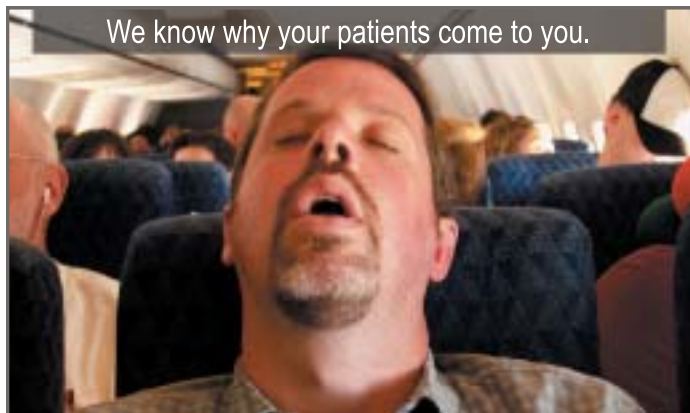


## NIGHTWALKERS PART II *by Frank Roman MD JD*



Restless Legs Syndrome (RLS) is defined as a neurological condition characterized by an urge to move, usually associated with paresthesia that occurs or worsens at rest and is relieved by activity. Recently the diagnostic criteria was updated by the International RLS (IRLS) study group in collaboration with the National Institutes of Health. The key RLS Diagnostic criteria are the following:

- 1) Urge to move legs accompanied or caused by uncomfortable sensations. This urge is quite compelling and irresistible, can be painful and involve any part of the lower extremities. In severe cases can also involve the arms.
- 2) Urge to move legs partially or wholly relieved by movement. These movements can include walking (thus the nickname), stretching or counter stimulus such as rubbing or pounding the legs, hot baths, etc. Unfortunately, symptoms resume when movement ends.
- 3) Urge to move legs begin or worsen during inactivity or rest. Increasing duration of rest is associated with greater probability and intensity of symptoms. Body position during rest makes no difference.
- 4) Urge to move legs worsen or occurs solely in the evening or night. Symptoms may have a circadian aspect. The time of day may predict occurrence and severity of symptoms independent of rest. Noteworthy, symptoms can occur anytime of day in patients with severe RLS.



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Current understanding of RLS pathophysiology suggests involvement of iron metabolism and dopaminergic dysfunction. It seems that all conditions compromising iron status will increase the risk of RLS. Impairments in CNS iron transport and metabolism have been demonstrated.

Decreases in iron concentration in the Substance Nigra and correlate with RLS severity.

RLS onset occurring before the age of 45 is slower in progression, has a greater familial pattern, more likely to be idiopathic and is less related to serum ferritin levels than late onset RLS. There is also data suggesting RLS is linked to at least 1 gene located on chromosome 12q. Certain lifestyle factors such as smoking, obesity, and inactivity can also lead to increase prevalence of RLS. Patients may also develop RLS as a result of a medical condition. Most common causes of secondary RLS include iron deficiency anemia, kidney failure, pregnancy, neurological lesions and many medications, for example antidepressants and dopamine antagonists.

It is important to differentiate RLS from:

Nocturnal leg cramps - usually experienced as painful muscular contractions which may be relieved with stretching.

Painful peripheral neuropathy - usually reported as numbness, burning, and pain. Symptoms are usually present throughout the day and relief not obtained during sustained rest.

Hypotensive Akathisias - Occurs in individual with orthostatic hypotension. Feeling of restlessness brought on by sitting still. Should not occur while lying down.

Arthritis - Pain and discomfort localized to joints. Does not have a circadian pattern as seen in RLS.

Volitional lower limb movements - Occurs in patients who fidget, much as foot tapping or leg rocking. Not associated with sensory symptoms or conscious urge to move and not circadian in nature.

Neuroleptic-induced akathisia - Most of the time a whole body sensation rather than centered only in the lower extremities with no circadian pattern, less associated sensations and often no relief with movement. Usually associated with history of specific medication exposure.

Burning or painful feet - No circadian pattern, predominant involvement of feet with repetitive movement of toes.

Certain subset of patients with RLS are iron deficient. A low serum ferritin level (less than 50ug/l) has been associated with RLS. Therefore, measurement of serum ferritin and iron saturation levels should be routinely checked. The treatment for iron-deficient RLS patients is ferrous sulfate 350mg with Vitamin C 500mg TID.

The primary treatment for RLS is Dopaminergic Agents, only two have FDA indication for RLS, Ropinirole (Requip) and Pramipexole (Mirapex). Recently, Pergolide (Permax) was taken off the market due to unacceptable adverse effects. For patients with daily symptoms, a dopamine agonist is preferred as first-line treatment. However, Levodopa's rapid onset of action makes it ideal for intermittent usage when symptoms occur only occasionally.

Another group of medications used for RLS are the sedative-hypnotics agents despite the paucity of data establishing efficiency for RLS. In all honesty, this class of medication may have been

*continued on page 69*

Inhaled Mass by the aerosol scientists. The important thing to remember about Inhaled Mass is that it expresses only the amount (mass) of drug that has been delivered to the respiratory system; it does not tell us how much of that delivery was actually retained in the respiratory tract or where it went. We have two other D-words for that.

The first of which is "deposition," which readily slips off the tongue of many practitioners who use it generously to describe anything having to do with the administration of aerosols. But, as we have just noted, the term delivery describes the amount of drug that is inhaled. Deposition is a very precise word, or at least it should be, because it describes only the amount of drug that is retained. In fact, the term "deposition fraction" is frequently used by aerosol scientists to describe the amount retained (deposited) as a percentage of the amount inhaled (delivered).

The last D-word is "distribution." Distribution pertains to the location in the respiratory tract that aerosol particles are deposited. We typically have no accurate idea about the distribution of aerosol particles when we administer a treatment. Arguably, it is important. For example, if we were trying to deliver and deposit an antibiotic aerosol in the endobronchial regions of the lungs, we would have failed if, for example, the majority of the distribution was to the trachea and mainstem bronchi. The converse is probably true; distribution of a bronchodilator aerosol to the alveoli, instead of major upper and middle airways probably will not help to relieve bronchospasm. Distribution is difficult to determine and must be estimated by in vivo techniques, usually by deposition lung imaging using radiolabeled aerosols that emit gamma rays that can be detected by a gamma scintillation camera positioned externally adjacent to the chest. This is a technique within the realm of Nuclear Medicine known as "lung scanning." Through the use of contemporary computerized lung scanning methodologies, regions of interest (ROI) can be defined on the lung scan, and the amount of gamma energy in each region can be determined as an index of the distribution of the delivered and deposited aerosol. Bluntly, it tells us where the aerosol went. Typical methods for describing distribution involve defining ROIs then comparing the gamma energy of one ROI to another. For example, central-to-peripheral, upper-to-lower, and right-to-left or, more specifically, a diseased area compared to the rest of the lung.

In summary, more precise usage of all 4 of the aerosol D-words would help us to say what we mean and mean what we say when it comes to describing aerosol therapy.

*Mike McPeck, RRT FAARC is President of Healthline Medical, Inc. Baldwin Park, CA. He is also an Assistant Professor for the RC Program at SUNY in Stony Brook, NY. He can be reached at michael.mcpeck@aerosol-medicine.com.*



**"You call it doing my homework, I call it intentional infliction of emotional distress"**

used due to the lack of available, FDA approved drugs or standard of care guidelines many years ago with the rationale and hope of sedating the patients to the point of not experiencing the restless legs. In essence these agents may mask RLS symptoms but do not treat the underlying cause. Tolerance seems to develop fairly quickly and there is a significant risk of abuse and daytime sedation. Despite these negatives, these agents may be beneficial in combination therapy for patients that cannot fall asleep despite relief of sensory symptoms. Common medication in this category include Clonazepam (Klonopin), Temazepam (Restoril), and Lorazepam (Ativan). Non benzodiazepines in this group include Zaleplon (Sonata), Zolpidem (Ambien), and Eszopiclone (Lunesta).

Third class of medications used for RLS are the anticonvulsants. Most common agents used are Gabapentin (Neurotin) and Carbanazepine (Tegretol). Gabapentin is usually preferred for tolerability and safety. Gabapentin is recommended as second or third line therapy but patients who report pain as a major symptom it can be a first line treatment. The last group of medications commonly used in RLS are the Opioids. Agents in this category include Propoxyphene (Darvocet), Hydrocodone (Vicodin) and Oxycodone (Percocet). Considered effective second or third line agents for patients who report frequent or nightly symptoms or first line if there is a significant pain component. Dependence and tolerance may occur.

One of the most common problem observed with treatment for RLS is Augmentation. Augmentation is by definition exacerbation of RLS symptoms, attributable to a specific therapeutic intervention. Common features include shift on onset of daily RLS symptoms to a time period that is equal or greater than 2 hours earlier than was typical before beneficial stable treatment and absence of any other medical, psychiatric, behavioral or pharmacologic factor that explains RLS symptoms exacerbation.

Atypical features of Augmentation include: Increased intensity temporally related to increased daily medication dose, decreased intensity temporally related to decreased daily medication dose and symptoms extended to previously unaffected body parts.

However, it is important to keep in mind there are certain symptoms that mimic augmentation, such as natural progression of RLS, temporary symptoms worsening due to external factors (sleeplessness, alcohol, caffeine.), medication (dopamine receptor blockers, antidepressants), tolerance and end of dose rebound.

Augmentation is primarily seen with dopaminergic agents. No reported cases with opiates, anticonvulsants, or other non-dopaminergic drugs.

As with many chronic diseases, it is important to empower the patients with education and resources. For RLS, these websites are recommended - The Restless Legs Foundation ([www.rls.org](http://www.rls.org)), National Institutes of Health ([www.ninds.nih.gov](http://www.ninds.nih.gov)) and Worldwide Education and Awareness of Movement Disorders([www.wemove.org](http://www.wemove.org))

Look forward to the day a cure is found and the name Nightwalkers is a euphemism for couples on a romantic rendezvous during the night.

*Frank Roman MD is a diplomat of the American Board of Sleep Medicine and a Partner, Neurosurgery and Neurology Associates of Massillon, OH. Dr. Roman also received his law degree from the University of Akron Law School.*