PRACTICE PARAMETER

Practice Parameters for the Dopaminergic Treatment of Restless Legs Syndrome and Periodic Limb Movement Disorder

An American Academy of Sleep Medicine Report

Standards of Practice Committee of the American Academy of Sleep Medicine

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Summary: Dopaminergic agents, particularly dopamine agonists, have been used with increasing frequency in the treatment of restless legs syndrome and periodic limb movement disorder. These evidence-based practice parameters are complementary to the Practice Parameters for the Treatment of Restless Legs Syndrome and Periodic Limb Movement Disorder, published in 1999.1 These practice parameters were developed by the Standards of Practice Committee and reviewed and approved by the Board of Directors of the American Academy of Sleep Medicine. Recommendations are based on the accompanying comprehensive review of the medical literature regarding the dopaminergic treatment of restless legs syndrome (RLS) and periodic limb movement disorder (PLMD), which was developed by a task force commissioned by the American Academy of Sleep Medicine. The following recommendations serve as a guide to the appropriate use of dopaminergic agents in the treatment of RLS and PLMD. Levodopa with decarboxylase inhibitor, and the dopaminergic agonists pergolide, pramipexole, and ropinirole are effective in the treatment of RLS and PLMD. Other dopamine agonists (talipexole, cabergoline, piribidel, and alpha-dihydroergocryptine) and the dopaminergic agents amantadine and selegiline may be effective in the treatment of RLS and PLMD, but the level of effectiveness of these medications is not currently established. Lastly, no specific recommendations can be made regarding dopaminergic treatment of children or pregnant women with RLS or PLMD.

Key Words: Dopaminergic agents, dopamine agonists, restless legs syndrome, periodic limb movement disorder

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INTRODUCTION

RESTLESS LEGS SYNDROME (RLS) AND PERIODIC LIMB MOVEMENT DISORDER (PLMD) HAVE PRIMARILY BEEN TREATED BY FOUR CLASSES OF MEDICATIONS: DOPAMINERGIC AGENTS, OPIOIDS, BENZODIAZEPINES, AND ANTICONVULSANTS. The previous practice parameter paper stated that, "dopaminergic agents are the best studied and most successful agents for treatment of RLS and PLMD."[1] Since the publication of the previous paper, dopaminergic agents, particularly dopamine agonists, have been the subject of increased study as therapy for RLS and PLMD. This article reports new evidence for the role of dopaminergic agents in the treatment of RLS and PLMD published since the first expert review, grades the evidence available, and supplements the 1999 practice parameters.

METHODS

On the basis of this review and noted references, the Standards of Practice Committee of the AASM, in conjunction with specialists and other interested parties, developed the recommendations included in this paper. In most cases, the conclusions are based on evidence from studies published in peer-reviewed journals that were evaluated as noted in the evidence tables of the companion review paper. However, when scientific data are absent, insufficient, or inconclusive, the recommendations are based upon consensus opinion. Those recommendations for which consensus opinion contributed to the recommendation are specifically indicated; otherwise consensus opinion was not used. The consensus opinion was based on review and discussion by the Standards of Practice Committee. The strength of each recommendation is based on the level of the evidence available or on consensus when evidence is lacking.

The Board of Directors of the AASM approved these recommendations. All authors of the accompanying review paper, members of Standards of Practice Committee, and the AASM Board of Directors completed detailed conflict-of-interest statements and were found to have none with regard to this subject.

These practice parameters define principles of practice that should meet the needs of most patients in most situations. These guidelines should not, however, be considered inclusive of all proper methods of care or exclusive of other methods of care reasonably directed toward obtaining the same results. The ultimate judgment regarding the propriety of any specific care must be made by the physician in light of the individual circumstances presented by the patient and the available diagnostic and treatment options. The current recommendations modify and replace previous recommendations[1], where applicable.

The AASM expects these guidelines to have a positive impact on professional behavior, patient outcomes, and possibly, health care costs. These practice parameters reflect the state of knowledge at the time of development and will be reviewed, updated, and revised, as new information becomes available. The articles entered in the evidence tables of the companion review paper were based on the Standards of Practice Committee's levels of evidence (Table 1) for evidentiary articles, which are used to support the strength of the recommendations (Table 2) in this

paper. Square-bracketed numbers in this paper refer to sections, tables, or references in the accompanying review paper. Other citations, noted by superscripted numbers, refer to the reference list at the end of this paper.

BACKGROUND

Recent work has resulted in several important findings related to the pathophysiology, epidemiology, and evaluation of RLS and PLMD. Several new studies suggest the involvement of the dopamine system [11-13] and depletion of iron stores [17-19] in RLS. PLM (periodic limb movement(s), [Table 2]) may be related to dopamine deficiency; it is more common in conditions with dopamine deficiency [22] and less common in conditions with dopamine excess [23]. Recent prevalence studies confirm the notion that RLS is common in populations of Northern and Western European extraction [24-28]; the prevalence may be lower in Asian populations [29,30]. PLMS (periodic limb movement(s) in sleep, [Table 2]) may be more common in younger groups than previously suspected, particularly in children with ADHD [31,32], and, although the high frequency of PLMS persists, the severity does not increase over time [33]. The International RLS rating scale, a subjective instrument used to assess RLS severity, has recently been validated in an international multi-center study [83], and has recently been used as a therapeutic outcome measure [36]. In addition, the suggested immobilization test (SIT) has been proposed as a supplementary method to assess the subjective and motor components of RLS [41]. Subtle respiratory disorders (e.g., upper airway resistance syndrome) may be responsible for the sleep complaints attributed to PLMD [8], and the excessive daytime somnolence associated with PLMS may not be due to leg movements themselves [42].

Levodopa was the dopaminergic agent most studied for RLS/PLMD treatment up to the time of the end date of the literature review for the prior practice parameter paper.[1] Since that time, other dopaminergic agents, especially dopamine agonists, have been the subject of increased study in the treatment of these disorders. This latter class of medication has been generally well tolerated; however, there have been reports of sudden, irresistible episodes of intense sleepiness ("sleep attacks") as an adverse effect with dopaminergic agents [43]. In particular, it had been reported that dopamine agonists may induce these sleep attacks in patients with Parkinson's disease; however, this sleepiness may occur with other treatments for Parkinson's disease [44,45], and the severity of the sleepiness may be different for this disease versus that of RLS [47].

The original practice parameter[1] emphasized the importance of limiting the pharmacologic treatment of RLS and/or PLMD to patients who meet specific diagnostic criteria, and the need for physicians to closely monitor the clinical response and adverse effects in individuals treated with medication. This is critical regardless of the medication used to treat RLS or PLMD. The accompanying paper reviews four different types of dopaminergic agents: levodopa, dopamine agonists, amantadine, and selegiline. The following recommendations reflect the evidence obtained from the current review, combined with the previous review[2] and practice guidelines[1].

Table 1—AASM Classification of Evidence

Recommendation Grades	Evidence Levels	Study Design
A	I	Large, well-designed, randomized and blinded controlled study with statistically significant conclusions on relevant variables
B	II	Smaller, well-designed, randomized and blinded controlled study with statistically significant conclusions on relevant variables
C	III	Well-designed, non-randomized prospective study with control group
C	IV	Well-designed, large prospective study with historical controls or careful attention to confounding effects or small prospective study with control group
C	V	Small prospective study or case series without control groups

Adapted from Sackett[3]

RECOMMENDATIONS

The following are additional or modified recommendations of the Standards of Practice Committee and the Board of Directors of the American Academy of Sleep Medicine, to supplement the previous practice parameter[1] . The classification of evidence was adapted from the suggestions of Sackett[3] (Table 1). Recommendations are given as standards, guidelines and options, as defined in Table 2. The readers are referred to the evidence tables and articles referenced in the review paper for guidance regarding dosing of medications that have been used in the treatment of RLS and PLMD.

1. Levodopa with decarboxylase inhibitor is effective in the treatment of RLS and PLMD. (Standard) [4.b; Table 3]

This recommendation adds evidence to the same recommendation of the previous practice parameter paper,[1] and is based on Level I, II, III, and V evidence for levodopa with decarboxylase inhibitor in the treatment of RLS and PLMD. A total of 21 studies (18 studies summarized in the prior practice parameter paper, 3 new studies) were used in the derivation of this practice parameter, attesting to the fact that up to now, this dopaminergic agent is the best studied as a treatment for RLS and PLMD. The main side effects complicating the use of this agent in clinical series are the high frequencies of RLS daytime augmentation (i.e., occurrence or worsening of daytime RLS symptoms with long-term medication usage, typically increased by higher doses) and early morning rebound of RLS symptoms, especially at higher dose levels.

2. The dopamine agonist pergolide is effective in the treatment of RLS and PLMD. (Standard) [4.c.ii; Table 4]

This recommendation adds evidence to the same recommendation of the previous practice parameter paper,[1] and is based on Level I, II, and V evidence for pergolide in the treatment of RLS and PLMD. In the largest of the clinical series [61] reviewed for this paper, 78.6% remained on pergolide long-term, despite adverse effects of nausea, congestion, and mild augmentation. In most cases, these adverse effects were either minor or could be adequately controlled; however, the development of pleuropulmonary fibrosis [62] or cardiac valvulopathy [63] has been reported in isolated case reports.

3. The dopamine agonist pramipexole is effective in the treatment of RLS and PLMD. (Guideline) [4.c.iii; Table 4]

This is a new recommendation, and it is based on Level II and V evidence. In the one Level II study [64], pramipexole was effective in relieving RLS sensorimotor symptoms by questionnaire assessment and reducing PLMS and PLMS-Waking index by polysomnogram. The four Level V studies [37,65,66,-67] showed subjective improvement in RLS

Table 2—AASM Levels of Recommendations

Term	Definition
Standard	This is a generally accepted patient-care strategy, which reflects a high degree of clinical certainty. The term standard generally implies the use of Level I Evidence, which directly addresses the clinical issue, or overwhelming Level II Evidence.
Guideline	This is a patient-care strategy, which reflects a moderate degree of clinical certainty. The term guideline implies the use of Level II Evidence or a consensus of Level III Evidence
Option	This is a patient-care strategy, which reflects uncertain clinical use. The term option implies either inconclusive or conflicting evidence or conflicting expert opinion.

Adapted from Eddy[4]

symptoms. The most common reported side effects in these studies were fluid retention/edema, daytime fatigue/sleepiness, gastrointestinal distress, insomnia/alertness, dizziness, and occasional augmentation of RLS.

4. The dopamine agonist ropinirole is effective in the treatment of RLS and PLMD. (Option) [4.c.iv; Table 4]

This is a new recommendation, and it is based on Level III and V evidence. The one Level III study was divided into subjective and objective outcome measures and was reported in two separate articles [68,69]. The study demonstrated improvement in somatic complaints and some sleep parameters (total sleep time, sleep efficiency) but worsening of stage shifts, and, during psychomotor tasks, there was enhancement of fine motor activity and a decrease in error rate. The Level V studies [38,70,71,72] revealed significant subjective improvement in RLS severity, and the one study [70] that also measured PLMS by PSG reported significant improvements in sleep efficiency and PLMS at the start of and following one month of treatment.

5. Other dopamine agonists (talipexole, cabergoline, piribedil, and alpha-dihydroergocryptine) may be effective in the treatment of RLS or PLMD, but the level of effectiveness of these agonists is not currently established. (Option) [4.c.v; Table 4]

This is a new recommendation, and it is based on Level V evidence. These dopamine agonists were each examined in only one open-label clinical series study. Talipexole was examined in 5 RLS subjects, and improvement was reported in some measures of sleep; however, quantitative data or statistics were not presented [73]. Cabergoline was examined in 9 RLS subjects, who reported a subjective relief of symptoms and experienced reductions in measures of PLMS, PLMA, and PLM awakening [Table 2], and some sleep parameters showed improvement [74]. Piribedil was examined in 13 RLS subjects; complete, partial, or no response was reported by the use of a rating scale in 8, 3, and 2 subjects, respectively [75]. Alpha-dihydroergocryptime was examined in 15 RLS subjects; only sleep duration and latency were reported as improved by subjective report, and 13 subjects experienced side effects [76].

6. The dopaminergic agents amantadine and selegiline may be effective in the treatment of RLS and PLMD, but the level of effectiveness of these agents is not currently established. (Option) [4.d; Table 5]

This is a new recommendation, and it is based on Level V evidence. Amantadine was examined in one Level V study [77] in 21 RLS subjects who were not well managed on their current medications. Eleven of these subjects reported some benefit (6 reported at least a 95% symptom reduction), and this treatment benefit continued for all but 2 of these 11 subjects followed 3 – 13 months post-treatment. Side effects of drowsiness were reported in 3 subjects, and fatigue in 2 subjects. Selegiline was examined in one Level V study [78] in 31 subjects with PLMD and a sleep-wake complaint. There was a significant decrease in PLMS by PSG following treatment.

7. No specific recommendations can be made regarding dopaminergic treatment of children or pregnant women with RLS or PLMD. [5.b]

This statement is reissued from the previous practice parameter paper,[1] and is based on Standards of Practice Committee consensus. To date, beyond case reports, there is only one study that examined the response to levodopa and pergolide in children, albeit with comorbid attention deficit-hyperactivity disorder [9]. There are very limited studies of RLS treatment in pregnancy [79,80], and none of these involved dopaminergic agents.

RECOMMENDATIONS FOR FUTURE RESEARCH

As discussed in the prior practice parameter paper,[1] there is a pressing need for well-powered, multi-center clinical trials using randomized double-blind, placebo-controlled study designs for the evaluation of RLS and PLMD treatments. This need is especially acute in the case of dopaminergic agonists, which will increasingly become the favored treatment for RLS and PLMD in the near future. Future studies should address long-term effectiveness, augmentation, and side effects for all medications used to treat these conditions. Finally, additional topics that warrant further study include side-by-side comparison of different medications, comparison of different routes of drug administration and dosing, and the effectiveness and risks of treatment in special populations such as the elderly, children, and pregnant women.

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