RESTLESS LEGS SYNDROME/WILLIS-EKBOM DISEASE DIAGNOSIS AND TREATMENT

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Diagnosis

Restless legs syndrome (RLS), also known as Willis-Ekbom disease, is fundamentally a clinical diagnosis, based on face-to-face evaluation of core symptomatic criteria. These criteria were updated by the International Restless Legs Syndrome Study Group in 2012 and published in 2014 (1). The four existing criteria from 2003 were largely unchanged and can be remembered with the acronym "URGE": U – **U**rge to move the legs, often accompanied by uncomfortable leg sensations; R – **R**est makes this urge worse; G – the urge **G**ets better with movement; E – urge is worse in the **E**vening or night. The major change in the 2012 criteria was the addition of a fifth criterion that requires exclusion of RLS mimics such as positional discomfort, myalgia, habitual foot tapping, etc, as the sole cause of the sensory symptoms. Periodic limb movements of sleep, which are repetitive movements of the limbs (most commonly the legs, measured via anterior tibialis EMG during sleep studies), are present in the majority of patients who have RLS and are considered a supportive feature for diagnosis. However, PLMS are known to have considerable night-to-night variability (2, 3). Their absence on a single night of monitoring does not serve to exclude a diagnosis of RLS and polysomnography is not required for RLS diagnosis. Furthermore, PLMS are commonly observed in patients who do not have RLS and their presence on a sleep study does not imply a diagnosis of RLS (4).

Treatment

Several classes of medications have been implicated in worsening RLS symptoms. These include dopamine antagonists (antipsychotic medications and the anti-emetic metoclopramide), anti-histamines (especially non-selective agents such as diphenhydramine), and anti-depressants. In a series of consecutive patients started on common second-generation anti-depressants and monitored for the development or worsening of RLS, rates of new or worsening RLS were highest in mirtazapine (28%) and lowest in citalopram (2%; no cases of RLS were seen in 25 patients treated with reboxetine, but this medication is not currently available in the United States) (5). Bupropion, while not superior to placebo for chronic treatment of RLS (6), is thought to be unlikely to worsen RLS based on its mechanism of dopamine and norepinephrine reuptake inhibition.

There are four medications that are currently approved by the US FDA for the treatment of RLS, which include, in order of FDA approval, ropinirole, pramipexole, gabapentin enacarbil, and rotigotine. All but gabapentin enacarbil are dopamine agonists; ropinirole and pramipexole are taken orally while rotigotine is available as a transdermal patch replaced every 24 hours. Gabapentin enacarbil is an alpha-2-delta calcium channel ligand, a pro-drug that is converted to gabapentin (but gabapentin and gabapentin enarcarbil do not have 1:1 equivalent dosing). Other alpha-2-delta ligands that are commonly used for the treatment of RLS, although are not FDA approved for this purpose, are gabapentin and pregabalin.

There have been few head to head trials to guide practice decisions regarding which medication should be prescribed as first line, and in which patients. A recent randomized controlled trial of pregabalin 300 mg versus pramipexole 0.25 mg or 0.5 mg, supported by the makers of pregabalin, demonstrated that both pregabalin and the 0.5 mg dose of pramipexole were superior to placebo at reducing RLS severity, although the 0.25 mg dose of pramipexole was not (7). Pregabalin resulted in a greater reduction in RLS severity than did pramipexole. Medication was stopped due to side effects in 28% of patients on pregabalin, 18% on 0.25 mg pramipexole, and 21% on 0.5 mg pramipexole (significantly favoring pramipexole). However, augmentation (i.e., a medication-induced worsening of RLS symptoms over time) was significantly more common in patients on higher dose pramipexole that on pregabalin (8% versus 2%; the rate of augmentation on lower dose pramipexole was 5% but not significantly different than pregabalin). Non-randomized studies have also found a similar, approximately 7-8% per year, rate of augmentation with dopamine agonists (8, 9). Because of this augmentation risk with dopamine agonists, a combined statement by the IRLSSG, the RLS Foundation, and the European RLS Study Group recommends consideration of alpha-2-delta ligand agents as first-line treatment or keeping dopamine agonist dose as low as possible (and not exceeding recommended maximum doses for RLS) (10). Treatment decisions also should be guided by patient comorbidities. For example, patients with pre-existing depression may benefit from dopamine agonists (to avoid the risk of worsening depression or suicidal ideation

related to alpha-2-delta ligand use), whereas patients with comorbid anxiety disorders may instead benefit from the anxiolytic effect of alpha-2-delta ligands for their RLS. A practical guide for choosing between alpha-2-delta ligands and dopamine agonists based on patient comorbidities can be found in the IRLSSG guidelines for long term treatment of RLS (11).

Multiple clinical trials have been performed using oral or intravenous iron therapy in patients with RLS, with or without comorbid iron deficiency. In meta-analysis, these studies demonstrate a significant benefit of iron for RLS (Trotti, unpublished data). The RLS Foundation practice algorithm recommends testing serum ferritin in all RLS patients, repleting iron with an oral iron supplement in those with ferritin < 50-75 mcg/L (11). In those whom oral iron is not tolerated, intravenous iron can be considered.

The first AAN practice guideline for the treatment of RLS was recently released (12). For treatment of RLS symptoms, the authors found strongest evidence in support of pramipexole, rotigotine, and gabapentin enacarbil (Level A). Cabergoline was also given a Level A recommendation in terms of efficacy, but it was noted that this is infrequently used in RLS because of the risk of cardiac valvulopathy. Ropinirole, pregabalin, intravenous ferric carboxymaltose, and oral ferrous sulfate with vitamin C (the latter only in those with serum ferritin $\leq$ 75 mcg/L) were given a recommendation of Level B. They found insufficient evidence in support of choosing pregabalin over pramipexole (Level U). For treatment-refractory patients, use of prolonged-release oxycodone/naloxone was given a Level C recommendation, with a note that the risks versus benefits of opiate use should be considered. This medication is not presently available in the United States. Moderately strong evidence was found in support of pneumatic compression devices (Level B). There was weak evidence against vibratory counter-stimulus devices for treating RLS symptoms specifically (Level C against) but weak evidence for these devices in improving subjective sleep measures in patients with RLS (Level C).

Quality measures for the care of adult patients with RLS have been proposed by the American Academy of Sleep Medicine. These focus on three key outcomes (13):

1) Improve accuracy of RLS diagnosis (process measures include using formal diagnostic criteria, such as those from the IRLSSG or the AASM, and measuring body iron stores with at least a serum ferritin)
2) Decrease RLS symptom severity (process measures include assessment of symptom severity and offering of evidence-based treatment)
3) Minimize treatment complications (process measures include counseling regarding potential medication side effects, assessing for impulse control disorders in patients on dopaminergics, and assessing for augmentation in patients on dopaminergics)

Pregnancy is a time of increased vulnerability to RLS symptoms, with the frequency and severity of RLS increasing with each trimester. Although RLS symptoms typical resolve shortly after delivery in those who did not have RLS predating their pregnancy (14), the presence of RLS during pregnancy can be problematic and requires special attention because of the possibility of pregnancy-related adverse medication effects. The IRLSSG has published a guideline for the management of RLS during pregnancy and lactation (15). This guideline emphasizes the importance of accurate diagnosis and use of non-pharmacologic strategies (assessment and treatment for iron deficiency with serum ferritin < 75 mcg/L, moderate intensity low-impact exercise, and avoidance of RLS triggers). In patients with symptoms that are refractory to these interventions and severe enough to warrant pharmacotherapy, recommendations during pregnancy are for carbidopa/levodopa ER 25/100 qhs or clonazepam 0.25 to 1 mg qhs (or low-dose oxycodone in very severe, very refractory cases). During lactation, gabapentin, low dose clonazepam, or low dose tramadol (the latter in very severe, very refractory cases) are recommended when necessary.

A number of cross-sectional and longitudinal studies have evaluated for associations between RLS and cardiovascular disease. Neither type of study has been uniformly supportive of an association between RLS and cardiovascular disease, but numerous studies have found such an association (16). Multiple mechanisms have been proposed for such a relationship. One key candidate is periodic limb movements of sleep, which are accompanied by elevations in blood pressure and heart rate (17, 18) and have been identified as a cardiovascular risk factor among normotensive elderly men in a longitudinal study (19). A recent placebo-controlled trial (funded by the drug manufacturer) of patients with RLS and PLMS evaluated the effect of rotigotine on nocturnal blood pressure (20). In 66 analyzed patients, rotigotine decreased episodes of nocturnal blood pressure elevations by 20-25% more so than placebo. However, whether or not treatment of PLMS (in people with or without RLS) results in a reduction in cardiovascular disease remains an important, unanswered question.

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