The Treatment of Restless Legs Syndrome and Periodic Limb Movement Disorder

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Abstract: A task force consisting of six authors reviewed the published literature on the therapy of the restless legs syndrome or periodic limb movements in sleep available in indices through April, 1998. They selected the 45 articles for detailed review which presented original investigations of therapeutic impact on the restless legs syndrome (RLS) or periodic limb movements (PLM) and which met minimal standards. These articles dealt with a range of pharmacological and other treatment modalities, although most dealt with medications and almost half of those concentrated on dopaminergic agents, especially levodopa in various formulations. Almost half of the articles reviewed used controlled methodologies, most commonly cross-over methodologies with randomized allocation of subjects. Multi-center studies with large numbers of subjects and long-term controlled studies were not found. Information was extracted from the articles and study design, clinical definition, evaluative measures, side effects, and outcomes were tabulated in 6 evidence tables and summarized in the accompanying text. This literature was evaluated for the nature of the studies performed and its coverage of potential therapies. The review concludes with comments on possible future directions for therapeutic investigation based on the current state of the literature.

1.0 INTRODUCTION

A NUMBER OF DEVELOPMENTS IN THE LAST DECADE AND A HALF HAVE MADE A REVIEW OF THERAPY in the Restless Legs Syndrome (RLS) and Periodic Limb Movement Disorder (PLMD) both timely and important. (Table I provides the various definitions associated with these periodic movements.) First, a growing number of studies of therapy in RLS and PLMD have appeared using increasingly sophisticated methodologies and designs. While these studies, as reviewed in this article, have covered a broad range of agents and procedures, they have concentrated in four classes of medications: dopaminergic agents, opioids, benzodiazepines, and anticonvulsants. Information is now available both about the efficacy and the disadvantages of using some of these agents. Second, the clinical features, diagnostic standards, epidemiology, and some aspects of the pathophysiology of RLS and PLMD have been studied and further clarified.[1-3] Third, a number of population surveys have indicated that the prevalence of RLS may be higher than previously suspected.[4-7] This makes it seem plausible that RLS is one of the most common and clinically significant sleep or movement disorders. PLMS, while not always of clinical significance, have also been found to be present in about half of older persons.[8] Finally, because knowledge about RLS and PLMD has developed recently, relatively little is known by physicians about these conditions and their treatments.[9,10] Providing a thorough review and generating standards for treatment of RLS and PLMD would benefit physicians specializing in sleep medicine as well as other physicians, including primary care providers, who are all likely to see patients with RLS.

RLS therapy has been reviewed by various authors.[1-3,11-16] However, none of these reviews used defined criteria for selecting articles or employed an evidence-based evaluation of therapy.

2.0 Methods

Medline searches for articles on RLS and PLMD were conducted through April, 1998. Key words for search included restless legs, both as a subject or text word; a combination of myoclonus and periodic; a combination of sleep with dyskinesia, myoclonus, or restless; and a combination of sleep, periodic, and movements. This search led to 588 articles and was supplemented by review of Current Contents and the Sleep Research indices to September, 1997 and by articles discovered during other research, if

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published prior to April, 1998. 328 articles, identified as potentially relevant based on abstracts, were obtained in full length and examined further. Articles to be entered into the evidence tables and used for our conclusions were required to be published after peer review and to meet two initial criteria: a minimum of 5 patients studied and a defined outcome that could be used to assess the therapy. Articles were eliminated in which there was inadequate definition of RLS or PLMS or in which the numbers of patients involved could not be clearly determined. Articles in all languages were considered for inclusion. Forty-five articles relevant to therapy and meeting criteria were then selected for analysis and tabulation. Two task force members analyzed each of these articles for design, definition of RLS and PLMD, exclusion and inclusion factors, subject character and dropout, outcome measures, side effects evaluated, biases, and conclusions. Discrepancies were resolved and evidence tables prepared based on these analyses. The level of evidence for the treatment-related data in each paper is listed in Tables 1-6, and was identified by members of the American Academy of Sleep Medicine Standards of Practice Committee according to criteria, as noted in the accompanying practice parameter paper.[17] Some articles, more recent than the review paper timeline, but relevant to therapy of RLS or PLMD are noted in the companion practice parameter paper.[17]

131 articles derived from the search did not meet the criteria for reviewable therapeutic articles, but were found useful as background articles. These articles were in languages comprehensible to the task force members, which included English, French, German, Italian, and Spanish.

The Board of Directors of the American Academy of Sleep Medicine approved this review. All authors of this review completed detailed conflict-of-interest statements and were found to have no significant conflicts with regard to this subject.

3.0 Background

While there were scattered mentions of conditions that might have been RLS beginning with Willis in 1672,[18] the first extensive description of RLS was a monograph by Ekbom[19] which delineated the clinical features and made initial therapeutic suggestions. Ekbom noted that both the opioids and sedative medications helped RLS,[20] but felt they carried disadvantages and recommended cholinergic vasodilators as therapy.

PLMS was first called nocturnal myoclonus[21] (Table I). However, the essential periodic nature of these movements and their association with RLS was first uncovered by Lugaresi and his colleagues.[22] Because they were known as myoclonus prior to their definition as periodic leg movements, the initial therapy suggested for PLMD was clonazepam, which had been found useful for other myoclonias.[23]

3.1 Definition and description of RLS and PLMD

While many of the clinical features of RLS were first delineated by Ekbom,[19] major work on characterizing the clinical features, epidemiology, and pathology of RLS and PLMD has been accomplished in the last decade.

3.1.1 Diagnostic criteria

RLS is still diagnosed clinically by evaluating the patient's history. While earlier diagnoses were based on global clinical impression, the trend has been for increasingly formalized diagnostic criteria. In recent years, consensus criteria for diagnosis have been proposed, although empirical validations have not been performed. The International Classification of Sleep Disorders (ICSD)[24] produced by the American Sleep Disorders Association in 1990 and updated in 1997 lists 3 minimal criteria for a diagnosis of RLS (Table II). Subsequently, the International Restless Legs Syndrome Study Group[25] in 1996 propounded 4 minimal criteria for the diagnosis of RLS (Table II). A validated questionnaire based on these clinical criteria could be useful in a preliminary diagnosis of RLS, either for epidemiological studies or as an element of clinical evaluation. However, although initial efforts in this direction have begun, such an instrument does not currently exist in final form. There is no questionnaire that has been properly validated with sensitivity and specificity within and across disease conditions established.

From their discovery, PLMS have been diagnosed with a direct recording of movements, usually via electromyography (EMG) (surface recordings of both anterior tibial muscles during polysomnography {PSG}), but in recent years through actigraphy (activity recording) as well. Diagnosis has depended on demonstrating that the movements were present and the diagnostic criteria have related to how to enumerate them and assess their significance. Coleman[26,27] established the first widely accepted formal criteria for counting them -- setting a criteria of EMG burst length (0.5 to 5.0 seconds), period (4 to 90 seconds), minimal train length (4 movements), and behavioral state (sleep). The American Sleep Disorders Association Atlas Task Force[28] has largely reaffirmed this definition, with the minor variations of a minimum separation time of successive movements of 5 seconds, and the requirement that movement amplitude on EMG be greater than 25% of a great toe dorsiflexion signal (performed without resistance to 30 degrees during calibration). Movements associated with respiratory events are usually classified separately. The periodic limb movement index (PLMI) is usually calculated as number of total PLMS divided by total sleep time. Similarly, the number of PLMS associated with arousals (as defined by the Sleep Disorders Task Force in 1992[28])[29] is used to generate a PLMS with arousal index (PLMAI).

Because PLMS may not always be clinically significant, there has been further need to define a disorder associated with them, periodic limb movement disorder (PLMD). First, there was a need to set a threshold for a minimum number or frequency of PLMS to establish PLMD. Most authors have set a PLMI of 5 or higher as significant, although this figure may be low,[30,31] especially in the elderly. The only formal diagnostic criteria for PLMD are found in the ICSD[24] which set minimal diagnostic criteria (Table III). In many studies of the effects of drugs on PLMD, the study groups have been defined predominantly by the presence of polysomnographic PLMS without clear specification of clinical consequences or the presence of restless legs syndrome.

The ICSD also provided unique severity and duration criteria for RLS and PLMD[24] (Tables IV and V). These ICSD criteria have not been experimentally validated. The International Restless Legs Study Group is in the process of validating a RLS severity rating scale, a preliminary version of which has already been used in clinical trials.[32,33] Clinically, most cases, except for those due to a secondary cause such as a medication or pregnancy, fall in the chronic category by ICSD guidelines and duration of illness is not a major factor in therapeutic trials.

3.1.2 Associated features related to sub-categories or evaluation

3.1.2.1 Epidemiology of RLS and PLMS

Earlier epidemiological studies using clinical diagnoses of interviewed patients found that 2 to 5% of patients could be diagnosed with RLS.[34-36] Five modern population studies employing restricted questionnaires in population sampling polls, asking about a subset of clinical features of RLS or PLMD, have found prevalence figures in adults ranging between 9 and 15%.[4-7,37] These studies have also indicated that prevalence increases with age, at least through the end of the sixth decade of life.[38] The increasing prevalence is due to continued incidence at older ages combined with the typical chronic course.[39] Recent case series examining age of RLS onset retrospectively have indicated that among adult patients, a substantial fraction (as large as 43%) report onset before the age of 20.[39-41] Several reports have documented the occurrence of RLS and PLMD in childhood with preliminary work suggesting the importance of a positive family history in diagnosis and a predominance of PLMD symptoms over RLS dysesthesias in children.[42,43]

Since the work of Lugaresi's group,[44] it has been considered that most, but not all RLS patients also have PLMS. In the most thorough polysomnographic study to date,[41] 80.2% of a series of RLS patients had more than 5 PLMS per hour on an initial PSG and an additional 7.6% had that number on a second PSG.

PLMS may occur in up to 6% of the general population,[45] and this increases with age.[26,27,45-47] A study by Coleman and colleagues[48] found PLMS in 20% of patients 60 years or older (adding those with RLS but not PLMS gave a total of 28% affected in this age group). Two later studies, requiring a PLMI greater than 5, found PLMS in 44% of subjects over 65 years of age[46] and in 58% of subjects over 60 years of age.[30]

In summary, RLS and PLMD are both common. RLS is a chronic condition which can begin at almost any age and whose prevalence increases gradually into old age. PLMS appear to increase dramatically in prevalence later in the life span until it is possible that a majority of those older than 60 will have a PLMI of at least 5.

3.1.2.2 Etiology, risk factors, co-morbid conditions and differential diagnosis

Etiology

The pathogenesis of RLS and PLMD remains unknown. Vascular, systemic, peripheral nervous system, genetic and central nervous system etiologies have been proposed.[1,3,14] Current evidence favors a disinhibition of normal central nervous system pacemakers, probably governed by multiple influences.[1] The dopaminergic system has been implicated, with neuropharmacological data indicating primary dopaminergic system involvement modulated by the opioid system and possibly other neurotransmitter systems.[1,11,49] The involvement of low iron stores, measured as ferritin, in provoking RLS suggests that iron levels are also involved in modulating RLS.[50-52] Because RLS symptoms follow a circadian cycle,[53] there is likely a provocative factor linked to circadian rhythm.

Localization of the key abnormality in RLS and PLMD has also been equivocal. While subtle peripheral nerve abnormalities may be found with RLS,[54] RLS does not inevitably follow or correlate with peripheral nerve damage. Recently, high-resolution functional magnetic resonance imaging has indicated involvement of thalamic, cerebellar, red nucleus and brainstem structures.[55] PET and SPECT studies have shown modest dopamine deficits in the basal ganglia,[56-59] but the significance of this finding remains unclear. Few RLS patients develop the motor abnormalities, such as Parkinsonism, associated with basal ganglia pathology. It may be that any basal ganglia dopamine deficiency is only a marker of a more signficant deficiency in another location.

Attempts to find a cortical locus for PLM using backaveraging have either found no potentials[44,60] or potentials that do not suggest cortical involvement similar to that demonstrated in myoclonias.[61] These results support a subcortical location for the generator of these movements. A number of recent studies[62-64] have found PLMS present in those with spinal cord injuries, including complete transec-

tion, supporting the idea that at least part of the oscillator underlying PLM is located within the spinal cord. While studies of reflex excitability in RLS or PLMD have given equivocal results,[65-68] one recent study[69] demonstrated increased excitability in flexor withdrawal reflexes in the legs of RLS patients during NREM sleep, when normal subjects show a decrease. This result suggests that state-dependent altered physiology may cause or facilitate some of the abnormal movements of RLS and PLMD.

Risk factors and Co-Morbid Conditions

Increased age, positive family history, pregnancy, uremia, and low iron stores have all been proposed as risk factors for RLS and/or PLMD. Not only does the prevalence of RLS increase with age, but the severity of the disorder also seems to increase with age and longer duration of symptoms.[39] Similarly, PLM prevalence appears to increase with age, rising dramatically after the age of 50.[45-47]

In idiopathic RLS, 3 recent studies have found a positive family history of RLS in 63%, 64% and 92% of cases.[39-41] One of those studies found a positive family history in only 13% of cases with neuropathic RLS,[40] suggesting that there may be two groups of patients -- those with familial, idiopathic RLS and those with sporadic, acquired, secondary RLS. Although no RLS gene linkage has yet been identified, an autosomal dominant pattern of inheritance has been found in several large pedigrees.[70-73]

The largest study on RLS during pregnancy reported a prevalence of 19% in 500 consecutively interviewed women, with 7% reporting severe symptoms and complete resolution of RLS in 96% by 4 weeks after delivery.[74] In renal dialysis patients, studies have reported a 20% to 57% prevalence of RLS.[75-82] No single factor has been found in uremia, but kidney transplant may produce substantial improvement, whereas dialysis does not.[83] Recent work has found serum ferritin levels to correlate inversely with the severity of RLS symptoms.[51,52]

Although most cases of RLS and PLMD appear idiopathic, a large number of comorbid conditions have been reported in association with RLS and PLMD. With a few exceptions, the majority of these comorbid conditions have an undetermined relationship to RLS and many likely represent coincidental occurrence.[1-3]

Differential diagnosis

In contrast to comorbidity issues, differential diagnosis should distinguish RLS dysesthesias from paresthesias and dyesthesias due to peripheral neuropathy, arthritic and muscular pain, neuroleptic-induced akathisia,[84] and the discomfort of painful legs/moving toes.[71] PLMS need to be distinguished from the normal phenomena of sleep starts[24] and phasic REM activity as well as the spectrum of abnormal sleep movements (rhythmic movement disorder, apnea or seizure related movements, and REM sleep behavior disorder). Satisfying the 4 RLS diagnostic criteria outlined in section 3.1.1 will typically distinguish RLS dysesthesias from other types of leg discomfort. To differentiate PLMS from other sleep related movements, PSG is generally needed. Most pathologic forms of "myoclonus", other than PLMS, are either typically suppressed during sleep, shorter in duration or have a much different periodicity.[1]

3.2 The evaluation of RLS and PLMD

Both subjective and objective measures have been used to determine therapeutic response in RLS and PLMD. The most sophisticated, controlled studies have tended to use both in order to give a more complete picture of the patient's state and therapeutic benefit. In this section, we review those measures commonly used in the studies as well as those which may find greater use in the future.

3.2.1 Subjective evaluations of symptoms

Typical evaluative questionnaires have called for assessment of symptom severity, including patient rated frequency, duration, and intensity of symptoms as well as daytime sleep propensity, sleep disturbance, somnolence, or daytime function. These measures are commonly used to establish treatment effects, but like all subjective measures have the bias of being "subjective". In controlled studies, subjective placebo effects as large as 30% have been reported.[85,86] Finally, such measures of RLS have never been validated for their sensitivity and specificity within and across diseased populations.

3.2.2 Polysomnography

As a standard methodology for "objective" measurement of RLS and PLMD, therapeutic trials have utilized polysomnography (PSG). Both PLMS and sleep parameters have been assessed. The most common measures utilized as therapeutic criteria are total PLMS, PLMI, PLMAI (See Table I), sleep efficiency and sleep latency. Arousals may also be independently analyzed.[87]

In using the PSG for assessment, several issues need to be addressed. First, not all patients with RLS have demonstrated a PLMI greater than 5 on PSG.[25] Therefore, not all patients can be meaningfully evaluated this way. Second, not all patients with PLMS have RLS symptoms, nor can we be sure they all share some common disorder.[88] It is inappropriate to assume therefore, that all treatments tested solely against PLMS are valid for all clinical conditions of RLS and PLMD. Third, the correlation between RLS symptoms and PSG findings (e.g. PLMS or sleep efficacy) have not been adequately studied.[89] These studies to date do suggest that changes in one of these may not always be

a good measure of changes in other aspects of RLS.[90-93]

An alternate PSG methodology, home recording, has not been used for therapeutic studies in RLS or PLMD.

3.2.3 Actigraphy and movement recording

Actigraphy using an ankle-placed activity meter has been proposed for economically measuring PLM. The major potential advantages are simple home recording and increased accuracy and sensitivity since recordings can be made over multiple nights, but a drawback is the inability to distinguish independent PLMS from apnea associated movements. Although global activity during the night has been used as a measure of PLM,[91] such general activity is non-specific and may not accurately reflect PLMS. Further developments have begun, however, to separate PLM from general activity[94] and associate activity with body position (standing, sitting, lying) as well as add computing power to the monitor to permit on-line enumeration of PLM.

3.2.3.1 Immobilization tests

Immobilization tests, developed primarily by Montplaisir and colleagues, attempt to provoke RLS symptoms by imposing rest. In the "Suggested Immobilization Test" (SIT), the patient sits on the bed with legs outstretched and eyes open and is instructed to not move the legs or other body parts. Anterior tibial EMGs record PLM, while patients signal the time or intensity of sensory discomfort. A 30 minute SIT was only partially successful as a measure of therapeutic response.[95] Subsequently, longer durations of 60 minutes[89] or 90 minutes[53] have been used. Symptoms seem to plateau at approximately 60 minutes.[89] For unclear reasons, PLM recorded during this test have sometimes had longer EMG bursts (greater than 5 seconds) than those recorded during the PSG.[89]

A variant, the "Forced immobilization test"(FIT),[96] employs actual physical restraint of the legs, but is uncomfortable for the patient and discriminates less well between RLS patients and controls. In another variant of the test,[97] the patient is allowed to move around if symptomatic and actigraphic measurement of leg movements is used as a measure of restlessness.

The SIT is currently the only developed objective assessment of the RLS movements during wakefulness, but it is limited by the need to perform the test in a laboratory type setting. So far, it has been used in relatively few therapeutic trials in RLS and its actual value will require further evaluation.

3.2.4 Other methods of evaluation (including quality of life)

The assessment of sleepiness or fatigue reported by PLMS patients can be assessed with both the patient's self report on the Stanford Sleepiness Scale (SSS) or the Epworth Sleepiness Scale (ESS) and the physiological assessment of sleepiness using the Multiple Sleep Latency Test (MSLT). In two studies, however, while other measures were significant, the MSLT did not show significant changes after treatment,[91, 95] perhaps because relaxation itself can provoke RLS symptoms which may then decrease sleepiness. Patients with PLMD alone are likely to be more amenable to accurate assessment using these subjective and objective measures of sleepiness.

A striking omission in the literature has been the relative paucity of quality of life information about RLS patients. While there are well developed and validated quality of life questionnaires (e.g., SF-36), these have not been used in the studies we reviewed nor adapted to RLS or PLMS. In recent years, informal scales have been used in some studies[98] and quality of life measures are included in the International Restless Legs Syndrome Study Group (IRLSSG) rating scale that is under development.

3.2.5 Summary of evaluative measures

Adequate therapeutic evaluations of RLS utilize some objective measures, since these are likely to be less influenced by the large placebo effects reported in some subjective studies. However, in the case of RLS, a mix of objective and subjective measures is needed to provide a full picture of overall therapeutic benefit since objective measures cannot assess all aspects of RLS, including effect on quality of life. The studies of PLMD only rarely assess the impact of the movements on patients' daytime functioning or sleep complaints, so they generally can be reduced to studies on the presence of PLM at night. PLM can probably be adequately assessed by current techniques of counting movements, but it is not clear which measure (PLMI, PLMAI, or total events) best correlates with disease impact. In terms of the measures used to assess therapeutic effect of RLS and PLMD, many of the studies reviewed do not present a complete picture.

4.0 Therapies in RLS and PLMD

In general, therapies for RLS and PLMD can be divided into two large categories: those interventions which have been systematically studied and reported in the literature and those interventions which have been found by personal exploration, anecdote, and clinical experience and disseminated informally, largely outside the medical and scientific profession. The first group of interventions, as revealed by our review, are predominantly pharmacologic in nature. The second group includes a wide range of behavioral, herbal, and nutritional therapies, which, though potentially quite important, remain outside of our purview.

4.1 Introduction to Therapies

We have grouped the evidence tables by treatment type. The six tables are: dopaminergic, opioid, benzodiazepine, anticonvulsant medications, medications drawn from other classes, and nonpharmacological therapy.

Several general comments can be made about the articles which met criteria as a group. First, it is important to understand that almost all of these studies show a systematic pattern of biases. Almost none of the studies involve parallel groups; instead, the major controlled design is a cross-over design with sequential assignment of patients to different exposures. In most cases, the initial exposure (usually active medication or placebo) is randomized. Many studies are also case series, usually open label studies of a single intervention. As a result, the major biases of these studies relate to the initial recruitment of the patients rather than to their assignment to different interventions. In general, subjects are patients who come to medical attention, which usually means those with greater access to medical care and more severe conditions. In the case of PLMD, this generally implies that the patient underwent PSG prior to recruitment, regardless of the initial complaint that brought the patient to a sleep laboratory. Most centers conducting studies are also university-based, so they experience the referral bias of such centers. In addition, all the studies reported are from the most developed countries and most have been done in centers whose patient populations are predominantly caucasian and of European ancestry. There are very few studies on special populations such as children (those under age 18), pregnant women, or the very old, although older subjects are well represented in a number of studies. A further issue with the literature is that information about those who were rejected for studies is not provided and, in general, there are no details about which patients dropped out of studies or why. Often, inclusion and exclusion criteria are given in only general terms or not discussed at all. Similarly, reporting of side effects seems to be meager or inconsistent. Many studies make no mention of them at all.

A second point is that the definitions of RLS and of PLMD have evolved. More recent studies may be examining better defined populations. Older studies of PLM may not have noted whether patients were adequately evaluated for RLS or other disorders and so were evaluating mixed populations with PLMD alone or PLMD associated with various other conditions.

4.2 Pharmacotherapy

The pharmacological treatment of RLS may go back over three centuries to Willis' successful treatment (and reported cure!) of a severely affected patient with an opiate preparation, laudanum.[18,99] Ekbom, while aware of the palliative efficacy of opiates and other sedative/hypnotic medications, felt vasodilators (generally cholinomimetic) were the most appropriate therapy, with the optimal balance of side effects and benefit.[19,20] The use of vasodilators dwindled without any published demonstration that Ekbom was misguided in his recommendations. Therapy for PLMD awaited the discovery and characterization of PLM in the course of sleep recordings.[22,100] The modern era of pharmacotherapy for these conditions then began with reports that benzodiazepines, a newer class of sedative/hypnotics, could alleviate RLS and PLMS.[23,101,102] Within several years, the three other major classes of medications, the dopaminergic agents,[103-106] opioids,[103,107,108] and the anticonvulsants[86,109] were also reported to be effective in these conditions. The last ten years have not seen further novel therapies, but a refinement in the studies reported, an increase in the number of agents investigated within individual classes, and a more acute awareness of the benefits and problems of these therapies. In recent years, most studies have focused on RLS. This may be due to the uncertain clinical status of PLMD.[110]

Despite the studies reported recently on RLS, relatively little is known about the long-term consequences of treatment. Some of the complications that affect patients with other diseases treated with the same agents (e.g. dyskinesias that are common in Parkinson's disease patients treated with dopaminergic agents) have not been reported in relatively long-terms studies (months to years in the case of dopaminergic agents) in RLS.[111,112] This may be due to a relatively intact striatonigral dopamine system in RLS patients. However, a number of significant complications of treatment have been noted, especially with use of the dopaminergic agents. The first problem noted was rebound, the tendency of symptoms to worsen at the end of a dosing period, leading to late night or morning recurrence of symptoms and PLMS.[105,113] This has been most common in cases of short acting dopamine agents such as regular release l-Dopa/carbidopa. A second common and important consequence reported after dopaminergic treatment is the apparent worsening of symptoms seen with long-term use of the medications, referred to as RLS augmentation,[114] which is seen most commonly with levodopa, and is increased by higher doses.[114-117] The symptoms of augmentation may present as a progressively earlier daily onset of RLS symptoms; consist of expansion of the symptoms beyond the legs (e.g., involving the trunk or upper limbs); and may be seen as an increase in symptom intensity or decrease in drug efficacy. Further increases in the medication may lead to greater augmentation, while discontinuing the medication will probably return the patient to a baseline level of symptoms. In contrast to rebound, augmentation is most prominent in the afternoon or evening, although in very severe cases it may be present at all hours. Clinical experience suggests that rebound and augmentation may occur with other agents, such as opioids,

but this has not been formally studied and clinical experience suggests it is not as common. A further problem, which has also not been formally studied, is that patients may experience a transient aggravation of symptoms for several days when they stop RLS therapy.

4.2.1 Dopaminergic medications

Dopaminergic therapy has largely tracked the therapeutic emphasis in Parkinson's disease, with an initial emphasis on levodopa followed by greater interest in dopamine agonists. Fifteen of the 18 studies listed in Table 1 [87,91,95,98,104-106,111-116,118-122] were conducted on levodopa compounded with a dopa-decarboxylase inhibitor (DDI), either carbidopa or benserazide. The other three deal with dopamine agonists. Seven of the studies listed in the table were conducted in a double-blind, cross-over designed manner; eight of them were also randomized. The remaining studies were clinical series, ranging from a sample size of six to fifty-one subjects.

We have reviewed 8 double-blind trials of levodopa, seven of which focused on patients with RLS (See Table 1). Four randomized cross-over studies using levodopa at a dose of 100 to 200 mg daily combined with DDI revealed significant decreases in the number of PLMS relative to placebo (See Table 1). Measures of sleep or arousal were less consistently decreased.[87,95,98,118] One study found comparable results in RLS patients with uremia and idiopathic patients.[98] Seventeen out of 20 subjects in one non-randomized crossover study preferred levodopa 250 mg to placebo.[106] Two randomized cross-over studies compared 200 mg daily levodopa against other agents. In one, levodopa decreased PLMS, PLMAI, and found better subjective response than a mild opioid, propoxyphene[91] (See Section 4.2.2 and Table 2 for opioid results). In the other,[104] levodopa was compared to dopamine agonists (bromocriptine, piribedil) and found to be significantly better than placebo in improving sleep quality. In the last double-blind trial,[119] 5 daily doses of 100 mg levodopa led to a significant reduction of PLMS in narcoleptics, but more disrupted sleep.

Seven clinical series examined levodopa therapy. One study reported that rebound and augmentation were very common in long-term levodopa therapy, especially of RLS patients (20% and 82%, respectively).[114] The same group found that 50% of long-term levodopa patients needed to be switched to a dopamine agonist, pergolide for adequate management, especially those with severe RLS.[115] Another study used a single evening dose of levodopa and found benefit restricted to the first part of the night.[105] Two studies found relatively sustained benefit on levodopa. One of the studies found benefit in all 20 patients studied, but the emergence of rebound in 7 (35%), requiring higher doses after 8 to 20 months.[113] In the second, at 2 year follow-up, 26 of 29 patients continued on levodopa at the end of the study, although 9 (31%) required higher doses.[111] A final study of uremic patients found no complete relief, but worsening when therapy was discontinued.[120]

In summary, the short-term, controlled studies have reported most consistent benefit from levodopa in reducing PLMS while long-term, open label studies have emphasized subjective benefit and tolerability. The greatest problems in treatment reported have been the emergence of rebound or augmentation which led either to dose increases or switching to another agent.

We reviewed only three studies of dopamine agonists in RLS patients. One small, controlled study of bromocriptine reported in 1988 found significant subjective relief and decreased PLMS in RLS patients.[122] No subsequent studies have examined this medication. Two studies have examined pergolide. Almost all reported subjective relief, although the longer-term study reported some augmentation.[116] The other study compared pergolide to levodopa and found better subjective relief and greater decreases in PLMS with pergolide.[121]

4.2.2 Opioid medications

Our review disclosed considerably fewer publications about opioid medications than about the dopaminergic agents, although opioid medications are prescribed by many physicians who treat RLS extensively.[123]

The four studies of opioids meeting study criteria are listed in Table 2.[91,108,124,125] Two are double-blind, randomized, placebo-controlled trials, using crossover methodology.[91,124] They examined oxycodone and propoxyphene, using both subjective ratings of RLS symptoms and polysomnographic measures to assess therapy. Oxycodone at a mean daily dose of 15.9 mg both improved subjective ratings and decreased PLMS,[124] with evidence for decreased arousals and improved sleep efficiency. Four patients did not experience worsened sleep-disordered breathing with the use of oxycodone. The study of propoxyphene examined a group of six patients with PLMD, three of whom also had RLS.[91] A daily dose of 200 mg of propoxyphene napthylate significantly decreased PLMAI, but not PLMI, while subjective benefit was not signficant.

The other two studies used a variety of opioids in open-label clinical series. One series found subjective improvement of RLS symptoms in all 6 patients,[125] but every patient was taking at least one other analgesic or sedative. The second series[108] found subjective benefit in all 5 patients, with marked improvement of awake dyskinesias and of PLMS each found in 3 of the patients.

Other case reports have found opioids useful for RLS in Parkinson's disease[126] and in a subset of patients with PLMD alone.[127] Long-term benefit for RLS with opioids has been reported, with little evidence for tolerance or

addiction, in limited series.[108,128]

4.2.3 Benzodiazepines

Studies of benzodiazepines have focused on clonazepam therapy, with additional studies that have tested several other, more recently available benzodiazepines. Only 3 studies of benzodiazepines in RLS have been reported.[85,129,130] Two double blind cross-over studies with small numbers of patients either found a modest benefit in leg symptoms and sleep[129] or no significant benefit compared to placebo.[85] The last study was a long-term open label study indicating significant benefit with few therapeutic problems in 24 patients.[129] Six studies have examined the impact of benzodiazepines on PLMD,[131-136] two of which were double blind. The majority of patients, except in one study,[132] did not have RLS, but all complained of either insomnia or EDS. A parallel design study[133] compared clonazepam to placebo and found a significant decrease in PLMS. A cross-over study examined triazolam[132] and found no significant improvement of PLMS, but better sleep and longer sleep latency on MSLT. Four uncontrolled studies[131,134-136] examined the effect of benzodiazepines on PSG measures of PLMS after clonazepam (3 studies), nitrazepam (1 study), or temazepam (1 study). The number of patients studied ranged between 6 and 14 and the duration of study varied from 2 days to 6 months. Three studies showed a significant decrease in PLMI,[134-136] while the last[131] showed a significantly decreased PLMAI, but not PLMI.

In summary, the studies reviewed generally report that benzodiazepines are helpful in the treatment of RLS and PLMD. However, their conclusions may be limited in view of the small sample sizes, the modest magnitude of treatment effects, and the difficulty in differentiating the nonspecific effects of benzodiazepines on sleep parameters from their specific actions on RLS and PLMD.

4.2.4 Anticonvulsant medications

Anticonvulsants were first studied for RLS and PLMD in the 1980's, beginning with carbamazepine, while more recently, gabapentin has been the subject of increased interest. All studies reviewed focussed on RLS patients. Three studies of carbamazepine met criteria for review;[86,93,109] one double blind, randomized parallel study with placebo control and two open label ones. The parallel trial[86] followed a large number of patients (174 completed the study) and demonstrated significant subjective improvement for both the drug and placebo groups, although carbamazepine was significantly more effective than placebo. More patients in the carbamazepine arm reported bothersome side effects and more dropped out due to side effects (6 vs. 2). A small open-label study with a crossover design, which included a placebo phase and involved upward titration of carbamazepine from 200 to 600 mg per day, found RLS severity subjectively improved with drug.[109] However, there was no statistical analysis and only 3 of the 6 subjects preferred the medication. The last study included 9 RLS subjects with PLMS and insomnia, whose bedime dose of carbamazepine was tritrated upward to a final dose between 3 and 7 mg/kg per day.[93] Subjective ratings and PSG measures of sleep efficiency and sleep latency were significantly improved by treatment but PLMS were not.

There have been two open label studies of gabapentin in RLS.[137,138] Both used subjective ratings, patient adjusted doses, and variable dose schedules. One study[137] titrated gabapentin up from 300 milligrams to a maximum of 2400 milligrams in 8 patients and found subjective improvement in half the patients after 1 week to 6 months follow-up. Two patients dropped out due to side effects. A second study[138] treated 16 patients for 6 to 18 months with 300 to 2000 milligrams a day of gabapentin and reported that every patient had a 50% or better subjective decrease of RLS symptoms.

While all of these studies of RLS showed some benefit from anticonvulsants, only one used a placebo control and that study with carbamazepine had a notably large placebo effect. The only study which examined sleep with PSG was a baseline/drug study that demonstrated some sleep benefit, but no significant decrease in PLMS with carbamazepine.

4.2.5 Medications active on the adrenergic systems

The first adrenergic medication reported as useful for RLS was the beta-blocker, propranolol.[35] More recently, studies have focused on clonidine, whose main action is to suppress noradrenergic activity by activating presynaptic inhibitory alpha-2 auto-receptors.[92] The only studies meeting review criteria are two double blind, controlled studies of clonidine in RLS.[92,139] One study[92] had a randomized, cross-over study of 10 patients whose dose was titrated over 2-3 weeks to reach a mean of 0.5 mg clonidine per day. Clonidine resulted in significant improvement compared to baseline in subjective measures and sleep latency, though PLMI was not significantly decreased. There was no correlation between plasma clonidine concentration and control of symptoms. Side-effects were frequent (8 of 10 patients); however, no patients left the study due to them. The second study[139] used a double-blind, parallel study of 10 patients treated with 0.15 mg clonidine daily compared to 10 treated with placebo. Clonidine significantly improved RLS symptoms, with 8/10 patients having complete relief of symptoms. There have also been a number of less formal reports, including one which reported efficacy in uremic RLS[140] in doses ranging between 0.1 and 0.9 mg per day. There are no reports of clonidine benefiting PLMD alone.

4.2.6 Other medications and delivery routes

A variety of agents beyond those already discussed have been suggested largely anecdotally in the literature to help RLS and PLMD (e.g. analgesics, sedatives, muscle relaxants, stimulants), but no studies of these agents met criteria. All published studies of pharmacologic agents in RLS and PLMD that met criteria for evidence based review used oral preparations. There is, however, a single case report of the successful use of epidural delivery of morphine[141] to an RLS patient with severe and unremitting disease. So, while it is possible that other routes (e.g. depot medications, intrathecal delivery) might be useful to provide sustained delivery in severely affected patients or to provide treatment to those unable to take medications by mouth (i.e. parenteral formulations, skin patches), these have not been examined more than minimally in the literature. In addition, while it is often the clinical practice to use combination therapy, especially in RLS,[123] there are no publications that have evaluated this practice. Another treatment strategy recommended in some reviews, rotating between successful agents, has also not been the subject of any published observations.

4.2.6.1 Miscellaneous medications

The only additional medication reported in an article meeting review criteria was a study of baclofen in 5 patients with PLMD[142] which used a single blind non-randomized cross-over trial of placebo and increasing doses of baclofen titrated to patient need over 15 days with nightly PSG. At all doses tested (20 to 80 milligrams per day), baclofen increased the number of PLMS, but decreased their amplitude and associated arousals. Sleep parameters also improved. No reported studies have employed baclofen in RLS.

4.2.6.2 Vitamins and minerals

The possible benefit of folic acid in RLS was first suggested in 1976.[143] One open-label study examined 16 patients with folic acid deficiency and a variety of neurologic problems (Table 5).[144] Fifteen were reported to have RLS. The RLS symptoms were reported to be improved with folic acid therapy in doses ranging from 1.25 to 30 mg daily.

Three studies have examined the use of iron in RLS therapy (Table 5).[50,51,145] A 1953 clinical series[145] reported relief of RLS in 29 patients, some anemic, treated with IV iron oxide (21 patients), oral iron (2 patients) and blood transfusions (6 patients). Two unblinded, open label studies[50,51] of iron supplementation in elderly RLS patients by one group showed subjective benefit from 320 milligram iron sulfate tablets taken 2 to 3 times a day. In one study[51], the serum ferritin levels correlated with symptom severity. Patients reliably responded if pre-treatment serum ferritin level was below 45 micrograms per liter.

4.2.6.3 Avoidance of specific medications

No studies meeting criteria have provided evidence of benefit from avoiding specific medictions. Two observational case studies have shown that dopaminergic or opioid antagonists can aggravate or reactivate the symptoms of RLS.[49,146] In addition, a number of clinical reports have suggested aggravation or provocation of RLS or PLMD by tricyclic antidepressants,[147] or serotonin reuptake blockers.[148] In contrast, some reports have suggested amelioration of RLS by different antidepressant classes.[149]

4.3 Non-pharmacological therapy

4.3.1 Accommodative strategies and sleep hygiene

No reports have formally studied the strategies and sleep hygiene practices of RLS or PLMD patients. Anecdotally, RLS patients themselves report that they often alter their sleep patterns to accommodate their RLS. For instance,[53] they may delay their hours of sleep into the middle of the night or remain active during hours when their symptoms might make sleep difficult. A study on the effects of sleep deprivation and circadian rhythm found that, although the circadian effect was the most important, sleep deprivation itself also exacerbated RLS symptoms.[53,150]

4.3.2 Behavioral and stimulation therapies

One study evaluated standard cognitive behavioral therapy for insomnia patients with PLMS[131] using a parallel group design with 16 patients and comparing the behavioral therapy to clonazepam (Table 6). Both agents improved sleep. Only behavioral therapy reduced daytime napping, but it did not reduce PLMS. Studies not meeting criteria but suggesting some benefits from behavioral treatment include two which used thermal feedback for PLMS.[151,152]

Because relief with motor activity, especially walking, is a key feature of RLS, walking or movement of the affected limb can be intentionally used to reduce RLS symptoms. Anecdotally, moderate amounts of regular exercise have been suggested to help symptoms, while excessive exercise is reported by patients to aggravate RLS symptoms. Hot baths or tasks requiring a large amount of concentration have also been reported anecdotally to reduce RLS symptoms. Counter-stimulation such as massage has also been suggested as helpful. Two studies of PLMS have also examined stimulation as a possible therapy (Table 6), one a double-blind crossover study of vibration compared to clonazepam[129] and an open label study of electrical foot stimulation.[153] Neither improved sleep but the second did

reduce the number of PLMS during the night.

4.3.3 Invasive therapies

One unblinded study on selected patients with documented venous insufficiency and complaints of RLS used intravenous sclerotherapy with sodium tetradecyl sulfate to obliterate the distended veins.[154] After a variable number (1 to 10) of treatments, 98% of patients reported notable improvement in RLS symptoms, although 28% of these relapsed by the two-year follow up.[154] This study has not been independently replicated.

4.3.4 Nutritonal considerations

There are no studies meeting study criteria which have examined the benefits of particular diets on RLS or PLMD. One uncontrolled study reported that abstinence from caffeine and all other xanthines led to complete remission of RLS discomfort for 10 patients[155] (Table 6), although five patients also used benzodiazipines concurrent with starting the withdrawal.

5.0 Discussion of therapies

5.1 Differences between RLS and PLMD

In the studies which met criteria, there have been distinct differences in which agents have been studied for RLS and which for PLMD alone. All studies of anticonvulsants, clonidine, folic acid, iron, sclerotherapy, and caffeine restriction; all but three studies of dopaminergic agents; and 3 of 4 studies of opioids have been based on an entry diagnosis of RLS. However, some of the studies on dopaminergic agents and opioids employed PLMS as a measure of RLS. In contrast, six of nine studies of benzodiazepines and all the behavioral studies as well as the baclofen study have used an entry diagnosis of PLMD. Two of the open label studies of dopaminergic therapy (levodopa, pergolide) provided some information showing similar initial but different long-term impact of the agents on RLS and PLMD alone.[114,115]

5.2 Secondary and primary RLS and PLMD

RLS treatment has been studied for two conditions in which RLS is believed to be secondary to another disorder; i.e. iron deficiency and end stage renal disease (see 3.1.2.2). PLMD treatment has been studied where PLMS are associated with narcolepsy. In cases of iron deficiency anemia or low ferritin, oral iron has been reported to reduce RLS symptoms in a limited number of cases.[51] Since iron replacement takes time and may be only partially successful, general medications may be necessary either transiently or permanently, but there have been no specific reports on their use in this condition. Dialysis itself does not appear to alter the RLS or PLMD secondary to end-stage renal disease, but the dialysate temperature may influence symptoms.[156] Erythropoietin supplementation may reduce symptoms and symptoms often largely resolve with kidney transplantation.[157,158] Two clinical trials meeting study criteria included patients with end-stage renal disease and found efficacy for levodopa.[98,120] One did not.[118] One trial with clonidine[139] revealed efficacy in this group of patients. Some case reports suggest efficacy for benzodiazepines.[77] Nephrologists, noting that carbidopa is a pyridoxine (B6) inhibitor, suggest providing an additional daily B6 supplement of 10 mg.[159] In considering other potential medications for dialysis patients, the elimination patterns of the medications and their active metabolites need to be considered (e.g. gabapentin is dialyzable, whereas meperidine, propoxyphene, valproic acid and carbamazepine are not[159]). PLMS occur commonly in narcolepsy,[160-163] and have been reported to be reduced by either levodopa[119] or bromocriptine.[163,164] These treatments, however, have not been reported to improve sleep or other narcoleptic symptoms. Specific studies have examined therapy in patients with such disorders as fibrositis[136] and venous insufficiency[154].

5.3 Relationship of therapy to disease severity

There is a lack of studies which differentiate cases with varying degrees of RLS or PLMD. Because of selection bias, patients with moderate to severe symptoms have been studied in most clinical trials. In a long-term open label study on dopaminergic agents, more severe patients developed early complications with levodopa therapy,[114] while mild patients and those with PLMD alone benefited from levodopa alone in lower doses (200 mg daily or less) and developed fewer complications. In one other preliminary report, gabapentin was found to be helpful for mild to moderate, but not severe, RLS.[165]

5.4 Therapy of special patient groups: children, pregnant women, the elderly

The evidence tables include no treatment studies meeting entry criteria on children, or on pregnant females but two specific to the elderly.[50,51] A few case reports have indicated individual responses in children with RLS or PLMD to: strict limit-setting in enforcing the child's sleep schedule, caffeine restriction, clonazepam, levodopa/carbidopa, pergolide, and clonidine.[42,43,72,166-168]

One clinical series examining RLS in pregnancy reported significantly fewer women on folate to have RLS (9%) compared to women on a vitamin without folate (80%).[169] In two cases of severe RLS, carbamazepine was found to provide relief.[170] However, carbamazepine has been associated with neural tube defects in humans, especially dur-

ing the first trimester.[171,172] Another study recommended treatment of anemia during pregnancy, based on a finding of increased prevalence of RLS in pregnancies complicated by anemia (24% vs 11%).[19] The risk from medications during pregnancy is classified by the FDA on the basis of data from humans and animals. Designations are category A,B,C,D,and X, varying from least to highest risk, with category A having no evidence for risk by controlled studies and category X contraindicated during pregnancy because of proven teratogenicity.[173] Very few of all medications fall in category A, because controlled studies are rarely done during pregnancy.[172]

Classification of medications for RLS is as follows: levodopa/carbidopa C, pergolide B (but limited data); clonazepam C, temazepam X; oxycodone B (but D if chronic use), propoxyphene C (but D if chronic use), codeine C (but D if chronic use);, carbamazepine C, gabapentin C; and clonidine C.[173] Benzodiazepine and opioids can cause a neonatal withdrawal syndrome when taken late in pregnancy.[172] Benzodiazepines, opioids, and anticonvulsants are excreted in breast milk and thereby can cause sedation in the breastfed infant.[173] Dopaminergic medications inhibit prolactin release, which diminishes lactation.[173] To receive up-to-date, evidence-based information on the safety and risk of drugs during pregnancy, physicians can consult a teratogen information service such as Motherisk Program (http://www.motherisk.org) or the Organization of Teratology Information Services (http://orpheus.ucsd.edu/ctis/).

Treatment of RLS and PLMD in the elderly is important since they have the highest prevalence of both disorders. The studies reviewed here do not report any distinctive response of the elderly to therapy. Two particular concerns in the elderly are the possible interactions with multiple other medications for different conditions and the tendency of various analgesic and sedative medications to cause excessive sedation.[174-176]

5.5 Therapy in special circumstances

RLS patients are particularly concerned about circumstance (i.e., surgery or cardiac catheterization) where they may be hospitalized and be required to stay in bed or hold their legs still. There have been no reports of agents used in this circumstance, but standard medications, delivered by a parenteral or transdermal route if oral agents are contraindicated, are possible choices. A consideration is whether any such therapy is likely to adversely affect hemodynamic or respiratory function.

6.0 Summary

Of the 45 evidentiary articles we have reviewed, almost one half have dealt with dopaminergic therapy, while the majority of the remainder have dealt with benzodiazepine, opioid, or anticonvulsant therapies. This predominant interest in dopaminergic therapy is also reflected in the more recent publications which we have not reviewed, but which are listed in the accompanying standards paper.[17] The agent most thoroughly studied, including open-label long-term studies, has been levodopa. The one form of secondary RLS studied most extensively is uremic RLS, which has been examined with several agents and found to be consistent with idiopathic RLS in patient response to levodopa and clonidine.

Based on this review, it is clear that there remain many areas to be studied in the therapy for RLS and PLMD: First, no agent has been studied in large, multi-center trials or in large-scale long-term studies. A consequence of the limited therapeutic trials in RLS and PLMD is that there are currently no drugs in the United States which have been approved with a specific indication for these conditions. Second, many agents which have shown preliminary positive results, such as dopamine agonists, many opioids, and the anticonvulsants, have not yet been thoroughly studied. For some of these, especially the dopamine agonists, more extensive studies are likely in the near future (and some studies too recent to be reviewed are listed in the accompanying standards article[17]). Third, except for rare case reports, studies have not addressed routes for drug administration other than the oral route. Fourth, studies have only minimally examined therapy in children or in pregnant women. Fifth, there are very few comparative studies which compare different agents in action on the same population of patients. It is, therefore, difficult to directly compare the relative efficacy of different agents or classes. Sixth, there have been no studies looking specifically at possible combination therapy, which has been reported to be used in current treatment regimens.[123] Seventh, few studies have attempted any assessment of quality of life effects. Eighth, there have been few published reports of nutritional, behavioral, or herbal therapies for RLS or PLMD.

While many agents could be more thoroughly explored and many new types of studies could be contemplated, at this point the most promising focus for further study might include those agents which have been shown in published studies to be successful. In dopaminergic therapy, the possible use of the dopamine agonists (pergolide, pramipexole, ropinerole, cabergoline, and others) needs much more investigation. Preliminary investigations suggest that these medications offer good acceptability and carry relatively robust benefit to risk ratios (see studies too recent to be reviewed listed in the accompanying standards article[17]). Supplementation of iron, which is involved in the dopamine synthetic pathway, may also provide another approach to dopaminergic therapy.[52]

Beyond the dopaminergic agents, there are a number of promising avenues to explore. More study of the opioids,

which are available for delivery by many routes, may also prove useful. The opioids may prove especially beneficial for very severe cases refractory to other medications. Further study of the anticonvulsants also seems warranted. Sclerotherapy should be further investigated with greater attention to diagnosis and more detailed evaluation of outcomes.

In the area of assessment, both subjective measures and objective recording, including actigraphy, should be further developed to provide more reliable evidence of therapeutic impact. Quality of life instruments are needed to document the benefits of treatment. And, finally, it seems clear that more attention still needs to be paid to long-term benefits and possible side effects and risks of the various treatment interventions.

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NOTE

This review contains explanatory tables that accompany the text and are given Roman numerals and evidentiary tables that include details of all the studies reviewed are are given Arabic numerals.

TABLE I - DEFINITIONS

PLM Periodic Limb Movement(s) - one or more movements which meet the criteria for relatively stereotyped repetitive periodic movements (criteria including number in series, period, duration, amplitude), but not restricted to the sleep state. When enumerated for a given period of observation, usually a full night, the sum is the #PLM.

PLMS Periodic Limb Movement(s) in Sleep - One or more PLM occurring in sleep. Usually used as the plural, to refer to all of such movements restricted to sleep which occur during a night's study or to the condition of having such movements, generally (e.g. "The patient has PLMS"). Most studies of PLM record only PLMS.

PLMD Periodic Limb Movement Disorder - A medical disorder with symptoms (See Table III for ICSD definition). Usually requires documentation of some minimum number or frequency of PLM plus some related clinical complaint such as daytime sleepiness.

PLMI Periodic Limb Movement Index - Number of PLM per hour. Usually refers to number of PLMS per hour of sleep for a whole night's sleep or part of it (e.g. the first third of the night, the sleep period when PLMS in RLS are concentrated).

PLMAI Periodic Limb Movement Arousal Index - Number of PLMS per hour of sleep associated with an arousal on polysomnography. If enumerated, one or more such movements are PLMA and their sum can be abbreviated as #PLMA.

NM Nocturnal Myoclonus - Older term used to refer to periodic movements largely identical to PLMS. Operational definitions for counting NM were not formally developed. Used today in some of the European literature, either in the original sense or to refer to movements enumerated like PLM. Condition can be called nocturnal myoclonus syndrome (NMS).

TABLE II - DIAGNOSTIC CRITERIA FOR RLS

International Classification of Sleep Disorders Criteria (1990, Revised 1997):

Essential Features:

Restless legs syndrome is a disorder characterized by disagreeable leg sensations that usually occur prior to sleep onset and that cause an almost irresistible urge to move the legs.

Diagnostic Criteria: Restless Legs Syndrome (780.52-5)

A. The patient has a complaint of an unpleasant sensation in the legs at night or difficulty in initiating sleep.
B. Disagreeable sensations of "creeping" inside the calves are present and are often associated with general aches and pains in the legs.
C. The discomfort is relieved by movement of the limbs.
D. Polysomnographic monitoring demonstrates limb movements at sleep onset.
E. There is no evidence of any medical or mental disorders that account for the movements.
F. Other sleep disorders may be present but do not account for the symptom.

Minimal Criteria: A + B + C

International RLS Study Group Criteria (1995):

1. A desire to move the limbs usually associated with paresthesias or dysesthesias
2. Motor restlessness (during wakefulness patients move the limbs in an attempt to relieve the discomfort)
3. Symptoms worse or exclusively present at rest with at least partial and temporary relief by activity
4. Symptoms worse in the evening or night.

TABLE III - DIAGNOSTIC CRITERIA FOR PLMD

International Classification of Sleep Disorders Criteria (1990, Revised 1997):

Essential Features:

Periodic limb movement disorder is characterized by periodic episodes of repetitive and highly stereotyped limb movements that occur during sleep.

Diagnostic Criteria: Periodic Limb Movement Disorder (780.52-4)

A. The patient has a complaint of insomnia or excessive sleepiness. The patient occasionally will be asymptomatic, and the movements are noticed by an observer.
B. Repetitive highly stereotyped limb muscle movements are present; in the leg, these movements are characterized by extension of the big toe in combination with partial flexion of the ankle, knee, and sometimes hip.
C. Polysomnographic monitoring demonstrates:
   1. Repetitive episodes of muscle contraction (0.5 to 5 seconds in duration) separated by an interval of typically 20 to 40 seconds.
   2. Arousal or awakenings may be associated with the movements
D. The patient has no evidence of a medical or mental disorder that can account for the primary complaint.
E. Other sleep disorders (e.g., obstructive sleep apnea syndrome) may be present but do not account for the movements.

Minimal Criteria: A + B

TABLE IV - ICSD CRITERIA FOR RLS SEVERITY AND DURATION

Severity

Mild: Occurs episodically with only mild disruption of sleep onset and causing little patient distress
Moderate: Occurs less than twice a week but results in significant delay of sleep onset, moderate disruption of sleep and mild impairment of daytime function
Severe: Occurs more than twice a week and results in severe disruption of sleep patterns and marked daytime symptoms

Duration

Acute: 2 weeks or less
Subacute: Greater than 2 weeks but less than 3 months
Chronic: 3 months or longer

TABLE V - ICSD CRITERIA FOR PLMD SEVERITY AND DURATION

Severity

Mild: Associated with a PLMI of 5-24 per hour and results in mild insomnia or mild sleepiness
Moderate: Associated with a PLMI of 25-49 per hour and results in moderate insomnia or sleepiness
Severe: Associated with a PLMI of greater than 50 per hour or a PLMAI of greater than 25 per hour and results in severe insomnia or sleepiness

Duration

Acute: 1 month or less
Subacute: Greater than 1 month but less than 6 months
Chronic: 6 months or longer

Table 1. L-Dopa Controlled Trials

Acetam, acetaminophen; ASA, acetylsalicylic acid; Bens, benserazide; Benz, benzodiazepine; Brom, bromocriptine; Carb, carbidopa; Clond, clonidine; Clonz, clonazepam; CO, crossover; CBZ, carbamazepine; DB, double blind; Diaz, diazepam; Fural, furaldehyde; Gabap, gabapentin; IBI, inter-burst interval; ICSD, International Classification of Sleep Disorders definitions (Tables II-RLS and III-PLMD); IRLSSG, International RLS Study Group criteria for RLS (Table II); L-dopa, levodopa; Nitr, nitrazepam; Nran, nonrandomized; Ns, non-significant; Orph, orphenadrine; OSAS, obstructive sleep apnea syndrome; Oxyc, oxycodone; PC, placebo control; Perg, pergolide; Prop, propoxyphene hydrochloride; Prop-N, propoxyphene napthylate; Ran, randomized; SB, single blinded; SBJ, subjective measure; SE, sleep efficiency; SIT, suggested immobilization test (See Section 3.2.3.1); SL, sleep latency; Sxs, symptoms; SWS, slow wave sleep; Temanz, temazepam; Triaz, triazolam; Trihex, trihexyphenidyl; TST, total sleep time; WASO, wake after sleep onset; *, significant difference; #PLM, count of PLM; #PLMA, count of PLMA; %REM, percent of REM sleep; %SWS, percent of slow wave sleep

Reference/ Evidence Level	Study design	Medication used: Agent; Duration; Administration protocol	Diagnostic criteria	Sample size / age / sex of subjects	Outcome measures	Side effects	Conclusions	Comments
Mont-plaisir (87) Level II	DB Ran CO with PC plus parallel control group	L-dopa/Bens; 2 wks for each phase with 1 wk washout; 100/25 mg, 1 dose 1h and 3 h before bed	RLS: clinical criteria (leg paresthesias at rest, worse in evening, delayed sleep onset)	n=12 (6 RLS, 6 controls)/ mean=54.5 yrs/ 6 M, 6 F	PLMS: #PLM, PLMI, K and K-alpha complexes	None reported	RLS vs. controls: Increased #PLM*, K complex (ns), K alpha complexes* Med vs Placebo: Decreased #PLM*, K complexes (n.s.), K-alpha complexes (n.s.)	Small sample size; examined K complex and K-alpha complex both with and without PLMS
Walker (118) Level II	DB Ran CO with PC	L-dopa/Carb CR; 1 wk for each phase with 1 wk washout; 100/25 mg, fixed dosage 1h before bed	RLS: ICSD PLMS: computerized scoring of leg movement from PSG (not standard PLMS criteria)	n=8 RLS (all with uremia, 5 completed)/ mean=68.2 yrs/ 1 M, 4 F	SBJ: structured questionnaires (RLS dysesthesias and sleep), Sleep: PSG measures PLMS: #PLM, PLMS with arousals	None reported	SBJ: No improvement Sleep: No change except increased SWS* PLMS: Decreased #PLM* and PLMS with arousals*	Patients had uremia; RLS histories unclear; 1 patient on sedatives during study
Trenk-walder (98) Level I	DB Ran CO with PC	L-dopa/Bens; 4 wks each phase; 100/25 mg, 1-2 tablets 1h prior to bedtime, mean final L-dopa dosage=146 mg	RLS: Variant of IRLSSG PLMS: Coleman (82) based on actigraphy and PSG	n=32 RLS (28 completed, 17 idiopathic RLS, 11 uremic RLS)/29-73 yrs/18 M, 10 F	SBJ: quantitative questionnaire, global symptoms Sleep: PSG measures PLMS: PLMI, PLMS with arousals	HA, dry mouth, GI symptoms, agitation after caffeine	SBJ: Improved sleep quality* and quality of life* Sleep: No effects PLMS: Decreased PLMI* and PLMS with arousals*	Some patients with uremia, errors in ascertainment of exposure to an intervention (30% of idiopathic RLS patients may have been treated)
Kaplan (91) Level II	DB Ran CO (L-dopa vs. Prop N) with PC	L-dopa/carb; ten days each medication; 4 day placebo. 100/25 & 200/50 mg, dosage at PSG=L-dopa/Carb 200/50 at bedtime; Prop N 200 mg at bedtime	RLS: ICSD PLMS: similar to Coleman (82) (bursts 0.5 - 5 sec duration, 5 - 120 sec IBI, $\geq$ 4 per series)	n=7 (6 completed, 3 RLS with PLMS, 3 PLMS alone)/ 44-72 yrs/ 2 M, 4 F	SBJ: global symptoms (sleep and day alertness), sleep diary (sleep/wake schedule) Sleep: PSG measures, MSLT PLMS: #PLM, PLMAI from PSG, actigraphy	L-dopa/carb: nausea, dizziness, constipation, blurred vision, augmentation Prop: depression, dizziness, nausea, tongue swelling	SBJ: Improved sleep (6/6 L-dopa/carb, 3/6 Prop, 2/6 placebo), more rested/awake (5/6 L-dopa/carb, 3/6 Prop, 1/6 placebo) Sleep: L-dopa/carb decreased sleep latency* and increased SWS*; MSLT: no effects PLMS: 100% of the patients responded favorably to L-dopa/carb with decreased PLMS* and PLMAI*	small sample size; four-day placebo period was also washout period

Table 1. L-Dopa Controlled Trials

Reference/ Evidence Level	Study design	Medication used: Agent; Duration; Administration protocol	Diagnostic criteria	Sample size / age / sex of subjects	Outcome measures	Side effects	Conclusions	Comments
Boivin (119) Level II	DB NRan CO with PC	L-dopa/Bens; 1 wk washout, placebo x 1 wk; 50/12.5mg at 900, 1300, 1700, 2100, 0300 x 1 wk; 100/25 mg at same times x 1 wk (PSG at this dosage)	ICSD classification (diagnosis of narcolepsy), PLMS criteria as defined by Coleman (82)	n=6 PLMS(all had narcolepsy with cataplexy)/18-63 yrs./2M, 4F	Sleep: PSG measures PLMS: #PLM, PLMI	None reported	Sleep: No effects except increased WASO* PLMS: Decreased #PLM in both halves of night* and PLMI*	Patients had narcolepsy; small sample size; split night analysis of PLMS
Brodeur (95) Level II	DB Ran CO with PC	L-dopa/Bens; 2 wks on each treatment, 1 wk washout in between; 100/25 mg or placebo, fixed protocol: doses 1h before bedtime and 3h after bedtime	General clinical criteria (paresthesias leading to an urge to move the legs at bedtime and prolonged SL)	n=6 RLS/mean=51.3 yrs./3 M, 3 F	SBJ: Questionnaires on specific symptoms (pain/paresthesia in arms/legs, arm/leg movements at bedtime, perceived SL and TST) Sleep: PSG measures, MSLT PLMS: PSG: #PLM, PLMI, PLMS with awakening, SIT: #PLM	None reported	SBJ: Reduced sxs* and perceived SL* Sleep: PSG: reduced SL*; MSLT: increased mean SL (n.s.) PLMS: Reduced PLMI*, total #PLM*, and PLMS with awakenings*; SIT: no significant changes	Small sample size; only 4 of 6 patients had PLM during SIT
Akpinar (104) Level II	DB Ran CO with PC	L-dopa/bens 200/50 (13 pts); Brom 2.5 mg (2 pts); Piribedil 40 mg (1 pt); 2 wks on drug or placebo then crossover for 2 wks; fixed dose, 1h before bedtime,	RLS: clinical criteria (leg discomfort, urge to move legs, insomnia) PLMS: operational definition (not specified)	n=16 RLS (13/16 also had PLM)/mean=50.8 yrs./7 M, 9 F	SBJ: Specific symptoms (sleep quality, number of awakenings, duration awake)	Nervousness, light-headedness, decreased speech (when on L-dopa/bens)	SBJ: Decreased number of awakenings* and time awake* for both moderate (n=10) and severe (n=6) patients, improved sleep quality (very good: 3 severe (50%), 9 moderate (90%); good: 3 severe, 1 moderate)	non-systematic group assignment; unclear sxs reporting; broke group down into moderate and severe patients
von Scheele (106) Level III	DB CO with PC	L-dopa/bens, fixed dosage (not given) vs placebo on alternate days until patient had preference (within 1 wk) or could not discriminate	Clinical criteria (not specified)	n=20 RLS/10-83 yrs./8 M, 12 F	Specific symptoms (leg discomfort)	None reported	SBJ: 17/20 (85%) patients preferred L-dopa*	

Table 1. Levodopa uncontrolled Trials

Reference/ Evidence Level	Study design	Medication used: Agent; Duration; Administration protocol	Diagnostic criteria	Sample size / age / sex of subjects	Outcome measures	Side effects	Conclusions	Comments
Allen (114) Level V	Clinical series	L-dopa/carb; at least 3 wks duration; 100/25 (1 patient used CR), 1/2-6 tablets/night in 1-2 doses, titrated to obtain satisfactory sleep; mean final dosage=238/60	RLS: IRLSSG PLMS: Coleman (82)	n=46 (30 RLS, 16 PLMD alone)/mean=57.5 yrs/26 M, 20 F	SBJ: Global and specific sxs, clinical rating of severity	Augmentation, rebound	SBJ: Augmentation in 82% of RLS pts and 31% of PLMD pts on L-dopa/Carb. Augmentation* greater for subjects with more severe RLS and higher dose of L-dopa/carb. Rebound occurred in 20% of RLS and 0% of patients with PLM. Despite patients having achieved satisfactory relief, 17/46 had to change medication because of augmentation.	Compares response of RLS and PLMD alone patients
Earley (115) Level V	Clinical series	L-dopa/carb; at least 2 mos duration; 100/25 or CR 200/50, 1/2-6 tablets/night in 1-2 doses, titrated to obtain satisfactory sleep; mean final dosage=260/65. Switch to perg (0.05 to 1.0 mg) if intolerable adverse effects or inadequate control; titrated for sxs relief, adverse effects, or up to 1.0 mg; mean final dosage=0.37 mg perg	RLS: IRLSSG PLMS: Coleman (82) PLMD: PLMS>25/hr in NREM, PLMAI>=5	n=51 (36 RLS, 15 PLMD alone)/ mean=58.8 yrs./ 26 M, 25 F	SBJ: Global and specific sxs, clinical rating of severity	L-dopa: augmentation, rebound, pain, emesis, SOB, HA, dizziness, anxiety Perg: augmentation, nausea, nasal congestion, pain, constipation, SOB, blurred vision, sleepiness, strange feelings, edema	SBJ: Patients with PLMD alone responded better to L–dopa* than RLS pts; 21/51 (39%) continued on L-dopa, 26/51 (50%) switched to perg; Severe RLS patients responded better to perg* with less augmentation* than with L-dopa.	Compares response of RLS and PLMD alone patients; breakdown of results by RLS severity
Becker (112) Level V	Clinical series	L-dopa/carb (100/25) and brom, adjusted clinically, 47 pts began on L-dopa, 2 on brom; 5 later switched to brom; mean duration 283 (SD=316) days; mean final L-dopa dosage=160 mg; (unknown brom dosage)	RLS: ICSD PLMS: ICSD	n=49 (RLS and/or PLMS, no breakdown; 47 completed)/ 23-79 yrs/ 36 M, 13 F	SBJ: Specific sxs and sleep quality: responders identified by reduced leg restlessness, improved sleep, and requested refills of meds	Nausea, emesis, muscular spasms, HA, rebound	SBJ: L-dopa/carb and brom offered clinically relevant improvement for RLS/PLMS complaints for 70.2% of pts after ≥ 6 months of therapy; 33/47 continued on L-dopa	Nine patients also had OSAS; 2 patients lost to F/U; analysis done retrospectively; no distinction RLS and PLMD alone

Table 1. Levodopa uncontrolled Trials

Reference/ Evidence Level	Study design	Medication used: Agent; Duration; Administration protocol	Diagnostic criteria	Sample size / age / sex of subjects	Outcome measures	Side effects	Conclusions	Comments
Guille-minault (113) Level V	Clinical series	L-dopa/carb 100/25 regular or CR 100/50; duration 11±2 months; at bedtime (7 patients had 2 doses CR 100/50 at night and 100/25 in morning to improve rebound)	RLS: clinical criteria (uncomfortable leg sensation with irresistible urges to move the legs) PLM: operational definition (≥4 movements, ≤90 sec apart) based on PSG or actigraphy	n=20 RLS with PLM/mean=64 yrs/ 8 M, 12 F	SBJ: specific sxs (discomfort), RLS sxs log, sleep logs Sleep: PSG measures PLM: PSG, actigraphy	Morning rebound developed in 7/20 subjects	SBJ: 20/20 (100%) responded initially to L-dopa; 13/20 (65%) reported continued efficacy at last F/U. Morning rebound in 7/20 patients, requiring 2 doses of L-dopa/carb CR 100/50 at night and 100/25 in the morning	
von Scheele (111) Level V	Clinical series	L-dopa/bens for at least 2 yrs; (50-600 mg) median L-dopa dosage=100 mg; 2 patients switched to brom (unknown dose)	RLS: clinical criteria (leg discomfort at rest, relieved by movement)	n=30 RLS/ 10–83 yrs/15 M, 15 F	SBJ: Specific sxs (restless legs, sleep length, awakenings)	2 had transient nausea	SBJ: L-dopa or brom provided long term relief for RLS in 28/29 (96.6%) patients*; with improved sleep* 22/29 (75.8%) and decreased awakenings* 17/29 (58.6%)	
Sandyk (120) Level V	Clinical series	L-dopa/carb; duration 1-3 mos; 100/25 (2-3 doses/day) or 250/25 (2 doses/day)	RLS: clinical criteria (unpleasant sensation, worse when immobile, ameliorated by movement, worse evening/night, frequent insomnia)	n=8 RLS with uremia/58-70 yrs./ 3 M, 5 F	SBJ: Specific Sxs(discomfort, sleep quality)	One patient reported gastrointestinal symptoms and postural lightheaded-ness	SBJ: 6/8 (75%) patients found satisfactory relief of RLS sxs	Patients all had uremia; small sample size; 2/8 patients had peripheral neuropathy
Mont-Plaisir (105) Level V	Clinical series	L-dopa (50-200) mg/bens in 4:1 ratio; duration at least 4 wks; variable dosage, titrated up from 50 to 200 mg L-dopa, mean final L-dopa dosage=164.3 mg	RLS: clinical criteria (discomfort in legs at rest, reduced by movement) PLMS: Coleman (82)	n=7 RLS, all with PLMS (5 patients studied with PSG after treatment)/ mean = 40.7 yrs/ 4 M, 3 F	SBJ: structured questionnaires for RLS, PLMS, sleep quality Sleep: PSG measures PLMS: #PLM, PLMI on PSG (night broken into thirds)	Late night rebound of PLMS	SBJ: 7/7 (100%) had ameliorated RLS*, improved PLMS*, decreased SL*, and decreased daytime fatigue; 5/7 (71.4%) had complete relief with L-dopa 100-200 mg Sleep: Improved SE*, decreased SWS latency*, awakenings* and WASO* PLMS: No change in total #PLM or PLMI, but decreased in first third of night* and rebounded in last third of night*	Small sample size; 4/7 patients were familial cases of severe RLS; examined impact on PLMS during thirds of night

Table 1. Agonists

Reference/ Evidence Level	Study design	Medication used: Agent; Duration; Administration protocol	Diagnostic criteria	Sample size / age / sex of subjects	Outcome measures	Side effects	Conclusions	Comments
Staedt (121) Level II	DB Ran CO without PC	Perg (0.125 mg) vs L-dopa (250 mg)/carb given; 16-day period followed by 1 day washout; 1-3h prior to sleep. Variable protocol: up to 0.25 mg of Perg, 500 mg of L-dopa, Perg mean final dose 0.159 mg/night, mean L-dopa final dose=363 mg	RLS: clinical criteria (restlessness & paresthesias present at night and/or day) PLMS: Coleman (82)	n=11 RLS/ 50–69 yrs./6 M, 5 F	SBJ: specific sxs (restlessness and paresthesias) Sleep: PSG measures PLMS: #PLM, NMS cluster disturbed time	Nausea (9 with perg, 1 with L-dopa) and constipation (2 with perg, 2 with L-dopa). All patients with nausea were successfully treated with domperidone.	SBJ: 2/11 (18.2%) patients reported partial, 9/11 (81.8%) patients complete relief of motor restlessness with perg; 1 patient with improved restlessness with L-dopa Sleep: Perg increased TST* compared to L-dopa; both meds decreased sleep latency and nocturnal awakenings compared to baseline PLMS: A mean decrease in NMS cluster disturbed time of 79% from control for Perg greater than 45% from control on L-dopa was found*	Nine patients were treated with L-dopa prior to the study with inadequate relief; short washout period of 3 days; 3 patients were also on temazepam throughout the study
Walters (122) Level II	DB Ran CO with PC	Brom; 30 days duration, 2 wk washout; 7.5 mg in 1-2 doses 3h before sleep; variable dose, mean brom 7.5 mg at time of PSG	RLS: Variant formalized criteria (included PLM and sleep disturbance, circadian pattern) PLMS: Coleman (82)	n=6 RLS with PLMS (4 patients studied with PSG)/40-68 yrs./ 4 M, 2 F	SBJ: Global and specific Sxs(restlessness and paresthesias) Sleep: PSG measures PLMS: #PLM, PLMI from PSG	One patient with nasal stuffiness and light-headedness	SBJ: 5/6 (83.3%) patients had partial improvement Sleep: Increased TST and SE PLMS: Decreased #PLM* and PLMI* in 4/4 (100%) patients studied by PSG	Small sample size
Silber (116) Level V	Clinical series	Perg; Average duration=25 mos; (0.05 mg) increased by 0.05 mg every 48-72 hrs until adequate response, side effects noted, or a maximum of 1.0 mg. Additional doses if necessary (7/15 took 2 or more doses daily). Mean perg final dose=0.26 mg. Three patients also on benz	RLS: ICSD criteria	n=20 RLS (10 patients studied with PSG, 9/10 had PLMS)/ 41-86 yrs./ 5 M, 15 F	SBJ: Specific Sxs: discomfort (rated RLS on 0-5 scale, with 0-1=complete or near complete control, 2-3=moderate control, 4-5=minimal or no control)	Side effects occurred in 12/20 (60%) patients (nausea, dizziness, insomnia, constipation, nasal stuffiness, urinary frequency, edema, visual disturbances): manageable augmentation occurred in 4/15 (26.7%) patients who continued on the perg long term.	SBJ: Perg was beneficial (moderate to complete control) in 19/ 20 (95%) patients, 15/20 (75%) continued on perg long term with continued benefit. Specifics of control: 9 patients had near-complete or complete control (scale score 0 or 1) while 10 had moderate control (scale score 2 or 3), and 1 had no control.	18/20 patients failed to respond well to other treatments (opioids, benzo-diazepines, L-dopa/carb). RLS was familial in 7 patients, associated with narcolepsy in 1 patient, and sertraline therapy in 1 patient.

Table 2. Evidence for Treatment of RLS/PLMD with Opioid Therapy (Section 4.2.2)

Reference/ Evidence Level	Study design	Medication used: Agent; Duration; Administration protocol	Diagnostic criteria	Sample size / age / sex of subjects	Outcome measures	Side effects	Conclusions	Comments
Walters (124) Level II	DB Ran CO with PC	Oxyc; 2 weeks each phase with titration; 2.5-25 mg daily, variable dosage, mean Oxyc at time of testing: 15.9 mg	RLS: IRLSSG. PLMS: variant of Coleman (82)(0.5-5 sec durtion; 5-90 sec apart; ≥ 4 per series)	n=11 with RLS + PLMS / 36 – 74 yrs./ 5 F, 6 M	SBJ: structured questionnaires (quantitative) Sleep: PSG measures PLMS: #PLM	Constipation, daytime lethargy (decreased at lower dose)	Oxyc compared to placebo: SBJ: improved RLS dysesthesias* (51%), motor restlessness* (53%), and daytime alertness* (38%) Sleep: decreased nocturnal arousals* (46%) and improved SE* (54%). PLMS: decrease #PLM* (65%)	Sleep apnea in 4 patients was not worse on oxyc.
Kaplan (91) Level II	DB Ran CO with PC	Prop-N 100 & 200 mg, L-dopa/Carb 100/25 & 200/50. Ten days each medication; 4 day washout. Dosage at time of testing: Prop-N 200 mg qHS	RLS: ICSD. PLMS: similar to Coleman (82) (0.5 - 5 sec duration, 5 - 120 sec IBI, ≥ 4 per series)	n=7 entered, 6 completed (3 RLS + PLMS; 3 PLMD alone)/ 44-72 yrs./ 4 F, 2 M	SBJ: global Sxs(sleep and day alertness) and sleep diary (sleep/wake schedule) Sleep: PSG measures, MSLT PLMS: #PLM, #PLM with arousals from PSG, actigraphy	Prop-N: depression, dizziness, nausea, and rash	Prop-N compared to placebo: SBJ: improved sleep (3/6 Prop-N, 2/6 placebo), more rested/awake (3/6 Prop-N, 1/6 placebo). Sleep: MSLT - no effects PLMS: decreased #PLM (ns), decreased #PLM with arousals* (57%)	Small sample size; only four day washout between treatments
Sandyk (125) Level V	Clinical series	2 patients: Oxyc 10 – 30 mg + ASA 650 mg – 1.95 gm. 4 patients: codeine 30 – 60 mg + acetam 325 – 650 mg + Temazepam 15 – 60 mg. Duration not specified; variable dosage	RLS: clinical criteria (leg discomfort, usually upon retiring, relieved by movement). PLMS: definition not specified	n=6 RLS, 5 also PLMS / 42 – 87 yrs./ 4 F, 2 M	SBJ: Specific Sxs (discomfort, sleep quality)	One patient: nausea, vomiting, hallucinations, daytime sleepiness, and increased dysesthesias on the night after stopping codeine + acetam + temazepam	SBJ: 6/6 subjects reported improvement of RLS Sxs	No patients on opioid alone (all on opioid combined with another medication).
Hening (108) Level V	Clinical series	Prop 130-260 mg, codeine 30-120 mg (with Acetam), Methadone 5-20 mg. duration: acute- 2 days or less, chronic- at least 4 weeks; variable dosage	RLS: clinical criteria (restlessness, dysesthesias, worse at night and during repose). PLMS: series of ≥5, at intervals of 4-60 sec	n=5 RLS + PLMS / 61 – 69 yrs./ 1 F, 4 M	SBJ: structured questionnaire for specific Sxs (leg discomfort, restlessness) Sleep: PSG measures. PLM: #PLM asleep and awake	No significant side effects or need for escalating doses	SBJ: 5/5 had marked decrease of RLS dysesthesias Sleep: 2/5 had improved sleep (defined as improvement in 3/6 PSG measures). PLM: 3/5 had marked decrease of awake movements and 3/5 of #PLMS	Small smaple size. Wide variance in type and dose of opioid used. All 5 remained on opioid (1.5 - 6 year duration)

Table 3. Evidence for Treatment of RLS/PLMD with Benzodiazepine Therapy (Section 4.2.3)

Reference/ Evidence Level	Study design	Medication used: Agent; Duration; Administration protocol	Diagnostic criteria	Sample size / age / sex of subjects	Outcome measures	Side effects	Conclusions	Comments
Edinger (131) Level II	Unblinded parallel study, clonz vs. cognitive behavioral	Cognitive behavioral therapy; Clonz; duration=4 weeks; 0.5 - 1.5 mg, 0.5 mg 3 days, increased 0.5 mg q 3 days as needed to maximum 1.5 mg	PLMS: Coleman (82) PLMD: insomnia complaint >6 months, PLMAI > 5/hr	n=16 / mean=66.1 yrs (15 completed -- 7 on behavior treatment, 8 on clonazepam)/ 7 M, 9 F	SBJ: structured questionnaires, sleep diary, Sleep and PLMS: home ambulatory monitoring measurements (medilog 9000)	Anxiety for 3 pts (1 on Clonz, 2 on cognitive behavioral therapy)	SBJ: Cognitive behavioral treatment alone reduced daytime napping. 71% on behavior and 87% on Clonz opted to continue treatment. Sleep: Both treatment about equally improve sleep at night*. PLMS: Clonz alone reduced PLMI (18%), PLMAI (44%).	No placebo control; unclear how many patients had RLS; statistics not clearly presented; One drop out unrelated to treatment.
Bonnet (132) Level II	DB Ran CO with PC	Triaz; 3 day duration; 0.125 & 0.25mg & placebo, fixed dosage	PLMS: operational definition using PSG (EMG activity at least 2x background lasting 0.5 - 5.0 seconds)	n=11 with PLMD/ 55 - 75 yrs./ 7 M, 4 F	SBJ: structured questionnaires, sleep diary Sleep: PSG measures PLMS: #PLM, #PLMA	None reported	SBJ: Low dose improved daytime alertness Sleep: Both doses improved SE, TST PLMS: No significant decrease	
Peled (133) Level II	DB Ran parallel with PC	Clonz 0.5-2mg (1 at 0.5mg, 4 at 1.0mg, 2 at 2.0 mg)/ 4 weeks, adjustment of dosage after each wk x 4 wks/ open label avg f/u 10.5 months	PLMS: Coleman (82)	n=20 with PLMD(10 drug, 10 placebo) / 30-70 yrs./ 12 M, 8 F	SBJ: global Sxs (degree of improvement) Sleep: PSG Measures PLMS, PLMI, PLMA	One pt reported dizziness, somnolence	Clonz vs. placebo: SBJ: Improved global assessment, 17/20 noted benefit Sleep: Improved sleep paramaters PLMS: Decreased PLMI (43%), PLMA	
Boghen (85) Level II	DB Ran CO with PC	Clonz; 4 weeks; 0.5mg fixed protocol, med taken 30 min before bedtime initially with increase to 4 times a day	RLS: clinical criteria	n=6 with RLS / 31 - 61 yrs./ 3 M, 3 F	SBJ: Two questionnaires (4 point scale for pts, 2 point – improved or no change, for rater)	Sleepiness	SBJ: No benefit compared to placebo on either pt or rater scale	

Table 3. Evidence for Treatment of RLS/PLMD with Benzodiazepine Therapy (Section 4.2.3)

Reference/ Evidence Level	Study design	Medication used: Agent; Duration; Administration protocol	Diagnostic criteria	Sample size / age / sex of subjects	Outcome measures	Side effects	Conclusions	Comments
Montagna (129) Level II	DB Ran CO with PC	Clonz; 1 week Clonz, 1 week placebo, 1 week vibrator; 1 mg, 1/2h before bedtime, fixed protocol	RLS: clinical criteria	n=6 / 44 - 61 yrs./ 3 M, 3 F	SBJ: quality of sleep, dysesthesias, nocturnal leg jerking (4 point scales)	Not reported	Clonz vs. baseline: Improved quality of sleep* (23%), dysaethesias* (26%; also improved vs. PC or vibrator); No improvement in leg jerking. 5/6 preferred Clonz.	Compared med to alternate therapy (vibration)
Mitler (134) Level III	NRan CO with baseline	Clonz 1 mg & temaz 30 mg; 2 wk washout; fixed dose 7 days	RLS: ICSD PLMS: ICSD	n=10 (2 with RLS, 8 with PLMD alone) / 47.1±10 yrs./ 6 M, 4 F	SBJ: structured questionnaire Sleep: PSG measures PLMS: PLMI, PLMA	Not reported	Sleep: Compared to baseline: both drugs improved sleep* as indicated by various measures on PSG (TST, SE, WASO). Temaz but not Clonz also reduced sleep latency. PLMS: both reduced PLMI* (clonz, 34%; temaz, 26%), PLMA; neither affected total #PLM or the #PLM without arousal.	no placebo control
Schenck (130) Level V	Clinical series	Clonz; 1 month; fixed dose 7 days, 1.35mg±1.04 mg average	RLS: clinical criteria (not specified)	n=24 with RLS and/or PLMD / mean=44.7 yrs./ 11 M, 13 F	SBJ: Global Sxs	Mild morning sedation, subjective memory loss	Clonz showed sustained efficacy with little adverse effects, dose escalation, or abuse (no quantification)	Criteria for RLS not specified; no clear breakdown into patients with RLS vs. those with PLMD alone
Ohanna (135) Level V	Clinical series	Clonz; 3-6 weeks; 0.5-2mg at bedtime	PLMS: Coleman (82)	n=20 with PLMD (14 with post drug use data) / 20 - 76 yrs./ 17 M, 3 F	Sleep: SE by PSG PLMS: #PLM, PLMI, PLMAI	None reported	SBJ: 11/14 reported decreased sleep disturbance; PLMS: decreased #PLM* (65%), PLMI*	Variation in duration of trial not explained
Moldofsky (136) Level V	Clinical series	Nitrz; (mean=6 months); start 5mg in one dose 45 min before bedtime, titrate to optimal in range 2.5-10 mg, variable period	PLMS: PSG measurements (measured both legs, took count from higher leg)	n=13 with PLMD, 2 also RLS / mean=53.3 yrs./ 10 M, 3 F	SBJ: structured questionnaires for global and specific Sxs Sleep: PSG measures,	One pt with sluggishness and impaired daytime concentration	SBJ: Improved global rating Sleep: Increased SE*, decreased PLMI, WASO*, wakenings*, arousal index*, PLMS: Decreased PLMI* (65%)	Pts all had fibrositis

Table 4. Evidence for Treatment of RLS/PLMD with Anticonvulsant Therapy (Section 4.2.4)

Reference/ Evidence Level	Study design	Medication used: Agent; Duration; Administration protocol	Diagnostic criteria	Sample size / age / sex of subjects	Outcome measures	Side effects	Conclusions	Comments
Telstad (86) Level I-II	DB Ran parallel with PC	CBZ; 5 weeks; begin 100 mg at bedtime. Increased by 100mg/week if needed to maximum of 300 mg. Ave dose 239mg at testing.	RLS: clinical criteria (unpleasant leg sensations at rest, worse at night)	n=181 RLS (174 completed) / 17 - 86 yrs./ 52 M, 122 F	SBJ: Global Sxs: analog scale for symptom severity and symptom improvement; number of attacks per week	34 drug and 20 placebo reported "unwanted side effects" (not specified)	SBJ: Both placebo and CBZ decreased the number of attacks*, but CBZ was significantly more effective than placebo*	Notably large beneficial placebo effect.
Lundvall (109) Level II	Ran CO with PC	CBZ; 28 days with gradual increase; start at 200 mg at bedtime, increased by 200 mg per week to a maximum dose 200 mg in am, 400 mg at bedtime (total 600 mg/day)	RLS: clinical criteria (based on sensations, not clearly specified)	n=6 RLS/37 – 71 yrs./ 4 M, 2 F	SBJ: Global Sxs: daily rating of attacks of 1) RLS sensations per day and number of days with attacks and 2) severity of RLS; MD and patient preference for drug or placebo or neither for further treatment.	2 patients with mild gastritis and sweating, dizziness, and vomiting	SBJ: 3 pts reported improvements and wanted to continue on CBZ. 3 pts reported insufficient improvement. All patients had lower scores for days with RLS and lower mean severity on drug compared to placebo.	No statistical analyses performed on data. Investigators wanted to study 20 patients but couldn't find others to meet criteria (note: no indication of how the six subjects were selected was provided).
Zucconi (93) Level V	clinical series	CBZ; duration 30-45 days; reached 3-7 mg/kg/day, 1-2 hr before bed, variable protocol, increased as necessary, final dose not stated. All patients had therapeutic levels of CBZ (5.7-8.7 micrograms/ml)	RLS: clinical criteria, PLMS: Coleman (82)	n=11 RLS (9 completed each phase of study, 2 subjects did not have leg movements on PSG) / 30 – 64 yrs./ 4 M, 5 F	SBJ: structured questionnaires, subjective assessment of RLS severity, sleep quality Sleep: PSG measures, PLMS: #PLM	Not measured	CBZ compared to baseline SBJ: improved in both subjective measures* Sleep: increased sleep efficiency*, decreased sleep latency* PLMS: not effected by treatment	RLS without PLMS excluded from final testing. Drug levels checked before assessment.

Table 4. Evidence for Treatment of RLS/PLMD with Anticonvulsant Therapy (Section 4.2.4)

Reference/ Evidence Level	Study design	Medication used: Agent; Duration; Administration protocol	Diagnostic criteria	Sample size / age / sex of subjects	Outcome measures	Side effects	Conclusions	Comments
Adler (137) Level V	Clinical series	Gabap; minimum of 1 week, up to 6 months; variable dosage (300 mg increased to 600 mg after 3 days), final 300-2400 mg/day (mean=1163 mg/day),	RLS: clinical criteria (not specified)	n=8 RLS (6 completed)/ 56 - 79 yrs./ 4M, 4F	SBJ: Structured questionnaire: O'Keefe scale (0-10)	Dizziness, nausea, drowsiness	SBJ: 4 of 8 beneficial response with 3 having complete resolutions of Sxs.	No statistics performed; 2 could not tolerate side effects and were discontinued from study.
Mellick (138) Level V	Clinical series	Gabap; 6 - 18 months; variable final doses, 300-2000 mg/day	RLS: Variant of IRLSSG	n=16 RLS / 36 – 75 yrs./ 9 M, 7 F	SBJ: Global Sxs, specific Sxs (discomfort, leg movements, sleep quality)	Dizziness, drowsiness, enhanced alcohol effect	SBJ: Percent symptom relief – 80-100% (11), 75% (3), 50% (2)	retrospective study; refereed letter to the editor; no statistics performed
General Comments on Table 4								Studies did not control for sedative effects of these drugs

Table 5. Evidence for Treatment of RLS/PLMD with Other Pharmacological Therapies (Sections 4.2.5 & 4.2.6)

Reference/ Evidence Level	Study design	Medication used: Agent; Duration; Administration protocol	Diagnostic criteria	Sample size / age / sex of subjects	Outcome measures	Side effects	Conclusions	Comments
Wagner (92) Level II	DB Ran CO with PC	Clond; 2-3 weeks; pts titrated to 0.1-1.0 mg (mean=0.5mg) over 2 weeks	RLS: IRLSSG PLMS: Coleman (82)	n=11 RLS (10 completed) / 29-61 yrs./ 8 M, 3 F	SBJ: structured quantitative questionnaire Sleep: PSG measures. PSG: PLMC, PLMI	Hypertension, dizziness, dry mouth, decreased cognition, sleepiness, constipation	Clond compared to placebo: SBJ: decreased RLS dyesthesias*, motor restlessness*, daytime fatigue* Sleep: only decreased SL*. PLMS: No change	
Ausser-winkler (139) Level III	DB Parallel design with PC(unclear if randomized)	Clond; 3 days; 0.075 mg twice a day/total 0.15 mg	RLS: clinical criteria (at least 2 bouts/day of more than 10 minutes of leg discomfort, restlessness, compulsion to move)	n=20 RLS / age and gender not specified	SBJ: Global Sxs: degree of improvement	None reported	Clond compared to placebo: SBJ: 3/10 showed "striking" decrease of symptoms. One of Clond group and 9 of placebo group showed no benefit. Overall difference in benefit favored clond*.	
Guille-Minault (142) Level III	SB Non-Ran CO with PC	Baclofen; 15 days; variable dose, 4 days placebo, 9 days titration up on baclofen from 20 mg to maximum of 160 mg, then 2 day placebo, PSG on each of 15 nights;	RLS: not specified PLMS: PSG measure, operational definition of PLMS (not specified) PLMD: ICSD	n=5 PLMS/ 52 – 71 yrs./ 2 M, 3 F	SBJ: Sleep diary Sleep: PSG measures PLM: #PLM, #PLMA	Not reported, although some implied	Sleep: decreased WASO, decreased fragmentation, increased TST and SWS. PLMS: all doses increased PLMS* over placebo, but percentage with arousal decreased.	On baclofen, PLMS period and amplitude decreased, duration unchanged
Nordlander (145) Level V	Clinical series	IV 2% iron oxide (100-200 mg iron per dose); 1-3 injections every 2-4 days (21 patients), oral iron (2 patients), blood transfusions (6 patients)	RLS: clinical criteria (not specified, but author describes paresthesia in bed forcing patient to move legs)	n=30 RLS, 29 treated with iron or blood transfusions; 10/21 patients treated with IV iron were anemic/ 19-83 yrs./ 12M, 18F	SBJ: Global Sxs, 4 point	None reported	IV iron, oral iron or blood transfusions completely relieved RLS for several months in all but 1 patient.	Outcome measures not based on severity of RLS.
O'Keefe (50) Level V	Clinical series	Iron sulphate; duration not reported; fixed dosage, 200 mg TID	RLS: Specific Sxs (bilateral leg discomfort, at night, urge to move, relieved by movement, sensation not paresthesias or pain)	n=15 RLS (4 with iron deficiency) / 65 yrs. or older / gender not specified	SBJ: reported benefits	None reported	SBJ: 3 out of 4 with anemia reported improvement	All pts were elderly

Table 5. Evidence for Treatment of RLS/PLMD with Other Pharmacological Therapies (Sections 4.2.5 & 4.2.6)

Reference/ Evidence Level	Study design	Medication used: Agent; Duration; Administration protocol	Diagnostic criteria	Sample size / age / sex of subjects	Outcome measures	Side effects	Conclusions	Comments
O'Keefe (51) Level III	Case control study, unblinded	Iron sulphate; ave 12 wk duration (range 8-20 weeks); 200 mg TID, fixed dosage,	RLS: clinical criteria (bilateral leg discomfort at night, urge to move legs, relieved by movement)	n=18 RLS enrolled, 15 completed / 70-87 yrs./ 5 M, 13 F	SBJ: structured questionnaires, global Sxs	None reported	SBJ: reduced RLS Sxs for pts with ferritin ≤ 45. Had only marginal benefit in pts with ferritin 45-100 mg/l range.	All pts were elderly
Botez (144) Level V	Clinical series	Folic acid; 6-12 months; variable dose, but 3 mg IM/wk or 5-30 mg po daily	RLS: clinical criteria (not specified, but author refers to cramps, joint pain, numbness in the arms and legs relieved by movement)	n=16 RLS/ 26 - 76 yrs./ 4 M, 12 F	SBJ: Global Sxs	None reported	SBJ: 15/16 patients with folate deficiency had RLS which resolved with folic acid treatment	Vague endpoint and clinical critera

Table 6. Evidence for Treatment of RLS/PLMD with Other Non-pharmacologic Therapies (Section 4.3)

Reference/ Evidence Level	Study design	Medication used: Agent; Duration; Administration protocol	Diagnostic criteria	Sample size / age / sex of subjects	Outcome measures	Side effects	Conclusions	Comments
Kanter (154) Level IV	Clinical series	Sclerotherapy with IV sodium tetradecyl sulfate. 1-10 treatments based on doppler-reflux in any saphenous trunk	RLS: ICSD	n=113 with RLS / 22 - 68 yrs./ 9 M, 104 F	SBJ: RLS discomfort	None reported	SBJ: Initial 98% success rate (complete resolution of Sxs or sustained marked improvement). Of successful pts, 4%, 8%, and 28% relapsed at 6, 12, and 24 months respectively	All patients were found to have venous insufficiency before treatment.
Edinger (131) Level II	Ran unblinded parallel study with no PC	Cognitive behavioral therapy vs. Clonz; duration=4 week;	PLMS: Coleman (82) PLMD: insomnia complaint >6 months, PLMAI > 5/hr	n=16 PLMS/ mean=66.1 yrs (15 completed --7 on behavior treatment, 8 on clonz)/mean=66.1 yrs/7 M, 9 F	SBJ: structured questionnaires, sleep diary, Sleep and PLMS: home ambulatory monitoring measurements (medilog 9000)	Anxiety for 3 pts (1 on clonz, 2 on cognitive behavioral therapy)	SBJ: Cognitive behavioral treatment alone reduced daytime napping. 71% on behavior and 87% on Clonz opted to continue treatment. Sleep: Both treatment about equally improve sleep at night*. PLMS: Cognitive behavioral therapy did not decrease PLMI or PLMAI significantly. Clonz alone reduced PLMI (18%), PLMAI (44%).	No placebo control; unclear how many patients had RLS; statistics not clearly presented; One drop out unrelated to treatment.
Kovacevic-Ristanovic (153) Level V	Open label	Single; 2-6 months; 30 minute electrical stimulation of the dorsiflexors of the feet and toes before bedtime [1.5 MA, frequency 47 Hz], on for 1.5 second and off for 1.8 second	PLMS: PSG measures (0.5-5 seconds, series of 5 or more, 5 to 90 seconds between movements)	n=8 PLMS/ 32 -66 yrs./ 6 M, 2 F	Sleep: PSG measures PLMS: #PLM	None reported	After one treatment: Sleep: Indices of sleep continuity did not change significantly. PLMS: Decreased #PLM*	
Montagna (129) Level II	DB Ran CO with PC	Clonz 1 mg, 1/2h before bedtime, fixed protocol, 1 week Clonz, 1 week placebo, 1 week vibrator	RLS: clinical criteria	n=6 RLS/ 44 - 61 yrs./3 M, 3 F	SBJ: quality of sleep, nocturnal leg jerking	None reported	Vibration: SBJ: less improvement of quality of sleep*, dysaethesia* compared to Clonz. PLMS: No improvement in leg jerking.	Small sample size; Patient selection
Lutz (155) Level V	Clinical series	Withdrawal from caffeine;t 5 of 10 pts on Diaz at the time of caffeine withdrawal.	RLS: clinical criteria (not specified)	n=10 RLS/ 14 - 46 yrs./ 4M, 6F	SBJ: Specific Sxs: discomfort (restless legs dysesthesias)	None reported	SBJ: All ten had complete relief of their RLS	Confounding factors: Two pts temporarily on Diaz and 3 on it long-term or not specified

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