



PHARMACEUTICALS USED TO TREAT RESTLESS LEGS SYNDROME

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This month's column will focus on the disorder of Restless Legs Syndrome (RLS) and some of the pharmaceutical compounds employed in its treatment. Following a brief overview of the symptoms, prevalence, and proposed pathophysiology of this disorder, we will review the pharmaceutical interventions routinely prescribed.

The first clinical description of (RLS) was provided in the mid 1600's by the English physician Thomas Willis who stated "Wherefore to some, when being abed they betake themselves to sleep, presently in the Arms and Legs, leaping and Contractions of the tendons, and so great a Restlessness and Tossing of their members ensue, that the diseased are no more able to sleep, than if they were in a Place of greatest torture." Over two hundred years later, the physician Ekbom coined the phrase "Restless Legs" and stated

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that "The syndrome is so common and causes such suffering that it should be known to every physician."

Today, RLS is recognized to be a chronic and progressive neurological disease characterized by unpleasant sensations in the legs as well as a compelling urge to move them. These symptoms occur most frequently during the evening or night, as well as during periods of rest. Approximately 5-15% of Northern European and Northern American populations are afflicted with RLS. Adverse outcomes associated with this disorder include hypertension, alcohol abuse, neurocognitive deficits and decrements in mental and physical health.

Those with RLS report an urge to move their limbs during daytime hours if they become confined in a delineated space for extended periods of time (i.e., sitting at a school desk). Unpleasant sensations in the limbs and/or urges to move the legs occurring in the evening often lead to difficulties with sleep onset or sleep maintenance. When these symptoms are experienced by children, they have often been incorrectly identified as "growing pains."

Periodic limb movements (PLMs), are another trait frequently occurring in patients with RLS. PLMs are defined by the International Classification of Sleep Disorders (ICSD) as periodic episodes of repetitive and highly stereotyped limb movements that occur during sleep. Four or more repetitive muscle contractions lasting 0.5-5 seconds and separated by 4 to 90 seconds are conventionally regarded as PLMs. But, the night-to-night variability in their occurrence, as well as variability in the intensity of daytime and evening sensory

symptoms, often leads to RLS being under appreciated or missed during a clinical evaluation.

Chronic sleep restriction and sleep fragmentation is one adverse outcome attributed to RLS and PLMs. This, in turn, is postulated to contribute to the deleterious physical, mental and social effects associated with this disorder. For example, adults with RLS manifest an increased incidence of hypertension, alcoholism, poor mental health and neurocognitive impairment. Consequently, the negative impact of RLS on quality of life is similar to that observed with other chronic disorders such as depression, heart failure and diabetes.

Recent epidemiologic and genetic linkage studies have begun to distinguish two forms of RLS; early onset (primary RLS), and late onset (secondary RLS). The early onset form typically begins in childhood or young adulthood with symptoms developing in a slowly progressive manner. Early onset RLS is inherited in an autosomal dominant fashion, shows genetic anticipation, is more prevalent in females (2:1), and is associated with at least two separate genetic loci. In addition, PLMs are thought to be more prominent in this form of the disease. In contrast, the late onset type is characterized by a later age of symptom onset (>45 yrs.), an equal female to male ratio, a rapidly progressive course, a relationship with low body iron and other associated identifiable causes such as diabetes, kidney disease, neuropathy, anemia and even nervous system trauma.

In addition to the intrinsic pathophysiological mechanisms previously described, certain extrinsic factors are associated with increased frequency and severity of symptoms. For example, H2 histamine blockers such as Zantac or Tagamet have been reported to worsen symptoms of RLS. In addition, caffeine, alcohol, and certain antidepressants such as Elavil are reported to worsen the frequency and severity of RLS/PLM symptoms.

Prevalence studies suggest that the onset of RLS increases with age, with a prevalence rate of 2% in children, 3% in 30 year-olds, and up to a 20% prevalence rate in 80 year-olds. Genetic epidemiological studies and linkage analyses also demonstrate that early onset RLS is a heritable trait, but the pathophysiological mechanisms of RLS are still unclear. Recently, much research has focused upon determining if reductions in extracellular dopamine levels within the CNS, or else deficiencies in post synaptic responsivity to dopamine, contribute to the symptoms RLS and PLMS.

Reduced levels of extracellular dopamine is central to several hypotheses regarding neurochemical substrates contributing to



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the symptoms of RLS. Yet, elucidation of the actual dopaminergic dysfunction remains enigmatic. For example, it may be that reduced synthesis or increased sequestration of dopamine within cell bodies and terminals leads to diminished extracellular dopamine. Alternatively, dopamine production and release may be normal, but the number and/or type of post synaptic dopamine receptors may be altered and result in RLS symptoms.

Deficiencies in central dopamine neurotransmission may contribute to the etiology of many RLS symptoms. The first link made between dopamine and RLS was based on the observation that many patients derived great relief from the administration of dopamine augmenting drugs. This was acknowledged by the American Academy of Sleep Medicine's 1999 Practice Parameters for the treatment of RLS and PLM, which stated that "Dopaminergic agents are the best studied and most successful agents for treatment of RLS and PLMD." Following multiple clinical trials with dopamine agents and FDA approval for several agents, in 2004 Littner et al. reported in the journal *Sleep* that "Levodopa with decarboxylase inhibitors, and the dopaminergic agonists pergolide, pramipexole, and ropinirole are effective in the treatment of RLS and PLMD." Despite the promise that dopamine augmenting compounds can reduce the symptoms of RLS, it should be mentioned that their use for RLS is currently only approved for adults; data are lacking with regards to their use for RLS in pediatric populations and during pregnancy.

The role of dopaminergic compounds for the treatment of RLS and PLMS is well accepted. When prescribing any type of dopaminergic medication (whether it be a precursor to dopamine, a dopamine agonist, or a compound that reduces dopamine metabolism), the potential for side effects such as nausea, gastrointestinal distress, reduced blood pressure and sleepiness need to be taken into account and discussed with a credentialed sleep medicine physician. In addition, as dopamine is a major neurotransmitter modulating mood, cognition, wakefulness and sleep, any type of dopamine precursor, agonist, or antagonist can result in acute thought and behavioral changes. Working with an experienced sleep medicine professional who can monitor any undesired effects during therapy is an important component of RLS management. Given that most RLS patients need very low doses of dopaminergic medications for symptomatic relief, the likelihood of a serious or adverse outcome is exceedingly remote.

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"Here's the problem: You can afford to go to Hawaii, but you can't afford to come back."