# 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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also with addiction, impulsivity, and anxiety.[15] Decreased binding suggests either increased endogenous opioid receptor occupancy or downregulation/internalization of the receptors.

There is evidence supporting opioid interactions with dopaminergic systems on the basis of *in vitro* and clinical data. Stimulation of opioid receptors, especially mu receptors, which are robustly associated with dopamine receptors, can facilitate dopamine release as demonstrated by microdialysis studies in mice and on functional imaging of dopamine receptor occupancy in humans.[16,17] Importantly, pretreatment of RLS with a dopamine antagonist will negate any benefit of opioids, also suggesting that opioids interact with or work via dopaminergic systems to treat RLS.[18] If naloxone, an opioid antagonist, is given to untreated subjects with RLS, no overt effect is seen,[19,20] but if given in a double-blind fashion to opioid-treated patients with RLS, the RLS signs and symptoms reappear, suggesting that naloxone blocks the beneficial effects of the opioid agonist.[21,22] However, naloxone does not block the beneficial effects of a dopamine agonist, suggesting that the dopaminergic response is not mediated via an opioid mechanism.[23]

## CLINICAL STUDIES

Despite how long opioid drugs have been used for RLS, there are few high-quality, placebo-controlled studies to support their use. A parallel-group study randomized 306 patients with moderate to severe RLS and previous unsuccessful treatment to receive flexibly dosed prolonged-release oxycodone/naloxone or placebo.[24] After 12 weeks, oxycodone/naloxone resulted in a greater symptom reduction than placebo as found using the International Restless Legs Syndrome Scale[25] (−8.15; 95% CI, −10.85 to −5.46), with a mean dose of oxycodone of 21.9±15.0 mg and that of naloxone of 11.0±7.5 mg. The Clinical Global Impression responder rate was significantly higher in the oxycodone/naloxone group (67%) than in the placebo group (35%). Sleep adequacy and quantity improved more in the oxycodone/naloxone group than in the placebo group as measured by the Medical Outcome Studies sleep subscales. Daytime somnolence was not different between groups. During a subsequent 40-week open-label phase involving 197 subjects, oxycodone/naloxone was titrated from 5 mg oxycodone twice daily to a maximum of 40 mg twice daily. Forty subjects discontinued therapy, including 6 because of lack of therapeutic effect and 21 because of adverse events. At the end of the 40 weeks, the mean daily oxycodone dose was 18.1±10.5 mg. Efficacy was maintained with a reduction in the International Restless Legs Syndrome Scale score from onset of the open-label phase. Drug withdrawal symptoms were noted in only 3 of 176 subjects. Prolonged-release oxycodone/naloxone is approved for the treatment of RLS in more than 20 European countries, including the United Kingdom, France, and Germany.

A small double-blind crossover study randomized 11 patients with moderate to severe RLS to receive oxycodone in divided doses (2 hours before and at bedtime) or placebo. On self-rated 0 to 4 scales, oxycodone (mean dose of 15.9 mg/d) improved RLS symptoms of motor restlessness and leg paresthesia better than placebo.[26] A retrospective long-term study of various opioids in refractory RLS showed that 20 of 36 continued on opioid monotherapy (mean, 5 years and 11 months) and only 1 patient discontinued because of the development of tolerance and addiction.[27]

Two open-label studies support the effectiveness of the chronic use of methadone for refractory RLS. One study evaluated 27 subjects who failed on average 5 or more previous treatments for RLS.[28] Seventeen remained on methadone for 23±12 months at a dose of 15.5±7.7 mg (range, 5-40 mg) and reported continued benefit and tolerability. Most patients who stopped methadone did so in the first month of therapy. Another longitudinal study reported on a consecutive series of 76 patients on methadone with primary RLS and complete data between 1997 and 2007.[5] Unlike dopamine agonist treatment, the long-term tolerability was excellent, without any evidence of augmentation. The median daily dose after 6 months of treatment was 10 mg. This did not increase in the first 3 years of use but did increase by a median of 5 mg and a maximum of 10 mg in those patients who had been followed for 4 to 7 years. No one who took methadone for at least a year subsequently discontinued it.

Methadone is frequently used to treat narcotic addiction because it has less abuse potential than do other narcotics.[29] In contrast to morphine and most other narcotics, its use does not cause intracellular forskolin-stimulated cyclic adenosine monophosphate accumulation, a mechanism thought to contribute to opioid tolerance.[30] Methadone also uniquely antagonizes *N*-methyl-D-aspartate receptors in the spinal cord,[31] an area heavily implicated in RLS symptom genesis.[32,33] Therefore, although there is no human clinical comparison of different opioid medications, there is scientific rationale to specifically support the use of methadone, especially when long-term treatment is required.

## USING OPIOIDS FOR THE TREATMENT OF RLS

### Indications

Restless leg syndrome is considered refractory to treatment when it is unresponsive to monotherapy with tolerable doses of first-line agents of both classes (dopamine agonists and alpha-2-delta ligands) due to inadequate efficacy, augmentation, or adverse effects.[3] Doses of dopamine agonists should generally not exceed those recommended to prevent the development of augmentation.[34] Before considering opioid therapy, physicians should consider other alternative approaches.[34]

1. Is there evidence for low systemic iron stores (serum ferritin concentration of <75 μg/mL)? Oral or intravenous iron therapy may relieve symptoms without the need for additional medications.[3,35]
2. Have other factors that might exacerbate RLS been considered, such as the use of drugs that can worsen symptoms, including antihistamines, serotonergic antidepressants, and dopamine antagonists, or the presence of other sleep disorders such as obstructive sleep apnea?
3. Has combination therapy been considered, using lower doses of agents of different classes? In patients with severe symptoms this may not be appropriate and in some patients with profound RLS associated with dopamine agonist augmentation, opioids may be indicated even if alpha-2-delta agents have not had an adequate trial.
4. In the case of dopamine agonist augmentation, has a 10-day washout period, without immediate substitution of an opioid, been considered? Although this may allow determination of the severity of baseline symptoms off all drugs, an exacerbation of RLS with profound insomnia very frequently develops during the washout period and this approach is appropriate only for some carefully selected patients.

Not all these options may be relevant or appropriate in every patient. The time of initiation of opioid therapy depends on many factors, including the severity of the symptoms and their effect on sleep and quality of life. Although the benefits and risks should be carefully weighed, appropriate patients should not be deprived of opioids simply because of fear of opioid use disorder.

### Precautions

Physicians are increasingly reluctant to prescribe long-term opioids because of recent heightened scrutiny by regulatory agencies and increased concerns of high rates of addiction and overdose recently publicized by organizations such as the Centers for Disease Control and Prevention.[6] However, as long as reasonable precautions are taken, this should not deter physicians from prescribing medications necessary for the health of their patients. Refractory RLS can be a devastating condition, resulting in profound insomnia, suicidal depression, and severely compromised quality of life.[36] Nevertheless, prescribers should act responsibly with an understanding of the opioid epidemic afflicting the United States and the legal requirements of individual states. Following simple standardized safety practices reduces risk to patients, allowing for effective use of the drugs (Table 1). Several guidelines for chronic opioid use for pain with evidence in support of the recommendations have been published, including examples of patient questionnaires and contracts.[6,37-39]

Before initiating opioid therapy, patients should be questioned about a personal or family history of alcohol or drug abuse (including prescribed medications), and present and past psychiatric disease. These factors increase the risk of opioid dependence, which is also higher in men and younger patients. Screening questionnaires


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**TABLE 1. Summary of Considerations in the Use of Opioids for Refractory RLS**

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| 1. Opioids should be considered for the treatment of RLS that is not adequately controlled with first-line agents due to poor response, adverse effects, or, in the case of dopamine agonists, augmentation. |
| 2. Factors that may be responsible for an inadequate response, especially low iron stores, the use of medications that can exacerbate RLS, or obstructive sleep apnea, should be considered. |
| 3. Alternative approaches should be considered when relevant, including using combination therapy of nonopioid agents or, in the case of dopamine augmentation, a 10-day washout period before substituting an opioid. These approaches are not appropriate for all patients. |
| 4. Before initiating opioid therapy, patients should be assessed for risk of opioid use disorder, state prescription drug monitoring programs should be queried, and a urine drug screen performed. |
| 5. Patients should be informed about expectations of treatment and the risks of opioids. |
| 6. Patients should be asked to sign an opioid contract, including at a minimum the following:<br>• An understanding of the side effects of opioids and the risk of opioid use disorder;<br>• That medications should be obtained from only a single provider and a single pharmacy;<br>• That early refill prescriptions will generally not be issued even if the medication is reported lost;<br>• That the dose should not be altered by the patients without discussion with the prescribing physician;<br>• That medication should not be shared with anyone else. |
| 7. Regular follow-up is needed, assessing effectiveness of therapy, side effects, and evidence for development of opioid use disorder. State prescription drug monitoring programs should be assessed regularly and a urine drug screen considered at least once annually, especially in high-risk patients. |
| 8. Testing initial response with a short-acting drug is reasonable, but long-acting or extended-release agents are preferred at night, with either short- or long-acting agents added during the day as needed. |
| 9. Treatment should commence with low doses, increasing as needed and tolerated, but the individual risk-benefit ratio should be carefully considered if doses above those listed in Table 2 are used, because such doses have been associated with increased overdose-related mortality. |
| 10. The choice of drug to be used depends on physician preference, patient factors, and cost, but the prescriber should be very familiar with dosing schedules and the individual differences between agents. |
| 11. Care should be taken with dosages when transitioning a patient between different opioids due to varying drug potencies and cross-tolerance. |

RLS = restless leg syndrome.

for depression and anxiety may be helpful, and validated tools are available to stratify risk, such as the Opioid Risk Tool[40] and the revised Screener and Opioid Assessment for Patients with Pain.[41] Opioids should not necessarily be withheld in patients at higher risk but more intensive monitoring may be needed.

Alternative therapies should be discussed with the patient, and the reasons for an opioid prescription should be documented in the medical record. Treatment aims should be specified and tailored to the patient's primary complaint related to RLS, such as inability to initiate sleep at night. It should be emphasized that complete relief of symptoms is not a realistic long-term goal in most patients. The goal should be to reduce symptoms to a level that provides sustainable improvement in sleep and overall quality of life. Potential adverse reactions should be described, including nausea, constipation, pruritus, myoclonus, drowsiness, and cognitive impairment. The possibility of precipitating or exacerbating obstructive or central sleep apnea, or the conversion of treated obstructive sleep apnea to central sleep apnea, should be considered. Opioids should not be taken together with alcohol and preferably not together with benzodiazepines. An electrocardiogram to assess the QT interval should be obtained before prescribing methadone and should be repeated after initiation of the drug, particularly when it is combined with other agents that may cause QT prolongation.

An opioid contract should be signed by each patient.[6] This should include an understanding of the risk of opioid use disorder, that medications should be obtained from only a single provider and a single pharmacy, that early refill prescriptions will generally not be issued even if the medication is reported lost, that the dose should not be altered by the patients without discussion with the prescribing physician, and that medication should not be shared with anyone. The patient should

**TABLE 2. Suggested Doses for Using Opioids in RLS**

| Drug | Starting total daily dose | Usual effective total daily dose |
|---|---|---|
| Tramadol (immediate or extended release) | 50 mg (100 mg ER) | 100-200 mg |
| Codeine | 30 mg | 60-180 mg |
| Morphine CR | 7.5-15 mg | 15-45 mg |
| Oxycodone (immediate or extended release) | 5-10 mg | 10-30 mg |
| Hydrocodone (immediate or extended release) | 10-15 mg | 20-45 mg |
| Methadone | 2.5-5 mg | 5-20 mg |

CR = controlled release; ER = extended release; RLS = restless leg syndrome.

be informed that state prescription drug monitoring programs will be interrogated. A urine drug screen can be performed before initiation of therapy, especially if there is suspicion of existing opiate use. Patients should be reassessed at regular intervals, usually every 3 to 6 months, to determine efficacy, side effects, and any evidence for opioid use disorder or misuse. In particular, practitioners should consider whether patients with multiple comorbid conditions may have supplies of opioids prescribed in the past for other disorders.[42] The prescription drug monitoring program data should be checked at each visit and random urine drug screens considered at least once yearly, especially in higher risk patients. The goals of urine drug screens are to determine whether the patients are taking any other unsuspected narcotic substance and to show that the patient is taking the prescribed opioid and not diverting it. Screens differ in the list of drugs tested, and physicians should familiarize themselves regarding which drugs are included in the specific screen ordered. In particular, assessment for tramadol or methadone may need to be specially requested. The interpretation of drug screens is complex and unexpected results should be discussed with the toxicologist or the laboratory performing the test before conclusions are reached. At follow-up visits, patients should be reassessed for the development of depression and anxiety and appropriately treated or referred.

## Drugs and Doses

Most published studies of opioids in RLS have used oxycodone or methadone.[24,26-28] There has been experience with other agents[27] but no comparative studies have been reported. Although lower potency drugs such as codeine or tramadol can be tried,[27,43] most patients with refractory symptoms will require the use of high-potency medications. Testing initial response with a short-acting opioid may be a reasonable initial option but in general, longer-acting and controlled-release drugs are preferred. This may be especially important at night, because short-acting opioids may not give adequate length of coverage and may be associated with end-of-dose rebound of RLS symptoms. However, shorter-acting drugs may be appropriate during the day when symptoms may be less severe, because lower doses can be used. Choice of a specific drug depends on individual prescriber and patient factors, including cost of medication.[44] Low doses should be given initially with titration to usual effective doses on the basis of efficacy and side effects. The timing of doses depends on symptoms: the first objective should be to give relief at night but some patients will require additional daytime doses. The goal should be to improve patient's quality of life but not to necessarily eliminate all RLS symptoms. Total daily doses above those listed in Table 2 may sometimes be needed, but the risk-benefit ratio should be carefully assessed because such doses have a significantly increased risk of overdose-related deaths in studies of patients with chronic noncancer pain.[45-47]

In an attempt to simplify the available choices, this article will restrict discussion to only a few of the more commonly used agents. Methadone is anecdotally considered to be the most effective opioid for RLS, but has variable pharmacokinetics and pharmacodynamics, is long acting, may cause prolongation of the electrocardiogram QT interval at high doses,[48] and reduce testosterone levels. Practitioners


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prescribing methadone should be knowledgeable about these unique features. Extended-release oxycodone is frequently used but similar medications include controlled-release morphine. Tramadol carries a risk of seizures particularly when the patient is also taking antidepressants. There is anecdotal evidence that tramadol may cause augmentation.[49-51] Table 2 lists the recommended initial and usually effective dose ranges but it should be noted that a minority of patients may require higher doses than those listed to obtain relief from symptoms. These doses are derived from limited published studies, anecdotal experience, and the approximate equivalence in strength of different agents.

It is important to emphasize that the doses of opioids used for refractory RLS are far lower than those used for the treatment of chronic pain syndromes. These lower doses markedly reduce the risk of opioid use disorder. In a study of nationwide US medical and pharmacy claims to Blue Cross and Blue Shield insurance companies in 2015, the rate of opioid use disorder in patients taking low-dose opioids for more than 90 days was 6/1000 patients, compared with 40/1000 patients using high-dose opioids, an almost 7 times lower frequency. Low-dose opioids were defined as less than 100 mg morphine or equivalent per day, an upper limit far higher than that recommended for RLS, suggesting that the rate of opioid use disorder in patients with RLS may be even lower.[52]

### Unresolved Clinical Questions

Further well-designed research studies are needed to resolve a number of clinical questions. The comparative effectiveness and side effects of different opioids in patients with refractory RLS need to be determined. Studies are needed to confirm the clinical impression that maintaining a low dose of a dopamine agonist or alpha-2-delta ligand may allow a lower dose of opioid to be used. Further long-term studies of safety and efficacy are needed. In particular, larger studies are needed to assess the risk of dose escalation and abuse of opioids prescribed for RLS.

There is no consensus on how to convert patients with refractory RLS from a dopamine agonist or alpha-2-delta ligand to an opioid.[34] One choice is to titrate the opioid to a therapeutic level and then slowly wean and discontinue the preexisting medication. However, in patients with severe augmentation, an alternative approach is to first taper down the previous drug before introducing an opioid. This allows evaluation of baseline symptoms off medication but often leads to transitory extremely severe RLS symptoms during the washout period. These varying approaches need to be systematically compared.

## CONCLUSION

In summary, a number of opioid medications in low dose appear effective in refractory RLS.[5] The risks of opioid use are relatively low, taking into account the much lower doses used for RLS compared with those in patients with pain syndromes. As long as reasonable precautions are taken, the risk-benefit ratio is acceptable and opioids should not be unreasonably withheld from such patients.

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**Abbreviations and Acronyms:** **RLS** = restless legs syndrome

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