Restless Legs Syndrome from Black's Medical Dictionary, 43rd Edition
(Also called Willis-Ekbom disease). A condition in which a person experiences unpleasant sensations, and occasionally involuntary movements, in the legs when at rest, especially at night. In most cases the cause remains a mystery.

Restless legs syndrome (RLS) is a sensorimotor disorder that affects 7–15% of the general population and almost 2% of children. Essential diagnostic criteria include an urge to move the legs usually accompanied or caused by uncomfortable and unpleasant sensations that begins or worsens during rest and is relieved by activity and is worse in the evening or night.

There are two types of RLS: primary and secondary. Primary is genetic or idiopathic and secondary is due to a precipitating disorder. The pathology of RLS is unknown. Strong evidence suggests involvement of iron and dopamine. Dopamine agonists are currently the treatment of choice. Opioids, gabapentin, and benzodiazepines may also be effective.

Keywords
- Dopamine
- International Restless Legs Syndrome Study Group (IRLSSG)
- Iron
- Periodic limb movements in sleep (PLMS)
- Restless legs syndrome (RLS)

Definition and History
Restless legs syndrome (RLS) is a neurological disorder associated with sensory and motor symptoms. Sir Thomas Willis published the original description of RLS in 1672. During the nineteenth century, RLS was considered a form of hysteria or neurasthenia. Theodor Wittmaack, a German physician, called the condition ‘anxietas tibiarum.’ RLS was not recognized as a neurological disorder until 1923 when H. Oppenheim described it as a genetic neurological disorder. In 1943, F. Gerard Allison described a phenomenon ‘leg jitters’ as a common minor ailment characterized by unpleasant, unlocalized restlessness in one or both legs associated with voluntary and involuntary limb jerks and sleep disturbance. Leg jitters, according to Allison, were sometimes relieved by ‘getting up and walking.’

In 1944, based on eight cases, Karl-Axel Ekbom, a Swedish neurologist, published a description of a new syndrome, Asthenia Curum Paraethetica (Irritable legs). From 1943 to 1944, Ebkom screened 4259 patients for irritable legs and identified 20 patients with moderate to severe symptoms.

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Thinking that people with mild symptoms did not seek medical treatment, Ekbom screened 503 patients from an outpatient neurological service and an additional 503 healthy people. Of the 1006 people screened, 65 people had mild RLS symptoms: 39 patients from the outpatient clinic and 26 healthy people.

In addition, Ekbom believed that there was an association between pregnancy and irritable legs. Ekbom questioned 486 postpartum women. Fifty-five of the women described leg paresthenias during pregnancy. In 1945, based on 169 cases and his extensive study, Ekbom published a comprehensive description of the disorder. Ekbom classified symptoms as predominantly sensory or painful and renamed the disorder RLS but noted that symptoms could occur in the arms.

Ekbom and his contemporary, Dr. Nil Brage Nordlander, lectured extensively on RLS. Ekbom described the disease as ‘so common that every practicing physician meets it.’ We now know that RLS affects 7–15% of the general population and almost 2% of children. The essential symptoms of RLS as described more recently by the International Restless Legs Syndrome Study Group (IRLSSG) are as following:

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

Types of RLS

RLS is classified as primary or secondary. Primary RLS is not associated with an underlying medical or neurological abnormality or caused by a drug. Although RLS can be genetic or sporadic, most primary RLS, especially with young onset and a positive family history, are genetic.

Secondary RLS is diagnosed when a precipitating illness, medical condition or causative drug can be identified. Secondary RLS is frequently associated with uremia, diabetes, neuropathy, gastric surgery, and conditions associated with iron deficiency such as pregnancy and frequent blood donations. There is also an association with fibromyalgia, rheumatoid arthritis, and multiple sclerosis. More recently hypertension and heart disease have also been linked to RLS.

Periodic Limb Movements and RLS

Periodic limb movements in sleep (PLMS) are repetitive highly stereotyped movements that occur involuntarily at predictable intervals. Polygraphic recordings done by Coccagna and Lugaresi et al. in 1962 documented that PLMS occurred in patients with RLS. Coccagna called these movements ‘nocturnal myoclonus.’ Approximately 80% of people with RLS have PLMS. Periodic limb movements also occur in wakefulness in RLS as determined by the Suggested Immobilization Test (SIT). Although the European discovery of the BTBD9 gene was driven by RLS, the simultaneous discovery of the same gene was driven by PLMS in the Icelandic population.

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PLMS occur commonly with other sleep disorders such as narcolepsy and REM sleep behavior disorder (RBD) as well as in isolation as an incidental finding on polysomnography.

The current polysomnographic scoring criteria for PLMS include four movements in a row, 0.5–10 s duration, and spaced 5–90 s apart, at least 8 μV elevation above the baseline EMG.

**Development of Diagnostic Criteria and Classification**

In 1979 and 1990, The Diagnostic Classification Steering Committee of the American Association of Sleep Medicine developed RLS diagnostic criteria, which were published in The International Classification of Sleep Disorders: Diagnostic and Coding Manual (ICSD). In the early 1990s, physicians and scientists dedicated to research on restless legs/periodic limb movements in sleep formed the International Restless Legs Syndrome Study Group (IRLSSG). The IRLSSG felt that the 1990 definition did not include all the essential features of RLS and mistakenly included some nonessential features as well. The IRLSSG currently consists of more than 130 physicians and scientists from 17 countries. In 1995, the IRLSSG published the original consensus definition of RLS. For better clarity, the IRLSSG updated the definition and diagnostic criteria for RLS. The IRLSSG published the updated definition in 2003. This new definition was incorporated into the new International Classification of Sleep Disorders (ICSD-2) in 2005. This definition now stands as the universal definition of RLS in 2008.

The consensus definition of RLS published by the IRLSSG and the International RLS Severity Scale were instrumental in subsequent RLS research leading to FDA approved medications.

**Pathogenesis/Pathophysiology**

The pathogenesis of RLS is unknown but appears to involve iron metabolism within the central nervous system, the neurotransmitter dopamine and genetic factors.

Iron is closely linked to secondary forms of RLS. Many of the illnesses that precipitate secondary RLS are characterized by decreased iron levels: renal failure, pregnancy, frequent blood donations. Patients with RLS and low ferritin levels improve with iron therapy. Researchers have found that severity of RLS symptoms increases inversely when serum ferritin levels are decreased below 50 μg l⁻¹.

Ferritin is the major storage protein for iron and has two parts L-ferritin and H-ferritin. Transferrin is the primary iron transport protein. Transferrin is manufactured primarily in the liver and does not cross the blood brain barrier. Cerebral transferrin is manufactured within the brain. When researchers compared the cerebral spinal fluid (CSF) levels and the serum levels of ferritin, iron, and transferrin in RLS patients compared to normal controls, they found that RLS patients with normal or elevated serum iron levels had lower CSF ferritin levels and higher CSF transferrin levels than controls, suggesting a selective reduction of CSF iron. Similarly, histological and immunohistochemical studies have reported reduced brain iron. Likewise, brain magnetic resonance imaging (MRI) studies demonstrate a reduction in iron in the substantia nigra and to a lesser degree the putamen of people with RLS.

Iron is intrinsically related to dopamine. The D2 dopamine receptor is a protein that contains iron and iron is a cofactor for tyrosine hydroxylase, an enzyme that controls the rate-limiting step in the conversion of tyrosine to levodopa, a precursor to dopamine. Although patients with RLS respond to dopamine, it is possible that dopamine is deficient due to defective acquisition or utilization of
iron by brain cells.

The role of dopamine in RLS is substantiated by the remarkable benefit of dopamine drugs for RLS symptoms, and the exacerbation of symptoms associated with dopamine receptor antagonists. Similarly, opioid agents can improve symptoms and opioid antagonists can exacerbate symptoms in RLS patients treated with opioids. Thus both the endogenous dopamine and opioid systems are implicated in the pathogenesis of RLS. Further studies suggest that it is the dopaminergic system that is primarily involved, and that this is modulated by opioids. Some researchers have hypothesized that decreased dopamine-D2 receptor stimulation is responsible for RLS symptoms.

Dopaminergic PET scan studies have shown modest and variable pre and postsynaptic deficits in the nigrostriatal pathways in many studies. However, it does not appear that the predominant abnormality is in the nigrostriatal dopamine pathway, the pathway involved in Parkinson’s disease. Rather, it is thought that the dopaminergic neurons in the A11 region of the hypothalamus are involved. The A11 neurons that project to the neocortex and dorsal raphe have local connections within the hypothalamus and descend to the spinal cord as the sole source of spinal dopamine. Diencephalospinal neurons terminate predominately in the dorsal horns of the spinal cord in areas that have sensory afferent input, interneurons, somatic motor neurons and the intermediolateral nucleus (IML).

Preliminary autopsy evidence also suggests that the endogenous opioids Beta endorphin and Met enkephalin are decreased in the thalamus of patients with RLS.

Genetics and RLS

The first chromosome linkage study suggested an autosomal recessive inheritance pattern (RLS1). Subsequent studies of other possible loci suggest an autosomal dominant inheritance pattern (RLS 2, RLS 3, RLS 4, and RLS 5).

Two genome-wide association studies were published based on data from Europe and Iceland. The European researchers studied people with a familial pattern and sporadic forms of RLS. The Icelandic researchers studied people with RLS and periodic limb movements. Both groups identified a common variant in an intron of BTBD9 on chromosome 6p. Additionally, the European researchers identified a MEIS1 gene on chromosome 2p and genes encoding mitogen-activated protein kinase MAP2K5 and the transcription factor LBXCOR1 on chromosome 15q. The MEIS1 gene is thought to be associated with limb development.

Epidemiology/Risk Factors

RLS affects 7–15% of the general adult population and almost 2% of children. Forty to 65% of people with RLS report a positive family history of RLS. A first-degree relative of a person with RLS has a 3–6 times greater risk of developing RLS.

RLS affects both genders and all ethnic groups. Caucasians and women have a higher incidence. Research suggests a lower incidence of RLS among persons from the Indian subcontinent and other Asian countries.

Clinical features and Diagnostic Criteria

Essential Criteria

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Restless Legs Syndrome is diagnosed primarily by the patient’s description of clinical symptoms. Adults with RLS must have four essential clinical symptoms: (1) An urge to move the legs usually accompanied or caused by uncomfortable and unpleasant sensations in the legs. (2) The urge to move or the unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting. (3) The urge to move or unpleasant sensations are partially or totally relieved by movement such as walking or stretching, at least as long as the activity continues. (4) The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night. Supportive and associated symptoms help confirm the diagnosis. Supportive and associated features are often present but are not essential to the diagnosis. These include a positive family history of RLS, improvement of symptoms with dopaminergic therapy, and the presence periodic limb movements during sleep or wakefulness. RLS almost invariably occurs in the legs but can involve the arms, torso, or face. Symptoms may be unilateral or bilateral.

Children diagnosed with RLS must have the four essential clinical features described above and be able to describe leg sensations in their own words. Alternatively, a child who cannot describe the leg sensations in their own words must meet all four essential clinical features and in addition meet two of the following: (1) sleep disturbance greater than expected for age, (2) a parent or sibling with definite RLS, (3) periodic limb movements that occur during sleep at a frequency greater than five movements per hour.

**Differential Diagnosis**

RLS must be differentiated from legs cramps, positional discomfort, neuroleptic-induced akathisia, and painful legs and moving toes syndrome.

In children RLS must be differentiated from motor tics, attention deficit hyperactivity disorder, muscle pains, leg cramps, Osgood–Schlatter’s disease, arthralgia and akathisia. Growing pains are thought to be the onset of RLS in some cases.

**Diagnostic Work-up/tests**

The diagnosis of RLS is based on the clinical history. Serum iron, ferritin levels and iron-binding capacity are essential to obtain in order to evaluate whether iron deficiency may play a role. Some researchers recommend checking vitamin B12, folate and magnesium levels, although there is less evidence for these as associated conditions. A polysomnogram is not indicated for diagnosis of RLS, but may be useful if assessment for periodic limb movements or other sleep disorder is suspected. All patients should undergo a physical and neurological examination. If suspected, peripheral neuropathy or radiculopathy can be documented by electromyography (EMG) and nerve conduction studies. Additional testing may be necessary to differentiate primary RLS from secondary RLS. The diagnostic tests recommended depend upon the suspected precipitating condition.

When the diagnosis of RLS is unclear a trial of dopaminergic medication may help confirm the diagnosis. Almost all patients with RLS will respond to dopaminergic agents.

The frequency and severity of symptoms should be documented and the patient classified as having intermittent RLS, daily RLS or refractory RLS.

**Management**

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Nonpharmacologic Therapy

Nonpharmacologic therapies that benefit people with RLS include: (1) mental distraction and mental alerting activities. There are case reports that mental distractions, such as playing the piano, can decrease symptoms. The mechanism is unknown but it is thought that mental distraction activates parts of the brain that block the perception of RLS symptoms. (2) Eliminating dietary triggers such as caffeine, alcohol, and tobacco; (3) hot or cold soaks; (4) massaging the legs; (5) adjusting the bedtime so that the patient goes to bed after symptoms stop; (6) if possible discontinue drugs known to exacerbate RLS symptoms: tricyclic antidepressants, SSRIs, H1 antihistamines, calcium channel blockers and dopamine antagonists; (7) walking or exercising the legs; (8) avoiding excessive exercise.

Pharmacologic Therapy

All medications used to treat RLS should be started at the lowest dose and increased slowly to an effective dose. Because medication half-life is different from peak effect, one recommendation is that medication should be dosed every three hours during the symptomatic period. The number of doses per day depends on the number of symptomatic hours per day.

Replace iron in patients with serum ferritin levels below 50 μg l⁻¹. Recommended dosing is 325 mg of ferrous sulfate three times a day with supplemental vitamin C 500 mg with each dose of ferrous sulfate. Reevaluate the serum ferritin level after 3 months of therapy. There is no indication to treat patients with iron who do not have a low ferritin, and iron overload may occur. Additionally, in patients with iron deficiency, an evaluation for the underlying cause of the deficiency should be undertaken.

In 1982, Akpinar reported that dopamine agonists improved RLS. In 2005 ropinirole, a nonergot dopamine agonist became the first Federal Drug Administration (FDA) approved medication for RLS. Since 2005 the FDA approved another dopamine agonist, pramipexole. Dopaminergic agonists drugs are regarded as the first line pharmacologic therapy for RLS. There are two types of dopaminergic drugs: ergot preparations and nonergot preparations. Bromocriptine, pergolide, and cabergoline are all ergot dopamine preparations. Prolonged use of ergot preparations is associated with cardiac valvular fibrosis and pulmonary fibrosis. Therefore ergot preparations are used with caution and monitoring for these side effects. Pergolide is no longer available for use in the United States.

Nonergot dopaminergic agents are the only FDA approved medications for RLS in the United States. The two that are approved include pramipexole (Mirapex®) and ropinirole (Requip®). The therapeutic dose of ropinirole ranges from 0.25 to 4 mg day⁻¹. Ropinirole should be started at 0.25 mg given 30 min before the onset of symptoms or 90–120 min before bedtime. The dose is increased by 0.5 mg weekly until alleviation of symptoms. The maximum dose is 4–6 mg day⁻¹.

Pramipexole is available in multiple dosage strengths and should be started at 0.125 mg, the lowest dose available. Medication is increased by 0.125 mg every 4–7 days as needed. The average dose prescribed is 0.5 mg day⁻¹. Some physicians increase pramipexole to a maximum dose of 2 mg day⁻¹.

Levodopa/carbidopa is an older dopaminergic agent with a short half-life. Levodopa/carbidopa is used when symptoms occur intermittently or in preparation for sitting for prolonged times. Because
of a tendency to cause more marked augmentation, daily use at higher dosages is not recommended.

Cabergoline is a long acting ergot dopaminergic agonist effective against RLS symptoms but seldom used to treat RLS in the United States due to cost and potential associated side effects.

Side effects of the dopaminergic drugs include nausea, light-headedness, daytime drowsiness, orthostatic hypotension and sleep attacks. Chorea and hallucinations are common side effects of dopamine agonist in Parkinson’s disease but are not reported in RLS. Compulsive gambling and compulsive shopping have been reported.

The most troubling side effects of dopaminergic agents in RLS are rebound and augmentation. Rebound occurs when symptoms increase at a time compatible with the half-life of the medication. Augmentation is a more common side effect and is particularly prominent with the use of levodopa. Augmentation is the earlier occurrence of RLS symptoms in the evening, requiring an earlier administration of medication. Furthermore, the symptoms are usually worse and may spread to other body areas besides the legs. The management of RLS augmentation includes avoiding chronic treatment with levodopa, use of longer acting dopamine agonists, earlier doses of the dopamine agonists if mild augmentation occurs, and a reevaluation for iron stores as a low ferritin has been associated with augmentation. For severe or recurrent augmentation, the dose of the dopamine agonist should be lowered or the dopamine agonist discontinued. Alternate therapy can then be chosen.

Other treatment options include the opioids, gabapentin, and benzodiazepines.

For severe RLS, opioids (codeine, propoxyphene, hydrocodone, methadone, oxycodone, or tramadol) are sometimes prescribed. There is little addiction or tolerance to opioids when used to treat RLS. Constipation, dizziness, nausea, and vomiting are side effects associated with opioids. Patients treated with opioids should be monitored for the development or exacerbation of sleep apnea.

Gabapentin (Neurontin) is an anticonvulsant frequently prescribed for painful RLS, daily RLS, and refractory RLS. The starting dose is 100–300 mg. The average dose is 300–1200 mg day$^{-1}$. The therapeutic range is 300–2700 mg day$^{-1}$. Side effects associated with gabapentin include ataxia and drowsiness.

Benzodiazepines, clonazepam (Klonopin®), temazepam (Restoril®), and triazolam (Halcion®), may reduce leg discomfort, decrease the urge to move and help patients sleep through periodic limb movements. High doses of benzodiazepines cause carry-over effects such as morning drowsiness and decreased cognition. Benzodiazepines are not recommended in patients with untreated or inadequately treated sleep apnea because benzodiazepines may increase apnea. Addiction and tolerance to benzodiazepines rarely occurs in patients without a previous history of addiction. Nonbenzodiazepine hypnotics (eszopiclone, zolpidem) are sometimes prescribed to help patients sleep but have not been shown to reduce RLS symptoms or periodic limb movements.

In 2004, the Medical Advisory Board of the RLS Foundation established treatment recommendations for RLS. This approach separates patients into one of three categories: intermittent symptoms, daily symptoms and refractory symptoms. Treatment is based on frequency

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and severity of symptoms.

Intermittent symptoms are treated with nonpharmacologic therapies alone or in combination with medications. Medications used to treat intermittent RLS include benzodiazepines, levodopa, low potency opioids (tramadol, propoxyphene, codeine), and dopamine agonists.

Dopamine agonists are the drugs of choice for treating daily RLS. Combination therapy is also used. Gabapentin and low potency opioids are also used for daily RLS. Nonpharmacologic therapies may also be helpful.

Refractory RLS is difficult to treat. Treatment may require a change in therapy to gabapentin or another dopamine agonist. Alternatively, refractory RLS can be treated by adding a benzodiazepine, opioids, or gabapentin. Refractory RLS may require high potency opioids. Combination therapy is also used.

Most medications prescribed to treat RLS are not recommended for pregnant women. Pregnant women should be evaluated for iron deficiency. Iron deficiency should be treated and the use of nonpharmacologic therapies encouraged. There is some evidence that folate, B12 and magnesium are helpful in pregnancy. When pharmacologic therapy is necessary, opioids are used with caution.

Children with RLS should be evaluated for iron deficiency anemia and treated as needed. Children who are not iron deficient or in whom symptoms are not controlled by iron therapy should be first treated with nonpharmacologic therapy. When medication is needed, nonergot dopaminergic agents are recommended. There is anecdotal evidence that gabapentin, benzodiazepines, or clonidine are also helpful.

Prognosis

Primary RLS is an idiopathic or genetic disorder with a familial pattern. When symptoms develop at an early age, progression of symptoms develops slowly and may not occur daily for many years. Although 15% of patients with RLS experience a remission in symptoms for a month or more, primary RLS is considered to be a chronic progressive disorder.

Secondary RLS remits when the precipitating condition resolves. Although some women who develop RLS during pregnancy will continue to have symptoms postpartum, most will be symptom free after pregnancy. There is anecdotal evidence that women who develop RLS during pregnancy have a higher incidence of RLS in later life.

Symptoms of primary and secondary RLS can usually be controlled by medication and nonpharmacologic therapies (Video 1 and Table 1).
Video 1

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<table>
<thead>
<tr>
<th>Motor restlessness during wakefulness</th>
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<tbody>
<tr>
<td>1. Tossing/turning in bed (patient 1)</td>
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<tr>
<td>2. Foot rubbing (patient 2)</td>
</tr>
<tr>
<td>3. Leg flexions (patient 2)</td>
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<tr>
<td>4. Leg stretching (patient 3)</td>
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<tr>
<td>5. Body rocking (patient 3)</td>
</tr>
<tr>
<td>6. Marching in place (patient 2)</td>
</tr>
<tr>
<td>7. Periodic myoclonus while awake (patient 1)</td>
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<tr>
<td>8. Clustered myoclonus while awake (patient 3)</td>
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<tr>
<td>9. Periodic movements in sleep involving legs (patient 4)</td>
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<tr>
<td>10. Periodic movements in sleep involving arm and legs (patient 4)</td>
</tr>
</tbody>
</table>

Table 1 and the accompanying video were first published by Walters A, Hening W, and Chokroverty S (1991) Review and videotape recognition of idiopathic restless legs syndrome. *Movement Disorders* 6: 105–110. The table and video are reproduced by permission of the Movement Disorders Society and the *Movement Disorders* journal.

See also
Akathisia; Periodic Limb Movements

Glossary

**A11 region**
A cluster of dopamine containing cells located in the diencephalon with projections to the spinal cord.

**BTBD9**
The symbol for (Broad-Complex-Tram-Track-Bric-A-Brac Domain 9) and is a gene encoding a BTB
(Poz) domain on Chromosome 6p.

**DMT1**
The abbreviation for divalent metal transporter 1. DMT 1 removes iron from endosomes and makes iron available to the intracellular labile iron pool.

**LBXCOR1**
The code name for ladybird homeobox 1 homolog (*Drosophila*) corepressor 1 and is located near MAP2K5 on chromosome 15q.

**MAP2K5**
The symbol for Mitogen-activated protein kinase 5 and is located on Chromosome 15q.

**MEIS1**
The symbol for Meis homeobox 1. MEIS1 is linked to embryonic proximal–distal limb formation. MEIS1 is located on chromosome 2p.

**MPT1**
The abbreviation for metal transporter 1 (ferroprotein) and is thought to be involved in cellular iron efflux.

**Periodic limb movements in sleep (PLMS)**
Repetitive stereotypic leg movements that reoccur throughout the night during sleep. Scoring criteria for PLMS include four movements in a row, 0.5–10 s duration, spaced 0.5–90 s apart, and at least 8 μV elevation above the baseline EMG.

**Restless legs syndrome (RLS)**
It is a sensorimotor disorder with four essential diagnostic criteria: (1) An urge to move the legs usually accompanied or caused by uncomfortable and unpleasant sensations in the legs. (2) The urge to move or the unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting. (3) The urge to move or unpleasant sensations are partially or totally relieved by movement such as walking or stretching, at least as long as the activity continues. (4) The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night.

**Further Reading**

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Relevant Websites

- [www.neurotalk.org](http://www.neurotalk.org) – An online support group for the discussion of brain, neurological, health, and mental health conditions.
- [www.rls.org](http://www.rls.org) – This is an organization of lay people interested in RLS.
- [www.sleepfoundation.org](http://www.sleepfoundation.org) – Provides comprehensive sleep medicine education and awareness programs for professionals and the general public.
- [www.wemove.org](http://www.wemove.org) – A comprehensive internet source for information on movement disorders.
- [www.irlssg.org](http://www.irlssg.org) – The International Restless Legs Syndrome Study Group (IRLSSG) is an organization of professionals committed to advancing basic and clinical research on Restless Legs Syndrome (RLS).

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