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Parasomnias: An Updated Review

Michael J. Howell

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Abstract Parasomnias are abnormal behaviors emanating from or associated with sleep. Sleepwalking and related disorders result from an incomplete dissociation of wakefulness from nonrapid eye movement (NREM) sleep. Conditions that provoke repeated cortical arousals, or promote sleep inertia lead to NREM parasomnias by impairing normal arousal mechanisms. Changes in the cyclic alternating pattern, a biomarker of arousal instability in NREM sleep, are noted in sleepwalking disorders. Sleep-related eating disorder (SRED) is characterized by a disruption of the nocturnal fast with episodes of feeding after an arousal from sleep. SRED is often associated with the use of sedative-hypnotic medications; in particular, the widely prescribed benzodiazepine receptor agonists. Recently, compelling evidence suggests that nocturnal eating may in some cases be a nonmotor manifestation of Restless Legs Syndrome (RLS). rapid eye movement (REM) Sleep Behavior Disorder (RBD) is characterized by a loss of REM paralysis leading to potentially injurious dream enactment. The loss of atonia in RBD often predates the development of Parkinson's disease and other disorders of synuclein pathology. Parasomnia behaviors are related to an activation (in NREM parasomnias) or a disinhibition (in RBD) of central pattern generators (CPGs). Initial management should focus on decreasing the potential for sleep-related injury followed by treating comorbid sleep disorders. Clonazepam and melatonin appear to be effective therapies in RBD, whereas paroxetine has been reported effective in some cases of sleep terrors. At this point, pharmacotherapy for other parasomnias is less certain, and further investigations are necessary.

M. J. Howell (✉)
Department of Neurology, University of Minnesota Medical Center, Sleep Disorders Center, University of Minnesota, Minnesota, MN, USA
e-mail: howel020@umn.edu

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Classification of Parasomnias

Parasomnias are typically classified by the sleep state from which they arise: non-rapid eye movement sleep (NREM) and rapid eye movement sleep (REM) (see Table 1) [1]. Central pattern generators, which are functional groups of neurons, give rise to the stereotyped parasomnia behaviors either through activation (in NREM parasomnias) or disinhibition (in Rapid Eye Movement Sleep Behavior Disorder [RBD]) [2].

NREM parasomnias include: confusional arousals, sleepwalking disorder, and sleep terrors. These behaviors arise when the cortex incompletely arouses from deep NREM sleep, often due to comorbid conditions that provoke repeated arousal or promote sleep inertia. Changes in the cyclic alternating pattern, a biomarker of arousal instability in NREM sleep, are noted in sleepwalking and related disorders [3].

Sleep-related eating disorder (SRED) is currently classified in the *International Classification of Sleep Disorders, 2nd edition* (ICSD-2) under "Other Parasomnia" [1]. However the vast majority of SRED cases emanate from NREM [4], and the complex amnestic behaviors with ambulation are striking similar to sleepwalking [5]. Furthermore, both SRED and sleepwalking are frequently triggered by sedating agents in the setting of underlying motor restlessness [6]. Thus, considering these similarities, SRED will be reviewed immediately after NREM parasomnias.

REM sleep behavior disorder is the most clinically relevant REM parasomnia. The loss of atonia in RBD is due to dysfunction of the REM-related neurons in the pons and frequently predicts the impending onset of neurodegenerative disease

Table 1 Parasomnia classification

	NREM	REM
Disorders	Confusional arousals	REM Sleep Behavior Disorder
	Sleepwalking Sleep terrors*	Isolated sleep paralysis
	Sleep-Related Eating Disorder†	

*Also known as night terrors

† SRED is currently classified under other parasomnia in the *International Classification of Sleep Disorders*, 2nd edition; however, based on evidence presented in this review recent evidence demonstrates that amnestic nocturnal eating is more typical of a nonrapid eye movement parasomnia (NREM)

REM = rapid eye movement

[7]. Isolated sleep paralysis is characterized by a persistence of REM atonia into wakefulness [1]. Parasomnia Overlap Disorder, a combination of sleepwalking and RBD, is common among parasomnia patient populations and currently classified as a variant of RBD [1].

NREM Parasomnias

NREM sleep parasomnias are characterized by abnormal nocturnal behavior, impaired consciousness, and autonomic nervous system activation due to impaired arousal. They typically arise from slow wave (N3) NREM sleep [1]. Distinguishing features include: duration, complexity, and type of behavior, as well as degree of amnesia. Precipitating factors include conditions that result in either sleep fragmentation (noise), increased homeostatic sleep pressure (sedatives, sleep deprivations), or both (obstructive sleep apnea) (see Table 2) [1].

Confusional arousals (CoA) are characterized by disoriented behavior during an arousal from NREM sleep, often with vocalizations and poor recall of events the following day. Although CoA typically lasts less than 5 minutes, episodes can occasionally last an hour. These prolonged episodes most commonly occur in the setting of poly-neuropharmacy, in particular sedative-hypnotics. This behavior is typically benign, however, occasionally the patient can become aggressive and violent [1].

Sleepwalking (SW) is the combination of ambulation with the persistence of impaired consciousness after an arousal from sleep. Patients typically have amnesia and the behaviors are inappropriate, such as placing car keys in the refrigerator or rearranging furniture to nonfunctional locations. Attempting to arouse the patient is often difficult and may paradoxically worsen confusion and disorientation [1]. This is in contrast to the dramatic, violent, but often readily reversible dream enactment behavior of RBD (see "REM Parasomnias" as follows).

SW can become prolonged and/or dangerous. Alarming reports have described leaving the house, automobile driving, and sometimes the discharge of loaded firearms. As with CoA, prolonged SW behaviors have been associated with sedative-hypnotic medications, in particular, the benzodiazepine receptor agonists; however, unlike CoA, SW frequently occurs in the setting of Restless Legs Syndrome (RLS) (see "Pathophysiology" as follows).

Sleep terrors (STs) are episodes of intense fear initiated by a sudden cry or loud scream and accompanied by increased autonomic nervous system activity. Most commonly STs occur in preadolescent children. Parents describe the patient as being inconsolable during events. In adults, STs can involve impulsively bolting out of bed without proper judgment in response to an imminent threatening image or dream fragment [1]. Severe injury or even death may result from leaping out of bed or jumping through a window. STs can last for more than 5 minutes and attempts to abort an episode frequently result in even greater agitation.

Variations of CoA and SW have been described in the ICSD-2. sexsomnia is characterized by recurrent amnestic

Table 2 NREM parasomnias

	CA	SW	ST	SRED
Sleep-state boundary	NREM/Wake	NREM/Wake	NREM/REM	NREM/Wake
Typical Duration*	<1 minute	1-20 minutes	5-20 minutes	5-20 minutes
Ambulation	-	+	−/+	+
Autonomic activation	-	-	+	-
Amnesia	+	+	+	−/+
Associated with RLS	-	+	-	+

* Events are usually more prolonged when associated with sedative hypnotics

CA = confusional arousal; NREM = nonrapid eye movement; REM = rapid eye movement; RLS = Restless Legs Syndrome; ST = sleep terror; SRED = sleep-related eating disorder; SW = sleepwalking

sexual behavior ranging from masturbation to sexual intercourse. This dramatic behavior has resulted in relationship strife with occasional forensic consequences (for more detail see Schenck et al. [8]). Another apparent variation is SRED (see as follows), manifesting with dysfunctional nocturnal eating often leading to weight gain. Interestingly, nocturnal eating is a common nonmotor manifestation of RLS [6, 9], and the misdiagnosis and treatment of RLS as insomnia (with sedative hypnotics) frequently leads to amnestic SRED [6].

Clinical Presentation

Although NREM parasomnias peak in childhood, they are not uncommon in adults with a prevalence range between 1 and 4% [1, 10–12]. NREM parasomnia behaviors occurs with spectrums of duration, autonomic activity, and impaired arousal. CoA are frequently of shorter duration compared to SW or STs. Prolonged (>60 minute) episodes have been associated with sedative-hypnotic medications [13]. In regard to autonomic function, CoA and SW have less activation compared to STs, which are characterized by increased heart rate, tachypnea, diaphoresis, and facial flushing. Although all of the NREM parasomnias have impaired arousal, attempts to wake a patient from an ST often results in a paradoxical increase in agitation. NREM parasomnia patients are at least partially amnestic for the nocturnal behaviors. Children with STs will not recall the dramatic events, which often leads to the bewilderment of concerned parents who witness the experiences [1].

Other sleep disorders are frequently associated with and contribute to NREM parasomnias. Obstructive sleep apnea (OSA) and RLS are the most commonly identified precipitating factors in patients with SW [13–15]. Other conditions that are associated with NREM parasomnias are also characterized by sleep fragmentation and/or increased homeostatic sleep pressure, including shift work, sedatives, environmental sleep disruption, and periodic limb movements (PLMs) [11].

Parasomnias are notoriously common in patients on sedative-hypnotic medications. One group of investigators noted a high frequency of SW and other amnestic complex behaviors among psychiatric patients who took benzodiazepine receptor agonist (BRA) medication [16, 17]. These findings are consistent with other reports of abnormal nocturnal behavior induced by BRAs, in particular zolpidem [13, 17–26]. In the setting of BRA-induced parasomnias, the behaviors are often prolonged and can include amnestic nocturnal eating (SRED), sexual activity (sexsomnia), and sleep driving. These complex amnestic behaviors frequently occur in the setting of central nervous system (CNS) polypharmacy or supratherapeutic doses. Not unexpectedly, there has been an increase in sleep-associated amnestic complex behavior in parallel to the contemporary rise in use of sedative-hypnotic medication [13].

Intriguingly, many cases of BRA-induced SW are noted to have comorbid RLS which could be easily misdiagnosed and treated as insomnia [6, 13]. Then, not surprisingly, BRA, which has a mechanism of action of suppression of memory, along with executive function, unleashes prolonged amnestic ambulating events by disinhibiting hippocampal and frontal lobe function [6, 13, 27].

SW has also been associated with a variety of other medications and medical conditions. Implicated agents have included antidepressants amitriptyline [28], bupropion [29, 30], paroxetine [31], and mirtazapine [32], the mood stabilizer, lithium [33, 34], the antipsychotics quetiapine [35] and olanzapine [36–38], the antihypertensive agent metoprolol [39], the anti-seizure agent topiramate [40], and the antibiotic fluoroquinolone [41]. Medical conditions associated with NREM parasomnias include migraine [42, 43], febrile illness [44], vitiligo [45], hyperthyroidism [46], as well as encephalitis and stroke [1]. These diverse conditions and medications likely induce NREM parasomnias through a final common pathway. The exact mechanism of that pathway has not yet been determined. One interesting possible explanation (i.e., the serotonin hypothesis will be described as follows).

Pathophysiology

SW and related disorders occur when there is an incomplete dissociation of NREM sleep into wakefulness. Two pathological processes may lead to this sleep–wake boundary dysfunction (see Table 3). First, phenomena that deepen sleep and enhance sleep inertia promote NREM parasomnias by impairing otherwise normal arousal mechanisms. Second, conditions that cause repeated cortical arousals lead to NREM parasomnias through sleep fragmentation. These abnormal arousals are often associated with the normal alternating arousal microstructure of NREM sleep, the cyclic alternating pattern (CAP) [3]. The complex amnestic behaviors that characterize these

Table 3 Provoking NREM parasomnias

	Increase sleep fragmentation	Increased sleep inertia	Both
Conditions	Noise	Sleep Deprivation	OSA
	Pain	Circadian Misalignment	Orexin dysfunction (narcolepsy)
	RLS/PLM	Sedative hypnotic medication	

NREM = nonrapid eye movement; OSA = obstructive sleep apnea; RLS/PLM = Restless Legs Syndrome/periodic leg movements

conditions are related to central pattern generators [2]. The isolated activation of these functional groups of motor neurons with a relative paucity of activity in brain regions that control executive function and memory account for the poor judgment and amnesia that characterize NREM parasomnias.

In the normal transition from light NREM sleep to wakefulness, consciousness emerges quickly, typically within seconds. The duration of a normal arousal depends on an intricate combination of variables, including duration of prior wakefulness, current sleep duration, depth of NREM sleep, circadian rhythm phase, effects of sedating or stimulating medications, and multiple genetic and environmental factors. Stimuli of endogenous and exogenous origins activate neurons in the brainstem and the basal forebrain. These regions subsequently promote wakefulness through both direct activation of the cerebral cortex and inhibiting the thalamic reticular neurons, thus blocking spindle oscillations. These alerting phenomena lead to suppression of slow wave activity (SWA) and more predominant fast cortical activity appears compatible with wakefulness [47].

The speed of the conversion from NREM sleep to wakefulness depends on the intensity of SWA. Most arousals into wakefulness arise from lighter stages (N1 or N2) of sleep with minimal SWA. The threshold for which stimulation is required to produce an awakening during light sleep is low. By comparison, the threshold for an awakening from deep NREM sleep (N3), characterized by nearly continuous SWA, is high, and awakenings are typically prolonged [48]. Subsequently, sleep inertia during N3 sleep arousals is strong (subjectively referred to as "sleep drunkenness") and promotes a return to somnolence.

In NREM parasomnias, impaired arousal mechanisms and the persistence of sleep drive result in a failure of the brain to fully transition into wakefulness. Indeed, most SW and related disorders arise out of N3 sleep. Thus sleep-promoting conditions, such as sleep deprivation and sedative-hypnotic medication will lead to NREM parasomnias.

Conversely, disorders that lead to fragmented NREM sleep precipitate SW and other disorders of arousal by increasing arousal frequency. OSA, noise, and orexin dysfunction (cause of sleep instability in narcolepsy) all promote parasomnias by fragmenting NREM sleep. In fact, CoA can be precipitated in the sleep laboratory through sleep deprivation, which promotes SWA, combined with a sudden loud noise (see management as follows) [49].

The chronic intermittent airway collapse in patients with OSA leads to NREM parasomnias through parallel mechanisms, sleep fragmentation, and an increased homeostatic sleep drive [3, 11, 13, 14].

Combinations of predisposing and precipitating factors frequently lead to SW. For example, CNS polypharmacy is often the setting for dangerous behavior, such as sleep driving [13, 50]. Other examples include patients with OSA who are prescribed sedative-hypnotic medication to assist with continuous positive airway pressure compliance. A similar situation, often in patients with RLS, which is misdiagnosed as having insomnia, and is subsequently treated with a BRA. As patients with RLS have a strong subconscious drive to ambulate, it is not unexpected that agents that suppress memory and executive function would lead to amenstic sleepwalking behaviors [6, 13].

Sleep Microarchitecture in NREM Parasomnias and the Cyclic Alternating Pattern

Patients with NREM parasomnias have essentially normal sleep based on commonly reported polysomnography (PSG) variables. In particular, evaluations of sleep macroarchitecture indicated either normal distribution of NREM sleep and its individual sleep stages [51–53] or slightly decreased N2 and higher N3 (slow wave) sleep [54] in these patients.

However, the microstructure of sleep in patients with NREM parasomnias often demonstrates several interesting findings. Commonly there is an increase in arousals, either related to PLMs, respiratory events, or spontaneously [54, 55]. Autonomic activation, as measured by heart rate variability, precedes cortical and behavioral arousals [56]. Furthermore, the density of SWA during the early sleep cycles is relatively decreased compared to controls [3, 57]. However, immediately preceding a confusional arousal, there is frequently an increase in SWA, commonly referred to as hypersynchronous delta (HSD) [54, 58, 59]. The cyclic alternating pattern (CAP), a marker of NREM instability, provides insight into these phenomena [60] (see paragraph below). Immediately post-arousal, typically there is a persistent slowing of brain activity as measured by surface electroencephalography (EEG) [53, 61].

The CAP is an intrinsic oscillation throughout NREM sleep between periods of cortical arousal and quiescence throughout NREM sleep. This oscillation typically occurs every 20 to 40 seconds and provides the scaffolding for normal (such as K complexes and delta bursts) as well as pathological NREM phenomena (confusional arousal and SW events) [62]. Patients who experience sleepwalking and sleep terrors have an increased number of CAP cycles and a higher CAP rate, which is a measure of NREM instability [3, 52, 63]. Furthermore, a subtype of cortical arousal in the CAP (phase A1) is characterized by HSD [62] and the majority of reports indicate SW, STs, and CoA are often preceded by a phase A1 run of HSD, indicating that these events are linked to the CAP [54, 58, 59]. Finally, it has been demonstrated that the CAP may be used as a biomarker for treatment response. In particular, resolution of CAP abnormalities in patients who are being treated for

sleep-disordered breathing (SBD) is associated with a resolution of SW behaviors [60].

The increase in CAP activity noted in parasomnias (increased type A1 arousals and increased CAP rate) indicates underlying NREM instability. Thus abnormal CAP activity is not likely to be the cause of parasomnias, but rather a marker of a sleep destabilizing process. Candidate processes include neuropsychiatric disease, medications, subtle respiratory events, as well as innate genetic factors. In fact, PLMs are also plausibly not directly causal to sleep instability, but instead are a manifestation of unstable CAP [2]. These insights suggest that the treatment of NREM parasomnias should be directed at resolving underlying sleep destabilizing processes and that the CAP changes (decrease in CAP rate and number of A1 events) may be used as a marker of treatment response.

Intracranial monitoring and neuroimaging in NREM parasomnia patients have indicated that the slowing of cortical activity post-arousal is not diffusely distributed and that certain regions may become more activated/wake-like and coexist with regions that are more slow/NREM sleep-like activity. One report captured a confusional arousal in a 20-year man who was undergoing intracerebral EEG monitoring for refractory epilepsy. The cingulate and motor cortices demonstrated an arousal followed by brain waves consistent with wakefulness, whereas in parallel the frontoparietal associative cortices had increased delta activity consistent with deep NREM sleep [64]. These findings were very similar to an SW event that was captured in a 16-year-old man with cranial single photon emission computed tomography. In this case, the parasomnia was characterized by activation (increased regional cerebral blood flow) of motor coordination pathways with a relative paucity of activation in the frontal lobe [65].

Sleep-Related Eating Disorder

Under normal human physiological conditions, nighttime is characterized by a prolonged period of fasting associated with sleep. Energy homeostasis is maintained through the sleep period by alterations in metabolism and appetite modulation. This stands in contrast to fasting during sedentary wakefulness, which demonstrates a progressive hypoglycemia for a 12-h duration [66]. The sleep-related fast is disrupted in SRED, characterized by recurrent episodes of nocturnal eating after an arousal with adverse consequences. The episodes are described as occurring in an involuntary, compulsive, or "out of control manner". Often, patients describe an inability to return to sleep without eating, and in this regard, it resemble other nocturnal compulsions that interfere with sleep, such as RLS. Amnestic SRED, as with SW, is often related to sedative-hypnotic medication use, most commonly zolpidem. These cases are often characterized by prolonged episodes with elaborate and sometimes dangerous food preparation [13, 21, 67–69].

Nomenclature

There is no uniform classification scheme for nighttime eating behaviors. Sleep and eating disorder researchers use divergent, but occasional, overlapping terminology that is perplexing and impedes clinical investigations [5]. The term "nighttime eating" is commonly used by eating disorder investigators to describe both evening hyperphagia (eating after the evening meal, but prior to initial sleep onset), as well as nocturnal eating (eating after an arousal from sleep, but prior to the final morning awakening). The SRED originated as a term to describe amnestic ambulation with eating (sleepwalking-like behavior). However, confusingly, SRED now includes nonamnestic behaviors. Thus, fully conscious, but dysfunctional nocturnal eating is considered SRED, according to the ICSD [1, 5].

For the purpose of this review, nocturnal eating (NE) will encompass all eating (dysfunctional and nondysfunctional) that occurs after an arousal from sleep, but prior to the morning awakening. SRED will be used as defined by current ICSD-2 criteria, meaning dysfunctional nocturnal eating that occurs in an involuntary manner. Importantly, the vast majority of reported SRED cases, and those described in this review are dysfunctional because they are in fact amnestic especially those associated with sedating medications (see Table 4).

Clinical Presentation

SRED is particularly common among patients with other sleep disorders (4-5% prevalence) [6, 16, 70, 71]. The most striking relationship is between SRED and RLS in which both eating and motor symptoms frequently coexist and fluctuate in

Table 4 Definitions and associations

Nocturnal eating (NE)	Eating that occurs after an arousal from sleep prior to final awakening. Includes both dysfunctional (SRED) and nondysfunctional eating
Sleep-related eating disorder (SRED)	Dysfunctional NE often with amnesia and sleepwalking behavior.
Restless Legs Syndrome (RLS)	A state of motor restlessness that interferes with sleep onset and maintenance. Strongly associated with NE and SRED.
Psychophysiological Insomnia (PI)	A state of cognitive hyper-vigilance that interferes with sleep onset and maintenance. Only rarely associated with NE and SRED.

parallel. In a survey of 88 RLS patients who presented to a sleep disorder center, 61% had frequent NE and 36% had SRED [6]. These findings are similar to a survey of 100 RLS patients who demonstrated a 33% prevalence of SRED [71]. Furthermore, the mistreatment of RLS with benzodiazepine receptor agonists frequently induces amnestic SRED. In contrast, dopamingic therapy resolves NE and SRED in parallel with motor restlessness [6, 71] (see "The Relationship between SRED and RLS" as follows).

At night SRED patients consume foods higher in carbohydrates and fats than typical daytime ingestion [4, 69]. Weight gain is commonly reported [1, 68, 69]. The majority of patients describe chronic unrelenting daily symptoms that may persist for decades prior to pursuing treatment [68, 69]. Nearly a quarter of SRED patients will experience greater than 5 episodes of nocturnal food ingestion [4]. The majority (60-83%) of reported SRED cases are female and frequently coexists with daytime eating disorders [4, 68–70].

Amnestic SRED most commonly occurs in the setting of sedative-hypnotic medications, in particular, the benzodiazepine receptor agonists [6, 16, 17, 21, 68]. These unconscious episodes may include nonfood ingestions, such as cigarettes, coffee grounds, or egg shells. Other patients will ingest substances they would otherwise avoid, such as patients with food allergies, diabetes, hyperlipidemia, or when undergoing general anesthesia the next day [69, 72, 73]. Patients may fall asleep with an oral bolus of food, which combined with the circadian decline in salivation places the patient at high risk of dental caries [72]. Finally, food preparation can include using the stove and/or oven in a haphazard manner increasing the risk for fires [69, 72, 73].

SW is commonly reported among patients with SRED. Three series have reported comorbid SW in 48 to 65% of patients with SRED. SW without eating may precede SRED and then once nocturnal eating develops it may become the predominant SW behavior [17, 68, 69].

Pathophysiology

SRED and Benzodiazepine Receptor Agonists

Several early reports noted that amnestic nocturnal eating was associated with sedating psychotropic medications. A 1981 case report described amnestic nocturnal eating after initiating a combination of chlorpromazine, amitriptyline, and methyprylon [74]. Subsequently, SRED has been reportedly induced with triazolam, lithium, olanzapine, risperidone, zopiclone, and zaleplon [16, 37, 72, 75, 76], as well as zolpidem extended-release formulation [77, 78].

The majority of drug cases are related to zolpidem, a benzodiazepine receptor agonist. The first series of zolpidem-associated SRED described 5 middle-aged patients, 2 of whom already had intermittent episodes of conscious nocturnal eating prior to starting zolpidem. Interestingly, all 5 had a history of RLS. Soon after initiating zolpidem, each patient described amnestic nocturnal eating that stopped with discontinuation [21].

Further reports have strengthened the relationship between zolpidem and SRED. In a series of 1235 patients at an outpatient psychiatry clinic, the combination of zolpidem and antidepressants posed the greatest risk for SRED [16]. In another report of 29 sleepwalkers with frequent BRA use, approximately two-thirds of the patients described a sleep-related eating behavior [17]. The vast majority of reports note improvement, if not outright resolution, once the agents were discontinued [20, 21, 79–82].

SRED frequently occurs when patients take supratherapeutic doses of zolpidem [26, 67, 83] in a desperate attempt to initiate sleep. BRAs enhance gamma amino butyric acid (GABA) activity at central GABA-A receptors resulting in hypnotic phenomena [13]. As these agents suppress executive function, it may be that zolpidem by itself does not activate SRED, but instead disinhibits the behavior in a patient population at risk for nocturnal feeding. Patients with RLS who are not on sedatives demonstrate a greater tendency toward wakeful, nonpathological, nocturnal eating [6, 71]. Conversely, when on sedatives, in particularly BRAs, patients with RLS frequently demonstrated amnestic SRED [6, 21, 71, 78]. (see section titled The Relationship between SRED and RLS).

Medication-Induced Amnesia

Impaired consciousness as a defining criterion for SRED has evolved since complete or at least partial unawareness was necessary for diagnosis. In the original series of 32 SRED patients, 84% claimed an impaired recall [68]. In another case series of 23 patients, 91% had incomplete consciousness and/or amnesia for the behavior [69]. Conversely, a subsequent report noted full awareness in all 26 patients after episodes of nocturnal eating in a sleep laboratory [4]. Currently, reduced awareness and subsequent amnesia is not a required diagnostic criterion for SRED in the ICSD-2 [1].

The discrepancy in consciousness among SRED reports may be best explained by the use of sedating medications [4, 84]. The first case reports of amnestic nocturnal eating were associated with sedative psychotropic medications, as well as other parasomnias [72, 74, 85]. Moreover, the majority of patients in the original series were taking hypnotic medication or had a previous history of SW [68]. Conversely, all 26 patients with full consciousness during nocturnal eating episodes in a sleep laboratory were drug free and only 1 had a history of SW [4].

The Relationship between SRED and RLS

In many cases of SRED, nocturnal food ingestion is best characterized as restless eating (i.e., to facilitate sleep). In this regard nocturnal feeding behaviors bear a striking similarity to the motor symptoms of RLS. In fact, reports have described that nocturnal eating is pervasive among RLS patients, including the original description by Ekbom [9] in 1960 [6, 71]. "They often have to get up and walk like a caged bear," to quote 1 of my patients, or "they go into the kitchen and get something to eat" [9]. Further similarities in epidemiology, polysomnographic phenomena, clinical course, and treatment response are reviewed here, which is suggestive of an intimate relationship between nocturnal food ingestion and RLS (see Table 5).

RLS is a disorder affecting approximately 8 to 10% of the population, and thus a common cause of sleep initiation and maintenance failure [1, 86, 87]. Furthermore, although RLS is distinct from, it is commonly confused with psychophysiological insomnia (PI). Thus, it may be expected that many patients with RLS will be mistakenly treated with therapies designed to treat PI, agents such as BRAs.

Table 5 Evidence that NE may often be a non-motor manifestation of RLS and medication-induced SRED is the mistreatment of RLS as PI

1. Nocturnal eating (NE) is pervasive among patients with Restless Leg Syndrome (RLS). In fact it was noted in Ekbom's [9] original 1960 description of RLS.
2. NE in RLS is not merely "killing time" as other disorders of sleep maintenance, such as psychophysiological insomnia (PI), are more likely to have prolonged nighttime awakenings but less likely to break the night time fast
3. Sleep-related eating disorder (SRED) is common in patients with RLS
4. RLS is nearly ubiquitous in cases of SRED. Thus far, every SRED report in which RLS was explicitly considered, RLS was found
5. The compulsive nature of NE is similar in character to the motor manifestations of RLS, and they arise, intensify, and subside in parallel
6. Dopaminergic phenomena on polysomnography (PSG), such as periodic limb movements (PLMs), bruxism, and rhythmic masticatory muscle activity are noted in both SRED and RLS
7. Despite suggestions to the contrary, dopaminergic therapies improve rather than exacerbate NE and SRED
8. In most cases of sedative-induced SRED, the underlying disorder for which the sedative was prescribed was not PI, but instead it was RLS, a condition that is easily confused with PI
9. Based on the finding of frequent NE in RLS, medications such as benzodiazepine receptor agonist (BRA), which suppress executive function, will disinhibit ambulation and eating. Furthermore, the patient will be amnestic for events due to BRA effects on memory
10. The rise of SRED reports parallels the widespread use of BRA
11. SRED is rarely noted when patients with RLS are rigorously excluded from BRA treatment trials

As with SRED, RLS has a higher prevalence in women [1, 86]. In addition, medication-induced SRED is more common in women [67, 83].

Similar to RLS [88], several features of SRED suggest an underlying dopamine dysfunction. First, dopamine mediates impulsive behaviors, such as motor restlessness, smoking, and binge eating [88, 89]. Second, a PSG study of 35 SRED patients demonstrated that 77% had PSG confirmation of wakeful RLS and periodic limb movement during sleep [4]. Third, rhythmic masticatory muscle activity and bruxism, dopaminergic phenomena [4, 90] associated with RLS [91], are commonly seen in SRED [4, 72]. In the original SRED case series, prominent rhythmic masticatory muscle activity was described during NREM sleep and after arousals [72]. Recently, rhythmic masticatory muscle activity was found in 29 of 35 patients diagnosed with SRED during their PSG evaluations [4].

Recently, 2 investigations demonstrated a high prevalence of both SRED and nondysfunctional nocturnal eating in patients with RLS. A community survey of 100 RLS patients revealed a high prevalence of SRED in RLS (33%) compared to normal population controls (1%) [71]. The authors pondered whether the compulsive nocturnal eating was related to an underlying RLS brain pathology or whether nocturnal eating was merely "killing time," as previously suggested [92]. This question was addressed in another study of 130 patients with either RLS or PI who presented to sleep disorders center. This report noted that 61% of RLS patients described either nondysfunctional NE (25%) or SRED (36%). Conversely, only 12% of patients with PI described NE, and no patients met the criteria for SRED. This study suggests that nocturnal eating in RLS is not merely "killing time," as PI patients were more likely to have prolonged (>5 minute) nightly awakenings (93%) compared to patients with RLS (64%) [6].

Intriguingly, the nocturnal feeding behavior of SRED closely resembles the motor activity of RLS, which is characterized by an underlying feeling (often poorly described) of discomfort in the lower extremities that compels the patient to move. Movement relieves the discomfort, and the patient is unable to reintiate sleep until the urge is addressed [93]. In SRED, patients state that after an awakening from sleep, they have a compulsion to eat (often without hunger) that interferes with sleep maintenance. Subsequently, once food is ingested, the feeling abates and sleep may be reinitiated [1, 71, 72, 94].

Compulsive nocturnal eating is not unexpected, as RLS patients often describe other nonmotor nocturnal urges [94]. Recently, 6 cases of nocturnal eating and nocturnal smoking were reported. Five of 6 cases either presented with (or were noted to have) RLS. Patients claimed that they would wake up and be unable to return to sleep without eating and/or smoking. In a follow-up study that investigated the

prevalence of sleep-related smoking, RLS patients demonstrated an increased prevalence (12%) compared to matched controls (2%). Interestingly, among RLS patients with nocturnal smoking, SRED was common (83%), and both phenomena often began simultaneously [94].

It has been debated whether SRED in RLS may be caused by dopaminergics because these agents are known to trigger daytime impulsive behaviors such as gambling [95–99]. However, through the preponderance of evidence, it is suggested that dopamine agents are not the cause of SRED. First, dopamine agents suppress feeding behavior in animal models [100]. Second, a review of the original SRED series noted that dopaminergic therapy resolved the dysfunctional eating in 7 of 8 patients in whom the treatment was attempted [72]. Later, two cases of SRED were noted to resolve with levodopa (in combination with buproprion and trazodone) [101]. Third, in a separate survey of patients with both SRED and RLS, 10 patients reported that nocturnal eating emerged prior to or concomitant with motor restlessness, and none reported that nocturnal eating emerged after the start of dopaminergic therapy. Also, RLS patients with SRED were not significantly more likely to use dopaminergic drugs compared to RLS patients without SRED. In fact, subjects whose nocturnal eating symptoms were under control were more likely to be on these agents than subjects who continued to have nocturnal eating [71]. Fourth, a double-blind treatment trial of pramipexole for SRED demonstrated improved sleep and reduced nighttime activity, and furthermore did not result in increased feeding activity [102]. Fifth, another series monitored therapy outcome in 44 RLS patients previously unexposed to dopaminergics. In this population, the frequency of both NE and SRED diminished by half with dopaminergics. In addition, only 1 patient reported an exacerbation of NE after dopamine agents were initiated, and there were no cases of dopaminergics inducing *de novo* NE. Consistent with other reports, nocturnal eating symptoms demonstrated a clinical response in parallel to motor RLS symptoms [6]. Finally, treatment with dopaminergic agents appears to improve other nonmotor manifestations of RLS that frequently coexist with SRED. In particular, all patients who reported a remission of nocturnal smoking had been treated with dopaminergic agonists [94].

Conceptually, as RLS patients are predisposed for NE, greater than 60% in 1 survey [6], then amnestic SRED would be the expected result when RLS patients are treated with agents that suppress memory, as well as executive function. Thus, it is not a surprise that 80% of RLS patients exposed to sedative-hypnotics had subsequent amnestic SRED or sleepwalking behavior [6]. Although RLS is a condition distinct from PI, it can be easily misdiagnosed and then mistreated as an insomnia related to cognitive hypervigilance. In 2002, the first case series of 5 patients with zolpidem-induced amnestic SRED was reported. Incidentally, all 5 patients were noted to have RLS [21]. Others have commented that RLS appears to be ubiquitous in the setting of zolpidem-induced SRED [103]. In fact, the author of this review is unaware of any zolpidem-induced SRED report in which RLS was explicitly considered, and subsequently was not discovered [6, 13, 21, 78, 79, 83, 103, 104].

Persuasively, zolpidem-induced SRED among patients with PI is rare. Among 25 PI patients treated with either a benzodiazepine or BRA, only 2 reported amnestic behavior, and in neither case did the events persist [6]. These findings are consistent with previous reports in which SRED and SW are rare (1% or less) in zolpidem-treated insomnia patients when RLS had been carefully excluded [27]. Therefore, 1 can conclude that in the absence of motor restlessness, sedative hypnotics are safe agents, and there is minimal risk of SW/SRED behaviors.

REM Parasomnias

REM Sleep Behavior Disorder

Under nonpathological circumstances, REM sleep is characterized by an activated brain state in combination with skeletal muscle paralysis, preventing dream enactment behavior (DEB). In RBD, normal atonia is lost and patients present with a complaint of DEB either by the patients themselves or by the bed partner [1]. The spectrum of DEB varies from small hand movements to violent activities, such as punching, kicking, or leaping out of bed. Examples of various RBD injuries have included: subdural hematoma, shoulder dislocation, cervical fracture, and lacerations severing arteries, tendons, and nerves [105].

Clinical Presentation

Previous reports of RBD prevalence varied, depending on whether a measurement of REM electromyography (EMG) tone by polysomnography was included in the diagnosis. Surveys have revealed that some DEB by clinical history alone is nearly universal. In a study of 1140 college-aged students, 98% acknowledged a history of at least 1 DEB symptom [106]. DEB is particularly common in recently postpartum women [107]. Violent behaviors during sleep are less common, but still notable, with a 2% prevalence identified by a phone survey [108]. Various reports have suggested that the prevalence of RBD appears to be approximately 0.5% [1, 109], with higher frequencies among patients with neurodegenerative disease, narcolepsy, or those taking antidepressant medications [1, 110, 111].

RBD appears to have an age and etiology-related bimodal distribution. Among younger adults (<40 years of age), RBD is most frequently noted with antidepressant medications, or in the setting of narcolepsy. Among older adults, RBD is typically spontaneous, and in the absence of a known toxin or acute CNS lesion presumed to be indicative of an impending synucleinopathy [7].

The majority of spontaneous and Parkinsonian RBD cases are male patients [7, 112]. However, there is evidence to suggest that female patients with RBD are underreported. A recent investigation noted that while the male-to-female ratio was 2:1, in older patients among those <50 years of age the ratio was 1.25:1. The younger cases were more often associated with antidepressant medications and autoimmune conditions, especially in women [113]. In addition, women present with less injurious dream enactment and are therefore less likely to receive medical attention [114]. Furthermore, due to the gender difference in life expectancy, elderly women are less likely to have bed partners than elderly men, and thus less likely to have witnessed parasomnia behaviors [114].

In RBD sleep-related vocalizations may be loud and aggressive (expletives are not uncommon). This is most often discordant from waking personality. In particular, the dream content experienced by patients with RBD is not associated with daytime aggressiveness [115]. In addition, RBD vocalizations need to be distinguished from sleep talking, which is common (during both NREM and REM), and more typical of daytime conversation and does not, in itself, represent pathology.

Some patients adopt extraordinary measures to prevent sleep-related injury (SRI); they may place obstacles to hinder exiting the bed or sleep in a room devoid of furniture. Patients and family members frequently deal with these behaviors for years prior to seeking medical attention.

Intriguingly, RBD may be partially therapeutic for obstructive sleep apnea. Normal REM atonia promotes upper airway collapse, and patients with OSA often deteriorate during REM. Thus, it has been suggested that the excessive EMG activity during REM in RBD may help protect against severe SDB [116]. Recently an investigation demonstrated that the greater the motor activity during REM in patients with RBD, the less severe the obstructive sleep apnea, as measured by apnea-hypopnea index [117].

Ancillary Features of Neurodegeneration

The majority of spontaneously developing RBD cases are related to synuclein CNS pathologies. When fulminate, these conditions include Parkinson's disease (PD), multiple system atrophy, dementia with Lewy bodies, and pure autonomic failure [118, 119]. These disorders are often heralded by SRI and all demonstrate pathological synuclein deposition in the CNS on postmortem evaluation.

Thus, it is expected that patients with RBD demonstrate various motor and cognitive features of Parkinson's disease and other Lewy body disorders. Motor testing reveals that patients with RBD demonstrate abnormalities on the Purdue Pegboard assessment, alternate tap test, and quantitative timed evaluation of standing and walking [120]. Further studies have demonstrated impairments in visuoconstructional skills [121–123], visuospatial learning [121], and color identification [120, 124]. Patients with RBD demonstrate lower scores on the Iowa Gambling Test, a marker of impaired decision-making [125]. Other investigations have revealed impairments in attention and executive function [7, 126].

Comorbid anosmia is frequently noted in cases of spontaneous RBD. Among 3 case series, 56 to 63% of RBD patients had impairments in smell identification, compared with 8 to 17% in age-matched controls [120, 127, 128]. RBD and anosmia, in combination with impaired color identification, places the patient at very high risk of impending PD [124].

Autonomic dysfunction is pervasive in patients with RBD. For example, orthostatic responses are impaired, falling between normal controls and PD patients. These findings are consistent with RBD as a part of an evolving neurodegenerative disorder [129]. Constipation, from enteric neuron pathology, is frequently reported [120], and when present along with impaired color vision, it also predicts progression to PD [130]. Cardiac scintography has demonstrated impaired autonomic innervation to the heart in patients with RBD and has been used to predict Parkinsonian syndrome. In particular, reduced uptake of (123) I-metaiodobenzylguanidine, indicating sympathetic involvement, has been demonstrated in RBD, PD, and dementia with Lewy bodies [131–133], but not in multiple system atrophy [7, 131–133]. These findings suggest that cardiac scintography in RBD may predict the onset of either PD/dementia with Lewy bodies (reduced metaiodobenzylguanidine uptake) or multiple system atrophy (normal metaiodobenzylguanidine uptake).

Pathophysiology

The suppression of motor activity during REM sleep is the cumulative result of multiple, currently poorly understood, pathways that terminate with spinal motor neurons most notably via the magnocellular reticular formation in the medulla [7].

Multiple areas of the brainstem may influence muscle tone during REM sleep. These include pontine REM-on (precoeruleus and sublateral dorsal) and REM-off (ventral

lateral portion of the peri-aquaductal grey matter and lateral pontine tegmentum) nuclei, as well as various related brainstem structures. Dysfunction in these structures, as well as their related neurotransmitters and pathways can result in REM sleep without atonia. [113, 118, 134–137].

Various forebrain circuits may unleash motor behaviors when REM motor activity is not suppressed. These CPGs give rise to stereotyped patterns of behavior such as startling, punching, or jumping (see CPGs and their role in parasomnias below).

Thus, several diverse pathologies can lead to RBD a final common pathway disorder. These pathologies include: synuclein neurodegeneration, non-synuclein neurodegeneration, orexin dysfunction, toxic etiologies, and direct CNS lesions. They all manifest in a loss of behavioral control during REM sleep and the enactment of dream mentation (see Table 6) [7].

Table 6 RBD etiologies

Synuclein neurodegeneration
Parkinson's disease
Dementia with Lewy bodies
Multiple system atrophy
Pure autonomic failure
Nonsynuclein neurodegeneration
Tauopathies
Progressive supranuclear palsy
Guadaloupean Parkinsonism
TAR DNA-Binding Protein 43 pathologies (TDP-43opathies)
Frontaltemporal dementia
Amyotrophic lateral sclerosis
Amyloidopathies
Alzheimer's disease
Trinucleotide repeat disorders
Spinal cerebellar ataxia type 3
Huntington's disease
Sleep state boundary dysfunction
Orexin dysfunction (narcolepsy)
Toxic
Tricyclic antidepressants
Tetracyclic antidepressants
Monoamine oxidase inhibitors
Serotonin-specific reuptake inhibitors
Serotonin-norepinepherine reuptake inhibitors
Acetylcholinesterase inhibitors
Lesions
Stroke (ischemic and hemorrhagic)
Demyelinating disease
Traumatic brain injury

RBD = rapid eye movement (REM) Sleep Behavior Disorder

Synuclein Neurodegenerative Etiologies

The brainstem nuclei that control REM sleep are often involved early in the natural history of synucleinopathies [7]. The premotor interval between the onset of RBD and the parkinsonian triad of resting tremor, bradykinesia, and cogwheel rigidity varies from months to decades [7]. Three case series all demonstrate that approximately 50% of patients convert to a neurological disorder 10 years after the start of RBD symptoms [138–140].

Neuroimaging reveals coincident and progressive dopaminergic abnormalities in RBD. Investigations have found reduced striatal dopamine transporters [141, 142] and dopaminergic innervation [143]. Prospectively, SPECT has demonstrated a serial decline in dopamine transporters consistent with degeneration [144].

By the time motor abnormalities develop in patients with Parkinson's disease, the majority of dopaminergic cells in the substantial nigra (SN) are dysfunctional. Among cases of RBD without parkinsonism SN hyperechogenicity on transcranial ultrasound indicates preclinical neuronal dysfunction [145].

Diffusion-tensor imaging has demonstrated decreased fractional anisotropy (meaning decreased neuronal fiber integrity) in the tegmentum of the midbrain and rostral pons, regions consistent with key areas in the regulation of REM sleep [146].

Non-Synuclein Neurodegenerative Etiologies

RBD has been associated with other neurodegenerative pathologies [7, 147, 148]. Diverse etiologies include cases of tauopathy related parkinsonian syndromes (Progressive supranuclear palsy, Guadaloupean parkinsonism) [149–151], TDP-43opathies (frontotemporal dementia, amyotrophic lateral sclerosis) [7, 152], amyloidopathies (Alzheimer's disease) [7, 153]. RBD has also been associated with some trinucleatide repeat disorders including spinal cerebellar ataxia type 3 (SCA3) [154–157] and Huntington's disease [158]. However, with the notable exception of SCA3, none of these conditions have prevalence rates similar to synuclein disorders. Moreover, these conditions are not typically preceded by RBD but instead develop RBD coincidentally or following other neurological deficits [7].

Orexin Dysfunction

Impaired orexin function can precipitate DEB, with up to 50% of narcolepsy patients also having RBD symptoms [159]. Orexin, a neuropeptide secreted from the lateral hypothalamus promotes state (wake, NREM, REM) stability

and prevents frequent transitioning. When deficient, such as in narcolepsy, REM-wake instability arises with wake-like motor activity in parallel to REM dream mentation [160, 161].

Toxic RBD

Psychoactive medications have long been noted to acutely precipitate or exacerbate DEB. Implicated medication classes include: tricyclic and tetracyclic antidepressants, monoamine oxidase (MAO) inhibitors, serotonin-specific reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and an acetylcholinesterase inhibitor [113, 162, 163]. Clomipramine and venlafaxine, when used to treat cataplexy, have also precipitated or exacerbated DEB [164–166].

While many of these agents are serotonergic the diversity of pharmacological mechanisms confirms that various pathways can lead to RBD. Furthermore, researchers have recently demonstrated two non-serotonergic toxic models of RBD. One group induced RBD with MPTP (toxic to dopaminergic neurons) in the marmoset [137]. The other group used a mouse model to demonstrate that impaired glycine and GABA-A activity triggers DEB [136]. These later findings compliment the therapeutic efficacy of clonazapam in many RBD cases (see section REM Sleep Behavior Disorder Treatment).

Medication induced RBD may in fact be the most prevalent form of RBD especially among the young [113, 163, 167]. It is uncertain whether these medications cause a de-novo induction of RBD or, whether patients would have otherwise developed RBD later [7].

Lesional RBD

Occasionally, reports have emerged of DEB following a focal CNS insult from various vascular, demyelinating, and traumatic etiologies [168–175]. Cranial imaging typically demonstrates pontine tegmentum pathology.

Isolated Sleep Paralysis

Isolated sleep paralysis (ISP) is the preservation of atonia after an arousal from REM sleep. Dream mentation may coexist with wakeful cognition resulting in hypnopompic hallucinations, often with a foreboding sense of terror. As ISP is a dissociated state with REM atonia persisting into wakefulness it is considered a REM parasomnia. ISP episodes usually last seconds and spontaneously resolve or are halted by external auditory or tactile stimulation from a bed partner. Sleep paralysis is part of the diagnostic quatrad of narcolepsy, along with hypnogogic/hypnopompic hallucinations, hypersomnolence, and cataplexy [1].

Sleep paralysis can also occur in the absence of narcolepsy (hence the name *isolated* sleep paralysis), but typically other sleep disorders are eventually discovered. Most commonly, these conditions include: OSA, sleep deprivation, and circadian misalignment [176, 177]. Patients usually describe ISP when supine, possibly indicating underlying airway obstruction [178].

The lifetime prevalence of sleep paralysis, based on a large systematic review, is estimated to be 7.6% of the general population, 28.3% of students, and 31.9% of psychiatric patients [179]. Familial cases suggest that some genetic factors contribute to ISP [1].

Diverse cultures often have similar paranormal or religious interpretations of ISP. Patients, typically without history of a thought disorder, will describe in vivid detail: alien abduction, sexual assault by animals, or demonic possession [180, 181].

Central Pattern Generators and Their Role In Parasomnias

The behaviors that characterize parasomnias span the broad range from inaudible vocalizations to complex behaviors. It has been noted that these automatisms often resemble stereotyped behavior noted in other primates as well as more genetically distant mammalian and reptilian species [182]. In fact nocturnal subconscious behavior frequently resembles “primitive” activity such as: defensive postures, violent gestures, and sexual movement [2, 183]. The presence of similar behaviors among animal groups with distant common ancestors suggests that they arise from shared brain structures, in particular subcortical regions, including the brainstem and spinal cord.

A unifying concept, the CPGs, explains this spectrum of activity. CPGs are functional groups of neurons that give rise to subconscious patterns of motor activity.

CPGs require a certain amount of activation or disinhibition to generate stereotyped or quasi-stereotyped motor activity. This has been elegantly described as the facilitation of a “kinetic melody” [2, 184]. During NREM parasomnias, intrinsic activation of an encoded motor plan occurs during the cortical arousal phase of the CAP (see previously) [2]. Thus, any process, such as sleep apnea, that leads to NREM instability promotes more frequent CPG behavioral activation [185]. External stimuli, such as a sudden noise can also promote activation of CPGs, and in fact this technique is used to clinically induce SW and CoA (see management as follows). Conversely, the loss of REM atonia in RBD leads to a disinhibition of CPGs, and injurious motor activity may emerge.

Furthermore, during NREM parasomnias, CPGs are activated in isolation from other brain structures that are important for normal wakeful behavior. In particular, imaging studies have revealed a paucity of activation in the dorsal lateral frontal cortex and hippocampal structures during NREM sleep [186]. Thus, with sudden arousals, the motor activity of SW (an expression of CPG activation) occurs in parallel with poor executive function and amnesia.

Importantly, by further impairing frontal lobe function, CPG behaviors are amplified in the setting of sedative hypnotic medication. This occurs through enhancement of GABA-A activity and is related to dose and binding affinity [13]. By hindering cortical arousal, sedative-hypnotics impede the conscious, executive "brake" on CPG behavior. Thus, elaborate inappropriate behaviors emerge as brain regions that encode motor behaviors are activated in parallel to frontal lobe inhibition. This is particularly relevant in the setting of pathological predisposed behaviors, such as the urge to ambulate in patients with RLS.

Serotonin Theory of Parasomnias

Although the molecular pathophysiology of NREM parasomnias is poorly understood, there is evidence that serotonergic pathways may be implicated [42, 187]. First, serotonergic agents have been known to induce SW [31, 33, 34, 188] and RBD [162], but conversely, they have been known to effectively treat other parasomnias, most notably ST [189, 190]. Second, serotonin provides activation to motoneurons [191, 192]. Third, this motor activity may be dissociated from consciousness [187, 193]. Fourth, serotonin activity is a plausible link between SBD and parasomnias such as serotonin neurons are activated by hypercapnic acidosis [187, 191, 194]. Fifth, disorders associated with SW, such as migraine [42, 43] and fever [44], are characterized by surges of serotonin [187]. Therefore, it has been suggested that serotonergic neurons, activated by nocturnal respiratory events, may pathologically trigger CPGs resulting in sleep-related motor activity [187]. This is an intriguing hypothesis; however, further research is needed, and any explanation should account for the discrepancy in the treatment between parasomnias.

Alternative Theory of Sleep Terrors

ST, although superficially similar to CoA and SW (in regard to abrupt arousal from slow wave sleep), may nevertheless originate in part from a distinctive neurophysiologic mechanism. [195]. In particular, it has been suggested that instead of an overlap between NREM and wakefulness, as implicated in other NREM parasomnias, ST may represent a disorder of transition between deep NREM sleep (N3) and REM sleep. This theory would explain several unique features of ST (i.e., the high autonomic activity and the apparent vivid mentation, both from REM, combined with very difficult arousability from N3). Furthermore, REM and NREM overlap may also explain the striking preponderance of ST in childhood because they have a greater proportion of both N3 and REM sleep. Intriguingly, the antidepressant medication paroxetine, an agent that can both induce SW [31] and treat ST [189, 190], is a potent REM suppressor [196]. Thus, if ST were due to pathological REM and NREM overlap, it would expected that paroxetine would block these phenomena. Conversely, paroxetine would not be expected to have a therapeutic effect on SW, a wake/NREM phenomena. However, based on the serotonergic effects of paroxetine, it would be expected to potentially worsen SW [187] (see "Serotonin Theory of Parasomnias" previously cited).

General Parasomnia Management

The first steps of parasomnia management include a severity assessment, identifying and treating comorbid sleep disorders, eliminating presumed inducing agents, and maximizing environmental safety. Most CoA and many SW episodes are benign and limited in duration. In these cases, patients may be given reassurance and are advised to avoid sleep deprivation and sedating agents. Situations that deserve more thorough investigation include violent/potentially injurious behavior, nonviolent dangerous behavior (such as leaving the house), dream enactment behavior, or if the parasomnia is associated with symptoms suggestive of another sleep disorder or neuropsychiatric condition [197].

Correctly diagnosing a parasomnia requires a detailed review of the sleep-wake complaints followed by a neuropsychiatric history and examination. A report from a bed partner is particularly helpful because many patients are unable to properly recall the nocturnal events by the time they are discussed with a clinician.

Recurrent, brief DEB occurring in the later half of the sleep period followed by complete alertness and orientation when awakening are features that help to distinguish RBD from other parasomnias. This presentation contrasts with SW, where there is often a lifelong history of prolonged, complex, nonviolent activities emanating from the first half of the sleep period with residual confusion [1].

In cases of suspected RBD, it is also useful to inquire about ancillary synuclein symptoms, such as difficulty with smell and bowel motility. When chronic, otherwise unexplained anosmia and constipation coexist with RBD, they are highly suggestive of an impending synuclein disorder.

Polysomnography

The primary role in the polysomnographic evaluation of parasomnias is to rule out conditions, such as SDB, as a cause of the nocturnal behaviors. The sleep fragmentation of OSA during REM or NREM sleep can lead to DEB or CoA/SW, respectively [55, 198] (see Table 7).

PSG with video monitoring is often helpful in the evaluation of parasomnias, even if abnormal behaviors do not arise during the sleep study [199–202]. Under routine conditions, PSG does not typically demonstrate CoA/SW or DEB. This is due to the intermittent nature of parasomnias, as well as the laboratory effect (foreign environment) decreasing N3 sleep compared to the home sleeping environment [203]. However, even without abnormal behaviors, PSG facilitates diagnosis as CoA/SW patients often demonstrate NREM sleep instability, whereas a lack of REM sleep atonia can help establish a diagnosis of RBD [204].

Sleep deprivation combined with forced awakening increases the likelihood of triggering a NREM parasomnia event during laboratory testing and thus helps facilitate diagnosis. In particular, 1 protocol recommends 25 h of sleep deprivation leading up to a PSG combined with an alarm awakening during slow-wave sleep. Using these methods, investigators reported that they can induce somnambulistic events in 100% of patients with a history of SW compared to only 30% of patients if sleep deprivation is not used. Importantly, no control subject without a history of SW demonstrated somnambulistic events using this combined method of sleep deprivation and forced arousals (a 100% sensitivity) [49].

In addition to NREM instability, CoA/SW PSG recordings often reveal a 10-second long build-up of hypersynchronous delta waves immediately preceding a parasomnia event (see discussion on CAP previously cited). Subsequently, postarousal EEG shows a persistence of slowed cortical activity that either evolves into wakeful EEG activity or returns to NREM sleep [53].

Polysomnography (PSG) is used to characterize SRED with commonly consumed nocturnal food made available at bedside to facilitate eating behavior. Similar to SW, SRED most commonly arises out of NREM sleep. One study documented that 44 of 45 feeding episodes in 26 patients arose from NREM sleep [4].

Polysomnographic criteria for RBD has been developed [205] and refined by the American Academy of Sleep Medicine [201], defining RBD as either sustained elevation of chin EMG activity (>50% of the 30-second epoch) or excessive bursts of transient muscle activity (at least half of all 3-second mini-epochs). Subtle dream enactment often involves only the forearms, and thus EMG monitoring of the upper extremities should be included. In addition, other common findings include a high percentage of N3 and PLMs [206].

Careful review of the PSG video can discern RBD from other motor parasomnias. One recent study blinded investigators to all PSG data except for the video monitoring. What they discovered is that RBD was discernable from other parasomnias based on appearance alone, as the motor activity was more typically repetitive, pseudohallucinatory, and frequently using hand babbling (limb wrist, flexed fingers-like a baby) [207]. Other REM sleep phenomena are often present, including snoring, and penile tumescence in males [208].

Sleep paralysis may be visualized during PSG with persistence of REM atonia, despite a wakeful EEG. After events, patients will frequently describe frightening dream mentation [209].

Table 7 PSG findings

	CA/SW	ST	SRED	RBD	ISP
Behavior	Disorientation, attempts to leave the bed, nondistressed	Screams, distressed, inconsolable	Eating	Dream enactment repetitive movements	Paralysis
Provoking maneuvers	Sleep deprivation with sudden arousal from N3	Sleep deprivation	Sleep deprivation food at bedside	None	Sleep deprivation
Originates	NREM	NREM	NREM	REM	REM
Reversible	-	-	-	+	+
NREM instability	+	+	+	-	-
REM atonia	+	+	+	-	+
					Persists into wakefulness
Other features	RLS, hypersynchronous delta	Increased HR	RLS, PLM, RMMA	Penile erection in males	Frightening dream mentation

CA = confusional arousal; HR = heart rate; ISP = isolated sleep paralysis; NREM = nonrapid eye movement; PLM = ; RBD = REM Sleep Behavior Disorder; REM = rapid eye movement; RLS = Restless Legs Syndrome; RMMA = rhythmic masticatory muscle activity; ST = sleep terror; SRED = sleep-related eating disorder; SW = sleepwalking

Environmental Safety

Environmental safety modification is a critical component in treating parasomnia cases with potential for sleep-related injury. The patient should be advised to remove any bedside object or furniture that could be injurious either to them or to a bed partner. Firearms should be removed from the bedroom and windows locked with curtains drawn to prevent lacerations. Bedroom door alarms are helpful ways to signal others that a sleepwalker is wandering; however, loud auditory stimuli could paradoxically worsen NREM parasomnias [49]. Conversely, a customized bed alarm with voice recording can prevent sleep-related injury in RBD [210] (see "RBD Management" as follows). Patients with a history of violent nocturnal behaviors should not sleep with a bed partner (at least until successful therapy has been achieved).

NREM Parasomnia Treatment

Reversing comorbid conditions characterized by frequent cortical arousal in sleepwalkers often dramatically diminishes nocturnal behaviors. Sixty SW patients were studied with PSG and followed for 1 year. A high number (n=53 patients) were diagnosed as having SDB. The majority of patients had only a mild burden of disease, often not reaching criteria for OSA, but instead upper airway resistance syndrome and did not demonstrate daytime sleepiness. However, the results were striking. Only 3 patients dropped out of the study, whereas of the remaining 50 all reported resolution of SW after treatment (42 reported continuous positive airway pressure, 8 upper airway surgeries). These dramatic results suggest that treatment of even mild, asymptomatic SDB may result in resolution of SW [55].

When SW is associated with sedative-hypnotics, it is of particular importance to reconsider the diagnosis for which the medication was originally prescribed. In these cases, patients may not have insomnia (for which the sedating agent was prescribed) but rather another disorder of sleep initiation such as RLS or a delayed circadian rhythm [6, 13, 21, 72, 78, 79]. Discontinuing offending agents will typical resolve the parasomnia particularly if another underlying condition is identified and treated [6, 13, 72]. Treatments include: dopamine agonists in RLS [211], and evening melatonin/morning light therapy in a delayed circadian rhythm [212]. Conversely in the setting of carefully diagnosed insomnia patients, those in whom other disorders are excluded, BRAs are well tolerated and SW rarely induced [6, 27]. Patients with insomnia can also be successfully treated with cognitive behavioral therapy [213].

Pharmacotherapy

If NREM parasomnia behaviors persist despite resolution of exacerbating disorders and removal of inducing agents pharmacological interventions may be considered. The most commonly prescribed agents include benzodiazepines and antidepressant medications. Efficacy depends upon which parasomnia is being treated. Antidepressants have some efficacy in the treatment of ST, whereas these agents may exacerbate SW. Suggesting that the disorders arise from distinct mechanisms (see alternative theory for ST above).

It is important to recognize that the evidence for all therapies is currently based on a small number of studies, typically case reports and case series. Only rarely have there been controlled clinical investigations and sample size was typically small. Furthermore, much of the evidence is contradictory [214], which is described as follows (see Table 8).

Benzodiazepines

Intermediate and long acting agents in the benzodiazepine class of sedative hypnotics (BZD) are the most commonly reported pharmacological treatments for NREM parasomnias. BZD act by increasing the chloride conductance through GABA-A receptors [215]. The use of BZDs in the

Table 8 Parasomnia treatments

	SW/CA	ST	SRED	RBD	ISP
Strong evidence-based treatments	All parasomnias appear to benefit from treating comorbid sleep disorders, eliminating provoking agents, and modifying the bedroom environment to prevent sleep-related injury				
Moderate* evidence-based treatments	None	None	Pramipexole	Clonazepam, melatonin	None
Weak† evidence-based treatment	None	Paroxetine, anticipatory awakenings	Topiramate	Customized bed alarm	None

*Large case series or small controlled trial without conflicting results

† Case series without conflicting results

CA = confusional arousal; ISP = isolated sleep paralysis; RBD = REM Sleep Behavior Disorder; ST = sleep terror; SRED = sleep-related eating disorder; SW = sleepwalking

treatment of NREM parasomnias is seemingly paradoxical, as other sedative-hypnotics such as benzodiazepine receptor agonists (BRA) can induce amnestic nocturnal behavior [13].

Clonazapem is commonly used as first line pharmacotherapy however studies show conflicting results. In 1996 a series of 170 patients with mixed sleep disorders (69 with SW/ST) treated with benzodiazepines, primarily clonazepam (n=136) and followed for clinical response [216]. The vast majority of all patients (86%) reported good control after an average follow up of 3.5 years. The authors reported that clonazapam efficacy was sustained with low risk of dosage escalation. A separate clinical case series reported on 6 SW patients who were initiated on clonazepam. SW was suppressed in 5 of 6 patients [217]. Conversely, a more recent report claims that clonazepam failed to demonstrate sustained efficacy in 5 SW patients. This investigation carefully excluded even subtle SDB. After 1 year, all patients treated with clonazepam dropped out of the study and reported a persistence of SW [55].

Antidepressant Medication

Agents with strong serotonergic actions, are occasionally effective in the treatment of some NREM parasomnia patients, most commonly ST (see serotonin hypothesis previously cited). One report described 2 patients with a history of ST combined with SW, both of whom failed diazepam therapy, but responded well to imipramine (a tricyclic antidepressant) [218]. Later, a 7-year-old girl with ST failed to respond to imiprimine, however, she had a compelling therapeutic response to trazodone (a phenylpiperazine antidepressant) [219]. In contrast to these successful ST cases, more recently a series of SW patients included 8 patients who were treated with various serotonergic agents and/or benzodiazepine. After a 1-year follow-up, all 8 patients described a persistence of SW [55].

Paroxetine appears to be particularly effective in the treatment of ST. In 1 report, 6 patients had a significant reduction if not outright elimination of ST events. The authors suggested that selective serotonin reuptake inhibitors may be uniquely effective for ST through serotonin effects on terror centers in the midbrain peri-aquaductal grey matter [190]. Conversely, there has been a report of paroxetine inducing SW [31] consistent with the suggestion that SW and ST arise through distinct pathophysiological mechanisms (see alternative theory of ST previously cited). Moreover these findings are in contrast to a dramatic elimination of SW behavior in patients who are effectively treated for SDB (see previously) [55].

Nonpharmacological Therapy

Psychotherapy may be helpful for managing some patients with NREM parasomnias. In 1981, 11 sleepwalkers reported that hypnotherapy was helpful with lasting improvement after 1 year. However, close scrutiny of the blinded, crossover portion of this study reveals no difference between the active and suggestive treatment groups [220]. Later, among 54 NREM parasomnia patients who presented with SRI behavior, 22 were taught self-hypnosis. Of these 22, 14 (64%) reported substantial benefit. However, separate data for SW and ST was not reported [221]. Later, the same investigators noted that 20 of 23 (87%) SW patients who underwent self-hypnosis training described significant improvement after greater than 6 months of follow-up [222]. More recently, however, only 3 of 11 (27%) sleepwalkers treated with physician-administered hypnosis described significant improvement after 18 months [223].

Anticipatory awakening is a commonly used method in childhood NREM parasomnias [197]. This technique involves purposefully arousing the parasomniac just prior to the onset of a typical episode. Sustained positive results in 4 children have been reported; however, there is negligible data in adults [224, 225]. This method appears to be a relatively low-risk therapy.

Sleep-Related Eating Disorder Treatment

The first goal in treating SRED is to eliminate implicated medications and correct comorbid sleep disorders, especially RLS. The majority of patients with drug-induced SRED notice improvement after inducing agents are discontinued [20, 21, 26, 67, 78–82]. Dysfunctional nocturnal eating can often be controlled outright by treating comorbid RLS (see "The Relationship between SRED and RLS" previously described) [6]. In cases of SRED associated with obstructive sleep apnea, continuous positive airway pressure may eliminate both the SDB and the nocturnal eating [72].

In cases without comorbid sleep disorders (or at least unrecognized comorbid sleep disorders), 2 classes of pharmacotherapies have been studied and appear to be potentially effective (i.e., dopaminergics and the antiseizure medication topiramate. However, as with other parasomnias, research on SRED therapy is still in its infancy. The original SRED case series noted that either bedtime levodopa or bromocriptine was effective in eliminating nocturnal eating in 8 patients [226]. Recently, pramipexole, a dopamine agonist, was investigated in a small, double blind, placebo-controlled, crossover trial. Pramipexole was well-tolerated and subjects noted improved sleep and reduced nighttime activity was documented with actigraphy [102]. An open-label trial of topiramate in 4 patients with nocturnal eating

demonstrated positive results. The agent was well-tolerated, repcorts of nocturnal eating were diminished, and weight loss (mean of 11.1 kg) was noted in all 4 individuals during an 8.5-month duration [227]. In another case series, 12 of 17 SRED patients treated with topiramate were treatment responsive. The agent was well-tolerated and for more than 1.8 years there was a mean weight loss of 9.2 kg among the treatment responders [228]. Finally a study of 25 SRED patients on topiramate reported that 17 (68%) of SRED patients were treatment responders. Adverse events were high however, and for more than 12 months, 41% of patients discontinued the medication [229].

REM Parasomnias Treatment

REM Sleep Behavior Disorder Treatment

Parasomnia management in general, but RBD management in particular, should initially focus on patient and bed partner safety by modifying the sleeping environment. Subsequently, the clinician should eliminate aggravating agents, as well as identify and treat comorbid sleep disorders. Most cases of toxic RBD are self-limited after discontinuation of offending medication, and DEB typically resolves if underlying REM-related OSA is treated.

When violent nocturnal behaviors persist, despite these interventions, or in situations with a high probability of injury, pharmacotherapy is appropriate [230]. The most commonly prescribed medications include clonazepam and/or melatonin [7, 231, 232]. The long-term efficacy and safety of these agents in the setting of progressive dementing illnesses is uncertain. Furthermore, based on the absence of large randomized, controlled trials, professional societies have found insufficient evidence to make definitive conclusions in regard to RBD therapy [233]. Instead, a consensus has arisen, based on original reports, case series, and small clinical trials [230].

Clonazepam

Clonazepam has been the most widely prescribed agent for RBD, and approximately 90% of patients initially respond well to low doses (0.5-1.0 mg) administered at bedtime [138, 234]. Clonazepam reduces phasic EMG activity during REM sleep with a minimal effect on tonic muscle activity [235]. The agent also appears to be effective in cases that have progressed to Parkinson's disease [236], as well as narcolepsy cases [159].

Although the majority of patients respond to clonazapam at first, long-term, follow-up studies are mixed. The results range from sustained benefit without dose escalation to others with a high incidence of dose escalation and treatment failure [138, 216, 237–239]. In 1 series, 58% of patients on clonazepam reported clinically significant adverse effects with 50% either stopping the agent or reducing the dose [239]. Clonazapam is particularly problematic in the setting of advanced neurodegenerative disease in which it has a prolonged duration of action that may result in morning sedation, as well as cognitive and gait impairment [210, 240].

Melatonin and Other Pharmacological Therapies

Alternative therapies have been reported, most notably high-dose melatonin (6–15 mg), either in combination with clonazapam or as sole therapy [232, 241–243]. In the setting of neurodegenerative disease, melatonin is a particularly intriguing option as it is only mildly sedating. Melatonin suppresses both phasic and tonic REM motor activity and its effect persists for weeks after the agent is discontinued [7, 232]. Other agents with some limited success include: imipramine, carbamazepine, levodopa, pramipexole, donepezil, sodium oxybate, triazolam, zopiclone, quetiapine, and clozapine [230, 231, 239].

Deep brain stimulation (DBS) treatments for Parkinson's disease have thus far not been therapeutic for comorbid RBD. Three case series of PD patients with RBD undergoing DBS noted improvements in subjective sleep quality and sleep architecture on PSG, however, little to no improvement in DEB or REM atonia [244–246]. These findings were not unexpected, as the current target of DBS, the subthalamic nucleus does not have a known effect on REM sleep. Intriguingly some investigators have started to perform DBS in the pons, near regions that control REM sleep [247].

Refractory RBD and Bed Alarm Therapy

Medication refractory RBD is a daunting and potentially life-threatening condition with limited management options. A patient exiting the bed while acting out a dream is particularly at high-risk of traumatic injury [105].

Intriguingly, the low arousal threshold and rapid transition to alert wakefulness from REM sleep offers a therapeutic window to halt behavior prior to SRI [248, 249]. Despite apparent unconsciousness during REM sleep, the brain is readily responsive to complex auditory sound processing [248, 250]. This contrasts with the high arousal threshold of NREM sleep often demonstrated by the inability to redirect or wake up SW patients (a NREM parasomnia) [49, 197].

A recent study of patients with medication refractory RBD and SRI, demonstrated the usefulness of a customized

bed alarm that delivered a calming message at the onset of DEB. Ideal voices, typically those of family members, were identified, and commands to halt DEB were then recorded. For example, "Peter, you are having a dream, lay back down." Subsequently, when the patient arose during sleep, the command emanated from a bedside speaker on a repeating loop until the patient returned to lying down on the pressure pad. Patients and bed partners described a robust sense of security since starting treatment and no serious SRIs were subsequently noted [210].

ISP Treatment

The vast majority of ISP cases can be successfully treated by correcting any underlying sleep disorder and optimizing the circadian timing and duration of sleep. Patients should also be reassured that ISP does not typically represent an underlying neuropsychiatric condition. In cases in which distressing events persist, serotonergic (REM suppressing) agents appear to have some benefit [251, 252].

Summary

Parasomnias represent abnormal behaviors that arise from sleep. They range from subclinical events only noticed by a wakeful bed partner to violent, potentially life-threatening dream enactment. Their etiology depends on the sleep state from which they arise (NREM or REM sleep). NREM parasomnias are treated by identifying and reversing conditions that lead to a stronger homeostatic sleep drive and/or fragment sleep. Correcting RLS, in particular, may help diminish sleepwalking behaviors in particularly amnestic SRED. RBD with violent dream enactment is often the cardinal feature of Parkinson's disease and related disorders, thus representing a biophysiological marker for early synnculein neurodegeneration. RBD is typically treated with low-dose clonazepam and/or high-dose melatonin.

Required Author Forms Disclosure forms provided by the author are available with the online version of this article.

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