Restless Legs Syndrome

MAX BAYARD, MD; THOMAS AVONDA, MD; and JAMES WADZINSKI, MD,
East Tennessee State University, Quillen College of Medicine, Johnson City, Tennessee

Restless legs syndrome is a common neurologic movement disorder that affects approximately 10 percent of adults. Of those affected with this condition, approximately one third have symptoms severe enough to require medical therapy. Restless legs syndrome may be a primary condition, or it may be secondary to iron deficiency, renal failure, pregnancy, or the use of certain medications. The diagnosis is clinical, requiring an urge to move the legs usually accompanied by an uncomfortable sensation, occurrence at rest, improvement with activity, and worsening of symptoms in the evening or at night. Restless legs syndrome causes sleep disturbances, is associated with anxiety and depression, and has a negative effect on quality of life. Treatment of secondary causes of restless legs syndrome may result in improvement or resolution of symptoms. Currently, there is little information regarding the effects of lifestyle changes on the symptoms of restless legs syndrome. If medications are needed, dopamine agonists are the primary medications for moderate to severe restless legs syndrome. Other medications that may be effective include gabapentin, carbidopa/levodopa, opioids, and benzodiazepines. (*Am Fam Physician.* 2008;78(2):235-240, 243. Copyright © 2008 American Academy of Family Physicians.)

▶ **Patient information:** A handout on restless legs syndrome, written by the authors of this article, is provided on page 243.

The online version of this article includes supplemental content at http://www.aafp.org/afp.

Restless legs syndrome (RLS) is a neurologic movement disorder that affects approximately 10 percent of adults.[1-3] About one third of those with RLS have symptoms of moderate to severe intensity that require medical therapy.[3] The prevalence of RLS increases with age,[1,2] although approximately one third of patients with RLS first experience symptoms before 18 years of age. RLS is more common in females.[2] There is a genetic predisposition to RLS, which is common in those with early-onset RLS. RLS may be a primary condition, or it may be secondary to iron deficiency, pregnancy, renal failure, the use of certain medications, or a spinal cord injury.

Pathophysiology

Research has identified abnormalities in dopamine and iron function in the central nervous system in individuals with RLS, although these relationships are not fully understood. Two studies have demonstrated enhanced circadian variation in dopamine activity in those with RLS compared with control patients.[4,5] Iron content in the substantia nigra and the putamen were lower in those with RLS than in control patients.[6] The levels of ferritin in the cerebrospinal fluid were significantly lower in patients with RLS than in controls, although serum levels were similar between the two groups.[7] Further, serum iron stores (measured by serum ferritin) have been shown to correlate inversely with RLS severity.[8,9] Iron is a cofactor in tyrosine hydroxylase, the rate-limiting enzymatic step in the conversion of tyrosine to dopamine.

Clinical Evaluation

The diagnosis of RLS is clinical. A focused history and physical examination, as well as a laboratory analysis, may identify conditions with similar symptoms or underlying causes of RLS. The history can reveal valuable information, such as: the frequency and severity of symptoms; previous treatments for RLS; current medications; family history of RLS; and use of caffeine, alcohol, or tobacco. A laboratory analysis is not necessary for the diagnosis, but it can help exclude secondary causes of RLS. Initial laboratory tests include a basic metabolic panel and ferritin level.

The four diagnostic criteria and three supportive criteria for RLS are listed in *Table 1*.[10] The differential diagnosis of RLS includes nocturnal leg cramps, claudication, peripheral neuropathy, and akathisia *(Table 2)*. Patients often have a difficult time describing the uncomfortable sensations of

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*	*Comments*
Obtain serum ferritin and consider replacing iron in patients with RLS with ferritin level less than 50 ng per mL (50 mcg per L).	C	9, 14	Expert panel and nonrandomized trial
Consider changing medications that may exacerbate symptoms of RLS.	C	14	Expert panel recommendation
If antidepressant therapy is used for patients with RLS, consider using bupropion (Wellbutrin).	C	14, 16	Expert panel and disease-oriented data showing decreased PLMS with bupropion compared with SSRIs
Dopamine agonists are effective treatment for moderate to severe RLS and are the preferred agents for most patients with daily RLS symptoms.	A	14, 17-24	Expert advice and RCTs with consistent findings

PLMS = periodic limb movements of sleep; RCT = randomized controlled trial; RLS = restless legs syndrome; SSRI = selective serotonin reuptake inhibitor.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see http://www.aafp.org/afpsort.xml.

RLS. They may complain of crawling, aching, or indescribable feelings in their legs, or they may just have the need to move.

The presence of periodic limb movements of sleep (PLMS) is supportive for the diagnosis of RLS. Approximately 80 percent of individuals with RLS experience PLMS, but less than one half of individuals with PLMS also have RLS.[10] Effective treatments for RLS typically decrease episodes of PLMS.

Table 1. Criteria for Diagnosis of Restless Legs Syndrome

Urge to move legs usually accompanied or caused by uncomfortable or unpleasant sensations in the legs (urge to move may not be accompanied by uncomfortable sensations, and arms or other body parts may be involved)
Urge to move or unpleasant sensation begins or worsens during periods of rest or inactivity
Urge to move or unpleasant sensation partially or totally relieved by movement (such as walking or stretching) as long as activity continues
Urge to move or unpleasant sensation worse in the evening or at night than during the day, or only occurs during the evening or at night; in very severe cases, worsening at night may not be noticeable, but must have been previously present
Supportive Clinical Features of Restless Legs Syndrome:
Periodic limb movements
Positive family history
Response to dopaminergic therapy

Adapted with permission from Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J, for the International Restless Legs Syndrome Study Group. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med. *2003;4(2):102,105. http://www.sciencedirect.com/science/journal/13899457. Accessed April 1, 2008.*

Children with RLS can be diagnosed using the same four criteria as adults *(Table 1[10])*. In addition, the child may describe in his or her own words some of the symptoms consistent with leg discomfort, or have at least two of the following: sleep disturbance, a biologic parent or sibling with RLS, or a polysomnographic-documented PLMS index of 5 or more per hour of sleep.[10]

RLS has a negative impact on quality of life.[3] Individuals with RLS are more likely to be depressed or anxious.[3,11] Insomnia and its consequences are common in RLS, with patients having trouble initiating and maintaining sleep.

RLS may be more common in patients with Parkinson's disease than in the general population; however, results from studies of this correlation are inconsistent and are confounded by concomitant use of dopaminergic agents in patients with Parkinson's disease.[12] RLS has not been shown to increase the risk of developing Parkinson's disease.

The severity of RLS symptoms and their effect on daily life can be assessed using the International Restless Legs Syndrome Study Group (IRLSSG) Severity Scale *(see online Figure A)*.[13] This is a validated, 10-question patient survey that can be used to quantify the severity of RLS and the patient's response to therapy. Each answer corresponds to a numerical value from 0 to 4, which is then totaled for all 10 questions. A score of 1 to 10 is considered consistent with mild RLS; 11 to 20 with moderate RLS; 21 to 30 with severe RLS; and 31 to 40 with very severe RLS.[13]

Table 2. Differential Diagnosis of Restless Legs Syndrome

Condition	*Distinguishing features*
Akathisia	An internal desire to move, most commonly associated with the use of neuroleptic medications; desire to move not necessarily associated with discomfort in the legs; symptoms are not worse at night
Nocturnal leg cramps	Sudden involuntary muscle contractions; palpable tightening of the leg muscles
Peripheral neuropathy	Etiologies include trauma, nerve compression, diabetes, nutritional disorders, infections, others; generally causes sensory disturbance; may or may not be more noticeable at night; not typically relieved by activity
Peripheral vascular disease	Primarily a consequence of atherosclerosis; cramping-type pains that are exacerbated by activity and improve with rest; symptoms not worse at night

Treatment

A consensus-based algorithm for the treatment of RLS has been developed based on whether symptoms are intermittent, daily, or refractory.[14] A summary of this approach is found in *Table 3*.[14]

SECONDARY RLS

If RLS is secondary to another underlying condition, treatment of that condition may improve or resolve the symptoms of RLS. For example, individuals with iron deficiency (with or without anemia) who also have RLS may receive symptom relief by taking supplemental iron. A ferritin level of less than 50 ng per mL (50 mcg per L) may cause or exacerbate RLS. Although levels above 10 to 20 ng per mL (10 to 20 mcg per L) are reported as normal, supplemental iron may improve symptoms in individuals with levels less than 50 ng per mL. Iron is not beneficial in individuals with ferritin above this level.

RLS is common during pregnancy, particularly during the third trimester, and will likely resolve with delivery. Individuals with RLS secondary to chronic kidney disease who undergo kidney transplant may experience resolution of symptoms.

LIFESTYLE FACTORS

Little information is available about the effects of lifestyle on the symptoms of RLS. Limiting caffeine, tobacco, and alcohol use may improve symptoms. Activities that provide mental stimulation may also provide relief. One survey showed a higher prevalence of RLS in persons who were sedentary and overweight.[1] A small randomized controlled trial (RCT) of 23 patients demonstrated improvement in symptoms of RLS with a program consisting of lower body resistance training and aerobic exercise.[15]

Table 3. Management of Restless Legs Syndrome

Intermittent RLS*
- Nonpharmacologic therapies
  - Administer iron replacement in patients who are iron-deficient
  - Consider effect of medications that may enhance RLS
  - Recommend mental alerting activities
  - Suggest abstinence from caffeine, nicotine, and alcohol
- Medications
  - Benzodiazepines
  - Carbidopa/levodopa (Sinemet)
  - Dopamine agonists
  - Low-potency opioids

Daily RLS†
- Nonpharmacologic therapy
- Dopamine agonists (drug of choice in most people with RLS)
- Gabapentin (Neurontin); if ineffective as first-line therapy, a dopamine agonist should be considered
- Low-potency opioids; if ineffective as first-line therapy, a dopamine agonist should be considered

Refractory RLS‡ (Consider referral to subspecialist)
- Change to different dopamine agonist
- Change to gabapentin
- Change to a high-potency opioid or tramadol (Ultram)
- Consider adding a second agent, such as gabapentin, a benzodiazepine, or an opioid

RLS = restless legs syndrome.

**—Intermittent RLS requires treatment when present, but does not occur frequently enough to require daily therapy.*

†*—Daily RLS occurs frequently enough to require daily therapy.*

‡*—Refractory RLS is treated daily with a dopamine agonist and results in one or more of the following outcomes: the initial response is inadequate despite adequate doses; the response has become inadequate over time, despite increasing doses; the treatment results in intolerable adverse effects; the treatment results in augmentation that was not controllable with additional earlier doses of the drug.*

Information from reference 14.

Table 4. Medications That May Exacerbate Restless Legs Syndrome

- Antihistamines
- Caffeine
- Dopamine antagonists including neuroleptics and antiemetics
- Lithium
- Selective serotonin reuptake inhibitors
- Tricyclic antidepressants

MEDICATIONS

Certain medications have been shown to exacerbate RLS *(Table 4)*. Cessation of these medications may improve symptoms. One study showed that all selective serotonin reuptake inhibitors researched increased PLMS. Conversely, bupropion (Wellbutrin) decreased the number of limb movements.[16] Because of the overlap between RLS

and PLMS, it is likely that bupropion would improve, or at least not exacerbate, symptoms of RLS. Currently, no RCTs on the effects of bupropion on the symptoms of RLS have been conducted.

Not all patients with RLS require medications to treat their symptoms. In a study of the prevalence of RLS, approximately 30 percent of individuals with RLS had symptoms that would be classified as moderate to severe.[3] In clinical trials, moderate to severe RLS generally refers to symptoms experienced at least 15 days per month or an IRLSSG severity score over 15.

Several classes of medications improve the symptoms of RLS *(Table 5 and online Table A)*. Dopamine agonists have been most extensively studied and are appropriate first-line treatments for moderate to severe RLS. Carbidopa/levodopa (Sinemet), opioids, anticonvulsants, and benzodiazepines are also effective. Some individuals may require medications from more than one class.

Dopamine agonists. Several RCTs have demonstrated the efficacy of dopamine agonists compared with placebo.[17-24] Dopamine agonists are chemically distinct from dopamine, although they activate neuronal dopamine receptors. The mechanism by which dopamine and dopamine agonists improve the symptoms of RLS is not fully understood. Pramipexole (Mirapex) and ropinirole (Requip) are both indicated for the treatment of moderate to severe RLS.

Table 5. Medications for the Treatment of Restless Legs Syndrome

Medication	*Starting dose*	*Adverse effects*	*Comments*
Non-ergotamine dopamine agonists Pramipexole (Mirapex) Ropinirole (Requip)	 0.125 mg 0.25 mg	Nausea, orthostasis, daytime somnolence; augmentation occurs, but less so than with carbidopa/levodopa (Sinemet)	Drugs of choice in most patients with moderate to severe daily RLS; pramipexole and ropinirole are FDA-indicated for the treatment of moderate to severe RLS Pramipexole: increase dose by 0.25 mg after four to seven days, up to 0.5 mg per day Ropinirole: increase to 0.5 mg on day three and to 1.0 mg on day eight; increase by 0.5 mg every week if needed to maximum of 4 mg per day
Carbidopa/levodopa	25/100 mg	Gastrointestinal upset and headache; augmentation common with daily dosing	Rapid onset of action, usually with first dose; beneficial for individuals requiring medications for intermittent symptoms
Gabapentin (Neurontin)	100 to 300 mg	Sedation, gastrointestinal discomfort	An appropriate first choice in individuals with RLS associated with neuropathic pain; consider use for daily RLS if dopamine agonist not effective; may be used with dopamine agonist in patients with refractory RLS
Opioids	Nightly dose varies by choice of opioid	Nausea, constipation; potential for abuse	Limited studies of effectiveness, but a reasonable choice in individuals with RLS associated with pain; may be used with dopamine agonist in patients with refractory RLS
Benzodiazepines Clonazepam (Klonopin) Zolpidem (Ambien)	 0.5 mg 5 mg	Daytime sleepiness; increased risk of falls at night; potential for abuse	Can be useful in intermittent RLS, particularly when insomnia is significant; may be used with dopamine agonist in patients with refractory RLS
Ergotamine dopamine agonists Cabergoline (Dostinex) Pergolide (Permax)	 0.5 mg 0.05 mg	Same as for non-ergotamine agonists; also have additional risk of cardiac valvulopathy	Effective in the treatment of moderate to severe RLS, but non-ergotamine dopamine agonists are preferred because of safety profile; neither cabergoline nor pergolide is FDA-indicated for treatment of RLS; pergolide recently removed from the U.S. market

FDA = U.S. Food and Drug Administration; RLS = restless legs syndrome.

Dopamine agonist dosing for RLS is lower than dosing for Parkinson's disease. Side effects of dopamine agonists include nausea, daytime somnolence, and orthostasis.

Cabergoline (Dostinex) and pergolide (Permax), which are ergot-derived dopamine agonists, are effective in RLS. However, the U.S. Food and Drug Administration has not indicated these drugs for the treatment of RLS. Ergot dopamine agonists have a small risk of causing cardiac valvulopathy,[25] which has led to the voluntary removal of pergolide from the market.

Carbidopa/levodopa. Levodopa is a dopamine precursor. It is typically combined with carbidopa, which serves to block the peripheral breakdown of levodopa. Carbidopa/levodopa is effective in the treatment of RLS,[26] but the development of augmentation limits its use in individuals requiring daily medications. With augmentation, symptoms of RLS may occur earlier in the day, with greater intensity, or in other body parts (e.g., the arms) than they did before therapy. Augmentation occurs in as many as 82 percent of patients with RLS receiving carbidopa/levodopa.[27] It can also occur with dopamine agonists, but not to the same degree. In two retrospective studies (60 and 59 patients) of pramipexole, augmentation developed in 33 and 32 percent of individuals, respectively.[19,28]

Gabapentin (Neurontin). Gabapentin was effective in treating RLS in limited studies.[29,30] In a crossover study (22 patients), individuals receiving gabapentin experienced improvement in symptoms.[29] In a small head-to-head study (16 patients), gabapentin and ropinirole demonstrated similar efficacy.[30] Gabapentin can be considered a first-line therapy when patients have neuropathic pain in addition to RLS.

Opioids. Opioids may improve symptoms of RLS. In a randomized double-blind crossover trial (11 patients), oxycodone (Roxicodone) treatment resulted in decreased RLS symptoms, decreased PLMS, and improved daytime alertness.[31] In a small RCT, propoxyphene (Darvon) was beneficial in the treatment of RLS, but less so than carbidopa/levodopa.[32] In an open label study (12 patients), tramadol (Ultram) taken at night improved RLS symptoms.[33]

Benzodiazepines. There is limited data on the effectiveness of benzodiazepines in treating the waking symptoms of RLS. They may be appropriate if sleep initiation is a problem.

Prognosis

RLS has a variable course, but symptoms tend to progress with advancing age. Some individuals may experience spontaneous improvement in their symptoms for a period of time, but symptoms tend to recur. Individuals with RLS secondary to an underlying condition may have improvement or resolution of symptoms if the underlying condition is treated. Medications, when needed, may provide relief of symptoms.

The Authors

MAX BAYARD, MD, is associate professor in the Department of Family Medicine at East Tennessee State University, Quillen College of Medicine, Johnson City, Tenn. He also is program director of the family medicine residency program at this institution. Dr. Bayard received his medical degree from East Tennessee State University and completed a family medicine residency at Bristol (Tenn.) Family Practice.

THOMAS AVONDA, MD, is assistant professor in the Department of Family Medicine at East Tennessee State University, Quillen College of Medicine. Dr. Avonda received his medical degree from Louisiana State University, in Baton Rouge, and completed a family medicine residency at Johnson City (Tenn.) Family Medicine.

JAMES WADZINSKI, MD, is chief resident at the East Tennessee State University Johnson City family medicine residency program. He received his medical degree from Saba University School of Medicine, The Bottom, Saba, Netherlands-Antilles.

Address correspondence to Max Bayard, MD, 917 W. Walnut St., Johnson City, TN 37604 (e-mail: bayard@etsu.edu). Reprints are not available from the authors.

Author disclosure: Nothing to disclose.

REFERENCES

1. Phillips B, Young T, Finn L, Asher K, Hening WA, Purvis C. Epidemiology of restless legs symptoms in adults. *Arch Intern Med*. 2000;160(14):2137-2141.
2. Phillips B, Hening W, Britz P, Mannino D. Prevalence and correlates of restless legs syndrome: results from the 2005 National Sleep Foundation Poll. *Chest*. 2006;129(1):76-80.
3. Hening W, Walters AS, Allen RP, Montplaisir J, Myers A, Ferini-Strambi L. Impact, diagnosis and treatment of restless legs syndrome (RLS) in a primary care population: the REST (RLS epidemiology, symptoms, and treatment) primary care study. Sleep Med. 2004;5(3):237-246.
4. Garcia-Borreguero D, Larrosa O, Granizo JJ, de la Llave Y, Hening WA. Circadian variation in neuroendocrine response to L-dopa in patients with restless legs syndrome. *Sleep*. 2004;27(4):669-673.
5. Earley CJ, Hyland K, Allen RP. Circadian changes in CSF dopaminergic measures in restless legs syndrome. *Sleep Med*. 2006;7(3):263-268.
6. 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):263-265.
7. 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):1698-1700.
8. Sun ER, Chen CA, Ho G, Earley CJ, Allen RP. Iron and the restless legs syndrome. *Sleep*. 1998;21(4):371-377.
9. O'Keeffe ST, Gavin K, Lavan JN. Iron status and restless legs syndrome in the elderly. *Age Ageing*. 1994;23(3):200-203.
10. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J, for the International Restless Legs Syndrome Study Group. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med*. 2003;4(2):101-119.

11. Sevim S, Dogu O, Kaleagasi H, Aral M, Metin O, Camdeviren H. Correlation of anxiety and depression symptoms in patients with restless legs syndrome: a population based survey. *J Neurol Neurosurg Psychiatry.* 2004;75(2):226-230.
12. Poewe W, Högl B. Akathisia, restless legs and periodic limb movements in sleep in Parkinson's disease. *Neurology.* 2004;63(8 suppl 3):S12-S16.
13. Walters AS, LeBrocq C, Dhar A, et al. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. *Sleep Med.* 2003;4(2):121-132.
14. Silber MH, Ehrenberg BL, Allen RP, et al., for the Medical Advisory Board of the Restless Legs Syndrome Foundation. An algorithm for the management of restless legs syndrome [published correction appears in *Mayo Clin Proc.* 2004;79(10):1341]. *Mayo Clin Proc.* 2004;79(7):916-922.
15. Aukerman MM, Aukerman D, Bayard M, Tudiver F, Thorp L, Bailey B. Exercise and restless legs syndrome: a randomized controlled trial. *J Am Board Fam Med.* 2006;19(5):487-493.
16. Yang C, White DP, Winkelman JW. Antidepressants and periodic leg movements of sleep. *Biol Psychiatry.* 2005;58(6):510-514.
17. Stiasny-Kolster K, Benes H, Peglau I, et al. Effective cabergoline treatment in idiopathic restless legs syndrome. *Neurology.* 2004;63(12):2272-2279.
18. Trenkwalder C, Hundemer HP, Lledo A, et al. Efficacy of pergolide in treatment of restless legs syndrome: the PEARLS Study. *Neurology.* 2004;62(8):1391-1397.
19. Silber MH, Girish M, Izurieta R. Pramipexole in the management of restless legs syndrome: an extended study. *Sleep.* 2003;26(7):819-821.
20. Winkelman JW, Sethi KD, Kushida CA, et al. Efficacy and safety of pramipexole in restless legs syndrome. *Neurology.* 2006;67(6):1034-1039.
21. Oertel WH, Stiasny-Kolster K, Bergtholdt B, et al., for the Pramipexole RLS Study Group. Efficacy of pramipexole in restless legs syndrome: a six-week, multicenter, randomized, double-blind study (effect-RLS study). *Mov Disord.* 2007;22(2):213-219.
22. Walters AS, Ondo WG, Dreykluft T, Grunstein R, Lee D, Sethi K, for the TREAT RLS 2 (Therapy with Ropinirole: Efficacy And Tolerability in RLS 2) Study Group. Ropinirole is effective in the treatment of restless legs syndrome. TREAT RLS 2: a 12-week, double-blind, randomized, parallel-group, placebo-controlled study. *Mov Disord.* 2004;19(12):1414-1423.
23. Trenkwalder C, Garcia-Borreguero D, Montagna P, et al., for the Therapy with Ropinirole, Efficacy and Tolerability in RLS 1 Study Group. Ropinirole in the treatment of restless legs syndrome: results from the TREAT RLS 1 study, a 12 week, randomised, placebo controlled study in 10 European countries. *J Neurol Neurosurg Psychiatry.* 2004;75(1):92-97.
24. Bogan RK, Fry JM, Schmidt MH, Carson SW, Ritchie SY, for the TREAT RLS US Study Group. Ropinirole in the treatment of patients with restless legs syndrome: a US-based randomized, double-blind, placebo-controlled clinical trial. *Mayo Clin Proc.* 2006;81(1):17-27.
25. Schade R, Andersohn F, Suissa S, Haverkamp W, Garbe E. Dopamine agonists and the risk of cardiac-valve regurgitation. *N Engl J Med.* 2007;356(1):29-38.
26. 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.
27. Allen RP, Earley CJ. Augmentation of the restless legs syndrome with carbidopa/levodopa. *Sleep.* 1996;19(3):205-213.
28. Winkelman JW, Johnston L. Augmentation and tolerance with long-term pramipexole treatment of restless legs syndrome (RLS). *Sleep Med.* 2004;5(1):9-14.
29. Garcia-Borreguero D, Larrosa O, de la Llave Y, Verger K, Masramon X, Hernandez G. Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. *Neurology.* 2002;59(10):1573-1579.
30. Happe S, Sauter C, Klösch G, Saletu B, Zeitlhofer J. Gabapentin versus ropinirole in the treatment of idiopathic restless legs syndrome. *Neuropsychobiology.* 2003;48(2):82-86.
31. Walters AS, Wagner ML, Hening WA, et al. Successful treatment of the idiopathic restless legs syndrome in a randomized double-blind trial of oxycodone versus placebo. *Sleep.* 1993;16(4):327-332.
32. Kaplan PW, Allen RP, Buchholz DW, Walters JK. A double-blind, placebo-controlled study of the treatment of periodic limb movements in sleep using carbidopa/levodopa and propoxyphene. *Sleep.* 1993;16(8):717-723.
33. Lauerma H, Markkula J. Treatment of restless legs syndrome with tramadol: an open study. *J Clin Psychiatry.* 1999;60(4):241-244.