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 prognostic marker for increased 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. Individuals with heart failure, stroke, or renal failure who have central sleep apnea 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. Events are often associated with arousal, but arousals are not required for the diagnosis. Central sleep apnea observed at high altitude occurs after ascent to high altitude, generally at least 2,500 meters above sea level. Central and obstructive sleep apneas may coexist; a diagnosis of central sleep apnea hypopnea requires that central events be > 50% of the total number of respiratory events.

Alterations in neuromuscular control of breathing can occur in association with medications or substances, which can cause or exacerbate impairments of respiratory rhythm and ventilation. Individuals taking medications with these effects may 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

Individuals with central sleep apnea hypopneas may present with sleepiness or insomnia. They may have 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 terminated obstructive events may be observed during sleep.

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, S3 heart sound, lung crackles, and lower-extremity edema, may be present.

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 < 45%, the prevalence has been reported to range from 15% to 44%. The gender ratio for prevalence in North America, Europe,

and Australia is even more highly skewed toward men than for obstructive sleep apnea hypopnea. Prevalence increases with age, and most individuals with the disorder are older than 60 years. Cheyne-Stokes breathing occurs in approximately 20% of individuals with acute stroke as assessed in Barcelona and Toronto. Central sleep apnea comorbid with opioid use occurs in approximately 24% of individuals taking opioids chronically for nonmalignant pain and similarly in individuals receiving methadone maintenance therapy as seen in several high-income countries. Higher opioid doses are associated with greater severity, especially at morphine-equivalent daily dosages > 200 mg. In children assessed in France and Canada, the prevalence ranges from 4% to 6%.

Development and Course

Polysomnography parameters for diagnosing central sleep apnea are different for children than for adults and comprise any of the following: 1) cessation of airflow and respiratory effort for more than 20 seconds, two breath cycles that are associated with an arousal from sleep, or > 3% oxygen desaturation; or 2) two breath cycles that are associated with bradycardia.

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 sex. 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. In children, central sleep apnea can be found in

individuals with congenital abnormalities, particularly Arnold-Chiari malformation, or comorbid medical conditions such as gastroesophageal reflux. Rarely, central sleep apnea resulting from a congenital condition may not manifest until adulthood (e.g., Arnold-Chiari malformation and congenital central hypoventilation).

Diagnostic Markers

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 with the number of central apneas and hypopneas > 50% of the total number of apneas and hypopneas. 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 central respiratory events are > 50% of the total number of respiratory events.

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. For example, central sleep apnea due to 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 breathing-related sleep 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.

Relationship to International Classification of Sleep Disorders

The *International Classification of Sleep Disorders*, 3rd Edition (ICSD-3), includes eight subtypes of central sleep apnea (central sleep apnea with Cheyne-Stokes breathing, central apnea due to a medical disorder without Cheyne-Stokes breathing, central sleep apnea due to high-altitude periodic breathing, central sleep apnea due to a medication or substance, primary central sleep apnea, primary central sleep apnea of infancy, primary central sleep apnea of prematurity, and treatment-emergent central sleep apnea). As in DSM-5, most of these diagnoses require a frequency of 5 or more central events per hour of sleep. In addition, ICSD-3 criteria also require the presence of signs or symptoms (e.g., complaints of insomnia or daytime sleepiness). Central events must constitute at least 50% of the total number of apneas and hypopneas. Primary central sleep apnea of infancy and primary central sleep apnea of prematurity have their own distinct criteria sets that differ from adult forms of central sleep apnea.

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:

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

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.

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.

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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

Subtypes of sleep-related hypoventilation include the following:

- *Idiopathic hypoventilation*, also referred to as *idiopathic central alveolar hypoventilation*, is characterized by reduction of tidal volume and elevated CO_2 during sleep, in the absence of any identifiable comorbidity that would account for the hypoventilation.
- *Congenital central alveolar hypoventilation* is a rare disorder associated with mutation of the gene *PHOX2B*. It typically manifests at birth.
- *Comorbid sleep-related hypoventilation* is due to one of numerous potential comorbidities, including pulmonary disease (e.g., chronic obstructive pulmonary disease [COPD]), chest wall abnormalities (e.g., kyphoscoliosis), neuromuscular disease (e.g., amyotrophic lateral sclerosis), and obesity (referred to as obesity hypoventilation), as well as use of medications or substances, especially opioids.

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

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 a 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 COPD, neuromuscular disorders, or obesity) is more common.

The prevalence of comorbid sleep-related hypoventilation due to obesity in the general population is estimated to be approximately 0.14%–0.6% based on national obesity rates and prevalence of obstructive sleep apnea across several countries. Increasing rates of obesity are associated with increasing prevalence of comorbid sleep-related hypoventilation

due to obesity. In individuals referred to a sleep clinic who have a body mass index > 35 kg/m^2, prevalence may be as high as 42%.

Development and Course

Idiopathic sleep-related hypoventilation is thought to be a slowly progressive disorder of respiratory impairment. When sleep-related hypoventilation 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.

Risk and Prognostic Factors

Environmental. Ventilatory drive can be reduced in individuals who are 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,