Evaluation and Management of RLS and PLMD

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Periodic Leg Movements of Sleep (PLMS)

Periodic Leg Movements of Sleep have been well defined as stereotyped involuntary movements occurring during sleep periods in a series of movements that for a given individual have a remarkably stable period, typically about 15–30 s. The naming and very loose criteria defining these have unfortunately created considerable confusion. The periodicity requirement became extended to include movements occurring with intermovement intervals (IMI) of 5–90 s ignoring movements with an IMI <5 s [1]. This has led to the identification of movements as periodic that are actually somewhat random without a well-defined mode describing their period. For example, some reports describe these as occurring for arms [2], leading to the unfortunate use of the term periodic limb movements. More careful analyses revealed that arm movements rarely show the well-defined modal period required for periodic phenomena [3]. They reflect somewhat randomly occurring frequent arm activity that is considered periodic because of an overly inclusive period requirements that have been used to define PLM.

Leg movements meeting the broad criteria for PLMS have also been found to occur in resting waking either during the night sleep period or for RLS patients when lying down attempting to rest without movement during the day in what has been called the suggested immobilization test [4]. These periodic leg movements in waking have been termed PLMW, but it should be again noted that the periodicity is not well established for these events during waking [5] except possibly when they occur in transitions into or out of sleep during the night's sleep period [6].

There is an extensive literature on PLMS that is exclusively based on EMG recordings of the anterior tibialis muscle. Thus, the considerable knowledge we have about PLM applies to activation of the anterior tibialis muscle that produces only a dorsiflexion and small inversion of the foot. This may occur with leg movements, but the PLM we measure is not a leg movement, nor does it involve any other part of the body. The foot dorsiflexion of PLM often occurs with activation of other muscles producing leg movements, but in one study about 39 % of the PLM occurred without any significant leg movement [7]. The appropriate terminology therefore is periodic foot dorsiflexions, but given the terminology history, the term periodic leg movements is acceptable with the caveat that the legs are often not moving.

The dorsiflexion of PLMS has been described as part of a larger envelope of episodic muscle activation, but the few studies attempting to document a more extended muscle pattern of periodic leg muscle activations during sleep have not provided a coherent picture except for the consistently primary role of the anterior tibialis muscle. Thus, when other leg muscles are recorded for observed periodic EMG events, the anterior tibialis is essentially always involved and usually is the first muscle to contract [8]. In about 13–39 % of the cases, it is the only muscle or movement involved [7, 9, 10]. Sometimes the anterior tibialis muscle activation of PLMS also occurs with activation of the extensor hallucis longus producing an extension of the big toe with some ankle dorsiflexion partially mimicking the Babinski's reflex [11]. PLMS occasionally occur with a triple flexion reflex at the ankle, knee and hip [10]. PLMS are too slow to be called myoclonus. PLMS typically last a few seconds (see Fig. 40.1). However, the movements may begin with one or more brief, myoclonic jerks that then blend into a more tonic phase; alternatively, a more sustained movement may terminate in a jerk [12, 13]. Movements are often bilateral, involving both feet, but may be predominant in one foot or alternate between feet. This may depend on sleeping position as well as biological factors. The most striking characteristic feature of PLMS is their repetitive, very periodic nature

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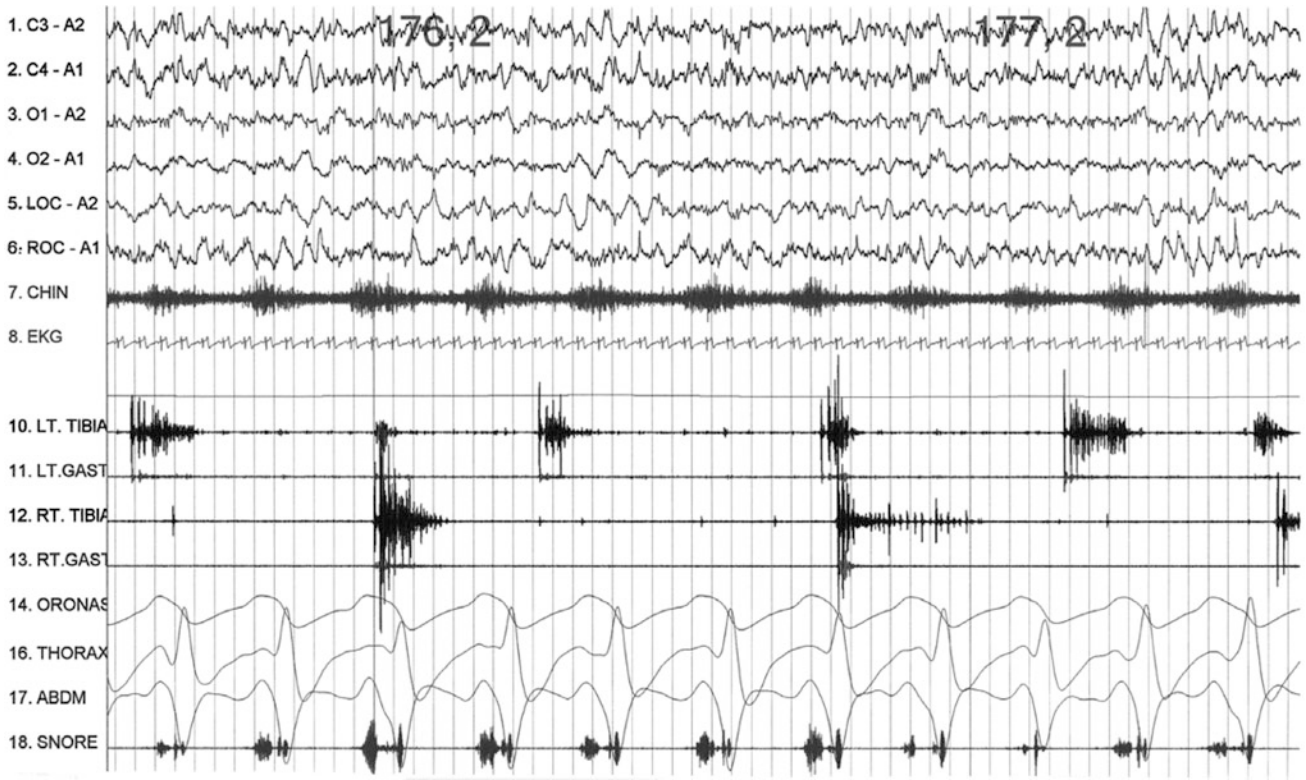

Fig. 40.1 Polysomnographic (PSG) recording showing periodic limb movements in sleep (PLMS) characterized by dystonic and dystonic–myoclonic electromyographic (EMG) bursts in left (LT) and right (RT) tibialis (TIBIA) and gastrocnemius (GAST) muscles during stage 2 (N2) non-rapid eye movement (NREM) sleep in an adult patient with restless legs syndrome (RLS). Top 4 channels show electroencephalograms (EEG) using international nomenclature (*A1* left ear; *A2* right ear; *ABDM* abdominal respiratory effort; *CHIN* submental EMG; *EKG* electrocardiogram; *LOC* left electro-oculogram; *ORONAS* oronasal airflow; *ROC* right electro-oculogram; *THORAX* chest respiratory effort)

providing a well-defined mode for the period or inter-movement interval (IMI). The variation in the inter-movement interval (IMI) between onsets of PLM approximates a lognormal distribution for the classically defined IMI ranging from 5 to 90 s. The average and standard deviation of the log IMI provides a measure of the periodicity and its spread which are both more stable over nights than is the measure of actual number of PLMS [14]. These measures with number of PLMS describe the periodic nature of the movements and the density with which they occur. There are also leg movements in sleep with IMI <5 that appear to be somewhat random in log space. An IMI of 10 s provides the best discrimination between these different distributions for short and long IMI. Thus, PLMS events are better described as occurring with IMI >10 s [15]. PLMS in moderate-to-severe RLS patients often occur in bouts of dozens to a hundred or more movements that last for many minutes. While most PLMS occur in stage 2 sleep, they also occur in all of the other stages of sleep including some in REM sleep and in waking during the sleep period [6].

Periodic Leg Movements of Sleep are defined by PSG recording. The current American Academy of Sleep Medicine (AASM) manual [16] and the World Association of Sleep Medicine (WASM) [1] criteria count movements if they occur in sleep as part of a series of four or more movements during any sleep stage including wake with IMI intervals of 5–90 s (in some older publications, intervals as short as 4 s or as long as 120 s have been accepted). Recent data have indicated the IMI interval for PLMS should be adjusted to be 10–90 s [15]. EMG activation must last 0.5–10 s. The number of movements associated with arousals may also be counted [1]. Box 40.1 lists the WASM criteria defining PLMS. Although patients may also have foot movement meeting the PLM criteria during wakefulness, only movements that occur during sleep are typically counted. A new measure, the periodicity index, is a ratio of all PLMS (with IMI range of 10–90 s) to all leg movements in sleep [17].

Box 40.1: Definition of Periodic Leg Movements in Sleep or Resting Wake (PLM)

Candidate leg movement (CLM) is defined by the following characteristics of a surface EMG recording of the anterior tibialis muscle

CLM onset occurs with EMG ≥ 8 μV above resting EMG.
CLM ends at the onset of the first 0.5 s with EMG always <2μV above resting EMG
CLM must be ≥ 0.5 and ≤ 10 s duration

Periodic leg movement (PLM) is a CLM that

has an intermovement interval (IMI) defined by onset from preceding CLM to onset of this CLM that is ≥ 5 and ≤ 90 s.

Is one of the 4 consecutive CLM that meet the IMI criterion above (giving 3 consecutive IMIs of 5–90 s).

Combining movements from two legs into one PLM event.

The movements from either leg should be counted.

Movement in one leg separated by less than 0.5 s from a movement in the other leg should be counted as a single leg movement.

From Zucconi et al. [1].

The biological basis for PLMS is particularly complicated by interaction with sleep state and the expression of these with spinal cord transactions. It is unclear how much the periodicity of PLMS stems from spinal versus brain activity, but certainly brain activity at least modulates PLMS expression and periodicity if not driving these. For example, neurotoxic lesions at the ventral mesopontine junction in cats produce increased leg movements in sleep that to some degree imitate PLMS [18]. The genetics of PLMS appear to match at least in part that for RLS with shared association for allelic variations in BTBD9, MEIS1, MAP2k4/SKOR1, TOX3, and PTPRD [19–21]. The possible genetic relation of RLS to PLMS is further supported by family history data indicating that increased PLMS occur with older adults without RLS who have an RLS relative but do not occur for those with a family member who has neither RLS nor significant number of PLMS [22]. PLMS also like RLS occur more with low serum ferritin, indicating a shared relation to impaired iron status [23]. Thus, occurrence of PLMS not attributed to medical conditions or medications may represent significant increased risk of RLS and accordingly may carry some of the health risks associated with RLS.

Individuals with elevated frequency of PLMS are often asymptomatic, but may have unrecognized sleep problems, particularly for those with higher rates of PLMS and/or more pronounced general leg movements occurring with the PLMS. Unfortunately studies do not provide information of the extent of general leg movement with the PLMS, so the potential for PLMS impact on sleep is not adequately described. Some small studies have indicated that the number of PLMS, disregarding any amplitude considerations, have little impact on sleep [24–26]. A larger population study, however, documented that PLMS with rates >15/h relate to poor sleep [27]. Amount of PLMS may relate to sleep disturbance more when the PLMS involve a greater spread of muscle activation not limited to the foot movement of the anterior tibialis, as is often clinically reported in RLS patients, but aside from limited data reported in one abstract [28], this has not been adequately documented. Bed partners sometimes complain more about the movements than the patients and are often an excellent source of information about the condition and its severity.

Periodic Leg Movements of Sleep may begin at any age, but prevalence increases markedly in healthy elderly people, with as many as 58 % having a PLMS index greater than 5 [29, 30]. Some studies have found no association between number of PLMS and either objective measures of sleep or symptomatic reports in the elderly, or only very weak associations [31]. Because of these findings, elderly patients with PLMS should only be treated when the PLMS can be linked to their sleep complaints, which usually means excluding other sources of sleep dysfunction.

Periodic Leg Movements of Sleep may occur as an isolated condition or may be associated with a large number of sleep, neurologic, or other medical disorders, and with medications such as neuroleptics and antidepressants. Among sleep disorders, the more striking associations are with narcolepsy [32–36] and RLS [37], because PLMS are common in these patients even at a relatively young age. PLMS are also common in patients with OSA [38] and RBD [39]. Patients with OSA may have a significant degree of PLMS, sometimes associated with significant sleep fragmentation even after successful treatment of their apnea [38]. The presence of PLMS in disorders involving the basal ganglia including Parkinson's Disease (PD) [40, 41], Lewy-Body Dementia [42], and MSA [43–45] is also noteworthy and may contribute to sleep problems in these disorders. Among medical conditions, the association of PLMS with uremia and end-stage renal disease is likely to be an important one related to mortality [46, 47] and to risks of stroke, cardiovascular disease, and cardiac structural abnormalities [48, 49]. PLMS have also been associated with increased risk of mortality for patients with systolic heart failure [50]. It has been reported that intrinsic and extrinsic lesions of the spinal cord may be associated with PLMS. This has been noted for multiple sclerosis [51, 52], radiculopathy [53], and transection [54]. It should be noted that the degree that these conditions produce leg movements with well-defined periodicity has not been well evaluated.

A number of studies have examined the relationship between PLM and other measures of central nervous system (CNS)/autonomic activity such as EEG, heart rate, and blood pressure. A general summary is that PLM are linked to periodic changes in activity level in different neural and neuro-responsive systems; furthermore, these modulations

do not appear to be caused by the PLM themselves, but are likely to be parallel phenomena produced by some common or associated biology [55–57]. Reducing the PLMS for RLS patients using dopamine agonists, however, appears to involve a biology that also reduces the associated cardiovascular changes. One suggestion is that the sympathetic nervous system may actually have a role in generating PLMS [58].

A specific feature of NREM sleep, the cyclic alternating pattern (CAP) is a recurrent alternation between "baseline" and more activated EEG patterns [59, 60]. PLM almost always occur during the activated ('A') phase of CAP [61]. The 'A phase' can be further subcategorized depending on the EEG frequencies most common: A1 activations consist primarily of slow waves while A3 activations are dominated by faster rhythms. The A3 phases are very strongly related to AASM-defined arousals. It has been proposed that a hierarchy of activations may be correlated with PLMS, with milder activations consisting solely of autonomic changes, slow waves, or K complexes while more intense ones are associated with EEG desynchronization and arousals [56, 57].

Periodic Limb Movement Disorder (PLMD)

Periodic Limb Movement Disorder is a condition diagnosed by excessive PLMS (>15/h for adults and >5/h for children) related to either significantly disturbed sleep at night or significant problems with functioning during the day that cannot be better explained by another disorder [62]. The prevalence and overall significance of PLMD is somewhat controversial. Individuals with elevated frequency of PLMS are often asymptomatic, but may have unrecognized sleep problems, particularly for those with higher rates of PLMS and/or more pronounced general leg movements occurring with the foot dorsiflexion of the PLMS. Unfortunately prior studies do not provide information of the extent of any general leg movement with the PLMS foot dorsiflexion, so the potential for PLMS impact on sleep is not adequately described. Small foot dorsiflexion no matter how many may not produce significant sleep or wake problems. Some small studies have found that the number of PLMS, disregarding any amplitude considerations, have little impact on sleep [24–26]. A large population study, however, documented that PLMS with rates >15/h relate to poor sleep [27]. Bed partners sometimes complain more about the movements than the patients and are often an excellent source of information about possible PLMD and its severity.

Restless Legs Syndrome

RLS is a neurological disorder of sensorimotor functioning predominantly characterized by an urge to move or restlessness focused on the legs that is provoked by rest, relieved by movement or CNS arousal, and increased with a circadian pattern during the evening and night [37]. RLS is a common disorder in the North American and European populations [63]. Associations with 16 specific allelic variants have been found by genome-wide association studies [21, 64–66]. However, while the degree of heritability determined by twin studies is relatively high (69 %) [67], the degree of familiarity is modest [68], and the 16 known RLS allelic variations account for a very small part (<15 %) of the familial pattern. The relative risk (Risch's lambda [69]) in first-degree relatives is in the range of 3–5 [68]. This suggests that RLS like other common diseases has a complex genetic diathesis that interacts with strong environmental factors. RLS, however, unlike other common diseases has one major well-defined commonly occurring environmental factor of iron deficiency [70]. Thus, all conditions compromising iron status produce increased risk of RLS. Conversely effectively all of the conditions that are associated with increased risk of RLS also have decreased iron status, e.g., pregnancy [71, 72], rheumatoid arthritis [73], and uremia [74, 75]. A unifying theme may be deficiency of iron in critical brain regions, particularly well documented for the substantia nigra and thalamus [76–83]. Box 40.2 lists major risk factors for RLS.

Box 40.2: Restless Legs Syndrome Risk Factors

Demographic and Lifestyle Factors

Increasing age
Female sex
Family history (early onset)
Living at high altitude
Smoking
Sedentary lifestyle
Caffeine
Alcohol consumption.

Medical, Surgical, and Neurological Conditions

Renal failure
Diabetes mellitus
Iron deficiency and anemia
Rheumatoid arthritis
Magnesium or vitamin B_{12} deficiency

Hypothyroidism
Heart failure
Surgical Gastric resection
Lung transplantation
Neurologic Polyneuropathies and radiculopathies
Parkinson's disease
Multiple sclerosis
Spinocerebellar ataxia (SCA3 or Machado–Joseph disease).

Other Factors
Pregnancy
Blood donations.

Medications (These may increase PLMS and also RLS)
Anti-histamines (only CNS-active)
Dopamine antagonists, e.g., antiemetics, antipsychotics (only CNS-active)
Serotonin and Norepinephrine reuptake inhibitors (SSRI, SNRI)
(Serotonin- and norepinephrine-releasing agents are also expected to increase PLMS and possibly RLS, but this has not been evaluated).

RLS significantly impacts patient's health and quality of life. Cross-sectional surveys have found RLS occurrence to be associated with general poor health, both physical and mental [63, 84–86], as well as specific disorders such as diabetes [87] and heart disease [88–90]. RLS may occur secondary to these disease states, particularly for cardiac diseases, rather than causing them [91]. RLS, in turn, relates to a diminished quality of life [63, 85, 92] and may be responsible for varied forms of psychological distress, particularly anxiety and depression [93, 94], impaired daily functioning [95], and loss of work productivity [96]. In vulnerable populations, such as dialysis patients, RLS occurs with increased mortality [96, 97]. Thus, there is evidence that RLS is provoked by a number of different disorders and also contributes to both morbidity and mortality. Much of this effect may occur through the impairment of sleep (Fig. 40.2) caused by RLS [98, 99]. Almost all studies have found RLS to be a chronic disease with both increasing prevalence (Fig. 40.3) and generally increasing severity with age [63]. Thus, RLS presents a cumulative burden substantially contributing to loss of quality of life and decreased health status in old age. Subjects with RLS report the same very poor health-related quality of life on the Medical Outcomes Short Form-36 as do those with other chronic diseases such as hypertension, congestive heart failure, and angina [85].

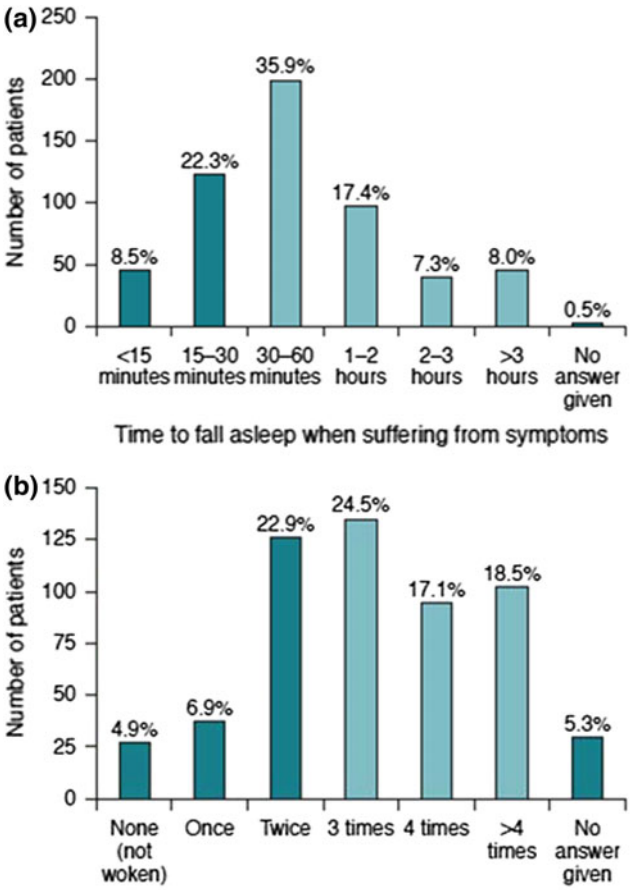

Fig. 40.2 Sleep impairment with RLS Fig. 40.1. Time to fall asleep (**a**) and number of reported awakenings (**b**) for RLS patients on nights when bothered by symptoms. *Unshaded bars* indicate those in the range considered abnormal and consistent with insomnia. Data are derived from RLS, Epidemiology, Symptoms, and Treatment (REST) general population study in the USA, France, Germany, Italy, Spain, and the United Kingdom. Reproduced with permission from Hening et al. [99]

Clinical Features and Diagnosis of RLS

restless legs syndrome was first extensively described by Karl Ekbom, a Swedish neurologist who named the condition and elucidated its clinical features [100–102]. Over the last decade, the key clinical features required for diagnosis have been determined through a consensus process [37, 103, 104] and include the 5 essential diagnostic features presented in Box 40.3. In addition, there are two significant specifiers that should be considered with the diagnosis: Clinical Course and Clinical Significance (see Box 40.3).

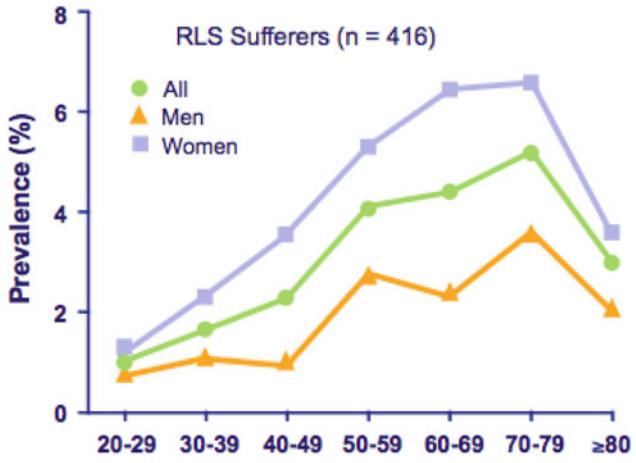

Fig. 40.3 RLS prevalence by age and gender. Population based sample of 15,391 adults ≥age 18 in Western Europe and the USA. RLS sufferer defined as those with RLS symptoms ≥2/week with moderate or severe distress when present. Note that there is little gender difference in the youngest group. Graph slightly modified from Allen et al. [63]

Box 40.3: Restless Legs Syndrome (Willis Ekbom Disease): Clinical Diagnostic Criteria

Adapted from Allen et al. [37].

Essential Diagnostic Criteria for RLS/WED

1. An urge to move the legs usually but not always accompanied by uncomfortable and unpleasant sensations in the legs.
2. The urge to move and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting.
3. The urge to move and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
4. The urge to move and any accompanying unpleasant sensations during rest or inactivity are worse in the evening or night than during the day or only occur in the evening or night (when symptoms are very severe, the worsening at night may not be noticeable but must have been previously present).
5. The occurrence of the above features is not solely accounted for by symptoms primary to another disorder or behavioral condition (e.g., myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping).

Specifiers for Clinical Course of RLS/WED

(a) Chronic-Persistent RLS/WED: untreated symptoms on average occurred ≥2/week for past year
(b) Intermittent RLS/WED: untreated symptoms occur on average <2/week for past year but with more than 5 lifetime events.

Specifiers for Clinical Significance

RLS/WED symptoms significantly impair social, occupational, educational, or other important areas of functioning

Special notes

1. Sometimes the urge to move occurs with discomfort involving arms as well as legs.
2. For very severe symptoms or in an advanced stage or in intractable cases relief with activity and/or the worsening in the evening may not be present, but then must have been previously present earlier in the course of the disease.
3. The specifiers for clinical course may not apply to children nor to special cases of provoked RLS/WED where frequency may be high but duration short, e.g., pregnancy.

Other body parts, especially the arms can be involved in RLS [105], especially during sever exacerbation of symptoms as occurs with RLS dopaminergic augmentation [106]. The legs, however, are almost always involved first and more prominently. RLS without leg symptoms at onset is at least rare [107], and the diagnosis requires involvement of the legs.

Clinical features supporting but not required for diagnosis [37] include familial aggregation [68, 108], significant numbers of PLM [4, 109] with established periodicity [110], prominent response to dopaminergic treatment [111], and daytime alertness despite significant sleep loss (Table 40.4). These supportive clinical features can be used to support diagnosis in uncertain cases, but the diagnosis must be based on evaluation of clinical history. The current diagnostic criteria apply to all conditions. Special problems with eliciting the sensory symptoms from children [112] and cognitively impaired elderly may require diagnosis guided by evaluating other conditions supporting the diagnosis (see Box 40.4).

Because frequent PLM are associated with RLS, the measurement of PLM has been proposed as a diagnostic test. The Montreal group has taken the lead in validating such a

test. They reported finding that the best discrimination for RLS from matched healthy controls was the PLMW per hour wake during sleep time but not dramatically better than the accuracy for PLMS per hour of sleep (92 % vs. 84 %). In contrast, somewhat unexpectedly the number of PLMW with arousal per hour of sleep had much lower accuracy (74 %) [109]. That study also included evaluation of the diagnostic accuracy of the Suggested Immobilization Test (SIT), a test designed to provoke RLS symptoms by having the subject remain sitting reclined in a bed without activity for a sustained period (usually an hour). The subject's rating of sensory discomfort provided about the same accuracy as the PLMS and PLMW, but there is an obvious problem of expectation for this sensory report from healthy versus diagnosed RLS patients. The PLMW from the SIT had poor accuracy (75 %). Work on evaluating the periodic nature of the PLM may provide better diagnosis, but this is only recently being considered [17].

To study responsiveness to dopaminergics, a test dose of levodopa was used. A greater than 50 % improvement of symptoms was strongly associated with a true RLS diagnosis, and a positive response to this test was a reliable indicator that a patient would subsequently benefit from dopaminergic treatment [113]. This has to be balanced against two larger clinical trials, where about 40 % of patients did not respond to the dopamine agonist ropinirole despite using a dose escalation to maximize treatment benefit [114, 115]. Thus, a failure to respond to dopamine treatment cannot be considered 100 % accurate for a negative diagnosis of RLS, and clearly there are always placebo responders in any clinical treatment.

Because there is, as of yet, no accepted laboratory marker for RLS, the standard for diagnosis remains a clinical one and is derived from the patient's history [116]. Laboratory evaluation is useful mainly to support the diagnosis of RLS and to identify any possible underlying medical condition (e.g., uremia) [116]. To determine RLS, in the clinic or the community, it is necessary to first establish the presence of the five diagnostic features noted previously. While earlier epidemiologic studies used ad hoc questions to ascertain the presence of RLS [117, 118], more recent ones have generated probes based on the first four diagnostic features [63, 119] [88, 95, 120–123]. A study at Johns Hopkins University, however, has demonstrated that up to 16 % of individuals without RLS may meet the original four diagnostic criteria [124]. Definitive diagnosis, therefore, requires discriminating RLS from its mimics as required by the 5th diagnostic criterion in the current diagnostic standard for RLS [37].

Several multi-question diagnostic instruments have been developed for epidemiologic studies. Two have been validated. One three-question instrument developed by Klaus Berger and endorsed at the National Institutes of Health (NIH) diagnostic consensus conference [104] had an inter-rater kappa of 0.67 between two experts who, however, had access to the questionnaire results [125]. This questionnaire, however, does not exclude mimics as required by the current diagnostic criteria. Another questionnaire developed at Johns Hopkins University was validated by independent clinician interview. It dealt somewhat with excluding mimics [126] and had a sensitivity of 89 % and specificity of 80 % in an American primary care practice. A much revised version of the questionnaire that specifically included items to exclude common mimics (Cambridge Hopkins RLS diagnostic questionnaire—CHRLSQ) was validated by the previously validated telephone diagnostic interview [127], had a sensitivity of 87 % and a specificity of 94 % in a population of blood donors [128]. The 13 items that are the validated diagnostic part of this questionnaire, the CHRLSQ-13, is available from the authors and has been used in clinical studies [70].

Two different approaches have been taken to make more definitive interview-based diagnoses for clinical or research purposes. First is a telephone interview, the Hopkins Telephone Diagnostic Interview for RLS (HTDI) [127]. This includes questions that address the diagnostic features, but also questions to assist with differential diagnosis and uncover mimics. Finally, there are questions concerning the key aspects of the disorder. Agreement with expert interviews was found to be 92 %, approaching the inter-rater reliability of two-expert face-to-face interviews of 96 % [127]. A second approach is a protocol that begins with questions about diagnostic features but then includes tests related to features supporting the diagnosis (see Box 40.4). This diagnostic interview includes questions on family history, a sleep study to look for PLM, a physical examination to exclude other causes for symptoms, and a dopaminergic challenge test [129]. It gives higher scores to patients with more frequent symptoms and therefore may not correctly identify those with sporadic symptoms. Its diagnosis is basically one of clinically significant RLS and is mainly useful in a sleep clinic or sleep laboratory setting.

Box 40.4: Conditions Supporting the RLS Diagnosis

- **Family History**: The prevalence of RLS among first-degree relatives of people with RLS is 3–5 times greater than in people without RLS.
- **Response to Dopaminergic Therapy**: Nearly all people with RLS show at least an initial positive therapeutic response to either L-dopa or a dopamine receptor agonist at doses considered to be very low in relation to the traditional doses of these medications used for the treatment of Parkinson's disease. This initial response is not, however, universally maintained.
- **Periodic Limb Movements** (during wakefulness or sleep): Periodic limb movements in sleep (PLMS) occur in at least 85 % of people with RLS; however, PLMS

also commonly occur in other disorders and in the elderly, but are uncommon in children.

- **Sleep Disturbance**: Disturbed sleep is a common major morbidity for RLS and deserves special consideration in planning treatment. This morbidity is often the primary reason the patient seeks medical attention.
- **Lack of profound daytime sleepiness**: The significant sleep disruption with moderate-to-severe RLS often fails to produce the expected profound daytime sleepiness (this may also occur for other hyperarousal conditions including some insomnias).

Overall either the CHRLSQ-13 or the HTDI (also appropriate for a clinical interview) provide the best general methods for diagnosis of RLS in studies.

Epidemiology, Biology, and Genetics of RLS

Prevalence of RLS in Different Ethnic Groups

It is not clear whether substantial and true differences exist between different ethnic groups in the prevalence of RLS. RLS must be defined clinically from history. Different groups with different languages unfortunately may respond differently when asked apparently equivalent questions about their medical history. Population-based studies, even when using several questions to diagnose RLS, vary in how many individuals detected have true RLS and how many of those with RLS are missed [125, 130]. A rough guide from one study with validation using trained physician diagnosis [131] is that the positive predictive value—how many of those identified with RLS actually have the disorder—is on the order of 40–60 % in studies using well-established diagnostic criteria based on the first 4 consensus diagnostic criteria without some screening required by the 5th diagnostic criterion. This means that less than half may actually have RLS. It is generally considered that false positives in such studies are more likely than false negatives, but this has not been tested.

Despite these methodological limitations, repeated studies have shown that there is a high prevalence of RLS in Western (European and European-derived) populations [63, 88, 95, 119–123]. It seems reasonable that the true rate in Western adults is on the order of 4–10 % for RLS at any frequency. One large-scale study, the REST population study conducted in the USA and Europe, found an overall prevalence of 7.2 % in adults [63]. That study used a questionnaire later found to have a positive predictive value of 59 % [131]. The study also looked at a measure of clinically significant RLS, a frequency of twice a week or more and moderate or greater distress when symptoms occurred and found a frequency of 2.7 %. A later study based on trained physician diagnosis found an overall frequency of approximately 4.4 % and confirmed the prior study showing clinically significant RLS frequency was 2.7 %; the prevalence of RLS with high impact of symptoms on patients life was 0.8 % [131]. These trained physician diagnosed rates are considered the most reliable estimates of RLS prevalence in the European and presumably white North American populations.

While several studies have suggested a lower prevalence in some non-Western countries [132–135]. other studies have found approximately the same prevalence as in the European/USA populations [136, 137]. In two methodologically rigorous studies, which used personal interviews to verify diagnosis, the frequency in Japanese elderly was around 1 % [134] and among Korean adults, 7.5 % [138]. The information on African Americans is scant. Very few African Americans seek treatment for RLS in clinics, and the previous published epidemiologic studies have not addressed the prevalence of RLS among African Americans. One preliminary study in Baltimore did not find a lower frequency in African Americans [139]. Given these uncertainties, it is not completely established that RLS is much more common in whites than in other ethnic populations.

Besides ethnicity, age and gender are strongly associated with RLS. Almost all studies [63, 88, 95, 119–123] have reported positive correlations of RLS with age (but see Sevim et al. [132]) that is more pronounced for women. Adults younger than 35 years appear to have no gender differences in prevalence [63], but after that prevalence increases significantly more for women than men. This critical age likely relates to pregnancy occurring since nulliparous women have the same risk of RLS as men [123, 140]. A systematic study of RLS frequency in children [141] found that 1.9 % of those 8–11 years of age and 2.0 % of those 12–17 years of age reported symptoms of RLS; 0.5 % of the younger group and 1 % of the older group had clinically significant RLS (twice a week and bothersome when occurring). There was no gender difference for children.

Incidence and Natural History of RLS

As noted above, RLS onset can occur at any age from childhood to old age for both genders. Incidence has been reported for one sample of American adults $\geq$ 40 years old to be 1.7 % per year [142]. RLS incidence per year in two different German population samples was 1.3 and 4.1 %. Persistence of RLS was low over 2–5 years at about 40–50 %, suggesting marked variability in RLS symptoms [143]. Unfortunately, these studies on incidence and persistence of RLS have been based on diagnostic methods that as noted above have low positive predictive values of about

50 %. The percentage falsely identified as having RLS (40–50 %) approximates the percentage not reporting persistence of RLS symptoms at the 2–5 year follow-up interview. Thus, it is unclear how many reporting on follow-up interview new onset or remission of symptoms were not those previously misclassified as RLS by the survey methods.

It has been assumed that the natural course of RLS is that of slowly progressive worsening, but while this is reported for some it is not always the case. Many cases report spontaneous remissions sometimes lasting years [144]. Although gradual worsening and spontaneous remissions are reported, the degree and rates of occurrence of these are not known. Three placebo studies of augmentation have reported evidence for definite spontaneous worsening of RLS during placebo treatment for 6 months at median 6 month rate of 1.0 % (<0.5, 1.0, and 6.0 %) [145–147]. The blinded comparison of pregabalin and pramipexole treatment [148] found approximately the same rate of RLS worsening on pregabalin (2.1 % for 12 months) consistent with the natural worsening on placebo. These studies would suggest that the natural progressive worsening beyond current moderately severe RLS occurs at a low rate of about 2 % of the patients over one year. But this remains to be better studied. Overall, it appears that the natural course of RLS is highly variable, including natural gradual worsening with changes in medical factors (e.g., iron status), periods of exacerbation, and also spontaneous remissions.

Secondary (Causally Related) and Comorbid Conditions for RLS

Elevated prevalence (>20 %) of RLS has been reported in studies based on clinical samples of persons with a number of medical conditions such as iron deficiency [70, 149], pregnancy [150–152], and uremia [153–155]. Their causative relation to RLS is supported by the reversibility of symptoms of RLS after treatment or resolution of iron deficiency anemia [156], pregnancy [151], and uremia [157]. Considerably higher prevalence of RLS has also been reported among these putatively causal comorbid conditions (iron deficiency [70], pregnancy [158], and uremia [159, 160]) even in Asian countries with low prevalence of RLS in the general population. One constant factor noted in these causally related conditions is that they typically predispose to low iron stores [161]. Decreased iron stores may also explain the finding that RLS may be more common among those who have been regular users of nonsteroidal anti-inflammatory medications that can cause gastrointestinal bleeding [162] and may be aggravated by blood donation [163] and may be more common among frequent blood donors [164] but not among those donating 3 times a year or less [165]. Such conditions may not only provoke RLS, but increase risk of RLS later in life. It has been also hypothesized that pregnancy similarly causes significant iron deficiency and may also cause lasting metabolic changes that predispose to increased RLS in later life [123, 166].

In some co-morbid neurologic conditions, the association with RLS is not so clearly related to iron metabolism, nor do any of these, unlike the iron-related ones noted above, show clear temporal patterns suggesting a causal relation, i.e., RLS resolved with treatment of the associated condition. These appear to be more comorbid rather than causal. It has long been suggested that neuropathy might predispose to RLS. Neuropathic findings have been reported in RLS patients [167, 168]. However, one study did not find an unusual prevalence in a neuropathy clinic [169], while another study reported that 30 % of neuropathy patients had RLS [170]. Radiculopathies [171, 172] and myelopathies may also cause or exacerbate RLS. There has also been an association between RLS and certain neurodegenerative conditions, including Machado–Joseph disease (SCA3) [173, 174], and demyelinating diseases such as multiple sclerosis [175–177]. Treatments of these conditions have not been reported to reduce RLS. In PD, RLS actually generally starts after beginning dopaminergic therapy [178], suggesting some analogs of the augmentation seen with dopaminergic therapy of RLS (see later).

RLS Biology

The cause of RLS remains unknown, though the functional abnormality is almost certainly neural in origin [179, 180]. A striking finding has been the almost universal response of RLS patients to medications that enhance dopamine system function [181]. Measures of dopamine dysfunction, however, have been equivocal or mixed [179, 182], but the larger imaging studies [183, 184], CSF studies [185], and autopsy studies [186] document increased not decreased dopamine in RLS. The reason that levodopa and dopamine agonists relieve the condition remains unclear but may reflect overcorrection of postsynaptic downregulation of response to dopamine [187, 188]. Drugs that antagonize the dopamine system may also unmask RLS symptoms, especially in treated patients [189, 190].

Studies have almost universally supported regional deficiency of brain iron in RLS despite normal peripheral iron (See Fig. 40.4). This most clearly involves the substantia nigra [76, 77, 81, 83, 191, 192] and the thalamus [79, 83]. Nigral iron deficiency has been shown in animals to produce increased striatal dopamine [193] as seen in RLS [184, 188]. Autopsy studies have suggested that the iron deficiency in RLS is associated with abnormal levels of cellular iron regulatory proteins [194, 195]. Brain iron deficiency is expected to cause RLS [188, 196] by producing a

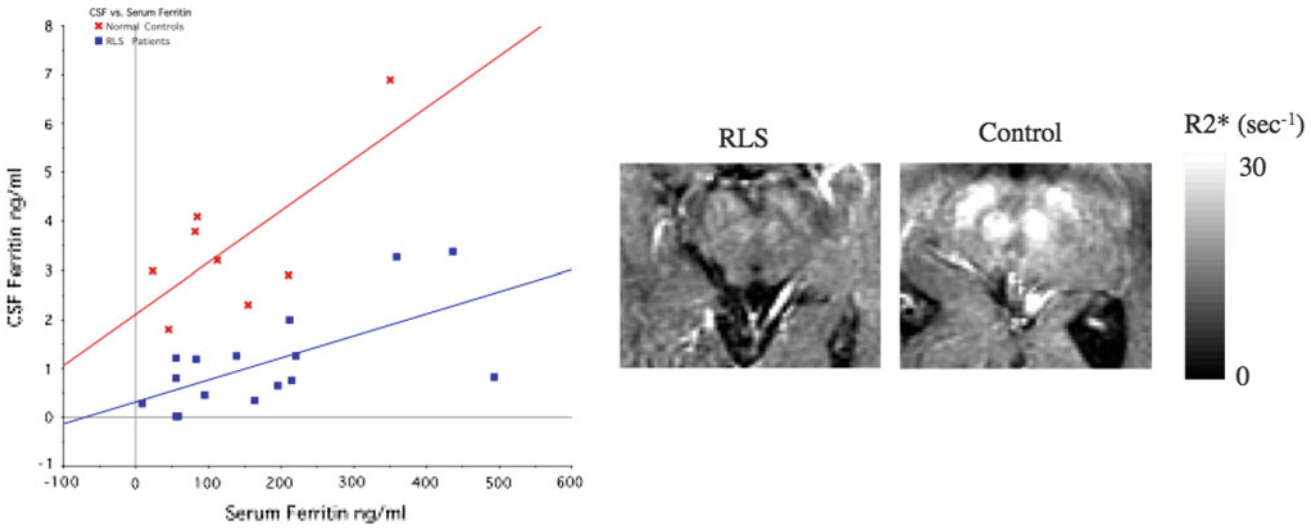

Fig. 40.4 Brain iron deficiency in RLS with normal levels of peripheral iron (serum ferritin *left graph*) but low levels of CSF ferritin (*left panel*) and also low levels of iron on MRI R2* (*right panel*)

dysregulation of brain dopamine function, perhaps related to altered amplitude of circadian dopamine variation. Recent identification of activation of hypoxic pathways in RLS [197, 198] indicates possible synergistic interaction between iron deficiency and hypoxia factors contributing to the dopaminergic dysfunction in RLS. Thus, COPD patients [199, 200] and those traveling or living at high altitudes [201] activating hypoxic pathways show higher rates or exacerbation of RLS.

It has been suggested on theoretical grounds that the A11 dopamine system, which descends to the spinal cord, could be involved in RLS, acting through D_3 dopamine receptors [202]. D_3 knockout mice show increased activity, as do mice with A11 lesions [203, 204]; however, these do not show the appropriate circadian pattern except when combined with iron deficiency [205]. Moreover, as noted above, RLS does not occur with neuronal loss and has increased not decreased dopamine; thus lesion studies reducing dopamine cells have somewhat limited usefulness. An autopsy study also failed to find any abnormalities in the A11 system of RLS patients [206].

The opioid system has also been suggested to be abnormal in RLS based largely on the therapeutic benefits of opioids for RLS [207–209]. A recent autopsy study documented decreased thalamic beta-endorphin cells [210], but an opioid imaging study failed to find significant difference from controls [211].

There is no evidence of neurodegeneration in RLS [212, 213]. Thus, RLS appear to have a pervasive functional abnormality in which brain systems are intact but have multiple abnormal functioning and interactions. Some limited evaluations of the resting state have documented abnormal interactions for RLS involving particularly the thalamus [214, 215]. Transcranial magnetic stimulation has also revealed increased excitability of the motor cortex in RLS [216–220] that is reduced by dopamine agonists [221, 222]. Further documenting the pervasive nature of the RLS brain abnormalities decreased myelination has been found in autopsy studies [223] and correspondingly decreased white matter in specialized MRI studies [223–225].

Overall, a mild brain iron deficiency possibly appears to be the most consistent abnormality reported for RLS and based on animal and clinical studies appears to largely explain the known biological abnormalities in RLS particularly those related to changes in dopamine [188]. Animal models of iron deficiency demonstrate increased activity that can occur in the hours before the primary sleep period, similar to RLS [226]. In this iron model of RLS causation, iron deficiency is expected to act principally through a dysregulation of brain dopamine function, perhaps related to altered amplitude of circadian dopamine variation [188]. The iron deficiency could also cause decreased myelination, white matter, resting state, and cortical excitability changes in RLS. The iron deficiency synergism with hypoxic pathways deserves special attention.

Familial Aggregation and Genetics in RLS

A striking finding in series of RLS cases is that some families have a high proportion of members with RLS [144, 153, 227, 228]. One obvious explanation would be that the disorder is under a large degree of genetic control. Three twin studies have suggested an elevated risk to monozygotic co-twins of affected individuals [67, 229, 230]. The first two studies suffered from major methodological limitations [229,

230]. The first study restricted to monozygotic twins had biased sampling from a clinical setting [231]. The second used general unvalidated questions for identification of RLS that cannot be considered accurate [230]. The third study used a preexisting twin sample with accurate diagnoses and found significantly greater concordance in monozygotic twins providing the heritability factor of 69 % [67].

The search for genetic determinants of RLS has been limited by two factors. First, the risk to first-degree relatives of patients has only been modest, on the order of three- to sevenfold [68]. Second, the frequency of RLS (4–10 % of adults) is quite high for a simple genetic disorder and suggests complex genetics likely involving environmental interaction. An initial approach to finding genetic determinants, searching for candidate genes active in the dopamine and iron pathways presumed to be involved in RLS did not reveal specific mutations contributing to RLS [232, 233]. One exception was the association of a fast metabolizer allele of monoamine oxidase A with RLS in women [234]. Another exception was the finding that variants in the neuronal nitric oxide synthase 1 gene (*NOS1*) are associated with RLS [235]. This gene is active in the nitric oxide/arginine pathway that is involved in sensory processing and affects both dopamine and endogenous opioid transmission. Multiple linkage analyses using large families with high rates of RLS occurrence failed to find any gene significantly related to RLS.

Genome-wide association studies in case-control populations, however, have found multiple specific allelic variations associated with an increased risk of RLS. Two groups initially reported significant associations in three genes [21, 66] *BTBD9* (6p), *MEIS1* (2p), and *MAP2K5/LBXCOR1* (15q). These genes do not have clearly known functions in adults, but are active during development, especially in the formation of the limbs. They are expressed within the nervous system [236]. One group found that *BTBD9* was better linked to the presence of increased PLM than to the purely subjective symptoms of RLS [21], underscoring the important connection between RLS and PLM. The group also found that serum ferritin, the best marker of body iron stores, was decreased in a dose-response fashion in patients with the RLS-PLM predisposing variant. Further association studies have identified RLS risk alleles in 5 other genetic regions. There are now a total of 16 allelic variations identified with increased risk of RLS. These occur on MEIS1, BTBD9, PTPDR, MAP2K5/LBXCOR1, TOX3, and the 2p14 region. The alleles are on intron (noncoding) portions of the genes. The functional relation of these genes to known biology of RLS is being explored. One important study documents the MEIS1 RLS alleles relating to a loss of function [237]. Knockout animal and fly studies have shown that BDBT9 and MEIS1 are both involved in the development of the dopamine system and also have effects on iron metabolism [238, 239]. Overall, these genetic data further support the strong relation between iron metabolism, dopamine, and RLS.

Evaluating the Severity and Impact of RLS

Standard Clinical tools have been developed and validated to evaluate the severity of RLS. The first of these was the Johns Hopkins Restless Legs Severity Scale (JHRLSS) that categorized the patients by time of onset of symptoms: mild for bedtime and evening only, moderate for afternoon before 6PM, and severe formorning before 12 noon [240]. This scale was designed to evaluate severity only for patients who had nearly daily symptoms, and the scale is rarely used today.

The second scale developed by the International Restless Legs Syndrome Study Group to evaluate RLS severity (IRLS) has become accepted as the primary scale for use in evaluating RLS severity (see Box 40.5). It has been well validated [241] and found to be responsive to changes in clinical estimates of RLS severity [242, 243]. This 10-item scale scores each item as 0–4 with 4 indicating greatest severity. Total scores of 0–10 indicate mild, 11–20 moderate, 21–30 severe, and 31–40 very severe RLS [241]. The IRLS has been found to have two factors, one for symptoms of RLS and the other for effects of RLS on life [244]. The IRLS scale has been translated into at least 15 different languages and is available from MAPI Research Trust at http://www.proqolid.org/.

The current diagnostic criteria for RLS also include added specifiers describing the RLS severity based on the clinical course as chronic-persistent (symptoms at least twice weekly for most of the past year) vs. intermittent (symptoms < twice weekly over the past year) [37].

Box 40.5: International Restless Legs Syndrome Study Group Rating Scale (IRLS)

(For permission to use contact: MAPI Research Trust at http://www.proqolid.org/).

The subject is given a copy of the questions. The clinician asks before each question:

"*In the past week…*"

The clinician not the patient records the subject's answers on the data sheet.

Each item is scored for 0—none, 1—mild, 2—moderate, 3—severe, 4—very severe (exceptions to this scoring are noted below)

1. Overall, how would you rate the RLS discomfort in your legs and arms?
2. Overall, how would you rate the need to move around because of your RLS symptoms?
3. Overall, how much relief of your RLS arm or leg discomfort did you get from moving around?
   4—No relief
   3—Mild relief
   2—Moderate relief
   1—Either complete or almost complete relief
   0—No RLS symptoms to be relieved
4. How severe was your sleep disturbance due to your RLS symptoms?
5. How severe was your tiredness or sleepiness during the day due to your RLS symptoms?
6. How severe was your RLS as a whole?
7. How often did you experience RLS symptoms?
   4—Very often (6–7 days in 1 week)
   3—Often (4–5 days in 1 week)
   2—Sometimes (2–3 days in 1 week)
   1—Occasionally (1 day in 1 week)
   0—Never
8. When you had RLS symptoms, how severe were they on average?
   4—Very severe (8 h or more per 24 h)
   3—Severe (3–8 h per 24 h)
   2—Moderate (1–3 h per 24 h)
   1—Mild (less than 1 hour per 24 h)
   0—None
9. Overall, how severe was the impact of your RLS symptoms on your ability to carry out your daily affairs—for example, carrying out a satisfactory family, home, social, school, or work life?
10. How severe was your mood disturbance due to your RLS symptoms—for example, angry, depressed, sad, anxious, or irritable?

The total score ranges from 0 to 40.

As a rough guide, the overall score divides into different levels of severity: 0 No, 1–10 Mild, 11–20 Moderate, 21–30 Severe, 31–40 Very Severe RLS.

(Note, IRLS is copyright protected and not to be used without permission. Fees may apply)

There are two well-validated disease-specific quality of life scales for RLS that have been used in the major clinical trials, i.e., the RLSQoL developed at Johns Hopkins [242, 245, 246] and the RLS-QoL developed in Germany [247]. The Hopkins scale is available from MAPI Research Trust at http://www.proqolid.org/, and it has been translated into several different languages.

Treatment of RLS and PLMD

A spectrum of treatment options, both non-pharmacologic (Box 40.7) and pharmacologic (Box 40.8), is available to address the wide range in severity and frequency of RLS symptoms. Before embarking on a decision to treat RLS or PLMD, some general comments about treatment guidelines are warranted (Box 40.6). For the purpose of treatment guidelines, patients can be classified (Table 40.1) into intermittent (usually mild), chronic, and persistent (usually moderate-to-severe with the added category of refractory or intractable [248] and into degree of clinical significance. These classifications depend on the intensity and frequency of symptoms, impairment of quality of life, and response to treatments. The IRLS, a validated clinical scale assessing RLS severity (Box 40.5), has been used as a primary end point in almost all clinical trials.

Box 40.6: General Treatment Guidelines for Restless Legs Syndrome (RLS)

Does the patient have RLS? (this must be established first).

- Does the patient have primary RLS or comorbid (secondary) RLS?
  (This distinction is important as the comorbid conditions must be identified and treated where possible).
- Always evaluate iron status and also determine if non-pharmacological treatment will suffice.
  (It is important to determine if mild or intermittent symptoms without significant disability can be managed by non-pharmacologic measures).
- Define RLS severity to guide treatment evaluation.
  Use the IRLSSG [see Box 40.5 and Table 40.1] or provide an overall clinical impression.
- Define end points in therapy and evaluate these on follow-up.
  For example, elimination of RLS symptoms or IRLS score <11, reduction or elimination of leg jerks during sleep as obtained by history from bed partner or polysomnography study, a significant reduction in IRLS scale score, quality-of-life improvement.

Box 40.7: Non-pharmacologic Treatment of Restless Legs Syndrome (RLS)

- Follow sleep hygiene measures (see Table 26.17 in Chap. 26).
- Consider discontinuing or reducing medications that can worsen RLS (see Box 40.2).

Table 40.1 Classification of RLS for treatment purpose

Categories	Key features
Mild (Intermittent) RLS	• Intermittent mild symptoms (< 2/week, mild-to-moderate distress when present) • Sometimes bothersome • Maybe predictable and situational
Minimal RLS	• IRLS score of 1–10 (see Box 40.5)
Moderate RLS	• Symptoms (significantly bothersome) occurring at least twice a week interfering with quality of life • IRLS score of 11–20
Moderately severe RLS	• Same as moderate RLS symptoms • IRLS score of 21–30
Severe RLS	• Significant and intense symptoms occurring daily interfering with daytime function and quality of life • IRLS score of 31–40
Refractory or intractable RLS	• Severe daily symptoms despite adequate doses of dopaminergic medication • IRLS score of 40 • Severe sleep disturbance • Impairment of quality of life and severely impaired daytime function

IRLSSG International Restless Legs Syndrome Study Group; RLS, restless legs syndrome
Modified and adapted from Hening et al. [327] and Silber et al. [328]

- Avoid substances that may trigger RLS (e.g., alcohol, smoking, caffeine-containing drinks).
- Exercise regularly at moderate intensity (avoid vigorous exercise, which may exacerbate RLS symptoms).
- Participate in mentally alerting activities (activities promoting alertness benefit RLS symptoms).
- Use counter stimulation measures (e.g., hot or cold showers, massage, getting up, and walking).
- Adjust sleep schedule to be somewhat delayed.
- Participate in patient support groups.

Important pharmacologic treatment options for RLS (see Box 40.8) include the α2δ ligands (particularly gabapentin enacarbil), the dopaminergic agents, the opioids, the sedative-hypnotics, and both oral and intravenous (IV) iron. Box 40.9 lists some general principles of pharmacotherapy for RLS. The first review and standards for RLS treatment were published in 1999 by the AASM [86, 249]. They established that clinicians managing RLS should be able to make an accurate diagnosis, understand primary and secondary RLS and the comorbidities of RLS, and follow patients at appropriate intervals to adjust treatment as needed. The most recent evidentiary reviews include one from the American Academy of Neurology [250]. A management paradigm has been published by the Medical Advisory Board of the RLS Foundation [248]. Two important treatment guidelines have been published by the International Restless Legs Syndrome Study group (ILRSSG): one for long-term treatment [251] and another important one in collaboration with the European RLSSG and the USA RLS foundation on initial treatment and managing augmentation [252].

Box 40.8: Pharmacologic Agents commonly used in Restless Legs Syndrome

Alpha-2-delta ligands:

Gabapentin enacarbil (approved), pregabalin, gabapentin

Dopaminergic medications:

Dopamine agonists: pramipexole (approved), ropinirole (approved), rotigotine patch (approved), cabergoline (not recommended*)
Levodopa combined with a decarboxylase inhibitor

Opioids (mild, moderate, strong):

Oxycodone/naloxone (approved in Europe)
Oxycodone, hydrocodone, methadone, buprenorphine

Benzodiazepines:

Clonazepam

Iron treatments:

Oral iron (in those with low serum iron or ferritin below 75 ng/ml)
IV iron (iron deficiency and non-responders to oral iron)
Ferric Carboxymaltose (FCM)

Low molecular weight dextran
Iron Sucrose (uncertain benefit for adults with RLS)

*concerns about fibrosis require added regular cardiac monitoring.

Box 40.9: Principles of Pharmacotherapy for Restless Legs Syndrome
Individualize the therapy.

- Start with monotherapy rather than polytherapy.
- Begin with a very small dose and gradually increase every 3–5 days to an optimal or maximal tolerable dose.
- Try monotherapy even in an apparently severe case using small-to-medium dose (a surprising number of such patients will respond satisfactorily).
- Try to convert patients on polytherapy (placed on treatment before referral to you) to monotherapy if possible (it is possible to do so in many such patients).
- Try to reduce the dose or eliminate some medications if patients complain of undesirable side effects from multidrug treatment.

Perform regular follow-up to monitor for side effects, progression of the disease, augmentation, tolerance, and rebound.

The treatment guidelines include as-needed medication for infrequent RLS, α2δ agents as preferred, and dopamine agonists as a second choice initial treatment for moderate-to-severe RLS, second-line treatment involves low-dose, very long acting dopamine agonists, moderate strength opioids, and combinations of α2δ agents, low-dose dopamine agonist and moderate strength opioids. An array of strategies (switching agents, combination treatment, strong opioid agents, IV iron) is used for refractory patients who fail other treatments. These reviews, particularly the ones from the IRLSSG, provide an easy route into the RLS therapeutic literature.

Pharmacologic Treatment of RLS (see Boxes 40.8, 40.9, 40.12, and Table 40.1)

Historic Note and RLS Augmentation

Opioids as the first treatment used for RLS [253, 254] were rapidly replaced by levodopa and then dopamine agonists when they became available. The dopaminergic medications showed more consistent and immediately effective treatment than opioids [255, 256] without the dependence and abuse problems. Gabapentin was also used to treat RLS, but the early results were somewhat mixed [257] complicated by its uneven uptake into blood and apparently less effect on PLMS. The dramatic efficacy of the dopaminergic treatment left little room for this alternate treatment except in non-responders. This changed with the awareness that treatment with the dopaminergics over 3–10 years produced a major problem of augmenting the RLS symptoms. RLS augmentation produced symptoms becoming more severe, more extensive, and occurring for more of the day especially in the afternoon and morning where they had not previously occurred [106]. Augmentation on the dopamine agonists did not usually appear until after 6 months to 10 years of treatment [258, 259]. Initially, there was some uncertainty if augmentation was iatrogenic or a natural progression of symptoms. It also was unclear if effective treatment by non-dopaminergic drugs might also produce significant augmentation. This issue was directly addressed in a major large clinical study comparing at therapeutically effective doses the dopamine agonist pramipexole with the α2δ ligand pregabalin over one year of treatment. The results of this study showed that pregabalin compared to pramipexole was equally or more effective and had significantly less augmentation. The one-year augmentation rate for pregabalin (1.7 %) was the same as that seen in other studies on placebo, indicating this reflected possible natural progression in this study without any dose increase and/or noise in the clinical measure of augmentation. In contrast, the 9 % augmentation on 0.5 mg pramipexole for one year demonstrated that augmentation was iatrogenic, not natural progression, and based on other studies probably occurred for all dopaminergic treatment of RLS. The study also demonstrated augmentation occurred mostly after the initial 6 months of treatment and was increased with higher dose (see Fig. 40.5). After this study, the treatment of RLS shifted from using dopamine agonists as the primary first-line treatment to instead using the α2δ agents as first line and dopaminergics only when there was a reason not to use the α2δ agents. Moreover, with increased experience, very severe and intractable cases of RLS have been identified and often require returning to using dopamine agonists, but those with very long half-lives, e.g., rotigotine, and also the initial drug used for RLS, i.e., opioids. Now with the most extreme RLS moderate and high potency opioids are used. The one relatively new treatment for RLS that at this point in 2016 is still being evaluated is intravenous (IV) iron. Given the RLS biology of brain iron deficiency, it is hoped that some treatment, possibly IV iron, could actually reduce this biological abnormality and thereby provide effective treatment. The range of current treatments is presented in brief here as they are currently (2016) recommended by the IRLSSG.

α2δ Ligands

The α2δ ligands have analgesic and anticonvulsant activity. They bind to the α2δ voltage gated calcium channel

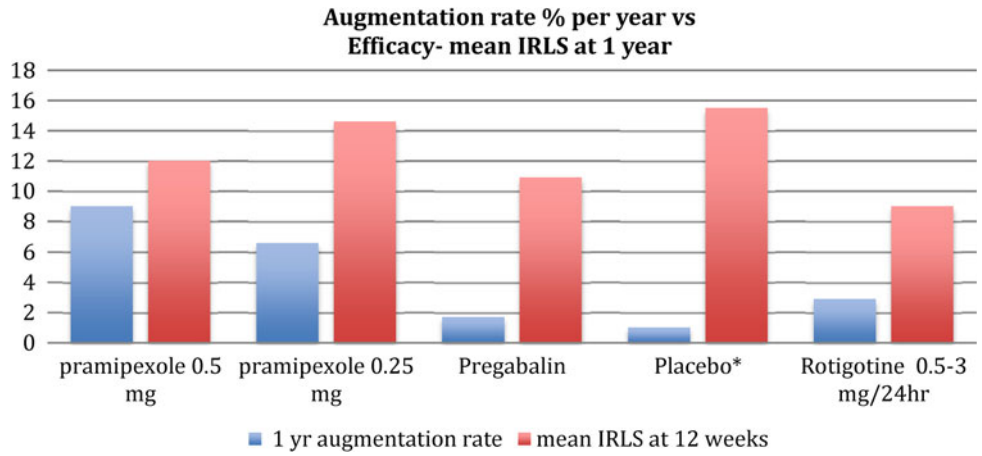

Fig. 40.5 Long-term treatment efficacy versus augmentation. *Red bars* indicate mean clinical severity of RLS on the IRLS scale after 12 weeks of treatment. *Higher values* indicate more severe RLS, with <10 considered minimal RLS, 10–15 mild RLS, >15 moderate RLS symptom severity. *Blue bars* indicate rates of RLS augmentation after 1 year of treatment. Higher values are more augmentation. The 1 % on placebo indicates natural progression without treatment, the values significantly higher than that indicate the percentage with drug induced worsening of RLS (augmentation). Note Pregabalin 300 mg in this study is as effective as pramipexole 0.5 mg with augmentation not significantly greater than for placebo. In contrast, pramipexole shows significant dose-related augmentation. Data sources for pramipexole: Allen et al. [37]; rotigotine: Benes et al. [147]; Placebo: Garcia-Borreguero et al. [145] and Benes et al. [147] pro-rated from 6 months data

reducing neurotransmitter release in pathways involving several neurotransmitters [260], including glutamate [261]. There are three α2δ ligands used for RLS: gabapentin enacarbil, pregabilin, and gabapentin. Gabapentin was initially used for RLS with generally good but mixed results in uncontrolled, open label trials for mild-to-moderate RLS. The studies were small, and results were considered inconclusive for a first-line treatment recommendation [257, 262]. Trials comparing gabapentin to other RLS treatments generally found gabapentin to be almost as effective, although somewhat less effective in reducing the PLMS [263, 264]. In a double-blind, cross-over study, gabapentin in doses of 600–2400 mg was more effective than placebo in treatment of RLS, but 13 % of the RLS patients continued to have abnormally high rates of PLMS [265]. Gabapentin is poorly taken up into the blood with wide variations between individuals and even across days in a given individual. This problem limits reliably delivering effective treatment and leads to needing larger doses. The other two α2δ ligands resolve that problem. One, gabapentin enacarbil is a pro-drug overcoming the gabapentin uptake problem. It reliably delivers gabapentin to the blood and maintains a reasonable blood level for 12–18 h with almost complete clearance in 24 h [266]. Large controlled clinical studies have documented efficacy with mostly mild side effects for gabapentin enacarbil treatment of RLS at single daily doses of 600–1200 mg [267–271]. This drug is now approved by US Food and Drug Administration (FDA) for treatment of moderate-to-severe RLS at a dose of 600 mg per day, although in the clinical studies effective doses range from 300 to 1200 mg. Pregabalin has a different chemical structure, and has none of the uptake problems of gabapentin. In controlled clinical trials compared to placebo, one dose of 100–300 mg pregabalin provided effective treatment for 12–16 h [148, 272–275] with higher doses up to 600 mg used for RLS with neuropathic pain [276].

The α2δ ligands currently recommend (Box 40.8) for initial first-line treatment of RLS based on adequate clinical studies are gabapentin enacarbil (300–600 mg once daily) and pregabalin (100–300 mg usually only once daily). Gabapentin is likely to be effective except for the problem of its variable uptake into blood. It also has not been evaluated in large clinical trials, so there may be other unknown limitations. Gabapentin use is thus complicated by a wide range of doses ranging from 300 to 2400 mg a day and a need to give it 1–3 times a day. Failure with gabapentin given its uptake problems does not mean the other α2δ agents will not be effective.

Cost is a significant issue. Gabapentin but not the other α2δ ligands are available as a generic at a lower price than the other α2δ agents.

Levodopa

Akpinar [277] and Montplaisir et al. [189] first reported a profound response of RLS symptoms to small doses of levodopa. Subsequent studies have consistently found that levodopa reliably ameliorates RLS symptoms, decreases PLM [255, 256], and improves sleep [181, 278], but in the

vast majority of cases daily chronic longer term use produces RLS *augmentation* [106, 146]. It is not recommended for daily use.

Dopamine Agonists

Dosing of dopaminergic agents for RLS differs from the typical dosing schedule in PD. Many RLS patients can be successfully managed with low doses given 2 h before symptom onset. Generally, a single dose taken at night can benefit those with late evening and bedtime symptoms, while more severe patients with significant evening symptoms can take one dose in the early evening and a second before bedtime. For the patient who develops a rapid escalation in RLS severity, with increasing medication requirements in the first 2 years of therapy, augmentation should be carefully considered.

Because of reports of fibrosis and valvulopathy with ergot-derived agonists (pergolide, bromocriptine, cabergoline) [279] non-ergot-derived agonists are preferred treatment. Ropinirole, pramipexole, and rotigotine have been approved for the treatment of RLS after several large multicenter studies [114, 115, 280–284]; they have also been shown to markedly decrease PLMS in RLS [285–287]. Rotigotine is provided as a transdermal patch that, unlike oral agents, provides continuous delivery over 24 h and sustains a near-constant blood level.

RLS Augmentation on Dopaminergic Treatment: Rates and Management

As noted above in the history of RLS treatment, augmentation is an iatrogenic increase in the severity of RLS with long-term dopaminergic treatment (see Fig. 40.5). It also occurs for tramadol [288]. Its primary manifestation is worsening of RLS and the progression of symptoms earlier in the day. This has been defined for clinical studies at the NIH RLS consensus conference [104] (Box 40.10). Based on a study of levodopa patients in which 60 % developed augmentation, a validated severity questionnaire has been developed [289]. A series of questions for early identification of augmentation have been proposed by the IRLSSG as part of their official guidelines for managing augmentation [252] (Box 40.11).

Box 40.10: NIH Workshop Diagnostic Criteria for RLS Augmentation

Adapted from Allen et al. [104].

RLS augmentation can be diagnosed if A and B are met

(a) Either of the following two criteria are met:
   1. Criterion 1: RLS symptoms occur at least 2 hours earlier than was typical during the initial course of beneficial stable treatment.
   2. Criterion 2: Two or more of the following key features of RLS augmentation are present:
      - An increased overall intensity of the urge to move or sensations is temporally related to an increase in the daily medication dosage, or a decreased overall intensity of the urge to move or sensations is temporally related to a decrease in the daily medication dosage.
      - The latency to RLS symptoms at rest is shorter than the latency either during initial therapeutic response or before treatment was instituted.
      - The urge to move or sensations are extended to previously unaffected limbs or body parts.
      - The duration of treatment effect is shorter than the duration during initial therapeutic response.
      - Periodic limb movements while awake occur for the first time or are worse than either during initial therapeutic response or before treatment was instituted. In addition to meeting one of these two criteria, the diagnosis requires both of the following:
      - Augmented symptoms meeting these criteria are present for at least 1 week for a minimum of 5 days.

(b) No other medical, psychiatric, behavioral, or pharmacologic factors explain the exacerbation of the patient's RLS and any symptoms meeting these criteria for augmentation.

Box 40.11: Indications for early identification of RLS augmentation

Adapted from Garcia-Borreguero et al. [252].

1. RLS/WED symptoms appearing earlier than before the drug was started?
2. Higher doses or dosing earlier in the day than after the first 2 months on treatment
3. Intensity of symptoms when present is worse than before starting treatment?
4. Symptoms occur for the first time in new parts of the body (e.g., arms) not affected before starting treatment.

Levodopa augmentation rates have been reported to occur in as many as 80 % of RLS patients, with 50 % of them requiring a change in medication [106, 290]. Dopamine agonists have slower development of augmentation with rates of 20–30 % over 3 years (20–30 %) [291–293] but persisting development at the rate of about 7–8 % new cases each year for over 9 years and presumably indefinitely [259, 294]. Any increasing dose requirement for relief of

increasingly intense symptoms may suggest tolerance. Tolerance does not itself cause augmentation with an earlier onset of symptoms or spread to other parts of the body. Tolerance, however, is often an early observable sign of augmentation [291] and should always be considered a warning sign of augmentation. Iron deficiency may be a predisposing factor for augmentation [295].

The treatment of augmentation involves primarily reducing or discontinuing the use of dopaminergic and switching to or adding a non-dopamine medication. The options are well described in the treatment guidelines provided by the IRLSSG [252]. The critical issue involves appreciating the importance of minimizing the use of dopaminergic medication for patients who develop augmentation. The continuously acting dopaminergic medication, rotigotine, appears to have fewer problems with augmentation and may provide a treatment for augmented RLS although often at higher than regulatory approved doses [296], but in general avoiding any dopaminergic medication is the safest way to minimize augmentation problems.

Anticonvulsants (Other than α2δ Agents)

Carbamezapine had in earlier studies demonstrated successful use in RLS [297–300]. However, clinical experience has not demonstrated as good a response as that seen with dopamine agonists or gabapentin. There are only limited case reports or small series with other anticonvulsants, such as lamotrigine [301, 302] and topiramate [303]; thus, these are usually tried only in patients who are unable to tolerate other agents.

Opioids

Moderate potency opioids (e.g., oxycodone, hydrocodone) are used mostly for second-line treatment, and the moderate-to-high potency opioids (methadone, buprenorphine) are used only for treatment of refractory RLS. Opioids have been documented to be effective in RLS [208, 209, 259, 304]. Because of individual variation in response to the different classes of opioids, it is often worthwhile trying more than one agent. Longer acting medications such as methadone often provide relief for some of the most severely affected patients, including those who have failed dopaminergic therapy [209, 304]. One opioid agent, tramadol, which also has serotoninergic properties, has been reported to cause augmentation [288, 305].

Sedative Hypnotics

Despite the early use of benzodiazepines for treating RLS and PLMD, the sedative-hypnotic agents do not have reliable effectiveness in eliminating RLS sensations or eliminating PLMS [306, 307]. They are best reserved for mild cases with primary sleep disruptions where they may enable the patient to sleep through the symptoms or as adjunctive therapy for persisting insomnia. When used alone, they may increase the risk of falls if during the night the patient awakens and gets out of bed to relieve the RLS symptoms.

Iron Treatment

The biological basis of RLS includes brain iron deficiency. Thus, iron unlike other treatments may correct the biology causing the disease and modify the course of the disease. Barriers to changing brain iron status include limited absorption of iron from the gut, regulation of iron transport across the blood brain barrier, and the biological problems with iron management that may have contributed to the development of the brain iron deficiency in the first place.

Oral iron treatment despite limitation of absorption from the gut is considered a primary treatment for all RLS patients based on the biology of RLS, general clinical experience, and one small placebo-controlled, double-blind clinical trial [308]. Iron transport from the gut to blood is generally extremely limited when serum ferritin values are high. Oral iron is unlikely to be effective for patients with higher values of serum ferritin as shown by failed benefit when given to RLS patients with a mean serum ferritin of 135 mcg/l [309]. In contrast, oral iron was shown to be effective treatment for RLS patients with serum ferritin ≤ 75 mcg/l [308]. Oral iron (usually iron sulfate 325 mg with vitamin C 100 mg taken once or twice a day) is recommended for all RLS patients with fasting morning serum ferritin ≤ 75 mcg/l and transferrin saturation <45 %. These serum values indicate iron levels are likely too low for RLS, and there is no indication for iron overload such as that associated with hemochromatosis. Oral iron treatment is usually continued if tolerated until serum ferritin increases to >100 mcg/l or transferrin saturation increases to >45 %. It can be reinstated as needed to keep serum iron levels high. Recent data on effects of oral iron on hepcidin levels indicate that taking oral iron more than once a day provides little extra benefit, and it may even suffice or be preferable to take it once every other day [310].

IV iron treatment bypasses the gut rapidly increasing iron in the blood available for transport to the brain. IV iron has been found to provide effective treatment in both open-label studies at doses of 500 mg of ferric carboxymaltose (FCM) [311] and 1000 mg iron dextran [312–314], and also two well-controlled clinical trials of 1000 mg of FCM [315, 316]. About half of the cases in these studies reported significant benefit from the iron treatment lasting for at least 2–4 months, and about 20 % of all patients reported essentially complete relief from RLS lasting for more than 6 months. Two controlled studies with 1000 mg IV iron sucrose failed to show significant benefit compared to placebo [317, 318], but the iron sucrose unlike iron dextran and FCM releases its iron rapidly and is thus less likely to provide the longer duration of iron availability needed for transport to the brain. Iron dextran at high molecular weight can produce

anaphylaxis and is therefore not recommended. This problem is much less for iron dextran at low molecular weight and may not be a significant problem at all for the other IV iron formulations. Curiously, IV iron appears to benefit about 40–60 % of RLS patients with long lasting benefit for 20–30 %, but some show no benefit at all even from a second added dose treatment [315]. The role of IV iron in treatment of RLS remains to be better developed, but it holds promise for at least some RLS patients.

Treatment of Refractory and Intractable RLS

Box 40.12 provides reasonable guidelines for treatment of intermittent and chronic persistent RLS. The situation is much more complicated for the severe RLS refractory to most of the treatments for RLS. The general guidelines for these patients is to first ensure adequate iron stores and if serum ferritin is < 100 mcg/l consider a trial on 1000 mg IV iron using one of the formulations that provides relatively slow release of the iron, e.g., ferric carboxymaltose. These infusions can usually be arranged through hematology clinics. The main pharmacological approach in these patients is the use of low doses of long half-life, potent opioids, e.g., methadone [259, 304], buprenorphine, or prolonged release oxycodone–naloxone [209]. The prolonged release oxycodone–naloxone has been approved for treatment of refractory RLS in Europe, but opioids are not approved for any use in RLS. All of these drugs need to be used carefully given the risk of dependence. The dose for these drugs will be below or at the low end of the doses used for treating pain. If higher doses are needed, care should be taken to ensure the drug is not treating some other condition, e.g., pain, or that dependence has not developed.

Box 40.12: Treatment Strategies for Mild, Moderate, Severe, and Refractory or Intractable Restless Legs Syndrome (RLS)

All RLS

Oral iron treatment if serum ferritin $\leq$75 mcg/l and transferrin saturation <45 %.

Mild or Intermittent RLS

Non-pharmacologic measures (NP)

Levodopa PRN (no more than once a week), low-dose α2δ ligand

Sedative-hypnotic PRN for sleep if needed and helpful.

Moderate-to-Moderately Severe RLS

α2δ agent nightly

Very low-dose dopamine agonist (with caution regarding augmentation)

Combination of α2δ agents and very low-dose dopamine agonist

Mild-to-moderate potency opioids.

Severe, Refractory RLS

Combination opioid and α2δ agents and low-dose dopamine agonists

Oxycodone–naloxone (approved for RLS in Europe)

High-potency opioids in very severe cases at very low doses (e.g., Methadone at 5–10 mg/day not to exceed 20 mg/day). Evaluate for possible IV iron treatment.

Pharmacologic Treatment of PLMD and PLMS

The periodic limb movement disorder (PLMD) occurs with high rates of PLMS (>15/h for adults and $\geq$5/h for children) associated with disrupted sleep or waking unrelated to other sleep disorders or to medications. The PLMS of PLMD may mark inflammatory processes and/or iron deficiency. The iron status should be carefully evaluated and oral or IV iron treatment considered even for low normal iron stores, provided transferrin saturation is <45 %. Iron treatment options are the same as that for RLS above, except treatment success can be evaluated by documenting decrease in the PLMS. Possible causes for the inflammation or low iron should also be evaluated and appropriate treatment considered.

Treatment of PLMD other than with iron starts with α2δ agents to reduce the PLMS and also generally improve sleep. Low-dose L-dopa and dopamine agonists are also very effective for reducing PLMS, but the dopamine treatment of PLMS without RLS can lead to the development of RLS [106] and therefore should be used very cautiously and only at very low doses. Opioids are of uncertain benefit. Clonazepam was demonstrated to improve sleep but not the PLMS [306]. In most cases, it is important to look for other causes of the sleep and daytime functioning complaints and determine that the treatment of the PLMS produced significant changes in these to justify continuing the treatment.

Treatment of PLMS without RLS or PLMD is not clearly indicated. Very high rates of PLMS themselves have been related to significant health, particularly cardiovascular health problems. High rates of PLMS may thus deserve some attention. PLMS are associated with the increase in heart rate [319] and rises in blood pressure [320–322]; it has been suggested that, untreated, they may lead to persistent diurnal hypertension, but this connection appears to be very limited [323]. It nonetheless provides a potential rationale for treating PLMS that occur without a related sleep complaint in vulnerable patients [320]. Treating sleep disruption with PLMS in RLS patients might be less effective than in those without RLS, because some arousals may persist in RLS patients even when PLMS are effectively suppressed [324]. In RLS patients, there may be a different relationship between movements and arousals than in those without RLS [325]: in RLS, the PLMS may be more closely connected to an underlying abnormality. Nonetheless, dopaminergic treatment reducing the PLMS for RLS patients has been

shown to significantly reduce the transitory heart rate and blood pressure increases during sleep [326]. Consideration regarding treatments to reduce PLMS needs to be carefully balanced by the adverse effects of treatments and the limited data indicating clear benefit for the treatments especially in otherwise healthy individuals.

Summary

RLS is the 2nd or 3rd most common neurological disorder after essential tremor and headache. It is often misdiagnosed, under-diagnosed, under-recognized, and mistreated or under-treated. RLS should be strongly considered in any subject complaining of leg discomfort or excessive restlessness of the legs while lying in bed in the evening and of having difficulty falling asleep or maintaining sleep or of non-restorative sleep. Most patients get relief from treatment with α2δ ligands or low-dose dopaminergic drugs. Long-term 5- to 10-year treatment benefits from dopaminergics appear to be severely limited by the augmentation problem. It is hoped, but unclear if the long term treatment with α2δ ligands will be better than dopaminergic treatment.

PLMD treatment benefits are somewhat unclear, but iron status should be evaluated and appropriate treatment considered if serum ferritin is low. PLMS without RLS or PLMD has uncertain clinical significance, except to indicate possible iron deficiency. They may, however, occur with significant unrecognized sleep disruption and treatment as PLMD can be considered. PLMS at very high rates may be associated with health and cardiovascular problems, but there are no data at this point to indicate treating the PLMS themselves provides clinical benefits.

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