ELSEVIER

Seminars in
Pediatric
Neurology

Restless Legs Syndrome and Periodic Limb Movement Disorder in Children and Adolescents

Matthew A. Picchietti,[a] and Daniel L. Picchietti, MD[b]

Restless Legs Syndrome (RLS) has been recognized as a common and treatable neurologic disorder in adults for some time, but the occurrence of RLS in children and adolescents has seen relatively delayed acceptance. A large, population-based study has recently reported a 1.9% and 2% prevalence of RLS in children and adolescents, respectively. RLS in children is closely associated with periodic limb movement disorder (PLMD), and symptoms of both may range from mild to severe. An early, accurate diagnosis of RLS or PLMD provides substantial benefits to an individual's quality of life, especially in cases of poor-sleep related intellectual or emotional dysfunction. Treatment plans should use emerging knowledge of how RLS and PLMD affect children and adolescents to correctly identify these disorders and aim to reduce or eliminate symptoms. Best-fitting therapy will consider severity of symptoms, comorbid conditions, and phenotypic variables. Promising progress has been made in understanding the genetic components of RLS as well as the role of iron deficiency in exacerbating symptoms. A review of current research on RLS and PLMD in children and adolescents is presented.
Semin Pediatr Neurol 15:91-99 **© 2008 Elsevier Inc. All rights reserved.**

Restless Legs Syndrome (RLS) is a common, treatable neurologic disorder, which in adults is characterized by a prominent urge to move the legs, typically associated with uncomfortable and unpleasant sensations.[1,2] Symptoms are worse at rest, relieved by movement, and most severe at night. The impact of RLS can be severe, with adverse effects on sleep,[3] cognitive function,[4] mood,[5] and quality of life.[6,7] Several large population-based studies in the United States and Europe have found prevalence of 5% to 10% in adults, with about one third affected to a moderate or severe degree.[6,8-13] However, it was not until the mid-1990s that detailed reports of pediatric RLS appeared in the medical literature.[14,15] Additional case reports and case series have followed.[16-27] Consensus criteria for the diagnosis of RLS in children and adolescents were published in 2003 after a workshop at the National Institutes of Health (NIH) (Tables 1 and 2).[2] These pediatric criteria evolved out of the adult RLS criteria and 2 previous versions of pediatric criteria.[15,28] Two major concepts were incorporated: more restrictive criteria for a definite diagnosis to limit age-related potential for error and separate research criteria for less definitive cases. The first diagnostic concept was agreed on to avoid overdiagnosis in children, and the second was intended to capture a broader spectrum of RLS in childhood for further research. Pediatric RLS research in the past 14 years has emphasized the familial occurrence of RLS, the association with periodic limb movements in sleep (PLMS), and the relationship to attention-deficit/hyperactivity disorder (ADHD) in some cases.

PLMS and Periodic Limb Movement Disorder

PLMS are brief jerks during sleep lasting between 0.5 to 5.0 seconds, typically occur at 20- to 40-second intervals, and are more common in the legs, feet, and toes than in the arms.[29-31] Patients are usually unaware of their own PLMS and of the associated arousals disturbing sleep. Blood pressure has been shown to increase significantly in association with PLMS.[32] In general, PLMS are more frequent with age and are associated with disorders of underactive dopamine function in central nervous system pathways.[33]

Diagnostic criteria for periodic limb movement disorder (PLMD) are (1) PLMS documented by polysomnography, (2) PLMS exceeding norms for age (≥5 per hour for children and adolescents), (3) clinical sleep disturbance, and (4) the ab-

[a]From the Department of Psychology, Southern Illinois University, Carbondale, IL.
[b]The University of Illinois and Carle Clinic Association, Urbana, IL.
Address reprint requests to Daniel Picchietti, MD, Department of Pediatrics, University of Illinois School of Medicine and Carle Clinic Association, 602 W University Ave, Urbana, IL 61801. E-mail: dpicchie@uiuc.edu

1071-9091/08/$-see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.spen.2008.03.005

Table 1 NIH Workshop Diagnostic Criteria for RLS in Children and Adolescents (2003): Definite RLS

Criteria for the diagnosis of definite RLS in children (2 to 12 years old)		
Child meets **all 4** of the following **adult essential criteria:** 1. An urge to move the legs 2. The urge to move begins or worsens when sitting or lying down 3. The urge to move is partially or totally relieved by movement 4. The urge to move is worse in the evening or night than during the day or only occurs in the evening or night		
AND		
The child uses his/her own words to describe leg discomfort. ■ Examples of age-appropriate descriptors: hurt, tickle, tingle, bugs, spiders, ants, static, want to run, and a lot of energy in my legs	OR	Two or 3 of the following supportive criteria are met: ■ Sleep disturbance inappropriate for age ■ Biological parent or sibling has definite RLS ■ The child has a sleep study documenting a periodic limb movement index ≥5 per hour of sleep. An acceptable alternative ending is index that exceeds 5/h.
Criteria for the diagnosis of definite RLS in adolescents (13 to 18 years old) The 4 essential adult criteria are met.		
For all: the condition is not better explained by another current sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder.		

sence of another primary sleep disorder or reason for the PLMS (including RLS) (Table 3).[2,31,34] It is the presence of clinical sleep disturbance and the lack of another specific sleep disorder that define PLMD as a disorder.

The relationship between RLS, PLMS, and PLMD is complex. Most individuals with RLS have PLMS,[35] and PLMS are considered to be supportive of an RLS diagnosis in both children and adults.[2] Also, new genetic evidence indicates the high prevalence of a sequence variant of BTBD9 (located on chromosome 6p) in RLS with PLMS, suggesting that this is a distinct phenotype, different from RLS without PLMS.[36] Some research has suggested PLMS may serve as an objective measure for RLS and be an endophenotype for certain RLS cases.[37] A diagnosis of PLMD appears to be particularly useful in young children less than 6 years of age who do not yet have well-developed language skills and therefore cannot adequately describe the sensory component of RLS. Also useful is the awareness that the PLMD diagnosis in some school-age children may evolve to "RLS with PLMS" over time, with many of the children in a recent case series developing the sensory component in early adolescence.[38]

Prevalence of RLS, PLMS, and PLMD

Several large population-based studies have found an adult RLS prevalence of 5% to 10% in the United States and Western Europe, with about one third affected to a moderate or severe degree.[6,8-13] Recently, a large pediatric population-based study, involving over 10,000 families in the United States and United Kingdom, found a prevalence of definite RLS in 1.9% of 8- to 11-year olds and 2.0% of 12- to 17-year olds.[39] A 2% prevalence suggests that RLS affects approxi-

Table 2 NIH Workshop Diagnostic Criteria for Restless Legs Syndrome in Children and Adolescents (2003): Probable and Possible RLS

Criteria for the diagnosis of probable RLS: for research use (0 to 18 years old)		
The child has a biological parent or sibling with definite RLS		
AND		
Child meets **all 3** of the following adult criteria: ■ An urge to move the legs ■ The urge to move begins or worsens when sitting or lying down ■ The urge to move is partially or totally relieved by movement	OR	The child is observed to have behavior manifestations of lower-extremity discomfort when sitting or lying, with movement of the affected limbs. The discomfort has characteristics of adult criteria 2, 3, and 4: worse during rest and inactivity, relieved by movement, and worse during the evening and night.*
*This last category is intended for young children or cognitively-impaired children, who do not have sufficient language to describe the sensory component of RLS.		
Criteria for the diagnosis of possible RLS: for research use (0 to 18 years old)		
The child has a biological parent or sibling with definite RLS	AND	The child has periodic limb movement disorder

Table 3 Diagnostic Criteria for PLMD

Criteria for the diagnosis of PLMD

A. Polysomnography shows repetitive, highly stereotyped limb movements that are:
- **0.5 to 10 seconds in duration**
- **Minimum amplitude of 8 microV above resting EMG**
- **In a sequence of 4 or more movements**
- **Separated by an interval of more than 5 seconds (from limb-movement onset to limb-movement onset) and less than 90 seconds (typically there is an interval of 20-40 seconds).**

B. The PLMS index exceeds 5/h in pediatric cases and 15/h in most adult cases.

C. There is clinical sleep disturbance or a complaint of daytime fatigue.

D. The PLMS are not better explained by another current sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder (eg, PLMS at the termination of cyclically occurring apneas should not be counted as true PLMS or PLMD).

mately 984,000 of the school-age pediatric population in the United States.[40] Similar to adult RLS prevalence studies, one quarter to half of the affected 8- to 17-year olds in this population were reported to have moderate to severe symptoms. In addition, this 2% prevalence is consistent with adult RLS studies that indicate childhood onset in approximately 25% of cases.[35,41,42] Pediatric RLS has been found to manifest without significant gender differences,[39] which is in contrast to the 2:1 female-to-male ratio seen in adult RLS.[8]

In clinic-based studies, a pediatric RLS prevalence of 5.9% was found at the Mayo Clinic Pediatric Sleep Disorders Clinic,[22] and another study found a prevalence of 1.3% in 12 pediatric practices.[43] In addition, a study that included a question about "leg restlessness at bedtime" found positive reports in 6.1% of Canadian children aged 11 to 13 years old.[44]

PLMS >5/h in children referred for sleep studies has been reported in 5.6%, 23%, and 26% of sequential cases.[45-47] In these studies, there was considerable comorbidity with sleep disorder breathing, although a subset of these children had no evidence for disordered breathing. Another study reported pediatric PLMD in 11.9% of a community survey and 8.4% of a sleep-referral population.[48] PLMS have been found to be significantly more prevalent among Caucasian children than African-American children.[49] In summary, neither pediatric RLS nor PLMD appear to be uncommon, although it is clear that some cases are mild and unlikely to require specific treatment.

Diagnosis in Children and Adolescents

Diagnosing RLS in children and adolescents is more challenging than with adults because symptoms may present somewhat differently or not yet be fully manifest. To help promote an accurate diagnosis, pediatric-specific diagnostic criteria for RLS were published in 2003 as the result of a consensus workshop at the National Institutes of Health in Bethesda, MD (Tables 1 and 2).[2] For adolescents, the adult diagnostic criteria should be used. For children 12 years or younger, either of the 2 definite RLS definitions may be used, although our extensive survey and clinical experience have shown that most children with definite RLS will meet criteria for the first or "definite 1 RLS" category. Definite RLS is intended for clinical use in children 12 years or younger, with probable and possible RLS intended for research in children and adolescents ages 0 to 18 years (Tables 1 and 2).

RLS diagnostic considerations include a description of RLS sensations by the child, the presence and nature of any sleep disturbance, investigation of differential or contributing factors, family history, physical examination, and, in some cases, a sleep study.

In children, a good way to ask about RLS is to first explain that we all have had feelings in our bodies, such as a stomachache or headache. Other feelings may or may not be something everyone experiences. It is then useful to ask, "When you are in bed at night, do your legs bother you?" If the response is positive, then, "Tell me more" can often help elicit the other 3 essential diagnostic features of RLS. If the response is negative, then asking the parent about the child having leg aches or "growing pains" at night may help with the recollection of any RLS-like sensations. The discomfort aspect of RLS can be addressed by asking, "Is that a good or bad feeling?" If "growing pains" are reported, these may or may not represent RLS.[23,50]

Restless legs sensations are typically described by the child using age-appropriate terms such as "they won't stay still," "they want to move," "tickle," "want to run," "bugs," "spiders," "ants," and "a lot of energy in my legs." The terms "urge" and "discomfort" are too difficult to understand for most young children, and, as a result, the simpler words should be accepted for diagnosis.[2]

The diagnosis of PLMD involves assessment for the 4 diagnostic criteria in Table 3.[2,31] In some children and adolescents, sleep disturbance and PLMS predominate as symptoms, and leg discomfort may be absent or too intermittent to diagnose RLS. One study found that chronic, clinical sleep disturbance preceded specific RLS feelings by 11 years in a series of children who eventually developed definite RLS.[38] Importantly, substantial normative data have shown that PLMS >5/h are uncommon in children, adolescents, and adults less than 40 years of age.[16,17,48,49,51-55] An overnight polysomnogram is needed to quantify the repetitive leg jerking and disturbed sleep associated with PLMD. For an accurate diagnosis, observation alone has not been found to be sufficient.[18,56] It is important that sleep studies are performed according to standard methodology and are properly scored.[31,34] In particular, digital sampling rates of at least 256 Hz, low impedances of less than 10,000 ohms, sensitivity limits of −100 and 100 microvolts, and avoidance of notch or high-frequency filters are recommended for the leg channels. Another important aspect is that night-to-night variability of PLMS has been documented in adults,[57-60] and cases of PLMS indices varying from normal to abnormal have been

Table 4 Differential Diagnosis of Pediatric Restless Legs Syndrome

Common, potential mimics of pediatric RLS:
■ Transient nerve compression
■ Sore muscles
■ Leg cramps
■ Dermatitis
■ Orthopedic problems
Less common in pediatric age range:
■ Peripheral neuropathy
■ Radiculopathy
■ Myopathy

observed in children and adolescents (Picchietti D, April, 2008 unpublished data).

Differential Diagnosis

Potential mimics of pediatric RLS should be considered during assessment (Table 4). Transient nerve compression is typically caused by sitting on or crossing the legs for extended periods of time. Muscles may be sore after intense physical activity. About 7% of children have nocturnal leg cramps, which usually occur infrequently. Dermatitis, such as eczema, psoriasis, contact dermatitis, and bug bites, all present with overt skin changes. Orthopedic problems such as a sprained ankle, patellofemoral conditions, Osgood-Schlatter disease, arthralgias, and arthritis are usually associated with physical findings and are typically worse with movement, not better as in RLS. Uncommon mimics in the pediatric age range include peripheral neuropathy, radiculopathy, and myopathy.

Secondary RLS has been described in adults, with renal failure and pregnancy as the conditions most frequently associated with this variant of RLS.[61] In children, primary, familial RLS appears to be most common, although RLS in pediatric dialysis patients has been described.[62]

PLMS are seen in other sleep disorders such as narcolepsy and rapid eye movement (REM) sleep behavior disorder as well as found in association with obstructive sleep apnea. PLMS may be induced or worsened by certain medications, particularly serotonergic antidepressants.[63] PLMS are common in spinal cord injury and multiple-system atrophy.[64,65] When PLMS and moderate to severe daytime sleepiness are present, testing for narcolepsy should be pursued because this severity of sleepiness is uncommon in children with RLS or PLMD.[18,38] Sleep starts (hypnic jerks) are typically limited to the transition from wakefulness to sleep, are not periodic, and are briefer than PLMS. Normal phasic REM activity is limited to REM sleep and typically occurs in bursts rather than in the 20- to 40-second periodicity usually seen with PLMS. In most forms of myoclonic epilepsy, movements are prominent during wakefulness.

Connection to Low Iron Levels

Remarkable data have shown serum ferritin levels below 50 ng/mL to be associated with increased severity of RLS in adults,[66,67] and an increased prevalence of RLS has been found in iron-deficiency anemia as well as in blood donors.[68,69] Further evidence supporting a role of iron in RLS and the related motor component, periodic limb movements in sleep, includes magnetic resonance imaing data,[70] autopsy data,[71] intravenous iron studies,[72,73] and the results of oral iron treatment in adult and pediatric cases.[20,66,74] In 2 pediatric RLS case series, serum ferritin levels were found to be less than median normative values for age and sex in 75% and 72% of cases, respectively.[22,38] In a sample of children with ADHD, serum ferritin <12 ng/mL was found more often in children with RLS than in children with ADHD alone.[75] Particularly at risk for iron deficiency are infants, toddlers, teens, and especially female adolescents who are menstruating or pregnant.

Although suboptimal ferritin levels do not appear to be the sole cause of RLS symptoms, iron deficiency may contribute to the severity or expression of RLS symptoms in a significant number of cases.

Association With Cognitive and Affective Problems

Poor sleep has been shown to impair cognitive functions, including attention and memory, as well as emotional regulation in childhood and adolescence.[76-78] When sleep deprived, children and adolescents are often overtly moody rather than sleepy. Poor sleep can result in negative affect, easy frustration, and difficulty controlling impulses and emotions.[79-81] In adolescents, a recent study found a lower grade point average in association with RLS symptoms.[82] In adult RLS, cognitive deficits have been described, including an approximate 26% prevalence of ADHD.[83,84]

Several studies have reported an association between ADHD, RLS, and PLMD in children and adolescents.[15-17,19,76,85,86] Although it is clear that these disorders are not always comorbid, studies to date suggest that about one quarter of school-age children with ADHD meet criteria for RLS and, conversely, that about one quarter with RLS meet ADHD criteria[39,75,87,88] With the exclusion of "motor restlessness" as part of the diagnostic criteria for RLS in 2003, there is no longer any overlap of the diagnostic criteria for ADHD and RLS,[2] and, as a result, it has become easier to differentiate these distinct but apparently related conditions.

Although the relationship between these 3 disorders is complex and not yet fully understood, it is possible that underactivity of dopamine is a common etiologic factor.[89-91] Furthermore, ADHD, RLS, and PLMS are all associated with low iron stores.[75,92-94] The finding of relative iron deficiency is consistent with pathophysiological models of these disorders because iron is needed for dopamine synthesis.[94] In cases of comorbidity, boosting ferritin levels to treat RLS symptoms is likely to improve ADHD symptoms.[95,96]

Depression and anxiety are common in adults with RLS, occurring much more frequently than in the general population.[97-99] Potentially relevant is that persistent insomnia is a very strong predictor of depression in adults[100-102] with an odds ratio of 39.8 in 1 study.[103] In children, it has also been

found that sleep problems predict the development of mood and anxiety disorders.[104,105] Although causation has not been proven, such a relationship has been posited and, if accurate, indicates an interesting opportunity for prevention.[106-108] In a recent pediatric RLS case series, 8 of 18 children had comorbid anxiety and/or depression, which in all cases developed after the historical onset of clinical sleep disturbance.[38]

Genetic Influences

In addition to the dopamine-deficiency model of RLS as an area of ongoing research, genetic contributions to RLS and PLMS have been investigated.[37]

RLS is highly familial in early-onset cases (ie, cases with symptoms first occurring before 35 to 40 years of age).[109,110] The adult RLS literature has reported 40% to 92% of early-onset cases being familial, with much lower rates in late-onset and secondary RLS.[37,41,42,111-114] In a population-based study of pediatric RLS, parental history indicative of RLS was found in 71% of children 8 to 11 years old and 80% of 12- to 17-year olds.[39] Remarkably, both biologic parents reported being affected in 16% of cases in this study. In the clinical setting, we have found a positive family history of RLS in a biologic first-degree relative to be helpful in raising diagnostic certainty of RLS in pediatric cases as well as indicating the possibility of RLS developing over time in children who do not meet full RLS criteria at the time of initial evaluation. However, there are instances in which this information is not available, such as cases in which the child is adopted.

In addition, results from linkage, association, and twin studies have found RLS to be a highly heritable trait.[37] The exact mode of inheritance remains controversial, with some studies implicating an autosomal-dominant pattern and others a pseudodominant autosomal-recessive mode of inheritance. Comprehensively, the current literature suggests that perhaps the best model may involve the presence of more than 1 dominant RLS gene, influenced by gender and environmental factors, such as iron status.

Two recent genome-wide studies have found a variant of BTBD9 on chromosome 6p to be implicated in RLS.[36,37] Interestingly, this common variant is likely a genetic determinant of PLMS. In 1 of these studies, the presence of a single allele resulted in twice the risk for RLS, with a double allele resulting in 4 times the risk.[36] In addition, serum ferritin levels were found to be decreased by 13% per allele. With this genetic variant, the population attributable risk of RLS with PLMS was approximately 50%.

Treatment Options

Better Sleep Habits

Research has shown that children and adolescents, including those with sleep disorders, benefit significantly from establishing a routine of good sleep habits. Parental involvement and supervision are paramount because children and adolescents are apt to experiment with limits on sleep, resulting in sleep deprivation that significantly aggravates their RLS symptoms and adversely affects daytime function. Typical sleep needs by age are 2 years old: 12 hours, with 1 nap included; 5 years old: 11 hours; 10 years old: 10 hours; teen: 9 hours; and adult: 7 to 8 hours. The Peds RLS NEWREST chart (Table 5) presents helpful sleep tips for individuals with RLS.

Table 5 Pediatric Behavioral Interventions

The Peds RLS NEWREST Chart: Tips for Better Sleep
N utritional needs. A healthy, age-appropriate, diet should be adopted. Any foods containing caffeine, such as chocolate, and drinks such as soda, energy drinks, iced tea, and coffee should be restricted, especially in the late afternoon and evening. Current dietary iron intake and the need for iron supplementation should be assessed.
E nvironment for sleeping. The bedroom should be relaxing, quiet, and only for sleeping. Find another room for studying, loud music, TV, and "timeout."
W atch for and report restlessness, uncomfortable leg sensations, and disturbed sleep, especially when these affect daytime function.
R egular sleep schedule with a routine bedtime and wakeup time even on weekends.
E xercise daily. Physical activity can reduce RLS sensations and increases deep sleep.
S top substance use that interferes with good sleep such as tobacco, alcohol, and recreational drugs.
T ake prescribed medicine and/or approved iron supplements consistently.

Iron Supplementation

Iron stores are easily measured by a simple, widely available blood test, serum ferritin. However, it should be recognized that ferritin levels can be falsely elevated because of inflammation, such as during a viral illness or in chronic inflammatory disorders. Although it is widely accepted that ferritin levels below 12 ng/mL are detrimental, there is now evidence that for RLS and PLMD "low normal" is not ideal. Saturation of peripheral iron stores typically occurs at ferritin levels of ≥80 to 100 ng/mL. In adult RLS cases, current consensus recommendations are to achieve a serum ferritin >50 ng/mL.[115] In children, therapeutic iron has been found to be of benefit for RLS,[20] PLMS,[74,116] and ADHD.[74,95,117] Clinical improvement with mean increases in ferritin levels from 40.8 to 74.1 ng/mL and 29.1 to 55.7 ng/mL were shown in the 2 larger of these studies.[74,95] Thus, current evidence suggests that achieving and maintaining serum ferritin above 50 ng/mL can be of benefit. Careful medical supervision of therapeutic iron administration is important because of the rare but serious complication of iron overload, which can occur in individuals genetically predisposed to hemochromatosis.[118]

Typically, iron stores increase slowly with supplemental iron over weeks to months, and buildup is delayed by physical growth and menstruation. Absorption of iron is less efficient when combined with calcium, so supplements are ideally taken at least 1 to 2 hours before or after dairy consumption. Vitamin C, contained in many fruit drinks, enhances iron absorption.

Pharmacologic Therapy

As with any clinical disorder, the decision to put a child or adolescent on medication can be difficult. In RLS and PLMD, the risks of medication must be balanced against the consequences of poor intellectual and emotional function because of the untreated sleep disorder. Typically, medication should be used in combination with nonpharmacologic treatments after such techniques have been tried and found to be ineffective and only when the sleep disorder is affecting daytime function. In some children and adolescents, nonpharmacologic interventions alone adequately treat RLS symptoms. The main goal of medication is improved daytime function through decreased RLS sensations, increased sleep quantity, and better sleep quality.

Medication Options

At the present time, there are no Food and Drug Administration–approved medications for pediatric sleep disorders.[119] Nonetheless, there is medical literature that supports the use of pharmacologic treatments in select pediatric cases. Medications used to treat children and adolescents with RLS include clonidine and clonazepam. Clonidine, the most commonly used medication for children's sleep, is particularly useful when there are severe sleep-onset problems.[120-122] Clonazepam is typically used to decrease RLS sensations and improve the quality of sleep in children. Clonazepam should be discontinued if it aggravates hyperactivity, as it is known to do in some cases of ADHD. Gabapentin can also reduce sensory and motor symptoms and improve sleep quality.[123,124] Temazepam and zolpidem have been used in adults and may be considered for use in older children and adolescents with RLS and severe, chronically disturbed sleep.[115,125]

Dopaminergics. Medications that increase dopamine have been shown to suppress RLS sensations and PLMS more effectively than any other class of medication and are considered the medications of choice for adults with moderate to severe RLS.[115,126] Dopaminergics that have been found to be effective for RLS include carbidopa/levodopa and the dopamine agonists pramipexole and ropinirole. These 2 dopamine agonists are Food and Drug Administration approved for use in adult RLS. Although data are limited, there have been published studies reporting use of dopaminergics in pediatric RLS.[18,21,22,24,38,47,127] Augmentation, which is the worsening of RLS symptoms as dopaminergic dosage is increased, occurs most commonly with carbidopa/levodopa but has also been reported with the dopamine agonists.[128,129] When augmentation is a side effect, reducing the dose or switching to another dopaminergic is usually effective.[115] Augmentation is more common when there is low serum ferritin.[130]

When there is comorbid ADHD, stimulant medication used to treat ADHD, such as methylphenidate and dextroamphetamine, has not been found to be problematic as long as the effects have worn off by bedtime.[16,131] In some cases, treatment of the sleep disorder may reduce or eliminate ADHD symptoms.[127] When there is comorbid depression or anxiety, the adult literature indicates improved results with treatment of disordered sleep and the preference of noradrenergic medication (such as bupropion) over serotonergic medication for depression.[98,132-135]

Monitoring

Sensitivity to the individual differences in pharmacologic response for pediatric RLS and PLMD patients is important because relatively wide variability in optimal dosages has been seen. In addition, medication use should be periodically monitored and be reassessed once iron stores have been increased.

Family Support

Positive parental involvement and support are important in the treatment of pediatric RLS and PLMD. Advocating for the child in school may be necessary for academic accommodations. Adolescent self-awareness of RLS and PLMD encourages better responsibility and understanding in overcoming symptoms. In addition, because RLS is highly familial, it is not unusual for a parent to be affected. Appropriate referral and treatment for the affected parent may be of substantial benefit for both the parent and child because of the high prevalence of cognitive dysfunction and depression in adults with RLS.

Conclusion

In the past 15 years, a substantial number of studies have been published on pediatric RLS and PLMD, resulting in greater awareness of these disorders and their significant effects on quality of life. The need for further research has been validated by prevalence studies indicating the common occurrence of RLS and PLMD. Recently, diagnostic criteria have been developed for children. The relationship between RLS, PLMD, and comorbid disorders is currently under further investigation. Emerging knowledge of how iron deficiency and genetics contribute to the manifestations of RLS and PLMD symptoms is promising. We hope that future RLS and PLMD research will lead to better validated treatment options for patients suffering from these disorders.

References

1. Earley CJ: Clinical practice. Restless legs syndrome. N Engl J Med 348:2103-2109, 2003
2. Allen RP, Picchietti D, Hening WA, et al: 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 4:101-119, 2003
3. Hornyak M, Feige B, Voderholzer U, et al: Polysomnography findings in patients with restless legs syndrome and in healthy controls: A comparative observational study. Sleep 30:861-865, 2007
4. Abetz L, Allen R, Washburn T, et al: The impact of restless legs syndrome (RLS) on sleep and cognitive function. Eur J Neurol 9:50, 2004 (suppl 2)
5. Hornyak M, Kopasz M, Berger M, et al: Impact of sleep-related complaints on depressive symptoms in patients with restless legs syndrome. J Clin Psychiatry 66:1139-1145, 2005

6. Allen RP, Walters AS, Montplaisir J, et al: Restless legs syndrome prevalence and impact: REST general population study. Arch Intern Med 165:1286-1292, 2005
7. Abetz L, Allen R, Follet A, et al: Evaluating the quality of life of patients with restless legs syndrome. Clin Ther 26:925-935, 2004
8. Berger K, Luedemann J, Trenkwalder C, et al: Sex and the risk of restless legs syndrome in the general population. Arch Intern Med 164:196-202, 2004
9. Bjorvatn B, Leissner L, Ulfberg J, et al: Prevalence, severity and risk factors of restless legs syndrome in the general adult population in two Scandinavian countries. Sleep Med 6:307-312, 2005
10. Hogl B, Kiechl S, Willeit J, et al: Restless legs syndrome: A community-based study of prevalence, severity, and risk factors. Neurology 64: 1920-1924, 2005
11. Tison F, Crochard A, Leger D, et al: Epidemiology of restless legs syndrome in French adults: A nationwide survey: The INSTANT Study. Neurology 65:239-246, 2005
12. Ulfberg J, Nystrom B, Carter N, et al: Prevalence of restless legs syndrome among men aged 18 to 64 years: An association with somatic disease and neuropsychiatric symptoms. Mov Disord 16:1159-1163, 2001
13. Ulfberg J, Nystrom B, Carter N, et al: Restless Legs Syndrome among working-aged women. Eur Neurol 46:17-19, 2001
14. Walters AS, Picchietti DL, Ehrenberg BL, et al: Restless legs syndrome in childhood and adolescence. Pediatr Neurol 11:241-245, 1994
15. Picchietti DL, Walters AS: Restless legs syndrome and periodic limb movement disorder in children and adolescents: Comorbidity with attention-deficit hyperactivity disorder. Child Adoles Psych Clinics North Am 5:729-740, 1996
16. Picchietti DL, England SJ, Walters AS, et al: Periodic limb movement disorder and restless legs syndrome in children with attention-deficit hyperactivity disorder. J Child Neurol 13:588-594, 1998
17. Picchietti DL, Underwood DJ, Farris WA, et al: Further studies on periodic limb movement disorder and restless legs syndrome in children with attention-deficit hyperactivity disorder. Mov Disord 14: 1000-1007, 1999
18. Picchietti DL, Walters AS: Moderate to severe periodic limb movement disorder in childhood and adolescence. Sleep 22:297-300, 1999
19. Chervin RD, Archbold KH, Dillon JE, et al: Associations between symptoms of inattention, hyperactivity, restless legs, and periodic leg movements. Sleep 25:213-218, 2002
20. Kryger MH, Otake K, Foerster J: Low body stores of iron and restless legs syndrome: A correctable cause of insomnia in adolescents and teenagers. Sleep Med 3:127-132, 2002
21. Guilleminault C, Palombini L, Pelayo R, et al: Sleepwalking and sleep terrors in prepubertal children: What triggers them? Pediatrics 111: e17-e25, 2003
22. Kotagal S, Silber MH: Childhood-onset restless legs syndrome. Ann Neurol 56:803-807, 2004
23. Rajaram SS, Walters AS, England SJ, et al: Some children with growing pains may actually have restless legs syndrome. Sleep 27:767-773, 2004
24. Konofal E, Arnulf I, Lecendreux M, et al: Ropinirole in a child with attention-deficit hyperactivity disorder and restless legs syndrome. Pediatr Neurol 32:350-351, 2005
25. Happe S, Treptau N, Ziegler R, et al: Restless legs syndrome and sleep problems in children and adolescents with insulin-dependent diabetes mellitus type 1. Neuropediatrics 36:98-103, 2005
26. Cortese S, Konofal E, Lecendreux M, et al: Restless legs syndrome triggered by heart surgery. Pediatr Neurol 35:223-226, 2006
27. Mohri I, Kato-Nishimura K, Tachibana N, et al: Restless legs syndrome (RLS): An unrecognized cause for bedtime problems and insomnia in children. Sleep Med, 2007, Oct 6 [Epub ahead of print]
28. Hornyak M, Happe S, Trenkwalder C, et al: Restless legs syndrome in childhood: A consensus proposal for diagnostic criteria. Somnologie 6:133-137, 2002
29. Recording and scoring leg movements. The Atlas Task Force. Sleep 16:748-759, 1993
30. ASDA: International Classification of Sleep Disorders, Revised: Diagnostic and Coding Manual. Rochester, MN, American Sleep Disorders Association 1997, p 401
31. American Academy of Sleep Medicine.: International Classification of Sleep Disorders, Second Edition: Diagnostic and Coding Manual. Westchester, IL, American Academy of Sleep Medicine, 2005
32. Pennestri MH, Montplaisir J, Colombo R, et al: Nocturnal blood pressure changes in patients with restless legs syndrome. Neurology 68: 1213-1218, 2007
33. Silber MH: Commentary on controversies in sleep medicine. Periodic leg movements are not more prevalent in insomnia or hypersomnia but are specifically associated with sleep disorders involving a dopaminergic mechanism. Sleep Med 2:367-369, 2001
34. Iber C, Ancoli-Israel S, Chesson A, et al: The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications (ed 1). Westchester, IL, American Academy of Sleep Medicine, 2007
35. Montplaisir J, Boucher S, Poirier G, et al: Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: A study of 133 patients diagnosed with new standard criteria. Mov Disord 12:61-65, 1997
36. Stefansson H, Rye DB, Hicks A, et al: A genetic risk factor for periodic limb movements in sleep. N Engl J Med 357:639-647, 2007
37. Winkelmann J, Polo O, Provini F, et al: Genetics of restless legs syndrome (RLS): State-of-the-art and future directions. Mov Disord 22: 449-458, 2007 (suppl 18)
38. Picchietti D, Stevens HE: Early manifestations of restless legs syndrome in childhood and adolescence. Sleep Med 2007 Nov 15; [Epub ahead of print]
39. Picchietti D, Allen RP, Walters AS, et al: Restless legs syndrome: prevalence and impact in children and adolescents—The Peds REST study. Pediatrics 120:253-266, 2007
40. United States: Children Characterisitics. 2006 American Community Survey. U.S. Census Bureau, 2006. Available at: http://factfinder.census.gov. Accessed January 08, 2008
41. Walters AS, Hickey K, Maltzman J, et al: A questionnaire study of 138 patients with restless legs syndrome: The 'Night-Walkers' survey. Neurology 46:92-95, 1996
42. Bassetti CL, Mauerhofer D, Gugger M, et al: Restless legs syndrome: A clinical study of 55 patients. Eur Neurol 45:67-74, 2001
43. Kinkelbur J, Hellwig J, Hellwig M: Frequency of RLS symptoms in childhood. Somnologie 7:34, 2003 (suppl 1)
44. Laberge L, Tremblay RE, Vitaro F, et al: Development of parasomnias from childhood to early adolescence. Pediatrics 106:67-74, 2000
45. Kirk VG, Bohn S: Periodic limb movements in children: prevalence in a referred population. Sleep 27:313-315, 2004
46. Chervin RD, Archbold KH: Hyperactivity and polysomnographic findings in children evaluated for sleep-disordered breathing. Sleep 24:313-320, 2001
47. Martinez S, Guilleminault C: Periodic leg movements in prepubertal children with sleep disturbance. Dev Med Child Neurol 46:765-770, 2004
48. Crabtree VM, Ivanenko A, O'Brien LM, et al: Periodic limb movement disorder of sleep in children. J Sleep Res 12:73-81, 2003
49. O'Brien LM, Holbrook CR, Faye Jones V, et al: Ethnic difference in periodic limb movements in children. Sleep Med 8:240-246, 2007
50. Walters AS: Is there a subpopulation of children with growing pains who really have restless legs syndrome? A review of the literature. Sleep Med 3:93-98, 2002
51. Montgomery-Downs HE, O'Brien LM, Gulliver TE, et al: Polysomnographic characteristics in normal preschool and early school-aged children. Pediatrics 117:741-753, 2006
52. Pennestri MH, Whittom S, Adam B, et al: PLMS and PLMW in healthy subjects as a function of age: Prevalence and interval distribution. Sleep 29:1183-1187, 2006
53. Traeger N, Schultz B, Pollock AN, et al: Polysomnographic values in children 2-9 years old: Additional data and review of the literature. Pediatr Pulmonol 40:22-30, 2005

54. Tayag-Kier CE, Keenan GF, Scalzi LV, et al: Sleep and periodic limb movement in sleep in juvenile fibromyalgia. Pediatrics 106:E70, 2000
55. Arens R, Wright B, Elliott J, et al: Periodic limb movement in sleep in children with Williams syndrome. J Pediatr 133:670-674, 1998
56. Hilbert J, Mohsenin V: Can periodic limb movement disorder be diagnosed without polysomnography? A case-control study. Sleep Med 4:35-41, 2003
57. Culpepper WJ, Badia P, Shaffer JI: Time-of-night patterns in PLMS activity. Sleep 15:306-311, 1992
58. Edinger JD, McCall WV, Marsh GR, et al: Periodic limb movement variability in older DIMS patients across consecutive nights of home monitoring. Sleep 15:156-161, 1992
59. Haba-Rubio J, Staner L, Macher JP: Periodic arousals or periodic limb movements during sleep? Sleep Med 3:517-520, 2002
60. Hornyak M, Kopasz M, Feige B, et al: Variability of periodic leg movements in various sleep disorders: Implications for clinical and pathophysiologic studies. Sleep 28:331-335, 2005
61. Gamaldo CE, Earley CJ: Restless legs syndrome: A clinical update. Chest 130:1596-1604, 2006
62. Davis ID, Baron J, O'Riordan MA, et al: Sleep disturbances in pediatric dialysis patients. Pediatr Nephrol 20:69-75, 2005
63. Yang C, White DP, Winkelman JW: Antidepressants and periodic leg movements of sleep. Biol Psychiatry 58:510-514, 2005
64. Lee MS, Choi YC, Lee SH, et al: Sleep-related periodic leg movements associated with spinal cord lesions. Mov Disord 11:719-722, 1996
65. Wetter TC, Collado-Seidel V, Pollmacher T, et al: Sleep and periodic leg movement patterns in drug-free patients with Parkinson's disease and multiple system atrophy. Sleep 23:361-367, 2000
66. O'Keeffe ST, Gavin K, Lavan JN: Iron status and restless legs syndrome in the elderly. Age Ageing 23:200-203, 1994
67. Sun ER, Chen CA, Ho G, et al: Iron and the restless legs syndrome. Sleep 21:371-377, 1998
68. Rangarajan S, D'Souza GA: Restless legs syndrome in Indian patients having iron deficiency anemia in a tertiary care hospital. Sleep Med 9:88-93, 2007
69. Ulfberg J, Nystrom B: Restless legs syndrome in blood donors. Sleep Med 5:115-118, 2004
70. Earley CJ, Barker PB, Horska A, et al: MRI-determined regional brain iron concentrations in early- and late-onset restless legs syndrome. Sleep Med 7:458-461, 2006
71. Connor JR, Boyer PJ, Menzies SL, et al: Neuropathological examination suggests impaired brain iron acquisition in restless legs syndrome. Neurology 61:304-309, 2003
72. Earley CJ, Heckler D, Allen RP: The treatment of restless legs syndrome with intravenous iron dextran. Sleep Med 5:231-235, 2004
73. Earley CJ, Heckler D, Allen RP: Repeated IV doses of iron provides effective supplemental treatment of restless legs syndrome. Sleep Med 6:301-305, 2005
74. Simakajornboon N, Gozal D, Vlasic V, et al: Periodic limb movements in sleep and iron status in children. Sleep 26:735-738, 2003
75. Oner P, Dirik EB, Taner Y, et al: Association between low serum ferritin and restless legs syndrome in patients with attention deficit hyperactivity disorder. Tohoku J Exp Med 213:269-276, 2007
76. Lewin DS, Di Pinto M: Sleep disorders and ADHD: Shared and common phenotypes. Sleep 27:188-189, 2004
77. Sadeh A, Gruber R, Raviv A: The effects of sleep restriction and extension on school-age children: What a difference an hour makes. Child Dev 74:444-455, 2003
78. Steenari MR, Vuontela V, Paavonen EJ, et al: Working memory and sleep in 6- to 13-year-old schoolchildren. J Am Acad Child Adolesc Psychiatry 42:85-92, 2003
79. Chervin RD, Dillon JE, Archbold KH, et al: Conduct problems and symptoms of sleep disorders in children. J Am Acad Child Adolesc Psychiatry 42:201-208, 2003
80. Dahl RE: The impact of inadequate sleep on children's daytime cognitive function. Semin Pediatr Neurol 3:44-50, 1996
81. Dahl RE, Lewin DS: Pathways to adolescent health sleep regulation and behavior. J Adolesc Health 31:175-184, 2002
82. Pagel JF, Forister N, Kwiatkowki C: Adolescent sleep disturbance and school performance: The confounding variable of socioeconomics. J Clin Sleep Med 3:19-23, 2007
83. Pearson VE, Allen RP, Dean T, et al: Cognitive deficits associated with restless legs syndrome (RLS). Sleep Med 7:25-30, 2006
84. Wagner ML, Walters AS, Fisher BC: Symptoms of attention-deficit/hyperactivity disorder in adults with restless legs syndrome. Sleep 27:1499-1504, 2004
85. Cortese S, Konofal E, Lecendreux M, et al: Restless legs syndrome and attention-deficit/hyperactivity disorder: A review of the literature. Sleep 28:1007-1013, 2005
86. Sadeh A, Pergamin L, Bar-Haim Y: Sleep in children with attention-deficit hyperactivity disorder: A meta-analysis of polysomnographic studies. Sleep Med Rev 10:381-398, 2006
87. Wiggs L, Montgomery P, Stores G: Actigraphic and parent reports of sleep patterns and sleep disorders in children with subtypes of attention-deficit hyperactivity disorder. Sleep 28:1437-1445, 2005
88. Silvestri R, Gagliano A, Calarese T, et al: Ictal and interictal EEG abnormalities in ADHD children recorded over night by video-polysomnography. Epilepsy Res 75:130-137, 2007
89. Allen R: Dopamine and iron in the pathophysiology of restless legs syndrome (RLS). Sleep Med 5:385-391, 2004
90. Wilens TE, Dodson W: A clinical perspective of attention-deficit/hyperactivity disorder into adulthood. J Clin Psychiatry 65:1301-1313, 2004
91. Roman T, Rohde LA, Hutz MH: Polymorphisms of the dopamine transporter gene: Influence on response to methylphenidate in attention deficit-hyperactivity disorder. Am J Pharmacogenomics 4:83-92, 2004
92. Konofal E, Lecendreux M, Arnulf I, et al: Iron deficiency in children with attention-deficit/hyperactivity disorder. Arch Pediatr Adolesc Med 158:1113-1115, 2004
93. Konofal E, Cortese S, Marchand M, et al: Impact of restless legs syndrome and iron deficiency on attention-deficit/hyperactivity disorder in children. Sleep Med 8:711-715, 2007
94. Earley CJ, Allen RP, Beard JL, et al: Insight into the pathophysiology of restless legs syndrome. J Neurosci Res 62:623-628, 2000
95. Konofal E, Lecendreux M, Deron J, et al: Effects of iron supplementation on attention deficit hyperactivity disorder in children. Pediatr Neurol 38:20-26, 2008
96. Picchietti D: Is iron deficiency an underlying cause of pediatric restless legs syndrome and of attention-deficit/hyperactivity disorder? Sleep Med 8:693-694, 2007
97. Sevim S, Dogu O, Kaleagasi H, et al: Correlation of anxiety and depression symptoms in patients with restless legs syndrome: A population based survey. J Neurol Neurosurg Psychiatry 75:226-230, 2004
98. Picchietti D, Winkelman JW: Restless legs syndrome, periodic limb movements in sleep, and depression. Sleep 28:891-898, 2005
99. Winkelmann J, Prager M, Lieb R, et al: "Anxietas tibiarum." Depression and anxiety disorders in patients with restless legs syndrome J Neurol 252:67-71, 2005
100. Breslau N, Roth T, Rosenthal L, et al: Sleep disturbance and psychiatric disorders: A longitudinal epidemiological study of young adults. Biol Psychiatry 39:411-418, 1996
101. Chang PP, Ford DE, Mead LA, et al: Insomnia in young men and subsequent depression. The Johns Hopkins Precursors Study. Am J Epidemiol 146:105-114, 1997
102. Taylor DJ, Lichstein KL, Durrence HH, et al: Epidemiology of insomnia, depression, and anxiety. Sleep 28:1457-1464, 2005
103. Ford DE, Kamerow DB: Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? JAMA 262: 1479-1484, 1989
104. Ong SH, Wickramaratne P, Tang M, et al: Early childhood sleep and eating problems as predictors of adolescent and adult mood and anxiety disorders. J Affect Disord 96:1-8, 2006
105. Gregory AM, Caspi A, Eley TC, et al: Prospective longitudinal associations between persistent sleep problems in childhood and anxiety and depression disorders in adulthood. J Abnorm Child Psychol 33: 157-163, 2005

106. Lustberg L, Reynolds CF: Depression and insomnia: Questions of cause and effect. Sleep Med Rev 4:253-262, 2000
107. Tsuno N, Besset A, Ritchie K: Sleep and depression. J Clin Psychiatry 66:1254-1269, 2005
108. Turek FW: Insomnia and depression: If it looks and walks like a duck. Sleep 28:1362-1363, 2005
109. Hanson M, Honour M, Singleton A, et al: Analysis of familial and sporadic Restless Legs Syndrome in age of onset, gender, and severity features. J Neurol 251:1398-1401, 2004
110. Whittom S, Dauvilliers Y, Pennestri MH, et al: Age-at-onset in restless legs syndrome: A clinical and polysomnographic study. Sleep Med 9:54-59, 2007
111. Lavigne GJ, Montplaisir JY: Restless Legs Syndrome and sleep bruxism: Prevalence and association among Canadians. Sleep 17:739-743, 1994
112. Ondo W, Jankovic J: Restless legs syndrome: Clinicoetiologic correlates. Neurology 47:1435-1441, 1996
113. Allen RP, Earley CJ: Defining the phenotype of the restless legs syndrome (RLS) using age-of-symptom-onset. Sleep Med 1:11-19, 2000
114. Winkelmann J, Wetter TC, Collado-Seidel V, et al: Clinical characteristics and frequency of the hereditary restless legs syndrome in a population of 300 patients. Sleep 23:597-602, 2000
115. Silber MH, Ehrenberg BL, Allen RP, et al: An algorithm for the management of restless legs syndrome. Mayo Clin Proc 79:916-922, 2004
116. Simakajornboon N, Kheirandish-Gozal L, Gozal D, et al: A long-term follow-up study of periodic limb movement disorders in children after iron therapy. Sleep 29:A76-A77, 2006 (abstr)
117. Konofal E, Cortese S, Lecendreux M, et al: Effectiveness of iron supplementation in a young child with attention-deficit/hyperactivity disorder. Pediatrics 116:e732-e734, 2005
118. Barton JC, Wooten VD, Acton RT: Hemochromatosis and iron therapy of restless legs syndrome. Sleep Med 2:249-251, 2001
119. Mindell JA, Emslie G, Blumer J, et al: Pharmacologic management of insomnia in children and adolescents: Consensus statement. Pediatrics 117:e1223-e1232, 2006
120. Newcorn JH, Schulz K, Harrison M, et al: Alpha 2 adrenergic agonists. Neurochemistry, efficacy, and clinical guidelines for use in children. Pediatr Clin North Am 45:1099-1022, 1998
121. Owens JA, Rosen CL, Mindell JA: Medication use in the treatment of pediatric insomnia: Results of a survey of community-based pediatricians. Pediatrics 111:e628-e635, 2003
122. Prince JB, Wilens TE, Biederman J, et al: Clonidine for sleep disturbances associated with attention-deficit hyperactivity disorder: A systematic chart review of 62 cases. J Am Acad Child Adolesc Psychiatry 35:599-605, 1996
123. Garcia-Borreguero D, Larrosa O, de la Llave Y, et al: Treatment of Restless Legs Syndrome with gabapentin: A double-blind, cross-over study. Neurology 59:1573-1579, 2002
124. Happe S, Sauter C, Klosch G, et al: Gabapentin versus ropinirole in the treatment of idiopathic restless legs syndrome. Neuropsychobiology 48:82-86, 2003
125. Hening W, Allen R, Earley C, et al: The treatment of restless legs syndrome and periodic limb movement disorder. An American Academy of Sleep Medicine review. Sleep 22:970-999, 1999
126. Hening WA, Allen RP, Earley CJ, et al: An update on the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. Sleep 27:560-583, 2004
127. Walters AS, Mandelbaum DE, Lewin DS, et al: Dopaminergic therapy in children with restless legs/periodic limb movements in sleep and ADHD. Dopaminergic Therapy Study Group. Pediatr Neurol 22:182-186, 2000
128. Allen RP, Earley CJ: Augmentation of the restless legs syndrome with carbidopa/levodopa. Sleep 19:205-213, 1996
129. Garcia-Borreguero D: Augmentation: understanding a key feature of RLS. Sleep Med 5:5-6, 2004
130. Trenkwalder C, Hogl B, Benes H, et al: Augmentation in restless legs syndrome is associated with low ferritin. Sleep Med 2007, Oct 5 [Epub ahead of print]
131. O'Brien LM, Ivanenko A, Crabtree VM, et al: The effect of stimulants on sleep characteristics in children with attention deficit/hyperactivity disorder. Sleep Med 4:309-316, 2003
132. Kim SW, Shin IS, Kim JM, et al: Bupropion may improve restless legs syndrome: A report of three cases. Clin Neuropharmacol 28:298-301, 2005
133. Malek-Ahmadi P: Bupropion, periodic limb movement disorder, and ADHD (letter). J Am Acad Child Adolesc Psychiatry 38:637-638, 1999
134. Nofzinger EA, Fasiczka A, Berman S, et al: Bupropion SR reduces periodic limb movements associated with arousals from sleep in depressed patients with periodic limb movement disorder. J Clin Psychiatry 61:858-862, 2000
135. Trivedi MH, Rush AJ, Carmody TJ, et al: Do bupropion SR and sertraline differ in their effects on anxiety in depressed patients? J Clin Psychiatry 62:776-781, 2001