Key sleep neurologic disorders: Narcolepsy, restless legs syndrome/Willis-Ekbom disease, and REM sleep behavior disorder

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Summary

Sleep disorders are frequent comorbidities in neurologic patients. This review focuses on clinical aspects and prognosis of 3 neurologic sleep disorders: narcolepsy, restless legs syndrome/Willis-Ekbom disease (RLS/WED), and REM sleep behavior disorder (RBD). Narcolepsy causes pervasive, enduring excessive daytime sleepiness, adversely affecting patients' daily functioning. RLS/WED is characterized by an uncomfortable urge to move the legs before sleep, often evolving toward augmentation and resulting in daylong bothersome symptoms. RBD causes potentially injurious dream enactment behaviors that often signify future evolution of overt synucleinopathy neurodegeneration in as many as 81% of patients. Timely recognition, referral for polysomnography, and longitudinal follow-up of narcolepsy, RLS/WED, and RBD patients are imperatives for neurologists in providing quality comprehensive patient care.

Sleep disorders are common comorbidities in neurologic patients. The focus of this review is clinical and prognostic aspects of 3 key neurologic sleep disorders: narcolepsy, restless legs syndrome/Willis-Ekbom disease (RLS/WED), and REM sleep behavior disorder (RBD) (table 1).

Narcolepsy and idiopathic hypersomnia

Narcolepsy has an incidence of 0.5–1.37/100,000 and a prevalence between 20 and 56.3/100,000 in the general population and causes enduring excessive daytime sleepiness with a tendency to inadvertently doze and the need to nap, most often requiring treatment with

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Table 1 Summary of clinical features of 3 key sleep neurology disorders: Narcolepsy, restless legs syndrome/Willis-Ekbom disease, and REM sleep behavior disorder

Disorder	General population prevalence, %	Core features	Prognosis	Diagnostic tests	Main treatments
Narcolepsy	0.0002–0.0006	Hypersomnia, cataplexy, hypnogogic hallucinations, sleep paralysis, sleep fragmentation	Lifelong	Polysomnography, multiple sleep latency test, CSF hypocretin (remains investigational currently)	Stimulants, anticataplectic medications (fluoxetine, venlafaxine, sodium oxybate)
Restless legs syndrome/ Willis-Ekbom disease	3–9	Urge to move legs at rest, evening predominance, temporary relief upon movement or getting up to walk	Usually chronic, may remit	None; polysomnography as adjunctive test	Iron replacement, dopamine agonists, gabapentin, tramadol, opiates
REM sleep behavior disorder	0.5–6.8	Dream enactment, typically violent or injurious behaviors (i.e., screaming, shouting, arm flailing, punching, kicking)	Chronic; may remit in antidepressant-associated cases; 50%–81% of idiopathic RBD may later develop PD, MCI, DLB, or MSA	Polysomnography with video recording	Melatonin, clonazepam

Abbreviations: DLB = dementia with Lewy bodies; MCI = mild cognitive impairment; MSA = multiple system atrophy; PD = Parkinson disease; RBD = REM sleep behavior disorder.

lifelong stimulant therapy and anticataplectic agents.[e1,1] Cataplexy, a sudden attack of atonia triggered by emotions, affects 64%–90% of patients with narcolepsy.[e2]

Patients with narcolepsy most often present initially in young adulthood but can manifest symptoms between childhood and the seventh decade. In addition to hypersomnolence and cataplexy, other pentad narcolepsy symptoms include hypnogogic or hypnopompic hallucinations (vivid dreamlike visual imagery at sleep onset or upon awakening), sleep paralysis (intrusion of REM muscle atonia into awakening, with resultant inability to move), and nocturnal sleep fragmentation with resultant sleep maintenance insomnia and poor sleep quality. However, the full pentad is seen in less than half of patients. Motoric instability is also prominent in narcolepsy, manifested by frequent periodic limb movements of sleep with or without waking, subjective restless legs symptoms, REM and non-REM parasomnias, and excessive fragmentary myoclonus.[e2]

Narcolepsy-cataplexy (NC) results from hypothalamic hypocretin deficiency, which has been tightly linked to the HLA DQB1*06:02 gene allele in more than 90% of patients with NC, implying a probable but yet unproven autoimmune pathophysiology that is further supported by associations with seasonal streptococcal and H1N1 infections, as well as H1N1 vaccinations, and genome-wide association findings of T-cell receptor alpha locus polymorphisms.[2,e1,e3–e4] CSF hypocretin is measurably low in approximately 90% of patients with NC but has a considerably lower diagnostic yield in narcolepsy without cataplexy, which is a considerably more heterogeneous disorder.

The mainstay of treatment for narcolepsy is stimulant therapy, with goals of improved alertness and functioning. Medications to improve alertness range from the wake-promoting agents modafanil and armodafanil on the milder end of the potency spectrum (although narcolepsy patients often respond selectively well) to stimulant medications such as methylphenidate or amphetamines such as dextroamphetamine and methamphetamine. Relevant clinical pharmacology of the wake-promoting and stimulant medications is summarized in table 2. Anticataplectic treatments (venlafaxine, selective serotonin reuptake inhibitor antidepressants such as fluoxetine) and sodium oxybate (which has US Food and Drug Administration indications for cataplexy and excessive daytime sleepiness)

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Table 2 Clinical pharmacology of wake-promoting and stimulant medications

	Main mechanism of action	Dosage	Duration of action (t½)	Typical adverse effects	Interactions
Wake-promoting agents					
Modafanil[a]	Unknown	100–400 mg	Intermediate (15 h)	Tremor, jitteriness, palpitations, hypertension, nausea, headache, rash	Oral contraceptives (CYP3A4 induction)
Armodafanil[a]	Unknown	150–250 mg+	Intermediate (15 h)	Tremor, jitteriness, palpitations, hypertension, nausea, headache, rash	Oral contraceptives (CYP3A4 induction)
Traditional stimulants					
Methylphenidate	DNRI	15–60 mg+	Short (2–4 h)	Tremor, jitteriness, palpitations, hypertension	MAOIs, SSRIs, SNRIs, TCAs, buproprion
Methylphenidate sustained-release	DNRI	18–72 mg+	Intermediate (3.5 h)	Tremor, jitteriness, palpitations, hypertension	MAOIs, SSRIs, SNRIs, TCAs, buproprion
Amphetamine/ dextroamphetamine[a]	DNRI	15–60 mg+	Intermediate (9–14 h)	Tremor, jitteriness, palpitations, hypertension, QTc prolongation	MAOIs, SSRIs, SNRIs, TCAs, buproprion
Dextroamphetamine[a]	DNRI	15–60 mg+	Long (10–28 h)	Tremor, jitteriness, palpitations, hypertension, QTc prolongation	MAOIs, SSRIs, SNRIs, TCAs, buproprion
Methamphetamine	DNRI	15–60 mg+	Intermediate (9–15 h)	Tremor, jitteriness, palpitations, hypertension, QTc prolongation	MAOIs, SSRIs, SNRIs, TCAs, buproprion
Nonstimulant analeptic/ anticataplexy drug					
Sodium oxybate[a]	Unknown	4.5–9.0 g	Short (0.5–1h)	Nausea, dizziness, somnolence, enuresis, tremor, sleepwalking	Alcohol, hypnotics (potentiated effects of these drugs)

Abbreviations: CYP3A4 = cytochrome P450 3A4; DNRI = dopamine norepinephrine reuptake inhibitor; FDA = US Food and Drug Administration; MAOI = monoamine oxidase inhibitor; QTc = corrected QT interval; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; t½ = half-life of drug; TCA = tricyclic antidepressant (the potential interaction with all these agents is largely theoretical concern for potentiation of serotonin syndrome); + = may occasionally be effective at higher dosages in selected patients with careful monitoring.
[a] FDA indicated for treatment of narcolepsy in adults over 18 years of age.

are also therapeutic mainstays. Patients with narcolepsy and related hypersomnia conditions should also receive counseling regarding safety concerns, including precaution against driving or operating dangerous machinery or other similarly dangerous activities or hobbies when they are drowsy.

Polysomnography may show a diagnostically shortened REM latency[3] and is important for excluding other primary sleep disorders such as sleep apnea and periodic limb movement

RLS/WED symptoms are seen in about one-third of pregnant women. When symptoms begin during pregnancy, they most frequently resolve during the postpartum state.

disorder. Definitive diagnosis usually requires a multiple sleep latency test (MSLT), which provides an objective measure of sleepiness in the evaluation of narcolepsy and other hypersomnias. An MSLT involves 4 or 5 scheduled daytime nap opportunities, usually at 9:00 and 11:00 AM and 1:00, 3:00, and 5:00 PM. Each nap is interpreted for sleep onset and presence of REM sleep. MSLTs in patients with narcolepsy usually demonstrate a mean sleep latency of less than 8 minutes, with 2 or more sleep-onset REM periods. However, abnormal MSLT findings are not specific for narcolepsy and may also be produced by other sleep disorders such as sleep apnea, circadian misalignment, or sleep deprivation. An MSLT supports a narcolepsy diagnosis when historical features are consistent and imitators have been appropriately excluded.

Narcolepsy is usually an enduring and nonprogressive condition. Unfortunately, due to its somewhat protean manifestations, narcolepsy remains underdiagnosed and diagnostic delays are common. Recent evidence suggests that earlier age of symptom onset and earlier life diagnosis influence the social morbidity of patients with narcolepsy. Narcolepsy patients with symptom onset prior to 30 years of age reportedly had higher educational levels, less frequent unemployment, and better perceived health than those diagnosed after age 30 years.[e5] Comorbid mood and anxiety disorders are also influential in lower perceived quality of life.[e5]
Other central hypersomnias include idiopathic hypersomnia, posttraumatic hypersomnia, and hypersomnia associated with Parkinson disease, myotonic dystrophy, and multiple sclerosis. Treatment with modafanil may be an effective option for sleepiness associated with these neurologic disorders.[4]

Restless legs syndrome/Willis-Ekbom disease

Restless legs syndrome (RLS), also known as Willis-Ekbom disease (WED), affects approximately 3%–9% of the general population and is more frequent in certain medical and neurologic patient populations, including those with chronic renal insufficiency (especially those receiving hemodialysis), pregnancy, multiple sclerosis, epilepsy, Parkinson disease, and myotonic dystrophy.[5,e6–e9] Diagnosis of RLS/WED is based on a thorough clinical history and requires 4 cardinal features of described leg symptoms: 1) an urge to move the legs, with or without uncomfortable leg sensations; 2) temporary relief of that feeling by movement; 3) symptoms solely or predominantly at rest; and 4) nocturnal worsening of symptoms. About 50% of patients with RLS/WED have a family history of the disorder. Symptom quality, location or distribution, temporal occurrence, frequency, and severity are variable. RLS/WED often involves an uncomfortable somatosensory dimension of a creepy-crawly or prickling discomfort below the knees in the shins or calves, although sometimes this occurs more proximally in the thighs or in the arms near the shoulders.

While periodic leg movements of sleep (PLMS) are seen in 80%–90% of patients with RLS/WED, PLMS are not necessary or sufficient for the diagnosis of RLS/WED. PLMS are also frequent as an incidental finding in up to 5%–15% of younger adults and between 45% and 70% of elderly individuals. Periodic limb movement disorder is diagnosed when PLMS appear to cause hypersomnolence in the absence of other causes such as sleep apnea, or when PLMS cause maintenance insomnia with frequent movement-related arousals. RLS/WED, however, remains a clinical diagnosis. While polysomnography is not necessary to diagnose RLS/WED, it may be a helpful adjunct when the clinical history is atypical by demonstrating periodic leg movements of wakefulness (the objective correlate of RLS/WED) or frequent PLMS and movement arousals, and for excluding sleep apnea.

Augmentation involves a worsening of RLS/WED symptoms in temporal expression, severity, and distribution, with increased intensity and frequency, earlier onset, and symptom spread to the trunk and arms. The pathophysiology of augmentation has been postulated to involve diverse, potentially overlapping mechanisms, including genetic susceptibility, dopaminergic hyperstimulation and reduced tuberoinfundibular dopaminergic receptor responsivity, and iron deficiency.[e9] RLS/WED is frequently worsened by deficient iron stores, which may alter dopaminergic neurotransmission.

Nonpharmacologic treatments can be tried, although iron replacement treatment—especially in patients with low normal or reduced ferritin levels—and pharmacologic treatment are the mainstays of RLS/WED management. Iron and pharmacologic treatments for RLS are outlined in table 3. Iron deficiency, or even low normal body iron stores, is thought to worsen or precipitate symptoms. Serum ferritin measurement should be considered (with iron replacement therapy initiated when serum ferritin values are below 50 μg/L), although the evidence for iron replacement in RLS/WED overall remains poor and further controlled trials are needed.[6] Iron therapy can cause gastrointestinal distress or constipation, and ferrous fumarate or gluconate with added vitamin C is often better tolerated than ferrous sulfate. Patients with RLS/WED receiving iron therapy need to be monitored for development of iron overload and hemochromatosis.

Table 3 Clinical pharmacology of treatments for restless legs syndrome/Willis-Ekbom disease

	Main mechanism of action	Dosage	Typical adverse effects	Interactions
Iron replacement				
Ferrous sulfate	Fe	324 mg TID	Nausea, constipation	None
Ferrous fumarate	Fe	200/125 mg TID	Nausea, constipation	None
Carbidopa-levodopa	DA	25/100 mg, 1–2 prn	Nausea, dizziness, sedation, ICD	No significant interactions
Pramipexole[a]	DA	0.125–1.0 mg qhs	Nausea, dizziness, sedation, ICD	No significant interactions
Ropinirole[a]	DA	1–4 mg+ qhs	Nausea, dizziness, sedation, ICD	No significant interactions
Rotigotine[a]	DA	1–4 mg+ qhs	Nausea, dizziness, sedation, ICD	No significant interactions
Gabapentin	A2-delta subunit presynaptic voltage-gated calcium receptor	300–1,200 mg+ qhs	Nausea, dizziness, pedal edema, weight gain	No significant interactions
Gabapentin encarbil[a]	A2-delta subunit presynaptic voltage-gated calcium receptor	600–1,200 mg+ qhs	Nausea, dizziness, pedal edema, weight gain	No significant interactions
Pregabalin	A2-delta subunit presynaptic voltage-gated calcium receptor	100–300 mg+ qhs	Nausea, dizziness, pedal edema, weight gain	No significant interactions
Tramadol	MOR	50–300 mg+ qhs	Nausea, dizziness, rash	No significant interactions
Oxycodone	MOR	5–15 mg	Nausea, dizziness, rash	No significant interactions
Methadone	MOR	5–20 mg	Nausea, dizziness, rash	No significant interactions

Abbreviations: DA = dopamine agonist; FDA = US Food and Drug Administration; Fe = iron replacement; ICD = impulse control disorder; MOR = mu opiate receptor agonist; + = may occasionally be effective at higher dosages in selected patients with careful monitoring.
[a] FDA indicated for treatment of moderate to severe primary restless legs syndrome in adults over 18 years of age.

RLS/WED symptoms are seen in about one-third of pregnant women. When symptoms begin during pregnancy, they most frequently resolve during the postpartum state.[e8]

Dopaminergic agonist medications (e.g., oral pramipexole or ropinirole) or transdermal rotigotine remain first-line therapies, although the adverse effect profile of dopaminergic therapies has led many to instead utilize alpha-2-delta calcium channel ligands (e.g., gabapentin 300–1,200 mg/day, gabapentin encarbil 600–1,200 mg/day, or pregabalin 50–300 mg/day) as initial therapies.[7] Dosing of these symptomatic treatments at least 1 hour prior to bedtime (or the time of habitual symptom onset, whichever is earlier) is usual. When earlier evening symptoms emerge, divided doses may need to be utilized, with precautions concerning drowsiness and other adverse effects. Carbidopa-levodopa may be used when patients with RLS/WED have only intermittent symptoms or for patients with limited financial resources, although nightly use of carbidopa-levodopa may raise the risk of augmentation. For patients who are intolerant or resistant to the dopaminergic drugs and gabapentin, other alternatives include clonazepam and tramadol. Treatment-refractory patients or those with severe augmentation may require opiate treatment with oxycodone 5–15 mg/day or methadone 5–20 mg/day.

Most patients with RLS/WED respond favorably to initial treatment, which controls about 70%–80% of patients.[e10] RLS/WED patients without frequent PLMS may have a more favorable treatment response.[e10] However, patients with greater RLS/WED symptom severity, particularly the elderly, have substantially poorer sleep quality and quality of life.[e11] Unfortunately, despite initial efficacy of near 70% with short-acting oral dopamine agonists, following long-term administration between 20% and 75% of patients develop features of augmentation, with approximately 8% developing augmentation annually over the initial 8 years of treatment.[8,e12] Augmentation appears to be less frequent with rotigotine treatment.[9,e13] Augmentation has been associated with more frequent, uncomfortable, and longer duration RLS/WED symptoms.[e12] Additionally, up to 17% of RLS/WED patients treated with dopamine agonists develop impulse control disorders (ICDs) such as pathologic gambling, shopping, punding, or related ICD behaviors requiring drug discontinuation.[10]

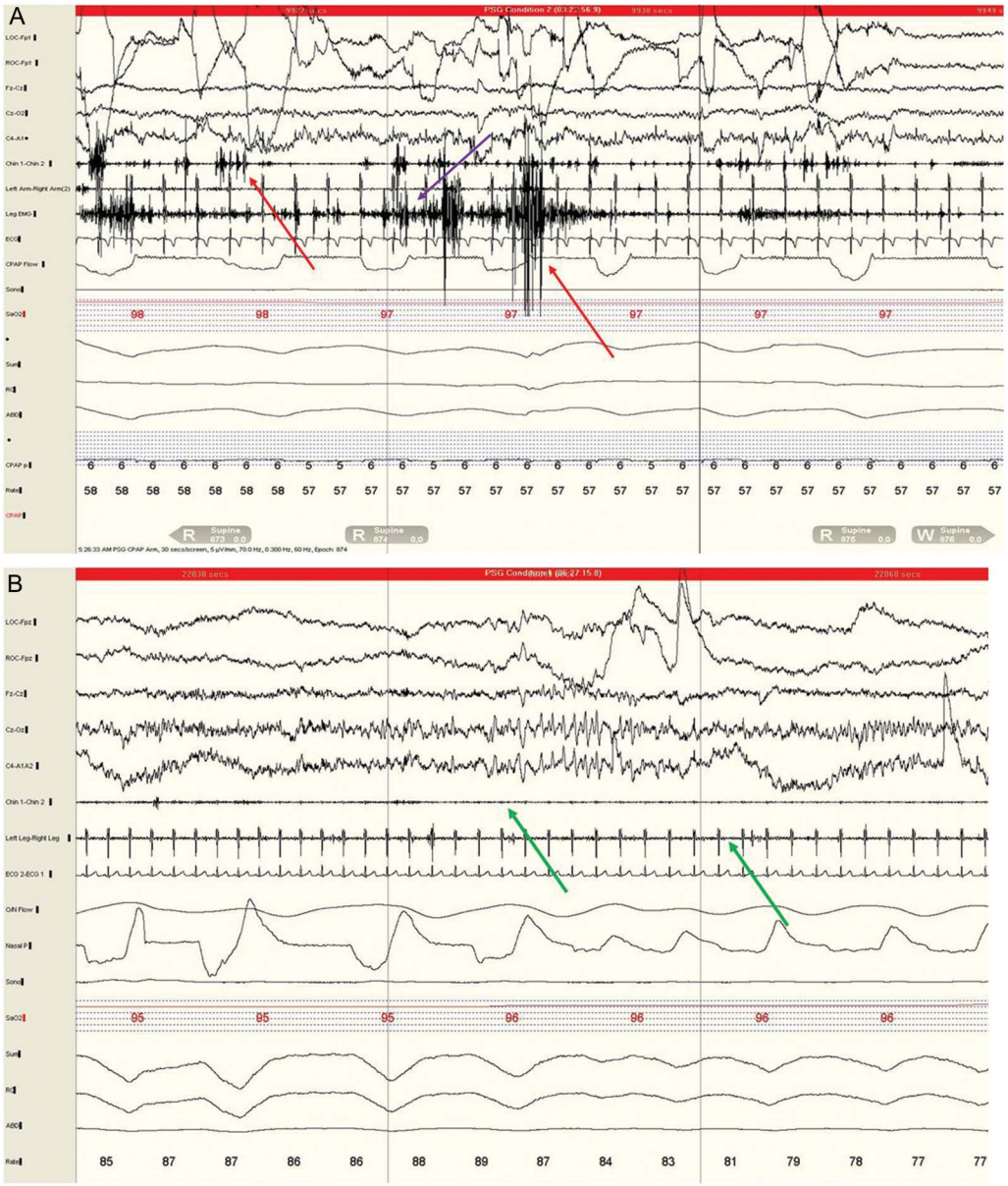
RLS/WED and PLMS may also be associated with hypertension and cardiovascular adverse events, although confirmation of a causative association is lacking and awaiting definitive longitudinal prospective cohort studies. A recent large cross-sectional study suggested that women who have frequent RLS/WED symptoms (15 or more days per month) have an elevated risk of hypertension.[e14] RLS/WED symptoms may be associated with worsened cardiovascular outcomes in patients with chronic renal insufficiency. In those receiving hemodialysis, RLS/WED symptoms were independently associated with higher short-term mortality and new cardiovascular events.[11] In renal patients with comorbid RLS/WED, patients with frequent PLMS also had evidence of left ventricular structural abnormalities when compared to those without PLMS.[e15]

REM sleep behavior disorder

REM sleep behavior disorder (RBD) affects between 0.5% and 7.0% of the general population and may lead to serious injury to patients or their bed partners.[12,13,e16,e17] RBD is characterized by dream enactment behavior and REM sleep without atonia (RSWA), an abnormal elevation of muscle tone during REM sleep (figure).[12,e17] Dream mentation in patients with RBD characteristically involves defending oneself against attackers or being chased, with witnessed dream enactment manifested by violent thrashing movements and screaming or shouting vocalizations.[12] Polysomnography is necessary for determination of RSWA, and video aids in the diagnosis through viewing of corresponding excessive phasic limb jerking and may infrequently capture diagnostic episodes of complex motor behavior indicative of dream enactment. Comorbid obstructive sleep apnea (OSA) affects approximately two-thirds of patients with RBD[14] and can sometimes mimic its symptoms. Treatment of OSA in patients with RBD may aid its control by reducing the frequency and severity of dream enactment episodes.

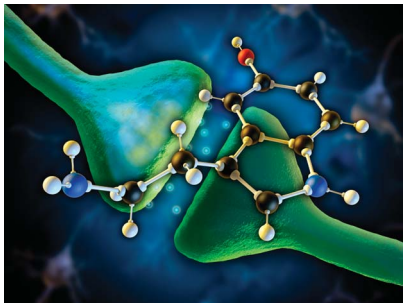
RBD is a core feature of synucleinopathy neurodegeneration, and idiopathic RBD (without other associated neurologic symptoms or signs at presentation) may herald the future

Figure REM sleep without atonia in a 30-second polysomnogram epoch in a 68-year-old man with REM sleep behavior disorder



Note the increased phasic muscle activity seen especially in the submentalis (chin) and anterior tibialis (leg) EMG channels (red arrows). The bursts of excessive activity are characterized as transient/phasic muscle activity, while a more sustained lower grade elevation of muscle tone lasting for longer than half of the epoch is described as tonic activity (seen in the leg channel, purple arrow). In this example, abnormal transient/phasic muscle activity excess is predominant, while there is underlying abnormal tonic activity confined to the leg EMG channel. An epoch of normal REM sleep muscle atonia is seen below for comparison, with normal tone in chin and leg EMG channels highlighted (green arrows).

development of overt memory, motor, or autonomic symptoms and evolve into mild cognitive impairment, dementia with Lewy bodies, and Parkinson disease.[12,15–19,e16,e17] Importantly, older adult patients newly diagnosed with idiopathic RBD have an approximately 50%–81% risk of developing impaired memory or autonomic function or parkinsonism during longitudinal follow-up, so all patients with RBD require serial neurologic examinations at least annually. RBD is a biomarker for synucleinopathy, signifying a potential therapeutic



Removal of antidepressants or substituting an alternative mood-stabilizing medication may improve or even stop dream enactment in younger adults with RBD.

time window for delivery of future neuroprotective therapies that could arrest or delay the development of more devastating cognitive and motor impairments.[12,19,20,e17]

However, RBD in young adults may instead be associated with mood disorder history, antidepressant medications (especially selective serotonin reuptake inhibitors), and narcolepsy. RBD and RSWA were also recently reported to occur in children and adolescents in whom a high index of suspicion should be maintained for narcolepsy and primary CNS hypersomnia.[e18,e19] Removal of antidepressants or substituting an alternative mood-stabilizing medication may improve or even stop dream enactment in younger adults with RBD. Longitudinal prospective cohort studies are necessary to determine whether RBD in children, adolescents, and young adults also signifies otherwise covert synucleinopathy, since RBD has been noted to precede the development of overt cognitive or motor manifestations by 50 years.[e20]

Falls or other injurious behavior to the patient or his or her bed partner may complicate RBD. Injuries occur in up to 55% of patients with RBD (most mild, such as bruises), but up to 11% experience serious injuries, including subdural hematoma requiring surgical intervention.[12,e21]

Treatment options include melatonin (initially at doses of 3 mg and gradually titrating toward 12 mg nightly or higher if needed), with the goal of suppressing frequent and potentially injurious dream enactment behaviors, or clonazepam 0.25–1.0 mg dosed to 2.0–3.0 mg nightly.[14,e22] The average effective reported doses are melatonin 6 mg and clonazepam 0.5 mg.[14] Great care should be taken to first exclude comorbid OSA in patients with RBD prior to use of clonazepam, a potential respiratory and upper airway suppressant, and clonazepam may have more adverse effects and potential drug interactions than melatonin. Melatonin is often a reasonable initial choice in elderly patients receiving polypharmacy and those with symptomatic neurologic disorders such as cognitive or autonomic impairment and parkinsonism.

CONCLUSION

Narcolepsy, RLS/WED, and RBD are each common public health problems encountered in neurologic practice. Recent evidence has shown that diagnosis in narcolepsy is often delayed, leading to a greater degree of social impairment. Earlier diagnosis and effective treatment of narcolepsy to improve alertness and prevent cataplectic attacks could affect patients' well-being and reduce potential for injury. RLS/WED, a frequent comorbidity in several neurologic patient types, not only causes considerable discomfort and sleep disturbance but also has recently been found to be possibly associated with hypertension and an increased risk for adverse cardiovascular events. In the meantime, while we await further definitive prospective cohort evidence concerning potential health risks in patients with RLS/WED, optimizing management and screening patients with RLS/WED for blood pressure and cardiovascular risk factors should be considered. RBD poses injury potential and signifies the need for careful longitudinal monitoring for symptoms and signs of cognitive, autonomic, and motor impairments. The common practical approach to these 3 conditions is that timely recognition, longitudinal follow-up, and optimization of treatment by neurologists are necessary to provide comprehensive care and may lead to improved patient quality of life, safety, and functioning.

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