Primary Sleep Disorders and Paroxysmal Nocturnal Nonepileptic Events in Adults With Epilepsy From the Perspective of Sleep Specialists

Madeleine Grigg-Damberger*† and Frank Ralls‡

Abstract: Sleep specialists are frequently referred adults with epilepsy to evaluate their sleep/wake complaints, sometimes to determine whether their paroxysmal nocturnal behaviors are epileptic or not. Many patients with epilepsy have at least one parasomnia (some more than one), and the sleep specialists are often asked to differentiate and treat these. Sleep specialists review which primary sleep disorders are more common in adults with epilepsy and how to evaluate and best treat these. The authors summarize (1) how to evaluate and differentiate parasomnias using video-polysomnography; (2) the value of sleep deprivation and loud auditory stimuli to increase the likelihood of provoking a non-rapid eye movement arousal parasomnia with a single night of video-polysomnography; and (3) how to score excessive muscle activity during rapid eye movement sleep to confirm a diagnosis of rapid eye movement sleep behavior disorder. The clinical semiology and video-polysomnography features of simple and complex sleep-related movement disorders and parasomnias are reviewed.

Key Words: Parasomnia, Polysomnography, Sleepwalking, Sleep terror, Nocturnal frontal lobe epilepsy, REM sleep behavior disorder.

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Sleep specialists are frequently referred adults with epilepsy to evaluate their sleep/wake complaints, sometimes to determine whether their paroxysmal nocturnal behaviors are epileptic or not. Many patients with epilepsy have at least one parasomnia (some more than one), and we are often asked to differentiate and treat these. Parasomnias are unusual or undesirable motor, behavioral, and/or experiential events that occur during (or in the transitions from and to) sleep (Kushida et al., 2005). Parasomnias are accompanied by varying combinations of complex motor movements, emotions, perceptions, dreaming, sensory experiences, hallucinations, thought images, and varying degrees of central nervous system sympathetic activation and arousal. If violent or dangerous, parasomnias can injure the patient (or those who attempt to intervene) and, when frequent, can disrupt the sleep/wake schedules and daytime functioning of the patient, bed partner, or family.

Some of these paroxysmal nocturnal behaviors (particularly complex sleep-related movement disorders or parasomnias) represent impaired sleep state synchronization or “state dissociation” disorders. Usually, transitions between wakefulness, non-rapid eye movement (NREM), and REM sleep occur smoothly and completely, but when more gradual or rapidly oscillating, the physiological markers of one sleep state can linger or intrude into another (Mahowald, 2009; Mahowald and Schenck, 2005). Narcolepsy with cataplexy is a prototypical state dissociation disorder in which (1) cataplexy is the sudden onset of REM sleep atonia while awake in response to an emotion-laden event; (2) sleep paralysis is an early or lingering appearance of REM sleep atonia; and (3) hypnic hallucinations fragments of REM sleep dreams persist into wakefulness. Table 1 summarizes the differential diagnosis of paroxysmal nocturnal events we consider in adults referred to sleep specialists.

EPIDEMIOLOGY AND RISK FACTORS FOR PARASOMNIAS

Parasomnias are particularly common in children and decrease in frequency with increasing age (Klackenberg, 1982). A longitudinal study of child development reported an overall prevalence of 40% for sleep terrors and 14.5% for sleepwalking in children aged 6 years or younger (Petit et al., 2007). An earlier study found that 40% of children (ages 6–16 years) have at least one episode of disorder of arousal (DoA) (mostly between ages 11 and 12 years), but only 2% to 3% of children have more than one DoA per month (Klackenberg, 1982). The majority of children who sleepwalk stop by the age of 13 years, but sleepwalking persists in 24% of frequent sleepwalkers, and 1% to 4% of adults sleepwalk. A telephone survey found that 2% of 4,972 adults in the United Kingdom reported sleepwalking, 2.2% sleep terrors, and 4.2% confusional arousals (Ohayon et al., 1999). However, only 0.4% of adults sleepwalk nightly (Piazzì et al., 2005).

Are parasomnias more common in children and/or adults with epilepsy? A prospective case-control study found a higher incidence of parasomnias among 89 children with idiopathic epilepsy compared with 49 siblings and 321 healthy control children using parental sleep questionnaires (Cortesi et al., 1999). Parasomnias were not more common in a prospective study of adults with a wide variety of different epilepsies and seizure types compared with healthy controls (Khatami et al., 2006). Sixty percent with epilepsy and 58% of the controls complained of at least one parasomnia: most often nocturnal leg cramps (25% vs. 17%), sleep starts (22% vs. 17%), and sleep talking (21% vs. 16%). Reports of sleep hallucinations, sleep paralysis, and violent acts during sleep occurred with equal frequency in patients and controls (16%, 4%, and 2%, respectively), as were shouting out when sleeping (4% vs. 3%). Nightmares and sleep-related bruxism were significantly more common but among control subjects and not the adults with epilepsy (16% vs. 6% and 19% vs. 10%, respectively). None of their study subjects reported sleepwalking or bedwetting.

However, NREM arousal disorders (DoA such as sleepwalking, sleep terrors, and confusional arousals) and sleep-related bruxism are significantly more common in patients and their relatives

From the *Department of Neurology, University of New Mexico School of Medicine; †Pediatric Sleep Medicine Services, University Hospital Sleep Disorders Center, University of New Mexico School of Medicine; and ‡Department of Pulmonary, Critical Care, and Sleep Medicine, University of New Mexico School of Medicine, Albuquerque, New Mexico, U.S.A.

Address correspondence and reprint requests to Madeleine Grigg-Damberger, MD, Department of Neurology, MSC10 5620, One University of New Mexico, Albuquerque, NM 87131-0001, U.S.A.; e-mail: MGriggD@salud.unm.edu.

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suggestive of OSA, 25% insomnia, and 17% EDS (Piperidou et al., 2006) an outpatient epilepsy clinic over a 10-month period had symptoms epilepsy patients (mean age 35 years) complained of EDS compared with 12% of the general adult population of 32,73 individuals found that 17% of epilepsy patients common in adults with epilepsy compared with healthy controls, but those who reported overall, quality of life (QoL) was reduced in patients with partial questionnaire compared with controls (de Weerd et al., 2004). Sleep complaints were two-fold higher (39% vs. 18%) of those with OSA and/or depression. An international cross-sectional survey present in those who have medically intractable or late-onset epilepsy, are male, older, or heavier (Hollinger et al., 2006; Malow et al., 2000; Manni et al., 2003). Thirty-nine percent of adults with medically intractable epilepsy had undiagnosed OSA [typically defined as a mean of at least five or more apneas and hypopneas per hour of sleep (mean number of apneas and hypopneas per hour of sleep [AHI] ≠5) on overnight polysomnography (PSG)] (Malow et al., 2000). AHI ≠5/hour are found in approximately 24% of men and 9% of women in the general adult population (ages 30–60 years) (Young et al., 1993, 1997). However, note that OSA in these patients was often mild (AHI 5–14/hour), and only 5% had AHI >20/hour (where >15/hour is moderate and >30–40/hour is severe).

Another study screened 283 unselected adults with epilepsy for OSA, identified 40 patients by questionnaire and interview judged to be “at risk for OSA,” and confirmed OSA (AHI ≥5) in 29 by in-laboratory PSG (Manni et al., 2003). OSA was mild in 67% (AHI 5–14/hour), moderate in 22% (15–29/hour), and severe in 11% (>30/hour). Epilepsy patients with OSA were more often male (15.4% men and 5.4% women), older (46 ± 15 years vs. 33 ± 12 years), sleepier (23% vs. 9%), heavier (28.5 ± 3.6 kg/m² vs. 23.3 ± 3.7 kg/m²), and had experienced their first seizure at an older age (32 years vs. 19 years).

Onset of OSA symptoms coincided with a clear increase in seizure frequency or the first appearance of status epilepticus in 29 patients (median age 56 years, 86% men) (Hollinger et al., 2006). Epilepsy patients who had OSA were more likely to complain of EDS (52% with OSA had an Epworth Sleepiness Scale score >10). They recommended considering OSA in epilepsy patients with poor seizure control and/or re-appearance of seizures after a seizure-free interval.

A case-control study of 53 older adults (mean age 59 years, 54% male) found OSA in 73% of men and 30% of women who presented to a tertiary epilepsy center with late-onset or worsening epilepsy (Chihorek et al., 2007). Of note, higher AHI (≥10) are common in older adults without sleep/wake complaints [found in 62% of 427 randomly selected community-dwelling elders (65 years or older)] (Anonymous, 1972). The authors also found the Epworth Sleepiness Scale as a useful screening tool in this population (mean score in those with OSA was 12 and those without OSA 6).

### Is One Night of Polysomnography Sufficient to Diagnose Obstructive Sleep Apnea in Patients With Epilepsy?

Is PSG data obtained from sleeping for the first time in the foreign environment of the sleep laboratory reliable? Alterations in normal sleep architecture observed when healthy adults sleep for the first time in a sleep laboratory (called First Night Effects) include longer time to fall asleep (sleep latency), lower sleep efficiency (percent of the time in bed spent sleeping), lower percentage of time spent in REM sleep, and reduced amounts of NREM 3 sleep time compared with the second night (Agnew et al., 1966). Two studies have found that adults with medically refractory epilepsy compared

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<th>TABLE 1. Differential Diagnosis of Paroxysmal Nocturnal Events in Adults Referred to Sleep Specialists</th>
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<td>● NREM Arousal disorder (confusional arousal, sleep walking, sleep terror)</td>
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<td>● REM sleep behavior disorder (RBD) and pseudo-RBD due to obstructive sleep apnea</td>
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<td>● Sleep-related rhythmic movement disorder with vocalization</td>
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<td>● Sleep-related expiratory groaning (catathrenia)</td>
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<td>● Post-traumatic stress disorder (PTSD)</td>
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<tr>
<td>● Sudden death when sleeping due to myocardial infarction, Brugada syndrome, untreated OSA, sudden unexpected death in epilepsy, and trauma</td>
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with nocturnal frontal lobe epilepsy (NFLE) (Bisulli et al., 2010). An individual with NFLE has a six-fold greater lifetime risk for DoA and five-fold for sleep-related bruxism compared with controls. The lifetime prevalence of a DoA in relatives of patients with NFLE was 4.7 times greater and nightmares 2.6 times greater compared with relatives of control subjects. NFLE predisposes patients and their relatives to the particular parasomnias (DoA and bruxism).

**CERTAIN PRIMARY SLEEP DISORDERS ARE COMMON IN ADULTS WITH EPILEPSY**

Many, but not all studies, report that obstructive sleep apnea (OSA), excessive daytime sleepiness (EDS), and sleep maintenance insomnia (difficulty staying asleep) occur more frequently in adults with epilepsy than the general population (de Weerd et al., 2004; Jenssen et al., 2006; Khatami et al., 2006; Piperidou et al., 2008; Soldatos et al., 2005). Thirty percent of 100 adults with epilepsy reported sleep complaints compared with 10% of 90 controls in a prospective study that used clinical interview and a standardized questionnaire to assess sleep/wake habits and disorders (Khatami et al., 2006). Adults with epilepsy were significantly more likely to have sleep maintenance insomnia (52% vs. 38%, P = 0.06). However, symptoms of sleep-onset insomnia (34% vs. 28%), EDS (19% vs. 14%), sleep apnea (9% vs. 3%), and restless legs (18% vs. 12%) were equally common in both patients and controls. The investigators found that EDS in the adults with epilepsy could be predicted by a history of loud snoring or restless legs symptoms (not by epilepsy type, seizure frequency, or number of antiepileptic medications prescribed). Sleep complaints were two-fold higher (39% vs. 18%) among 486 adults with partial epilepsy who responded to a mailed questionnaire compared with controls (de Weerd et al., 2004). Overall, quality of life (QoL) was reduced in patients with partial epilepsy compared with healthy controls, but those who reported disturbed sleep had the lowest QoL scores.

Several other well-designed studies have found that EDS is more common in adults with epilepsy compared with healthy age-matched controls, often then associated with symptoms suggestive of OSA and/or depression. An international cross-sectional survey of 35,327 individuals found that 17% of epilepsy patients complained of EDS compared with 12% of the general adult population (Soldatos et al., 2005). Twenty-eight percent of 124 consecutive epilepsy patients (mean age 35 ± 13 years, 55% male) who visited an outpatient epilepsy clinic over a 10-month period had symptoms suggestive of OSA, 25% insomnia, and 17% EDS (Piperidou et al., 2008). The authors found that (1) OSA symptoms were significantly more common among men and older patients; and (2) insomnia was an independent predictor for reduced QoL. However, Jenssen et al. (2006) found that scores on the Beck Depression Inventory suggestive of moderate to severe depression best predicted a complaint of EDS in patients with epilepsy, whereas sleep apnea scores contributed only minor independent effects.

**Untreated Obstructive Sleep Apnea May Be More Common in Epilepsy Patients With Poorly Controlled Seizures**

The current medical literature suggests that OSA is more likely to be found in those who have medically intractable or late-onset epilepsy, are male, older, or heavier (Hollinger et al., 2006; Soldatos et al., 2000; Manni et al., 2003). Thirty-nine percent of adults with medically intractable epilepsy had undiagnosed OSA [typically defined as a mean of at least five or more apneas and hypopneas per hour of sleep (mean number of apneas and hypopneas per hour of sleep [AHI] ≠5) on overnight polysomnography (PSG)] (Malow et al., 2000). AHI ≠5/hour are found in approximately 24% of men and 9% of women in the general adult population (ages 30–60 years) (Young et al., 1993, 1997). However, note that OSA in these patients was often mild (AHI 5–14/hour), and only 5% had AHI >20/hour (where >15/hour is moderate and >30–40/hour is severe).

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with normal age- and gender-matched controls tend to not have more NREM 1 and 2 sleep and less REM and NREM 3 sleep not just the first night but also the second (Marzec et al., 2005; Selwa et al., 2008).

However, for most patients with epilepsy, one night of PSG was sufficient to confirm (or exclude) a PSG diagnosis of OSA (Li et al., 2004; Scholle et al., 2003; Verhulst et al., 2006). Selwa et al. (2008) found that 29 patients had OSA (AHI ≥5). The results of the first study usually confirmed (or excluded) the diagnosis (Selwa et al., 2008). The median difference between AHI nights between nights 1 and 2 was only 3.25/hour. One patient had an AHI of 0 on the first night and 5.8 on the second. Three patients had an AHI >5 on the first night but not on the second. Twenty-nine patients had an AHI >5 on both nights, and 7 had an AHI <5 on both nights.

Can Treating Obstructive Sleep Apnea in Adults With Epilepsy Improve Seizure Control?

One prospective study examined the effects of treating OSA with continuous positive airway pressure (CPAP) in adults with medically refractory epilepsy (Malow et al., 2008). Investigators found that seizures were reduced ≥50% compared with their baseline in 28% of patients treated with CPAP versus 15% treated with sham CPAP (Malow et al., 2008). Six other small retrospective case series have reported that CPAP improved epilepsy control in some (but not all) when used (Beran et al., 1997; Chihorek et al., 2007; Devinsky et al., 1994; Hollinger et al., 2006; Oliveira et al., 2000; Vaughn et al., 1996). A clear reduction in seizure frequency was observed in four of five adults with epilepsy and OSA treated with CPAP, particularly those who used it faithfully (Devinsky et al., 1994).

CPAP in 12 adults with epilepsy led to a significant reduction in EDS and seizure frequency in 4 (Hollinger et al., 2006). Three of 10 adults with epilepsy became seizure-free after their OSA was treated; one had a >95% reduction in seizure frequency and three others had >50% when their OSA was treated (two with positional therapy to avoid sleep supine and eight with CPAP) (Vaughn et al., 1996). Four patients with medically refractory epilepsy had >50% reduction in their seizure frequency after CPAP use for 6 to 24 months, and antiepileptic medications were discontinued in two of these patients attributing their seizures to the OSA (Beran et al., 1997). Treating eight adults with epilepsy (six with CPAP for OSA, two prescribed supplemental oxygen for chronic obstructive pulmonary disease) led to reduced interictal spasms during sleep (Oliveira et al., 2000).

SLEEP-RELATED EPILEPTIC SEIZURES IN ADULTS FROM THE PERSPECTIVE OF SLEEP SPECIALISTS

We regard sleep-related epileptic seizures as an “epileptic” parasomnia. We understand that sleep (particularly NREM) is a powerful activator of interictal epileptiform discharges, certain seizure types, and particular epilepsy syndromes. Frontal lobe seizures are especially activated by sleep (Bazil and Waleczak, 1997; Crespel et al., 2000; Herman et al., 2001). One study found that 57% of partial seizures during sleep arose from the frontal, 44% lateral temporal, 40% mesial temporal, and 13% parieto-occipital regions (Herman et al., 2001). Skeletal motor inhibition and desynchronization of EEG during REM sleep are thought to explain why seizures rarely occur during REM sleep (Foldvary-Schaefer and Grigg-Damberger, 2006).

Sleep-related hypermotor seizures are often initially misdiagnosed as NREM disorders of arousal (confusional arousal, sleep-walking, or sleep terrors) (Derry et al., 2006b; Guilleminault et al., 1998; Hughes, 2007; Lugaresi et al., 1991; Meierkord et al., 1992; Montagna, 1992; Nobili, 2007; Oldani et al., 1998; Silvestri and Bromfield, 2004). Most nocturnal hypermotor seizures emanate from the frontal lobe, but one-third are temporal lobe in origin (Mai et al., 2005; Nobili et al., 2004) and some from insula (Ryvlin et al., 2006). Table 2 summarizes the clinical features of nocturnal hypermotor seizures (Combi et al., 2004; Nobili, 2007; Provini et al., 1999, 2000; Terzaghi et al., 2007; Timper et al., 2005).

Patients with NFLE often have attacks of varying severity; the minor ones are hard to distinguish from arousals seen in healthy normal controls. Table 3 summarizes the range of minor, mild, and moderate seizures seen in patients with NFLE (Provini et al., 1999; Zucconi et al., 1997). Zucconi et al. studied the video-PSG features of arousals in patients with NFLE and controls. They found that “normal” nonepileptic arousals from sleep (1) had no dystonic or repetitive features; (2) the motor behaviors were slower, less repetitive, and less stereotyped; and (3) fewer in number (Zucconi et al., 1997).

NFLE usually begins in middle to late childhood or adolescence. The mean age of onset in one series of 100 patients was 14 ± 10 years (but the range was 1–64 years; Provini et al., 1999). The mean age of onset was 7.5 years among 22 children with NFLE (Sinclair et al., 2004). The majority (78%) of 100 patients with NFLE deny precipitating factors for their seizures, but 18% reported psychologic stress as a trigger, three said seizures occurred after sleep deprivation and in one near her menses (Provini et al., 1999). A case series of 100 patients with NFLE reported that occasional daytime seizures occurred in 30%, <20% had ever had a generalized convulsion, the neurologic examination was normal in 92%, and the brain MRI normal in 86% (Provini et al., 1999).

Longer lasting nocturnal frontal lobe seizures can lead to “episodic nocturnal wandering” but more often are temporal lobe in origin (Mai et al., 2005; Nobili et al., 2002, 2004; Plazzi et al., 2005; Tai et al., 2010). Tai et al. (2010) found that postictal wandering was predominantly associated with temporal rather than extratemporal seizures, particularly those arising from the nondominant temporal lobe. Patients prone to “wandering” did so in a minority of their seizures (14%). Most temporal lobe seizures with postictal wandering began during wakefulness. The authors speculated that relatively greater sparing of suprasylvian motor structures after temporal lobe seizures may favor complex automatic wandering behaviors in the postictal state. Fifty to 80% of patients with temporal lobe epilepsy have nocturnal seizures, but nearly all have seizures when awake. Nocturnal temporal lobe seizures tend to be less frequent, do not cluster, and usually do not have the hyperkinetic motor activity of NFLE.

Nocturnal Frontal Lobe Epilepsy Often Has a Familial or Genetic Basis

A family history of sleep-related epilepsy is present in 30% of patients with NFLE (Aridon et al., 2006; Marini and Guerrini, 2007; Provini et al., 1999; Zucconi et al., 1997). The mean age of onset in one series of 100 patients was 14 ± 10 years (but the range was 1–64 years; Provini et al., 1999). The mean age of onset was 7.5 years among 22 children with NFLE (Sinclair et al., 2004). The majority (78%) of 100 patients with NFLE deny precipitating factors for their seizures, but 18% reported psychologic stress as a trigger, three said seizures occurred after sleep deprivation and in one near her menses (Provini et al., 1999). A case series of 100 patients with NFLE reported that occasional daytime seizures occurred in 30%, <20% had ever had a generalized convulsion, the neurologic examination was normal in 92%, and the brain MRI normal in 86% (Provini et al., 1999).

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TABLE 2. Clinical Features of Nocturnal Hypermotor Seizures

- An abrupt, often explosive, onset awakening the patient from grossly undisturbed NREM 2 sleep
- Asymmetric dystonic or tonic postures
- Thrashing, pedaling, and kicking of the lower extremities
- Tend to be “fairly” stereotyped in appearance for the individual patient
- Brief (typically lasting 20–30 seconds, less than 1–2 minutes)
- Patients are often aware during the seizure but say that they cannot control their movements or vocalizations
- No postictal confusion or amnesia
- 20% have no scalp-recorded ictal EEG activity accompanying them

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Oldani et al., 1998; Scheffer et al., 1994). NFLE has an autosomal dominant pattern of inheritance with an estimated 70% penetrance of the trait. More than 100 families with autosomal dominant NFLE (ADNFLE) have been identified, but mutations in the genes coding for various subunits of the neuronal nicotinic acetylcholine receptor (alpha2, alpha4, and beta2 on CHRNA4, CHRNA2, and CHRNβ2) on three different chromosomes (8p12.3-8q12.3, 15q4, and 20q13.1-13.3) have been identified in only a few studies (Aridon et al., 2006; De Marco et al., 2007; Díaz-Otero et al., 2008; Hoda et al., 2008; Marini and Guerrini, 2007; Phillips et al., 1995). The gene mutations of NFLE appear to confer a gain of function, leading to an increased sensitivity to acetylcholine (Hoda et al., 2008; Marini and Guerrini, 2007).

NFLE most often begins between ages 5 and 7 years in familial cases, 90% before the age of 21 years (Aridon et al., 2006). Patients with ADNFLE typically have normal neurologic examination, intellect, and brain MRI. Most studies suggest the clinical features and video-EEG findings of ADNFLE do not differ from sporadic NFLE (Marini and Guerrini, 2007). ADNFLE is typically lifelong, although seizures often become less frequent and milder by middle age (Aridon et al., 2006), which is attributed to a loss of nicotinic acetylcholine receptors with aging. NFLE may be associated with subtle deficits in cognitive flexibility compared with controls (Wood et al., 2010).

**Scalp Ictal EEG Often Normal in Patients With Nocturnal Frontal Lobe Epilepsy**

Probably, the greatest challenge when diagnosing NFLE is that 80% of adults with it have no IEDs in their EEGs awake or asleep, 20% have no scalp-recorded ictal EEG activity, and 25% have normal interictal and ictal EEGs (Oldani et al., 1998). In another study, 44% of patients with NFLE had a normal ictal EEG during video-EEG recording (Provini et al., 1999). The lack of scalp ictal EEG activity in NFLE has been attributed to the following: (1) muscle artifact often obscures the tracing; (2) events often last <20 to 30 seconds; (3) little or no postictal slowing; and/or (4) the epileptic focus is “buried” in the mesial frontal or inferior frontopolar regions “hidden” from scalp EEG recordings.

The diagnosis in these patients is confirmed by recording multiple seizures, noting their relatively stereotyped nature and clinical semiology. It is feasible to confirm the diagnosis with a single night of video-PSG because patients with NFLE tend to have multiple seizures. Provini et al. (1999) found that 100 patients with NFLE averaged 3 ± 3 (range 1–20) seizures per night of video-PSG and a mean of 20 ± 11 seizures per month (61%, >15 seizures per month).

The diagnosis of sleep-related epilepsy in adults is best confirmed by video-EEG, continuous prolonged inpatient recording if needed (Vignatelli et al., 2007). Oldani et al. (1998) compared the diagnostic reliability of routine video-EEG, daytime video-EEG after sleep deprivation, and nocturnal video-PSG to diagnose NFLE in 23 patients. All patients had normal video-EEG when awake. Nocturnal video-PSG confirmed the diagnosis in 87% of patients and daytime video-EEG with sleep deprivation in 52%. Overnight video-PSG is best reserved for NFLE patients in whom OSA or concomitant DoA is suspected.

Eighty percent of adults with NFLE have scalp-recorded ictal EEG activity. When unilateral, it is low-voltage paroxysmal fast activity, rhythmic theta activity, or flattening of the EEG over the frontocentral, fronto-central-temporal, frontotemporal, or parasagittal regions. A unilateral onset may be followed by early or late contralateral propagation. NFLE ictal EEG patterns when bilateral are usually maximal over the frontal, frontocentral, or frontotemporal regions, begin as either rhythmic fast or low-voltage fast activity, and sometimes lateralize to the size of the epileptogenic focus.

Patients with NFLE may complain that their seizures disrupt their sleep (and often they do). A case-control study found that 50% of 33 patients with NFLE complained of nocturnal awakenings compared with 22% of controls; 36% of patients complained of EDS (11% of controls), and those who complained of EDS were more likely to report frequent nocturnal awakenings (Vignatelli et al., 2006).

Vignatelli et al. (2007) evaluated the ability of six physicians (one sleep expert, two epilepsy experts, and three trainees in sleep medicine) to correctly diagnose NFLE (ranging from very brief paroxysmal arousals to nocturnal wandering) in 104 patients. Substantial to almost perfect inter-rater reliability was observed for more prolonged events or those with hypermotor or dystonic features. However, inter-rater reliability was at times only fair when raters were forced to distinguish brief paroxysmal arousals from equally brief nonepileptic arousals, especially when a patient had only one event in a single night of recording. The level of agreement between experts and trainees (with some training) was similar especially for longer lasting seizures. The authors argue that video recording (without the ictal EEG correlate that is often lacking) is probably sufficient to reliably diagnose NFLE when characterized by hypermotor or asymmetric dystonic seizures.

**Treatment Strategies for Nocturnal Frontal Lobe Epilepsy**

Carbamazepine is an appropriate first drug for NFLE, often effective at low doses (Oldani et al., 1998; Provini et al., 1999). Carbamazepine rendered 20% of 100 consecutive NFLE patients seizure-free and reduced seizure frequency by ≥50% in another 48% of patients (Provini et al., 1999). The effectiveness of carbamazepine in controlling seizures in ADNFLE may be related to its particular ability to inhibit mutated nicotinic acetylcholine receptors (Picard et al., 1999). Oxcarbazepine may also be effective for...
children with NFLE (Di Resta et al., 2010; Raju et al., 2007). Topiramate given as a single 50 to 300 mg dose at bedtime completely controlled NFLE in 25% of 24 adults with NFLE, while another 68% experienced ≥50% reduction (Oldani et al., 2006).

Particularly interesting are reports of tobacco use or nicotine patches improving AD Flem in 22 adults with NFLE (Brodtkorb and Picard, 2006). Although NFLE seizures persisted in the seven adults with NFLE who did not use tobacco, seizure fluctuations (including long remissions) corresponded to changes in tobacco habits in several patients. One patient who recently had begun treatment with transdermal nicotine experienced improvement. Nicotine normalized the intracellular subunit stoichiometry of nicotinic receptors in cultured cell lines carrying mutations linked to AD Flem (Son et al., 2009). Although evidence is limited, consider a trial of transdermal nicotine patches for medically refractory NFLE.

Approximately 30% of cases of sporadic NFLE are medically refractory. Patients with medically refractory NFLE may be candidates for tailored frontal lobe resections (Nobili et al., 2007; Sinclair et al., 2004). Nearly three-fourths (73%) of 21 cases of medically refractory NFLE became seizure-free after tailored frontal lobe epilepsy focus resections, and seizure control improved in another 23% (Nobili et al., 2007).

**HOW DO SLEEP SPECIALISTS EVALUATE PARASOMNIAS IN ADULTS?**

When asked to diagnose paroxysmal events or abnormal movements during sleep, we begin by asking whether these only occur around or during sleep (Walters, 2007). If these also occur while awake, consider whether the patient has a movement disorder when awake. Contrary to older teachings, most diurnal movement disorders (including tremor, dystonia, chorea, hemiballismus, and myoclonus) persist or intermittently recur in sleep (albeit more intermittent and reduced in frequency and duration than when awake).

Then, obtain a detailed description of the events regarding (1) stereotyped or variable; (2) consciousness is preserved before, during, and/or after them; (3) number and time(s) of occurrence related to sleep onset; (4) precipitating factors; (5) recall of the events; (6) potential to cause injury; (7) daytime consequences of them including cognitive slowing or daytime sleepiness; and (8) sleep/wake habits of the individual searching for irregular sleep/wake patterns in question (e.g., stereotypical, repetitive, or focal) (Kushida et al., 2005).

Unfortunately, the habitual nocturnal event may not be captured by one night of in-laboratory video-PSG. One to two consecutive nights of v-PSG provided valuable diagnostic information in 69% of 41 patients whose paroxysmal motor behaviors were “prominent,” 41% of 11 patients referred for minor motor activity in sleep, and 78% of 36 patients with known epilepsy (Aldrich and Jahnke, 1991). Another study found that video-PSG was diagnostic in 65% and “helpful” in another 26% of 100 consecutive adults referred for frequent sleep-related injuries; video-PSG identified DoA in 54, REM sleep behavior disorder (RBD) in 36, sleep-related dissociative disorders in 7, nocturnal seizures in 2, and OSA in 1 (Schenck et al., 1989). Unfortunately, only one-third of patients with paroxysmal nocturnal events will have a typical spell a single night of video-PSG (Aldrich and Jahnke, 1991; Blatt et al., 1991).

The AASM recommends that video-PSGs be done to diagnose parasomnias need (1) “additional EEG derivations in an expanded bilateral montage” to diagnose paroxysmal arousals or other sleep disruptions thought to be seizure-related when the initial clinical evaluation and results of a standard EEG are inconclusive; (2) recording surface electromyographic (EMG) activity from the left and right anterior tibialis and extensor digitorum muscles; (3) good audiovisual recording; and (4) a sleep technologist present throughout the study to observe and document events (Kushida et al., 2005).

We typically use bandpass of 0.3 to 35 Hz when reviewing in-laboratory PSG, but in patients with suspected or known epilepsy, we set the high-frequency filters to 70 Hz. We also review portions of the recording using vertical screen times (epochs) of 10 or 15 seconds, whereas we typically score sleep stages using 30-second epochs. The AASM encourages that polysomnographers and electroencephalographers who are not experienced or trained in recognizing and interpreting both PSG and EEG abnormalities should seek appropriate consultation or should refer patients to a center where this expertise is available (Kushida et al., 2005).

If the goal is to differentiate epileptic seizures from nonepileptic events, especially frontal lobe seizures, 18 channels of EEG are needed when recording video-PSG (Foldvary-Schaefer et al., 2006). That said, recording 18 channels of EEG during v-PSG did not improve the ability to recognize frontal lobe seizures. Adding 7 or 18 channels of EEG improved the accuracy of temporal lobe seizure detection (sensitivity 67% for 4 channels, 82% for 7, and 86% for 18) (Foldvary et al., 2000).

**Indications for Video-Polysomnography When Evaluating Parasomnias in Adults**

The American Academy of Sleep Medicine (AASM) clinical practice parameters recommend in-laboratory video-PSG (V-PSG) be used to evaluate parasomnias that are unusual or atypical because of patient’s age at onset; the time, duration, or frequency of occurrence of the behavior; or the specifics of the particular motor patterns in question (e.g., stereotypical, repetitive, or focal) (Kushida et al., 2005). Comprehensive in-laboratory video-PSG is not routinely indicated for “typical” sleep terrors or sleepwalking in young children (Kushida et al., 2005). However, video-PSG is usually warranted to evaluate parasomnias in adults which (1) begin or recur in adulthood; (2) occur more than 2 to 3 times per week; (3) are potentially injurious or have caused injury to the patient or others; and (4) could be seizure-related but the initial clinical evaluation and a standard EEG inconclusive (Kushida et al., 2005).

Clinical features that warrant concern for sleep-related epileptic seizures are as follows: (1) events occur any time of the night, occur just after falling asleep, or shortly before awakening in the morning; (2) multiple events a night; and/or (3) occasional occurrence of these events when awake or during a brief nap. If we suspect that the nocturnal events are sleep-related epilepsy and the patient has not had an EEG with sleep, we request one first. If the first (or second with 24-hour of sleep deprivation) routine EEG with sleep is normal and our clinical suspicion for a sleep-related epilepsy remains, we request continuous inpatient video-EEG monitoring (long-term monitoring) for 2 to 5 days.

Unfortunately, the habitual nocturnal event may not be captured by one night of in-laboratory video-PSG. One to two consecutive nights of v-PSG provided valuable diagnostic information in 69% of 41 patients whose paroxysmal motor behaviors were “prominent,” 41% of 11 patients referred for minor motor activity in sleep, and 78% of 36 patients with known epilepsy (Aldrich and Jahnke, 1991). Another study found that video-PSG was diagnostic in 65% and “helpful” in another 26% of 100 consecutive adults referred for frequent sleep-related injuries; video-PSG identified DoA in 54, REM sleep behavior disorder (RBD) in 36, sleep-related dissociative disorders in 7, nocturnal seizures in 2, and OSA in 1 (Schenck et al., 1989). Unfortunately, only one-third of patients with paroxysmal nocturnal events will have a typical spell a single night of video-PSG (Aldrich and Jahnke, 1991; Blatt et al., 1991).

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<table>
<thead>
<tr>
<th>Simple Sleep-Related Movement Disorder</th>
<th>Clinical Features</th>
<th>Video-EEG or PSG Features</th>
<th>Neurophysiological Basis</th>
<th>Epidemiology and Sleep/Wake Timing</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep starts (hypnic jerks)</td>
<td>In sleep/wake transition, 1–2 abrupt myoclonic flexion jerks (generalized or partial, often asymmetric), often accompanied by a feeling of falling, a sensory flash, and/or a bit of dream-like imagery</td>
<td>A single brief EMG burst lasts &lt;250 milliseconds, often occurs asymmetrically and simultaneously, or sequentially in various muscles, and often causes a brief EEG arousal</td>
<td>Sudden descending brainstem reticular formation volleys activated by the instability of the system in the wake/sleep transition</td>
<td>Occur occasionally in 70% of general adult population</td>
<td>Reassurance/Avoid sleep deprivation or insufficient sleep which may provoke them</td>
</tr>
<tr>
<td>Sleep paralysis</td>
<td>Upon awakening or going to sleep, transient inability to move despite being fully awake</td>
<td>REM sleep patterns, eye movements, and respiration spared</td>
<td>A brief persistence or intrusion of the skeletal muscle motor suppression of REM sleep into wakefulness</td>
<td>Occurs most often and frequently in narcolepsy with cataplexy</td>
<td>Reassurance/Avoid sleep deprivation</td>
</tr>
<tr>
<td>Hypnagogic foot tremor</td>
<td>Single short trains of rhythmic 1–2/second oscillating movements of the toes or whole foot of one or both feet most often wake/sleep, but often linger into stages NREM 1 or NREM 2 sleep, and may recur after sleep-related arousals</td>
<td>A series of single-phasic EMG bursts lasting 300 to 700 milliseconds recurring at 1 to 2/second for 10 to 20 seconds (Wichniak et al., 2001) May alternate from leg to leg</td>
<td>May be another manifestation of sleep-related periodic limb movements</td>
<td>8% of 375 consecutive patients complaining of disturbed sleep and 5% of 20 healthy young controls (Wichniak et al., 2001) 70% in one series were taking selective serotonin reuptake inhibitors (Chervin et al., 2003)</td>
<td>Usually do not disturb sleep or need treatment</td>
</tr>
<tr>
<td>Propiospinal myoclonus</td>
<td>Series of involuntary myoclonic jerks that begin in the upper rectus abdominus or lower intercostal muscles and propagate rostrally to the upper intercostals and caudally to the lower abdomen muscles when trying to fall asleep or relax, usually disappear NREM 2 sleep onset</td>
<td>EMG of PSM shows spontaneous intermittent rhythmic or arrhythmic brief myoclonic bursts, which usually arise in the upper rectus abdominus or lower intercostal axial muscles followed by propagation rostrally to upper intercostal and caudally to the abdominal muscles at slow conduction velocities of 2 to 16 milliseconds (Montagna et al., 2006)</td>
<td>Myoclonic jerk time-locked to brain averaging have shown that PSM does not originate in the cerebral cortex. PSG can develop within days or weeks of cervical trauma, suggesting that it may represent a partial release of a spinal central pattern generator (Brown et al., 1994), propagated up and down the spinal cord by slow conducting pathways, such as propiospinal fibers (Chokroverty et al., 1992)</td>
<td>Rare can cause severe sleep-onset insomnia May occur after trauma. Can coexist with restless legs syndrome or periodic limb movements</td>
<td>Clonazepam (0.5–2 mg) before bed usually provides partial relief for patients with PSM who complain of inability to fall asleep because of the PSM (Montagna et al., 2006)</td>
</tr>
<tr>
<td>Simple Sleep-Related Movement Disorder</td>
<td>Clinical Features</td>
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<td>Treatment</td>
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<tr>
<td>Sleep-related bruxism</td>
<td>Grinding or clenching of teeth during sleep, which often occurs with or after arousals</td>
<td>Recurring episodes of bruxing movements of masseter and temporalis muscles accompanied by the noise of grinding teeth, which usually follow an arousal, and sometimes concludes with a swallow, and can occur in any stage of sleep but most often NREM 1 or NREM 2</td>
<td>Sleep-related release of brainstem central pattern generators</td>
<td>8% of young to middle-aged adults and 3% of older persons (Lavigne et al., 2008)</td>
<td>Mouth guard or mandibular advance appliance worn when sleeping or clonazepam taken before bed are the most successive treatments for SB (Landry et al., 2006; Huynh et al., 2007; Landry-Schönbeck et al., 2009)</td>
</tr>
<tr>
<td>Sleep-related faciomandibular myoclonus</td>
<td>Spontaneous myoclonic jerks of the facial, masticatory, and sometimes sternocleidomastoid muscles during NREM sleep without the tonic EMG masticatory activity typical of sleep bruxism</td>
<td>Spontaneous myoclonic jerks in facial, masseter, and neck muscles during NREM sleep</td>
<td>Sleep-related release of brainstem central pattern generators</td>
<td>May cause tongue-biting; Sometimes mistaken for sleep-related epilepsy (Dylgjeri et al., 2009)</td>
<td></td>
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<tr>
<td>Excessive fragmentary myoclonus</td>
<td>Small muscle twitches about the mouth, fingers, or toes or small muscle twitches that resemble muscle fasciculations because they cause no movement across a joint space (Broughton et al., 1985)</td>
<td>Very brief (75–150 milliseconds) EMG bursts in various muscles which occur asynchronously and asymmetrically in a sustained manner without clustering for at least 20 minutes of sleep (Medicine 2005). EEG-EMG back averaging has shown that these are not generated by the cerebral cortex (Vetrugno et al., 2002)</td>
<td>Incidental finding in PSG; patients are usually unaware of the movements nor do they affect sleep onset or sleep quality, or need treatment. Occasionally, a bed partner asks for an explanation for them</td>
<td></td>
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</table>

Arousal from sleep can lead to a temporary loss of control of the neomammalian cortex provoking emergence of different types of motor behaviors, which are genetically determined and species-specific central pattern generators.
Finally, when should we retreat to the epilepsy monitoring unit to confirm sleep-related events are epileptic? Prolonged inpatient video-EEG monitoring is often a better choice in adults with undiagnosed paroxysmal nocturnal events when (1) the nocturnal behaviors do not occur nightly or every other night; (2) a primary sleep disorder (e.g., OSA) is unlikely; (3) a history of postictal agitation or wandering exists; and/or (4) cooperation of the patient is questionable.

Alternative Methods for Diagnosing Parasomnias

Derry et al. (2006a) designed a frontal lobe epilepsy and parasomnias (FLEP) scale to assess the likelihood a paroxysmal nocturnal event was likely to be NFLE based on the clinical history alone. The FLEP consists of a series of questions based on an initial series of cases and clinical expertise. Responses to the questions asked in the FLEP scale that favored nocturnal seizures were events last <2 minutes, occur ≥3 to 5 times per night, and behaviors during them are highly stereotyped. PNE (paroxysmal nocturnal events), which begin after age 55 and/or have highly variable clinical semiology, are unlikely to be NFLE. A patient with a score of 0 or less on the FLEP scale is very unlikely to have epilepsy, and any patient with a score of +1 to +3 is very likely to have epilepsy, whereas video-EEG or PSG monitoring is needed for those with a FLEP score of +1 to +3. For NFLE, the FLEP scale had a sensitivity of 71%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 91% (Derry et al., 2006a).

Manni et al. (2008) also found that the FLEP scale usually identifies NFLE, but it is less reliable for differentiating sleepwalking from epileptic nocturnal wandering and distinguishing RBD from epilepsy. Manni et al. evaluated the reliability of the FLEP scale in 71 subjects (mean age 54 ± 21 years, 85% men) of whom 11 had DoA, 14 NFLE, and 46 idiopathic RBD; the FLEP scale incorrectly diagnosed 4 (6%) of the patients (specifically NFLE patients who had epileptic nocturnal wandering). FLEP scores were in the equivocal range (+1 to +3) in 31% of the patients requiring video-PSG or video-EEG.

The diagnostic yield of home video recordings in capturing “spells” in children has been reported and studied (Beun et al., 1994; Sartori et al., 2008; Sheth and Bodensteiner, 1994; Stephenson et al., 2004; Woody, 1985). These are simple to request and obtain if events are frequent enough, and families have readily available camcorders, digital cameras, or cell phones to record the events. However, too often, the crucial beginning of an event is lost.

SLEEPWALKING AND SLEEP TERRORS IN ADULTS

Most adults referred to sleep specialists for parasomnias have NREM disorders of arousal (DoA), which include confusional arousals, sleepwalking, sleep terrors, sleep-related eating, or sexual behaviors (Hughes, 2007; Plazzi et al., 2005; Schenck et al., 2007; Vetrugno et al., 2006). As discussed earlier in the Introduction section, 40% of children have at least one episode of sleepwalking, but only 2% to 3% have more than one a month; most stop walking by age 13, 24% continue to sleepwalk, and 2% to 4% of adults sleepwalk but only 0.4% nightly.

Risk factors for confusional arousals in adults were age younger than 35 years, OSA, a bipolar or anxiety disorder, or shift or night work (Ohayon et al., 2000). In an earlier study, Ohayon et al. (1999) found that bipolar disorder increased the odds ratio for confusional arousals in an adult 13 times, an adjustment disorder...
three-fold, shift work or daytime sleepiness two-fold. However, adults who reported sleep terrors were three to five times more likely to be reported by those who also had symptoms suggestive of OSA, nightmares more than once a month, consumed alcohol at bedtime, or were prone to violent or injury-causing behaviors during sleep. Table 5 lists factors that predispose, prime, or perpetuate DoA.

Clinical Semiology of NREM Arousal Disorders

DoA most often occur 90 to 180 minutes after sleep onset in a transition from NREM 3 (occasionally NREM 2) sleep to wakefulness or REM sleep. DoA typically last for a few minutes, are nonstereotyped, and can be provoked by sensory stimuli (OSA, a loud noise, or bright light half-awakening the patient). Patients during DoA appear confused, disoriented, and are slow to respond. Their eyes are open (as opposed to closed during RBD or NREM), visual inspection functions but objects are often misidentified (e.g., trying to use the bedside water glass as a telephone receiver, the closet as a bathroom). They have little or no responsiveness to their external environment and exhibit automatic behaviors. They are difficult to arouse from an event, and if aroused, they recall only fragmentary dream-like images (often of being trapped or attacked). Varying degrees of central nervous sympathetic activation accompany DoA: mild for “passive” sleepwalking, moderate in confusional arousals, markedly for sleep terrors, or “agitated” sleepwalking. Episodes end with a return to sleep and retrograde amnesia for the events (although some adults can recall fragments of some events).

During a confusional arousal, the patient often suddenly sits up in bed, may then fumble with bedclothes, trash, flail or kick, moan, whimper, and/or utter often unintelligible words. Sleep sex is abnormal sexual behavior occurring when sleeping and classified as a variant of confusional arousal in the second edition of the International Classification of Sleep Disorders. First described by Guillemini et al. in 2002, 11 patients (7 men) exhibited atypical sexual behaviors when asleep. These included loud sexual vocalizations, fondling their bedpartner, sexual intercourse with or without orgasm, sexual assault, and atypical for the particular individual’s awake deviant sexual behaviors. “Passive” sleepwalking often begins as a confusional arousal but the patient leaves the bed, walking toward a sound, light, or a particular room. While sleepwalking, the person may eat, urinate in a closet or next to the toilet, or walk outside.

Sleep terrors and agitated sleepwalking often begin with bedclothes flail, kick, moan, whimper, and/or utter often unintelligible words. Sleep sex is abnormal sexual behavior occurring when sleeping and classified as a variant of confusional arousal in the second edition of the International Classification of Sleep Disorders. First described by Guillemini et al. in 2002, 11 patients (7 men) exhibited atypical sexual behaviors when asleep. These included loud sexual vocalizations, fondling their bedpartner, sexual intercourse with or without orgasm, sexual assault, and atypical for the particular individual’s awake deviant sexual behaviors. “Passive” sleepwalking often begins as a confusional arousal but the patient leaves the bed, walking toward a sound, light, or a particular room. While sleepwalking, the person may eat, urinate in a closet or next to the toilet, or walk outside.

Sleep terrors and agitated sleepwalking often begin with a bloodcurdling scream or cry, the patient exhibiting severe agitation, greater fear, more vocalization, and marked sympathetic arousal with mydriasis, tachycardia, tachypnea, and sweating. They flee to the toilet, or walk outside.

<table>
<thead>
<tr>
<th>TABLE 5. Precipitating, Priming or Exacerbating Factors for New Onset or Late Recurrence of Sleepwalking or Sleep Terrors in Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stressful life events (changes in sleep environment, family, or workplace conflicts) preceded SW in 56% of the adult subjects they studied</td>
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<tr>
<td>Cumulative partial sleep deprivation</td>
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<tr>
<td>Obstructive sleep apnea</td>
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<td>Shift or night work</td>
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<tr>
<td>Bipolar or anxiety disorder</td>
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<tr>
<td>Alcohol use</td>
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<tr>
<td>Intercurrent infection with or without fever</td>
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<tr>
<td>Extreme fatigue or exercise</td>
</tr>
<tr>
<td>Sedative-hypnotics (especially zaleplon, zolpidem, and zopiclone)</td>
</tr>
</tbody>
</table>

agitation when touched or held; innocent attempts by bystanders to touch or direct them may then lead to injury (to themselves or others). Violent DoA in adults can cause injury to patient or bedpartner, and self-injury during a DoA is misdiagnosed as suicide (pseudosuicide) (Mahowald et al., 2003). Agitated sleepwalkers are more often an adolescent or adult. Even violent DoA usually last a few to rarely as long as 30 minutes, often followed by a calm return to bed or sleep somewhere else in the house or outside.

Video-Polysomnographic Features of NREM Arousal Disorders

DoA usually emerge from NREM 3, occasionally from NREM 2 sleep (Schenck et al., 1998; Zadra et al., 2004). The onset of DoA event is best identified by the appearance of tachycardia from NREM 3 sleep: the acceleration of the heart rate is typically greatest for a sleep terror or agitated sleepwalking, moderate for confusional arousal, and least for passive sleepwalking.

EEG during a DoA event in 38 adult sleepwalkers (mean age 29 years, 55% men) was characterized by either regular rhythmic hypersynchronous delta or theta activity or high-amplitude delta intermixed with alpha or beta activity (Schenck et al., 1998). A case-control study compared PSG in 24 adult sleepwalkers (18–25 years old) and 12 age-matched controls (Blatt et al., 1991). Sleepwalkers had more 30-second epochs of sleep containing hypersynchronous delta waves (60 ± 60 vs. 2 ± 3), a greater percentage of NREM 3 sleep time with hypersynchronous delta waves (25% ± 21% vs. 1% ± 2%), more NREM 3 sleep interruptions (8 ± 5 vs. 4 ± 2), and a greater percent of their total sleep time spent in NREM 3 (31% ± 12% vs. 23% ± 7%).

Studies comparing sleep microarchitecture and EEG power in adults with sleepwalking or sleep terrors to controls report that patients with sleepwalking/sleep terrors have (1) increased number of brief arousals from NREM 3 sleep especially during the first NREM cycle of a night; (2) reduced delta power of the slow-wave activity especially during first NREM cycle; (3) slower decay of EEG delta power of NREM 3 sleep across recurring cycles of NREM sleep; and (4) alterations in cyclic alternating pattern during NREM sleep consistent with increased NREM 3 sleep instability. More work is needed to see whether individuals with DoA can be identified by abnormalities in their sleep microarchitecture.

Techniques for Activating NREM Arousal Disorders in the Sleep Laboratory

Montplaisir et al. developed “activation” techniques that increased the likelihood of capturing a patient’s sleepwalking or sleep terror event in a single night of in-laboratory recording. Patients would arrive at their customary bedtime, remained awake the entire night, and then permitted to fall asleep 1 hour later than their usual wake time (i.e., 25 hours of prior wakefulness). To further provoke DoA events, investigators subjected patients (and controls) to six auditory stimuli [AS, 3 seconds of a pure sound at 1,000 Hz presenting in ascending intensities of 10 dB (from 40 to 90 dB)] with a minimal interval of 1 minute between two stimuli. The AS was delivered to the patient or control subject by earphones inserted into both ears. Whenever possible, the first and second groups of AS were presented during NREM 3 sleep during the first and second NREM-REM sleep cycles.

Using this technique, the investigators found that they could trigger 1 to 3 sleepwalking events in 30% of 10 patients with DoA by sounding a 40 to 70 dB buzzer during NREM 3 sleep. After 25 hours of total sleep deprivation, the AS provoked DoA behaviors in 100% of their subjects (and none of their controls). A few sleepwalking events were induced from NREM 2 sleep. No episodes were induced from REM sleep. Sleep deprivation nearly tripled the percentage of auditory stimulus trials that induced a behavioral
Genetic Predisposition to Disorders of Arousal and Other Parasomnias

Genetic predisposition for DoA is the most significant predisposing factor for DoA in children (Hublin and Kaprio, 2003; Kales et al., 1980; Petit et al., 2007). Psychopathology is usually not a factor in young children with arousal disorders (Petit et al., 2007). Psychopathology is often a significant factor when sleepwalking first appears in older teens and adults, but partial sleep deprivation, situational stress, and genetics often contribute.

Genetic predisposition is also a significant factor for DoA in adults. Hublin et al. (1997) found in a study population of 11,220 Finnish adults (33–60 years) that 3.9% of men and 3.1% of women reported sleepwalking (weekly in only 0.4%). Twenty percent of the men and 18% of the women who were sleepwalkers as children continued to sleepwalk as adults. Only 0.6% of the adult sleepwalkers reported never sleepwalking as a child. The authors found that they could attribute 66% of the phenotypic variance to genetic influences in men and 57% in women with a history of sleepwalking as children; 80% in men and 36% in women in the adult sleepwalkers. In a later study, they found that other parasomnias (bruxism, nightmares, and sleepwalking) are also much more common in families of individuals affected by sleepwalking (Hublin et al., 2001).

NREM Arousal Disorders Expression of a Sleep-Related Loss of Inhibition of Central Pattern Generators

DoA are thought to represent the release or expression of central pattern generators (CPGs): standing, walking, vocalization, eating, aggression, and sexual behaviors (Tassinari et al., 2005, 2009). CPGs (listed in Table 6) are genetically determined neuronal aggregates in the mesencephalon, pons, and spinal cord, which code for species-specific motor behaviors and emotions essential for survival (e.g., feeding, locomotion, defense, and copulation) (Tassinari et al., 2005). After infancy, CPGs are usually suppressed by the cerebral neocortex when awake. However, CPGs released from neocortical inhibition during DoA often lead sleepwalkers to the kitchen to eat (often foods they would not eat when awake), to the cerebral neocortex when awake. However, CPGs released from neocortical inhibition during DoA often lead sleepwalkers to the kitchen to eat (often foods they would not eat when awake), to urinate (next to the toilet or in a closet), or outside (through a window or door).

Tassinari et al. (2005) argue that the clinical semiology of NFLE and many parasomnias [DoA, bruxism, periodic limb movements during sleep (PLMS), faciomandibular myoclonus, and catathrenia] are similar because they reflect release of neocortical inhibition of the same CPGs during sleep. The higher prevalence of sleepwalking in families with NFLE may reflect that both occur when CPGs are disinhibited (Bisulli et al., 2010; Tassinari et al., 2009; Tinuper et al., 2010).

Treatment Strategies for NREM Arousal Disorders in Adults

DoA in adults are often triggered by conditions and/or substances that increase NREM 3 sleep or make arousal from sleep more difficult (Table 5). Identifying, avoiding, or treating these are sufficient treatment for DoA. Further treatment strategies for DoA in adults are provided in Table 7. We consider pharmacotherapy for DoA in adults when they (1) are frequent; (2) are danger to the patient or others; (3) are chronic; (4) cause undesirable secondary consequences (EDS and weight gain from nocturnal eating); (5) are sufficiently distressing to the patient or family; and/or (6) cause legal issues regarding sexual or violent behavior. When medication is needed in adults with DoA, sleep specialists often first prescribe clonazepam (0.5–2 mg QHS). The value of clonazepam to suppress frequent DoA in adults is based on five small case series, which together show that 83% of 61 sleepwalkers responded to it (Harris and Gronstein, 2009). The effectiveness of clonazepam for suppressing DoA is thought to be related to inhibition of arousals or locomotor activity rather than pharmacological suppression of NREM 3 sleep.

REM Sleep Behavior Disorder

RBD is a parasomnia characterized by abnormal and often violent motor behaviors and complex vocalizations in which patients appear to enact their dreams while in REM sleep (Trotti, 2010). Skeletal muscles (except those innervating eye muscles and the diaphragm) are normally paralyzed during REM sleep (preventing dream enactment behavior). Skeletal atonia is normally present throughout a REM sleep period interrupted by intermittent phasic bursts of rapid eye movements and facial and limb phasic muscle twitches (Fig. 2). We differentiate but do not score phasic and tonic REM sleep in a PSG: so-called “tonic” REM sleep is characterized by an EEG background of low-voltage mixed frequencies (and sometimes diffuse alpha activity at frequency 1–2 Hz slower than the waking dominant posterior rhythm) and chin muscle atonia with superimposed periods of “phasic” REM sleep with runs or bursts of rapid eye movements, saw tooth waves, phasic muscle twitches, and irregular respiration (Fig. 3). The tonic and phasic components of REM sleep are markedly altered in patients with RBD, with partial or complete loss of tonic chin EMG atonia normally seen throughout a period of REM sleep and excessive amounts of phasic EMG activity in the chin and limb channels (Fig. 3).

| TABLE 6. Emergence of Different Central Pattern Generators in Parasomnias and Nocturnal Frontal Lobe Epilepsy |
|---------------------------------------------------------------|--------------------------------------------------|
| Central Pattern Generator Type                | Range of Motor Behaviors                        |
| Alimentary                                      | Bruxism, chewing, swallowing, lip smacking      |
| Defensive/predatory                             | Biting, teeth chattering, faciomandibular myoclonus |
| Emotional                                       | Universal facial expression (fear) and encoded vocalizations |
| Locomotor                                       | Pedaling (supine), tetrapod progression (prone), fugue (wandering), cyclic (periodic) leg movements, bimanual pedal activity |
| Copulatory                                       | Repetitive pelvic thrusting                      |

| TABLE 7. Treatment Strategies for NREM Sleep Disorders of Arousal (DOA) in Adults |
|---------------------------------------------|---------------------------------------------|
| ● Regular bed- and wake-times with adequate amounts of sleep |
| ● Avoid sleep restriction, sleep deprivation, jet lag, and night or shift work |
| ● Avoid visual, auditory, or tactile stimuli especially during the first third of the night which may trigger an event |
| ● Decrease noise, light, pain, nocturia, or dyspnea, which may contribute to partial arousal |
| ● Avoid extreme exercise, fatigue, and emotional or situational stress |
| ● Search for and treat sleep apnea, restless legs, narcolepsy, and gastroesophageal reflux |
| ● Avoid alcohol, antipsychotics, antidepressants, antihistamines, sedative-hypnotics, and benzodiazepines |
| ● Clonazepam may cause excessive daytime sleepiness or disinhibition |
REM sleep without atonia (RSWA) was first induced experimentally by making bilateral lesions in the dorsolateral pontine tegmentum of cats (Jouvet, 1965; Mahowald and Schenck, 2004). Depending on the size and extent of the brainstem lesions, the cats could stand, walk, attack, and “act out their dreams” during REM sleep, culminating in attacking behaviors when they extended the lesions into midbrain interrupting amygdalar pathways. First described in humans by Schenck and Mahowald (Schenck et al., 1986), RBD is an uncommon condition diagnosed in 34 (4.8%) of 703 consecutive patients referred to a tertiary sleep center (Frauscher et al., 2010). Only 17% were referred specifically for suspected RBD, 60% only reported RBD symptoms when specifically questioned, and clinical RBD behaviors were incidentally found on video-PSG in 24% (Frauscher et al., 2010). Sleep-related injuries (bruises, abrasions, lacerations, fractures, choking episodes, running into walls or glass doors, and rarely subdural hematomas) to the patient or bed partner were the presenting complaint in 33% to 85% of patients with RBD (Olson et al., 2000; Schenck et al., 1989, 1993).

RBD usually presents after age 50, although any age group can be affected (Chiu et al., 1997). Chronic RBD most often affects older men: 87% of 93 consecutive patients with RBD seen at the Mayo Clinic over a 4-year period were men (Olson et al., 2000). A male predominance is observed in most other large case series (Iranzo et al., 2006; Postuma et al., 2009a; Schenck et al., 1993). Estimates of the prevalence of RBD in the general population range from 0.38% (Chiu et al., 2000) to 0.5% (Ohayon et al., 1997).

RBD can be idiopathic or secondary. Secondary RBD can be related to neurodegenerative disorders, other neurologic disorders, sleep disorders, or medications, including withdrawal states (Aurora et al., 2010). Symptomatic RBD in older adults is most often associated with an α-synucleinopathy, which manifests as dementia with Lewy Bodies (DLB), Parkinson’s disease (PD), or multiple system atrophy (MSA) (Boeve and Saper, 2006; Boeve et al., 2001, 2003, 2004, 2007; Gagnon et al., 2006a; Iranzo et al., 2006; Mahowald et al., 2007; Postuma et al., 2006b; Stiasny-Kolster et al., 2005; Weyer et al., 2006). Between 38% and 65% of patients with “idiopathic” RBD followed longitudinally subsequently developed a α-synucleinopathy 10 to 29 years after the onset of RBD (Iranzo et al., 2006; Postuma et al., 2009a; Schenck et al., 1996, 2003). Based on a prospective longitudinal study of 93 iRBD patients, Postuma et al. (2009) recently estimated that the 5-year risk of neurodegenerative disease was 18%, increasing to 41% and 52% at 10 and 12 years, respectively.

RBD is often the first clinical sign of an α-synucleinopathy, preceding other early nonmotor signs (olfactory dysfunction and depression) of Parkinsonism and/or dementia by years or decades (Boeve et al., 1998; Claassen et al., 2010; Iranzo et al., 2006; Postuma et al., 2009b; Stiasny-Kolster et al., 2005; Weyer et al., 2006). A recent retrospective study showed that RBD preceded other signs or symptoms of synucleinopathy by as long as 50 years (median interval 25 years) (Claassen et al., 2010). However, RBD behaviors that typically
appear early in the course of synucleinopathies may lessen or disappear later (Boeve et al., 1998; Bugalho et al., 2011). RBD can be misdiagnosed as sleep-related epilepsy, agitated sleepwalking, nocturnal panic attacks, nocturnal hallucinations, agitated delirium in intensive care units, sundowning, and/or intentional spouse abuse. Some patients with RBD also have OSA, nocturnal epilepsy, confusional arousals, and/or sleepwalking.

For example, dream enactment behavior during REM sleep can be observed in patients with severe OSA. Iranzo et al. reported 16 adults with severe OSA (mean AHI of 68 ± 19/hour) who were thought likely to have RBD because they complained of dream-enacting behaviors and unpleasant dreams (Iranzo and Santamaria, 2005). However, skeletal atonia was preserved during REM sleep in these patients with “pseudoRBD,” and CPAP therapy eliminated the abnormal behaviors, unpleasant dreams, daytime sleepiness, and snoring.

Epilepsy coexisting with RBD was found by Manni et al. (2007) in 10 (12.5%) of 80 older adults (mean age 71 ± 7 years, 47 men) with epilepsy. RBD episodes preceded seizure onset by 4.5 years in six subjects and followed it by 9.7 years in four. RBD has also been observed in 10% to 15% of patients with narcolepsy with cataplexy (Billiard, 2009; Dauvilliers et al., 2007; Schenck and Mahowald, 1992), and others have RSWA without clinical RBD (Dauvilliers et al., 2007). RBD in patients with narcolepsy needs to be distinguished from sleepwalking, PLMS, and abnormal dreaming, all more common in these patients. Medications prescribed to treat their cataplexy can induce or aggravate RBD.
The personality, temperament, and behaviors during RBD episodes may mean that the extrapyramidal system is bypassed in these patients during REM sleep. RBD is also more intelligible speech during their RBD episodes than when the patients singing, dancing, saluting, marching, clapping, or snapping their fingers (Oudiette et al., 2009).

RBD behaviors are often more plentiful and severe at the end of the night when REM sleep is most plentiful (Irzano et al., 2009). Paroxysmal motor RBD behaviors were more likely to occur in phasic portions of REM sleep (when rapid eye movements and saw tooth waves are seen) rather than in tonic REM sleep (Manni et al., 2009). A case-control study of five PD patients with RBD found that limb jerking was the most common behavioral expression of RBD (Frauscher et al., 2007).

Speech in RBD events can vary from mumbling to logical sentences. A particularly interesting study by De Cock et al. (2007b) found that 38% of 53 PD patients moved much better and had louder more intelligible speech during their RBD episodes than when awake. The authors speculated that improved motor and vocal abilities during RBD events may mean that the extrapyramidal system is bypassed in these patients during REM sleep. RBD is also a dream disorder: patients report that the content of their dreams become increasingly violent and disturbed. Their dreams often involve frighteningly unfamiliar people or animals, confrontation, attacking or chasing themes, and the behaviors often depict the sleeper depending himself. The personality, temperament, and behavior of RBD patients awake are discordant with their nocturnal aggressive behaviors.

**Video-Polysomnographic Features of REM Sleep Behavior Disorder**

Video-PSG confirmation of RSWA is required to diagnose RBD (Kushida et al., 2005). RBD is diagnosed by (1) excessive amounts of phasic and/or tonic submentalis and/or excessive phasic limb EMG activity during REM sleep on video-PSG; (2) the presence of abnormal REM sleep clinical dream enactment behaviors during video-PSG and/or a clinical history of sleep-related injurious, potentially injurious, or disruptive behaviors; and (3) exclusion of substance abuse; other medical, neurologic, psychiatric, or sleep disorder; or medication(s) that better explain the sleep disturbance (Aurora et al., 2010; Iber et al., 2007; Medicine, 2005; Walters et al., 2007).

To score excessive tonic and/or phasic EMG activity during REM sleep, we use scoring criteria published by the AASM in 2007 (Iber et al., 2007). A 30-second epoch of REM sleep is regarded as containing excessive tonic activity when the amplitude of the chin EMG is of higher amplitude than its lowest amplitude during NREM sleep for 50% or more the epoch (Fig. 3). Excessive phasic EMG activity in REM sleep is scored by subdividing the 30-second PSG epoch into 10 consecutive 3-second mini-epochs, identifying and tallying the number of 3-second mini-epochs that contain phasic EMG activity lasting 0.1 to 5.0 seconds, which is at least four times as high as the baseline EMG activity. If five or more 3-second mini-epochs of a 30-second epoch of REM sleep contain excessive phasic EMG activity, the REM sleep epoch is regarded as containing excessive phasic EMG activity (Fig. 4).

If a video-PSG contains excessive EMG activity during REM sleep but the patient has no clinical history suggestive of dream enactment behaviors and none seen on the PSG, we say that the PSG shows RSWA. Because many of the RBD motor and/or vocal behaviors usually last only a few seconds, we have found it particularly useful to review carefully epochs of REM sleep in the video-PSG when the excessive phasic motor activity is observed, confirming clinical manifestations of RBD that are easily missed. However, clinical confirmation of RSWA and/or RBD may be missed by a single night of video-PSG. Zhang et al. (2008) retrospectively analyzed video-PSG of 55 patients with RBD who have at least two consecutive video-PSGs. They found (1) weak first night effects with increased REM sleep latency, increased NREM 1 sleep, and increased mean number of arousals per hour of sleep (arousal index); (2) they could diagnose RBD in 95% of patients by recording and carefully analyzing the amounts of REM-related EMG activity, RSWA, and motor events observed on video-PSG; (3) no significant difference in the amounts of phasic and tonic EMG activity during REM sleep between nights 1 and 2 but dream enactment motor events varied between nights; (4) interstudy agreement were lowest for video analysis (kappa coefficients of 0.64, 0.51, and 0.31 between nights 1 and 2 for REM sleep-related EMG activity, RSWA, and video analysis); and (5) they were able to diagnose RBD even in patients with concomitant OSA, use of CPAP, or clonazepam treatment. Note that dream enactment behaviors are more susceptible to night-to-night variability, so a single night of video-PSG in a patient with no clinical history of RBD might be labeled only RSWA.

Patients with RBD characteristically exhibit excessive tonic activity in their chin EMG and/or excessive phasic activity in their chin and/or limb EMG. In routine PSG, we only record EMG from the chin and anterior tibialis leg muscles. We add surface EMG electrodes to the wrist extensors when recording patients with suspected RBD (Aldrich and Jahnke, 1991; Chesson et al., 1997; Frauscher et al., 2007; Kushida et al., 2005).

**Scoring REM Sleep in Patients With REM Sleep Without Atonia**

Epochs of REM sleep in a PSG is scored first and foremost by the presence of low or absent chin muscle activity, soon followed by rapid eye movements, saw tooth waves, and an EEG background of continuous low-amplitude mixed frequencies (Fig. 2). Burns et al. (2007) developed a computerized metric to assess chin EMG variance to confirm RSWA in patients with RBD. They thought that a normal chin EMG during REM sleep should be below the lowest 5% of its amplitude during NREM sleep.

We must score REM sleep in patients with RSWA and RBD “ignoring” the chin EMG: (1) the onset of a REM sleep period is identified by the first rapid eye movement in the presence of EEG activity typical of REM sleep (low-amplitude mixed frequencies and...
absence of sleep spindles or K-complexes); (2) offset of REM sleep by a specific marker of another sleep stage (sleep spindle, K-complex, EEG arousal, or wakefulness) or the absence of rapid eye movements for 3 minutes; (3) if an epoch of REM sleep is disrupted by movement arousals or artifact, continue to score REM sleep as long as rapid eye movements, increased motor activity with erratic behavior, or incongruous vocalizations were used to identify reappearance of REM sleep if the EEG signals were consistent with REM sleep (low-voltage mixed frequencies) and alpha frequencies absent; and (4) if a patient has OSA fragmenting REM sleep by excluding EMG increases from respiratory-induced arousals and snoring artifacts (Dauvilliers et al., 2007; Iranzo and Santamaria, 2005; Lapierre and Montplaisir, 1992).

**Which Muscles Should We Record to Identify REM Sleep Without Atonia in a Polysomnogram?**

Unfortunately, the AASM rules for scoring RSWA and clinical RBD in a PSG do not specify which (and how many) skeletal muscles should be recorded during a video-PSG to confirm RBD or RSWA. Recent studies show that excessive phasic EMG activity and RSWA during REM sleep is (1) more frequent in distal than proximal limb muscles; (2) more frequent in upper limbs than lower limbs; and (3) RSWA cannot be scored based on chin EMG alone but requires recording and scoring of excessive phasic EMG activity in the upper and lower distal limb muscles.

Frauscher et al. (2008) recorded 13 different muscles in 17 RBD patients (9 with PD) to determine which combination of muscles provides the highest rates of phasic EMG activity during REM sleep in patients with RBD. They found that the greatest amounts of excessive phasic EMG activity during REM sleep was observed in the mentalis, flexor digitorum superficialis, and extensor digitorum brevis muscles. This combination of muscles detected 82% of all mini-epochs containing phasic EMG activity while only 55% of excessive phasic activity would be scored if only the chin EMG was recorded.

Bliwise and Rye (2008) recorded EMG activity from five muscle groups (mentalis, left/right anterior tibialis, and left/right brachioradialis) in 11 patients with RBD compared with 31 elderly controls (without RBD or PLMS). They found that the greatest amounts of excessive phasic EMG activity during REM sleep in patients with RBD compared with healthy older controls were recorded from the mentalis and brachioradialis muscles.

**When Is the Lowest Percentage of Excessive Muscle Activity in a Polysomnogram Considered REM Sleep Without Atonia?**

The AASM rules for scoring RBD and RSWA in a PSG only specify what constitutes excessive tonic or phasic EMG activity in a 30-second epoch of REM sleep (Burns et al., 2007; Fantini et al., 2005; Ferri et al., 2008; Frauscher et al., 2007; Mayer et al., 2008; Sforza et al., 1997). In defense of this omission, there was simply no enough evidence (or even expert consensus) available to write a rule for this. However, recently published studies are providing evidence to guide us.

Montplaisir et al. (2010) retrospectively reanalyzed video-PSG data in 80 patients with idiopathic RBD and 80 age- and gender-matched controls. Clinical RBD by history was confirmed in the video-PSG in 82%. Based on the case-control data, they were able to draw receiver operating characteristic curves for each of the REM sleep EMG parameters to determine cut-off values showing the highest sensitivity and specificity in discriminating RBD patients from controls. They found a tonic chin EMG density (percentage of 2-second mini-epochs of REM sleep) ≥30%, phasic chin EMG
density ≥15%, and ≥24 leg movements per hour of REM sleep would correctly identify RBD in 82% of their 80 patients but misidentified it in one control. Five patients with RBD by history and on video-PSG did not fulfill any of these PSG criteria. Unfortunately, this study collected from earlier studies could not provide crucial cut-off values for the upper limbs, which in other studies show the most plentiful excessive phasic activity during RSWA and RBD. They also found no between-group differences in sleep architecture with comparable values for total sleep time, sleep efficiency, REM sleep percent, efficiency, and mean number of rapid eye movements per epoch of REM sleep (REM density).

Montplasir et al. emphasized that their data showed an absence of a bimodal distribution, which suggests the loss of skeletal muscle atonia and/or the increase of excessive phasic activity during REM sleep in RBD represents a continuous process reflecting underlying disease progression. Supporting this contention, Iranzo et al. (2009) found that the percentages of excessive muscle activity in mentalis, biceps brachii, and anterior tibialis muscles during REM sleep was significantly greater in all five muscles recorded in 11 patients with idiopathic RBD when a second PSG was recorded a mean of 5 years later. Chin tonic EMG activity alone increased from 30% to 54% (Iranzo et al., 2009).

Consens et al. (2005) used computerized quantitative analysis techniques to identify and compare EMG activity from submentalis, forearm extensors, and anterior tibialis muscles in 9 patients with possible or probable RBD and 14 controls. They tallied the percentage of 30-second REM epochs with at least 15 seconds of tonic EMG activity and the percentage of 3-second REM mini-epochs that contained phasic EMG bursts from chin and bilateral surface EMG from the electrodes placed over the forearm extensors and anterior tibialis from two or more consecutive PSGs for each subject. They further devised an “RBD PSG score,” which was a combined measure of the proportion of 30-second epochs of REM sleep containing elevated muscle tone and the measure for the proportion of 3-second mini-epochs containing burst activity. Of note, the abnormalities found on the first night of PSG confirming RBD correlated well with those found on the second night (p > 0.70, P < 0.0001), confirming again that the RSWA seen in one night of PSG is more often comparable to that seen the next night.

They found the mean percentage (±SD) of REM sleep epochs containing excessive tonic chin EMG activity were 29% ± 19% in those with RBD compared with 22% ± 18% in the controls. The mean percentage of 3-second mini-epochs of REM sleep containing excessive phasic muscle activity was 50% ± 41% in the patients versus 30% ± 38% in controls. The mean PSG RBD scores were 40% ± 22% in those with RBD compared with 26% ± 24% in controls (P = 0.02). Consens et al. suggested that ≥10% of REM sleep spent with elevated EMG tone or phasic burst activity would confirm a diagnosis of clinical RBD (based on the receiver-operator curves), providing a sensitivity of 89% but a specificity of only 57%.

Ferri et al. have developed a “REM sleep atonia index (RAI)” to identify abnormally elevated submentalis muscle amplitude during REM sleep in patients with idiopathic RBD, narcolepsy with cataplexy (with and without RBD), and normal age-matched controls using computerized quantitative analysis (De Carli et al., 2004; Ferri et al., 2008, 2010). They define RAI as the ratio between the percentage of EMG 1-second mini-epochs with average amplitude ≤1 μV and the total mini-epochs (excluding those with 1 < amplitude ≤2 μV). Mathematically, the RAI can vary from 0 (absence of mini-epochs with amplitude ≤1 μV and consistent with complete RSWA), to 1 (stable EMG atonia).

After correcting for signal noise, they report that RAI values <0.8 were strongly indicative of RSWA, values 0.8 to 0.9 less evident (and often seen in older but not young controls), and >0.9 present in majority of controls. Three-fourths of their subjects with idiopathic RBD had RAI <0.9, and all with RBD and MSA had RAI <0.8. In another study, Ferri et al. (2008) found that RAI was lower (greater percentage of REM sleep with excessive tonic chin EMG) in 34 patients with narcolepsy with cataplexy compared with age-matched normal controls. Seventeen of the patients with narcolepsy had PSG-confirmed RBD. Those with RBD had more phasic chin EMG activity than those without RBD, but the elevated tonic chin EMG values did not differ between those with and without RBD.

### Symptomatic Forms of REM Sleep Behavior Disorder

Frauscher et al. (2010) found RBD in 34 (4.8%) of 703 consecutive patients referred to a tertiary sleep center. RBD was idiopathic in 11 patients and symptomatic in 23; causes of symptomatic RBD were parkinsonian syndromes in 11, antidepressants in 7, narcolepsy with cataplexy in 4, and pontine infarction in 1. Using logistic regression analysis, the investigators found that the presence of a parkinsonian syndrome increased the odds ratio a patient would have RBD by 16.8 times, narcolepsy with cataplexy (odds ratio 10.7). The odds ratio of RBD increased 1.5 years for every 10-year increase. However, secondary RBD can also develop in patients with neurologic disorders that are not synucleinopathies and have been observed in patients with brain lesions that most often involve the pontine tegmentum. Table 8 summarizes other neurologic and neurodegenerative disorders and medications associated with chronic RBD. Because the frequency of RBD is so much greater among patients with DLB, MSA, and PD with dementia, we cite the medical literature regarding this in these patient populations.

### Dementia With Lewy Bodies

DLB is the second most common late-life dementia and probably accounts for approximately 20% of all late-onset dementias, 10% to 15% at autopsy (McKeith et al., 2005). RBD occurs in 50% to 80% of patients with DLB (Boeve et al., 2004). The percentage of patients with DLB who have RBD is likely to be greater than reported because many patients deny having it. One study found 59% of 17 patients with video-PSG-confirmed RBD were unaware of their RBD behaviors and 18% could not recall

<table>
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<th>TABLE 8. Other Neurological Disorders Associated With REM Sleep Behavior Disorder</th>
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<tr>
<td>Narcolepsy with cataplexy (10%–15%, others have RSWA without clinical RBD) (Billiard 2009; Davviliers et al., 2007; Schenck and Mahowald 1992)</td>
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<tr>
<td>Parkinson’s disease due to Parkinson mutations (10%–15%) (Iranzo et al., 2005; Plazzi et al., 1998; Tachibana and Oka, 2004)</td>
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<tr>
<td>Paraneoplastic limbic encephalitis with voltage-gated potassium channel antibodies (five cases) (Iranzo et al., 2003)</td>
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<tr>
<td>Guadalpean Parkinsonism (78%) (De Cock et al., 2007a; Iranzo et al., 2009)</td>
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<tr>
<td>Progressive supranuclear palsy (&lt;5%) (Arnulf et al., 2005; Cooper and Josephs, 2009; Montplasir et al., 1997; Pareja et al., 1996)</td>
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<tr>
<td>Huntington’s disease (12%) (Arnulf et al., 2008)</td>
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<td>Spinocerebellar ataxia type 3 (Friedman et al., 2003; Iranzo et al., 2003; Syed et al., 2003)</td>
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<td>Pure autonomic failure (Weyer et al., 2006)</td>
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<td>Chiari malformations (20%) (Henriquez-Filho and Pratesi, 2008)</td>
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<tr>
<td>Structural lesions most often involving the pontine tegmentum (Kimura et al., 2000; Plazzi and Montagna, 2002; Tippmann-Peikert et al., 2006)</td>
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<tr>
<td>Ischemic infarction, multiple sclerosis, brain stem tumor, trauma, or surgery</td>
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unpleasant dreams (Iranzo et al., 2009). A diagnosis of RBD in a patient with Parkinsonism or dementia warrants consideration of DLB. Diagnostic criteria for probable DLB is suggested by the presence of dementia and RBD with at least one of the three core features of visual hallucinations, fluctuating cognition, or Parkinsonism (McKeith, 2006).

Recognizing DLB is clinically important because patients with it often have (1) an extreme sensitivity to the side effects of neuroleptics; (2) a good response to cholinesterase inhibitors; and (3) their episodes of disturbed consciousness or “delirium” misdiagnosed. DLB tends to have a more rapid progression than Alzheimer’s disease (mean survival 8 ± 3 years) and two-thirds are men (in contrast to the predominance of Alzheimer’s disease in women (McKeith et al., 2005). Consider DLB in patients who have unexplained recurrent delirium, episodic disturbances of consciousness, syncope, and sleep disorders.

Parkinson’s Disease

RBD occurs in approximately 15% to 50% of patients with PD (Comella et al., 1998; De Cock et al., 2008; Gagnon et al., 2002; Lee et al., 2009). Another third of PD patients have RSWA on their PSG without any clinical history of RBD behaviors or symptoms (Gagnon et al., 2002). RBD may be even more common in PD because 65% were unaware of their RBD symptoms and 24% did not recall violent dreams (Iranzo et al., 2005).

Recent studies suggest that PD patients with RBD may have a different neurodegenerative profile than those without RBD (Bliwise et al., 2010; Bugalho et al., 2011; Kumru et al., 2007; Postuma et al., 2008). PD patients with RBD were (1) more likely to have rigid-akinetic PD and less likely to have tremor-predominant PD (Bliwise et al., 2010; Bugalho et al., 2011; Kumru et al., 2007; Postuma et al., 2008); (2) more often were older, had a longer duration of PD, and were more disabled (Lee et al., 2010); and (3) have orthostatic hypotension (71% compared with 27%, without RBD) (Postuma et al., 2008).

A few studies have examined whether sleep architecture and phasic EMG activity is different in PD patients with rigid-akinetic and tremor-predominant forms, especially because RBD is much more likely to develop or be present in those with rigid-akinetic PD. Higher percentages of excessive phasic EMG activity during REM and NREM sleep were found in patients with rigid-akinetic PD compared with tremor-predominant PD (Bliwise et al., 2010). PD patients with RBD are more likely to have showed EEG backgrounds when awake compared with PD patients without RBD (Gagnon et al., 2004) and poorer performance in executive function, verbal memory, and visuospatial dysfunction on neuropsychological testing than PD without RBD (Vendette et al., 2007).

Multiple System Atrophy

RBD is often the initial symptom of MSA (Tison et al., 1995). Clinical RBD was reported in 69% of 39 consecutive cases of MSA, and 90% had RSWA on their video-PSG (Plazzi et al., 1997). As MSA patients with RBD are often unaware of their RBD behaviors or disturbing dreams, the percentage of MSA with clinical RBD may be underestimated without video-PSG (Tachibana and Oka, 2004). RBD is a red flag for the diagnosis of MSA (Köllensperger et al., 2008).

Consider MSA in a RBD patient who has axial rigidity (less often a jerky postural tremor) and a history of (1) symptomatic orthostatic hypotension or urinary incontinence beginning <1 year after the onset of the Parkinsonism; (2) early postural instability and falls <3 years after onset; and (3) rapid progression to wheelchair within <5 years despite dopaminergic therapy (Iranzo et al., 2005; Köllensperger et al., 2008; Plazzi et al., 1997). Consider MSA in any older woman who has or develops RBD because no gender predominance is observed in MSA. MSA patients with RBD on video-PSG had higher percentages of RSWA, greater periodic limb movement indexes, and less total sleep time when compared with PD patients with RBD (Iranzo et al., 2005). Some of the highest percentages of RSWA are observed in patients with MSA.

Treatment Strategies for REM Sleep Behavior Disorder

The first step in the treatment of RBD is to remove drugs that can precipitate or worsen it. Drugs used to treat depression or anxiety which have been reported to cause or worsen RBD include paroxetine, fluoxetine, imipramine, venlafaxine, and mirtazapine (Onofrj et al., 2003; Parish, 2007; Schenck et al., 1992; Schutte and Doghmaji, 1996; Teman et al., 2009). Fluoxetine or sodium oxybutyrate is used to treat cataplexy in patients with narcolepsy with cataplexy and can induce or aggravate their RBD (Abiri et al., 2007; Ahmed, 2008; Schenck and Mahowald, 1992). Other drugs that have been reported to cause RBD include isopropyl (a beta-blocker), rivastigmine, and withdrawal from alcohol or barbiturates, but all of these are based solely on case reports (Aurora et al., 2010b; Iranzo and Santamaria, 1999; Yeh et al., 2010).

Many drugs do seem to increase EMG activity in PSG, worsen symptoms of restless legs syndrome and PLMS, and cause or exacerbate RBD and/or RSWA. Hoque and Chesson (2010) recently analyzed evidence for drugs causing excessive EMG activity in patients with restless legs, periodic limb movements, RBD, and RSWA. They found that the strongest evidence for drug-induced restless legs syndrome were for escitalopram, fluoxetine, t-dopa/carbidopa, pergolide, l-thyroxine, minserain, mirtazapine, olanzapine, tramadol, bupropion, citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine for periodic limb movements and clomipramine, selegiline, and phenelzine for drug-induced RBD/RSWA.

If a drug that is aggravating RBD cannot be discontinued (too often the case in patients with concomitant depression treated with venlafaxine or a selective serotonin reuptake inhibitor), try reducing the daily dose. Consider prescribing bupropion to treat depression in patients with RBD because it does not worsen RBD, restless legs syndrome, or PLMS (Kim et al., 2005; Lee et al., 2009; Nozinger et al., 2000; Yang et al., 2005).

The next step in treating RBD is to secure the bedroom and protect the patient and bed partner from injury. Safety measures to protect the patient and bed partner from RBD behaviors include padding bedrails, pillow or plastic screen barricades, pad sharp corners and move furniture away from the bed, remove dangerous objects from bedroom, locks on doors and windows, motion-detected alarms, and consider having the patient sleep on a mattress on the floor or in another bedroom (Abad and Guillemainault, 2004; Olson et al., 2000; Schenck and Mahowald, 1991). Of note, active restraints should not be used because sudden twisting movements during RBD events may lead to greater injury (Aurora et al., 2010).

RBD warrants pharmacotherapy to (1) prevent injuries in patients with violent dream enactment; (2) reduce the intensity of the unpleasant dreams; and (3) permit the bed partner to sleep safely and comfortably near the patient (Aurora et al., 2010). Unfortunately, there are no randomized, double-blind controlled or head-to-head clinical trials of pharmacologic therapy for RBD. Most often clonazepam or melatonin (and sometimes in combination) are prescribed to treat RBD.

Small case series and case reports have found clonazepam effective in treating RBD in the majority (90%) of patients (Comella et al., 1998; Fantini et al., 2005; Gagnon et al., 2006b; Iranzo et al., 2005, 2009; Massironi et al., 2003; Nomura et al., 2003; Olson et al., 2000; and Santamaria, 1999).
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epochs of RSWA remained lower in patients who then were crossed (39% vs. 27%, reduced the number of 30-second REM sleep epochs of RSWA 4-week period. Compared with baseline, melatonin significantly treat RBD than clonazepam because it has few side effects (Aurora argues that melatonin may be a better first choice of a medication to... patients with epilepsy improves seizure control; (6) why is sleep macro- and microarchitecture altered in patients with epilepsy; and (7) the link between particular epilepsies, nonepileptic parasomnias, sleep fragmentation, and arousal to understand how to best improve overall function and that a multidisciplinary model will best serve patients with these disorders.

**REFERENCES**


Boeve BF, Silber MH, Ferman TJ. REM sleep behavior disorder in Parkinson’s


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Montagna P. Nocturnal paroxysmal dystonia and non-rapid eye movement disorder different from bruxism. Mov. Disord. 2007;12:1819–1822.


