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Behavioral Sleep Medicine Interventions for Restless Legs Syndrome and Periodic Limb Movement Disorder

Wilfred R. Pigeon, PhD, CBSM and **Michael Yurcheshen, MD**
University of Rochester Medical Center, Rochester, NY USA

SYNOPSIS

Restless Legs Syndrome (RLS) and Periodic Limb Movement Disorder (PLMD) are sleep disorders that are commonly seen in clinical practice. The standard treatment recommendations for these disorders are pharmacologic; most recently both conditions are most typically managed with pramipexole or ropinerole, which are FDA approved for the treatment of RLS. A mix of behavioral suggestions is included in treatment algorithms for providers as well as in patient education materials. While these suggestions have considerable merit, they are typically not delivered as an intervention, but instead provided as a series of helpful tips. There is emerging evidence for providing such suggestions as a more active and comprehensive intervention as part of a cognitive-behavioral package as well as for exercise therapy and cognitive behavioral therapy for insomnia to be delivered as active treatments for RLS and/or PLMD.

Keywords

Restless Legs Syndrome; Periodic Limb Movement Disorder; Behavioral; Cognitive-Behavioral; Behavioral Medicine; Relaxation

Restless Legs Syndrome (RLS) and Periodic Limb Movement Disorder (PLMD) are sleep disorders that are commonly seen in clinical practice, both by primary care providers and by sleep specialists. Unlike the vast majority of movement disorders, these conditions do not improve with sleep. The standard treatment recommendations for these disorders are pharmacologic, although behavioral interventions for these conditions are increasingly recognized, albeit under-utilized.

Restless Legs Syndrome and its Pharmacologic Management

Although the first descriptions of RLS were recorded as early as 1672, Stephen Eckbolm is largely credited with the first modern report of the condition, identifying 8 patients with the condition in 1945 [1–2]. Since these earliest accounts, diagnostic criteria for the condition have been established and refined [3–4]. In the most recent version of the *International Classification of Sleep Disorders*, RLS is grouped with other sleep related movement disorders.

Corresponding Author: Wilfred R. Pigeon. Ph.D., C.BSM, Sleep & Neurophysiology Research Laboratory, University of Rochester Medical Center, 300 Crittenden Boulevard-Box PSYCH, Rochester, NY 14642-8409, Telephone: 585.275.3374; Fax: 585.276-2531, Wilfred_Pigeon@URMC.rochester.edu, Michael Yurcheshen, M.D., Strong Sleep Disorders Center, 919 Westfall Road - Building A; Suite 100, University of Rochester Medical Center, Rochester, NY, 14618, Telephone: 585.341.7575, Michael_Yurcheshen@URMC.rochester.edu.

Although this syndrome does not *necessarily* involve stereotyped movement, RLS is included among the movement disorders of sleep because of its close association with PLMD and PLMW (periodic leg movements of wake). RLS has 4 features [5], which include 1) a strong, "nearly irresistible", urge to move the legs; 2) the sensations are worsened with inactivity; 3) the sensations are improved or relieved with movement; and 4) the symptoms are exacerbated at night.

In clinical practice, not all of these features are necessary to make a diagnosis of RLS; there is also some variability in how frequently symptoms occur. In children under 12 years of age, the condition can include probable or definite RLS, and diagnostic criteria are slightly different [4–5].

This utilitarian description, however, in some ways minimizes the degree of sleep disruption that many of these patients experience. In some cases, the discomfort is so disruptive that afflicted patients wander nightly, sometimes for hours, until they finally collapse with exhaustion. The sensation has been described variably, and some descriptors of the sensation include "tingling", "stinging", or a "creepy-crawly" feeling. In up to 50% of cases, symptoms are severe enough to involve the upper extremities in addition to (or in rarer circumstances, instead of) the lower extremities [6].

It is estimated that RLS has an incidence of about 5–15% in the general population, and most studies suggest it is up to twice as common in women [7–8]. RLS is commonly idiopathic, but many secondary causes of this condition have been identified. These secondary causes include, but are not limited to, neuropathy, diabetes, renal dysfunction, spinal stenosis, pregnancy, side effects from drugs/medications (such as antipsychotics or antiemetics), and iron or vitamin deficiency. A discussion of the secondary causes of RLS is beyond the scope of this article, however, a recent online review of RLS includes an extensive discussion [9]. Other, less common, causes of RLS have also been described. For instance, in a recent case series, 5 patients with Chiari-I malformation were found to have RLS [10]. Some familial cases of RLS have also been identified, suggesting a genetic component. Indeed, a handful of genetic loci and polymorphisms of susceptible genes (including the BTBD9 gene) associated with RLS have been discovered [11–12]. Depending on the cause, symptoms may fluctuate. Pregnancy is a common example, with many women describing symptoms only during the term of pregnancy, but never before or after.

There has been some evidence that "idiopathic" Restless Legs Syndrome may actually be a harbinger of neurodegenerative conditions such as Parkinson's Disease [13]. Confirmatory evidence of a definitive relationship between these conditions is lacking. A recent epidemiologic study also links between RLS and vascular disease [14]. Causality and directionality in this association has not been firmly established.

The typical workup for RLS includes a diligent clinical encounter with close attention paid to sleep and past medical history. The physical examination should include a neurologic examination, particularly of the lower extremities. A comprehensive laboratory workup is of variable utility. Serum ferritin levels are often drawn, and some practitioners advocate for supplementing iron if the level is below 50 ug/ml, although currently there are no clinical trials or even guidelines to support this practice. Although CSF iron studies appear more sensitive for RLS, a lumbar puncture for such an evaluation is not recommended [15]. Neuroimaging of the lumbosacral spine and EMG/nerve conduction studies are not indicated in every patient. Polysomnography is not routinely required in most cases of RLS, and an estimated 10–20% of patients with RLS will have a polysomnogram free of any remarkable surface EMG finding [16]. This said, information from a nocturnal PSG can be useful in questionable cases of RLS, or to identify the degree of sleep disruption from associated nighttime movements. The

Suggested Immobilization Test (SIT) is a procedure where a patient rates their level of leg discomfort while surface EMG tracings of leg movements are recorded [17]. This test is used infrequently in clinical practice.

If a specific cause of RLS is identified, treating the underlying condition can be helpful in alleviating symptoms. Some examples include addressing any reversible causes of renal dysfunction, or delivery, when pregnancy is the proximal cause [18]. The relationship between glucose control and RLS is just beginning to be explored [19].

Treatment for the idiopathic from of RLS is most commonly pharmacologic. Standards of practice and algorithms for pharmacologic treatment have been developed, but the treatment landscape has changed since 2004 when these guidelines were published [20–21]. Specifically, dopamine D2 agonists have become first line treatment for this condition [22]. According to the American Academy of Sleep Medicine (AASM) 2004 Practice Parameters, levodopa/carbidopa and pergolide are considered “standards” for treatment [20]. Since that time, pramipexole and ropinerole have become FDA approved for treating RLS, and many practitioners use these agents first to treat RLS. Evening administration at doses that are generally significantly less than what would be required for treatment of Parkinson’s Disease are usually effective. The most common side effects of these dopamine agonists include nausea and sleepiness. Dopamine dysregulation syndrome is uncommon, but should be considered when using dopamine agonists. Other agents that show significant efficacy include, but are not limited to, gabapentin and clonazepam [23–24]. Side effects to gabapentin include non-specific drowsiness, nausea, and dizziness, among others. Clonazepam has a longer half-life than many benzodiazepines, and therefore seems to carry a lower risk of abuse, however, clonazepam abuse does occur and this possibility remains at least a possible concern.(25) Opiates can also be quite effective; it is also worth noting that some (although not all) opiates are among the few RLS agents that are considered to be pregnancy risk category B. Dependency is an consideration with the use of any opiate. Supplemental iron (oral or intravenous) is sometimes effective in cases of iron deficiency (ferritin <50 mcg/l), but the evidence for this approach to date is based on case series, and controlled clinical trials are forthcoming [26–27]. Finally, magnesium may be a useful treatment in some cases [28–29]. There are few, if any, head to head clinical trials comparing these agents. A complete discussion on the specific therapeutic management of RLS is beyond the scope of this review, but considerations of comorbidities, tolerance, and augmentation, among others, will dictate which agents to use and when.

Periodic Limb Movement Disorder and its Pharmacologic Management

This condition, initially referred to as nocturnal myoclonus, is characterized by nighttime limb movements during sleep. Sydmonds first described the condition in 1953 [30]. Unlike RLS, no discomfort in the limbs is necessary for the diagnosis of PLMD. Patients might be completely unaware of the presence of these movements, were it not for a bed partners’ complaints. Of course, many patients with limb discomfort (of any kind) may also have co-morbid PLMD. These patients may or may not meet diagnostic criteria for RLS. Most patients with RLS also have PLMD [16]. PLMD is closely related to Periodic Limb Movements of Sleep with one significant difference: patients with PLMD have a sleep complaint, such as insomnia or daytime sleepiness.

PLMD is a relatively uncommon disorder. One study estimated that 3.9% of the adult population has PLMD, but these cases were identified by self report, and were not confirmed with polysomnography [31]. PLMD can also occur in children. A 2004 case series suggested that 23% of prepubertal children presenting to a sleep disorders clinic had periodic limb movements on polysomnography [32]. As with sleep disordered breathing, the consequence of nighttime sleep disruption in a pediatric patient may not result in sleepiness, but rather in

behavioral concerns. Specifically, ADHD symptoms appear to be common in pediatric patients with nocturnal sleep disruption from PLMD [33].

PLMD is diagnosed through a combination of history along with polysomnographic data. Again, it is most often a bed partner's observation that a patient moves during the night. Particularly astute bed partners may notice that the movements are more likely to occur in the first half of the night. Non-REM sleep, when leg movements are far more common than in REM sleep, predominates in the first half of the night. There is variability in the timing of these movements, however, and many patients' movements may continue throughout the entire sleep period.

On polysomnography, surface EMG activity from limb leads is recorded during the night. Using criteria recently established by the AASM, a limb movement can be scored if it has a duration 0.5–10 seconds, and has at least an 8 microvolt increase over the baseline resting EMG amplitude [34]. If four of these movements occur within 5 to 90 seconds, the movements can be scored as a periodic leg movement series (PLMS). An PLMS index of greater than 15 movements per hour in adults, and greater than 5 in children should arouse suspicion for PLMD [35]. By strict criteria, movements that are precipitated by respiratory disturbances (such as apnea) should not be scored, and movements in this setting should not be considered periodic leg movement disorder. There is ongoing and considerable debate about whether disease severity, as assessed by PLMS index, has any correlation to patient complaints.

Correlative movements to this EMG activity can sometimes be witnessed using video monitoring. Classic clinical reports have characterized these movements as a partial or complete "triple flexion" response, with extension of the great toe, dorsiflexion of the ankle, and occasional flexion of the knee and hip [36]. The movements, however, can often be more vigorous, causing significant disruption to a bed partner's sleep.

Much has been written about clinical significance criteria for PLMD and how many if not most of these cases do not rise to this level and do not require treatment. [37] Clinical judgment is often a guide in these cases. If these limb movements are uncovered on polysomnography that is otherwise devoid of other obvious causes for daytime sleepiness, then they should certainly be addressed. Many times, however, limb movements on PSG are simply incidental and do not require treatment.

Because it can be difficult to determine if the limb movements noted on polysomnography are incidental to sleep complaints, or if they are germane, treatment for PLMD can be more complicated than for RLS. If there is an identified cause of the PLMD (i.e. arthritis, RLS), then treatment of the primary condition is recommended. The 2004 AASM guidelines consider treatment for restless legs syndrome and periodic limb movement of sleep to be one and the same [20]. The recommendations discuss a host of treatments, but ropinerole and pramipexole have since become leading agents in treatment of PLMD. Occasionally, several agents might be tried before an effective one is identified. In the absence of limb discomfort, judging treatment efficacy can be somewhat challenging. Again, a bed partners' reports are important to judge efficacy, as are patient reports of any improvements in sleep continuity and/or daytime sleepiness or fatigue.

Behavioral Sleep Medicine Interventions for RLS and PLMD

Behavioral sleep medicine (BSM) approaches to RLS and PLMD do exist, but the level of empirical support for their use is less complete than the body of evidence that exists for the use of BSM interventions in chronic insomnia, pediatric sleep disorders, and even CPAP adherence. Nonetheless, some BSM principles are already embedded in the existing treatment guidelines for RLS and PLMD. As conditions that tend to be chronic, RLS and PLMD are also

appropriate targets for chronic disease management interventions with which practitioners in general behavioral medicine will be familiar. There are also some data that support the direct and targeted treatment of RLS/PLMD with cognitive and behavioral interventions; some being specific to BSM and others, again, coming from general behavioral medicine.

While pharmacologic management is the standard of care for both RLS and PLMD, treatment guidelines and algorithms as well as patient information pamphlets highlight a number of non-pharmacologic suggestions. These are most well-developed for RLS, but most of the suggestions apply to PLMD as well. The list of such approaches/suggestions can be quite extensive and detailed [21]. They include eliminating medications that may cause or exacerbate RLS symptoms especially dopamine blocking agents (e.g. neuroleptics), but also antiemetics and antihistamines (found in many over-the-counter allergy and sleep aids), as well as avoiding antidepressants that may cause or exacerbate PLMs, especially the selective serotonin reuptake inhibitors (SSRIs). Other suggestions include maintaining a healthy weight and diet, getting moderate exercise, using support groups, and taking a hot bath, cold shower and/or brief walk before bedtime. With the exception of exercise (reviewed below), none of these suggested is based on anything other than anecdotal reports. The suggestions also usually mention some version of employing good sleep hygiene.

In terms of sleep hygiene for RLS/PLMD, there are a two main points that bear highlighting. First, the avoidance of alcohol, caffeine and nicotine may be underscored because of their potential contribution to RLS symptoms and/or PLMs. Second, other sleep hygiene practices may or may not have any utility for patients with RLS/PTSD. Particularly when sleep hygiene is provided to patients as a handout or pamphlet, there is no indication that this helps promote sleep in any patient group. In this regard it is important for providers not familiar delivering BSM interventions that sleep hygiene has little to no demonstrated efficacy as a monotherapy for insomnia. Moreover, even when it is delivered as part of a multi-pronged intervention, sleep hygiene as a psycho-educational therapy, is an active process with patient-provider interaction, goal-setting, between-session homework assignments and follow-up. In addition, it is equally important to note that some sleep hygiene or “tips for good sleep” include in them a suggestion that is not considered a sleep hygiene instruction, but a stimulus control instruction. In particular the suggestion to “use the bedroom only for sleep and sex” is a stimulus control instruction (without providing rationale for and complete instructions for stimulus control) and is in direct conflict with the suggestion “to maintain a regular bed and wake time” that is often an item on the same list. This is confusing to patients who may consistently go to bed at a regular time to abide by the latter instruction, regardless of whether they are sleepy, and get up at the same time each morning, despite waking much earlier than their rise time. In such cases, following good sleep hygiene may actually contribute to the development or maintenance of insomnia. A thorough BSM approach to sleep scheduling for patients with RLS/PLMD would be a much preferred approach than the standard sleep suggestions provide.

The treatment of co-morbid insomnia or insomnia-like presentations in RLS/PLMD can be directly targeted with the cognitive-behavioral therapies for insomnia (CBT-I) that are the focus elsewhere in this issue. As with many medical and psychiatric conditions, RLS/PLMD may directly precipitate insomnia or directly exacerbate pre-existing insomnia. One manner by which this may occur is that when nocturnal RLS symptoms and/or PLMs lead to repeated full awakenings, one or more such awakenings may lead to lengthy wake times and difficulty reinitiating sleep. As is the case with going to bed before being sleepy and remaining in bed for more than 15–20 minutes following final awakening in the morning, these can set the stage for excessive time in bed relative to total sleep time, and potentially to conditioned arousal as seen in psychophysiologic insomnia. In one study, PLMD patients did not differ from primary insomnia patients in terms of sleep hygiene factors (reading in bed), stimulus control behaviors (lying awake in bed), cognitive arousal, and physical arousal, while both groups differed

significantly from normal sleepers on each of these domains [36]. Thus, at least for patients with PLMD there can be an insomnia-like presentation. In such cases, or when co-morbid insomnia is diagnosed in RLS or PLMD, CBT-I should be considered.

To date, there remains only one controlled trail of CBT-I in RLS/PLMD. In this study by Edinger and colleagues [37], 16 patients with PLMD were randomly assigned to receive 4 weekly sessions of CBT-I or 4 weeks of clonazepam at 0.5 to 1.0 mg. Both groups had significant improvements in self-reported sleep variables with no between group-differences, except that the CBT-I group had significantly more reductions in daytime napping and the clonazepam group had significantly more reductions in PLM arousals. One consideration, when delivering CBT-I, is the possibility that sleep deprivation can worsen RLS. If this is a concern, than the sleep restriction component of CBT-I may be modified to limit this possibility by replacing it with sleep compression [38]. On the other hand, in the seminal study of sleep restriction therapy for insomnia [39], two study participants who had both RLS and PLMD demonstrated significant improvements in sleep with no reports of increased RLS symptoms. Overall, CBT-I, with some potential modifications on a patient-specific basis, can be considered a potentially promising approach to both RLS and PLMD with further empirical work clearly needed.

The role of exercise remains a somewhat confusing topic with respect to RSL/PLMD. As noted above, ‘moderate’ exercise is often suggested for RLS. This is based on several factors. First, RLS symptoms tend to increase with prolonged inactivity and to be alleviated with physical activity. On the other hand, some individuals report exacerbation of symptoms with exercise. Specific findings on the topic have been mixed with one study showing an increased risk for RLS associated with physical activity prior to bedtime [40] and another showing an increased risk for RLS associated with lack of exercise [41]. The discussion is aided by the existence of two randomized controlled trials of exercise therapy. The first such study was a crossover trial conducted in 13 patients with PLMD subsequent to spinal cord injury in which participants received 200 mg L-DOPA and 50mg benserazide for 30 days or exercise on an ergometer 3 times a week for 45 days [42]. Despite the limitations of this design and the small sample size, both treatments resulted in significant reductions in PLM index from 35.1 to 19.9 for L-DOPA and from 35.1–18.5 for the exercise program. Such studies bear replication in other RLS/PLMD populations.

The second exercise study was conducted in 23 patients with RLS who were randomized to receive a 12 week trial of exercise therapy or a control condition [43]. Both groups received basic instructions in lifestyle management that included cigarette and alcohol cessation, avoidance of excessive caffeine, and proper sleep hygiene, with no specific goals being set or follow-up on these suggestions. The exercise intervention consisted of lower body resistance training exercises and 30 minutes of treadmill walking, which took place 3 times per week for 12 weeks at a local community center (participants were free to do more or less than instructed). Compared to the control group, the exercise group achieved significant reductions in RLS symptom severity at a 6 week assessment, which was maintained at the 12 weeks. Notably, the control group had no improvements from baseline at either time point, an indirect test of the utility of lifestyle instructions for RLS. While these are small trials, they begin to clear up some confusion with respect to exercise and suggest that an exercise program (as opposed to a suggestion to exercise), may be a promising approach to managing RLS/PLMD.

Although spontaneous, episodic, or treatment specific remission of RLS/PLMD does occur, for many patients these are chronic conditions. Comprehensive non-pharmacologic approaches to other chronic diseases, either independent from or in concert with pharmacologic interventions, share some similarities with treatments for RLS/PLMD. For instance, one such approach, albeit untested in any controlled fashion, exists for RLS in the form of a patient guide

that greatly expands the standard suggestions for RLS [44]. In addition, Hornyak and colleagues have recently published results of an uncontrolled trial of CBT for RLS [45]. In this preliminary study, 25 participants with RLS (15 medicated and 10 unmedicated) took part in a weekly 90 minute group therapy sessions for 8 weeks. The intervention included modules on psychoeducation about RLS symptoms and treatments, mindfulness-based breathing relaxation, cognitive therapy for sleep disturbances, stress-reduction and coping strategies, cognitive therapy for depression, and identifying and managing individual triggers for RLS. Overall, participants reported significant improvements on subjective scales of RLS severity and quality of life (including satisfaction with sleep) at post-treatment and these gains were maintained at a 3 month follow up assessment. While further work is needed in this are, this study provides the first evidence that a comprehensive behavioral medicine approach can be implemented with positive outcomes for RLS patients.

Summary

RLS and PLMD are most often treated pharmacologically as is suggested by standards of practice. While treatment algorithms and patient materials do highlight the use of non-pharmacologic approaches, these are seldom delivered in any systematic or rigorous manner. Nonetheless, several behavioral sleep medicine approaches are available to assist in the management of RLS/PLMD. The first, and perhaps the most obvious use of a BSM approach in these conditions, is in the case of diagnosed co-morbid insomnia or the presence of several insomnia-like symptoms, where CBT-I would be indicated. Due caution is noted in utilizing the all-too-pervasive lists of sleep hygiene and sleep tips as “hand-out” therapies. Except when such services are not available, there is little rationale for providing sleep hygiene instructions alone apart from multi-component CBT-I. Second, the recent evidence supporting exercise therapy for PLMD and RLS and comprehensive CBT for RLS highlight their potential utility. Third, BSM and general behavioral medicine strategies can target lifestyle factors contributing to pathophysiology. Fourth, similar behavioral medicine approaches can be undertaken to help patients cope with their conditions using a model of chronic disease management. In addition, any or all BSM approaches may be useful for patients experiencing augmentation or tolerance to medications, and accordingly during a “drug holiday”.

The use of BSM approaches in RLS and PLMD represent not only an under-utilized set of strategies that can be delivered to patients, but also an area with a number of empirical questions to be addressed. Most, if not all, of the BSM interventions reviewed require additional support before being considered evidence based treatments. Exercise therapy and comprehensive CBT in particular, deserve some further assessment in randomized, controlled trial designs. There is also ample opportunity to assess various combinations of therapies including modifying CBT-I to include exercise therapy and/or components of CBT for RLS. Similarly, research designs that could evaluate these BSM approaches as adjuvants to standard medication management would be informative.

In sum, it is incumbent upon the sleep medicine field to more fully include BSM approaches in the management of RLS and PLMD. The emerging findings suggest that patients may benefit from a more multi-disciplinary approach than is typically the norm, while underscoring the importance of conducting additional clinical research in this area.

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