

# Sleep Health Newsletter™

Fall 1999

David P. White, M.D., Editor

*Dear colleague,*

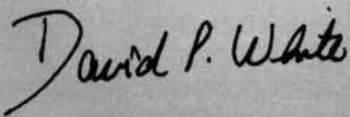
Our Fall issue of the Sleep Health Newsletter™ focuses on a sensory-motor disorder referred to as Restless Legs Syndrome (RLS). The feature article addresses the symptoms of restless legs syndrome, as well as its prevalence, diagnosis, causes and treatments. Our case study highlights the treatment of a 37-year-old male police officer with complaints of sleep onset and sleep maintenance insomnia secondary to restless legs syndrome. In addition, this quarter's featured abstract examines the latest therapies for RLS.

The intent of this newsletter is to help primary care physicians and other healthcare professionals stay up-to-date on the latest diagnostic techniques and therapeutic regimens that may benefit their patients with sleep disorders.

If you have any suggestions about subjects that future issues ought to contain, or if you would like to order extra issues of this newsletter or perhaps add a colleague's name to our mailing list, we encourage you to do so by calling 617-527-2227, ext. 214, and ask to speak to Assistant Newsletter Editor, Steve Danehy.

I certainly hope that this newsletter will be helpful to you in diagnosing, treating and supporting your patients with sleep disorders.

Sincerely,



David White

**David P. White, M.D.**

*Dr. White is an Associate Professor of Medicine at Harvard Medical School, past President of the American Sleep Disorders Association (ASDA) and, through his position at Boston's Brigham & Women's Hospital, the Medical Director of Sleep HealthCenters® LLC.*

## “Restless Legs Syndrome, Periodic Limb Movements of Sleep”

Author: John Winkelman, M.D., Ph.D.

The Restless Legs Syndrome (RLS), often accompanied by periodic limb movements (PLMs), is characterized by an uncomfortable sensation such as a "creepy crawly" feeling in the lower extremities. Often the syndrome is accompanied by motor restlessness (such as a need to pace or move the lower extremities) to alleviate the discomfort. The symptoms are classically worse at rest and at night. Occasionally, the upper limbs can also be affected. Bedtime is a major problem for RLS patients because rest, particularly lying down in bed, is associated with dysesthesia and irresistible leg movements that may consequently interfere with the ability to fall asleep. Therefore, patients with RLS commonly complain of sleep onset insomnia. However, many patients also experience paresthesia on awakenings in the middle of the night, and thus suffer from further difficulties returning to sleep following nocturnal awakenings. The pathophysiology of the disorder is currently poorly understood, although this is an area of active ongoing research.

The prevalence of RLS is estimated to be 5% of the population, but many researchers and clinicians believe this is an underestimation. Many patients do not seek medical care for this disturbing nocturnal movement disorder. In addition the severity of RLS varies greatly throughout a patient's lifetime, and can be intermittent (i.e., at times symptoms are severe and at other times absent). Of note, caffeinated drinks tend to result in an increase of RLS symptoms.

Eighty percent of patients with RLS have associated PLMs, although PLMs may exist in the absence of any RLS symptoms. While RLS commonly presents with sleep initiation insomnia, PLMs are a major cause of sleep fragmentation and can result in ineffective sleep and consequently contribute to excessive daytime sleepiness. While the diagnosis of RLS is a clinical one (based on the above symptoms), the diagnosis of PLMs is usually made by polysomnographic recordings during sleep. It is characterized by rhythmic movements during sleep, most frequently extension of the big toe and dorsiflexion of the ankle. Occasionally the movements include also flexion of the knee or hip. PLMs are measured by monitoring the EMG of the anterior tibialis muscles during a polysomnogram. Each movement lasts 0.5-5 seconds, and the movements occur at a frequency of 1-3 movements per minute. In order to group movements together and diagnose them as "periodic", the gap between each two consecutive movements has to be less than 90 seconds, and there has to be a sequence of at least 4 events. PLMs

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1-877-SLEEPHC (877-753-3742).

## Restless Leg Syndrome Author: John Winkelman, M.D., Ph.D.

cont. from pg. 1

cluster into episodes, each of which lasts several minutes or even hours. Many of them, as stated, result in arousals and sleep fragmentation.

The prevalence of PLMs increases with age. It is considered uncommon before the age of 30 years, about 5% among 30-50 year-olds, approximately 30% over the age of 50 years, and as high as 44% among individuals over 65 years old.

When dealing with a patient who is diagnosed with RLS or PLMD, it is important to rule out a potentially causative medical condition. A number of such underlying causes for RLS have been reported and should be considered in the initial evaluation. These include medications (mainly SSRIs – Selective Serotonergic Reuptake Inhibitors, Lithium and Tricyclic Antidepressants), iron deficiency anemia, peripheral neuropathy, uremia, spinal cord tumors or myelopathies.

The initial treatment for RLS/PLMs would be elimination of

underlying causes. For instance, discontinuation of SSRIs or correction of iron deficiency anemia will often result in symptomatic

improvement. Otherwise, the treatment includes dopaminergic agonists, hypnotics (e.g., benzodiazepines), and opioids (see table). The goal of therapy for PLMD is to consolidate sleep, whereas with RLS the goal is to alleviate discomfort and improve quality of life. Recent evidence suggests that long-acting dopaminergics [e.g., long acting L-dopa/carbidopa (Sinemet CR) and pramipexole (Mirapex)] provide optimal relief of symptoms and improvement in sleep quality.

In summary, both PLMs and RLS should be considered

in the differential diagnosis of both insomnia and excessive daytime sleepiness, since both disorders are relatively common and can result in difficulties falling and maintaining sleep. Both respond well to therapy if properly diagnosed and treated. □

### Treatment of RLS/PLMS

1. Exclude underlying causes – iron deficiency, uremia, peripheral neuropathy, SSRIs (e.g., fluoxetine, sertraline, paroxetine), tricyclic antidepressants:

#### Commonly Used Drugs:

##### Dopaminergics:

Ldopa/carbidopa

Pramipexole

Pergolide

##### Hypnotics:

Clonazepam

Lorazepam

Trazodone

##### Opiates:

Oxycodone (sustained-release)

Propoxyphene

#### Dosage Range

25/100 - 50/200

0.125 - 1.0 mg

0.05 - 0.5 mg

0.5 - 1.0 mg

0.5 - 2.0 mg

50 - 100 mg

10 - 40 mg.

32 - 65 mg.

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*“The prevalence of RLS is estimated to be 5% of the population, but many researchers and clinicians believe this is an underestimation.*

*Many patients do not seek medical care for this disturbing nocturnal movement disorder.”*

John Winkelman, M.D., Ph.D.

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For more information about RLS contact:

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**Dr. Winkelman** is an Instructor in Psychiatry and Medicine at Harvard Medical School, has performed extensive research in RLS and is a member of the Medical Advisory Board of the Restless Legs Syndrome Foundation. His work has been published in peer-reviewed journals such as *Sleep*, *American Journal of Kidney Diseases* and *Journal of Clinical Psychiatry*. He is Medical Director of the Sleep HealthCenter® affiliated with Brigham and Women's Hospital.

**Dr. Fogel**, a graduate of the Columbia University College of Physicians and Surgeons, recently concluded a clinical fellowship in Pulmonary and Critical Care Medicine at Massachusetts General Hospital. He now serves as a Fellow in the Sleep Disorders Program at Brigham and Women's Hospital in Boston.

The *Sleep Health Newsletter* is published by Sleep HealthCenters®, LLC as an educational service to healthcare professionals. The Editor invites submissions of original work for consideration in future issues. Manuscripts of 1500 words or less should be mailed to Assistant Newsletter Editor, Steve Danehy, c/o RTA, 2345 Washington St., Newton Lower Falls, MA 02462.

## Case Study: Restless Legs Syndrome by Robert Fogel, M.D.

### Initial Evaluation:

Mr. K, a 37-year-old white male police officer who presented to us with complaints of sleep onset and sleep maintenance insomnia secondary to restless legs syndrome. He first noted the onset of a "crampy" "crawling" sensation in his lower extremities approximately 10 years prior to this evaluation. These symptoms would generally appear in the late evening, especially when he was sitting down or when he attempted to fall asleep. Rubbing his calves and thighs would provide some relief, but many times he felt that he had to get up and walk for relief. The restless feeling in his legs and need to move made it very difficult for him to fall asleep at night. If he woke up in the middle of the night, it was also difficult to return to sleep. In addition, his wife told him that his legs were constantly "kicking" in his sleep and in the morning he often found the blankets and sheets in a heap on the floor by his bed. He was diagnosed with Restless Legs Syndrome (RLS) and probable Periodic Limb Movements of sleep (PLMs) by his internist approximately 5 years ago. Initially he was managed with Temazepam 30 mg each night, which provided only minimal improvement in symptoms and sleep quality. He had briefly been started on L-dopa/carbidopa (Sinemet) but this had been unsuccessful.

His current sleep schedule is that he gets into bed at approximately 11:30 PM, having taken his Temazepam 1 hour earlier. His sleep onset latency varies from approximately 15 minutes to greater than an hour due to the uncomfortable feeling in his lower extremities. He generally awakens once or twice per night and requires approximately 30 minutes to return to sleep. He wakes up at 7AM generally feeling "groggy" and unrefreshed. He feels somewhat sleepy throughout the day, but does not take any naps. He drinks 3-4 cups of coffee each day.

He denied any symptoms consistent with other sleep disorders such as sleep apnea, narcolepsy, or sleepwalking.

### Past Medical History: Medications:

1. Chronic Low Back pain . . . . . Temazepam 30mg, QHS
2. Irritable Bowel Syndrome . . . . . Zantac 150 mg BID

### Physical Examination:

Detailed physical examination including neurological exam was normal.

### Discussion 1:

This patient demonstrates the classic presentation of Restless Legs Syndrome (RLS) as well as Periodic Limb Movements of sleep (PLMs). These include an uncomfortable, "crawling" sensation in the legs that is relieved by movement, a predilection for the feeling to occur in the evening hours and difficulty with sleep onset secondary to these movements. In addition, his wife's complaints of his constantly moving legs and the disruption of the bedsheets are highly suggestive of PLMs. The great majority (>80%) of those with RLS will also suffer from PLMs. However, the diagnosis of PLMs is usually confirmed after nocturnal polysomnography. No obvious secondary cause of RLS could be discerned in this case (such as SSRI use, renal failure or symptoms of iron-deficiency). However, his caffeine intake could very well be exacerbating the problem. While benzodiazepines are often used as hypnotics to improve sleep quality in patients with RLS/PLMs, it is less clear if they actually decrease the number of movements. Long-acting dopaminergic agonists (such as Sinemet CR) are generally thought of as first-line therapy for relief of symptoms with RLS. However, when instituting this therapy it was also felt to be important to avoid benzodiazepine withdrawal.

It was recommended that Mr. K. begin therapy with Sinemet CR 50/200 to be taken 1 hour prior to bedtime. In addition, the Temazepam was to be discontinued and zolpidem (Ambien) 10 mg, QHS begun. The hope was that the hypnotic medication could be discontinued once adequate relief of RLS occurred. He was encouraged to decrease his caffeine intake as well.

### Follow-Up:

On initial follow-up 2 months later, Mr. K was doing extremely poorly. He continued to suffer from symptoms of RLS with no improvement in his sleep quality. In fact, it was actually somewhat worse. It was taking him an hour to fall asleep, and he was having several prolonged awakenings during the night. He had taken to remaining in bed until approximately 11AM (12 hours) although he was only getting 6-7 hours per sleep.

At this point it was recommended that Mr. K increase his dose of Sinemet CR to 2 tablets one hour prior to bedtime. He was switched from Ambien to Trazodone 100 mg. as a longer-acting

hypnotic in the hope of consolidating sleep throughout the night. In addition, Mr. K was encouraged to limit his time in bed to no longer than 7.5 hours.

Unfortunately, at a second follow-up, Mr. K. still complained of difficulty with sleep onset due to the uncomfortable feeling in his legs. While he felt that symptoms were somewhat improved, he continued to require 45 minutes to fall asleep and awoke at least once during the night. He had decreased his caffeine intake to one cup of coffee in the morning.

Due to his continued symptomatology Mr. K was switched from Sinemet to pramipexole (Mirapex), a new very long-acting dopaminergic antagonist. This was begun at a dose of 0.125 mg and was titrated up to 0.5 mg over several weeks. The Trazadone was continued. With this regimen, Mr. K had substantial improvement in his symptoms and sleep quality. While he still had some symptoms of RLS he was able to fall asleep at 11:30 PM within 15 minutes and slept soundly through the night until 7AM. He felt more alert during the daytime.

### Discussion 2:

This case is illustrative in a number of respects. First, it was unusual in that Sinemet will provide immediate relief of symptoms of RLS in at least 80% of people. However, it is not uncommon for people who have initial relief with Sinemet to develop problems later on with an earlier time of onset of RLS symptoms. Second, patients often respond positively to a different drug in the same class after having a poor response to an initial treatment attempt, as was the case here. Patients with severe RLS may also require therapy with multiple classes of agents for optimal relief. It would have been acceptable for the clinician in this case to have considered a trial of an opioid medication for relief, although many are wary of their use given the potential for abuse and dependence. It is unclear how opioids work in the treatment of RLS/PLMs, although preliminary evidence for an abnormality of cerebellar opiate receptors is emerging. In this case, with failure of initial therapy one may also have wanted to search for an occult iron-deficiency as an exacerbating factor, as this may well respond to iron supplementation, or to perform polysomnography to exclude other potential disrupting influences on sleep, such as obstructive sleep apnea. □

## Abstract of Note ...

### RESTLESS LEGS SYNDROME IMPROVED BY PRAMIPEXOLE

#### A double-blind randomized trial

Jacques Montplaisir, MD, PhD, CRCPC; Alain Nicolas, MD, PhD; Régine Denesle, BA; and Baltazar Gomez-Mancilla, MD, PhD

**Article Abstract - Background:** Restless legs syndrome (RLS) is characterized by leg paresthesia associated with an irresistible urge to move. Currently used dopaminergic agents, such as levodopa, pergolide, and bromocriptine, offer incomplete control of sensory and motor symptoms and induce severe side effects. **Objective:** To assess the safety and efficacy of pramipexole, a full D3-receptor agonist, in the treatment of RLS. **Methods:** Ten RLS patients were studied before and after two 1-month treatments (placebo and pramipexole) administered in a double-blind crossover fashion. The severity of sensory and motor manifestations was assessed by 1 week of home questionnaires and 2 consecutive nights of sleep laboratory recordings. The indexes of periodic leg movement during sleep (PLMS) and during wakefulness (PLMW) were used as primary outcome variables. **Results:** Pramipexole dramatically reduced the PLMS index to normal values (Wilcoxon,  $p = 0.005$ ). The PLMW index was also significantly reduced (Wilcoxon,  $p = 0.007$ ). Pramipexole also alleviated leg discomfort at bedtime and during the night as measured by the home questionnaires. **Conclusions:** Pramipexole is the most potent therapeutic agent ever tested for RLS. Measures of both sensory and motor functions returned to normal values after treatment. Moreover, these results further support the hypothesis that D3 receptors play a major role in the physiopathology of this condition.

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