REVIEW PAPER

An Update on the Dopaminergic Treatment of Restless Legs Syndrome and Periodic Limb Movement Disorder

A Review by the Restless Legs Syndrome Task Force of the Standards of Practice Committee of the American Academy of Sleep Medicine

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Abstract: This paper reviews evidence from April, 1998 through April 2002 for the dopaminergic treatment of the restless legs syndrome (RLS) and periodic limb movement disorder (PLMD). There has been increased study of dopaminergic agents for the treatment of these conditions since publication of a review paper and practice parameters that covered all types of medical treatment of RLS and PLMD in 1999. For this reason, the Restless Legs Syndrome Task Force and the Standards of Practice Committee decided to update the evidence on dopaminergic treatment of these conditions. This paper reviews the literature on levodopa, dopaminergic agonists (pergolide, pramipexole, ropinirole, talipexole, cabergoline, piribidel, DHEC), and other dopaminergic agents (amantadine, selegiline).

Abbreviations: DB, double blinded; DHEC, alpha-dihydroergocryptine; F, female; ICSD- International Classification of Sleep Disorders (6); IRLSSG, diagnosis by International RLS Study group criteria (34); M, male; PD, Parkinson's disease; PLM, periodic limb movement(s); PLMA, periodic limb movements(s) with arousal; PLMAI, periodic limb movement arousal index (PLMA per hour of sleep); PLMI, PLMS index (PLMS per hour of sleep); PSG, polysomnography (sleep study); QHS, nightly at bedtime; QOL, quality of life; SBJ, subjective measure; SE, sleep efficiency; SR, sustained release (formulation of levodopa compound); TIB, time in bed; TX, therapy

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1. INTRODUCTION

RESTLESS LEGS SYNDROME (RLS) IS A SENSORIMOTOR DISORDER CHARACTERIZED PRIMARILY BY MOTOR RESTLESSNESS WHICH IS BROUGHT ON BY REST AND ACCENTUATED LATER IN THE DAY AND DURING THE EARLY NIGHT IN THOSE WITH NORMAL CIRCADIAN ACTIVITY RHYTHMS. According to the recently revised diagnostic criteria, RLS is a clinical diagnosis which depends first on establishing the key features of the disorder (Table 1) and then on excluding potential mimics such as cramps.[1,2] Although work has advanced in understanding the pathophysiology and genetics of the disorder, there is currently no recognized objective test for the disorder. A combination of a provocative test conducted in the evening (suggested immobilization test-SIT) with measurement of sensory discomfort and the presence of frequent periodic limb movements (PLM) during awake epochs of the standard polysomnogram (PSG) can produce a high degree of diagnostic accuracy (reported sensitivity of 82%, specificity of 100% on sample tested).[3] In general, a significant number of PLM during sleep (PLMS) have been found in 80 to 90% of patients with RLS,[4] but the absence of such movements, especially after only a single study, does not exclude the diagnosis of RLS provided the diagnostic criteria are satisfied.

PLM (See Table 2 for definition of abbreviations) are repetitive movements that primarily involve the legs and that occur maximally during NREM sleep. While most PSG only record movements during sleep (PLMS), some do also consider those PLM occurring during wake (PLMW). Standard criteria for PLM include their occurrence in a series of 4 or more movements spaced by intervals of 5 to 90 seconds (onset to onset) with EMG burst durations of 0.5 to 5 seconds that rise to 1/4 of the EMG biocalibration amplitude.[5,6] It has recently been proposed that the burst duration be allowed to be as long as 10 seconds for PLMW, speculating that the involuntary muscle activity may be extended by a voluntary component that lengthens the burst.[7] PLM are themselves only a finding, whereas periodic limb movement disorder (PLMD) is a clinical condition which involves a sleep complaint associated with the finding of excess numbers of PLMS[6]. To make a diagnosis, it is generally necessary to exclude other sleep disorders as the source of the sleep complaint. Recently, it has been appreciated that such disorders should include upper airway resistance syndrome which often is not apparent with routine PSG studies.[8]

In 1999, the Standards of Practice Committee of the AASM (Andrew L. Chesson, Jr., MD, chair) published an initial set of standards for the management of the restless legs syndrome (RLS) and periodic limb movement disorder (PLMD).[9] These standards were based on a literature review of therapeutic trials, which covered the period ending with April 1998.[10] It was evident at that time that there were an increasing number of reports of therapeutic trials in RLS being published. It subsequently became clear that the large majority of new articles focused on dopaminergic agents, particularly levodopa (combined with a decar-

Table 1—Clinical Features of the Restless Legs Syndrome

Diagnostic Features

1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs.
2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting.
3. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching.
4. The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night.

Supportive clinical features

1. Positive Family history
2. Positive Response to dopaminergic therapy
3. Presence of periodic limb movements (during wakefulness or sleep)

Associated features of RLS

1. Variable clinical course, but typically chronic and often progressive.
2. Physical examination normal in idiopathic/familial forms.
3. Sleep disturbance is a common complaint in more affected patients.

Diagnostic features are those mandatory for a definite clinical diagnosis.
Supportive clinical features are those which may increase the probability of a diagnosis in doubtful cases, such as is common in children.
Associated features are typical, but do not contribute to diagnosis.

Modified from [1]

boxylase inhibitor) in various formulations and dopamine agonists. The literature prior to 1998 contained a number of articles dealing with levodopa formulations, but there were few articles on dopamine agonists and none on the newer, non-ergot dopamine agonists, pramipexole and ropinirole, which were first registered in Europe and the United States for other therapeutic uses at around the time of completion of the evidence review. It was, therefore, felt that an additional review was necessary to examine the evidence for use of the dopaminergic agents and especially the newly introduced agonists. In the four years prior to April, 2002, there were a sufficient number of publications to make at least an initial evidence based review of these agents. This review does not cover the full range of RLS therapies that are recommended for use; there were insufficient new publications in the intervening period to add significantly to the earlier review of agents other than the dopamingeric medications. Those interested in the general treatment of RLS need to read this supplementary review in conjunction with the earlier review which covers all agents.

2. METHODS OF LITERATURE SEARCH AND REVIEW

Literature searches were first conducted in January 2001, and then updated in August 2001 and finally, April 2002. The search was performed through Medline using the search terms: restless legs, periodic leg movement, periodic limb movement, and nocturnal myoclonus. A Pub Med search was also done. Search terms were applied both to the keyword field and as a text search. A total of 227 papers were derived from the searches and reviewed for relevance to the therapeutic literature based on their abstracts. 56 papers were selected for detailed consideration and four were added by task force member recommendation from other search resources. Of these, 27 met the criteria of having a focus on RLS treatment with a minimum of 5 patients studied, a clear indication of RLS or PLMD diagnosis for study entry, and use of a pharmaceutical agent which was primarily active on the dopamine system.

All articles selected for inclusion in the review were examined by one task force member who prepared a detailed report according to a modified worksheet. This report was then reviewed by a second task force member. Discrepancies were resolved by the chair. The material was then put into evidence tables grouped by class of agent: levodopa formulations, dopamine agonists, and other dopaminergic agents (Evidence Tables 3 through 5). All articles were reviewed for: mode of RLS diagnosis , means of quantifying PLM (usually only PLMS) or PLMD diagnosis where relevant, entry and exclusion criteria, number of subjects and age and gender breakdowns, agent used, schedule of administration and dosage at evaluation, outcome measures and results, including indication of significance of statistically tested results, and study conclusions. Possible biases and other distinctive characteristics of individual reports were noted as comments. Evidence levels were assigned based upon the following scheme:

Level 1 – Large, well designed, randomized, blinded and controlled study with statistically significant conclusions on relevant variables.

Level 2 – Smaller, well-designed, randomized and blinded controlled study with statistically significant conclusions on relevant variables.

Level 3 – Well designed non-randomized prospective study with control group

Level 4 – Well designed, large prospective study with historical controls or careful attention to confounding effects or small prospective study with control group

Level 5 – Small prospective study or case series without control groups

All authors of this paper, members of Standards of Practice Committee, and the AASM Board of Directors completed detailed conflict-of-interest statements and were found to have no significant conflicts with regard to this subject.

Table 2

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. 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.

3. BACKGROUND

During the three-year period between the final draft of the previous review and the current review, there was active research on the pathophysiological basis of RLS and PLM, the epidemiology and genetics of RLS, and the means of identifying patients and assessing their severity.

a. Update on pathophysiology

The most important recent developments in understanding the pathophysiology of RLS, has focused on the possible involvement of the dopamine system in RLS. In an additional recent development, it has been found that an abnormality of the body's use and storage of iron may underlie the dopamine abnormality. Several lines of evidence support this hypothesis. Imaging studies using ligands targeted to pre- and postsynaptic dopamine sites have found evidence for a modest reduction of dopamine function in the striatum, perhaps more in the putamen than in the caudate.[11,12,13] It is not clear whether this modest difference suggests that these brain areas are involved in RLS or whether this effect is merely part of a more general dopamine dysfunction. The actual tracts involved in the generation of the disorder may lie elsewhere. In addition, not every study has found an abnormality of dopamine system imaging.[14] However, none of the studies were done at a time of day when patients were likely to suffer their greatest symptoms, nor have they been able to focus on dopamine tracts other than the nigrostriatal tract. Some additional results have shown only equivocal or unclear evidence for involvement of the dopamine system. The use of metoclopramide to unmask RLS symptoms in untreated patients, though seemingly effective in some patients, did not reach statistical significance compared to placebo in a small series.[15] A study of CSF in RLS patients obtained during the daytime when patients were not symptomatic found no difference from controls in the dopamine metabolite, homovanillic acid.[16] Therefore, the strongest evidence for dopamine involvement in RLS remains pharmacological and not necessarily physiological.

Iron deficiency has also been found to be common in RLS. There is an inverse relationship between iron stores and severity of RLS symptoms.[17] Recent results have documented the relative depletion of brain iron stores in RLS patients. CSF ferritin has been found to be low in idiopathic RLS patients[18] and MRI imaging of brain iron has found depletion of iron in the substantia nigra of such patients which is related to RLS severity.[19] Depletion of iron and alteration in levels of iron proteins has now been confirmed on autopsy.[20] Dopamine and iron vary across the circadian cycle with nadirs reached near the maximum of RLS symptoms. Iron is needed for dopamine synthesis and, at least in animal models, iron deficiency during early life can result in lifetime abnormalities of the dopamine system. These findings on iron deficiency have been included in a comprehensive model which explains how iron deficiency could lead to the dopamine abnormalities underlying RLS.[21]

It has also been hypothesized that PLM are related to deficiencies in dopamine and are therefore more common in conditions with this deficiency, such as disorders with Lewy body pathology,[22] and less common in conditions of dopamine excess, such as schizophrenia.[23]

b. Update on epidemiology

Four recent studies are consistent with the idea that RLS is a common condition, at least in populations derived from Western Europe. Phillips and colleagues[24] who studied a population sample in Kentucky, USA, using a questionnaire that was based on the International RLS Study Group criteria (IRLSSG), found that 10% of respondents reported experiencing RLS symptoms 5 or more nights a month. A study of working age women in Sweden (aged 18 to 64 years) found that 11.4% of these young to middle aged adults reported symptoms of RLS that matched the IRLSSG diagnostic criteria [25] whereas a similar study of men found that 5.8% were affected[26] There were significantly elevated complaints of sleep problems and daytime performance disruption due to inadequate sleep in these women compared to those without RLS symptoms. In Chile, a Southern cone country with a predominant European population base, 13% of the relatives of hospital outpatients were found to meet diagnostic criteria for RLS.[27] In a population study of the elderly in Augsburg,[28] Rothdach and colleagues used a 3 question screen to determine RLS. 10.2% of the elderly were diagnosed with RLS, women at a higher prevalence (13.9%) than men (6.2%).

In recent years, a number of epidemiological studies have examined RLS prevalence in other population groups. Two studies from Asia[29,30] found lower prevalence in Japanese (3%) and Singapore (0.1%) populations than those typical of Northern and Western European populations.

Studies of PLM have been based on enumeration of nighttime movements and have usually only counted PLMS. Recent studies have suggested that PLMS may be more common in younger groups than previously suspected. They may be particularly common in children with ADHD.[31,32] Longitudinal studies in older adults have found that a high frequency of PLMS persists, but the severity of PLMS does not increase over time.[33]

c. Update on diagnosis of RLS and PLM

A consensus conference held at the National Institutes of Health in Bethesda, Maryland recently clarified and modified the original diagnostic criteria established in 1995 by the International RLS Study group (IRLSSG).[34] As shown in Table 1, this conference revised and rearranged, but did not substantially alter the diagnostic criteria.[1] The major changes are deletion of the diagnostic criteria of motor restlessness, which was reported to have been difficult to apply, and the establishment of provocation by rest and amelioration with activity as separate diagnostic criteria. It is unlikely that use of the modified criteria would alter the patient population studied. This workgroup also proposed initial criteria for the diagnosis of RLS in children and in the cognitively impaired elderly, as well as a new definition for PLM in children. Meantime, a number of associated diagnostic instruments are under development.[2,35] Combined with the new diagnostic features, these should facilitate better RLS diagnosis in the future and facilitate screening for therapeutic studies. Almost all papers under review now use the IRLSSG 1995 criteria as the diagnostic standard,[34] as indicated in the evidence tables. Attempts to provide an objective diagnostic test for RLS have been made, but have not yet reached a generally accepted level of utility. Such tests use the SIT and PSG to examine sensory symptoms and motor manifestations (PLM) of RLS. Single measures provide a reasonable level of sensitivity and specificity (80% or more), but the combination of sensory discomfort during the SIT and PLMW index can improve specificity (100% reported).[3] This may therefore be helpful as a confirmatory test if it is positive, but does not rule out RLS if negative.

New criteria have also been proposed for scoring PLMW, since EMG potentials may last longer in that state, perhaps due to voluntary prolongation of muscle activity.[7] Montplaisir and colleagues have proposed that burst duration up to 10 seconds be permitted.[7]

d. Update on evaluation of RLS

This period demonstrated the gradual development and validation of a number of rating scales. The full evaluation of RLS involves understanding its basic symptoms, its impact on sleep, and its impairment of quality of life. Therapeutic trials have examined various of these aspects and use both subjective measures (specific to RLS or general, like the SF-36 quality of life scale) and objective measures (sleep studies, actigraphy) to determine the severity of RLS and its response to treatments. Because RLS is primarily a subjective disorder – in fact, it can be considered a chronic pain syndrome if the discomfort has a painful quality – the major office evaluation uses subjective ratings to determine severity. A recent subjective instrument, the International RLS rating scale, has been validated in an international multicenter study (IRLSSG, submitted) and has also been used in a large multi-center drug trial as a measure of therapeutic efficacy.[36] Partial versions of this scale were used in some of the articles under review.[37,38] This instrument measures both primary disease symptoms and disease impact. It is dominated by a single severity factor, but it appears to have two primary aspects that are related to the severity of the symptoms and their impact on sleep and quality of life.

Additional subjective measures include sleep logs or quality of life scales. A one question Hopkins RLS scale ranks severity by time of day of symptom onset, with more severe disease manifesting earlier in the day.[39] This scale has been validated against polysomnographic measures of severity such as PLMS index (PLMI) and sleep efficiency. In addition, there is an international multicenter study under way to develop a specific rating scale for augmentation (Diego Garcia-Borreguero, MD, oral communication, February, 2004: DGarciaBorreguero@fjd.es), a problem identified as important for dopaminergic treatment of RLS.[40]

Standard sleep measures remain useful measures of sleep initiation, continuity, and sufficiency. These are often combined with measures of PLMS amount, frequency, and association with arousals. Recently, the suggested immobilization test (SIT) has been proposed as a possible auxiliary measure, examining the ability of a period of imposed rest to induce subjective and motoric features of RLS.[41]

In evaluation of PLMS and possible diagnosis of periodic limb movement disorder (PLMD), the association between PLMS and subtle respiratory defects such as upper airway resistance syndrome has suggested that these conditions be monitored when a diagnosis of PLMD is being considered, since they may be the cause of sleep complaints by themselves. The PLMS in this situation may only be incidental associates of the respiratory disturbances.[8] Also, excessive daytime somnolence associated with PLMS may not be due to the leg movements, but merely an associated condition, such that treatment suppressing the leg movements may not resolve the somnolence.[42]

4 INTRODUCTION: SURVEY OF THE DOPAMINERGIC AGENTS

As articles reviewed below indicate, the emphasis upon the dopaminergic treatments continues a trend noted in the prior review and indicates considerable effort has been made to develop evidence supporting this mode of treatment. The studies meeting our criteria for inclusion in this review almost all indicate treatment benefits from dopaminergic medications. These include 17 articles showing efficacy of a dopamine agonist, 3 articles reporting treatment benefit for levo-dopa and one article each showing some benefit from amantadine and selegiline, drugs presumed to act on the dopaminergic system because of their positive effects in treatment of Parkinson's disease (PD). The three following sections review each of these classes of dopaminergic medications. Not only have these medications reduced the patients' subjective report of the severity of RLS symptoms in general but also in several instances they have been shown to improve overall sleep and reduce the excessive nocturnal motor activity characteristic of RLS. The one adverse effect from these medications that appears to be receiving more attention than

in prior studies is that of drowsiness and sleepiness in the daytime. Thus the current literature consistently reports efficacy of the dopaminergic drugs and also appears to indicate some adverse problems with daytime drowsiness, fatigue or sleepiness, occurring even for treatment with amantadine. However, monitoring of sleepiness has not been extensive and its importance and degree are unclear.

In recent years, it has been reported that dopamine agonists can induce irresistible and sudden sleepiness (sleep attacks) in Parkinson's disease (PD) patients with resulting automobile accidents[43] The initial report spurred multiple investigations which have now suggested that EDS in PD patients can occur with many different treatments.[44,45] There are likely two related but different effects in PD patients: first is an increase in the experience of significant daytime sleepiness or drowsiness similar to that observed with many other medications such as the benzodiazepines. The second, more serious possible adverse effect, involves a sudden and unexpected onset of sleepiness. The adverse effect of daytime drowsiness from treatment with dopamine agonists is reported for both RLS and PD patients, although the complaint appears to be more common for PD (51% for one sample of 638 non-demented PD patients[46] compared to reported 20-30% for RLS patients, as shown in the adverse effects column for dopamine agonists of table 4). Sudden sleep attacks occurred, however, in only 3.8% of 420 Parkinsonian drivers, and in only 3 drivers (0.7%) did this occur without warning.[46] A review of these patients revealed that a history of daytime sleepiness, such as documented by the Epworth Sleepiness Scale (ESS), was found in most of those with sleep attacks.[46] No sudden, unexpected sleep attacks were reported for RLS patients. In summary, although sleepiness has been reported as a side effect of dopaminergic agents in some RLS patients, it is not clear that this would include an important number of sleep attacks. The degree of sleepiness experienced in RLS patients is likely less than that of PD patients, who have a very different pathology, who show a likely tendency towards EDS independent of treatment [47] and who take very different doses of the medications.

4B. LEVODOPA

Our previous[10] review summarized the results of 18 studies of levodopa in the management of RLS, including eight double blind trials. The effectiveness of the drug in reducing PLMS and RLS was clearly demonstrated, leading to the designation of use of levodopa as a guideline for treatment of RLS and PLMD.[9] Clinical series emphasized, however, the high frequency of daytime augmentation (up to 82%) and early morning rebound (20-35%) associated with levodopa treatment, especially at higher dose levels.

We reviewed two recent double-blind, placebo controlled, crossover trials of levodopa, both using actigraphic measurements of PLMS and quality of life measures. The first study was designed to explore the duration of levodopa response and to assess how long the drug must be taken for a therapeutic effect to become apparent.[48] Regular release levodopa (100-200 mg) and benserazide were administered one hour before bed for four weeks, followed by four weeks placebo. The results showed that the effect of levodopa on PLMI was confined to the first 4-6 hours in bed. A significant reduction of PLMI occurred the first night the drug was taken and the effect wore off the night following discontinuation of therapy. Patients' ratings of sleep latency, sleep quality and life satisfaction all improved significantly with the drug. However, there was a significant increase in physicians' ratings of RLS severity during the day with the drug compared to placebo, suggesting the start of augmentation.

The second study explored one possible approach to the problem of the short duration of action of levodopa.[49] Slow release levodopa (100-200 mg) with benserazide was added to 100-200 mg regular-release levodopa for 4 weeks. Patients were selected if RLS in the first half of the night had responded to regular-release levodopa, but PLMS had increased in the second half of the night in association with later prolonged awakenings. The PLMI was significantly reduced between the 3rd and 7th hour after lights out in the combination treatment sequence compared to the sequence in which only regular release levodopa was taken. Patients' ratings of sleep quality, RLS severity at night and time awake in the second half of the night all improved significantly. Augmentation developed in 27% of patients on combination therapy and 17% on the regular release drug alone.

The question of whether dopaminergic therapy relieves symptoms of attention deficit and hyperactivity disorder (ADHD) in children who also have RLS or PLMS was explored in an open label study of five children.[50] After six months of therapy with 400 mg levodopa daily in divided doses, the PLMI and the index with arousals significantly fell and measures of ADHD improved. The study was not able to determine whether the effect on ADHD was mediated via reduction in PLMS or through an independent mechanism.

In summary, recent studies have emphasized the short duration of regular release levodopa in reducing PLMS; reported that levodopa is effective the first night it is used, thus supporting feasible intermittent use of the drug; found that a combination of regular and slow release levodopa before bed provides a longer duration response compared to regular release levodopa alone; reported improvement in quality of life indices with levodopa use; provided prospective information indicating a high frequency of daytime augmentation even after only four weeks use of the drug; and provided some preliminary data suggesting that further exploration of the role of levodopa in treating children with both ADHD and RLS/PLMS may be warranted.

4.C.I. SPECTRUM OF ACTION IN BINDING OF AGONISTS

The dopaminergic agents discussed in this paper include the following: pergolide, pramipexole, ropinerole, talipexole, cabergoline, piribedil and alpha-dihydroergocryptine (DHEC). Pergolide, cabergoline and DHEC are all ergot derivatives with predominately D2 receptor agonist properties; and partial or complete D1 agonist properties.[51,52,53] They all appear to have affinity for D3 and D4 receptors, which is lower than that for D2. Pramipexole, ropinerole, piribedil and talipexole are non-ergot dopamine agonists. Their highest affinity is for D3 receptor followed by D2 and then D4 receptor. Talipexole appears to have only partial agonists properties at the D3 receptor. None appear to have an effect on the D1 receptors.[52,53]

4.C.II. PERGOLIDE

In the 1999 AASM review of treatment for RLS and PLMD, only two published studies of pergolide were available.[54,55] The practice parameter report noted sufficient evidence to recommend pergolide treatment as a guideline but not as a standard.

The current review found seven new studies of pergolide, of which one attained Level 1 evidence and two attained Level 2 evidence.[50,56,57,58,59,60,61] Wetter et al. found RLS symptoms, PLMS and sleep all improved on pergolide at a mean dose of 0.51 mg.[56] Earley et al. also reported RLS and PLMS significantly improved with pergolide.[57] In uremic patients, Pieta et al. reported improved subjective measures but not objective PLM or sleep measures.[58] Three clinical series in adults have noted long-term favorable results with pergolide.[59,60,61] In the largest of these studies, adverse effects of nausea (41%), congestion (41%) and very mild augmentation (27%) were noted, but 78.6% remained on pergolide long-term.[61] Domperidone has been used to manage nausea in some of the studies.[56,61] In the only study involving children, Walters et al. reported favorable results in two children based on improvements in polysomnographic, cognitive and behavioral measures.[50]

Overall, a number of studies, including those providing high levels of evidence, have been published reporting pergolide to be effective in the treatment of primary, adult RLS and PLMD. Nausea and congestion are common adverse effects, but rarely has augmentation been reported severe enough to warrant discontinuation. Recent reports of single cases and small series detail rare, but serious complications of pergolide use which are typical of ergot medications: the development of pleuropul-

monary fibrosis[62] or cardiac valvulopathy.[63] For uremic patients with RLS there may be potential benefit. Further study in childhood RLS and PLMD is needed.[50]

4.C.III. PRAMIPEXOLE

The only double-blind, randomized, cross over trial with placebo control had eleven subjects of which only ten completed the trial.[64] The maximum dose of pramipexole was 1.5 mg. The dose was escalated on a weekly basis over four weeks. Pramipexole was significantly effective in treating sensory and motor symptoms as measured by RLS severity questionnaire, PLMS and PLMW index by polysomnogram. However, sleep efficiency did not improve. The four remaining studies were open-label clinical series looking at long-term effectiveness and side effects. In these trials [37,65,66,67] pramipexole was used in a dose range of 0.125mg to 2.5mg. The treatment period ranged from 1 to 10 months. The sample size ranged from 7 to 24 subjects. The outcome measures were all subjective ratings scales. All of these studies reported a "significant" improvement in subjective ratings with the use of medications. The common side effects noted in the trials were fluid retention/edema, sleepiness/fatigue during the day, GI disturbance, insomnia/alertness, dizziness and occasional augmentation or worsening of RLS.

These studies consistently report a benefit to the use of pramipexole in the treatment of RLS in adults. The actual duration and degree of effectiveness is unclear given the limited number of high-quality, placebo-controlled trials.

4.C.IV. ROPINIROLE

The evidence for support of ropinirole in the treatment of RLS is based on five studies (six publications). One study was a single-blinded, non-randomized cross over trial. This study was divided into subjective and objective outcome measures and reported in two separate articles.[68,69] The patients spent three sequential nights in the sleep lab: The first night for adaptation, the second night with placebo and the third night with ropinirole, which was given at a dose of 0.5mg on just the third night. The subjects performed psychomotor tasks and had a standard all-night polysomnogram. The study demonstrated that there was a first night effect with improvements from the first night to the second night. Comparing the drug night to the placebo night, they report an increase in total sleep time and sleep efficiency but more frequent stage shifts. On psychomotor tasks there was a decrease in somatic complaints, enhancement of fine motor activity, and a decrease in error rate. There were also four, open-label clinical series[38,70,71,72] which varied in the duration of treatment from 31 days to 10 months. The dose ranged from 0.25mg to 4mg. The sample sizes were small (5 to 16 subjects). Subjective measures were used in all three studies but PLMS (PSG) were measured in only one study.[70] That study reported improvements in sleep efficiency and PLMS based on PSG, both immediately after beginning of treatment and after a month of using ropinirole. All studies reported significant improvements of subject's ratings of symptom severity while on treatment.

4.C.V. OTHER AGONISTS

There have been four other dopaminergic agents used in treating RLS. All four studies (using talipexole, cabergoline, piribidel, and DHEC) were open-label clinical series. Five subjects were treated with talipexole for four weeks with doses ranging from 0.4 to 0.8 mg given at bedtime.[73] The authors reported a "significant increase in both sleep efficiency and percent stage 2 and a significant decrease in percent stage 1, percent stage awake and number of arousals". There were no data or statistics given in the paper. Cabergoline was given to nine subjects once a day for twelve weeks.[74] The dose ranged from 1-3 mg per day. Polysomnographic data demonstrated a significant reduction in PLMS, PLMA and PLM awakening. Total sleep time was increased and sleep latency was shortened along with an increase in sleep efficiency. All subjects reported improvement of symptoms based upon a severity scale. Piribedil was given as a total daily dose of about 100mg (range 25 – 350) for a median duration of 8 months (ranging from less than one month to 15 months[75]). The causes of RLS in the 13 patients included Parkinson's disease (4), neuropathy/ polyradiculopathy (6) and idiopathic (3). A ten-point subjective rating scale was used as the endpoint. Treatment produced complete, partial, or no response in eight, three and two subjects respectively.[75] DHEC was given to 15 subjects in doses ranging from 10 mg to 40 mg per day.[76] Thirteen out of 16 subjects experienced side effects with nausea, vomiting and abdominal pain being the most common. The outcome measures were a visual analog scale for symptom severity, and patient recordings of duration and quality of nocturnal sleep, sleep latency and frequency of sleep interruption. The sleep duration and sleep latency were reported as improved.

Overall these studies provide only modest, preliminary evidence of efficacy. They provide level 4 and 5 evidence to support use of these dopamine agonists.

d. Other dopaminergic agents

Amantadine was developed as a prophylaxis and treatment for influenza and serendipitously was found to be useful for treatment of Parkinson's disease.

Among its actions, it is considered to enhance dopaminergic activity. In one unblinded, uncontrolled study, amantadine in doses ranging from 100 – 300 mg/day (taken 1 to 3 times a day as needed.) was evaluated as an add-on treatment for 21 adult RLS patients who were not adequately treated by their current medications.[77] About half of the patients (11 of 21) reported some benefit with six (29%) reporting at least 95% reduction in symptoms. The outcome variables showed statistically significant treatment effects. None of the subject factors predicted response to amantadine. The adverse effects of amantadine did not include augmentation but did include drowsiness for three patients and fatigue for two, somewhat like the problems with daytime alertness noted for other dopaminergic treatments. Follow-up evaluations of the 11 patients reporting benefit from amantadine were obtained for three – 13 months after treatment. The treatment benefit continued for all but two of the patients. During this follow-up period two patients weaned themselves off their other RLS medication (levo-dopa). Overall these are promising results for an open-label trial suggesting amantadine has a place in the treatment options for RLS. One somewhat troubling aspect of the study was the number of patients already on treatment for their RLS who had such limited benefit from their treatment and the apparent relative failure of this medication for treatment of patients with augmentation. The degree of benefit for patients not on any medication remains to be determined in future studies.

Selegiline is an irreversible MAO inhibitor that at lower doses selectively inhibits MAO-B. This action is considered to effectively decrease synaptic dopamine reuptake and enhance dopaminergic activity. Selegiline has a short metabolic half-life of less than 1 hour and is metabolized into amphetamine and methamphetamine. It has been evaluated in one study for the treatment of PLMD for patients selected to have a sleep-wake complaint but no other major sleep disorder.[78] Patients with RLS were explicitly excluded. In 31 patients evaluated with polysomnograms before and after treatment there was a significant decrease in PLMS. Patients took selegiline during the daytime in equally divided doses early in the morning and again at noon times. A forced escalation of dose every two weeks from 5 to 10 and then 15 mg twice a day was followed by a maintenance dose chosen by the patient as the most effective. The maintenance dose was continued for another six weeks to seven months before repeating the PSG evaluation. Average ± standard deviation decrease in PLMS per hour for all subjects was 20.7 ± 23.8. There was also a mild non-significant decrease in sleep efficiency and increase in sleep latency. Although the patients selected their doses based on clinical benefit, the study did not report any systematic data on clinical changes associated with this treatment other than the decrease in PLMS. Overall this study supports the concept that enhanc-

ing CNS dopaminergic activity reduces PLMS. It is not certain if this would apply to the PLMS of RLS patients, but this seems likely. The lack of a blinded placebo control must be noted since the decrease observed may be a regression to mean effect for patients chosen to have a large number of PLMS. The clinical significance of these findings is much less certain. The lack of any report on clinical benefits aside from decreased PLMS and the report that the medication was continued at a dose considered to be effective by the patient further limits conclusions that can be drawn from this study. These patients were presumably selected from a group started on the selegiline treatment and the subjects reported were the ones who continued on the treatment long enough to have the repeat PSG. No information is provided about the number of subjects who started but did not complete this treatment schedule. Those completing the study may have improved clinically for reasons other than the medication use.

5. SUMMARY OF DOPAMINERGIC THERAPIES STUDIED

a. Agents

The new studies show a shift from the previous review of therapy in RLS. While we have not considered therapies other than dopaminergic, these agents have provided the vast majority of therapeutic trials reported in this period, although trials with anticonvulsants, opioids, and metals have continued to be reported. Within the studies on dopaminergic agents, two trends can be discerned: First, there has been a shift from a concentration on levodopa, to a focus on other agents, especially dopamine agonists. Second, a much wider variety of agents has now been tried in RLS. This is again true of the dopamine agonists, eight having been the subject of trials during this period. Other agents such as apomorphine have been tried, but not reported in papers reaching our inclusion criteria. It is to be expected that additional agonists may be studied in the near future.

b. Patients Studied

The majority of patients with RLS studied have been those who are middle-aged to elderly. One study, however, has examined the response to levodopa and pergolide in children with co-morbid ADHD.[50] Although there has not been a systematic study of the aged, individuals over 65 years of age have been included in many of the studies.

To date, there have been very limited studies of RLS treatment in pregnancy.[79,80] None have reported the use of dopaminergic agents. There are few studies of secondary RLS, although some of the studies have included patients with uremia, neuropathy, or fibromyalgia. One study was restricted to patients on dialysis.[58]

Most studies include patients with moderate to severe RLS. Because there has not been a standardized means of assessing severity, it is difficult to make comparisons across studies. Some studies have concentrated on those with previous medication failures, which is likely to be a more severe group. One distinct change in the current study period is the marked decrease in studies aimed at PLMD. Only one study specifically targeted this group. [78] This is likely due to the controversies regarding the morbidity of PLMD.[22,42,81,82]

c. Strengths and Weaknesses of Studies

Although the number of reported studies in the time period covered (<4 years) indicates that there is a substantial increase in the investigation of therapeutic modalities for RLS, there remain certain key deficits in the kinds and scope of studies that have been undertaken. First, almost all of the studies are small scale or of modest size. Very few studies are multicenter or include large numbers of subjects; large multicenter studies have only been reported in abstract form.[36] This deficiency may be remedied in the next few years. Second, most of the studies cover shorter time periods, although several open studies have examined responses over several months to a year or more. Good, multi-year data are lacking. Third, there are no new comparative studies reported in this time period, making it difficult to perform direct comparisons of different agents. Fourth, the major issue of augmentation, raised by earlier studies of levodopa and pergolide,[40] has not been systematically studied. Those papers reporting studies on agonists which describe augmentation report lower levels than seen with levodopa. What is currently lacking, in this regard, is a means of assessing augmentation. Trials with a scale to assess augmentation are now under way (Diego Garcia-Borreguero, MD, oral and email communication, February, 2004: DGarcia Borreguero@fjd.es).

Studies have continued to rely on monitoring of subjective response and sleep measures, including PLMS. The more compelling studies use both objective and subjective measures. Few studies have used statistical corrections for the number of comparisons. Clear designation of primary and secondary endpoints has often not been made. A validated rating scale, the IRLSSG, has been used in several studies, sometimes in a truncated form.[37,38] An international multi-center validation of this form has now been published.[83] In addition, a number of other quality of life scales are undergoing formal validation (Richard Allen, PhD, Johns Hopkins University, oral and email communication, September, 2003; RichardJHU@aol.com). Which measures should be the primary outcome measures, whether subjective ones or sleep measures, remains uncertain. Objective sleep measures, including PLM counts, may only reflect a portion of the morbidity in RLS. In PLMD, the objective measures are clearly necessary, but may not be sufficient to guarantee a clinically meaningful outcome.

New types of assessment are emerging, but have not yet become standard. The Suggested Immobilization Test (SIT), which can provoke symptoms in most patients,[41] has not yet been used to measure therapeutic response. Actigraphy, which can measure generalized activity, [84] count leg kicks,[85] and provide some assessment of sleep,[86] has been used in a few studies, but has not been fully exploited for longer term assessment of subjects.

d. Coverage of Different Agents and Modalities

The succession of agents studied for RLS have largely depended on when the agents became available to treat other conditions such as PD, pain, epilepsy, and insomnia. Therefore, levodopa and bromocriptine were first studied when approved for use in PD, followed by pergolide, and other more recently approved agonists. To date, there are no medications in the United States for which RLS is an approved indication, although the appearance in abstract form of large multicenter and multinational studies sponsored by pharmaceutical companies suggests that indications may be approved in the near future.

In the future this situation may change and RLS may not be so dependent on initial indications for other conditions. The only medication now approved for RLS is a levodopa/benserazide compound used in Europe whose approval was based on one of the larger studies reported in this review. [48]

Doses of dopaminergic agents used to treat RLS have often not been systematically explored and, particularly for the dopamine agonists, the doses indicated in the evidence tables may only be initial efforts to focus in on the range of effective doses. One general observation that can be made, however, is that the dose ranges found effective are almost universally well below those most commonly used to treat PD. The development of augmentation may be related to higher dosages and thus there may be a good rationale to aim for administration of the lowest effective dose for all of these dopaminergic agents.

All the agents reported in this period have been oral agents, although subcutaneous injections[87] or intrathecal administrations[88] have been reported in abstracts or case reports as useful in RLS. Development of other routes for treatment of PD, such as skin patches, suggests that similar methods may be available for RLS in the future. Parenteral or transcutaneous routes will be helpful for those unable to receive oral meds, such as those in the perioperative period or those intubated in critical care units.

e. Overall Assessment and Future Recommendations.

The recent period demonstrates that dopaminergic agents are currently of greatest interest for treatment of RLS. Extrapolating from current trends, it would appear that the dopamine agonists are likely to be the favored agents for therapeutic trials in the next decade. Almost all studies have reported positive outcomes. No study of idiopathic RLS has reported treatment failures with a dopaminergic agent, although some have shown relatively weak benefits. It is of interest that almost all Parkinsonian medications have been studied in RLS and reported to benefit the condition. The solitary exception is the anticholinergics, which may indicate some differential pathophysiology of the two disorders.

Although formal meta-analyses have not been done, the studies we have reviewed show substantial efficacy by different measures, mostly tolerable side effects, and, in the mid-term at least, no severe complications (such as levodopa-induced dyskinesias or mental changes, which may occur in PD). Initial peripheral side effects and augmentation remain the most troubling side effects. The former were managed in several studies by use of domperidone, a peripheral dopamine blocker not approved for use in the United States. The studies report lower levels of augmentation for the agonists and there is at least a clinical impression that longer half-life agents may be less likely to induce manifest augmentation. The development of a validated rating scale for augmentation should help assess this complication of treatment. The issue of sleepiness, raised for treatment of PD, has had quite limited study in relation to RLS.

Studies are underway to validate instruments that can assess quality of life or economic impact of RLS and improvement through treatment. Some modest efforts in this direction have already been reported, as we have reviewed, but more extensive efforts and the development of more closely targeted instruments will add critical information to the picture of RLS and its impact.

In the near future, it seems highly likely that there will be large multicenter trials undertaken by the pharmaceutical industry. It is not clear that the academic environment can support such studies, although that cannot be ruled out. Hopefully, these studies will be able to assess long-term benefits. Other issues that will need study include the development of augmentation and the problems of sleepiness induced by treatment. The academic environment may be well suited to developing comparative studies, perhaps focusing on specific issues such as the development of augmentation.

There is a lack of studies using different administration routes and special populations. These can perhaps best be addressed in the academic setting, but may be later-phase studies carried out if drugs are approved for RLS in the United States or Europe. Children seem most likely to be studied. The elderly make up part of the population currently studied, but they may need systematic review or analysis through age-stratified studies. The recent initiation of diagnostic criteria for children and the cognitively compromised elderly should facilitate studies in those populations. Pregnant women remain the most difficult population to study and, in this regard, work on RLS may be dependent on evolving information from drug studies done outside the field. The treatment of secondary RLS with dopaminergic agents remains another issue. Finally, more attention must be made to categorizing patients by level of severity and examining those with different needs for once daily dosing, multiple daily doses, or only situational or intermittent treatment.

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REFERENCES

1. Allen RP, Hening WA, Montplaisir J, et al. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology: A report from The RLS Diagnosis and Epidemiology workshop at the National Institute of Health. Sleep Med 2003;4(2): 101-119.
2. Hening W, Allen RP, Thanner S, et al. The Johns Hopkins telephone diagnostic interview for the restless legs syndrome: preliminary investigation for validation in a multi-center patient and control population. Sleep Med 2003; 4(2): 137-141.
3. Michaud M, Paquet J, Lavigne G, Desautels A, Montplaisir J. Sleep laboratory diagnosis of restless legs syndrome. Eur Neurol 2002;48(2):108-113.
4. Montplaisir J, Boucher S, Poirier G, Lavigne G, Lapierre O, Lesperance P. Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. Mov Disord 1997;12(1):61-65.
5. The Atlas Task Force. Recording and scoring leg movements. Sleep 1993;16(8):748-759.
6. Diagnostic Classification Steering Committee of the American Sleep Disorders Association. The International Classification of Sleep Disorders: Diagnostic and Coding Manual. Rochester, Minnesota: American Sleep Disorders Association; 1997.
7. Michaud M, Poirier G, Lavigne G, Montplaisir J. Restless Legs Syndrome: scoring criteria for leg movements recorded during the suggested immobilization test. Sleep Med 2001;2(4):317-321.
8. Exar EN, Collop NA. The association of upper airway resistance with periodic limb movements. Sleep 2001;24(2):188-192.
9. Standards of Practice Committee of the American Academy of Sleep Medicine. Practice parameters for the treatment of restless legs syndrome and periodic limb movement disorder. Sleep 1999; 22(7): 961-8.
10. Hening W, Allen R, Earley C, Kushida C, Picchietti D, Silber M. The treatment of restless legs syndrome and periodic limb movement disorder. An American Academy of Sleep Medicine Review. Sleep 1999 ; 22(7): 970-999.
11. Staedt J, Stoppe G, Kogler A, et al. Nocturnal myoclonus syndrome (periodic movements in sleep) related to central dopamine D2-receptor alteration. Eur Arch Psychiatry Clin Neurosci 1995; 245(1): 8-10.
12. Turjanski N, Lees AJ, Brooks DJ. Striatal dopaminergic function in restless legs syndrome: 18F-dopa and 11C-raclopride PET studies. Neurology 1999; 52(5): 932-7.
13. Ruottinen HM, Partinen M, Hublin C, et al. An FDOPA PET study in patients with periodic limb movement disorder and restless legs syndrome. Neurology 2000; 54(2): 502-4.
14. Eisensehr I, Wetter TC, Linke R, et al. Normal IPT and IBZM SPECT in drug-naive and levodopa-treated idiopathic restless legs syndrome. Neurology 2001; 57(7): 1307-9.
15. Winkelmann J, Schadrack J, Wetter TC, Zieglgansberger W, Trenkwalder C. Opioid and dopamine antagonist drug challenges in untreated restless legs syndrome patients. Sleep Medicine 2001; 2(1): 57-61.
16. Earley CJ, Hyland K, Allen RP. CSF dopamine, serotonin, and biopterin metabolites in patients with restless legs syndrome. Movement Disorders 2001; 16(1): 144-9.
17. Sun ER, Chen CA, Ho G, Earley CJ, Allen RP. Iron and the restless legs syndrome. Sleep 1998; 21(4): 371-7.
18. Earley CJ, Connor JR, Beard JL, Malecki EA, Epstein DK, Allen RP. Abnormalities in CSF concentrations of ferritin and transferrin in restless legs syndrome. Neurology 2000; 54(8): 1698-700.
19. Allen RP, Barker PB, Wehrl F, Song HK, Earley CJ. MRI measurement of brain iron in patients with restless legs syndrome. Neurology. 2001; 56(2): 263-65.
20. Connor JR, Boyer PJ, Menzies SL, et al. Neuropathological examination suggests impaired brain iron acquisition in restless legs syndrome. Neurology 2003, 61 (3): 304-9
21. Earley CJ, Allen RP, Beard JL, Connor JR. Insight into the pathophysiology of restless legs syndrome. J Neurosci Res 2000; 62(5): 623-8.
22. Montplaisir J, Michaud M, Denesle R, Gosselin A. Periodic leg movements are not more prevalent in insomnia or hypersomnia but are specifically associated with sleep disorders involving a dopaminergic impairment. Sleep Medicine 2000; 1(2): 163-167.
23. Ancoli-Israel S, Martin J, Jones DW, et al. Sleep-disordered breathing and periodic limb movements in sleep in older patients with schizophrenia. Biol Psychiatry 1999;45(11): 1426-1432.
24. Phillips B, Young T, Finn L, Asher K, Hening WA, Purvis C. Epidemiology of restless legs symptoms in adults. Archives of Internal Medicine 2000; 160(14): 2137-141.
25. Ulfberg J, Nystrom B, Carter N, Edling C. Restless Legs Syndrome among working-aged women. European Neurology 2001; 46(1): 17-9.
26. Ulfberg J, Nystrom B, Carter N, Edling C. Prevalence of restless legs syndrome among men aged 18 to 64 years: an association with somatic disease and neuropsychiatric symptoms. Movement Disorders 2001; 16(6): 1159-63.
27. Miranda M, Araya F, Castillo JL, Duran C, Gonzalez F, Aris L. [Restless legs syndrome: a clinical study in adult general population and in uremic patients]. [Spanish]. Revista Medica De Chile 2001; 129(2): 179-86.
28. Rothdach AJ, Trenkwalder C, Haberstock J, Keil U, Berger K. Prevalence and risk factors of RLS in an elderly population: the MEMO study. Memory and morbidity in Augsburg elderly. Neurology 2000; 54(5): 1064-8.
29. Kageyama T, Kabuto M, Nitta H, et al. Prevalences of periodic limb movement-like and restless legs-like symptoms among Japanese adults. Psychiatry Clin Neurosci 2000; 54(3): 296-8.
30. Tan EK, Seah A, See SJ, Lim E, Wong MC, Koh KK. Restless legs syndrome in an Asian population: A study in Singapore. Movement Disorders 2001; 16(3): 729-32.
31. Picchietti DL, Walters AS. Moderate to severe periodic limb movement disorder in childhood and adolescence. Sleep 1999; 22(3): 297-300.
32. Chervin RD, Archbold KH, Dillon JE, Pituch KJ, Panahi P, Dahl RE, et al. Associations between symptoms of inattention, hyperactivity, restless legs, and periodic leg movements. Sleep 2002;25(2):213-218.

33. Gehrman P, Stepnowsky C, Cohen-Zion M, Marler M, Kripke DF, Ancoli- Israel S. Long-term follow-up of periodic limb movements in sleep in older adults. Sleep 2002;25(3):340-343.
34. The International Restless Legs Syndrome Study Group (Arthur S. Walters MD — Group Organizer and Correspondent). Towards a better definition of the Restless Legs Syndrome. Mov Disord 1995;10:634-642
35. Allen RP, Earley CJ. Validation of a diagnostic questionnaire for the restless legs syndrome (RLS) (Abstract). Neurology 2001; 56, (Supp 3): 4A.
36. Trenkwalder C, Brandenburg U, Hundemer HP, Lledo A, Quail D. A randomized long-term placebo controlled multicenter trial of pergolide in the treatment of RLS - The Pearls study. Neurology 2001; 56, (Suppl 3): A 5.
37. Becker PM, Ondo W, Sharon D. Encouraging initial response of restless legs syndrome to pramipexole [see comments]. Neurology 1998 Oct; 51(4): 1221-3.
38. Ondo W. Ropinirole for restless legs syndrome [see comments]. Movement Disorders 1999; 14(1): 138-40.
39. Allen RP, Earley CJ. Validation of the Johns Hopkins restless legs severity scale. Sleep 2001; May; 2(3): 239-42.
40. Allen RP, Earley CJ. Augmentation of the restless legs syndrome with carbidopa/levodopa. Sleep 1996; Apr; 19(3): 205-13.
41. Michaud M, Lavigne G, Desautels A, Poirier G, Montplaisir J. Effects of immobility on sensory and motor symptoms of restless legs syndrome. Mov Disord 2002; 17(1): 112-115.
42. Nicolas A, Lesperance P, Montplaisir J. Is excessive daytime sleepiness with periodic leg movements during sleep a specific diagnostic category? European Neurology 1998; 40(1): 22-6.
43. Frucht, S, Rogers JD, Greene, PE, Gordon, MF, Fahn S. Falling asleep at the wheel : motor vehicle mishaps in persons taking pramipexole and ropinirole. Neurology 1999; 52, (9).1908-10.
44. Ondo WG, Dat Vuong K, Khan H, Atassi F, Kwak C, Jankovic J. Daytime sleepiness and other sleep disorders in Parkinson's disease. Neurology 2001; 57, (8): 1392-6.
45. Pal S, Bhattacharya KF, Apapito C, Chaudhuri KR. A study of excessive daytime sleepiness and its clinical significance in three groups of Parkinson's disease taking pramipexole, cabergoline and levodopa mono and combination therapy. J Neurol Transm 2002; 108, (1): 71-7.
46. Hobson DE, Lang AE, Martin WR, et al. Excessive daytime sleepiness and sudden onset sleep in Parkinson disease: a survey by Canadian Movement Disorders Group.JAMA 2002; 287 (4):455-463.
47. Rye DB, Bliwise DL, Dihenia B, Gureki P. Daytime sleepiness in Parkinson's disease. J Sleep Research 2000; 9, (1).63-69.
48. Benes H, Kurella B, Kummer J, Kazenwadel J, Selzer R, Kohnen R. Rapid onset of action of levodopa in restless legs syndrome: a double-blind, randomized, multicenter, crossover trial. Sleep 1999; 22(8): 1073-1081.
49. Collado-Seidel V, Kazenwadel J, Wetter TC, et al. A controlled study of additional sr-L-dopa in L-dopa-responsive restless legs syndrome with late-night symptoms. Neurology 1999 ; 52(2): 285-90.
50. Walters AS, Mandelbaum DE, Lewin DS, Kugler S, England SJ, Miller M. Dopaminergic therapy in children with restless legs/periodic limb movements in sleep and ADHD. Dopaminergic Therapy Study Group. Pediatric Neurology 2000; 22(3): 182-86.
51. Coldwell MC, Boyfield I, Brown T, Hagan JJ, Middlemiss DN. Comparison of the functional potencies of ropinirole and other dopamine receptor agonists at human D2 (long), D3 and D4. 4 receptors expressed in Chinese hamster ovary cells. Br J Pharmacol 1999; 127, (7): 1696-1702.
52. Standaert D, Young A. Treatment of central nervous system degenerative disorder. In: Hardman J, Limbird L, Editors. The Pharmacologic Basis of Therapeutics. 10th ed. New York: McGraw-Hill- 2001: 549-568.
53. Markstein R. Dopamine receptor profile of co-dergocrine (Hydergine) and its components. Eur J Pharmacol 1982; 86, (2): 145-155.
54. Silber MH, Shepard JW, Wisbey HA. Pergolide in the management of restless legs syndrome: an extended study. Sleep 1997; 20, (10): 878-82.
55. Staedt J, Wassmuth F, Ziemann U, Hajak G, Ruther E, and Stoppe G. Pergolide: treatment of choice in restless legs syndrome (RLS) and nocturnal myoclonus syndrome (NMS). A double-blind randomized crossover trial of pergolide versus L-Dopa. Journal of Neural Transmission 1997; 104(4-5): 461-8.
56. Wetter TC, Stiasny K, Winkelmann J, et al. A randomized controlled study of pergolide in patients with restless legs syndrome [see comments]. Neurology 1999; 52(5): 944-50.
57. Earley CJ, Yaffee JB, Allen RP. Randomized, double-blind, placebo-controlled trial of pergolide in restless legs syndrome. Neurology 1998; 51(6): 1599-602.
58. Pieta J, Millar T, Zacharias J, Fine A, Kryger M. Effect of pergolide on restless legs and leg movements in sleep in uremic patients. Sleep 1998; 21(6): 617-22.
59. Noel S, Korri H, Vanderheyden JE. Low dosage of pergolide in the treatment of restless legs syndrome [letter]. Acta Neurologica Belgica 1998; 98(1): 52-3.
60. Staedt J, Hunerjager H, Ruther E, Stoppe G. Pergolide: treatment of choice in Restless Legs Syndrome (RLS) and Nocturnal Myoclonus Syndrome (NMS). Longterm follow up on pergolide. Short communication. Journal of Neural Transmission (Budapest). 1998a; 105(2-3).
61. Stiasny K, Wetter TC, Winkelmann J, et al. Long-term effects of pergolide in the treatment of restless legs syndrome. Neurology 2001; 56(10): 1399-402.
62. Danoff SK, Grasso ME, Terry PB, Flynn JA, Pleuropulmonary disease due to pergolide use for restless legs syndrome. Chest 2001 Jul: 120 (1): 313-316.
63. Pritchett AM, Morrison JF, Edwards WD. Valvular heart disease in patients taking pergolide. (comment) Mayo Clinic Proceedings 2002 Dec; 77 (12):1280-1286.
64. Montplaisir J, Nicolas A, Denesle R, Gomez-Mancilla B. Restless legs syndrome improved by pramipexole: a double-blind randomized trial. Neurology 1999; 52(5): 938-43.
65. Lin SC, Kaplan J, Burger CD, Fredrickson PA. Effect of pramipexole in treatment of resistant restless legs syndrome. Mayo Clinic Proceedings 1998; 73(6): 497-500.
66. Montplaisir J, Denesle R, Petit D. Pramipexole in the treatment of restless legs syndrome: a follow-up study. Eur J Neurol 2000 May; 7 Suppl 1: 127-31.
67. Stiasny K, Moller JC, Oertel WH. Safety of pramipexole in patients with restless legs syndrome. Neurology 2000; 55(10): 1589-90.
68. Saletu B, Gruber G, Saletu M, et al. Sleep laboratory studies in restless legs syndrome patients as compared with normals and acute effects of ropinirole. 1. Findings on objective and subjective sleep and awakening quality. Neuropsychobiology 2000; 41(4): 181-9.
69. Saletu M, Anderer P, Saletu B, et al. Sleep laboratory studies in restless legs syndrome patients as compared with normals and acute effects of ropinirole. 2. Findings on periodic leg movements, arousals and respiratory variables. Neuropsychobiology 2000; 41(4): 190-9.
70. Estivill E, de la Fuente V. [The efficacy of ropinirole in the treatment of chronic insomnia secondary to restless legs syndrome: polysomnography data]. [Spanish]. Revista De Neurologia 1999a Nov 1-1999a; 29(9): 805-7.
71. Estivill E. de la Fuente V. [The use of ropinirol as a treatment for restless leg syndrome]. [Spanish]. Revista De Neurologia 1999b May 16-1999b May 31; 28(10):962-3.
72. Galvez-Jimenez N, Khan T. Ropinirole and restless legs syndrome [letter; comment]. Movement Disorders 14[5], 890-2. 1999 Sep.
73. Inoue Y, Mitani H, Nanba K, Kawahara R. Treatment of periodic leg movement disorder and restless leg syndrome with talipexole. Psychiatry & Clinical Neurosciences 1999; 53(2): 283-5.
74. Stiasny K, Robbecke J, Schuler P, Oertel WH. Treatment of idiopathic restless legs syndrome (RLS) with the D2-agonist cabergoline—an open clinical trial. Sleep 2000; May 1, 23(3): 349-54.
75. Evidente VG. Piribedil for restless legs syndrome: a pilot study. Mov Disord 2001;16(3):579-581.
76. Tergau F, Wischer S, Wolf C, Paulus W. Treatment of restless legs syndrome with the dopamine agonist alpha- dihydroergocryptine. Mov Disord 2001; 16(4): 731-5.
77. Evidente VG, Adler CH, Caviness JN, Hentz JG, Gwinn-Hardy K. Amantadine is beneficial in restless legs syndrome. Movement Disorders 2000; 15(2): 324-7.
78. Grewal M, Hawa R and Shapiro C. Treatment of periodic limb movements in sleep with selegiline HCL. Movement disorders 2002; 17, (2): 398-401.
79. Botez MI, Lambert B. Folate deficiency and restless legs syndrome in pregnancy (letter). NEJM 1977; 297:670.
80. McParland P, Pearce JM. Restless legs syndrome in pregnancy- case reports. Clin Exp Obst Gyn 1990; 17: 5-6.
81. Mendelson WB, Are periodic leg movements associated with clinical sleep disturbance? (see comments) Sleep 1996; 19(3): 219-23.
82. Karadeniz D, Ondze B, Besset A, Billiard M. Are periodic leg movements during sleep (PLMS) responsible for sleep disruption in insomnia patients? European Journal of Neurology 2000; 7(3): 331-6.
83. The International Restless Legs Syndrome Study Group. The International Restless Legs Syndrome Study Group rating scale for Restless Legs Syndrome. Sleep Medicine 2002; 4(2): 121-132.
84. Hening WA, Youssef E, Wagner ML, Walters AS . The use of actigraphically determined activity ratios to measure the presence of excessive motor activity in the Restless Legs Syndrome. Sleep 2001; Supplement (Abstract): A356.
85. Gorny S, Allen R, Krausman D, Earley C. Accuracy of the PAM RL system for automated detectionof periodic leg movements (Abstract). Sleep 1998; 21, (Supp): S183.
86. Pollak CP, Stokes PE, Wagner DR. Direct comparison of two widely used activity recorders. Sleep 1998; 21(2): 207-12.
87. Reuter I, Ellis CM, Ray Chaudhuri K. Nocturnal subcutaneous apomorphine infusion in Parkinson's disease and restless legs syndrome. Acta Neurologica Scandinavica 1999 ; 100(3): 163-7.
88. Jakobsson B. and Ruuth K. Successful treatment of restless legs syndrome with an implanted pump for intrathecal drug delivery. Acta Anaesthesiol Scand 2002; 46(1): 114-7.

Table 3 - Levodopa

Reference/ Evidence Level	Study design	Agent/Duration/ Administration protocol	Diagnostic criteria / Inclusion Criteria	Sample size (completed) / age range (mean age) / gender of subjects	Adverse Effects	Outcome measures / Results	Conclusions	Comments
48 / Benes Level 1	DB, Randomized, cross-over with placebo control	L-dopa with benserazide vs. placebo/ two 4-week phases/ Initially 1 capsule (100/25 or placebo); could be increased during the first 3 weeks to maximum of 2 capsules if RLS persists. 27 subject went to 200/50 and 28 subjects went to 2 placebo	IRLSSG/ a) RLS stable for 2 weeks with screening; b) sleep disruption shown by sleep latency > 30 min or sleep efficacy ≤ 85%; c) PLM > 5/hr (PSG); Exclusion: sleep apnea	41 (32) / 25-75 / 19F, 13M	Self reported only, side effects with L-dopa: , worsening RLS (2), reduced sexual drive (1), diarrhea(2), nausea(1), muscle weakness (1). There were 25 adverse events reported while on placebo	Comparisons were made between drug and placebo phases. PLM: Actigraphy on 3 consecutive nights/decreased PLMI overall* , in the first half* but not in the second half of sleep ; decreased TIB without PLMS*/ SBJ: questionaires on QOL, sleep latency and duration/all improved*	L-dopa significantly reduced PLMS and improved the subjects' reported QOL including sleep	Patients studied required demonstrated sleep difficulties and PLMS; 4 subject were on dialysis
49 / Collado-Seidel Level 1	DB, Randomized, cross-over with placebo control	4 weeks added drug – 4 weeks placebo/ SR 100/25 or 200/50, 1 hr before bed. (pt determined dose based on sleep quality) Mean SR dosage at end of drug period: 142 mg L-DOPA (24 subjects on SR and 28 on placebo increased to 2 capsules); regular release 100mg in 23, 200 mg in 7 patients	IRLSSG/ a) PLMAI >5 by PSG OR SE<85% OR Sleep latency >25 min AND b) improvement in RLS first half of night with standard levodopa AND c) ≥ 2 awakenings, > 20 min or 1 awakening > 1hour in 2nd half of the night AND d) > 30% increase in PLMI 2nd half of the night by actigraphy.	37 (30) / 58 ±10 / 11M, 19F	Dry mouth (3); nightmares (2); others (1); depression (4); 26.7% augmentation w/ treatment, 16.7% augmentation w/ placebo.	Improvement determined by measuring drug versus placebo phases. PLM: Actigraphic assessment of PLMS using ICSD criteria/ improvement in PLMI*, TIB without leg movements* SBJ: Analog scales for sleep quality; RLS severity (1-10) and QOL (1-7)/ Improvement in sleep quality*; RLS severity at night*, Gen. well-being*; Only QOL score improvement was "weariness"*	Combination of regular and SR L-Dopa was effective, but some augmentation developed. SR effects lasted 3-7 hrs;	All patients were documented failures on RR L-DOPA only in 2nd half of night and additionally had documented poor sleep generally with PLM causing arousal. Statistics done comparing drug and placebo phases.

Reference/ Evidence Level	Study design	Agent/Duration/ Administration protocol	Diagnostic criteria / Inclusion Criteria	Sample size (completed) / age range (mean age) / gender of subjects	Adverse Effects	Outcome measures / Results	Conclusions	Comments
50 / Walters Level 5	Unblinded clinical series, No control	SR carbidopa/ 5 with L-DOPA 25/100; 2 with Pergolide/ 6 months study/ 4 doses daily (including QHS), variable, 300-600 mg L-dopa daily, 0.4-1.0 mg Pergolide daily	IRLSSG/ a) PLMI by PSG >5 b) ADHD by DSM-IV criteria c) history of either RLS or PLMS	8 (7) / 4-18 / 6M, 1F	None were noted	Sleep: PSG/No significant changes/ PLM: PSG/ decreased total PLM*/ SBJ: a) global RLS-subjective/in 6 with history of RLS, symptoms all improved b) ADHD: Connors scale and psychological testing for ADHD with 5 pt scale/ reduced inattention*, oppositional-defiant behavior score*, child behavior checklist*, and visual memory*.	ADHD symptoms as well as PLMS were improved by dopaminergic therapy in an open label trial; RLS subjective benefit was also noted in those with RLS	Study restricted to children with ADHD and sleep problems . 5 subjects were failures on stimulant drugs. Five patients continued to receive TX for 3 years with reported continued subjective improvement.

* = statistically significant (P< .05 or better)

Table 4 - Dopamine Agonists

Reference/ Evidence Level	Study design	Agent/ Duration/ Administration protocol	Diagnostic criteria / Inclusion Criteria	Sample size (completed) / age range (mean age) / gender of subjects	Adverse Effects	Outcome measures / Results	Conclusions	Comments
37/ Becker Level 5	Unblinded, clinical series	Pramipexole/ at least 4 weeks variable dose: 0.125 – 2.5 mg (mean: 0.73 mg), could be one (2 hr before bedtime) to 3 doses depending on symptom timing	IRLSSG/ moderate to severe RLS, by clinical assessment; All had 1-8 (mean 3.4) prior TX for RLS including; 19 with levodopa	23 (23) / 31-87 (mean 55.2)/ 11 F, 12 M	Clinical self-report: sleepiness, fluid retention, groggy by day, mood elevation, worse RLS. At least 6 (26%) with daytime sleepiness –4 resolved with dose adjustment.	SBJ: a) 6 question rating scale (0 – 24)/ decrease from mean of 17 to 7.8*/ b) patient preference of drug/ 17 of 23 preferred drug	Pramipexole effective in treatment of RLS.	No indication of when in study previous TX was stopped or duration of this treatment, except it was more than 4 weeks; patients may have been having Sx augmentation from prior use of levodopa. Limited report of adverse effects, but sleepiness appeared to be a common problem.
38 / Ondo Level 5	Unblinded clinical series, no control	Ropinirole/ 2-7 months (mean = 3.9 months)/ 0.25 – 4.0 mg per day upward titrated to effective dose, variable nighttime doses	IRLSSG / Currently in Treatment for RLS	16 (13) / 39-75 / gender not reported	Impressionistic: Pan -corporeal - rash & lower extreme edema in (1); sedation, nausea, fatigue, dyspnea, shoulder pain, acne, hypomania, all in single cases	SBJ: a) abbreviated IRLS/ total score declined from 18.6 → 7. 7*; b) 10 reported marked improvement, 3 moderate improvement. 10 of 13 continuing on medication preferred this to prior treatment.	Ropinirole is effective enough to justify larger, double-blinded, controlled study.	Patients already on RLS treatment. Patients included those with neuropathic pain. Patients unique to those in movement disorder clinic. Patients selected from population presenting to a movement disorder clinic.

Reference/ Evidence Level	Study design	Agent/ Duration/ Administration protocol	Diagnostic criteria / Inclusion Criteria	Sample size (completed) / age range (mean age) / gender of subjects	Adverse Effects	Outcome measures / Results	Conclusions	Comments
50 / Walters Level 5	Unblinded clinical series, no control	SR carbidopa/ 5 with L-DOPA 25/100; 2 with Pergolide/ 6 months study/ 4 doses daily (including QHS), variable, 300-600 mg L-dopa daily, 0.4-1.0 mg Pergolide daily	IRLSSG/ a) PLMI by PSG >5 b) ADHD by DSM-IV criteria c) history of either RLS or PLMS	8 (7) / 4-18 / 6M, 1F	None were noted	Sleep: PSG/No significant changes/ PLM: PSG/ decreased total PLM*/ SBJ: a) global RLS-subjective/in 6 with history of RLS, symptoms all improved b) ADHD: Connors scale and psychological testing for ADHD with 5 pt scale/ reduced inattention*, oppositional-defiant behavior score*, child behavior checklist*, and visual memory*.	ADHD symptoms as well as PLMS were improved by dopaminergic therapy in an open label trial; RLS subjective benefit was also noted in those with RLS	Study restricted to children with ADHD and sleep problems . 5 subjects were failures on stimulant drugs. Five patients continued to receive TX for 3 years with reported continued subjective improvement.

Reference/ Evidence Level	Study design	Agent/ Duration/ Administration protocol	Diagnostic criteria / Inclusion Criteria	Sample size (completed) / age range (mean age) / gender of subjects	Adverse Effects	Outcome measures / Results	Conclusions	Comments
56 / Wetter Level 1	DB, randomized cross-over with placebo control	Pergolide/ 2 weeks or more/ self titration to maximum 0.75 mg 2 hrs before bedtime; mean – 0.51 mg; patients also took 3 doses daily domperidone throughout study	IRLSSG/ PLMI >5 on PSG, sleep latency >25 minutes, sleep efficiency < 85%, no significant organ dysfunction based on history and labs.	30 (28) / 28 – 70 (57.2±8.9) / 16F, 12M	Self reporting, On pergolide: nausea (12); headache (6); rhinitis (6); vomiting (5); abdomen pain (4); dizziness (4); abnormal vision (3) ; diarrhea (3); rash (3); dry mouth (2); vivid dreams (1). On placebo: headache (9); abdomen pain (7); constipation (4); nausea (3); rash (3).	All comparisons between drug and placebo grops. PLMS: PSG/ decreased PLMI* (in all sleep stages), PLMAI* Sleep: PSG/ increased TST*, SE*, stage 2%*, SWS%*, but also awakenings*; decreased wake time* SBJ: a) 5 point scale of sleep quality/improved*, b) sleep diary/improved sleep latency*,TST*, number awakenings*; c) 10 point symptom scales for RLS severity, urge to move/improvement at 3 time points*: bedtime, night, day; d) QOL scale (0-50)/ improved both measures*, life satisfaction, negative feelings e) Clinical global impression (7 point scale for illness severity, global change, therapeutic effect, side effects worse than benefit)/ all better on drug*	Pergolide given as single low-to-medium bedtime dose with domperidone is well tolerated and effectively treats sleep problems and waking symptoms of RLS	No adverse events were so severe as to lead to drop out from pergolide. 2 dropouts, one due to withdrawal of consent; second due to GI discomfort on placebo. All patients took domperidone to reduce peripheral side effects of pergolide. 10 patients without prior treatment, 17 with levodopa in past year.

Reference/ Evidence Level	Study design	Agent/ Duration/ Administration protocol	Diagnostic criteria / Inclusion Criteria	Sample size (completed) / age range (mean age) / gender of subjects	Adverse Effects	Outcome measures / Results	Conclusions	Comments
57/ Earley Level 2	DB, randomized, parallel design with placebo control	Pergolide/ 5 days stable after titration, (14-18 days)/ variable, 0.05 mg, titrated by patient up to max. of 0.3 mg at dinner & 0.35 mg QHS over 14 days	IRLSSG/ Required baseline PSG with ≥ 15 PLMI	16 (15) / 43-80 / 8F, 8M	Monitored Weekly: 4 each with stomach pain, constipation, ↑ dreaming on drug; 2 each with itchy eyes and taste on placebo. No rebound or augmentation noted.	a) PLM: by PSG/ 70% improvement in PLMI*/ b) Sleep: by PSG/ 23% improvement in sleep efficiency*. c) SBJ: global improvement (0 – 100 %), hrs/day with RLS after noon until 1 hr of sleep or 1 hr lying still w/o RLS/ mean 74% decrease in number of hrs per day with RLS*	Pergolide is an effective agent in treatment of RLS in short-term.	
58 / Pieta Level 2	DB, randomized cross-over with placebo control	Pergolide/ 10 nights/ began at 0.05 mg and increased by 0.05 mg every 2nd night to a final dose of 0.25 mg. 1 week washout for cross-over.	IRLSSG/ a) PLM by actigraphy and PSG b) severe RLS patients on hemo- or perotoneal dialysis w/ sleep disturbance or daytime sleepiness and willingness to stop hypnotic and dopaminergic meds	14 (8) / (42.5) / 5F, 3M	Nausea and nightmares (2), and enuresis (1)	PLM/Actigraphy -- % of time in bed occupied by movement and PSG – 5-fold increase of EMG activitiy over baseline with duration > 0.5 sec but < 30 seconds, interval > 1 sec apart/ decreased PLM only during the first hour in bed by actigraphy*; no decrease over the whole night by PSG Sleep: PSG/ no significant change in SE, TST, latency to persistent sleep SBJ: 5 pt scale rating sleep quality and severity of RLS/ 5 of 8 reported both improved	In uremic RLS, pergolide provided some subjective improvement but little objective improvement.	Severe patients with uremia were selected for the study. Two patients had sleep apnea as well. Non-standard PLM measurements were used. No statistics on subjective measures.

Reference/ Evidence Level	Study design	Agent/ Duration/ Administration protocol	Diagnostic criteria / Inclusion Criteria	Sample size (completed) / age range (mean age) / gender of subjects	Adverse Effects	Outcome measures / Results	Conclusions	Comments
59 / Noel Level 5	Unblinded clinical series, no control	Pergolide/ 2-13 months (mean 5.6)/ 0.1 mg – 0.3 mg daily, variable, start at 0.025 mg, increase by same dose every 2 days	IRLSSG	10 (7) / 20-73 / not stated	Impressionistic: Rash (1), nausea (1), orthostatic hypotension (1). No augmentation or rebound reported	SBJ: qualitative motor restlessness, leg discomfort, difficulty falling asleep, nocturnal awakenings. 7/10 tolerated drug; 6/7 same dose (0.1 – 0.3) with significant improvement over 2 – 9 months; 1/7 after 10 months needed increase in dose from 0.15 → 0.3 .	Pergolide is effective and well tolerated in mild RLS over several months (of responders, only 1 of 7 had RLS more than 1 year)	Relied on patient global impression, no formal scales or subjective measures and no statistics provided. Mild patients were included in the study; 4/10 without prior treatment.
60 / Staedt Level 5	Unblinded clinical series, no control	Pergolide and 3/8 also on 20 mg temazepam/ 517 ± 117 days/ variable dose -- 0.23 mg ± 0.104 mg	General clinical criteria	10 (8) / (58.2±5.4) / 4M, 4F completed	Dry nose (1), nausea (2), flatulence (2), TIA (1). Appears 3/8 had augmentation (occasional mild RLS on following afternoon)	PLM: PSG/ decreased PLMS cluster time* Sleep: PSG/ increased SWS*, REM sleep*, TST*, TIB* SBJ: RLS All patients reported "complete RLS relief"	Authors recommend Pergolide as first line agent, adding 30 mg domperidone during first week.	Unconventional PLM measure (cluster time) This is an open extension of a previous reported crossover trial. Patients had RLS for 4.2 ± 2.9 yrs. Information on study use of domperidone not clear.
61 / Stiasny Level 5	Unblinded, long term follow-up study	Pergolide/ 426.4 ± 92.3 days/ variable, 'lowest effective dose': at measurement, 0.37 ± 0.15 mg; domperidone given as needed for nausea (13 of 22 subjects)	IRLSSG and ICSD/ Patients were in prior DB, PC study of pergolide	28 (22) / 28-70 (57.2 ± 8.9) / 16F, 12M	In those who completed study: Nausea (9= 41%), nasal congestion (9= 41%), very mild augmentation (6= 27%). 5 of 6 dropouts also had side effects contributing to withdrawal.	Results at last follow-up compared to baseline before earlier study. PLMS: PSG/ decreased PLMI*/ Sleep: PSG/ improved SE*/ SBJ: sleep questionnaire, QOL questionnaire, sleep diary, RLS severity scale/ improved RLS measures* and SE*, TST*	This open label follow-up study shows continued benefit of pergolide. Nausea, nasal congestion, and very mild augmentation were common side effects.	78.6 % remained on pergolide long term. 6 dropped out, 5 with side effects, 1 also with loss of efficacy; 1 decided not to take more meds. Subjective scales not validated.

Reference/ Evidence Level	Study design	Agent/ Duration/ Administration protocol	Diagnostic criteria / Inclusion Criteria	Sample size (completed) / age range (mean age) / gender of subjects	Adverse Effects	Outcome measures / Results	Conclusions	Comments
64 / Montplaisir Level 2	DB, randomized cross-over with placebo control	Pramipexole/ 4 weeks/ taken 1 hour before bedtime; wk 1= 0.375 mg, wk 2= 0.75 mg, wk 3= 1.5 mg, but decrease to previous dose if persistent side effects	IRLSSG/ sleep onset or maintenance insomnia > 3 nights/ week for at least 1 year	11 (10) / 30-61 (49.3±11.5) / 5F, 5M completed	GI side effects (9), dizziness (4), daytime fatigue (3); all mild and usually resolved with time or dosage decrease	PLM: PSG/ decrease of total PLMS*, PLMI*, PLMAI*, PLMW index*/ SBJ: rated RLS on a 0-3 scale, daily for 1 week prior to each of the 4 recording sessions / decrease: severity of RLS*,	Pramipexole was effective in treating sensory and motor symptoms of idiopathic RLS.	
65 / Lin Level 5	Unblinded clinical series, no control	Pramipexole/ 2-3 months/ final dose 0.125 mg – 0.5 mg/day (mean 0.3 mg), one dose daily 8 pm or 2 hrs before bed.	ICSD/ prior Tx failure with benzodiazepines, opiods, levodopa or pergolide. Reemergence of RLS after initial successful dopaminergic TX All had prior Levodopa TX	16 (15)/ 36-78/ gender not reported	Number of patients checking items from a list of common side effects – stiffness & fatigue, (5 or 33%) sleepiness (4 or 27%), headache, insomnia, involuntary movement, & pain (3 or 20%) Depression, dreams, infection, light-headedness, & tremor (1 or 7%)	SBJ: 3 VAS (-4 to +4: much worse to much better) for patient subjective improvement/ mean scores: leg restlessness (2.5); insomnia (3.0); involuntary leg movements (3.0) corresponding to improvement in 12, 11, and 10 patients respectively	Pramipexole can be considered an effective agent in the treatment of RLS even after failure of other therapies, including other dopaminergic therapies.	4 patients had fibromyalgia. Side effect report based on current symptoms on drug; not change from prior TX. Outcome measures based on change and retrospective comparison. Because information not presented on end of prior TX, baseline condition might have been affected by drug withdrawal and augmentation, thereby enhancing the outcome measures. One patient dropped out due to increased insomnia.

Reference/ Evidence Level	Study design	Agent/ Duration/ Administration protocol	Diagnostic criteria / Inclusion Criteria	Sample size (completed) / age range (mean age) / gender of subjects	Adverse Effects	Outcome measures / Results	Conclusions	Comments
66 / Montplaisir Level 5	Unblinded clinical series, no control	Pramipexole/ 7.8 months ± 3 months/ initial dose 0.25 mg 1 hour before bedtime, 0.25 mg/week- increase by 0.25 mg as needed, at end, mean dose, 0.5 mg (0.25 - 0.75 mg range)	IRLSSG assumed	7 (7)/ 43-62 (55.4±8.1)/ 3F, 4M	Self-report of daytime sleepiness (1) and nausea (1).	Assessment 1 week before TX, separate to 1month after TX started; and at last month (mean 7.8 months) SBJ: Structured questionnaires and RLS global symptoms 0-3 (none to severe) / significantly decreased leg restlessness at bedtime* and nighttime* but not at daytime or evening at both first month and last month time points.	Continued benefit for RLS subjective leg restlessness after several months of use.	Patients were selected from a previous treatment population and had already experienced a positive effect of medication. Long-term study
67 / Stiasny Level 5	Unblinded clinical series, no control	Pramipexole/ duration not specified/ mean dosage 0.37 mg ± 0.17 (range 0.125- 0.75 mg)	Dx Criteria not specified/ all patients in an outpatient clinic treated with pramipexole for RLS	24 (24) / 46-79 (62.1±7.6) / 15F, 9M	Dry nose (1), constipation (1), dry mouth (1), arrhythmias (1),	SBJ: a) Sleepiness symptom questionnaire and phone interview F/U if sleepy/ No sudden, unexpected sleep attacks b) Epworth sleepiness scale (ESS)/ mean ESS score was normal: 6.5±4.6 c) 7 point scales on efficacy of current treatment and RLS severity / 22/24 were satisfied with current treatment and 23/24 noted RLS to be improved	There is no significant risk for sudden unexpected sleep episodes in RLS patients treated with pramipexole The majority noted RLS to be improved and were satisfied with treatment.	Measuresments only made while patients were on therapy for unknown duration; no statistics and no objective measures

Reference/ Evidence Level	Study design	Agent/ Duration/ Administration protocol	Diagnostic criteria / Inclusion Criteria	Sample size (completed) / age range (mean age) / gender of subjects	Adverse Effects	Outcome measures / Results	Conclusions	Comments
68 / Saletu Level 3	Subjects blind to treatment non-randomized crossover with placebo control	Ropinirole/ 3 consecutive nights: adaptation (1st night);placebo (2nd night) and drug (3rd night)/ 0.25mg at 19:00 and 0.25 mg at 22:00 hrs given on the 3rd night	IRLSSG and ICSD/ a) PLMS > 5/hr by PSG b) stable for 2 weeks before study.	12(12) / 35-74 (57.2±11.7) / 8F, 4M	Not reported	Results on drug night compared to placebo. Sleep: PSG/ increased TST, SE, % Stage 2, but (worsened) stage shifts / SBJ Sleep/Wake Quality scales/ decreased somatic complaints*, PSYCHO: tests of alertness and motor function/ improved fine motor activity* and decreased error rates*	A single nighttime dose of .5mg resulted overall in very limited improvements in sleep architecture, and in measures of awakening quality	Only two 0.25 mg doses of ropinirole or 2 placebo tablets for a single night. Unclear if patients had previous treatment. 57 statistical comparisons were made as regards to sleep (PSG), subjective sleep/wake quality, objective wake quality, and psychophysiological measures. No corrections were applied for multiple comparisons.
69 / Saletu Level 3	Subjects blind to treatment non-randomized crossover with placebo control	Ropinirole/ 1 night/ 0.25 mg doses at 1900 and 2230	IRLSSG and ICSD/a) insomnia or EDS, b) PLMS index of > 5/hr and 18-65 yrs	12 (12) / 35-74 (57.2 ±11.7) / 8F, 4M	None reported	PLM: PSG, 1- 20 sec duration, ≥ 5 movements with interval between 4-90 seconds, amplitude 3X baseline/ reduced PLMI*, PLMAI*	Ropinirole was beneficial and well tolerated.	Acute study. Non-standard definition for PLM. Patients had sleep complaints and documented PLMS.

Reference/ Evidence Level	Study design	Agent/ Duration/ Administration protocol	Diagnostic criteria / Inclusion Criteria	Sample size (completed) / age range (mean age) / gender of subjects	Adverse Effects	Outcome measures / Results	Conclusions	Comments
70 / Estivill Level 5	Unblinded clinical series, no control	Ropinirole/ 30 days/ 7 day washout before test, studied 2 nights (with or without 0.25 mg fixed dose) before and after 30 days of daily treatment	IRLSSG/ a) PLM index >5 b) 5 yrs insomnia	5 (5) / (53±9) / 3F, 2M	Not Reported	Compared nights with and without meds (night 1 to 0, night 31 to 30) PLM: PSG/ decreased total PLMS* both test nights with meds Sleep: PSG/ increased TST*, SE* both test nights with meds SBJ: sleep quality questionnaire (Spiegel)*, improved on med nights	Ropinirole benefits both sleep and PLMS in longstanding RLS with Insomnia.	Small open label study with objective measures; patients all had PLMS and sleep complaint One patient increased dose to 7.5 mg
71 / Estivill Level 5	Unblinded clinical series, no control	Ropinirole / 12 months/ 0.25 mg 15 mins before bed, fixed, 5 patients given additional psychoactive sleep meds after 1st month if sleep not better	IRLSSG/ 5 yr history of RLS without successful treatment and complaints of insomnia.	15 (15) / (43±7) / 8F, 7M	Not Reported	SBJ: sleep quality questionnaire (Spiegel) and RLS symptom questinnaire/ improved from all having bad sleep at baseline to 10 having good sleep at 7 days, 1 month to all having good sleep at 3, 6, 12 months with added sleep meds; all reported RLS symptoms gone from 7 day assessment	Ropinirole benefits refractory RLS patients from first night with benefits lasting 12 months. Patients may require, however, additional medications to improve insomnia	Only SBJ measures. Patients were medication failures, level of previous medications not specified. After one month, results derived from combination therapy in 5 of 15 patients. No statistics provided.
72 / Galvez-Jimenez Level 5	Unblinded clinical series, no control	Ropinirole/ average of 9.8 months (range 2-19) / variable dose, mean daily dose 2.8 mg (range 0.25-6 mg)	IRLSSG/ patients failed standard RLS treatment of 2 or more RLS drugs	8 (8) / 60-77 (67) / 6F, 2M	None reported	SBJ: IRLSSG questionnaire, 0-24 scale/ RLS symptom severity decreased by an average of 72% on ropinirole	Ropinirole was beneficial in patients with RLS who had previously failed other treatment.	

Reference/ Evidence Level	Study design	Agent/ Duration/ Administration protocol	Diagnostic criteria / Inclusion Criteria	Sample size (completed) / age range (mean age) / gender of subjects	Adverse Effects	Outcome measures / Results	Conclusions	Comments
73 / Inoue Level 5	Unblinded clinical series, no control	Talipexole/ 4 weeks/ 0.4 or 0.8 mg bedtime dose	General clinical criteria	5(5) / (51.4)/ gender not reported	One subject reported sleepiness in the morning.	PLM: PSG/ decreased PLMS count for each third of night: 87(21.2) to 25.6(4.3); 53.8(8.4) to 16.2(2.9); 54.6(16.7) to 15(6.7) Sleep: PSG/ no values were given; authors state a "significant increase in both sleep efficacy and % stage 2 and a significant decrease in % stage 1, % stage awake, number of arousals". SBJ: scales with 4 levels, none to considerable symptoms (0 to 3)/ no values were given but the authors report significant improvement in ratings of PLMD and sleep	Drug decreases PLMS and improved RLS symptoms and sleep architecture.	Small population with ill-defined criteria for RLS. 2 subjects had uremia. The actual data and statistical values for improved symptoms and sleep architecture were not given.

Reference/ Evidence Level	Study design	Agent/ Duration/ Administration protocol	Diagnostic criteria / Inclusion Criteria	Sample size (completed) / age range (mean age) / gender of subjects	Adverse Effects	Outcome measures / Results	Conclusions	Comments
74 / Stiasny Level 5	Unblinded clinical series, no control	Cabergoline/ once a day for up to 12 weeks/ variable titration by patient (mean dosage 2.1 mg; range 1 to 4)	IRLSSG/ a) PLMI (PSG) > 5 b)sleep efficiency < 85% Exclusion; apnea/hyponea >5/hr	9(9) / 38-64 (54.1± 8.7) / 7F, 2M	Not reported	PLM: PSG/PLMW index*, PLMI*, PLMAI* Sleep: PSG/ increased TST* , SE* SBJ: 10 point symptom scale (severity: none to very strong), Hamburger VAS for QOL/ averaged symptom ratings improved at sleep onset*, during the night * and day*; Hamburger VAS improved for 4 of 5 items listed	Cabergoline is effective and well tolerated in restless legs syndrome patients with severe RLS and those who developed augmentation under levodopa therapy.	7 of 9 Subjects had augmentation on L-dopa, Five of nine subjects were still on levodopa on entering trial, including baseline assessment and then withdrawn during the cabergoline titraton. Rating scales not validated. No statistics given for results on Hamburger VAS.
75 / Evidente Level 5	Unblinded clinical series, no control	Piribedil/ 0 to 15 months/ variable, begun at 50 mg at bedtime and increased by 50 mg every 5-7 days until benefit or intolerable of side effects. 25-350 mg at testing (mean 120). Domperidone (10-20 mg) given 30 mins before every dose of piribedil.	IRLSSG/ idiopathic RLS (3), associated neuropathy (5), uremia + neuropathy (1), or Parkinson's disease (4).	13 (13) / 39-87 (66) / 6F, 7M	Sleepiness and mental clouding (1), chest pain and palpitations (1); none had augmentation.	SBJ: 2 RLS severity scales/ RLS score decreased from 9.97 to 2.62*	Piribedil was effective for RLS	Patients with neuropathy responded as well as the others.

Reference/ Evidence Level	Study design	Agent/ Duration/ Administration protocol	Diagnostic criteria / Inclusion Criteria	Sample size (completed) / age range (mean age) / gender of subjects	Adverse Effects	Outcome measures / Results	Conclusions	Comments
76 / Tergau Level 5	Unblinded clinical series, no control	Alpha-DHEC/ 4 weeks after one week off all meds/ 5 mg at bed for 4 days, 10 mg qhs for 3 days, then individual titration BID if necessary, maximum of 60 mg/day; average dose was 23.1 ± 8.6 mg	IRLSSG	16 (15) / 40-72 (57) / 10F, 6M	Self report and exam The commonest were nausea (6); abdomen pain (3); vomiting (1). 5 patients needed domperidone for side effects.	Comparison of baseline (drug free week) to final. SBJ: 1 -- 4 VAS, a) overall complaint, b) parasthesia, c) motor restlessness, d) involuntary movement. 2 -- Estimation of sleep duration, latency, number of awakenings/ All VAS, estimated sleep duration, and latency improved*, but not estimated awakenings.	DHEC reduced all symptoms compared to baseline. Adverse effects, mostly GI, can be managed, no augmentation noted.	No data is given as to what Tx doses exist prior to study. Used non-validated , unique subjective measures. Used rank test for statistics. 11 patients elected to continue DHEC monotherapy at end of study.

* = statistically significant (P < .05 or better)

Table 5 - Other Dopaminergic Agents

Reference/ Evidence Level	Study design	Agent; Duration; Administration protocol	Diagnostic criteria / Inclusion Criteria	Sample size (completed) / age range (mean age) / gender of subjects	Adverse Effects	Outcome measures / Results	Conclusions	Comments
77 / Evidente Level 5	Unblinded clinical series, No control	Amantadine/ < 1 month to 13+months/ increase by 100 mg every 3-5 days, effective daily dose range: 100-300 mg; Mean 227 mg/day. Dose time matched to symptom occurrence, night only or day and night.	Diagnostic criteria not stated	21/ 46-84 (mean 70±9)/ not stated	Self reported: drowsiness (3), fatigue (2), insomnia (2), dry mouth (1), leg edema (1), weight loss (1)	SBJ: RLS rating scale from 0-10, decreased from 9.8(0.6) to 6.6(3.8)*(Wilcoxin's signed rank test). RLS global improvement in responders (0 – 100%= (complete resolution of Sx). Mean 69% (range 25 – 100%) .	Half of patients are benefited acutely by amantadine as an add-on medication with long-term benefit in a minority.	Rating scale not validated but changes in rating scale correlated with patient global rating of improvement (r=0.97). Results reported only for responders. Subjects did not discontinue prior treatment, but were held on constant doses during study. No augmentation/ rebound in 8 responders continuing on treatment for 6+ months. 3 responders stopped treatment: 2 for adverse effects; 1, loss of benefit.

Reference/ Evidence Level	Study design	Agent; Duration; Administration protocol	Diagnostic criteria / Inclusion Criteria	Sample size (completed) / age range (mean age) / gender of subjects	Adverse Effects	Outcome measures / Results	Conclusions	Comments
78 / Grewal Level 5	Unblinded, clinical series, retrospective selection	Selegiline/ variable 6 wk titration to optimal dose 3 to 7 months after starting drug; med taken twice a day up to 30 mg maximum	PLMS, standard criteria, with sleep complaint to establish PLMD/ PSG study showing PLMI >5 and excluding other sleep disorders, including RLS as well as neurological disorders	31 (31) /mean age (55.6)/ 18 M, 13 F	None reported, but sleep measures deteriorated	PLMS: PSG/ PLMI* (mean decrease 35.6 to 14.5). Sleep: PSG/ mean sleep latency increased 25.6 to 35.3 minutes; mean sleep efficiency decreased 80.2 to 76.3%;	Selegiline useful and well tolerated in PLMD patients who have daytime sleepiness.	Patients selected from unknown number screened. Since sleep was actually worse after TX, medication may be acting simply as daytime stimulant. Patients excluded if on other TX active on RLS/PLMS or caffeine

* statistically significant (P < .05 or better)