Restless Legs Syndrome and Other Movement Disorders of Sleep
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Disclosures

- I have no financial or relationship disclosures.

- I will be discussing off-label uses of certain medications for the treatment of restless legs syndrome.
Restless Legs Syndrome/Willis-Ekbom Disease

- Restless legs syndrome (RLS), also known as Willis-Ekbom disease (WED), was accurately described by Thomas Willis in 1685 (along with treatment by opiates), but first delineated as a unique condition by Dr. Karl-Axel Ekbom in 1945 when he described a “hitherto overlooked disease in the legs.”
Karl-Axel Ekbom

- Karl-Axel Ekbom (1907-1977) was a Swedish neurologist.
- Recognized link between RLS and iron deficiency.
Karl-Axel Ekbom
Thomas Willis 1621-1685

- Thomas Willis (1621-1685) was an English physician especially interested in anatomy, neurology, and psychiatry.

- He is known for pioneer research on the anatomy of the brain, spinal cord, peripheral nerves, and muscles. His most notable discovery was the "Circle of Willis."

- His text on the brain and nerves (Cerebri anatome of 1664), is the work that first coined the term neurology.

- Willis was the first to number the cranial nerves in the order in which they are now usually enumerated by anatomists.

- He coined the term mellitus in diabetes mellitus. An old name for the condition is "Willis's disease". He observed what had been known for many centuries elsewhere, that the urine is sweet in patients (glycosuria).
Thomas Willis
Restless Legs Syndrome/Willis-Ekbom Disease

Restless legs syndrome (RLS) is diagnosed clinically by the presence of five criteria:

1. An urge to move the legs that is usually, but not always, accompanied or caused by uncomfortable and unpleasant leg sensations.

2. The symptoms begin or worsen during rest or inactivity.

3. The symptoms are partially or totally relieved by movements such as walking or stretching for at least as long as the activity continues.

4. The symptoms only occur or are worse in the evening or night than during the day.

5. The symptoms are not solely accounted for as being primary to another condition (such as leg cramps, or positional discomfort).
Nailing Down Dysesthesias

- The patients’ subjective descriptions, however, are quite varied and tend to be suggestible and education dependent. The sensation is always unpleasant but not necessarily painful. It is usually deep within the legs and commonly between the knee and ankle.

- In a study of RLS patients, the most common terms used, in descending order of frequency included: "need to move", "crawling", "tingling", "restless", “cramping”, “creeping”, "pulling", "painful", "electric", "tension", "discomfort", and "itching.” 5

- Patients usually deny any “burning” or “pins and needles” sensations, commonly experienced in neuropathies or nerve entrapments, although neuropathic pain and RLS can co-exist.

- The key is to rephrase their description into a question asking if that makes you want to move your legs, is it better while moving, and are the symptoms worse in the evening/night.
More Diagnostic Pearls in RLS

- Essentially all patients report transient symptomatic improvement by walking, although some employ stationary bike riding or kicking. Other therapeutic techniques reported by patients include rubbing or pressure, stretching, and hot water. Symptom relief strategies all increase sensory stimulation to the legs and are generally alerting.

- Other clinical features typical for RLS include the tendency for symptoms to gradually worsen with age, improvement with dopaminergic treatments, a positive family history of RLS, and periodic limb movements while asleep (PLMS).
More RLS Diagnostic Pearls

- RLS symptoms may alternate between legs and may be asymmetric.

- It is not unusual for patients with severe RLS to describe similar symptoms in the arms and occasionally the trunk.

- Later in the disease course, the relief by movement may be less evident (but should have been present earlier).
Diagnostic Mimickers of RLS in Approximate Decreasing Order of Importance

- Nocturnal leg cramps
- Positional discomfort
- Habitual foot tapping (akathisia)
- Fibromyalgia
- Arthritis
- Venous stasis
- Leg edema
- Painful peripheral neuropathy
- Painful legs and moving toes syndrome
Sleep-related Leg Cramps

- These are painful contractions of the muscles of the leg or foot with resultant tightness or hardness.

- They occur most frequently at night, waking the patient from sleep.

- Generally are helped by stretching the affected muscle, often by standing.

- Usually idiopathic, but may occur in neuromuscular disorders, myopathies, ALS, and in electrolyte disturbances or more exotic causes such as peripheral nerve hyperexcitability (neuromyotonia/Isaac syndrome).

- Treatment is with quinine, but the benefits are modest, and it can cause thrombocytopenia and cardiac arrhythmias.
Positional Discomfort

- Body **positional discomfort syndrome**, is an entity where patients simply can’t find a comfortable position in which to rest, and may include superimposed neuropathic or radicular pain, and generalized anxiety.
Habitual Foot Tapping

- **Akathisia** is the inability to hold still (e.g., pacing, jiggling your leg), and may often part of RLS/WED.

- Generalized akathisia can be differentiated from RLS as it is perceived of as an ‘inner’, generalized, psychic sensation versus a focal, sensorimotor disturbance, and fails to demonstrate a circadian pattern of expression.

- Hypotensive akathisia typically only occurs while seated (compared with lying), and fails to demonstrate a circadian pattern of expression.
Periodic Limb Movements of Sleep

- **Periodic limb movements of sleep** (PLMS) were originally called nocturnal myoclonus and first described almost 50 years ago.
- They are diagnosed by clinical history and PSG.
- A PLM must be 0.5 to 10 seconds with minimum amplitude of 8 microvolts increase in the anterior tibial surface EMG voltage above the resting EMG.
- At least four leg movements separated by 5-90 seconds between onsets of successive movements must occur in succession to be scored as PLMS (leg movements associated with arousals from respiratory events during sleep are excluded).
- They usually do not persist in REM sleep.
- They are **known to occur in 80-88% of RLS patients**, but most patients with PLMS do not have RLS. They occur in 80% of patients with narcolepsy, and 71% of patients with RBD. They also occur more in PD patients.
- They are common in patients with OSA, are noted during titration PSG’s, and also increase in frequency as one ages (29.0% of subjects over age 49).
- Must occur on PSG > 5.0 per hour in children, and **15.0 per hour in adults**, and must be accompanied by a clinical sleep complaint or complaint of daytime fatigue attributable to PLMS to formally give a diagnosis of **Periodic Limb Movement Disorder** (PLMD).
Rhythmic Movement Disorder

- The movements of **rhythmic movement disorder** (RMD) consists of stereotyped contractions of large muscle groups at 0.5 Hz to 2 Hz during drowsiness or sleep.
- They are most frequent in light NREM sleep but may sometimes be seen in REM sleep.
- The head or trunk may rock from side to side or back to front, and occasionally the legs may flex and extend.
- One subtype is head banging (jactatio capitis nocturna), another is body rocking.
- In order to be classified as a disorder, they must interfere with normal sleep, cause bodily injury or daytime impairment.
- RMD is common in early infancy and childhood but can persist into adulthood. Intellectually handicapped children may be especially prone to RMD.
- Patients explain that they use the movements for soothing, sleep-inducing tactics.
- Protective headgear, or benzodiazepines may be used.
Nocturnal Myoclonus and Tics

- **Nocturnal myoclonus** (hypnic jerk, hypnagogic jerk, sleep start, or night start), is an involuntary twitch which occurs during hypnagogia, just as a person is beginning to fall asleep, often causing them to awaken suddenly for a moment. Physically, hypnic jerks resemble the "jump" experienced by a person when startled, often accompanied by a falling sensation. A higher occurrence is reported in people with irregular sleep schedules. It may be treated with clonazepam if severe and refractory to proper sleep habits and improved sleep hygiene (which is the best way to treat them).

- **Tics** are semivoluntary habits or mannerisms (from branchial arch derived muscles), that are often familial. They have a strong obsessive-compulsive association.
Spinal and Cortical Myoclonus

- **Spinal myoclonus** are segmental jerks of the trunk as well as of limb muscles, involving only one or two adjacent spinal segments and not propagated. They may be treated by benzodiazepines, baclofen, carbamazepine, and tetrabenazine.

- **Cortical myoclonus** are irregular and asynchronous jerks involving mainly distal limb and facial muscles. They may be treated with anti-epileptic drugs.
Propriospinal Myoclonus (PSM) is characterized by flexion or extension rhythmic jerks arising in axial muscles (pertaining to the trunk or head) and spreading to more caudal and rostral segments. They may be treated with benzodiazepines.

In PSM a spinal generator is believed to recruit axial and limb muscles via slowly conducting propriospinal pathways to produce the myoclonic jerks.

Several cases of PSM have been reported and multiple sclerosis, cervical trauma, thoracic herpes zoster, HIV infection, excision of cervical hemangioblastoma, thoracic arachnoid cyst, syringomyelia, and ischemic myelopathy have occasionally been described as associated lesions. In many cases, however, PSM remains idiopathic. PSM may be spontaneous and stimulus-sensitive and may be worse with the patient leaning back or lying in bed, as an effect of posture.

In three previous reported cases PSM showed a striking relationship with vigilance level, since it occurred in a semirhythmic fashion only during the wakefulness period preceding sleep onset. In these patients jerks recurred every 10—20 seconds and were of such intensity as to cause severe sleep-onset insomnia. The jerks were absent during sleep proper. It was speculated that changes in supraspinal control peculiar to the pre-dormitum stage set the spinal generator responsible for PSM into motion. This peculiar relationship of PSM with relaxed wakefulness and the ensuing disturbance of sleep allowed the proposition that PSM may represent a disorder of the sleep-wake transition period in some patients.
Painful Legs and Moving Toes Syndrome

- **Painful legs and moving toes** is a nosologic entity that consists of severe pain of the feet with burning sensation and repetitive, semicontinuous, undulating movements of the toes (as opposed to gross body stretching and walking characteristic of RLS, and the gross and intermittent periodic flexions of the hip, knee, and ankle seen in PLMS).

- It is not necessarily worse at night or relieved by activity.

- A drug response profile that mimics that for RLS and the presence of PLMS suggests that this entity may represent a phenotypic variant of RLS/PLMS.
Definitions RLS in Children

- RLS in children can be difficult to diagnose. Although some children report classic RLS symptoms that meet inclusion criteria, other complain of “growing pains”, (16, 17) and some appear to present with an attention deficit hyperactivity disorder (ADHD) phenotype.

- Kotagal et al reported that children with RLS have lower than expected serum ferritin levels and in most cases appear to inherit the disorder from their mother. (18)

- NIH diagnostic criteria for RLS in children is less well validated but emphasizes supportive criteria such as a family history of RLS, sleep disturbances, and the presence of PLMS, which is much less common in pediatric controls.

- The exact relationship between RLS and ADHD is not known. Children diagnosed with attention deficit hyperactivity disorder, however, often have PLMS (19-22) and meet criteria for RLS. 19 Children with ADHD also have a higher prevalence of a parent with RLS (23) and children diagnosed with PLMS often have ADHD. (24)

- Dopaminergic treatment of RLS/PLMS in children also improves ADHD symptoms. (25)

- Therefore, there is clearly some association between RLS and ADHD.
Frequency of RLS in Medical Conditions

- **Anemia**: is associated with a very common prevalence.
- Blood donation: 25% (women), and 15% (men)
- **Renal failure/hemodialysis**: ~70% (Caucasians), and ~50% (African-Americans)
- **Pregnancy** (particularly third trimester): > 30%
- Charcot-Marie-Tooth 2: ~35%
- Spinocerebellar ataxias ((SCA)1–3): ~30%
- **Parkinson’s disease**: > 20%
- Insomnia: > 20%
- **Attention Deficit Hyperactivity Disorder** (ADHD): > 12%
Epidemiology Summary

- Initially believed to be a rare condition, later studies suggested a prevalence as high as 10-15%.

- However, recent large epidemiological studies in the United States and Europe have determined that the true prevalence for RLS that causes moderate distress and occurs at least twice a week is in the range of 1.5-3.0%.

- RLS is more common in women than men.

- The incidence increases with age, and symptoms may progress with time; however, many patients experience unexplained remissions lasting at least a month.
Etiology and Pathophysiology

- Over **50% of RLS patients have a family history** of the disorder that is usually inherited in an autosomal dominant pattern. Multiple loci and several polymorphisms associated with RLS have been identified.

- The gene most frequently reported in multiple populations is **BTBD9 on chromosome 6p** with protein product widely expressed in the brain.
Etiology and Pathophysiology

- **CSF ferritin** levels are lower in patients with RLS than in controls (even in the absence of systemic iron deficiency). MRI and transcranial sonography have shown reduced iron stores in the basal ganglia and autopsy studies have demonstrated decreased substantia nigra iron, ferritin, and transferrin receptor concentrations with increased transferrin (a pattern suggestive of low iron stores).

- Abnormalities in the transport of iron across the blood-brain barrier in RLS may be the underlying mechanism.
Etiology and Pathophysiology

- RLS gets better with dopaminergic agonists and worsens with dopaminergic blockade, suggesting that dopamine deficiency may be at the heart of the disorder.

- RLS is associated with **down-regulation of the D2 receptors** in the putamen, and the degree of loss of receptors in RLS correlates with severity of disorder.

- The levels of **tyrosine hydroxylase** (the rate-limiting enzyme in the for dopamine synthesis) are increased in the substantia nigra in RLS, presumably as a compensatory mechanism to reduced dopamine receptors.
Etiology and Pathophysiology

- Major secondary causes of RLS include acquired iron deficiency, chronic renal failure, peripheral neuropathy, certain medications, and pregnancy.

- In chronic renal failure, the proposed mechanisms are lower levels of erythropoietin (makes red blood cells), and iron deficiency.

- These medications include most of the antidepressants (with the probable exception of bupropion), dopamine antagonists (atypical antipsychotics such as clozapine, risperidone, olanzapine, quetiapine, and ziprasidone used to treat psychoses, and anti-nausea medications such as metoclopramide), and possibly antihistamines.
Etiology and Pathophysiology

- RLS is often precipitated or exacerbated by pregnancy.

- Women who had restless legs syndrome (RLS) while pregnant were four times more likely to have the condition again after their pregnancies, and were three times more likely to have the chronic form of the condition, according to a small European study.
Consequences of RLS

- Sleep-onset insomnia and sleep maintenance insomnia are reported in 50% to 85% of patients.

- Studies have shown an increased prevalence of depression and anxiety in patients with RLS compared to controls.
Vascular Consequences of RLS?

- Recently (2012), a possible relationship between vascular disease and RLS has been hypothesized. Many of the cross-sectional studies performed have methodologic flaws, and the few prospective studies are contradictory; some, but not all, suggest a higher incidence of vascular disease after diagnosis of RLS or PLMS, but with low odds ratios.

- Proposed mechanisms for such a relationship include the effects of sleep deprivation and arousals from PLMS causing excessive sympathetic stimulation.

- Because of the uncertainty of the findings, the relatively low increased risk, and the lack of interventional studies, current therapeutic decisions should not be made based on concern about vascular risk.
Investigation of RLS

- The diagnosis of RLS is made clinically on **history**.

- Polysomnography (PSG) is **not** routinely indicated unless an additional sleep disorder (such as obstructive sleep apnea) is suspected. Polysomnographic evaluation is usually reserved for patients in whom the diagnosis is in doubt, in cases where PLMS are suspected to be severe and result in arousals, or if other sleep disorders are suspected. There are several potential diagnostic dilemmas.

- About 85% of patients with RLS will have elevated PLM indices on PSG (especially in older patients), but such a finding is nonspecific.

- **Secondary causes** of RLS should be considered (anemia etc).

- **Medications** that can cause/exacerbate RLS should be noted (antidepressants).
Investigation of RLS

- In most cases, only a simple evaluation is justified for clinically typical RLS.

- **Serum ferritin**, and possibly **iron binding saturation**, for serum iron deficiency, and electrolytes for renal failure may be obtained. Nerve conduction velocities (NCV) and electromyogram (EMG) may be performed in cases without a family history of RLS, atypical presentations (i.e. sensations beginning in the feet or superficial pain), in cases that have a predisposition for neuropathy (i.e. diabetes) or when physical symptoms and signs are consistent with a peripheral neuropathy. If EMG/NCV abnormalities are found they should be further evaluated.

- Recall that ferritin is an acute phase reactant, and may be elevated in the setting of a recent infection or chronic inflammatory disorders, as well as hemochromatosis, hemosiderosis, and adult-onset Still’s disease.
Treatment of RLS

- The development of validated rating scales and standardized diagnostic criteria have vastly improved the quality of RLS treatment trials. Although multiple medications have demonstrated outstanding efficacy, all are felt to provide only symptomatic relief, rather than any “curative” effect.

- Therefore, treatment should only be initiated when the benefits are felt to justify any potential side effects and costs. Treatment decisions also need to consider the chronicity and general progressive course of RLS.

- Over time, both dosing and medication changes are often required to maximize benefit, and minimize the risk of tolerance and side effects.
Dopaminergic Agonists

- The non-ergot dopaminergic agonists (DA’s) pramipexole, ropinirole, and rotigotine are approved by the FDA for the treatment of RLS.
- Extensive controlled trials have demonstrated their effectiveness.
- Ropinirole doses should be approximately $4 \times$ higher than those of pramipexole (and doses are considerably lower than for those used in Parkinson’s disease).
- Maximum approved doses are 4 mg for ropinirole, and 1.0 mg for pramipexole.
Dopaminergic Agonists

• Generally, treatment should be started at 0.25 mg for ropinirole or 0.125 mg pramipexole about 1-2 hours before symptoms start and increased every few days until relief is obtained.

• Some patients will require an afternoon dose as well as in the evening.

• Rotigotine is supplied as a once daily transdermal patch with doses of 1-3 mg.

• Side effects include hypersonolence, orthostatic hypotension, lightheadedness, nausea, vomiting, nasal congestion, and leg edema. Skin irritation may occur with rotigotine.

• Long term usage is often limited by augmentation, impulse control disorders (ICD), and hypersonolence.
Dosing Titrations for DA’s

- **Ropinirole** may be started at 0.5 mg PO q 1 to 2 hours prior to RLS onset. You can increase by 0.5 mg **q 3 days** but should not exceed a total of 4 mg. One can break up dosages; taking second courses later in the evening.

- **Requip XL** avoids multiple plasma level peaks and troughs of regular ropinirole over 24 hrs. Can be given as 2mg/day for **1-2 weeks** and increased by 2 mg increments up to 8 mg per day (for PD). Available in 2, 4, and 8 mg tablets. Don’t exceed 4 mg for RLS.

- **Pramipexole** may be started at 0.125 mg PO q 1-2 hours prior to RLS onset. You can increase by 0.125 mg **q 3 days**, but should not exceed a total of 0.75 mg.
Dopaminergic Agonists

- Ropinirole has a half life of 7 hours (24 hours in the XL preparation), and is a D3 > D2 receptor agonist. Elimination is hepatic.

- Pramipexole is D3 > D2 receptor agonist, and has a half life of 8-13 hours. Elimination is renal.

- Rotigotine is D3 > D2 agonist, with a half life of 5-7 hours. Elimination is renal.

- All are Pregnancy class C.
Ergot Derivatives?

- The ergot agonists include bromocriptine, cabergoline, and pergolide.

- The ergot derivatives have been shown to increase the risk of retroperitoneal, pericardial and pleuropulmonary fibrosis.

- Cabergoline: D2 > D3 agonist, half life is **80 hours**, elimination is hepatic.

- Pergolide: D2 > D3 agonist, half life is 27 hours, elimination is renal.

- Bromocriptine: D2 > D3 agonist, half life is 12-14 hours, elimination is hepatic.
Carbidopa-Levododopa

- Carbidopa inhibits decarboxylation of peripheral levodopa. It does not cross the blood-brain barrier and does not affect the metabolism of levodopa within the central nervous system.

- Carbidopa-levodopa half life is about 1.7 hours, elimination is renal.

- Dose is 25/100 mg PO prn. Useful as an emergency “fire extinguisher” treatment for RLS patients (ie on long flights or car rides).
Augmentation

- **Augmentation** is the development of worsening RLS progressively earlier in the day after administration of dopaminergic medication in the afternoon or evening. It occurs more often with carbidopa-levodopa.

- It may take the form of earlier onset of symptoms, worsening of preexisting symptoms, or spread of symptoms to the arms.

- In one study, augmentation develops in at least 42% of patients treated with pramipexole who were followed for a median of 9.7 years, and other studies have shown similar frequencies.

- This may be initially managed by adding a supplementary dose of medication earlier in the day, but in many patients worsening augmentation will eventually develop, requiring discontinuation of the drug.
Impulse Control Disorders

- Impulse control disorders (ICD’s) occur in 6% to 17% of patients taking dopamine agonists for RLS and may only manifest 9 months or longer after starting therapy.
Impulse Control Disorders

- Reckless generosity
- Impulsive cigarette smoking
- Transvetitism
- Kleptomania
- Hoarding
- Obsessive painting
- **Hobbyism**
- Computer addiction
- **Punding** (intense, time-consuming preoccupation and fascination with seemingly meaningless rituals or stereotyped activities eg arranging and rearranging objects)
- Walkabout (excessive aimless wandering or driving)
- **Pathologic gambling**
- Excessive spending
- **Pathologic sexuality**
- Dopamine Dysregulation Syndrome
Dopamine Dysregulation Syndrome

• **Dopamine dysregulation syndrome** (DDS) is an addiction-like overuse of dopaminergic medication above and beyond the need to control RLS and despite harmful side effects (eg dyskinesias, psychosis, and aggressive behavior).

• **D3 receptor** stimulation has been implicated in the addiction process (most heavily concentrated in the nucleus accumbens).

• The dopamine agonists have specific affinity for D3 > D2, and little or no affinity for D1. Thus DA’s stimulate pathways that govern reward behavior, pleasure, and addiction more avidly than the dopamine derived from levodopa therapy.
Anti-epileptics

• **Gabapentin, pregabalin** (enantiomer), and **gabapentin enacarbil** (pro-drug) are calcium channel alpha-2-delta ligands that have all been shown to be effective in the management of RLS, but only gabapentin enacarbil has been approved by the FDA for this purpose.

• The mechanism of action for treatment in RLS has **not been clearly established**.

• The mean effective dose for gabapentin is 1800 mg, and 300 mg for pregabalin. They may be given 1-3 times per day, based on effectiveness and patient tolerance. Gabapentin enacarbil is administered in a dose of 600 mg once daily in the late afternoon.

• Class side effects include **hypersomnia, dizziness**, unsteadiness, weight gain, and edema.

• Augmentation has **not** been reported.

• Half lives are **6.3 hours** for pregabalin, and **4.7 hours** for gabapentin.

• All are renally excreted, and **Pregnancy class C**.
Opioids

- Opioid medications are highly effective in RLS.

- High potency agents may be needed in RLS refractory to other medications.

- **Oxycodone** (10-20 mg), hydrocodone, and **methadone** (5-15 mg) have been used successfully.

- Tramadol is the only opioid in which augmentation has been reported (and it lowers seizure threshold!).

- Side effects include itch (mast cell degranulation, not allergy), nausea, constipation, sleepiness, cognitive impairment, **exacerbation of OSA**, and **central sleep apnea**.

- Metabolized primarily in the liver.
Benzodiazepines

- Despite their past widespread use, there is little data to support the use of benzodiazepines for RLS. Clonazepam was among the earliest drugs reported to be successful in treating RLS.

- In the opinion of most experts benzodiazepines do help facilitate sleep but seldom improve RLS cardinal features.

- These can be used successfully in mild cases of RLS and as adjunct therapy for residual insomnia. They probably work by inducing sleep rather than by specifically targeting the symptoms of RLS.
Iron Supplementation

- If ferritin is less than **50 ng/dL**, and/or iron saturation is less than **20%**, consider supplementation with ferrous gluconate or ferrous sulfate (especially in patients with drug-resistant, refractory, or chronic RLS).

- Iron should be administered apart from food, generally in 2-3 doses, with a daily amount of elemental iron of 150 mg to 200 mg.

- **Vitamin C** (200 mg) should be added to each dose to enhance absorption.

- Serum ferritin should be re-checked after **6 months**.

- Intravenous iron may be considered in malabsorption cases or in people intolerant or oral iron preparations (iron gluconate or iron sucrose should be used, as iron dextran carries a risk of anaphylactic reaction).
Iron Supplementation

- Although open label oral iron supplementation has been reported to improve RLS 174, the only controlled study of oral iron supplementation failed to improve RLS symptoms. 175 Oral iron, however, has numerous limitations related to absorption and tolerance.

- In contrast, the administration of high dose (1 gram) intravenous iron can dramatically increase serum ferritin levels. An open label study of intravenous iron demonstrated robust efficacy. 176 Controlled trials of iron dextran with uremic RLS also show efficacy. 177

- Additional studies with different iron preparations are ongoing.
Non-pharmacologic Management of RLS

- Practice regular moderate exercise.
- Reduce caffeine, alcohol, and nicotine use.
- Consider withdrawal of predisposing medications.
- Advise about regular walking, bicycling, massage, or soaking of the affected limbs.
- Mind alerting techniques may also be useful (computer, games or puzzles).
Conclusions

- RLS is a common disorder causing considerable morbidity.
- Diagnosis is purely clinical.
- Many effective therapies are available, but the side effects of each class of medication should be considered in determining optimal treatment.
- Consider checking serum ferritin and iron saturation levels.


Bibliography


Bibliography


