Non–Rapid Eye Movement Sleep and Overlap Parasomnias

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ABSTRACT

Purpose of Review: This article reviews the spectrum of non–rapid eye movement (non-REM) sleep parasomnias, including sleepwalking, confusional arousals, and sleep terrors, which represent the range of phenotypic disorders of arousal from non-REM sleep that occurs in children and adults.

Recent Findings: The *International Classification of Sleep Disorders, Third Edition* (*ICSD-3*) classifies parasomnias according to the sleep stage they emerge from: REM, non-REM, or other. Demographics, clinical features, and diagnosis of non-REM parasomnias are reviewed in this article, and an up-to-date synopsis of guidelines for management strategies to assist in the treatment of these sleep disorders is provided.

Summary: The non-REM parasomnias are most common in children and adolescents but may persist into adulthood. They can be distinguishable from REM parasomnias and nocturnal epilepsies, and, importantly, may lead to injury. Additionally, other parasomnias in this spectrum include sleep-related eating disorder and sexsomnia. Overlap parasomnia disorder includes one or more manifestations of a non-REM parasomnia seen in combination with REM sleep behavior disorder, representing an apparent erosion of the normally distinct stages of non-REM and REM sleep. A similar yet much more extreme dissociation of states underlies agrypnia excitata and status dissociatus, which represent rare, severe dissociations between non-REM, REM, and wake states resulting clinically in oneiric behaviors and severe derangement of normal polysomnographic wake and sleep stage characteristics. Management of non-REM and overlap parasomnias and state dissociation disorders include ensuring bedroom safety and prescription of clonazepam or hypnosis, in select cases, although in children and adolescents with noninjurious behaviors, non-REM parasomnias are often age-limited developmental disorders, which may ultimately remit by adulthood, and, in these cases, counseling and education alone may suffice. Timely and accurate recognition of the non-REM and overlap parasomnias is crucial to limiting potential patient injury.

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INTRODUCTION

Parasomnias are characterized by abnormal nocturnal behaviors, experiences, and autonomic responses emanating from sleep.[1] Parasomnias are categorized according to the sleep stage they emerge from as rapid eye movement (REM) sleep parasomnias, non-REM sleep parasomnias, or state-independent parasomnias (which are classified as "other" in the *International Classification of Sleep Disorders, Third Edition* [*ICSD-3*]) (**Table 6-1**).[1] The key common clinical characteristics of non-REM parasomnias are recurrence of episodes of incomplete awakening from sleep and amnesia. These episodes can have variable clinical presentations of disruptive abnormal behavior, such as ambulation, eating, and talking during sleep. If

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KEY POINTS

- Parasomnias are categorized according to the sleep stage they emerge from as rapid eye movement sleep parasomnias, non–rapid eye movement sleep parasomnias, or other (state-independent) parasomnias.
- Non–rapid eye movement parasomnias occur mostly during slow-wave sleep (sleep stage N3) but can also arise from sleep stage N2.
- Any factor increasing the propensity for sleep fragmentation (eg, pain, restless legs syndrome symptoms and periodic limb movements, obstructive sleep apnea events, or extrinsic stimuli such as loud noises) can lead to partial cortical arousal with impaired consciousness.

TABLE 6-1 Classification of Parasomnias[a,b]

▶ **Non-Rapid Eye Movement Sleep Parasomnias**
Confusional arousals
Sleepwalking (somnambulism)
Sleep terrors
Sleep-related eating disorder
Sexsomnia[c]
▶ **Other Parasomnias**
Exploding head syndrome
Sleep-related hallucinations
Sleep enuresis
Parasomnias due to a medical disorder
Parasomnias due to a medication or substance
Parasomnia, unspecified
▶ **Isolated Symptoms**
Sleeptalking (somniloquy)
▶ **Parasomnia Overlap Disorders[c]**
Status dissociatus[c]

[a] Data from the American Academy of Sleep Medicine.[1]
[b] Excludes rapid eye movement (REM)–related parasomnias.
[c] Not included in the *International Classification of Sleep Disorders, Third Edition*.

left untreated, the nocturnal episodes can lead to clinical consequences in the patient, such as injuries and distress to the patient's family. The general criteria for disorders of arousal from non-REM sleep are outlined in Table 6-2.[1]

PATHOPHYSIOLOGY OF NON–RAPID EYE MOVEMENT SLEEP PARASOMNIAS

The varying clinical phenotypes of disorders of arousal from non-REM sleep include confusional arousals, sleepwalking, and sleep terrors; all these share the same presumed underlying pathophysiologic mechanism of an incomplete transition from non-REM sleep to the awake state when sleep-wake boundary dyscontrol occurs. Non-REM parasomnias occur mostly during slow-wave sleep (sleep stage N3) but can also arise from sleep stage N2.[2] Several physiologic phenomena can precipitate the occurrence of these parasomnias by impairing complete cortical arousal out of the sleep state. Any factor increasing the propensity for sleep fragmentation (eg, pain, restless legs syndrome [RLS] symptoms and periodic limb movements, obstructive sleep apnea [OSA] events, or extrinsic stimuli such as loud noises) can lead to partial cortical arousal with impaired consciousness.[3]

Disorders of arousal may be exacerbated by conditions that promote the homeostatic sleep drive, such as sleep deprivation and sedating medications,

TABLE 6-2 General Diagnostic Criteria for Disorders of Arousal[a]

A. Recurrent episodes of incomplete awakening from sleep
B. Lack of or inappropriate response to intervention or redirection during episodes
C. Limited or no cognition or dream imagery
D. Partial or complete amnesia for the event
E. Nocturnal disturbance is not explained by other sleep, psychiatric, or medical disorder or medication/substance use

[a] Data from the American Academy of Sleep Medicine.[1]

by increasing the threshold for arousal. These conditions hinder the normal sleep-wake transition by enhancing sleep inertia and thus lead to emergence of the abnormal nocturnal behavior.

Pressman[4] has eloquently conceptualized a model for the non-REM disorders of arousal. A patient with an intrinsic *predisposition* is *primed* by influences such as sedating medications that hinder normal cortical arousal. Consequently, *precipitating* factors such as OSA or environmental disruption (eg, noise) trigger a disordered arousal from non-REM sleep (this is analogous to, yet distinct from, the 3P model for the etiology of insomnia disorder discussed in the article ''Chronic Insomnia Disorder'' by Alon Y. Avidan, MD, MPH, FAAN, and David N. Neubauer, MD,[5] in this issue of *Continuum*).

Non-REM parasomnia behaviors are manifested as arousal associated with disorientation, amnestic behavior, and confusion. The individual becomes ensnared in a state between non-REM and wakefulness due to disintegration of discrete boundaries between sleep and wake states. The physiologic responses are reminiscent of primordial instinctive behavioral manifestations, such as locomotion, aggression, and feeding, in conjunction with amnestic behavior during these nocturnal episodes.[1] The higher prevalence of non-REM parasomnias in the pediatric population also suggests that developmental immaturity of sleep-wake boundary regulation is an additional vulnerability factor that occurs at younger ages.[1]

In addition to the environmental and metabolic factors discussed, genetic elements have been suggested. Studies have demonstrated a high prevalence of human leukocyte antigen (HLA) DQB1*05:01 and HLA DQB1*04 alleles in various non-REM parasomnias.[6,7] An autosomal dominant trait for sleepwalking at chromosome 20 has also been identified.[8] Factors and conditions associated with the arousal parasomnias are listed in **Table 6-3**.

CONFUSIONAL AROUSALS

Confusional arousals are partial awakenings from slow-wave sleep, also known as sleep drunkenness and Elpenor syndrome. The individual typically sits up in a disoriented state and has some automatic behavior, such as mumbling, low-intensity vocalizations, confused motoric activity without

TABLE 6-3 Factors and Conditions Associated With Arousal Parasomnias

▶ **Predisposing Factors**
Genetic factors
Human leukocyte antigen (HLA) DQB1*05 and HLA DQB1*04 alleles
Chromosome 20q12-q13.12 locus
Maturational factors
Ambulating disorders
Restless legs syndrome (for sleepwalking)
▶ **Priming/Precipitating Factors**
Enhancing slow-wave sleep
Sleep deprivation
Circadian misalignment
Impairing cortical arousal
Central nervous system suppressant drugs
Increasing sleep fragmentation
Extrinsic stimuli
Periodic limb movements
Obstructive sleep apnea
Medical disorders such as gastroesophageal reflux disease
Psychiatric disorders and stress

KEY POINT

■ Conditions that exacerbate disorders of arousal include those that promote the homeostatic sleep drive, such as sleep deprivation and sedating medications, by increasing the threshold for arousal.

KEY POINTS

- Confusional arousals are partial awakenings from slow-wave sleep. The individual typically sits up in a disoriented state and has some automatic behavior, such as mumbling, low-intensity vocalizations, confused motoric activity without ambulation, and sympathetic hyperactivity.
- Sleepwalking is the disorder of arousal manifesting with prominent ambulatory behavior.

ambulation, and sympathetic hyperactivity. Confusional arousals are more common in pediatric populations, the prevalence being up to 17%,[9] while in adults, the prevalence is reported to be only 3% to 4%.[10] The episode is typically brief in duration, lasting for a few minutes, and associated with diminished or altered responsiveness to external stimuli. Occasionally, the event might be prolonged, particularly with sedative hypnotic use.[11,12] Partial or complete amnesia is noted, with an absence or only vague recollection of the episode afterward. According to *ICSD-3*, several criteria should be met for the diagnosis, as outlined in **Table 6-4**.[1]

TABLE 6-4 Diagnostic Criteria for Confusional Arousal[a]

A. The disorder fulfills general criteria for non–rapid eye movement sleep disorders of arousal
B. The episodes consist of patient demonstrating confused behavior after arousal while in bed
C. Absence of terror or ambulation out of bed

[a] Data from the American Academy of Sleep Medicine.[1]

SLEEPWALKING

Sleepwalking (somnambulism) is the disorder of arousal manifesting with prominent ambulatory behavior.[1] A large 2015 prospective study revealed the overall pediatric prevalence (ages 2.5 to 13 years) of sleepwalking to be 29.1%, with the peak observed at age 10.[13] The prevalence increased to 47.4% for children with one parent with a history of sleepwalking and up to 61.5% for children with both parents having a history of sleepwalking, supportive of a significant hereditary influence.[13] The prevalence of sleepwalking is decreased in adults, seen in only 1% to 4%,[1,13] although a 2014 study proposed that noninjurious sleepwalking is actually 12%, much higher than previously recognized.[14]

The nocturnal episodes can range from aimless wandering to complex, protracted, inappropriate behaviors, such as urinating in the closet, driving an automobile, or leaving the house unclothed in extreme weather conditions.[1] During an episode, sleepwalkers typically do not respond to attempts at redirection. Forceful restraining is not advised unless a high risk for injury exists. Occasionally, unintentional self-injurious actions, such as walking off a balcony or operating a motor vehicle, can result in grave consequences.[15] Sleepwalking tends to occur in the first half of the night, akin to the other non-REM disorders of arousal, and is related to the greater predominance of slow-wave sleep (sleep stage N3) in the first few hours of sleep. The *ICSD-3* diagnostic criteria for sleepwalking are listed in **Table 6-5**.

In adults, sleepwalking is frequently associated with other sleep disorders, such as RLS and OSA, as well as with use of sedative hypnotic medications,

TABLE 6-5 Diagnostic Criteria for Sleepwalking[a]

A. The disorder fulfills general criteria for non–rapid eye movement sleep disorders of arousal
B. Arousals are associated with ambulation and other complex behaviors out of bed

[a] Data from the American Academy of Sleep Medicine.[1]

in particular, the commonly prescribed benzodiazepine receptor agonists. Other than the priming and precipitating conditions previously mentioned, other medical conditions such as vitiligo, hyperthyroidism, migraines, febrile illness, head injury, encephalitis, stroke, and chronic pain syndrome have also been implicated.[1,16] In addition to the benzodiazepine receptor agonists,[11] a wide variety of other medication types have been implicated as provoking influences for sleepwalking, including antidepressants (amitriptyline, bupropion, paroxetine, mirtazapine), antipsychotics (quetiapine, olanzapine), antihypertensives (propranolol, metoprolol), antiepileptic drugs (topiramate), antiasthma agents (montelukast), and antibiotics (fluoroquinolones).[1,12]

A common and clinically relevant scenario is zolpidem-induced sleepwalking, among other amnestic behaviors during sleep, such as sleep-related eating disorder, often associated with the predisposing factor of underlying RLS. Since RLS frequently mimics insomnia,[1] the use of hypnotic drugs in patients with RLS is unfortunately common and may lead to sleepwalking and other related amnestic behaviors during sleep.[12] Thus, caution may be indicated when a sedative hypnotic is given to patients predisposed to ambulation due to RLS and motor restlessness or with underlying cognitive impairments, especially those with memory and executive dysfunction that may disinhibit amnestic behaviors and the primitive instinct of locomotion; in these settings, sleepwalking and other amnestic behaviors may emerge as complications of hypnotic therapy.[11,12]

SLEEP TERRORS

Sleep terrors (also known as night terrors or *pavor nocturnus*) are a dramatic disorder of arousal that start with a piercing scream at the onset of an abrupt arousal with autonomic hyperactivity and behavioral manifestation of intense fear. The prevalence of sleep terrors in children varies widely, from 14.7% to 56%.[1,13] In adults, the prevalence is reported as much lower at 2.2%,[1,11] with a relatively constant rate of 2.3% to 2.6% in those 15 to 64 years of age, decreasing to 1% in those older than 65 years of age.[1]

Sleep terrors consist of episodes of intense fright accompanied by loud crying or screaming in which the patient appears terrified and inconsolable. Increased autonomic activity results in tachypnea, tachycardia, mydriasis, diaphoresis, and increased muscle tone.[1] Patients are generally amnestic for episodes of sleep terror, although occasionally in adults, partial amnesia might be noted with vague recollection of a fragment of apparent dream mentation associated with the experience, such as a description of the ceiling collapsing or a fire in the bedroom.[12] Typically, the behaviors are noninjurious but can cause significant parental distress and sleep disruption (**Case 6-1**). Attempts to console the patient can lead to paradoxical increase in aggression.[12] The diagnostic criteria for diagnosis of sleep terrors are listed in **Table 6-6**.[1]

CLINICAL EVALUATION OF NON–RAPID EYE MOVEMENT DISORDERS OF AROUSAL

Comprehensive historical accounts of witnessed events obtained from the patient and a collateral historian, especially the parents in children or a bed partner in adults, is crucial for the diagnosis of parasomnia disorders. The patient's signs during an event further aid in supporting the suspected diagnosis (eg, in a patient with night terrors, the patient may exhibit tachycardia, palpitations, and diaphoresis,

KEY POINTS

- Sleep terrors consist of episodes of intense fright accompanied by loud crying or screaming in which the patient appears terrified and inconsolable. Increased autonomic activity results in tachypnea, tachycardia, mydriasis, diaphoresis, and increased muscle tone.
- Comprehensive historical accounts of witnessed events obtained from the patient and a collateral historian, especially the parents in children or a bed partner in adults, is crucial for diagnosis of parasomnia disorders.

Case 6-1

A 5-year-old girl presented with her parents, who described distressing nightly behaviors that had been occurring over the past year. After going to sleep at about 8:00 PM, she would awaken with a scream at about 11:00 PM seemingly confused and very difficult to console. Attempts to calm her only resulted in increased agitation. During an episode, the child would sweat profusely and breathe rapidly, and her heart raced. Her mother felt that during these episodes the girl was ''possessed by a demon.'' She recently contacted emergency services as she was convinced the child was having a seizure. These events lasted approximately 15 minutes, and then the girl fell back asleep. In the morning, she had no recollection of events. The child's napping schedule had recently changed as she had started kindergarten, resulting in much shorter naps. She had a normal medical history. Her examination was normal.

The patient was diagnosed with sleep terrors, and her parents were reassured that this condition did not represent a neurologic emergency. Efforts were made with the child's school to allow for a longer nap, which led to resolution of the episodes. At 1-year follow-up, the sleep terrors had not recurred.

Comment. This case demonstrates several clinical aspects typical of sleep terrors, including age-related onset during childhood, high parental concern, nighttime sleep disturbance, and association with a stressor such as change in school setting and daytime napping behaviors. In this case, liberalizing the patient's daytime napping led to decreased sleep homeostatic drive at night and led to resolution of the child's sleep terror events.

which help to distinguish the diagnosis from other disorders of arousal such as sleepwalking). In cases in which details are not clear, video-EEG polysomnography can be performed to assist in the diagnosis.

TABLE 6-6 Diagnostic Criteria for Sleep Terrors[a]

A. The disorder fulfills general criteria for non–rapid eye movement sleep disorders of arousal
B. The arousal is characterized by sudden fright manifested by terrifying scream/ vocalization at the onset
C. Events comprising intense fear and signs of autonomic arousal, mydriasis, tachycardia, tachypnea, and diaphoresis

[a] Data from the American Academy of Sleep Medicine.[1]

DIFFERENTIAL DIAGNOSIS OF NON–RAPID EYE MOVEMENT PARASOMNIAS

The non-REM disorders of arousal should be distinguished from other sleep-related disorders with potential similar clinical presentation, which include REM sleep behavior disorder (RBD), sleep-related epilepsy, sleep-related dissociative disorder, alcohol- and drug-related behavioral manifestations during sleep, OSA, and psychogenic spells or malingering.

RBD may be differentiated from non-REM disorders of arousal by several distinctive features, including complex dream enactment behaviors, which parallel described dream mentation and often involve defense against attack or aggression, and its more frequent occurrence in the second half of the night. Video-polysomnography can help

differentiate these disorders, sometimes directly by capturing actual events but also by assessing for the loss of skeletal muscle atonia (as measured by EMG) during REM sleep, which is supportive of the alternative diagnosis of RBD. For more information on RBD, refer to the article ''Rapid Eye Movement Sleep Behavior Disorder and Other Rapid Eye Movement Sleep Parasomnias'' by Birgit Högl, MD, and Alex Iranzo, MD,[17] in this issue of *Continuum*. Sleep-related epilepsy is exhibited by stereotypical repetitive behavior with bicycling, rocking, or running leg movements or, less often, by episodic nocturnal wandering episodes. In such cases, a full EEG montage should be conducted simultaneously with polysomnography to delineate the nature of these events. A history of significant psychosocial pathology, including sexual abuse, should raise concern for a possible diagnosis of a dissociative disorder. Aggravating factors, such as RLS and OSA, should also be carefully screened for and addressed, since effective treatment of these sleep comorbidities may reduce the propensity that provoke arousals from non-REM sleep, thereby decreasing the occurrence of non-REM disorders of arousal. Clinical characteristics of various parasomnias are listed in **Table 6-7**, and their polysomnographic findings are listed in **Table 6-8**.

POLYSOMNOGRAPHIC EVALUATION OF PARASOMNIAS

The American Academy of Sleep Medicine (AASM) has published practice guidelines for the evaluation of parasomnias.[18] According to the AASM, comprehensive in-laboratory video-polysomnography is indicated if the parasomnias are:

- Atypical or unusual in terms of age, onset, duration, or specific behavior
- Frequent in occurrence, (more than 2 or 3 times a week)
- Potentially injurious
- Potentially originating from epileptogenic activity, if prior evaluation has been inconclusive

These practice parameters further recommend use of expanded EEG and EMG channels with good-quality video.[18]

For pediatric cases, the AASM suggests performing comprehensive video-polysomnography, with extended EEG and EMG montages if OSA is suspected or parasomnia-related arousals are violent.[19] The purpose of such an evaluation is to identify a reversible sleep disorder for which treatment could lead to resolution of the parasomnia and prevention of injury. Because of their intermittent nature, nocturnal episodes might not be recorded during a single-night study, but features such as non-REM sleep instability, epileptiform abnormalities, and changes in REM sleep atonia can help support a clinical diagnosis. The yield can be increased significantly by the combination of prior sleep deprivation with forced awakening from auditory stimuli, but this approach is only rarely applied in clinical practice and should be pursued only with appropriate oversight, such as driving restriction before and after the study and seizure/injury precautions in the sleep laboratory.[19]

In confusional arousals, sleep terrors, and sleepwalking, a buildup of hypersynchronous delta frequency EEG activity is variably associated with the arousal from sleep or may occur preceding the event. Following arousal, persistent slow cortical activity is variable, evolving into either normal waking background alpha activity or a return to the non-REM sleep state.[12] A segment of a typical polysomnographic tracing of confusional arousal is illustrated in **Figure 6-1**.

KEY POINT

■ For pediatric parasomnias, the American Academy of Sleep Medicine suggests performing comprehensive video-polysomnography, with extended EEG and EMG montages if obstructive sleep apnea is suspected or parasomnia-related arousals are violent.

TABLE 6-7 Distinguishing Clinical Characteristics of Various Parasomnias

Parasomnia	Behavior	Autonomic Symptoms	Amnesia	Provoking Factors	Sex	Timing	Duration
Confusional arousal	Disoriented, simple to complex movements in the bed	Absent	Present	Sleep deprivation with forced awakening	No predominance, but injurious in males	First part of night	Several minutes, rarely prolonged
Sleepwalking	Ambulation, leaving the bed, wandering	Absent	Present	Sleep deprivation with forced awakening, restless legs syndrome	No predominance, but injurious in males	First part of night	Several minutes to prolonged
Sleep terrors	Distraught, agitated, screaming, inconsolable	Present	Present	Sleep deprivation with forced awakening	No predominance, but injurious in males	First part of night	Several minutes
Sleep-related eating disorder	High-calorie, bizarre eating after arousal from sleep	Absent	Present/ variable recall	Sleep deprivation, restless legs syndrome, hypnotic use	Females more than males	Usually first part of night	Several minutes
Sleep enuresis	Loss of bladder control while asleep	Absent	Present	Sleep deprivation, increased fluid intake	Males more than females	Anytime	Seconds to minutes
Sexsomnia	Abnormal sexual behavior during sleep/partial arousal	Absent	Present	Sleep deprivation	Males more than females	Anytime	Minutes
Rapid eye movement (REM) sleep behavior disorder	Dream-enacting movements/ vocalizations	Absent	Variable recall	None	Males more than females	About 2 hours after sleep onset	Seconds to minutes

KEY POINT

- The primary goal of managing parasomnias is to ensure the safety of the patient and cosleeper.

MANAGEMENT OF NON–RAPID EYE MOVEMENT PARASOMNIAS

Various strategies to control non-REM parasomnias are discussed below.

Environmental Safety

The primary goal of managing parasomnias is to ensure the safety of the patient and cosleeper. Environmental modifications (eg, removing sharp or otherwise potentially harmful objects, furniture, and weapons from the bedroom; securing windows and other outlets; using door alarms) may prevent problematic consequences. Careful consideration should be given to addressing any reversible predisposing, priming, or precipitating factors, as discussed in the

TABLE 6-8 Differentiating Polysomnographic Findings of Various Parasomnias

Parasomnia	Sleep Stage	Non–Rapid Eye Movement (REM) Instability	REM Sleep Atonia	Other Features
Confusional arousal	Non-REM	Present	Present	Hypersynchronous EEG delta activity
Sleepwalking	Non-REM	Present	Present	Restless legs syndrome
Sleep terrors	Non-REM	Present	Present	Increased heart rate
Sleep-related eating disorder	Non-REM	Present	Present	Restless legs syndrome, periodic limb movements, rhythmic masticatory muscle activity
Sleep enuresis	Non-REM/REM	Present	Present	
Sexsomnia	Non-REM	Present	Present	
REM sleep behavior disorder	REM	Absent	Absent	Periodic limb movements, irregular heart and respiratory rate

EEG = electroencephalogram.

section on pathophysiology. In particular, treatment of any comorbid sleep disorders, such as OSA and RLS, and removal of offending sedative agents significantly reduce the occurrence of disorders of arousal.[20]

Pharmacotherapy

If the parasomnia behavior persists after treatment of comorbid sleep conditions and removal of offending drugs and precipitating factors, then pharmacologic intervention can be considered. The evidence basis for pharmacotherapy of the parasomnias is extremely sparse and, at times, contradictory. Benzodiazepines and antidepressants are the mainstay of pharmacotherapy, depending on the type of disorder of arousal. Clonazepam is frequently used as a first-line agent to treat non-REM parasomnias of disordered arousal, although other intermediate and long-acting benzodiazepines may also be used. In a series of 69 patients with sleepwalking and sleep terrors treated with clonazepam and other benzodiazepines, 86% of patients showed significant improvement after an average follow-up of 3.5 years with sustained benefit.[21] Various serotonergic antidepressants have also been used for the treatment of non-REM parasomnias, especially for sleep terrors. One report showed a substantial response to imipramine in two patients with sleepwalking and sleep terrors,[22] while other case reports suggested convincing responses to trazodone[23] or paroxetine.[24] Antidepressants may improve sleep terrors by virtue of serotonergic effects on the mesencephalic periaqueductal gray matter.[24]

Behavioral strategies, such as psychotherapy, have also been employed for treatment of non-REM parasomnias with some success.[25] For benign parasomnias such as confusional arousals and sleep terrors in children, parents can be reassured about the generally noninjurious nature of the episodes and informed that events are frequently outgrown.

For persistent episodes of sleep terror in children, anticipatory awakenings

KEY POINTS

- Treatment of any comorbid sleep disorders, such as obstructive sleep apnea and restless legs syndrome, and removal of offending sedative agents significantly reduce the occurrence of disorders of arousal.
- Clonazepam is frequently used as a first-line agent to treat non–rapid eye movement parasomnias of disordered arousal, although other intermediate and long-acting benzodiazepines may also be used.

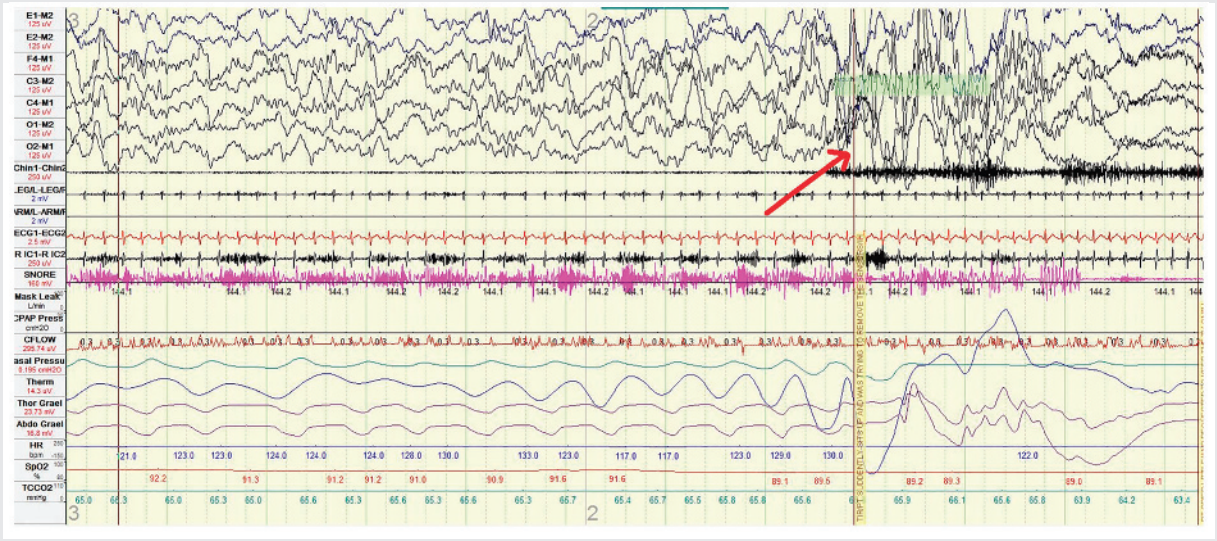

FIGURE 6-1 A 30-second polysomnographic tracing showing an arousal arising from sleep stage N3 (slow-wave sleep) (*red arrow*), showing hypersynchronous slow-wave activity and increase in muscle tone followed by normal wakefulness.

KEY POINTS

- For persistent episodes of sleep terrors in children, anticipatory awakenings 15 to 20 minutes before the typical time of occurrence has been shown to be highly effective in aborting the episodes.
- Sleep-related eating disorder is a condition characterized by recurrent episodes of typically amnestic binge eating of high-calorie food and sometimes bizarre pica-type ingestions after partial arousal from non–rapid eye movement sleep.

15 to 20 minutes before the typical time of occurrence has been shown to be highly effective in aborting the episodes.[25] Hypnotherapy has also been employed, with variable benefit from 27% to 87% reported in different case series for non-REM parasomnias.[26]

SLEEP-RELATED EATING DISORDER

Sleep-related eating disorder is a condition characterized by recurrent episodes of typically amnestic binge eating of high-calorie food and sometimes bizarre pica-type ingestions after partial arousal from non-REM sleep. The community prevalence of sleep-related eating disorder is currently not well characterized. Schenck and colleagues[27] found the prevalence of sleep-related eating disorder was 0.5% in a sleep clinic referral population. In college students, the occurrence was 4.6%,[28] and sleep-related eating disorder was found to affect 3.4% of patients in a depression clinic.[29,30] Sleep-related eating disorder has a 60% to 83% female preponderance, consistent with eating disorders and incongruent with other disorders of arousal.[1,30]

The episodes of sleep-related eating in sleep-related eating disorder are not driven by hunger but seem to comprise involuntary compulsive eating after partial arousal from sleep. Episodes consist of ingestion of peculiar combinations of items; carbohydrate-rich foods; or inedible or toxic materials such as raw or frozen meat, pet food, or buttered cigarettes. Sleep-related eating disorder can lead to multiple adverse consequences, such as weight gain, injuries sustained from careless handling of food items during an episode, precipitation or exacerbation of diabetes mellitus, hypercholesterolemia, or dental caries. The frequency of episodes ranges from a few times a week to multiple times per night.[1] The criteria for diagnosis of sleep-related eating disorder are listed in **Table 6-9**.[1]

The pathophysiologic mechanism of sleep-related eating disorder is not established, although it has been proposed that several heterogeneous factors may play a causative role. Most

researchers agree that sleep-related eating disorder is a variant of sleepwalking since it is characterized by partial or incomplete arousals from sleep, involves ambulation culminating in feeding behavior, and is affected by the usual predisposing influences for non-REM disorders of arousal, especially RLS, as well as other precipitating conditions as previously discussed.[28] Patients with sleep-related eating disorder share many similarities with somnambulists, including that both conditions originate from non-REM sleep and that 60% of patients with sleep-related eating disorder have a history of past or concurrent sleepwalking (**Case 6-2**).[1,27,30] Wakeful nocturnal eating is a common nonmotor manifestation of RLS; thus, misclassification of RLS as insomnia and resulting treatment with sedative hypnotic medication, especially zolpidem, can lead to the emergence of amnestic sleep-related eating disorder.[11,12,31]

Zolpidem is the most common agent that induces sleep-related eating disorder, but a wide range of other psychotropic medications, including benzodiazepines, mirtazapine, quetiapine, lithium carbonate, and anticholinergic drugs, have also been reported.[1] Several other factors have been associated with sleep-related eating disorder, including alcohol and other substance use, cessation of smoking, acute stress, onset of narcolepsy, autoimmune hepatitis, and encephalitis.[1]

Sleep-related eating disorders should be distinguished from other conditions such as night eating syndrome and the nocturnal occurrence of other eating disorders, such as bulimia nervosa, binge eating disorder, binge/purge type anorexia nervosa, and Kleine-Levin syndrome. Night eating syndrome is characterized by excessive eating at night before bedtime or after awakening from sleep but, unlike sleep-related eating disorder, is associated with fully preserved awareness and intentional eating. In contrast to daytime eating disorders, compensatory behavior such as induced vomiting or laxative use is not noticed in sleep-related eating disorder, although other eating disorders can occur concurrently. Kleine-Levin syndrome is a complex disorder of recurrent periodic hypersomnia, cognitive impairment, hypersexuality, and hyperphagia during wakefulness

KEY POINTS

- Most researchers agree that sleep-related eating disorder is a variant of sleepwalking since it is characterized by partial or incomplete arousals from sleep, involves ambulation culminating in feeding behavior, and is affected by the usual predisposing influences for non–rapid eye movement disorders of arousal.
- Night eating syndrome is characterized by excessive eating at night before bedtime or after awakening from sleep but, unlike sleep-related eating disorder, is associated with fully preserved awareness and intentional eating.

TABLE 6-9 Diagnostic Criteria for Sleep-Related Eating Disorder[a]

A. Recurrent episodes of dysfunctional eating occurring after arousal from main sleep period

B. Presence of at least one of the following with recurrent involuntary eating

1. Consumption of peculiar form or combination of food or inedible/toxic substances
2. Sleep-related injurious/potentially injurious behavior noted during food preparation/pursuit
3. Adverse consequences from recurrent nocturnal eating

C. Partial or complete loss of awareness during the episode with subsequent impaired recall

D. Disturbance is not explained by another sleep, mental, or medical disorder or medication/substance use

[a] Data from the American Academy of Sleep Medicine.[1]

KEY POINT

■ Dopamine agonists and topiramate have been used as pharmacotherapy for sleep-related eating disorder.

Case 6-2

A 44-year-old woman presented with amnestic nocturnal eating, which had resulted in a 20 kg (44 lb) weight gain over the previous 6 months. She experienced events involving sleepwalking to the kitchen and eating large portions of chocolate, peanut butter, and crackers. She would often wake up with a distended abdomen and chocolate spread on her fingers. She was found once by her husband, who said that she was ''in a trance.'' These events occurred approximately 4 to 5 times per week. Her diabetes mellitus was poorly controlled, and her dentist found three new dental caries.

These behaviors began after she started receiving zolpidem for ''insomnia.'' She had been reluctant to stop the drug since it was helping her fall asleep at night. However, further careful history revealed that she did not have hypervigilant insomnia, but instead her difficulty falling asleep was related to overwhelming discomfort in her legs compelling her to move her legs and walk at night. Before zolpidem therapy, she would often spend hours awake at night ambulating through the house and sometimes having a small snack.

The patient was diagnosed with sleep-related eating disorder and restless legs syndrome (RLS). Zolpidem was discontinued and pramipexole started, which resolved the difficulty with sleep initiation, and she had no further episodes of sleep-related eating disorder.

Comment. This case is a classic example of insomnia caused by RLS mistreated with zolpidem. She had no recollection of the nocturnal eating episodes with preference for carbohydrate-rich food items, which led to consequences such as poor oral hygiene and hyperglycemia. Thus, it is important to recognize this condition and address it in a timely manner. The treatment of underlying RLS not only improved her insomnia but also controlled the sleep-related eating disorder episodes.

with eventual return to baseline and thus can be easily separated from the symptomatology of sleep-related eating disorder. For more information on Kleine-Levin syndrome, refer to the article ''Narcolepsy and Other Central Hypersomnias'' by Yves Dauvilliers, MD, PhD, and Lucie Barateau, MD,[32] in this issue of *Continuum*.

The goal of treatment in sleep-related eating disorder is to eliminate any precipitating factors, such as hypnotic medications, and to recognize and treat any contributing comorbid sleep disorders, especially RLS. Removal of any offending drug, along with treatment of RLS and OSA, has been shown to resolve many cases of sleep-related eating disorder.[29–31] Dopamine agonists and topiramate have been used as pharmacotherapy for sleep-related eating disorder. In an original case series, Schenck and colleagues[33] showed improvement in 52% of patients (14 of 27) who received dopamine agonist agents. A randomized controlled trial of pramipexole up to 0.36 mg/d showed decrease in nocturnal activity by actigraphy and subjective improvement in sleep.[34] Topiramate has been proposed to exert anorexigenic actions.[29] According to Winkelman,[35] 68% of patients responded to topiramate, with a mean dose of 135 mg/d, but the discontinuation rate was high because of side effects. Schenck and Mahowald[36] also showed good response with topiramate treatment, which was well tolerated over 1.8 years.

SEXSOMNIA

Neurologists should be aware of sexsomnia for several reasons. Neurologists are often consulted for evaluation of unusual behaviors, including sleep-related abnormal sexual behaviors (sexsomnia). Rarely, sexual behavior may arise from nocturnal seizures, which can often be successfully treated, and sexsomnia may be comorbid with neurologic disorders such as Parkinson disease and narcolepsy.

The first classification of sleep-related disorders associated with abnormal sexual behaviors and experiences was published in 2007,[37] with an update in 2015.[38] Sexsomnia and sleep-related eating disorder are considered ''appetitive'' parasomnias, and they can be comorbid in the same patient. Sexsomnia is classified as a subtype of non-REM parasomnia disorders of arousal in *ICSD-3*,[1] with sexual behaviors that emerge during partial arousals from slow-wave (delta or stage N3) sleep, as is typical of the other non-REM parasomnias.

In a large series of 49 patients, sexsomnia was male predominant (75%), with a mean age of onset of 28 years and mean age at presentation of 35 years. A broad range of sexual behaviors was reported, including sexual intercourse/attempted intercourse (49%), fondling the bed partner (40%), agitated/assaultive sexual behaviors (37%), masturbation (23%), sexsomnia with minors (20%), sexual vocalizations (19%), and spontaneous sleep orgasm (4%). Not surprisingly, sexsomnia can lead to adverse legal consequences. The forensic implications of sexsomnia have recently been reviewed.[38] Shift work was a trigger for sexsomnia in one predisposed patient, and selective serotonin reuptake inhibitor (SSRI) therapy for depression was a trigger for sexsomnia in another patient. In four cases of sexsomnia associated with Parkinson disease, onset was noted with the initiation or dose increase of pramipexole therapy. None of the patients had a prior history of parasomnia, sexual disorder, or impulse control disorder. A detailed medication history with the bed partner's assistance is critical in the evaluation of a patient with sexsomnia, along with a detailed history of any parasomnia, sleep-disordered breathing, medical-neurologic-psychiatric problems, or family history.

Treatment data are limited; however, in one series, 86% of patients had control of sexsomnia with bedtime clonazepam, and 100% (4 of 4) of patients with comorbid OSA had resolution with control of OSA on nasal continuous positive airway pressure.

Ten cases of ictal/presumed ictal sexsomnia have been described, demonstrating a striking contrast between the high rate of recall for ictal sexsomnia episodes and the virtually complete amnesia for sexsomnia (parasomnia) episodes in all but two cases. In the 5 of 7 patients with reported treatment data, antiepileptic drug therapy completely suppressed the ictal sleep-related sexual seizures.[38]

PARASOMNIA OVERLAP DISORDER

Parasomnia overlap disorder is a condition with clinical features of both non-REM parasomnias and RBD. While overlap parasomnia disorder is currently classified as a subtype of REM parasomnias,[1] some believe it may be a distinct entity because of several differentiating features, such as occurrence at a younger age and more frequent presentation with non-REM parasomnias compared to REM-related behaviors.[39,40] Overlap parasomnia disorder can also be seen secondary to various disorders such as narcolepsy, multiple sclerosis, brain tumors,

KEY POINTS

- Sexsomnia is classified as a subtype of non–rapid eye movement parasomnia disorders of arousal in the *International Classification of Sleep Disorders, Third Edition*.
- Parasomnia overlap disorder is a condition with clinical features of both non–rapid eye movement sleep parasomnias and rapid eye movement sleep behavior disorder.

KEY POINTS

- Status dissociatus is a state of complete disintegration of wake/non–rapid eye movement/rapid eye movement sleep boundaries that is without identifiable sleep stages and with behavioral and motor manifestations of oneirism (dream-enactment behaviors).
- Agrypnia excitata is an extreme form of status dissociatus, with near-continuous motor and sympathetic hyperactivity, loss of N3 sleep stage (slow-wave) architecture, and dissociation of conventional non–rapid eye movement sleep markers.

rhombencephalitis, brain trauma, spinocerebellar ataxia type 3, psychiatric disorders, substance abuse, and alcohol withdrawal.[1,41] Polysomnographic evaluation demonstrates the presence of non-REM parasomnias and non-REM sleep architecture instability as well as dream enactment behavior in REM sleep with loss of normal REM sleep atonia (showing increased muscle tone during REM sleep).

Status Dissociatus

Status dissociatus is a state of complete disintegration of wake/non-REM/REM sleep boundaries that is without identifiable sleep stages and with behavioral and motor manifestations of oneirism (dream-enactment behaviors). An admixture of various polysomnographic markers of different states with unidentifiable sleep staging is noted, with the patient appearing asleep behaviorally but having complex motor behavior typical of dream enactment. The pathophysiologic basis is considered to be related to γ-aminobutyric acid–mediated (GABA-ergic) thalamolimbic dysfunction.[37] Status dissociatus can be seen acutely in alcohol withdrawal, subacutely in autoimmune encephalitis (associated with anti–*N*-methyl-D-aspartate [NMDA] receptor antibodies and anti–voltage-gated potassium channel complex [VGKC] antibodies),[40,42] and on a chronic basis in α-synuclein neurodegenerative disorders such as Parkinson disease, multiple system atrophy, and dementia with Lewy bodies.

Agrypnia Excitata

Agrypnia excitata is an extreme form of status dissociatus, with near-continuous motor and sympathetic hyperactivity, loss of sleep stage N3 (slow-wave) architecture, and dissociation of conventional non-REM sleep markers such as K complexes and sleep spindles. Agrypnia excitata may be seen in association with alcohol withdrawal, Morvan syndrome, or fatal familial insomnia and other prion diseases.[1] These patients exhibit gestures mimicking semipurposeful tasks in a confused hallucinatory state, termed as *oneiric stupor*, which is the behavioral marker of agrypnia excitata.[40,41]

Careful clinical history with polysomnographic evaluation and diagnostic workup for a possible underlying etiology are warranted. Management includes treating comorbid sleep disorders such as OSA or RLS and optimization of sleep and environmental safety. Clonazepam is the most frequently used agent for this rare parasomnia disorder.[39,40] Alprazolam, temazepam, carbamazepine, and melatonin use have also been reported.[40] For autoimmune etiologies, immunotherapeutic agents such as steroids, IV immunoglobulin (IVIg), and plasma exchange have been used in some cases of status dissociatus associated with autoimmune encephalopathy.[39]

CONCLUSION

Non-REM parasomnias include sleep terrors, confusional arousals, and sleepwalking and are most frequent in children and young adults. Non-REM parasomnias are typically benign in most children; therefore, in most cases, parental counseling, education, and watchful waiting can be undertaken. However, in adults, non-REM parasomnias can be potentially injurious, so counseling and education to ensure a safe bedroom environment should be undertaken in all adult patients, and treatment with behavioral therapies (eg, hypnosis) or pharmacotherapy with clonazepam should be considered in cases with significant injury potential. Sexsomnia is less frequently reported but shares a similar pathophysiology. Rare variants of the non-REM parasomnias include overlap parasomnia disorder, status

dissociatus, and agrypnia excitata, and in these cases, underlying etiologies such as neurodegenerative or autoimmune disorders should be sought. Timely recognition and proper management are warranted in all cases to avoid adverse consequences.

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