The Appropriate Use of Opioids in the Treatment of Refractory Restless Legs Syndrome

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Abstract

Restless legs syndrome (RLS) is a distinct disorder, differing from chronic pain in many ways. Refractory RLS is characterized by unresponsiveness to dopamine agonists or alpha-2-delta ligands due to inadequate efficacy, augmentation, or adverse effects. This may result in severely impaired quality of life, profound insomnia, and suicidal depression. Opioid therapy is a mainstay in the management of these patients. This article summarizes the basic science and clinical evidence in support of their use, including the positive result of a large controlled multicenter study of 306 subjects, and outlines an approach to their use in clinical practice. Treatable explanations for RLS refractoriness, such as low iron stores, and other therapeutic options, such as combination therapy, should be considered before prescribing opioids. The agents most commonly used are oxycodone and methadone, but tramadol, codeine, morphine, and hydrocodone can also be considered. Controlled-release medication should be used for evening dosage and short-acting drugs, if needed, during the day. Effective doses are considerably lower than used for chronic pain (oxycodone 10-30 mg daily; methadone 5-20 mg daily) and the risk of opioid use disorder is relatively low. However, sensible precautions should be undertaken, including assessing opioid risk with standard questionnaires, using an opioid contract, using urine drug screens, consulting state prescription drug monitoring programs, and frequent reevaluation of effectiveness and side effects. Opioid use in selected patients with refractory RLS may be life-transforming with favorable risk-benefit ratio.

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Restless legs syndrome (RLS) is a common disorder, with about 2% of the population afflicted with symptoms occurring at least twice a week and resulting in moderate or severe distress.[1,2] Most patients obtain at least initial relief with first-line agents, specified as dopamine agonists (pramipexole, ropinirole, rotigotine patch) and alpha-2-delta ligands (gabapentin, gabapentin enacarbil, pregabalin).[3] However, adverse effects prevent their use in some patients and the therapeutic effect can wear off with time. Importantly, as many as 50% to 70% of patients using dopamine agonists develop drug-induced augmentation over 10 years,[4,5] characterized by earlier symptom onset, involvement of arms and trunk, and shorter duration of relief from treatment. When RLS becomes unresponsive to monotherapy with first-line agents of both classes due to inadequate efficacy, augmentation, or adverse effects, it is considered refractory to treatment.[3]

The worsening epidemic of prescription and illicit opioid abuse has made many caregivers wary of prescribing opioids. Current consensus is that opioids have only a limited role in the management of chronic pain in the absence of malignancy or end-of-life care.[6] In contrast, published clinical trials and case series demonstrate the considerable effectiveness of opioids in treating refractory RLS, a distinct disorder with a different etiology, pathophysiology, and epidemiology from chronic pain syndromes.[7] Differentiating features of the disorder include the identification of several risk alleles by genomewide association studies, brain iron deficiency, and abnormalities in the dopamine system. Despite this, patients with RLS frequently report

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difficulty obtaining opioid prescriptions from providers.

The aim of this article is to summarize the basic science and clinical evidence supporting the use of opioids for the treatment of refractory RLS and to outline a responsible approach to their use. It is our opinion that the risk-benefit ratio of opioid use in patients with RLS who are selected according to our guidelines is positive and that risk can be minimized as long as reasonable precautions are followed.

CLINICAL NEED

Refractory RLS is a common clinical problem. The following case scenario illustrates a typical patient with RLS refractory to first-line therapies who is an excellent candidate for opioid therapy.

A 59-year-old woman with a family history of RLS in her father and brother presented with worsening RLS symptoms over 25 years. Pramipexole had been prescribed 15 years previously at a time when her symptoms occurred only after going to bed, delaying sleep onset by an hour. Initially a dose of 0.25 mg taken 2 hours before going to bed gave full relief. As time passed, symptoms began earlier in the day and eventually started whenever she sat down after 1 PM, also occurring in her arms. The dose of pramipexole had been increased to 1 mg daily. Pramipexole was discontinued a year before presentation and a rotigotine patch was substituted at 3 mg daily. Initially this was effective but over several months the effect wore off with recurrence of symptoms during the day and night, persisting after withdrawal of the drug. Pregabalin 300 mg in the evening failed to control symptoms adequately and caused feelings of depression. She did not snore and was not obese. Serum ferritin level was 135 μg/mL and transferrin saturation was 27%. At the time of presentation, the patient was sleeping only 3 hours a night and could not sit down without symptoms after 1 PM.

PRECLINICAL STUDIES: OPIOID PATHOPHYSIOLOGY IN RLS

Opioid medications stimulate G-protein–linked mu, kappa, delta,[8] and opioid receptor like-1 receptors,[9] which are found throughout the nervous system, especially in the spinal cord, brainstem, and thalamus. These are preserved throughout evolution, and serve other purposes in addition to their overt human clinical role in analgesia. Pathophysiologic understanding of RLS is incomplete and likely multifactorial.[7] Major clues include therapeutic responses, most specifically with dopaminergics, iron, and opioids. Other lines of research demonstrate abnormalities in iron, dopamine, hypocretin, opioid, and glutamatergic systems, and peripheral nerve sensory processing.

In a postmortem study evaluating opioid pathology,[10] 5 brains from patients with RLS and 6 brains from controls without other neurological disease were stained with antibodies for beta-endorphin, met-encephalin, and leu-encephalin, and cell numbers counted in a blinded fashion. In the thalamus, beta-endorphin–positive cells were reduced by 37.5% (P=.006; effect size, 2.16), and met-encephalin cells by 26.4% (P=.028; effect size, 1.58) in patients with RLS compared with controls but there was no difference in leu-encephalin cells. In the substantia nigra, there were no differences in beta-endorphin, met-encephalin, or leu-encephalin. Tyrosine hydroxylase staining for dopamine cells was normal. RLS pathology in the thalamus is also implicated by voxel-based magnetic resonance imaging studies, which inconsistently show increased pulvinar size,[11,12] reduced single-photon emission computerized tomography scan *N*-acetylaspartate:creatine ratio and *N*-acetylaspartate concentrations in the medial thalamus,[13] and functional magnetic resonance imaging studies, which show increased activity in the thalamus and cerebellum while RLS symptoms are present. Although these studies do not specifically implicate opioid systems, opioid receptors are very abundant in the thalamus.

Daytime positron emission tomography imaging using the nonspecific opioid ligand [11C] diprenorphine did not differentiate between human RLS and controls. Correlations were, however, found between mu-receptor–binding potential in amygdala, medial thalamus, anterior cingulate, and orbitofrontal cortex and RLS subjects' reported severity as measured by the International RLS Study Group severity scale.[14] These 4 regions have been shown to have varying degrees of interconnection and are associated not only with emotion and reward in decision making but

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