292.89 fluoxetine-induced sexual dysfunction, with onset after medication use).

ICD-10-CM. The name of the substance/medication-induced sexual dysfunction begins with the specific substance (e.g., alcohol, fluoxetine) that is presumed to be causing the sexual dysfunction. The diagnostic code is selected from the table included in the criteria set, which is based on the drug class and presence or absence of a comorbid substance use disorder. For substances that do not fit into any of the classes (e.g., fluoxetine), the code for "other substance" should be used; and in cases in which a substance is judged to be an etiological factor but the specific class of substance is unknown, the category "unknown substance" should be used.

When recording the name of the disorder, the comorbid substance use disorder (if any) is listed first, followed by the word "with," followed by the name of the substance-induced sexual dysfunction, followed by the specification of onset (i.e., onset during intoxication, onset during withdrawal, with onset after medication use), followed by the severity specifier (e.g., mild, moderate, severe). For example, in the case of erectile dysfunction occurring during intoxication in a man with a severe alcohol use disorder, the diagnosis is F10.281 moderate alcohol use disorder with alcohol-induced sexual dysfunction, with onset during intoxication, moderate. A separate diagnosis of the comorbid severe alcohol use disorder is not given. If the substance-induced sexual dysfunction occurs without a comorbid substance use disorder (e.g., after a one-time heavy use of the substance), no accompanying substance use disorder is noted (e.g., F15.981 amphetamine-induced sexual dysfunction, with onset during intoxication). When more than one substance is judged to play a significant role in the development of the sexual dysfunction, each should be listed separately (e.g., F14.181 mild cocaine use disorder with cocaine-induced sexual dysfunction, with onset during intoxication, moderate; F19.981 fluoxetine-induced sexual dysfunction, with onset after medication use, moderate).

Diagnostic Features

The major feature is a disturbance in sexual function that has a temporal relationship with substance/medication initiation, dose increase, or substance/medication discontinuation.

Associated Features Supporting Diagnosis

Sexual dysfunctions can occur in association with intoxication with the following classes of substances: alcohol; opioids; sedatives, hypnotics, or anxiolytics; stimulants (including cocaine); and other (or unknown) substances. Sexual dysfunctions can occur in association with withdrawal from the following classes of substances: alcohol; opioids; sedatives, hypnotics, or anxiolytics; and other (or unknown) substances. Medications that can induce sexual dysfunctions include antidepressants, antipsychotics, and hormonal contraceptives.

The most commonly reported side effect of antidepressant drugs is difficulty with orgasm or ejaculation. Problems with desire and erection are less frequent. Approximately 30% of sexual complaints are clinically significant. Certain agents, such as bupropion and mirtazapine, appear not to be associated with sexual side effects.

The sexual problems associated with antipsychotic drugs, including problems with sexual desire, erection, lubrication, ejaculation, or orgasm, have occurred with typical as well as atypical agents. However, problems are less common with prolactin-sparing antipsychotics than with agents that cause significant prolactin elevation.

Although the effects of mood stabilizers on sexual function are unclear, it is possible that lithium and anticonvulsants, with the possible exception of lamotrigine, have adverse effects on sexual desire. Problems with orgasm may occur with gabapentin. Similarly, there may be a higher prevalence of erectile and orgasmic problems associated with benzodiazepines. There have not been such reports with buspirone.

Many nonpsychiatric medications, such as cardiovascular, cytotoxic, gastrointestinal, and hormonal agents, are associated with disturbances in sexual function. Illicit substance use is associated with decreased sexual desire, erectile dysfunction, and difficulty reaching orgasm. Sexual dysfunctions are also seen in individuals receiving methadone but are seldom reported by patients receiving buprenorphine. Chronic alcohol abuse and chronic nicotine abuse are associated with erectile problems.

Prevalence

The prevalence and the incidence of substance/medication-induced sexual dysfunction are unclear, likely because of underreporting of treatment-emergent sexual side effects. Data on substance/medication-induced sexual dysfunction typically concern the effects of antidepressant drugs. The prevalence of antidepressant-induced sexual dysfunction varies in part depending on the specific agent. Approximately 25%–80% of individuals taking monoamine oxidase inhibitors, tricyclic antidepressants, serotonergic antidepressants, and combined serotonergic-adrenergic antidepressants report sexual side effects. There are differences in the incidence of sexual side effects between some serotonergic and combined adrenergic-serotonergic antidepressants, although it is unclear if these differences are clinically significant.

Approximately 50% of individuals taking antipsychotic medications will experience adverse sexual side effects, including problems with sexual desire, erection, lubrication, ejaculation, or orgasm. The incidence of these side effects among different antipsychotic agents is unclear.

Exact prevalence and incidence of sexual dysfunctions among users of nonpsychiatric medications such as cardiovascular, cytotoxic, gastrointestinal, and hormonal agents are unknown. Elevated rates of sexual dysfunction have been reported with methadone or high-dose opioid drugs for pain. There are increased rates of decreased sexual desire, erectile dysfunction, and difficulty reaching orgasm associated with illicit substance use. The prevalence of sexual problems appears related to chronic drug abuse and appears higher in individuals who abuse heroin (approximately 60%–70%) than in individuals who abuse amphetamines or 3,4-methylenedioxymethamphetamine (i.e., MDMA, ecstasy). Elevated rates of sexual dysfunction are also seen in individuals receiving methadone but are seldom reported by patients receiving buprenorphine. Chronic alcohol abuse and chronic nicotine abuse are related to higher rates of erectile problems.

Development and Course

The onset of antidepressant-induced sexual dysfunction may be as early as 8 days after the agent is first taken. Approximately 30% of individuals with mild to moderate orgasm delay will experience spontaneous remission of the dysfunction within 6 months. In some cases, serotonin reuptake inhibitor–induced sexual dysfunction may persist after the agent is discontinued. The time to onset of sexual dysfunction after initiation of antipsychotic drugs or drugs of abuse is unknown. It is probable that the adverse effects of nicotine and alcohol may not appear until after years of use. Premature (early) ejaculation can sometimes occur after cessation of opioid use. There is some evidence that disturbances in sexual function related to substance/medication use increase with age.

Culture-Related Diagnostic Issues

There may be an interaction among cultural factors, the influence of medications on sexual functioning, and the response of the individual to those changes.

Gender-Related Diagnostic Issues

Some gender differences in sexual side effects may exist.

Functional Consequences of Substance/Medication-Induced Sexual Dysfunction

Medication-induced sexual dysfunction may result in medication noncompliance.

Differential Diagnosis

Non-substance/medication-induced sexual dysfunctions. Many mental conditions, such as depressive, bipolar, anxiety, and psychotic disorders, are associated with disturbances of sexual function. Thus, differentiating a substance/medication-induced sexual dysfunction from a manifestation of the underlying mental disorder can be quite difficult. The diagnosis is usually established if a close relationship between substance/medication initiation or discontinuation is observed. A clear diagnosis can be established if the problem occurs after substance/medication initiation, dissipates with substance/medication discontinuation, and recurs with introduction of the same agent. Most substance/medication-induced side effects occur shortly after initiation or discontinuation. Sexual side effects that only occur after chronic use of a substance/medication may be extremely difficult to diagnose with certainty.

Other Specified Sexual Dysfunction

302.79 (F52.8)

This category applies to presentations in which symptoms characteristic of a sexual dysfunction that cause clinically significant distress in the individual predominate but do not meet the full criteria for any of the disorders in the sexual dysfunctions diagnostic class. The other specified sexual dysfunction category is used in situations in which the clinician chooses to communicate the specific reason that the presentation does not meet the criteria for any specific sexual dysfunction. This is done by recording "other specified sexual dysfunction" followed by the specific reason (e.g., "sexual aversion").

Unspecified Sexual Dysfunction

302.70 (F52.9)

This category applies to presentations in which symptoms characteristic of a sexual dysfunction that cause clinically significant distress in the individual predominate but do not meet the full criteria for any of the disorders in the sexual dysfunctions diagnostic class. The unspecified sexual dysfunction category is used in situations in which the clinician chooses *not* to specify the reason that the criteria are not met for a specific sexual dysfunction, and includes presentations for which there is insufficient information to make a more specific diagnosis.

Gender Dysphoria

In this chapter, there is one overarching diagnosis of gender dysphoria, with separate developmentally appropriate criteria sets for children and for adolescents and adults. The area of sex and gender is highly controversial and has led to a proliferation of terms whose meanings vary over time and within and between disciplines. An additional source of confusion is that in English "sex" connotes both male/female and sexuality. This chapter employs constructs and terms as they are widely used by clinicians from various disciplines with specialization in this area. In this chapter, *sex* and *sexual* refer to the biological indicators of male and female (understood in the context of reproductive capacity), such as in sex chromosomes, gonads, sex hormones, and nonambiguous internal and external genitalia. Disorders of sex development denote conditions of inborn somatic deviations of the reproductive tract from the norm and/or discrepancies among the biological indicators of male and female. *Cross-sex* hormone treatment denotes the use of feminizing hormones in an individual assigned male at birth based on traditional biological indicators or the use of masculinizing hormones in an individual assigned female at birth.

The need to introduce the term *gender* arose with the realization that for individuals with conflicting or ambiguous biological indicators of sex (i.e., "intersex"), the lived role in society and/or the identification as male or female could not be uniformly associated with or predicted from the biological indicators and, later, that some individuals develop an identity as female or male at variance with their uniform set of classical biological indicators. Thus, *gender* is used to denote the public (and usually legally recognized) lived role as boy or girl, man or woman, but, in contrast to certain social constructionist theories, biological factors are seen as contributing, in interaction with social and psychological factors, to gender development. *Gender assignment* refers to the initial assignment as male or female. This occurs usually at birth and, thereby, yields the "natal gender." *Gender-atypical* refers to somatic features or behaviors that are not typical (in a statistical sense) of individuals with the same assigned gender in a given society and historical era; for behavior, *gender-nonconforming* is an alternative descriptive term. *Gender reassignment* denotes an official (and usually legal) change of gender. *Gender identity* is a category of social identity and refers to an individual's identification as male, female, or, occasionally, some category other than male or female. *Gender dysphoria* as a general descriptive term refers to an individual's affective/cognitive discontent with the assigned gender but is more specifically defined when used as a diagnostic category. *Transgender* refers to the broad spectrum of individuals who transiently or persistently identify with a gender different from their natal gender. *Transsexual* denotes an individual who seeks, or has undergone, a social transition from male to female or female to male, which in many, but not all, cases also involves a somatic transition by cross-sex hormone treatment and genital surgery (*sex reassignment surgery*).

Gender dysphoria refers to the distress that may accompany the incongruence between one's experienced or expressed gender and one's assigned gender. Although not all individuals will experience distress as a result of such incongruence, many are distressed if the desired physical interventions by means of hormones and/or surgery are not available. The current term is more descriptive than the previous DSM-IV term *gender identity disorder* and focuses on dysphoria as the clinical problem, not identity per se.

Gender Dysphoria

Diagnostic Criteria

Gender Dysphoria in Children 302.6 (F64.2)

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least six of the following (one of which must be Criterion A1):

1. A strong desire to be of the other gender or an insistence that one is the other gender (or some alternative gender different from one's assigned gender).
2. In boys (assigned gender), a strong preference for cross-dressing or simulating female attire; or in girls (assigned gender), a strong preference for wearing only typical masculine clothing and a strong resistance to the wearing of typical feminine clothing.
3. A strong preference for cross-gender roles in make-believe play or fantasy play.
4. A strong preference for the toys, games, or activities stereotypically used or engaged in by the other gender.
5. A strong preference for playmates of the other gender.
6. In boys (assigned gender), a strong rejection of typically masculine toys, games, and activities and a strong avoidance of rough-and-tumble play; or in girls (assigned gender), a strong rejection of typically feminine toys, games, and activities.
7. A strong dislike of one's sexual anatomy.
8. A strong desire for the primary and/or secondary sex characteristics that match one's experienced gender.

B. The condition is associated with clinically significant distress or impairment in social, school, or other important areas of functioning.

Specify if:

With a disorder of sex development (e.g., a congenital adrenogenital disorder such as 255.2 [E25.0] congenital adrenal hyperplasia or 259.50 [E34.50] androgen insensitivity syndrome).

Coding note: Code the disorder of sex development as well as gender dysphoria.

Gender Dysphoria in Adolescents and Adults 302.85 (F64.1)

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least two of the following:

1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics).
2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics).
3. A strong desire for the primary and/or secondary sex characteristics of the other gender.
4. A strong desire to be of the other gender (or some alternative gender different from one's assigned gender).
5. A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender).
6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender).

B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:

With a disorder of sex development (e.g., a congenital adrenogenital disorder such as 255.2 [E25.0] congenital adrenal hyperplasia or 259.50 [E34.50] androgen insensitivity syndrome).

Coding note: Code the disorder of sex development as well as gender dysphoria.

Specify if:

Posttransition: The individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one cross-sex medical procedure or treatment regimen—namely, regular cross-sex hormone treatment or gender reassignment surgery confirming the desired gender (e.g., penectomy, vaginoplasty in a natal male; mastectomy or phalloplasty in a natal female).

Specifiers

The posttransition specifier may be used in the context of continuing treatment procedures that serve to support the new gender assignment.

Diagnostic Features

Individuals with gender dysphoria have a marked incongruence between the gender they have been assigned to (usually at birth, referred to as *natal gender*) and their experienced/expressed gender. This discrepancy is the core component of the diagnosis. There must also be evidence of distress about this incongruence. Experienced gender may include alternative gender identities beyond binary stereotypes. Consequently, the distress is not limited to a desire to simply be of the other gender, but may include a desire to be of an alternative gender, provided that it differs from the individual's assigned gender.

Gender dysphoria manifests itself differently in different age groups. Prepubertal natal girls with gender dysphoria may express the wish to be a boy, assert they are a boy, or assert they will grow up to be a man. They prefer boys' clothing and hairstyles, are often perceived by strangers as boys, and may ask to be called by a boy's name. Usually, they display intense negative reactions to parental attempts to have them wear dresses or other feminine attire. Some may refuse to attend school or social events where such clothes are required. These girls may demonstrate marked cross-gender identification in role-playing, dreams, and fantasies. Contact sports, rough-and-tumble play, traditional boyhood games, and boys as playmates are most often preferred. They show little interest in stereotypically feminine toys (e.g., dolls) or activities (e.g., feminine dress-up or role-play). Occasionally, they refuse to urinate in a sitting position. Some natal girls may express a desire to have a penis or claim to have a penis or that they will grow one when older. They may also state that they do not want to develop breasts or menstruate.

Prepubertal natal boys with gender dysphoria may express the wish to be a girl or assert they are a girl or that they will grow up to be a woman. They have a preference for dressing in girls' or women's clothes or may improvise clothing from available materials (e.g., using towels, aprons, and scarves for long hair or skirts). These children may role-play female figures (e.g., playing "mother") and often are intensely interested in female fantasy figures. Traditional feminine activities, stereotypical games, and pastimes (e.g., "playing house"; drawing feminine pictures; watching television or videos of favorite female characters) are most often preferred. Stereotypical female-type dolls (e.g., Barbie) are often favorite toys, and girls are their preferred playmates. They avoid rough-and-tumble play and competitive sports and have little interest in stereotypically masculine toys (e.g., cars, trucks). Some may pretend not to have a penis and insist on sitting to urinate. More

rarely, they may state that they find their penis or testes disgusting, that they wish them removed, or that they have, or wish to have, a vagina.

In young adolescents with gender dysphoria, clinical features may resemble those of children or adults with the condition, depending on developmental level. As secondary sex characteristics of young adolescents are not yet fully developed, these individuals may not state dislike of them, but they are concerned about imminent physical changes.

In adults with gender dysphoria, the discrepancy between experienced gender and physical sex characteristics is often, but not always, accompanied by a desire to be rid of primary and/or secondary sex characteristics and/or a strong desire to acquire some primary and/or secondary sex characteristics of the other gender. To varying degrees, adults with gender dysphoria may adopt the behavior, clothing, and mannerisms of the experienced gender. They feel uncomfortable being regarded by others, or functioning in society, as members of their assigned gender. Some adults may have a strong desire to be of a different gender and treated as such, and they may have an inner certainty to feel and respond as the experienced gender without seeking medical treatment to alter body characteristics. They may find other ways to resolve the incongruence between experienced/expressed and assigned gender by partially living in the desired role or by adopting a gender role neither conventionally male nor conventionally female.

Associated Features Supporting Diagnosis

When visible signs of puberty develop, natal boys may shave their legs at the first signs of hair growth. They sometimes bind their genitals to make erections less visible. Girls may bind their breasts, walk with a stoop, or use loose sweaters to make breasts less visible. Increasingly, adolescents request, or may obtain without medical prescription and supervision, hormonal suppressors ("blockers") of gonadal steroids (e.g., gonadotropin-releasing hormone [GnRH] analog, spironolactone). Clinically referred adolescents often want hormone treatment and many also wish for gender reassignment surgery. Adolescents living in an accepting environment may openly express the desire to be and be treated as the experienced gender and dress partly or completely as the experienced gender, have a hairstyle typical of the experienced gender, preferentially seek friendships with peers of the other gender, and/or adopt a new first name consistent with the experienced gender. Older adolescents, when sexually active, usually do not show or allow partners to touch their sexual organs. For adults with an aversion toward their genitals, sexual activity is constrained by the preference that their genitals not be seen or touched by their partners. Some adults may seek hormone treatment (sometimes without medical prescription and supervision) and gender reassignment surgery. Others are satisfied with either hormone treatment or surgery alone.

Adolescents and adults with gender dysphoria before gender reassignment are at increased risk for suicidal ideation, suicide attempts, and suicides. After gender reassignment, adjustment may vary, and suicide risk may persist.

Prevalence

For natal adult males, prevalence ranges from 0.005% to 0.014%, and for natal females, from 0.002% to 0.003%. Since not all adults seeking hormone treatment and surgical reassignment attend specialty clinics, these rates are likely modest underestimates. Sex differences in rate of referrals to specialty clinics vary by age group. In children, sex ratios of natal boys to girls range from 2:1 to 4.5:1. In adolescents, the sex ratio is close to parity; in adults, the sex ratio favors natal males, with ratios ranging from 1:1 to 6.1:1. In two countries, the sex ratio appears to favor natal females (Japan: 2.2:1; Poland: 3.4:1).

Development and Course

Because expression of gender dysphoria varies with age, there are separate criteria sets for children versus adolescents and adults. Criteria for children are defined in a more con-

crete, behavioral manner than those for adolescents and adults. Many of the core criteria draw on well-documented behavioral gender differences between typically developing boys and girls. Young children are less likely than older children, adolescents, and adults to express extreme and persistent anatomic dysphoria. In adolescents and adults, incongruence between experienced gender and somatic sex is a central feature of the diagnosis. Factors related to distress and impairment also vary with age. A very young child may show signs of distress (e.g., intense crying) only when parents tell the child that he or she is "really" not a member of the other gender but only "desires" to be. Distress may not be manifest in social environments supportive of the child's desire to live in the role of the other gender and may emerge only if the desire is interfered with. In adolescents and adults, distress may manifest because of strong incongruence between experienced gender and somatic sex. Such distress may, however, be mitigated by supportive environments and knowledge that biomedical treatments exist to reduce incongruence. Impairment (e.g., school refusal, development of depression, anxiety, and substance abuse) may be a consequence of gender dysphoria.

Gender dysphoria without a disorder of sex development. For clinic-referred children, onset of cross-gender behaviors is usually between ages 2 and 4 years. This corresponds to the developmental time period in which most typically developing children begin expressing gendered behaviors and interests. For some preschool-age children, both pervasive cross-gender behaviors and the expressed desire to be the other gender may be present, or, more rarely, labeling oneself as a member of the other gender may occur. In some cases, the expressed desire to be the other gender appears later, usually at entry into elementary school. A small minority of children express discomfort with their sexual anatomy or will state the desire to have a sexual anatomy corresponding to the experienced gender ("anatomic dysphoria"). Expressions of anatomic dysphoria become more common as children with gender dysphoria approach and anticipate puberty.

Rates of persistence of gender dysphoria from childhood into adolescence or adulthood vary. In natal males, persistence has ranged from 2.2% to 30%. In natal females, persistence has ranged from 12% to 50%. Persistence of gender dysphoria is modestly correlated with dimensional measures of severity ascertained at the time of a childhood baseline assessment. In one sample of natal males, lower socioeconomic background was also modestly correlated with persistence. It is unclear if particular therapeutic approaches to gender dysphoria in children are related to rates of long-term persistence. Extant follow-up samples consisted of children receiving no formal therapeutic intervention or receiving therapeutic interventions of various types, ranging from active efforts to reduce gender dysphoria to a more neutral, "watchful waiting" approach. It is unclear if children "encouraged" or supported to live socially in the desired gender will show higher rates of persistence, since such children have not yet been followed longitudinally in a systematic manner. For both natal male and female children showing persistence, almost all are sexually attracted to individuals of their natal sex. For natal male children whose gender dysphoria does not persist, the majority are *androphilic* (sexually attracted to males) and often self-identify as gay or homosexual (ranging from 63% to 100%). In natal female children whose gender dysphoria does not persist, the percentage who are *gynephilic* (sexually attracted to females) and self-identify as lesbian is lower (ranging from 32% to 50%).

In both adolescent and adult natal males, there are two broad trajectories for development of gender dysphoria: early onset and late onset. *Early-onset gender dysphoria* starts in childhood and continues into adolescence and adulthood; or, there is an intermittent period in which the gender dysphoria desists and these individuals self-identify as gay or homosexual, followed by recurrence of gender dysphoria. *Late-onset gender dysphoria* occurs around puberty or much later in life. Some of these individuals report having had a desire to be of the other gender in childhood that was not expressed verbally to others. Others do not recall any signs of childhood gender dysphoria. For adolescent males with late-onset gender dysphoria, parents often report surprise because they did not see signs of gender