Long-term Safety, Dose Stability, and Efficacy of Opioids for Patients With Restless Legs Syndrome in the National RLS Opioid Registry

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Abstract

Background and Objectives

Restless legs syndrome (RLS) is a sensory-motor neurologic disorder. Low-dose opioids are prescribed for patients with refractory or augmented RLS. The long-term safety, dose stability, and efficacy of these medications for RLS treatment is still unclear. In this study, we report the 2-year longitudinal data in a sample of patients treated with opioids for RLS in the community.

Methods

The National RLS Opioid Registry is an observational longitudinal study consisting of individuals taking a prescribed opioid for diagnosed and confirmed RLS, most of whom experienced augmented symptoms from dopamine agonists. Information on opioid dosages, side effects, past and current concomitant RLS treatments, RLS severity, psychiatric symptoms, and opioid abuse risk factors was collected at initial Registry entry and every 6 months thereafter by surveys on REDCap. No feedback or intervention was provided by the study staff to local providers.

Results

Registry participants (n = 448) with 2-year longitudinal data available were mostly White, female, older than 60 years, and, at Registry entry, had been on opioids for a median of 1–3 years at a mean morphine milligram equivalent (MME) of 38.4 (SD = 43.5). No change in RLS severity in the overall cohort was observed over the 2-year follow-up period. The median change in daily opioid dose from baseline to 2 years was 0 MME (interquartile range = 0–10). While 41.1% of participants increased their dose during the follow-up period (median increase = 10 MME), 58.9% decreased their dose or saw no change. Only 8% and 4% saw increases of >25 MME and >50 MME, respectively. Ninety-five percent of those who increased opioid dose >25 or >50 MME had one of the following features: switching opioids, discontinuation of nonopioid RLS treatment medications, at least mild insomnia at baseline, a history of depression, male sex, younger than 45 years, and opioid use for comorbid pain.

Discussion

Low-dose opioid medications continue to adequately control symptoms of refractory RLS over 2 years of follow-up in most of the participants. A minority of patients did see larger dose increases, which were invariably associated with a limited number of factors, most notably changes in opioid and nonopioid RLS medications and opioid use for a non-RLS condition. Continued longitudinal observations will provide insight into the long-term safety and efficacy of opioid treatment of severe, augmented RLS.

Classification of Evidence

This study provides Class IV evidence that opioid doses increase in roughly 40% of patients, in most by small amounts, over a 2-year period when prescribed for adult refractory restless leg syndrome.

Glossary

GAD-7 = generalized anxiety disorder-7 scale; **IRLS** = International Restless Legs Syndrome Study Group Severity Scale; **ISI** = insomnia severity index; **MDD** = major depressive disorder; **MME** = morphine milligram equivalent; **PHQ-9** = Patient Health Questionnaire; **RLS** = restless legs syndrome; **RLSF** = Restless Legs Syndrome Foundation.

Restless legs syndrome (RLS) is a sensory-motor neurologic disorder characterized by an irresistible urge to move the legs often concurrent with leg discomfort. Symptoms are worst at night and are commonly described by patients as unbearable.[1] RLS symptoms and their deleterious impact on sleep are associated with high levels of morbidity in affected patients.[2]

Dopamine agonist medications are commonly used as first-line treatment for RLS and are initially very effective in most patients.[3] Unfortunately, only a small subset of patients continues to benefit from these medications beyond 10 years, and many develop a worsening of symptoms known as augmentation.[4] First-line options for those with dopaminergic augmentation include iron supplementation (for those with low or low-normal iron indices) or α2δ agents such as gabapentin, pregabalin, and gabapentin enacarbil; however, these are not always efficacious or well tolerated.[5] Low-dose opioid medications are also effective in patients who have become refractory to first-line RLS treatments, particularly with augmentation to dopamine agonists.[6] Small studies have shown that these medications can control RLS symptoms over 2–10 years with minimal dose escalation.[7-9]

Rapidly escalating national rates of opioid misuse, abuse and use disorder, and fatal overdose make for an uncertain risk: benefit of this class of medications, even at very low doses, for augmented or refractory RLS. Furthermore, an increasingly strict regulation of their use makes clinicians even more hesitant to prescribe this class of medication.[10] Dose escalation of opioids is believed to increase the risk of substance use disorders and adverse outcomes.[11] Guidelines suggest various clinical factors to stratify the individual risk of dose escalation and risk of misuse/abuse before initiating opioid therapy in patients with chronic noncancer pain,[12] but it is unclear whether such guidelines and clinical tools are relevant for the use of opioids in RLS. Larger-scale multicenter data on the long-term efficacy, complications, and rates of abuse, diversion, and overdose in patients using opioids for RLS are badly needed to establish their safety and efficacy in this population.

The RLS National Opioid Registry was developed to collect longitudinal observational data on RLS treatment efficacy, dosage changes, medication tolerability, RLS severity, and sleep, mood, and anxiety symptoms in a national sample of patients using prescribed opioids for RLS. In this study, we presented data on the first 2 years of participant follow-up. The primary aim of this analysis was to examine the characteristics of long-term opioid medication treatment for RLS, including (1) efficacy for RLS, (2) changes in opioid dose, and (3) risk factors of opioid dose increases.

Methods

Participants

Patients were recruited through Restless Legs Syndrome Foundation (RLSF) advertising or by brochures provided to patients by treating physicians, many of whom practiced in groups certified by the RLSF as RLS Quality Care Centers. Recruitment occurred between December 2017 and September 2019. To meet eligibility criteria, participants had to be taking a prescribed opioid daily for diagnosed RLS and had a previous therapeutic response to a dopamine agonist medication. The requirement for a response to a dopaminergic agent was to better ensure the presence of RLS. Patients were assured that the information they provided for the Registry would not be shared with other healthcare professionals, including their RLS prescribing physician. Similarly, besides survey collection, no clinical oversight, support, or recommendations were provided to any participant or prescriber.

Evaluation

At enrollment, participants' RLS diagnosis was confirmed by a trained research coordinator using the Hopkins telephone diagnostic interview, an instrument validated to exclude common RLS mimics.[13] Baseline information on initial and current opioid dosages, side effects, past and current RLS treatments, augmentation history,[14] current RLS severity through the International Restless Legs Syndrome Study Group Severity Scale (IRLS),[15] psychiatric history and current symptoms through the Patient Health Questionnaire (PHQ-9),[16] and Generalized Anxiety Disorder-7 scale (GAD-7),[17] sleep disturbance through the Insomnia Severity Index (ISI),[18] and opioid abuse risk factors through the Opioid Risk Tool[19] was collected through a phone interview and online (REDCap) survey. Online follow-up surveys were performed every 6 months thereafter. Comprehensive details on recruitment, inclusion and exclusion criteria, and questionnaire items can be found in our previous publication on 1-year longitudinal data from this cohort.[20]

All opioid dosages were converted to morphine milligram equivalents (MME) using established conversion ratios.[21] Conversion ratios for common opioids were as follows: methadone: 4 (for doses ≤20 mg), 8 (21–40 mg), 10 (41–60 mg), and 12 (>60 mg); oxycodone: 1.5; and hydrocodone: 1.

Each questionnaire was assessed on a continuous scale unless noted otherwise. Statistical tests used for this analysis were

χ^2, Mann-Whitney, Wilcoxon signed-rank, and Spearman correlations. Logistic regression analyses were performed using a forward selection method with a threshold of $p < 0.1$. In the regression models, multicollinearity of all covariates was found to be at an acceptable level (variance inflation factors were all <1.2). All significance values reported were 2-sided, and analyses were performed using the Prism GraphPad 9 software and Microsoft Excel.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Institutional Review Board of Mass General Brigham, the parent organization of Massachusetts General Hospital. All patients provided verbal informed consent before participating in the registry.

Data Availability

Anonymized data reported in this study will be shared on requests from qualified investigators.

Results

Overview

Five hundred participants were originally enrolled in the registry. Of these original 500 participants, 24 discontinued opioid treatment, 14 were lost to follow-up, 5 were deceased, 4 missed the 2-year survey but remained in the registry, and 3 withdrew before their 2-year follow-up. An additional 2 participants completed the 2-year survey, but their opioid dosing information was uninterpretable and therefore excluded, leaving 448 with opioid dosing data. This constitutes a 94.9% retention rate among those who did not discontinue opioid medications or become deceased.

Table 1 summarizes the baseline characteristics of the 448 analyzed 2-year follow-up sample. Participants were mostly female (57%), predominantly 60 years or older (72%), and almost all White (98%). Participants had been taking opioids for a median of 1–3 years on entry into the registry, and almost all (n = 399; 89%) had a history of dopamine agonist augmentation, assessed by a clinical interview using augmentation diagnostic criteria.[14]

There were no significant differences in age, sex, or baseline IRLS, ISI, GAD-7, or PHQ-9 scores between those who continued participation at 2 years and those for whom 2-year data were unavailable. However, the median baseline daily MME for whom the 2-year follow-up was unavailable was significantly lower than that for participants remaining in the registry (20.0 vs 30.0; $p = 0.03$).

Opioid side effects reported at year 2 were very similar to those at baseline. The only difference >5% was appetite change (reported by 6% of participants at year 2 vs 12% at baseline). The most common side effects reported at 2 years were constipation (47%), drowsiness/fatigue (23%), itching (19%), sweating (17%), and stimulation/wakefulness (9%). Only 6% of participants (n = 25) endorsed "feelings of euphoria, warmth, intense relaxation, or giddiness" from their opioid medication(s). No

Table 1 Baseline Demographics of the 2-Year Study Sample

No. of participants	448
Age (y)	65.0 ± 10.7
Sex	
Female	257 (57.4%)
Race	
White	440 (98.2)
Native American/Alaska Native	4 (0.8%)
Asian	3 (0.6%)
Other	4 (0.8%)
Body mass index (kg/m²)	27.8 ± 6.4[a]
Highest education level	
Graduate school	203 (45.3%)
College graduate	136 (30.4%)
Partial college	84 (18.8%)
High school or lower	25 (5.6%)
Duration of current opioid	
Less than 6 mo	75 (16.7%)
6 mo–1 y	50 (11.2%)
1–3 y	116 (25.9%)
3–5 y	69 (15.4%)
5–10 y	63 (14.1%)
10+ y	75 (16.7%)
Family history of RLS	271 (60.6%)[b]
History of augmentation	399 (89.9%)[c]
Questionnaires	
ISI	10.6 ± 6.6
IRLS	13.0 ± 9.7
GAD-7	3.6 ± 4.0[b]
PHQ-9	5.7 ± 5.3[b]

Abbreviations: GAD-7 = Generalized Anxiety Disorder-7 Scale; IRLS = International Restless Legs Syndrome Study Group Severity Scale; ISI = Insomnia Severity Index; PHQ-9 = Patient Health Questionnaire; RLS = restless legs syndrome.
Values are shown as either mean ± SD or count (percentage of sample).
[a] n = 445.
[b] n = 447.
[c] n = 444.

serious side effects were reported by participants who continued in the registry or those who discontinued opioids and were no longer included in this summary.

Self-reported reasons for opioid discontinuation included side effects (n = 6), prescriber's unwillingness to prescribe opioids for RLS (n = 5), symptoms being controlled without opioids
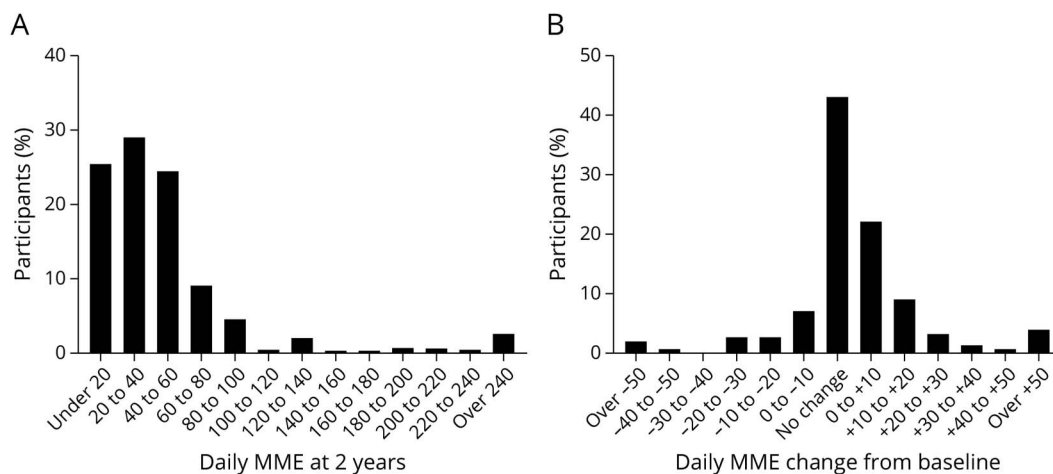
MME = morphine milligram equivalent

(n = 2), "augmentation" (n = 2), tolerance (n = 1), medication ineffectiveness (n = 1), or a combination of reasons (n = 2). An additional 5 participants discontinued their opioid medication for unknown reasons.

RLS Medication Changes

More than four-fifths of participants (81.3%, n = 364) who remained on prescribed opioids and completed 2-year surveys were on the same opioid type(s) as at baseline. An additional 1.8% (n = 8) added a new opioid, 2.7% (n = 12) removed an opioid, and 14.3% (n = 64) switched to a new opioid medication. Nearly half of participants who switched to a new opioid (n = 28; 43.8%) switched to methadone. More than one-tenth of participants (13.6%) added a dopamine agonist and/or an $\alpha_2\delta$ ligand during the 2-year follow-up period, whereas 10.0% removed such a medication.

At baseline, 23.9% (n = 107) of participants had treated their RLS with iron (either IV or oral supplement). At 2 years, 27.5% (n = 123) of participants reported currently taking iron supplements by mouth or having received an iron infusion in the past 6 months. Moreover, at 2 years, of the 47.5% (n = 211) of participants who had their blood iron levels checked in the past 6 months, 13.3% (n = 28) reported high iron levels, 16.1% (n = 34) reported low iron levels, and 70.6% (n = 149) reported normal iron levels.

Opioid Dose Changes

At the 2-year follow-up, the median daily MME was 30.0 (methadone = 7.5 mg, oxycodone = 20 mg) (Figure 1A), which was the same as at baseline. The median change in MME from baseline was 0 (Figure 1B). The mean daily MME at 2 years (excluding 4 outliers) was 43.5 (SD = 51.8), compared with a mean MME of 38.4 (SD = 43.5) at baseline. More than two-fifths (42.0%; n = 188) of patients were on the exact opioid regimen (i.e., opioid type and dosage) as at registry entry.

Roughly two-fifths of participants (41.1%, n = 184) increased their opioid dose from baseline to 2 years. Of those who increased opioid dose, more than half (54.9%, n = 101) increased by 10 MME or less (see Table 2 for detailed breakdown).

A portion of participants saw dose increases that resulted in them crossing risk thresholds established by the Centers for Disease Control and Prevention[22]: a total of 36 participants (8.0%) increased their daily MME dose from below 50 MME to ≥ 50 MME, and 15 participants (3.3%) increased their daily MME dose from below 90 MME to ≥ 90 MME.

Opioid dose increases of any size from baseline to 2 years were independently associated with the following factors: switching specific opioid medication (OR 3.54, 1.93–6.74), being on prescribed opioid(s) for <1 year at baseline (OR 1.91, 1.22–2.99), stopping a dopamine agonist or $\alpha2\delta$ ligand (OR 2.57, 1.28–5.32), and having a baseline ISI score of more than 10 (OR 1.66, 1.11–2.50) (Table 3).

Just 8.0% (n = 36) of all participants increased their opioid dose by > 25 MME (translating to a methadone dose change of 6.25 mg if dose was ≤20 mg or 2–3 mg if dose was >20 mg, or an oxycodone dose of 16.67 mg) over the 2-year follow-up period. Such larger dose increases (>25 MME) were independently associated with the following factors: switching specific opioid medication from baseline to 2 years (OR 4.58, 2.01–10.24), stopping a dopamine agonist or $\alpha2\delta$ ligand (OR 4.27, 1.61–10.85), having a baseline ISI score of more than 10 (OR 3.16, 1.38–8.03), reporting a history of major depressive disorder (MDD) at baseline (OR 2.84, 1.30–6.51), and the use of opioid(s) for non-RLS comorbid pain (OR 2.73, 0.95–7.18) (Table 3). Nearly all participants (35/36 = 97.2%) who increased by > 25 MME satisfied at least one of these 5 conditions. By contrast, among participants who did not satisfy any of these conditions (n = 111), less than 1% saw

Table 2 Registry Participants' Current Opioid Doses and Percentages With Changed Opioid Dose From Baseline to 2-Year Follow-up

| Opioid | Count | Daily dose (mg) | | % Who changed opioid dose (MME) | | | | | | |
| | | BL median | 2-year median | Decreased | Same | Increased | | | | |
						All	≤10	10.1–25	25.1–50	>50
Total	448			15.8	43.1	41.1	22.3	10.7	4.0	4.0
Methadone	190	10	10	11.1	56.8	32.1	18.9	7.4	2.6	3.2
Oxycodone	52	10	10	15.4	42.3	42.3	25.0	15.4	0	1.9
Hydrocodone	48	10	10.6	25.0	45.8	29.2	25.0	2.1	2.1	0.0
Tramadol	25	100	150	12	40	48	40.0	8	0.0	0.0
Oxycontin	21	20	20	0	90.5	9.5	0.0	4.8	4.8	0.0
Buprenorphine	18	2	2	22.2	50.0	27.8	5.6	11.1	5.6	5.6
Morphine	12	52.5	37.5	25	66.7	8.3	0.0	8.3	0.0	0.0
Codeine	7	48	50	0.0	14.3	85.7	71.4	14.3	0.0	0.0
Hydromorphone	5	10	4	40.0	40.0	20.0	0.0	20.0	0.0	0.0
Fentanyl	2	37.5	50	0.0	50.0	50.0	0.0	0.0	0.0	50.0
Pentazocine	2	225	225	0.0	100.0	0.0	0.0	0.0	0.0	0.0
Oxymorphone	1	10	10	0.0	100.0	0.0	0.0	0.0	0.0	0.0

Abbreviation: BL = baseline; MME = morphine milligram equivalent.

dose increases >25 MME during the follow-up period (0.9%; n = 1). Male sex had a trend association (OR 2.15, 0.99–4.71). Notably, baseline RLS severity (as assessed by IRLS) and Opioid Risk Tool scores were not associated with >25 MME dose increases from baseline to 2 years.

Opioid dose increases of >50 MME (n = 18) during the 2-year follow-up period were independently associated with male sex (OR 4.86, 1.48–18.69), use of opioid(s) for non-RLS comorbid pain (OR 7.02, 2.01–23.79), stopping a dopamine agonist or α2δ ligand (OR 6.67, 1.73–24.96), switching specific opioid medication from baseline to 2 years (OR 4.45, 1.38–13.95), a reported history of MDD at baseline (OR 4.14, 1.31–15.15), and an age of 45 years or younger at baseline (OR 7.07, 1.16–36.32) (Table 3). Nearly all participants who increased dose by > 50 MME satisfied at least one of these 6 criteria (17/18 = 94.4%). On the contrary, of the 89 who did not satisfy any of these conditions, only 1 increased dose by > 50 MME (1.1%). Again, baseline RLS severity and Opioid Risk Tool scores were not associated with such opioid dose increases.

Individuals who started their opioid medication less than 1 year before entering into the registry saw markedly lower rates of increase from 1-year follow-up to 2-year follow-up (26.3%, n = 20) than during the first year (48.7%; n = 37; p = 0.004). These participants also saw lower rates of large increases in the second year of follow-up: being on a prescribed opioid medication for RLS for <1 year at registry entry was associated with

>25 MME increases during the first year of follow-up (OR 4.28, 1.74–11.00) but not during the second year of follow-up.

Less than one-tenth of participants increased opioid dose during each of the first 2 years of follow-up (n = 42). These participants had lower baseline daily MME values than other participants (17.3 vs 30.0; p = 0.007). These individuals also had higher baseline IRLS scores, although this difference was not significant (16.5 vs 12.0; p = 0.27). On the 2-year surveys, the participants who increased doses both years had higher daily MME than others (40.0 vs 30.0; p = 0.009), and higher IRLS scores (15.0 vs 12.0; p = 0.08).

RLS Symptoms
Of the 448 participants who remained on prescribed opioids and completed 2-year surveys, IRLS, ISI, and PHQ-9 scores did not change from baseline to 2 years. RLS symptom severity remained in the low-to-moderate range (2-year IRLS mean = 13.6) (Figure 2A), consistent with severity at baseline (IRLS mean = 13.0) and at 1 year (IRLS mean = 13.9). Sleep disturbance remained consistently common in this population from baseline (ISI mean = 10.6), to 1 year (ISI mean = 10.4) and to 2 years (ISI mean = 10.2). There was a slight increase in GAD-7 scores (3.6 vs 4.1; p = 0.003).

Large and roughly equivalent fractions of the cohort had increases (45.9%) or decreases (42.8%) in the IRLS score during follow-up (Figure 2B). The only significant association with change in IRLS from baseline to the 2-year follow up was
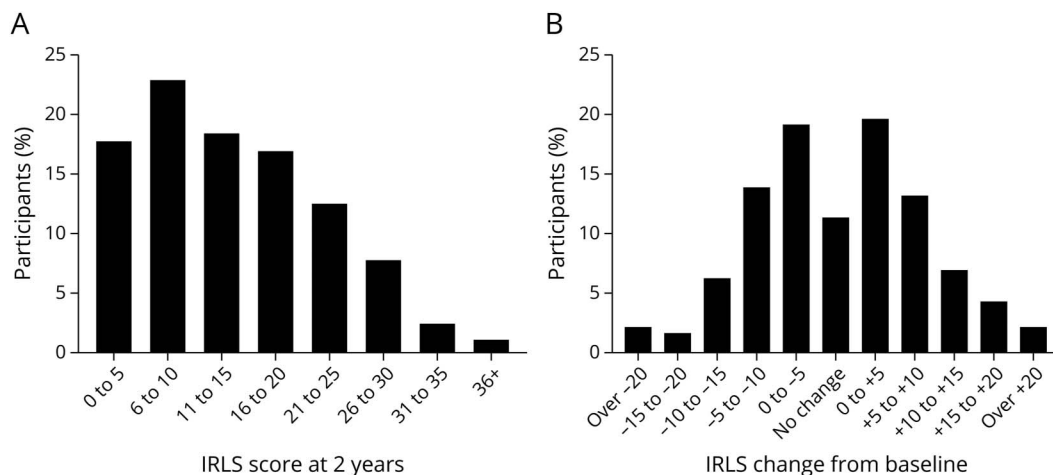
Table 3 Independent Associations at 2-Year Follow-up

Factor	OR	95% CI	*p* Value
Any MME increase >0 (n = 448)			
Switched opioids from baseline to 2 y	3.542	1.93–6.74	<0.0001
On opioid for under 1 y at baseline	1.907	1.22–2.99	0.0047
Stopped dopamine agonist or an α2δ ligand from baseline to 2 y	2.568	1.28–5.32	0.0089
Sleeping difficulties at baseline (ISI >10)	1.664	1.11–2.50	0.0136
MME increase >25 (n = 440)			
Switched opioids from baseline to 2 y	4.577	2.01–10.24	0.0002
Stopped dopamine agonist or an α2δ ligand from baseline to 2 y	4.269	1.61–10.85	0.0026
Sleeping difficulties at baseline (ISI >10)	3.155	1.38–8.03	0.0097
Reported major depressive disorder at baseline	2.843	1.30–6.51	0.0103
Using opioid for comorbid pain condition	2.732	0.95–7.18	0.0489
MME increase >50 (n = 440)			
Using opioid for comorbid pain condition	7.022	2.01–23.79	0.0017
Stopped dopamine agonist or an α2δ ligand from baseline to 2 y	6.673	1.73–24.96	0.0044
Switched opioids from baseline to 2 y	4.447	1.38–13.95	0.0101
Male sex	4.858	1.48–18.69	0.0129
Reported major depressive disorder at baseline	4.144	1.31–15.15	0.0205
Age ≤45 at baseline	7.066	1.16–36.32	0.0221

Abbreviations: ISI = Insomnia Severity Index; MME = morphine milligram equivalent.

the baseline IRLS score ($r = -0.51$, $p < 0.001$). Almost a quarter of participants (23.8%) continue to experience severe RLS (indicated by IRLS score >20). Severe RLS at year 2 was independently associated with the following factors: having a baseline ISI score of more than 10 (OR 3.75, 2.29–6.31), reporting painful RLS at baseline (OR 2.03, 1.26–3.26), use of opioid(s) for non-RLS comorbid pain (OR 3.01, 1.13–8.07), and an age of 45 years or younger at baseline (OR 1.63, 1.01–2.62) (Table 4). Individuals taking non-opioid RLS medications in addition to prescribed opioid(s) (dopamine

Figure 2 (A) Total IRLS Distribution at 2 Years and (B) Changes in IRLS From Baseline to 2 Years

IRLS = International Restless Legs Syndrome Study Group Severity Scale

Table 4 Independent Associations With High IRLS Score (>20) at 2-Year Follow-up (n = 448)

Factor	OR	95% CI	*p* Value
Sleeping difficulties at baseline (ISI >10)	3.750	2.29–6.31	<0.0001
Painful RLS at baseline	2.027	1.26–3.26	0.0035
Using opioid for comorbid pain condition	3.007	1.13–8.07	0.0267
RLS onset at young age	1.630	1.01–2.62	0.0431

Abbreviations: IRLS = International Restless Legs Syndrome Study Group Severity Scale; ISI = Insomnia Severity Index; RLS = restless legs syndrome.

agonist and/or α2δ ligand, 48.4% of participants) had higher 2-year IRLS scores than those on opioid monotherapy (15.9 vs 11.5; *p* < 0.001).

Comparison of Most Commonly Used Opioids

The most commonly used opioid in this sample was methadone (used by 50.9% of participants at 2 years; n = 228), followed by oxycodone (15.0%; n = 67), hydrocodone (11.6%; n = 52), oxycontin (7.1%; n = 32), and tramadol (6.7%; n = 30). IRLS scores at 2 years were significantly lower for participants using methadone (median = 10.0) than for participants taking oxycodone (19.0; *p* < 0.0001) or hydrocodone (18.0; *p* < 0.0001). 2-year ISI scores were also lower for participants taking methadone (median = 9.0) compared with participants using oxycodone (median = 13.0, *p* < 0.0001) or hydrocodone (12.0, *p* = 0.02). PHQ-9 and GAD-7 scores were significantly lower for participants using methadone when compared with participants taking oxycodone, but not compared with participants prescribed hydrocodone.

Among those who switched from another opioid to methadone (n = 28) during the follow-up period, 2-year IRLS scores were significantly lower than at baseline (11.1 vs 18.8; *p* < 0.001). However, most participants of this group (85.7%, n = 24) did see increases in daily MME from baseline to 2-years (median increase = 20 MME). Registry participants who switched to opioids other than methadone had slightly worse RLS severity than at baseline (16.3 vs 15.4; *p* = NS).

Table 2 summarizes a comparison of daily opioid doses and percentages who changed dose among participants who remained on specific opioids during the 2-year follow-up period. The percentage of participants who increased dose did not significantly differ between participants on methadone, oxycodone, and hydrocodone, and the regression analysis did not reveal any of these 3 medications to be significantly associated with dose increases at 2 years.

Reported side effects differed slightly between participants prescribed the 3 most common opioids. The most commonly reported side effects among participants taking methadone were constipation (59%), drowsiness (25%), sweating (19%), and itching (17%). Commonly reported side effects on

oxycodone were constipation (40%), itching (28%), drowsiness (27%), and sweating (19%). Last, the most common side effects among participants using hydrocodone were constipation (31%), itching and drowsiness (both 21%), and sweating (10%).

Classification of Evidence

This study provides Class IV evidence that opioid doses increase in roughly 40% of patients, in the majority by small amounts, over a 2-year period when prescribed for adult refractory restless leg syndrome.

Discussion

Opioids are prescribed for patients with RLS when they are refractory to, or intolerant of, first-line treatments (α2δ agents, dopamine agonists) or have severe augmentation to dopamine agonists. Controlled trials[6] demonstrate that efficacious opioid doses for such patients are low compared (mean MME = 33) with the doses of those with chronic opioid use for noncancer pain in which MME are roughly 60 MME.[23,24] The aim of this analysis was to assess the longitudinal efficacy and stability of opioid dosing for patients with refractory RLS.

Methadone was the most commonly prescribed opioid in our participants. Although the only large clinical trial with opioids was with oxycodone ER,[6] methadone has become the standard treatment in refractory, augmented patients due to its long half-life (which corresponds to the prolonged daily duration of most augmented patients' symptoms) and relatively lower risk of misuse due to once daily dosing and lack of euphoric effects.[25] For this reason, the few small long-term studies with opioids for refractory RLS have also all primarily used methadone.[7-9]

The median opioid dose change was 0 MME, and RLS symptom severity was unchanged from baseline to 2 years in this large cohort of the National RLS Opioid Registry. These findings suggest that prescribed opioid medications can control RLS symptoms over time with minimal dose escalation, consistent with previous small, long-term studies of opioid therapy in RLS that demonstrated relatively stable dosing over 2–10 years of follow-up.[7,8]

RLS severity in the overall cohort was unchanged from baseline, with overall low-to-moderate symptoms. Roughly equivalent fractions of the Registry participants had increases as decreases in IRLS over the 2-year follow-up period. There were no consistent associations with change in RLS severity over the follow-up period (other than baseline severity), and thus, these changes on an individual level may be explained by a multitude of factors such as medication switches, dose alterations, augmentation, and natural progression of disease.

Although most of the participants either decreased or did not change their opioid dose during the follow-up period, there

was a notable minority of participants who increased their dose. While most increases were small, 4% of participants increased the dose by 25–50 MME and another 4% increased the dose by > 50 MME. These individuals deserve particular attention because larger dose escalations and higher doses raise the risk for dangerous side effects and overdose.

A small number of discrete factors accounted for nearly all individuals with opioid dose increases >25 or >50 MME. Discontinuation of a nonopioid RLS therapeutic medication or the use of the opioid to additionally treat a non-RLS comorbid pain condition might be considered predictable associations with larger MME increases during the 2-year follow-up period. Eliminating dopaminergic agents, as is recommended in the context of augmentation of RLS symptoms, usually necessitates a greater therapeutic burden carried by the opioid. Similarly, in patients using prescribed opioids for a non-RLS comorbid pain condition, increases in opioid doses may be related to exacerbation of the other non-RLS pain conditions, in which opioids are often prescribed at higher doses than in the treatment of RLS. In fact, opioid dose escalation does occur in those with chronic noncancer pain conditions, although its frequency and causes are uncertain.[23,24,26]

Switching from one opioid to another during the follow-up period was also associated with larger opioid dose increases. Because registry participants switching to methadone made up a large portion of the individuals who switched opioids during the follow-up period (43.8%), this finding may largely be an artifact of the high MME conversion ratio used for methadone in this analysis. As such, nearly all participants who switched to methadone saw a substantial increase in daily calculated MME (median increase = 20 MME). Of note, there is some controversy and uncertainty regarding the optimal equivalence determination for methadone.[27,28] Furthermore, the nonlinear relationship of methadone dose to MME may contribute to the elevated number of participants with large MME increases as, for instance, an increase in methadone dose from 20 to 25 mg is calculated as a 40-MME increase.

Male sex and younger age were both found to be independently associated with especially large dose increases of >50 MME. Both these factors have previously been associated with opioid dose escalation and/or high dose prescribing in chronic noncancer pain.[29-32] A history of depressive disorder was also associated with opioid dose increases of both >25 and >50 MME. Similar to younger age and male sex, depression has been associated with high-dose opioid prescribing in chronic noncancer pain.[31] Given the high comorbidity of RLS and depression,[33,34] this association with larger dose increases is worth noting.

Of the original 500 RLS Registry participants, 2-year data were unavailable for 10% of participants. Of note, the median baseline MME for these participants was significantly lower than that for remaining participants who continued using the prescribed opioids. However, there were no significant differences in age, sex, or baseline IRLS between the 2 groups.

Considering that the 2 most common reasons provided for discontinuation were side effects and unwillingness of the prescriber to continue opioid treatment, it seems possible that both side effects and prescriber reluctance contributed to the lower baseline doses observed in this group.

Participants who were on opioids for less than a year at entry into the registry were significantly less likely to see dose increases during year 2 of follow-up when compared with that during year 1. This suggests that individuals just starting opioid medications for RLS may require dose increases early on, but that further dose increases are less frequent because an optimal dose is achieved approximately 1 year into treatment.

Patients with RLS, particularly those with daytime symptoms from dopamine agonist–related augmentation, are often prescribed methadone due to its long duration of action. Participants switching to methadone from another opioid during the 2-year follow-up had significant reductions in RLS symptom severity scores after the switch. By contrast, participants switching to other opioids did not see similar decreases in RLS severity. This suggests that methadone may be particularly effective for controlling RLS symptoms, although future comparative trials are needed to test this. As previously mentioned, most individuals switching to methadone did see MME increases, although this may be an artifact of the high conversion ratio used in this analysis.

This study is limited in its generalizability due to Registry participants being predominantly White, elderly, and highly educated. Thus, an extrapolation of these results to more diverse and younger populations should be performed with caution. Some baseline data are also limited in their reliance on participants' recollection of events, occurring sometimes decades in the past (e.g., age of symptom onset, mental health history, etc).

It is important to note that Registry participants' care is managed by participants' own providers without any intervention from the Registry research team at Massachusetts General Hospital, which provides no clinical feedback or guidance to either participants or to providers. In fact, most RLS providers are likely unaware of their patients' involvement in the registry.

In conclusion, this analysis provides preliminary evidence from a large national registry that low-dose opioids can control RLS symptoms over time with minimal dose escalation in most patients with refractory, augmented RLS. Continued data collection may help in identifying those patients with RLS for whom opioids continue to be effective and well tolerated at low doses.

Study Funding

Disclosure

Publication History

Appendix Authors

Name	Location	Contribution
John Weyl Winkelman, MD, PhD	Massachusetts General Hospital; Harvard Medical School	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Benjamin Wipper, BA	Harvard Medical School	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
Jordana Zackon, BA	Massachusetts General Hospital	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data

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