

COMMENTARY

Opioids and restless legs syndrome: a double-edged sword

Commentary on McCarter SJ, Labott JR, Mazumder MK, et al. Emergence of restless legs syndrome during opioid discontinuation. *J Clin Sleep Med*. 2023;19(4):741–748. doi:10.5664/jcsm.10436

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Opioids have been used to treat restless legs syndrome (RLS) for hundreds of years.¹ More recently, 2 randomized controlled trials have demonstrated the efficacy of this class of medications for RLS.^{2,3} The larger study enrolled refractory patients, who, even though they were resistant to other treatments, had a beneficial therapeutic response to oxycodone/naloxone at low–moderate doses. Further, large-scale, open-label observational studies demonstrate the continued efficacy of these medications (predominantly methadone) over 2–10 years for RLS, although a minority require small dose increases over time.^{4–8}

In general medical practice, opioids are primarily used for the treatment of both acute and chronic pain. They are also administered outside of medical practice by those with opioid use disorder (OUD). Discontinuation of chronic opioids is often unsuccessful for a variety of reasons, including the aversive symptoms of opioid withdrawal. Opioid withdrawal symptoms are monitored in medical detoxification settings with the use of clinical scales employing both behavioral and physiological indicators; chief among these are the COWS (Clinical Opioid Withdrawal Scale⁹) and the SOWS (Subjective Opioid Withdrawal Scale¹⁰).

“Restlessness” has long been recognized as one of the cardinal features of opioid withdrawal and is 1 of the 10 items in the COWS assessment. Only recently has it been recognized that this restlessness is in fact RLS, directly as a consequence of opioid withdrawal (“secondary RLS,” like that due to pregnancy, iron deficiency, or end-stage renal disease). Two recent studies have documented an incidence of RLS of approximately 50% in patients undergoing inpatient detoxification for OUD.^{11,12} Although RLS as an opioid withdrawal symptom is widely recognized among those with OUD, the medical community, even those working in detoxification programs, is mostly unaware of this. Unfortunately, for many of those with substantial RLS symptoms during opioid withdrawal, a return to opioids is perceived as the only recourse for their relief.

In this issue of the *Journal of Clinical Sleep Medicine* McCarter et al¹³ report a 36% incidence of RLS, with maximum appearance 2 weeks after discharge, for patients with chronic pain attending a 15-day outpatient program supporting withdrawal from long-term use (mean = 87 months) of opioids. Symptoms were moderate–severe. Those with withdrawal-related RLS had nearly double the opioid doses at admission to the program than

those without such emergent symptoms, and morphine milligram equivalents > 20 at admission was a strong predictor of such symptoms. The majority of those with withdrawal-related RLS symptoms had remission of symptoms by 3 months after discharge from the program. They did not present data on longer-term outcomes of opioid use.

RLS diagnosis in clinical practice, where symptoms can be precisely assessed, is often straightforward. However, RLS ascertainment by brief self-administered surveys is much more difficult. This is particularly true where patients have conditions with symptoms that overlap with the core features of RLS (eg, Parkinson’s disease,^{14,15} multiple sclerosis,¹⁶ adrenoleukodystrophy,¹⁷ akathisia,¹⁸ peripheral neuropathy¹⁹). For this reason, a recent International Restless Legs Syndrome Study Group task force strongly recommended that, where feasible, prevalence studies should always employ confirmatory follow-up clinical interviews²⁰ following such self-administered surveys.

It should be noted that the studies cited above examining incidence of opioid withdrawal–related RLS, including that by McCarter et al, used the Cambridge-Hopkins brief questionnaire, a self-completed survey that asks about the core diagnostic features of RLS and the presence of common mimics.²¹ However, none of the studies cited above, including our own, used follow-up clinical interviews. Given that opioid withdrawal includes multiple symptoms that mimic RLS²² (ie, generalized restlessness, anxiety, neuropathy, muscle cramps), both RLS prevalence and incidence figures in these studies must be considered tentative. In particular, the 27% RLS prevalence in patients entering the detoxification program in the McCarter et al study, while taking opioids, and with 52% of their patients taking alpha-2-delta ligands at therapeutic RLS doses, raises eyebrows.

Regardless of the precise incidence of RLS in the context of opioid withdrawal, the important issue is that it is not uncommon. RLS is not only distressing and produces substantial sleep disturbance but it may in fact interfere with opioid abstinence. Both opioid withdrawal symptoms,²³ as well as sleep disturbance, independently²⁴ contribute to relapse to opioid use. Anecdotally, patients with OUD describe a return to opioid use directly related to seeking relief from RLS. RLS also has other relevant substantial morbidity, including suicide and self-harm

events.²⁵ On the other hand, case reports suggest^{26,27} that, like most cases of both “primary” and “secondary” RLS, opioid withdrawal–related RLS is treatable with dopaminergic agonists. To examine this issue more carefully, a National Institute of Drug Abuse–funded trial of²⁸ short-term pramipexole treatment of opioid withdrawal–related RLS is underway, examining the hypothesis that not only RLS symptoms and sleep disturbance are effectively treated with this dopaminergic agonist in a detoxification setting but that opioid craving and detoxification treatment adherence are improved.

As was the case 30 years ago for primary RLS prior to the success of randomized controlled trials and educational initiatives, the first steps in advancing treatment of opioid withdrawal–related RLS are recognition of the problem and appropriate diagnosis. The McCarter et al paper in the current issue of the Journal is a valuable addition to this process. If short-term dopamine agonists prove successful in the treatment of RLS in the acute period of opioid withdrawal, their use in this context may be an important advance in reducing the morbidity of opioid withdrawal, maintaining participation in detoxification programs, and thus improving outcomes in OUD.

CITATION

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