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# What is Restless Legs Syndrome (RLS)?

**Restless Legs Syndrome (RLS)**, also known as **Ekbom's syndrome**, is a neurological condition associated with abnormal sensations in the legs. It is estimated that 5% of the general population and as many as 10% of those over the age of 65 have this disorder.

## There are four primary features of RLS:

- **Uncomfortable sensation in the legs with a clear need or urge to move the legs**. The sensation may be described in many different ways, from aching and pulling to creepy crawling feelings. The sensations can also be painful, not just uncomfortable. In the end, all sufferers can clearly identify a need or urge to move the legs as a driving force behind their complaint. These sensations usually occur in the calf area, but may be felt anywhere from the thigh to the ankle. One or both legs may be affected. For some people, the sensations are also felt in the arms. People with RLS have an irresistible urge to move the affected limb when the sensations occur.

- **The symptoms are worse at night**. Symptoms may present only at bedtime or they may start in the evening when trying to sit for any period of time. Sleep problems are common with RLS because of the difficulty it causes in getting to sleep. Some individuals may have symptoms throughout the day, but these symptoms will always be worse at night and better sometime in the morning.

- **The symptoms come on with rest**. Whether trying to lie quiet at bedtime or sitting through a long plane flight during the day, the sensations are likely to strike. Whether trying to sit through a movie or quietly reading a book, the symptoms will make what used to be an enjoyable event a most unbearable one. You cannot rest; you cannot relax; you cannot sleep another night.

- **The symptoms are relieved with movement**. All sufferers learn quickly that getting up and walking will immediately relieve the symptoms. However, as soon as the individual settles back into a restful state, the symptoms will usually return. Any movement of the legs will usually bring about some immediate, although temporary relief. If the legs are not moved, they may jump on their own. In some individuals, there may be semi-involuntary movements of the legs preceded by only a very brief sensation. Most individuals with restless legs syndrome will have rhythmic or semi-rhythmic movements of their legs while they are asleep. Although they may not be aware of their movement, usually their bed partner is. It is this movement of the legs, this constant walking to ward off the sensation that gives the viewer the perception of the sufferer being restless, thus the term "Restless Legs Syndrome".

Next: What are the causes of RLS?

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# Causes of Restless Legs Syndrome

In the last 20 years, there has been a substantial amount of research into understanding the cause of RLS. From that research there appears to be three factors which are pertinent to the disease: brain concentrations of iron, brain dopamine concentrations and genes.

## Role of Iron in RLS

The single most consistent finding and the strongest environmental risk factor associated with RLS is iron insufficiency. Professor Nordlander first recognized the association between iron deficiency and RLS, and reported that treatment of the iron deficiency markedly improved, if not eliminated, the RLS symptoms. Despite this strong association between serum iron insufficiency and RLS, only about 15% of the RLS clinical population appears to have peripheral iron deficiency (serum ferritin < 50 mcg/l). To account for this, Professor Nordlander in proposing his "iron deficiency" hypothesis of RLS stated: "it is possible…that there can exist an iron deficiency in the tissues in spite of normal serum iron". This hypothesis has led investigators to examine whether the brain could be deficient in iron in the face of otherwise normal serum iron measures.

All studies to date support the concept of diminished brain iron in patients with RLS even when blood tests indicate that their iron stores are normal. Using "spinal tap" also called "lumbar puncture" techniques, which involves placing a needle deep into the lower part of the spine (similar to an epidural), one can obtain cerebrospinal fluid that contains proteins and chemicals that exist inside the brain. Using cerebrospinal fluid (CSF), studies have shown that the iron storage protein, ferritin, is low in RLS patients despite these patients not being anemic and having normal serum levels of iron and ferritin. Magnetic Resonant imaging, also called MRI, can also be used to measure brain iron. Studies using MRI have shown decreased iron concentrations in the substantia nigra, one of the primary brain regions where dopamine-producing cells reside. One study using MRI found a strong relation between iron concentrations in the substantia nigra and the severity of the RLS symptoms. Through the generous efforts of RLS Foundation, a Brain Bank has been set up to collect brains from RLS patients who wish to donate their brains after they die. Using tissues from those donated brains, studies have shown markedly diminished iron and iron storage protein in the substantia nigra consistent with iron insufficiency in the dopamine cells.Overall the studies support the concept of iron dysregulation in brains of patients with RLS, particularly in dopamine-producing cells.

Gaps in our knowledge. Despite the substantial body of research on peripheral iron regulation, we still know very little about how iron is regulated by the blood-brain barrier or by the different cells within the brain. Also there is a relative lack of research on the effects of having iron insufficiency and on exactly how a brain region can be low in iron yet other organs in the body have normal levels?

## Role of Dopamine in RLS

Because of the marked improvement in RLS symptoms seen with drugs that stimulate the dopamine system and because of the RLS-like symptoms produced with drug that block the dopamine system, the dopamine system has been implicated RLS. CSF has also been used to evaluate dopamine system, and although this is a crude method for assessing the dopamine system in the brain, the data indicated possible increase in brain dopamine production. Imaging studies using special radioactive chemicals have found reduced receptor and transporter function in the brain of more severely affected RLS patients. Tissues from the Brain Bank have shown that the dopamine cells are normal in appearance and number and give no indication that the cells are damaged in anyway. These studies also found that the dopamine receptors were decreased and the proteins associated with producing dopamine (tyrosine hydroxylase) were increased. The composite results suggest the presence of increased production and release of dopamine but the proteins, called receptors, that bind the dopamine and transmit the dopamine signal to other cells, may not be working normally. The increase in dopamine may be the brain cells response to the poor signal. When you cannot hear the voices clearly on the TV, you turn up the volume. Cells interact with each other in the similar manner: if a cell cannot "hear" the message (i.e., dopamine) from another cell, it feedbacks to tell the other cell to increase the amount of message (i.e., dopamine). Thus despite the increase in dopamine, the end result may be a decrease in the effect that dopamine has on certain brains cells at certain times of the day (i.e., evening and night time) leading to the develop of RLS symptoms.

Gaps in our knowledge. The mechanism by which iron influences dopamine function is still unclear. Iron deficiency affects other systems in the brain, which potentially could affect the dopamine systems. There is recent work done here at Johns Hopkins which suggests that another chemical in the brain, glutamate, may be equally important in causing some of the symptoms experienced by RLS patients. Brain cells in culture and brains from animals show similar changes in the dopamine activity when the iron levels are made to go low. Brain cells in culture and brains from animals are what is referred to as "models" of the disease. We can uses these models to examine the connections between iron and dopamine or glutamate, which could potential be used to understand what is happening in the human brain and specifically what is happening in RLS.

## Role of Genes in RLS

Understanding how genes can affect our lives is quite complex. The simplest concept is when a specific gene is damaged, for example, hemophilia or sickle cell disease. In these diseases, the damaged gene results in an abnormal protein being made or in no protein at all being made. When we talk about how genes are related to blood pressure, heart disease, Alzheimer's disease, or RLS then the role of the gene is more difficult to understand because usually these common disorders do not result from one damaged gene but rather from interaction of several genes under certain environmental conditions. Most of us are born with normal hearts but over time, because of the interaction between environmental factors (aging, high cholesterol, smoking, increased blood pressure, diabetes, etc) and genes, some people will progress to having a bad heart. RLS is also related to environmental factors and genes. The single largest know environmental factors is low iron levels. Low iron may occur before birth, during infancy, as a child, during pregnancy or later in adult life. The low iron may resolve long before one even develops RLS symptoms, but the low iron condition may set into motion set of conditions that eventually lead to getting RLS. There are several genes (BTBD9, MEIS1, MAP2K5/LBXCOR1, PTPRD, TOX3,) in which a small natural variation in the genes structure is associated with an increased "risk" of developing RLS. Having one of these natural genetic variations does not necessarily give you the disease, it only increases your risk of one day developing RLS. For example, the change in the BTBD9 gene associated with increased risk of developing RLS is present in about 75% of patients who have RLS but also present in about 65% of patient who never had RLS. We know from studies that there is some point of interaction between several of the genes

and iron regulation, thus supporting the concept of an interaction between your iron levels at some point in your life and several genes that may trigger the onset of RLS.

Gaps in our Knowledge. The function of these genes in adult brain, let alone in RLS, remains unclear. The RLS-risk genes in relation to the primary iron management proteins may be upstream and may determine when and how iron is changed. Alternatively, RLS susceptibility genes may be downstream from the iron changes and thus may act to modify the consequences of the changes in iron. The more important question is: how does the cell metabolism-iron management proteins relation change or the iron-dopamine relation change when these RLS-risk genes are varied?

Next: RLS Symptoms

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# Symptoms of Restless Legs Syndrome (RLS)

## Do You Think You Might Have RLS?

- Have you ever had unpleasant or uncomfortable feelings in your legs that occurred mainly while you were either sitting or lying down?
- Have you ever felt the need or urge to move your legs that occurred mainly while you were sitting or lying down?
- While you are actually walking around, do you get any relief from these feelings?
- Are these feelings in your legs more likely to occur while you are resting than when you are physically active?
- Are these feelings in your legs worse at night or in the evening than at other times of the day?

If you have answered yes to these questions, you may suffer from Restless Legs Syndrome.

Next: RLS Treatment

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# Treatment for Restless Legs Syndrome (RLS)

## Medicine/Drug Therapy

Unfortunately, there is no known cure for restless legs syndrome. At the present time, there is no one drug which works for everybody, but most individuals with restless legs syndrome will find some benefit and relief with the currently available medications.

The medications presently available for treating this disorder can be divided into several categories.

- **Dopamine-Related Medications**
  Dopamine is a chemical that is produced by certain cells in the brain and this group of drugs functions to either increase the amount of dopamine made by the cell (levodopa) or increase the dopamine signal to other surrounding cells by mimicking dopamine in the brain. The dopamine-related drugs include levodopa, pramipexole, ropinirole and rotigotine. These drugs are also used for Parkinson's Disease. However, there is no indication that RLS is related to, or is a precursor of, Parkinson's Disease. These medications are likely to be effective in reducing symptoms in 90% of patients with restless legs syndrome. Excessive sleepiness, increased compulsive behavior and more commonly, paradoxical worsening of symptoms, referred to as "augmentation", may occur with these medications after extended use.
- **Opiates**
  Dr. Willis in his description of this disease in 1685s also reported on the benefits of opiates for treating the symptoms. Thus for over 300 years opiates remained the only truly effective treatment for this disease. This category of medications includes codeine, hydrocodone, oxycodone, morphine, hydromorphone, methadone, buprenorphine and pentazocine. It is estimated that 85-90% of patients with RLS will respond very well to opiates. An analysis of drug responses in RLS over a 2 -10 year period showed that 85% of RLS patients who started on methadone were still on it compared to less than 20% of those started on a dopamine drug. The median starting dose for methadone in this study was 10 mg per day with a range between 2.5 mg and 20 mg per day. It is important to realize that RLS for a majority of patients is not about pain; it is an abnormal, uncomfortable sensation. Tolerance to the opiates when treating RLS seems to be less of a problem than that seen with treatment of chronic pain disorders.
- **Benzodiazepines Receptor Agonist (BRA)**
  This group of drugs is also known as sleeping pills and has valium-like effects. The structure of the parent compound was designated as a "benzodiazepine". Later research identified the specific target of the benzodiazepine drugs and designated it as the "benzodiazepine receptor". This receptor interacts with a larger receptor called the GABA receptor. More recently, new drugs have been developed, which do not have the benzodiazepine structure of the previous parent compound but still bind to the benzodiazepine receptor, so the new classification of these drugs is "Benzodiazepine Receptor Agonist". Clonazepam was the treatment of choice for RLS for many years but it is not clear that any one of this class of drugs is better than another for treating RLS. The newer BRAs including Zolpidem (Ambien), Eszopiclone (Lunesta), and Zaliplon (Sonata) are shorter acting agents than clonazepam and may be equally effective. The BRAs are most effective in those with mild symptoms.
- **Alpha-2 delta Drugs**
  These include gabapentin and pregabalin, which pharmacologically affect calcium channels by interacting with one of the channel proteins, alpha-2 delta protein. These drugs are also used to treat patients with pain from nerve damage, even in those without RLS. Therefore, the benefits seen in RLS associated with peripheral neuropathy may be related to reducing the pain, which may trigger or intensify the RLS.
- **Iron Supplementation**
  The significance of low iron in causing RLS is outlined in the segment on Causes of Restless Legs Syndrome. Since the 1950, it has been known that iron therapy even without the presence of anemia has benefits for RLS symptoms. Studies have shown a strong relation between body iron stores as determined by serum ferritin and the severity of the RLS symptoms. A study has shown that in patients whose serum ferritin was < 75 µg/l, oral iron therapy (325 mg ferrous sulphate twice a day on an empty stomach) on average improved RLS symptom after 3 months. A randomized, double-blind study of the effects of giving a 1000 mg of iron in a pint of fluid through a vein in the arm (intravenously) versus no iron, found that nearly 50% of patients had moderate or greater improvement in their symptoms. A little over 20% of those in the study had a near complete resolution of their RLS symptoms with the iron infusion. All of the patients in this study had normal hemoglobins (i.e., not anemic) and had a range of serum ferritin that were mostly in the normal range.
  Oral iron equivalent to 65 mg elemental iron may be given once, twice or three times a day. It should NOT be given with solid or liquid food/dietary supplements or with milk. It should be given on an empty stomach an hour before eating or two hours after eating along with 100-200 mg of vitamin C. An iron panel (early morning fasting blood to check iron, ferritin, TIBC, and percent iron saturation) should be done every three months to check on progress of the treatment. The goal is to get the serum ferritin above 100 µg/l. If the patient cannot tolerate the iron or if after 6 months there has been very little change in the iron stores than consider an iron infusion.
  Iron infusion bypasses the gastrointestinal tract, which acts to limit absorption of iron when iron is given orally. There are several different formulations of iron designed for intravenous treatment. There are two formulation of iron dextran. The older version of iron dextran, Dexferrum, has a much higher rate of type-I allergic reaction then the newer low molecular weight (LMW) iron dextran (INFed). The estimate rate of type-I allergic reaction for INFeD is between 1 per 100,000-200,000 infusions. Up to a 1000 mg as a single infusion has been reported to be used safely. Ferric carboxymaltose (Ferinject) has been used with RLS patients with repeated infusions of 500 mg given 5 days apart. Sodium ferric gluconate (Ferrlicit) has been used in single doses of 100-250 mg. Iron sucrose (Venofer) has been used in single dose of 100-200 mg. Ferumoxytol has been used in single dose 510mg.

  The maximum effect of an iron infusion may not be seen before 4-6 weeks post infusion. At 6 weeks after the initial infusion, an early-morning, fasting iron panel should be repeated. An iron panel should be repeated in about 2-3 months to make sure the iron stores are stable.

## Non-Drug Related Treatment Options

There are some non-drug related treatments that most patients suffering with this disorder already appreciate. Hot baths, massaging and rubbing the legs, applying hot or cold packs, restricting the amount of caffeine or alcohol and partaking in moderate physical exercise will all bring about some level of relief from the symptoms. But in the end, many of these will not permit the patient to have a good night of sleep.

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# Problems with Dopamine Drugs

Levodopa and the dopamine agonists (e.g., ropinirole, pramipexole, rotigotine), though proven to be very effective agents for managing RLS, may lead to the development of three common problems when used chronically: augmentation, compulsive behavior and sleepiness. These three problems will not occur in everyone on dopamine agents but when these symptoms do occur, patients should reduce or get off the medication. Exchanging one dopamine drug for another is likely to provide, at best, only temporary relief from these side effects.

- Augmentation is the commonest long-term side effect. Studies show about 7% of patients per year who are on dopamine agonist will develop augmentation. So even if patients have been well treated on a dopamine agonist for 5 years, they can still develop augmentation. If the dose of the drug that you initially started with has more than doubled over the years, you likely have augmentation and will likely require increasing doses. If your symptoms, when they do break though, are more severe, intense and unbearable now than when you first initiated the medication, then you are probably augmented. If you now have moderate to severe symptoms in the early evening, afternoon or even morning, which was not the case years ago when you first started the medication, than you are probably augmented.
- With augmentation the brain becomes more and more dependent on these dopamine drugs. The brain does not see “ropinirole” or “pramipexole”, it see these drugs as just more dopamine in the system. Essentially over time the brain, seeing all this extra dopamine, decides it does not need to make as much. So the brain starts turning back its own natural production of dopamine and grows increasingly dependent on these drug, which mimic dopamine. So the patient essentially develops increasing physical dependence on the drug. If the patient reduces the drug or tries to stop the drug, the patient’s greatest fear of severe RLS is realized. Adding alternative drugs like Gabapentin or an opiate (e.g., oxycodone) may have temporary benefits, but an increase in some or all of the medications is inevitable. My approach to treating this drug-related problem is to “detox” patient off the medication, which is essential to work with the patient to withdrawal them from the dopamine drugs before I institute alternative treatments. Getting off the dopamine drug allows restoration of the natural brain levels of dopamine.
- Sleepiness associated with dopamine drugs has several forms. First, patients may complain of becoming severely sleepily soon after taking the medication. Second, some patients may complain of having problems staying awake throughout the day even if they are not taking the drug during the day. Third, patients may not necessarily feel overly tired during the day, but if they sit or rest at all, they cannot stay awake.
- Compulsive behaviors can take on any form (e.g., shopping, eating, gambling, sexual activities). Less obvious forms may involve subtle personal behaviors like thoroughness or tidiness. I had a patient who lost his job because he was so compulsive about doing the job thoroughly that he never got jobs done. Often the patient is not aware of the compulsion, though the spouse or family members are. If a behavior is out of character and excessive in nature then think about the drug causing it. Reducing the dose may help but there is no guarantee that the symptoms will not come back even at the lower dose.

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