

Practice Parameters for the 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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Abstract: These are the first clinical guidelines published for the treatment of Restless Legs Syndrome (RLS) and Periodic Limb Movement Disorder (PLMD) providing evidence-based practice parameters. They were developed by the Standards of Practice Committee and reviewed and approved by the Board of Directors of the American Academy of Sleep Medicine. The guidelines provide recommendations for the practice of sleep medicine in North America regarding the treatment of RLS and PLMD. Recommendations are based on the accompanying comprehensive review of the medical literature regarding treatment of RLS and PLMD which was developed by a task force commissioned by the American Academy of Sleep Medicine. Recommendations are identified as standards, guidelines, or options, based on the strength of evidence from published studies that meet criteria for inclusion.

Dopaminergic agents are the best studied and most successful agents for treatment of RLS and PLMD. Specific recommendations are also given for the use of opioid, benzodiazepine, anticonvulsant, and adrenergic medications, and for iron supplementation. In general, pharmacological treatment should be limited to individuals who meet diagnostic criteria and especially who experience insomnia and/or excessive sleepiness that is thought to occur secondary to RLS or PLMD. Individuals treated with medication should be followed by a physician and monitored for clinical response and adverse effects. It would be desirable for future investigations to employ multicenter clinical trials, with expanded numbers of subjects using double-blind, placebo-controlled designs, and an assessment of long-term response, side effects, and impact of treatment on quality of life. Evaluation of special groups such as children, pregnant women, and the elderly is warranted. Key words: practice guidelines-practice parameters-sleep disorders-restless legs syndrome-periodic limb movement disorder-treatment.

INTRODUCTION

RESTLESS LEGS SYNDROME (RLS) IS AN AWAKE PHENOMENON CHARACTERIZED BY 1) an intense, irresistible urge to move the legs, usually associated with sensory complaints (paresthesia or dysesthesia); 2) motor restlessness; 3) worsening of symptoms at rest and relief with motor activation; and 4) increased severity in the evening or at night.¹

Periodic limb movements of sleep (PLMS) are an asleep phenomenon characterized by periodic episodes of repetitive and highly stereotyped limb movements.² In patients

with periodic limb movement disorder (PLMD) the individual with PLMS has a complaint of insomnia and/or excessive sleepiness with no other disorder to explain the symptoms. Occasionally, patients with PLMS are asymptomatic and the movements are noticed by an observer. The stereotypical movements usually involve the leg and are characterized by extension of the great toe in combination with flexion of the ankle, knee, and sometimes hip.² The two syndromes (RLS and PLMD) are distinct by definition but can co-exist. Approximately 80% of individuals with RLS have evidence of PLMS on polysomnography.³ The diagnosis of RLS is based upon the history, while PLMD requires polysomnographic confirmation.

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METHODS

On the basis of the accompanying review⁴ and noted references, the Standards of Practice Committee of the American Academy of Sleep Medicine, 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 which were evaluated as noted in the evidence tables in the accompanying background paper. However, when scientific data are absent, insufficient or inconclusive, the recommendations are based upon consensus opinion. The strength of each recommendation is based on the level of the evidence available.

The Board of Directors of the American Academy of Sleep Medicine approved these recommendations. All members of Standards of Practice Committee and the 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 judgement 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 and resources. For the use of medication, data regarding side effects, medication effects, and the need for monitoring patients (clinically and by laboratory parameters) are based on current information. The reader should refer to the updated PDR and literature for any new information which might influence these guidelines.

The American Academy of Sleep Medicine 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.

This position paper is referenced by square-bracketed numbers to the relevant sections in the accompanying background paper.⁴ Other citations are noted and refer to the reference list at the end of this paper. The Standards of Practice Committee's assessments of the levels of evidence for each of the 45 evidentiary articles, which are used to support the strength of the recommendations in this paper, are recorded in the evidence tables in the background paper [Tables 1-6].

BACKGROUND

In his initial report on RLS, Ekbom estimated the prevalence to be 5%.⁵ More recent studies using questionnaires

and population sampling polls suggest perhaps a higher prevalence [3.1.2.1]. Symptoms may begin at any time from infancy to old age but peak onset is in middle age. Prevalence increases with age, and the severity of symptoms may fluctuate greatly throughout a patient's lifetime.⁶ Despite a growing recognition of the relatively high prevalence of RLS and PLMD, the two disorders are probably underdiagnosed and undertreated by most physicians.⁷ In addition, symptoms from RLS and PLMD may have a major impact on the patient and bed partner, including severe insomnia, anxiety, depression, marital discord, and social dysfunction.^{2,6} A recent increase in clinical and basic research may signal an exciting era of new insights into RLS and PLMD, including greater understanding of the best treatments for these conditions.⁷

A limited number of subjects have participated in studies which demonstrate that dopaminergic agents, opioids, benzodiazepines, anticonvulsants, and some adrenergic agents have beneficial effects on RLS symptoms and/or the movements or sleep disturbance associated with PLMD. Duration of follow-up of subjects in controlled studies has been relatively brief, usually days to a few months. The limited number of subjects and short follow-up in these studies have not allowed adequate assessment of side effects during long term treatment. Adverse drug reactions occur and they can be serious.⁸ Clinicians must have an appreciation of side effects to establish a benefit to risk ratio for clinical intervention in their patients.

Although not available specifically in the RLS/PLMD studies, there are large scale randomized, double-blind, placebo-controlled studies and long experience in other diseases with clinical use of the agents demonstrated effective for RLS and PLMD. Caution in interpretation of some of these data is needed, however, especially due to dosage differences for various other disorders. If the dosage of medication employed or the characteristics of another disease predispose to side effects that would not be experienced by a RLS or PLMD patient, information from such studies would not be directly applicable. For example, pergolide was studied as adjunctive therapy in patients already under treatment with levodopa/carbidopa for advanced Parkinson's Disease. In that setting, the rate of dyskinesias reported for pergolide is likely higher than if pergolide were used alone and the appearance of dyskinesia using dopaminergic agents, at recommended RLS/PLMD doses, has been an uncommonly reported problem. Nevertheless, RLS and PLMD are not uncommon in patients with Parkinson's Disease,⁹ so consideration of the side effects of combination therapy can be relevant in some patients on these medications. The issue of augmentation of symptoms is not an issue in other disorders, but may be important with RLS and may require attention by the physician [4.2].

For guidance to clinicians concerning drugs used in the management of RLS and/or PLMD, information about the

TABLE 1—IMPORTANT SIDE EFFECTS OF MEDICATIONS WHICH HAVE BEEN USED FOR TREATMENT OF RESTLESS LEGS SYNDROME AND PERIODIC LIMB MOVEMENT DISORDER

MEDICATION	DOSAGE RANGE	DISEASE/PATIENTS STUDIED	SIDE EFFECT	PERCENT AFFECTED (ACTIVE/PLACEBO)	REFERENCE
Levodopa/ carbidopa	25/100 QID or 50/200 CR QID	Parkinson/1015	Dyskinesia Nausea Hallucinations	12-17/# 6/# 4/#	(12)
Pergolide with levodopa/ carbidopa	.05-1.0 mg TID	Parkinson/189	Dyskinesia Nausea Hallucinations Rhinitis Constipation Pain	62/25 24/13 14/3 12/5 11/6 7/2	(13)
Pramipexole	.125-1.5 mg TID	Parkinson/388	Somnolence Insomnia Nausea Constipation Hallucinations	22/9 17/12 28/18 14/6 9/3	(14)
Narcotic analgesics	Variable	Pain control	Respiratory depression Nausea Somnolence Pruritus Constipation Urinary retention	* * * * * *	(15)
Clonazepam	1-3 mg	Epilepsy/574	Somnolence Depression Incoordination	37/10 7/1 6/0	(16)
Triazolam	.25 mg	Insomnia/1003	Drowsiness Dizziness Memory impairment	14/6 8/3 1/?	(17)
Gabapentin	300-600 mg TID	Epilepsy adjunct/543	Fatigue Dizziness Somnolence Ataxia	11/5 17/7 19/9 13/6	(18)
Carbamazepine	200-400 mg TID	Epilepsy/72	Fetal malformation	26/#	(19)
	200-400 mg TID	Epilepsy/236	Rash Hyponatremia Hepatotoxicity Blood disorders	11/# 2/# 1/# <1/#	(20)
	200-400 mg TID	Epilepsy/101	Ataxia (early) GI problems Sexual dysfunction Discontinued due to toxicity	33/# 27/# 13/# 12/#	(21)
Clonidine	0.1-0.2 mg daily or TTS 1-3	Hypertension/ 2681	Reduced blood pressure Dermatitis Systemic (dry mouth, somno-lence, dizziness, headache	89/# 15/# 8/#	(22)

signifies no large scale, placebo-controlled trials. * signifies no large scale controlled studies.

most frequent side effects has been assembled in Table 1. Table 1 is based on a sample of representative articles from the therapeutic literature. Frequent as well as serious side effects are listed. It should be noted that some of these listed side effects are reported at treatment doses used in disorders other than RLS/PLMD and may not be as likely to occur in dosage schedules as recommended for RLS/PLMD. Data on side effects may change as new evidence appears; therefore, updated PDRs should be consulted. The effects of large intentional overdoses and of interactions with other medications need to be considered clinically, but are not listed in Table 1. Risks associated with medications in pregnancy are discussed in the review paper [5.4], and are summarized below. Clinicians are often concerned about the potential addictive effects of narcotic medication. Nevertheless, addiction caused by therapeutic use of oxycodone with acetaminophen, for example, especially when used once daily at bedtime, is unusual.^{10,11} Carbamazepine therapy may be associated with blood dyscrasias, hepatotoxicity and fetal malformations, which are potentially serious side effects, yet carbamazepine is a common therapy for multiple disorders.

For proper management of the patient with RLS and/or PLMD, the physician must weigh the potential benefits of treatment of the patient's symptoms against the potential side effects associated with medication. In the absence of proof of disturbed sleep from periodic limb movements, the need for treating an asymptomatic individual with medica-

tion is questionable.

There are no controlled clinical trials which assess the safety and effectiveness of medications for RLS or PLMD during pregnancy. Risk of injury to the fetus must be taken into account when considering pharmacological treatment during pregnancy. The FDA classifies risk from medication during pregnancy on the basis of data from humans and animals. Designations are category A, B, C, D, and X, varying from least to highest risk, with category A having no evidence for risk by controlled studies and category X contraindicated during pregnancy because of proven teratogenicity. [5.4]

Classification of medications for RLS and PLMD is as follows: levodopa/carbidopa C, pergolide B (limited data), clonazepam C, temazepam X, oxycodone B (but D if chronic use), propoxyphene C (but D if chronic use), codeine C (but D if chronic use), cabamazepine C, gabapentin C, and clonidine C. Benzodiazepines and opioids may cause a neonatal withdrawal syndrome when taken late in pregnancy. Benzodiazepines, opioids, and anticonvulsants are excreted in breast milk and can cause sedation in the breastfed infant. Dopaminergic medications inhibit prolactin release, which diminishes lactation [5.4]. Thus, women of childbearing potential should be counseled appropriately concerning use of these medications.

TABLE 2—AASM Classification of Evidence

RECOMMENDATION GRADES	EVIDENCE LEVELS	STUDY DESIGN
A	I	Randomized well-designed trials with low-alpha & low-beta errors*
B	II	Randomized trials with high-beta errors*
C	III	Nonrandomized controlled or concurrent cohort studies
C	IV	Nonrandomized historical cohort studies
C	V	Case series

ADAPTED FROM SACKETT²³

*Alpha error refers to the probability (generally set at 95% or greater) that a significant result (e.g., $p < 0.05$) is the correct conclusion of the study or studies. Beta error refers to the probability (generally set at 80% or 90% or greater) that a nonsignificant result (e.g., $p > 0.05$) is the correct conclusion of the study or studies. The estimation of beta error is generally the result of a power analysis. The power analysis includes a sample size analysis which projects the size of the study population necessary to ensure that significant differences will be observed if actually present.

TABLE 3—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 EDDY²⁴

RECOMMENDATIONS

Following the safety and general recommendations sections, each of the medications for which practice parameter recommendations were considered will be addressed. The classification of evidence was adapted from the suggestions of Sackett²³ (Table 2). Recommendations are given as standards, guidelines and options, as defined in Table 3. Unless otherwise specified, the recommendations in this paper are supported by Level II to Level V evidence.

A. General treatment and safety recommendations

1. Pharmacological treatment of RLS and/or PLMD should be limited to patients who meet specific diagnostic criteria. [3.1; 5.1] (Standard)

Diagnostic criteria are available and are based on a patient's history and/or bed partner observations for RLS, and the patient's history combined with polysomnography for PLMD² [3.1; 3.2]. Assessment of severity and the relationship between the patient's symptoms and impact on general well-being help establish indications for treatment. PLMD patients experience insomnia or excessive daytime sleepiness. RLS patients experience insomnia, EDS, and/or waking restlessness and discomfort. Effective communication between the well-informed patient and physician assists in balancing the benefit from medication with potential side effects. RLS and PLMD are not the same disorder and treatment of the two is not always identical. As a result, differentiation of RLS and PLMD may be important [3.0; 3.1.1; 5.1].

2. The physician who evaluates and treats patients with RLS and/or PLMD should be aware of the existence of idiopathic and secondary forms, and should be knowledgeable about risk factors and co-morbid conditions for these disorders. [3.1.2.2] (Standard)

The presence of secondary forms and comorbid conditions can be important in influencing treatment options or indicating the need for treatment of underlying disorders [3.1.2.2; 5.2].

3. Individuals with RLS and/or PLMD who are being treated with medication should be followed by a physician at appropriate intervals and monitored for adverse side effects, augmentation, & tolerance.[4.0;5.0] (Standard)

The physician should have an awareness of side effects and other medication effects, and should work with the patient to balance potential benefits against potential adverse effects from medications (see Background section). This process requires periodic reevaluation to monitor the overall benefit-risk ratio for the individual patient. The physician should also assess for the emergence of other sleep problems or other underlying conditions which may

influence symptoms of RLS or PLMD. For example, coexistence of sleep apnea may influence the selection of sedating medications which might improve PLMD but at the potential risk of worsening apnea or oxyhemoglobin desaturation.⁶ Follow-up laboratory-based assessment may be required to accomplish these goals.

B. Specific treatment recommendations

1. Levodopa with decarboxylase inhibitor and pergolide are effective in the treatment of RLS and PLMD. [4.2.1] (Guideline)

This recommendation is based upon Level II, III, and V evidence. The dopaminergic agents are the best studied and the most successful agents for treatment of RLS and PLMD. Levodopa is the agent most thoroughly reported. Bromocriptine has been evaluated in fewer studies than pergolide with less substantial data [4.2.1]. Two studies with pergolide resulted in subjective RLS benefit and some reduced PLMS [4.2.1]. Sustained release formulations of levodopa with decarboxylase inhibitor have similar efficacy to non-sustained release, based on limited data [4.2.1]. Studies on other dopamine agonists using larger numbers of patients with good study designs are underway and will be published soon. The reader should refer to recent literature for data from clinical trials with newer agents such as pramipexole, ropinerole, cabergoline and others. The issue of long term benefit is not addressed adequately in studies performed to date and this will require additional study.

2. Oxycodone and propoxyphene are effective in the treatment of RLS and PLMD. [4.2.2] (Guideline)

This recommendation is based upon Level II and V evidence. Relatively few opioids have been adequately studied. Oxycodone may be more effective than propoxyphene, but direct comparisons between agents is lacking. Other opioids may be of benefit but this has not been tested. Risks of side effects, optimal dosage, and misuse potential of these agents still need to be adequately addressed in experimental designs. Treatment success with opioids may be more consistent for RLS than for reduction of periodic limb movements.

3. Carbamazepine is effective in the treatment of RLS. [4.2.4; 5.1] (Guideline)

This recommendation is based upon Level II evidence. In studies which met inclusion criteria, carbamazepine has been shown to benefit RLS symptoms but not PLMD symptoms [5.1].

4. Clonazepam is effective in the treatment of PLMD and possibly RLS. [4.2.3] (Option)

This recommendation is based upon limited Level II, III, and V evidence. Mixed results are reported with benzodiazepines, including limited data on response in the treat-

ment of RLS. Differentiation between direct effect of clonazepam on PLMD versus non-specific effects on sleep are not clear. More studies on benzodiazepines are needed.

5. Gabapentin is effective in the treatment of RLS. [4.2.4;5.1] (Option)

This recommendation is based on limited Level V evidence, which consists of only two open-label studies.

6. Clonidine is effective in the treatment of RLS. [4.2.5] (Option)

This recommendation is based on limited Level II and III evidence. Subjective evidence suggests benefit for RLS symptoms but without objective improvement of PLMD symptoms.

7. Iron supplementation is effective in the treatment of RLS in patients with iron deficiency. [4.2.6.2;5.2] (Option)

This recommendation is based upon level III to V evidence. Iron therapy may be more effective for patients with lower iron stores, but data are limited.

8. No specific recommendations can be made regarding treatment of pregnant women with RLS or PLMD. [5.4]

The review paper discusses the association between pregnancy and RLS and PLMD [3.1.2.2] and provides some information on treatment in this patient group [5.4].

The Background section of this paper also reviews the FDA classification of risk associated with medication during pregnancy, and discusses important aspects of side effects from medications that may be used to treat RLS or PLMD during pregnancy. Data from individual studies are not adequate to support specific recommendations, however.

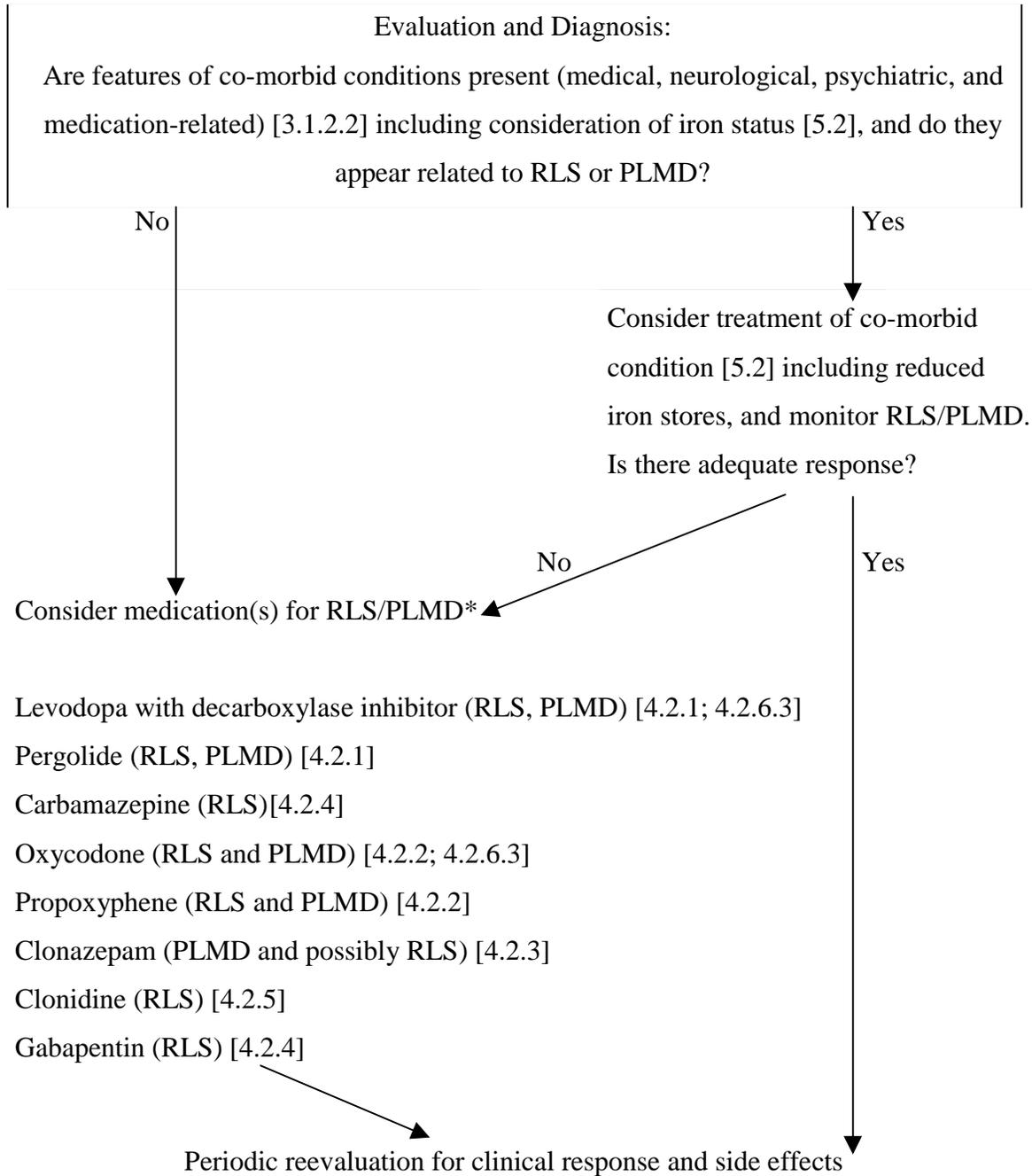
9. No specific recommendations can be made regarding treatment of children with RLS or PLMD. [5.4]

Benzodiazepines, anticonvulsants, alpha-adrenergic, and opioid medication classes have been used widely in children for treatment of other medical disorders, but no acceptable trials have been performed in children with RLS or PLMD [5.4].

RECOMMENDATIONS FOR FUTURE RESEARCH

Investigations to identify the best treatment for RLS and PLMD should include well-powered, multicenter clinical trials using randomized double-blind, placebo-controlled study designs. Future series should assess long term response and side effects, provide direct comparison within and between pharmacological classes of medication, evaluate combination therapy for patients with symptoms refractory to single drug treatment, and evaluate the impact of treatment on quality of life. Evaluation of special groups such as children, pregnant women, and the elderly is warranted.

Treatment Flow Diagram For Symptomatic RLS or PLMD Patients



*See preceding discussions in Specific Treatment Recommendations for details.

ADDENDUM

Several articles have been published since closure of the review paper MEDLINE search which may be relevant to clinical decision making. Articles on dopamine agents including pramipexole,²⁵⁻²⁷ pergolide,²⁸⁻³⁰ and L-dopa,³¹ gabapentin,³² and magnesium therapy³³ are available. The reader is urged to seek these and additional new articles appearing in this active area of research.

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