Nature and Science of Sleep

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ORIGINAL RESEARCH

Prevalence of Current Restless Legs Syndrome Symptoms Among Patients Treated with Buprenorphine/Naloxone for Opioid Use Disorder

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Objective: The purpose of this study was to determine the prevalence of Restless Legs Syndrome (RLS) in patients with Opioid Use Disorder (OUD) taking buprenorphine/naloxone maintenance therapy, and to assess symptom frequency, severity, and sleep disruption due to RLS.

Methods: Surveys inquired about demographic information, amount of time on maintenance treatment, previous drug use, current prescribed medications and alcohol use, and RLS symptoms. Participants were determined to have definite, probable, possible, or no RLS symptoms based on pre-established criteria from the Cambridge-Hopkins Questionnaire.

Results: The sample (n=129) was 33.3% female, 81.5% white, and the mean age was 40.6 years (SD=11.9). The median duration of buprenorphine/naloxone use was 3 years. 13.2% of participants had definite/probable RLS symptoms; these symptoms tended to be of moderate severity, occur at least 5–15 times a month, and disrupt sleep to a moderate degree. Of the 17 participants with definite/probable RLS symptoms, just four were taking a medication commonly used to alleviate RLS. An additional 7.0% had possible RLS symptoms.

Conclusion: Relatively high rates of current RLS symptoms were observed; the prevalence of clinically significant RLS was notably higher than that seen in the general population or in previously assessed clinical populations. RLS is common in those acutely withdrawing from opioids, and our data demonstrate that these symptoms are present in a sizable portion of patients on OUD maintenance therapy. Most patients with definite/probable current RLS symptoms did not report taking prescribed medications that have established efficacy for RLS.

Keywords: opioid use disorder, restless legs syndrome, maintenance therapy, buprenorphine, sleep disorders

Introduction

Restless Legs Syndrome (RLS) is a movement disorder characterized by an urge to move the legs that is precipitated by rest, relieved by movement, and most pronounced in the evening or at night.[1] RLS leads to substantial difficulty with both sleep onset and maintenance.[2] Both primary and secondary RLS are associated with substantial long-term detrimental effects on health, cognition, quality of life, and mortality.[3–8] The prevalence of clinically significant RLS in the general population has been estimated at roughly 3%, with higher rates generally seen amongst the elderly and in women.[3]

Opioids have demonstrated efficacy for RLS and are approved for that indication in Europe.[9] The converse is also true, as case series demonstrate that RLS is common among those with opioid use disorder experiencing opioid withdrawal,[10–12] with one reporting symptoms that persisted beyond the initial phase of withdrawal.[13] Another study observed high rates of RLS symptoms (27.8%) among patients on long-term opioids for chronic pain entering an outpatient prescription opioid tapering program; further, 36% of the participants without RLS symptoms at baseline developed de novo symptoms at some point during their taper period.[14] These data as well as clinical

Received: 27 June 2023
Accepted: 10 October 2023
Published: 21 October 2023

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observations suggest that patients with opioid use disorder (OUD) on long-term buprenorphine/naloxone maintenance therapy are likely to have an increased probability of RLS compared to the general population, but the prevalence is unknown.

As opioid withdrawal symptoms are an important determinant of relapse,[15] addressing all such symptoms, including RLS, even in those using medication for OUD, is an important component of relapse prevention. Further, sleep disruption during protracted withdrawal from opioids may confer risk for poor outcomes.[16–18] This study thus aimed to provide prevalence and symptom severity information about RLS during buprenorphine/naloxone maintenance treatment.

Methods

This study was conducted in 2016 and 2017 at Lemuel Shattuck Hospital (LSH), a public health and teaching hospital in Boston, Massachusetts. To be included in the study, participants had to be greater than 17 years old, have a diagnosis of OUD, and be actively receiving buprenorphine/naloxone maintenance treatment through the outpatient office-based opioid treatment program at LSH. This outpatient treatment program served Boston-area patients of all gender identities who were predominantly Caucasian (roughly 85% of patients) and publicly insured (roughly 90%). Patients in the clinic were directly observed taking medication during the buprenorphine/naloxone induction period but were not regularly observed taking treatment after this point. However, patients were required to provide urine samples for drug testing at least monthly to maintain buprenorphine/naloxone prescriptions.

Patients presenting to the clinic for a regularly scheduled visit were asked to participate in the study; all patients were given the opportunity to refuse participation. With the help of nurses at the hospital, participants completed questionnaires which included the following items: demographic information including age, gender (ie patients were asked what gender they identified with, and not the sex that they were assigned at birth), height, weight, race; amount of time on buprenorphine/naloxone maintenance treatment; previous recreational drug use (ie before starting buprenorphine/naloxone); medications currently used for depression, anxiety, RLS, and/or pain; current alcohol use; and the Cambridge-Hopkins RLS Questionnaire, a widely-used and validated RLS diagnostic instrument.[19]

All participants provided verbal informed consent, and this study was approved by both the Mass General Brigham Institutional Review Board and the Massachusetts Department of Public Health.

Based on responses to the Cambridge-Hopkins Questionnaire, patients were categorized as having definite, probable, or possible RLS symptoms. A determination of definite RLS was made if a participant answered positively to the four essential RLS criteria and if common mimics were not endorsed. Patients were determined to have probable RLS symptoms if they answered positively to all questions but responded "don't know" on a question asking if symptoms were due to muscle cramps. Lastly, patients were determined to have possible RLS symptoms if they responded positively to all questions except for the one about changing leg position ("Will simply changing leg position by itself once without continuing to move usually relieve these feelings?"). A final determination of RLS symptom status in those with ambiguous answers was made by a trained sleep medicine physician, who reviewed the responses to the questionnaires (JWW).

Patients reporting symptoms characteristic of RLS were asked about symptom frequency (<1x/month, 2–4 days/month, 5–15 days/month, most days, daily), severity (mild, moderate, severe, very severe), and sleep disturbance caused by these symptoms (none, mild, moderate, severe, very severe). Participants were also asked how RLS symptoms had changed compared to when they were using unprescribed opioids.

When responses to individual survey questions were left blank or were ambiguous, the rest of the survey responses were analyzed, and the sample sizes were noted in the Results section.

Statistical analyses included Chi-square tests (for categorical variables) and Mann–Whitney *U*-tests (for continuous unpaired data).

Results

Demographics/Clinical Characteristics

Demographic and clinical information is shown in Table 1. The demographic characteristics of the study sample were similar to those of the clinic population as a whole. Participants (n = 129) were primarily male (n = 86; 66.7%), white (n

Table 1 Sample Characteristics

	All	Definite/ Probable RLS	Possible RLS	No RLS
n	129	17	9	103
Age	40.6 (11.9)[a]	39.4 (10.7)	38.4 (8.0)	41.0 (12.5)[b]
% Female	33.3%	29.4%	33.3%	34.0%
% White	81.5%[c]	82.4%	66.7%	82.7%[d]
Previous Drug Use (At Least Once per Week Before Starting Buprenorphine/Naloxone)				
Opioids by Mouth	55.0%	64.7%	55.6%	53.4%
Snorting Heroin	29.5%	17.6%	33.3%	31.1%
IV Opioids	77.5%	82.4%	88.9%	75.7%
Cocaine	31.8%	23.5%	66.7%	30.1%
Benzodiazepines	19.5%	29.4%	33.3%	16.5%
Marijuana	27.1%	47.1%	33.3%	23.3%
Current Prescription Medication and Alcohol Use				
Time on Buprenorphine/Naloxone Maintenance Therapy (Years)	3.3 (3.0)[e]	3.8 (2.8)	3.9 (3.7)[f]	3.2 (3.0)[g]
Use of Medication for Anxiety and/or Depression	45.7%	58.8%	33.3%	44.7%
Use of Medication(s) for Pain	27.9%	35.3%	55.6%	24.3%
Use of Medication Known to Treat RLS	29.5%	23.5%	66.7%	27.2%
Use of Medication Known to Worsen RLS	24.0%	35.3%	11.1%	23.3%
Alcohol (At Least 1 Drink/Week)	11.8%[h]	17.6%	11.1%	10.9%[i]

Notes: Drugs considered to treat Restless Legs Syndrome (RLS) were dopamine agonists, alpha-2-delta calcium channel ligands (gabapentin, pregabalin), sedative hypnotics, and clonidine. Drugs considered to worsen RLS were selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, mirtazapine, quetiapine, and risperidone. Continuous variables are expressed as mean (SD) and categorical variables as percentage. [a]n = 128; [b]n = 102; [c]n = 124; [d]n = 98; [e]n = 114; [f]n = 8; [g]n = 89; [h]n = 127; [i]n = 101.

= 101; 81.5%), and the mean age was 40.6 years (SD = 11.9). The median duration of buprenorphine/naloxone use was 3 years (n = 114; range: 1 week to 15 years). Approximately half of the sample (n = 59) reported currently using medications for depression and/or anxiety, and approximately 10% (n = 15) reported drinking at least one alcoholic drink per week. Over one-quarter of participants reported using medications for pain (n = 36); the most commonly reported were ibuprofen (n = 15) and gabapentin (n = 10).

Nearly 80% of participants reported a history of IV opioid use (n = 100; 77.5%), over half had previously used oral opioids (n = 71; 55.0%), one-third had used cocaine (n = 41; 31.8%), 27.1% (n = 35) had used marijuana, and 19.5% (n = 25) had used benzodiazepines.

RLS Prevalence

Over one-tenth of participants were determined to currently have either definite/probable (n = 17; 13.2%) RLS symptoms, and another 7.0% (n = 9) had possible RLS symptoms (Figure 1). When comparing individuals with definite/probable RLS symptoms to individuals with no current RLS symptoms, the two groups were similar in terms of demographic information, time on buprenorphine/naloxone maintenance therapy, and current alcohol use (Table 1).

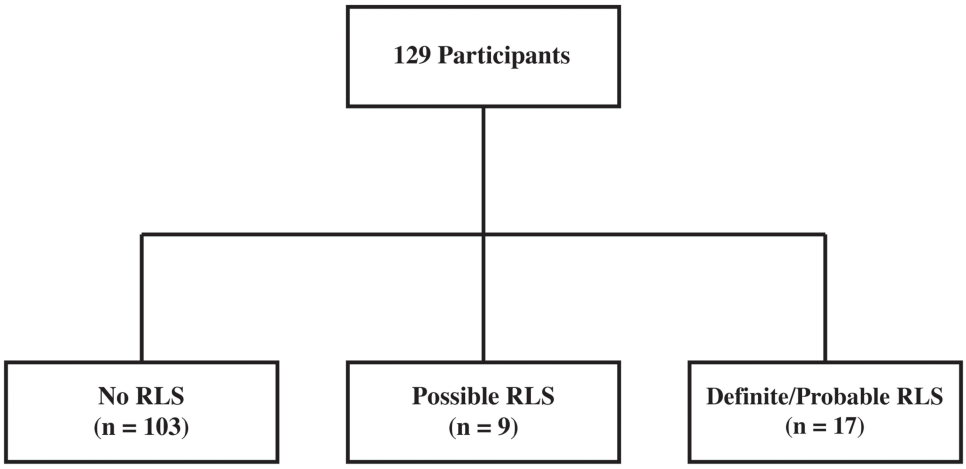

Figure 1 Determinations of current Restless Legs Syndrome (RLS) symptom status. Participants were classified as currently having definite, probable, possible, or no RLS symptoms based on responses to the Cambridge-Hopkins RLS questionnaire.

RLS Medications

Just four (23.5%) of the 17 participants with definite/probable RLS symptoms reported taking a non-opioid medication commonly used to relieve such symptoms (eg dopamine agonists, alpha-2-delta calcium channel ligands, sedative hypnotics, clonidine). Two-thirds of the individuals with possible RLS symptoms (n = 6; 67%) reported taking such medications, though all of these individuals reported using the medications for depression, anxiety, or pain rather than for RLS.

Of the 103 participants without current RLS symptoms, 27.2% (n = 28) reported taking a non-opioid medication commonly used to alleviate such symptoms. Three of these participants explicitly reported using these medications (two taking gabapentin and one taking ropinirole) specifically in order to treat RLS. The other 26 of these individuals reported taking them for either depression, anxiety, or pain.

Approximately one-quarter of all participants (n = 31; 24.0%) were taking a medication known to provoke RLS symptoms, such as a selective serotonin reuptake inhibitor or a serotonin and norepinephrine reuptake inhibitor. Six of the individuals with definite/probable RLS symptoms (35.3%) were taking such a medication.

Characterization of Those Currently Experiencing Definite/Probable RLS Symptoms (n=17)

Time on Buprenorphine/Naloxone Maintenance Therapy

Participants reporting definite/probable RLS symptoms had been on maintenance therapy for an average of 3.8 years (SD = 2.8). Nearly half (n = 8; 47.1%) had been on buprenorphine/naloxone therapy for five years or more (see Table 2).

RLS Symptom Frequency

RLS symptoms tended to occur at least five to fifteen days per month (n = 11; 64.7%).

RLS Symptom Severity

The majority of participants with definite/probable RLS reported their symptoms as moderate severity (n = 13; 76.5%). Just one reported mild symptoms (5.9%), whereas three (17.6%) experienced severe or very severe symptoms.

Sleep Disturbance Associated with RLS Symptoms

All participants reported that their symptoms disturbed sleep to at least some degree. This sleep disturbance was moderate for the majority of individuals (n = 11; 64.7%), although four individuals reported the disturbance to be either severe or very severe (23.5%).

Table 2 Characterizing Those Experiencing Definite/Probable Restless Legs Syndrome (RLS) Symptoms (n=17)

	Count (%)
Time on Buprenorphine/Naloxone Maintenance Therapy	
Under 1 year	4 (23.5%)
1 year to less than 5 years	5 (29.4%)
5 years or more	8 (47.1%)
RLS Symptom Frequency	
1 day per month or less	2 (11.8%)
2–4 days per month	4 (23.5%)
5–15 days per month	8 (47.1%)
Most days	3 (17.6%)
RLS Symptom Severity	
Mild	1 (5.9%)
Moderate	13 (76.5%)
Severe	2 (11.8%)
Very Severe	1 (5.9%)
Sleep Disturbance due to RLS Symptoms	
None	0 (0.0%)
Mild	2 (11.8%)
Moderate	11 (64.7%)
Severe	2 (11.8%)
Very Severe	2 (11.8%)

Comparison of Current RLS Symptoms to Previously Experienced Symptoms

Participants were asked how RLS symptoms had changed compared to when they were using unprescribed opioids (n = 15). Over half (n = 8; 53.3%) of participants said that their symptoms were now improved, two (13.3%) reported worse symptoms currently, and one (6.7%) reported that symptoms had not changed. Over one-fourth (n = 4; 26.7%) of participants said that they did not experience RLS symptoms when previously using unprescribed opioids.

Discussion

Approximately 13% of participants in this sample on buprenorphine/naloxone maintenance therapy for OUD were currently experiencing definite/probable RLS symptoms. These participants experienced RLS symptoms that tended to occur at least once per week, be of moderate severity, and notably disrupt sleep. An additional 7% were currently experiencing possible RLS symptoms. Of note, the rate of clinically significant RLS symptoms (as defined in the Allen et al. REST study: occurring at least twice per week and of at least moderate severity) observed in this sample is higher than the rate of roughly 2% observed among individuals under 50 in the general population.[3] Although RLS prevalence in clinic populations is slightly higher than that of the general population, the frequency of clinically significant RLS symptoms observed in this sample surpasses some of the most credible prevalence estimates for outpatient clinic

visitors.[20,21] Further, we observed these high rates of RLS in a sample consisting largely of men, who have a lower prevalence of RLS than women.[3]

Although the number of patients reporting the defining symptoms characteristic of RLS was not as high as what has been observed in those acutely withdrawing from opioids (approximately 50%),[12] these results suggest that there is still a relatively high prevalence of RLS symptoms among patients who are past withdrawal and on maintenance therapy for OUD, aligning with previous anecdotal reports.[13] Notably, these results suggest that RLS symptoms may persist for many years following acute opioid withdrawal and the onset of maintenance therapy; nearly half of the participants with definite/probable RLS symptoms had been taking buprenorphine/naloxone for five years or more. These findings are alarming given that RLS has been associated with increased risk for adverse health consequences, including depression and anxiety, cardiovascular disease, and overall mortality.[5,6,22]

These findings are of clear importance with the United States currently in the midst of the most devastating drug crisis in its history; recent statistics estimate that roughly three million Americans meet the criteria for OUD,[23] and that over 100,000 in the United States died from drug overdoses in 2021 alone.[24] Although the opioid epidemic has affected virtually all parts of US society, certain socioeconomic groups have seen disproportionate numbers of overdose deaths, including younger Americans and non-Hispanic white men.[25] Our primarily young, non-Hispanic white, and male sample is roughly representative of opioid users in the United States.

This study is descriptive and therefore cannot elucidate a mechanism for this relatively high rate of RLS among patients with OUD on buprenorphine/naloxone maintenance therapy. Alterations in the endogenous opioid system and related circuits are known to occur in patients with OUD, which may predispose these individuals to experiencing RLS symptoms.[26] Though speculative, we find it possible that the partial opioid agonism of buprenorphine may be sufficient to suppress certain OUD symptoms such as cravings, but not potent enough to suppress RLS in some patients. It is also conceivable that the opioid antagonist effects of naloxone may exacerbate RLS symptoms to some degree, though an oxycodone-naloxone combination has previously been found to effectively treat RLS.[9] This logic begs the question of whether patients using methadone, a full opioid agonist with demonstrated efficacy for RLS,[27,28] might see lower rates of RLS symptoms. Further, although patients at this clinic were required to submit urine samples for drug testing at least monthly in order to maintain buprenorphine/naloxone prescriptions, they were not directly observed each time that they took their treatment. Thus, it is possible that some patients were not taking the buprenorphine/naloxone as prescribed (eg sharing and/or selling the medication), which could have lead to opioid withdrawal and potential exacerbation of RLS symptoms. Lastly, it is possible that the iron status of patients with OUD may predispose these individuals to RLS symptoms. Although iron levels were not assessed in this study, OUD has been associated with decreased food consumption and malnutrition, which may result in iron deficiency,[29] a well-known risk factor for the development of RLS.[30]

In most cases, RLS symptoms can be effectively treated with first-line treatments such as dopamine agonists and alpha-2-delta calcium channel ligands. Just four of the 17 patients with definite/probable RLS symptoms reported taking such a medication or another commonly used to relieve RLS. Thus, RLS seems to be undertreated in this sample. However, participants were only specifically asked to list medications used for depression, anxiety, RLS, and/or pain, and it is possible that participants were taking RLS-relieving medications for a different indication.

Over one-quarter of participants without current RLS symptoms reported taking a medication known to alleviate RLS. Three of these individuals were taking such medications for RLS itself (and were not included in those with current RLS), whereas the rest reported taking the medications for depression, anxiety, or pain relief. It is likely that the rate of RLS symptoms in this sample would have been even higher without this relatively high usage of dopamine agonists, alpha-2-delta calcium channel ligands, sedative hypnotics, and clonidine. Clinicians should be mindful of the ability of such medications to treat RLS symptoms, and that discontinuation may lead to exacerbation of RLS and potentially be a risk factor for relapse. Similarly, physicians should be aware that numerous drugs, including selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors, may provoke RLS symptoms and should be cautious when prescribing such medications in this population; nearly one-fourth of the present sample reported using such agents.

Individuals currently experiencing RLS symptoms reported relatively high levels of marijuana, benzodiazepine, and pain medication usage compared to those not reporting current RLS symptoms. Due to the cross-sectional nature of this

study, it is impossible to determine whether onset of RLS symptoms preceded use of these substances, or vice versa. However, we find it plausible that in the absence of an effective treatment for RLS, some participants were using these agents in an effort to alleviate RLS symptoms and thus improve sleep.

This study had several key limitations. First, this sample was relatively small and larger studies on this topic should be conducted. Additionally, determinations of RLS symptom status were made based on survey responses; although the survey used to classify RLS status was a validated and well-known instrument (the Cambridge-Hopkins RLS Questionnaire), which is a more elaborated version of the 4-question screening questionnaire widely used in RLS prevalence studies,[31–35] a clinical interview to confirm diagnosis would have been optimal and should be utilized in future studies in this population.[36] Additionally, it is unclear how many patients at the clinic refused participation in the study and there is thus some potential for selection bias. Further, characterization of both RLS and OUD symptoms was relatively restricted: the International Restless Legs Scale, the tool most widely used to assess RLS symptom severity, was not employed,[37] sleep disturbance due to RLS symptoms was only detailed using a simple global question, and OUD severity was not assessed. Information on buprenorphine/naloxone dosing was not collected, limiting our ability to associate this with RLS symptoms. Lastly, this sample consisted largely of white participants, and generalizability to other races may be limited, though the demographic makeup of this study was similar to other studies looking at buprenorphine/naloxone use in the outpatient setting.[38,39]

Despite these limitations, this study did have strengths that warrant attention. First and foremost, to the best of our knowledge, this is the first study assessing the prevalence of RLS in patients using any form of medication-assisted maintenance therapy for OUD. These novel findings align with those of the previously noted studies revealing elevated rates of RLS in other populations of patients which have been exposed to opioids, such as those receiving medical detoxification for OUD as well as in individuals undergoing supervised outpatient prescription opioid tapering.[12,14] Further, the survey used to classify RLS status was a validated and well-known instrument (the Cambridge-Hopkins RLS Questionnaire), completion was assisted by RNs, and a trained sleep medicine physician made the final RLS classifications.

This work paves the way for future research assessing the relationship between RLS and OUD. Building upon limitations of this work, RLS prevalence in patients on OUD maintenance therapy must be assessed using clinical interviews, and with larger and more diverse samples. Additionally, it would be prudent to examine whether RLS rates differ in patients on OUD maintenance therapy with methadone and/or naltrexone, given the different mechanisms of these agents. Lastly, and perhaps most importantly, research should assess the treatment of RLS symptoms in patients with OUD and its potential role in preventing relapse. RLS and its resulting sleep disturbance can be extremely distressing, and individuals with untreated symptoms report using non-prescribed opioids to control their symptoms.[9] Similarly, in one study, sleep disturbance, the most common consequence of RLS, was associated with attrition from opioid detoxification.[18] A National Institute of Drug Abuse-funded trial of RLS treatment with pramipexole in patients with OUD undergoing opioid detoxification is currently underway, which will assess whether this medication can effectively control RLS symptoms and improve sleep in this setting, and further, whether this can improve engagement and retention in treatment.[40] Similar studies should be conducted in individuals receiving OUD maintenance therapy.

Conclusion

In this cross-sectional study, we observed relatively high rates of current RLS symptoms in patients being treated with buprenorphine/naloxone maintenance therapy for opioid use disorder. Although these RLS symptoms tended to be of at least moderate severity and led to disruptions in sleep, the majority of patients with such symptoms were not receiving a medication that would alleviate them. RLS symptoms can greatly interfere with sleep and quality of life, and those with untreated or partially treated symptoms may be motivated to use unprescribed opioids to control them. Furthermore, individuals suffering from RLS are at an increased risk of numerous psychiatric and cardiovascular illnesses. With this in mind, we suggest that physicians, nurses, and other healthcare practitioners caring for patients with OUD are trained on RLS screening and made aware that there are non-opioid medications that can effectively treat this condition.

Acknowledgments

The abstract of this paper was presented at SLEEP 2021 (the annual meeting of the Associated Professional Sleep Societies, LLC) as an abstract presentation with interim findings. The poster's abstract was subsequently published in *Sleep* (https://doi.org/10.1093/sleep/zsab072.528). The authors would like to thank Jane Dunning, RN and Ron Jacobs, RN for their help with this project.

Funding

PI Sundry Fund.

Disclosure

JWW receives royalties from UpToDate; consultation fees from American Regent, Azurity, Avadel, Emalex, Idorsia, Noctrix, and Disc Medicine; and research support from Merck, NIDA, the RLS Foundation, and the Baszucki Brain Research Fund. The other authors report no conflicts of interest in this work.

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