



ORIGINAL ARTICLE

# Baseline and 1-year longitudinal data from the National Restless Legs Syndrome Opioid Registry

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## Abstract

**Study Objectives:** Restless legs syndrome (RLS) is a sensory-motor neurological disorder. Low dose opioid medications are prescribed for treatment-refractory RLS. We describe baseline and 1-year longitudinal dosing and symptom outcomes for the National RLS Opioid Registry.

**Methods:** Individuals currently taking a prescribed opioid for diagnosed RLS are included in the registry. Information on initial and current opioid dosages, side effects, past and current concomitant RLS treatments, RLS severity, psychiatric history, and opioid abuse risk factors were collected at baseline. Follow-up online surveys were performed at 6 months and 1-year.

**Results:** Participants ( $n = 500$ ) are primarily white, elderly, educated, and retired. Half of all subjects are on opioid monotherapy. Nearly 50% of all subjects are taking methadone, and one-quarter are taking oxycodone formulations. The median total daily opioid dose is 30.0 morphine milligram equivalents (MME). At baseline, three-quarters of registry participants had been taking a prescribed opioid for RLS for more than 1 year and one-third for more than 5 years, and had mild-moderate RLS symptoms. At 1-year follow-up, 31.2% increased dose (median = 10 MME) and 16.0% decreased dose of their opioid. An MME increase  $\geq 25$  was associated with: opioid use for non-RLS pain, <1 year of opioid use, opioid switch to methadone, and discontinuation of non-opioid RLS medications which, combined, accounted for 91.7% of those with 1-year follow-up increases  $\geq 25$  MME.

**Conclusions:** In refractory RLS, prescribed opioids are generally used at low doses with good efficacy. Longitudinally over 1 year, roughly one-third of participants increased their prescribed opioid dose, though generally by small amounts, with larger dose increases accounted for by predictable features.

### Statement of Significance

Restless legs syndrome (RLS) is a sensory-motor neurological disorder characterized by an irresistible urge to move the legs. Although dopamine agonists and alpha-2-delta calcium channel ligands are effective treatments for this disorder, low dose opioid medications are prescribed for patients with treatment-refractory RLS. However, there are only limited data regarding the long-term safety and efficacy of prescribed opioid medications in the treatment of RLS. The RLS National Opioid Registry is a longitudinal observational study that will provide important information about long-term symptom control, dose escalation, and complications in patients using prescribed opioids for RLS. In this article, we present the baseline and 1-year longitudinal characteristics of the RLS Registry participants.

**Key words:** restless legs syndrome; opiates; observational studies

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## Introduction

Restless legs syndrome (RLS) is a sensory-motor neurological disorder characterized by an irresistible urge to move the legs and leg discomfort. Symptoms are provoked by rest, relieved with movement, and worst in the evening or at night [1]. Clinically significant RLS is present in roughly 3% of the general population [2]. Such sufferers describe these leg sensations as unbearable and the physical distress and lack of sleep associated with RLS contribute to high levels of morbidity.

Dopamine agonists have been the mainstay of medical treatment and most patients with RLS initially experience prompt suppression of symptoms upon treatment with these agents [3]. Unfortunately, only a minority of patients continue to benefit from dopaminergic drugs beyond 10 years [4]. Even worse, these treatments can lead to a worsening of RLS severity, known as augmentation, in 30%–50% of patients [5].

Low dose opioid medications are frequently prescribed for patients who have developed augmentation to dopamine agonists [6]. Opioids, even at low doses, are often dramatically effective for RLS in controlled, short-duration studies [7]. In contrast to dopamine agonists, small uncontrolled studies suggest that low dose opioids continue to control symptoms over at least a decade with minimal dose escalation and no evidence of augmentation [4, 8, 9].

Large-scale multicenter data on the long-term efficacy, dose escalation, and complications in patients using prescribed opioids for RLS is needed to establish their safety and efficacy in this population and the National RLS Opioid Registry is an attempt to address this issue.

In this article, we describe the baseline and 1-year longitudinal characteristics of the National RLS Opioid Registry participants.

## Methods

### Participants

A total of 500 adult (24–90 years) patients were recruited from media circulated by the Restless Legs Syndrome Foundation (RLSF) or by brochures provided to patients by treating physicians, many of whom practiced in groups certified by the RLSF as RLS Quality Care Centers (QCC). Roughly 40% of participants were referred from QCC sites (primarily Johns Hopkins, Massachusetts General Hospital, Yale New Haven Hospital, Stanford Sleep Clinic, and Mayo Clinic), however, the majority of participants came from outreach by the RLS Foundation or through social media. Recruitment occurred between December 2017 and September 2019. Participants who were currently taking a prescribed opioid daily for diagnosed RLS and had a previous therapeutic response to dopaminergic agonists were eligible for enrollment into the registry. The requirement for a response to a dopaminergic agent was to better ensure the presence of restless legs syndrome. Patients were specifically told that identifying information from the registry would not be shared with their RLS prescribing physician or other healthcare professionals.

### Standard protocol approvals, registrations, and patient consents

All participants provided verbal informed consent. The study was approved by the Institutional Review Board of Partner's Healthcare,

the parent organization of Massachusetts General Hospital. Participants were not compensated for their participation.

### Evaluation

Participants underwent a 45-min phone interview, during which a trained research coordinator confirmed their RLS diagnosis using the Hopkins telephone diagnostic interview, a validated, structured instrument that attempts to exclude major RLS mimics [10]. We collected information on demographics, initial and current opioid dosages, side effects, concomitant RLS medications and dosages, past RLS treatments, augmentation history [11], other current CNS medications, RLS severity using the International Restless Legs Syndrome Study Group severity scale [12], psychiatric history, suicidal ideation pre- and post-opioid treatment using the Columbia Suicide Severity Rating Scale [13], and opioid abuse risk factors using the Opioid Risk Tool (ORT) [14]. The ORT is a self-report screening tool that has scorable components relating to sex, family and personal history of substance abuse, age, history of preadolescent sexual abuse, and psychiatric disease. Based on their responses, patients receive a score ranging from 0 to 26: A score of  $\leq 3$  indicates low risk for opioid abuse, 4–7 indicates moderate risk, and  $\geq 8$  indicates high risk, according to a validation study among pain management patients [14]. Patient Global Impressions of Change (compared to before prescribed opioid use for RLS) and Severity were also collected during the phone interview. Following the phone interview, participants completed a baseline online survey, which collected information on comorbid health conditions, all current medications, family history of RLS, the impact of RLS on quality of life (using a survey based on the Johns Hopkins RLS Quality of Life questionnaire) [15], painful RLS (using adjectives from the McGill Pain Inventory) [16], napping, exercise, drug and alcohol consumption, insomnia severity [17], daytime sleepiness [18], and depression and anxiety symptoms [19–21]. Online surveys were submitted, and all data stored, in Research Electronic Data Capture (REDCap), without subject identifying information, under a unique study ID.

At the 6-month and 1-year anniversaries of their baseline interview, all subjects were emailed links to surveys which they completed online via REDCap, typically within 2 weeks. These surveys included questionnaires that were administered during the initial phone interview and online survey as well as changes in RLS and non-RLS medications, changes in health, and opioid side effects. If responses were unclear, a study coordinator contacted the participant via email or phone to provide clarification. If there was ambiguity regarding prescribed opioid dosing, clarification was established by querying their state prescription drug monitoring programs. If a participant did not respond to three email solicitations to complete a survey, they were considered lost to follow-up.

### Statistical analysis

All opioid dosages were converted to morphine milligram equivalents (MME) using established conversion ratios: methadone: 4 (for doses  $\leq 20$  mg), 8 (21–40 mg), 10 (41–60 mg), 12 ( $>60$  mg); oxycodone: 1.5; hydrocodone: 1; tramadol: 0.1 [22].

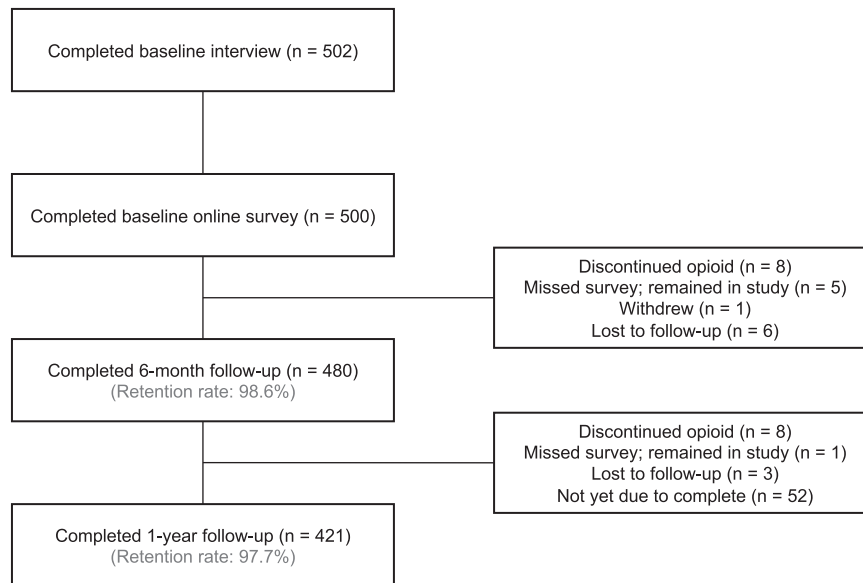


Figure 1. Participant flow diagram.

Table 1. Baseline demographics

Demographics	
Number of participants	500
Age (years) (n = 497)	65.1 ± 10.8
Gender	
Female	284 (56.8%)
Race	
White	491 (98.2%)
Native American/Alaska Native	4 (0.8%)
Asian	3 (0.6%)
Other	4 (0.8%)
Body mass index (kg/m <sup>2</sup> )	28.0 ± 6.3
Highest education level	
Graduate school	228 (45.6%)
College graduate	147 (29.4%)
Partial college	93 (18.6%)
High school or lower	32 (6.4%)

Questionnaires were assessed on a continuous scale unless otherwise noted. When data were missing, analysis was performed using all available values. Data from participants lost to follow-up were not included in the analyses of changes from baseline to 1-year. Statistical analyses included Chi-square tests (for categorical variables), Mann-Whitney tests (for non-normal, continuous unpaired data), Wilcoxon signed-rank tests (for non-normal, continuous paired data), and Spearman's correlations (for continuous data). Logistic regression analysis was used to assess associations of higher baseline MME and IRLS scores, and dose increases at 1-year; all models were adjusted for age and sex. Regression analyses were performed using a forward selection method (threshold:  $p < 0.1$ ) and consisted of data from all subjects. Multicollinearity of the covariates was examined and found to be at an acceptable level (variance inflation factors  $< 1.2$  for all). Odds ratios with 95% confidence intervals were reported.

All significance values reported were two-sided, and all analyses were performed using the Prism GraphPad 8 software.

## Data availability

Anonymized data reported in this article will be shared upon requests from qualified investigators.

## Results

### Baseline data

#### Overview

A total of 575 people were screened for eligibility, and 502 met inclusion and exclusion criteria. Ineligible candidates were either not taking a prescribed opioid regularly, did not have any previous therapeutic response to a dopamine agonist, or did not have an email address. Of the 502 participants who were interviewed and enrolled, 2 did not complete the baseline online survey (see Figure 1 for participant flow). Therefore, full data at registry entry (hereafter called baseline) is available for 500 participants who comprise the RLS opioid registry database.

#### Demographics and RLS history

The participant population is 57% female ( $n = 284$ ) and 72% are 60 years or older ( $n = 359$ ), with the mean age being  $65.1 \pm 10.8$  years old (range 24–90 years). This population is primarily white ( $n = 491$ ; 98%) and well-educated (see Table 1). Participants in the registry represent 44 different US states and 6 countries.

Almost two-thirds of participants ( $n = 305$ ; 61%) report a known family history of RLS, and 36% first experienced RLS symptoms before the age of 20 ( $n = 182$ ). Prior to initiating any prescription treatment for RLS, 54% of participants reported experiencing RLS symptoms every day ( $n = 268$ ).

#### RLS treatment/medical history

As an inclusion criterion, all participants had previously used and reported benefit from a dopamine agonist for RLS; nearly all ( $n = 445$ ; 89%) had a history of dopamine agonist augmentation according to clinical interview using augmentation diagnostic criteria [11].

**Table 2.** Baseline prescribed opioids and symptoms

Opioid	Count <sup>†</sup> (%)	Daily dose (mg)			Daily dose (MME)*			Symptom and mood scales (mean ± SD)		
		Median	Q1	Q2	Q3	IRLS	ISI	PHQ-9		
Methadone	228 (45.6%)	10.0	20	40	41.3	10.3 ± 9.2	9.5 ± 6.6	5.3 ± 4.9		
Oxycodone <sup>‡</sup>	122 (24.4%)	15.0	9.8	22.5	36.6	17.7 ± 9.4	12.5 ± 5.9	7.0 ± 5.5		
Hydrocodone	72 (14.4%)	10.0	7.5	10	18.8	16.5 ± 9.8	12.4 ± 6.9 <sup>§</sup>	5.1 ± 4.7 <sup>§</sup>		
Tramadol	43 (8.6%)	100.0	5	10	15.6	13.8 ± 9.5	11.0 ± 6.3	4.5 ± 3.8		
Morphine	19 (3.8%)	30.0	17.5	30	60	11.7 ± 8.7	9.2 ± 6.4	6.3 ± 7.0		
Buprenorphine	19 (3.8%)	2.0	22.5	52.5	60	12.2 ± 10.1	8.8 ± 8.0	6.8 ± 7.5 <sup>¶</sup>		
Codeine	12 (2.4%)	39.0	4.5	5.9	16.3	12.1 ± 8.3	11.8 ± 4.9	6.1 ± 4.9		
Hydromorphone	10 (2.0%)	9.0	20	36	58	13.2 ± 11.1	11.2 ± 8.7	7.5 ± 6.8		
Fentanyl	5 (1.0%)	25.0 <sup>¶</sup>	60	60	90	21.8 ± 15.0	19.0 ± 6.1	17.6 ± 6.7		
Oxymorphone	2 (0.4%)	12.5	–	37.5	–	12.0 ± 17.0	17.0 ± 4.2	5.0 ± 1.4		
Pentazocine	2 (0.4%)	225.0	–	83.3	–	0.0 ± 0.0	3.0 ± 1.4	1.0 ± 1.4		

Q, quartile; IRLS, International Restless Legs Syndrome Study Group severity scale; ISI, Insomnia Severity Index; PHQ-9, Patient Health Questionnaire.

\*CMS conversion ratios were used. Ratios for common opioids were as follows: methadone: 4 (for doses ≤20 mg), 8 (21–40 mg), 10 (41–60 mg), 12 (>60 mg); oxycodone: 1.5; hydrocodone: 1; tramadol: 0.1.

<sup>†</sup>The total count adds up to over 500 as numerous participants were taking two opioid medications.

<sup>‡</sup>Includes both oxycodone and OxyContin.

<sup>§</sup>n = 71.

<sup>¶</sup>n = 18.

<sup>¶</sup>Unit is µg/h.

The most common prior RLS treatment medications were ropinirole (n = 342; 68%) and pramipexole (n = 320; 64%). Levodopa had been used by 36% of participants (n = 178) and rotigotine had been used by 24% (n = 122). Hydrocodone (n = 69; 14%) was the most commonly used prescribed opioid prior to their current treatment and gabapentin (n = 285; 57%), clonazepam (n = 130; 26%), and pregabalin (n = 116; 23%) were the most commonly used non-FDA-approved prior RLS treatments. Less than a fifth of patients had IV iron infusions in the past.

Hypertension (n = 183; 37%), hypercholesterolemia (n = 172; 34%), gastrointestinal/digestive problems (n = 149; 30%), peripheral neuropathy (n = 118; 24%), and thyroid problems (n = 110; 22%) were the most commonly reported medical conditions. The average BMI of this sample is 28.0 ± 6.3.

### Psychiatric history and symptoms

Over half of the RLS opioid registry participants have a history of psychiatric illness (n = 266; 53%), primarily depression (n = 212; 42%), and anxiety disorders (n = 157; 31%). Roughly 20% (n = 98) use serotonergic antidepressants. One-fifth (n = 102; 20%) of participants reported current moderate to severe levels of depression at enrollment in the registry, according to the PHQ-9 (mean = 5.71) [18]. Over one-third (n = 183; 37%) of participants recalled having passive suicidal thoughts and behaviors, and 22% active suicidal ideation (n = 110), prior to initiating prescribed opioid medications for RLS. At registry enrollment, on opioid treatment, these proportions were reduced significantly, with 13% of participants reporting passive (n = 67), and 7% active (n = 35), suicidal ideation (p < 0.0001 for both).

Three-quarters of participants (n = 380; 76%) were low risk for opioid abuse based upon the ORT. A small percentage of participants (n = 28; 6%) were considered high risk.

### Baseline RLS medication treatments

Approximately half of all participants were taking a prescribed opioid as their only RLS treatment (n = 266; 53%) at registry

enrollment. Almost half of all participants were taking methadone (n = 228; 46%), with an additional 25% taking oxycodone formulations (n = 123): 18% (n = 88) taking oxycodone, 4% (n = 22) taking OxyContin (Purdue Pharma L.P., Stamford, CT), and 3% (n = 13) on both (see Table 2). Of the 47% of participants who were taking another RLS-related medication in addition to opioid treatment, α2δ ligands (n = 152; 31%) and dopamine agonists (n = 125; 25%) were most common. Benzodiazepines were used by 7% of participants (n = 35), with the most common being clonazepam (2%; n = 11) and diazepam (2%; n = 8). One-fifth of subjects reported using marijuana products at least a few times per year (20%; n = 98); 6% (n = 32) used such products a few times a week, and an additional 4% (n = 19) reported using marijuana a few times a day.

Opioid doses were positively skewed with 79% of registry participants (n = 396) having an MME <50 and 33% (n = 163) <20 (Figure 2). The mean total daily prescribed opioid dose at baseline in the 500 participants (excluding 4 outliers) was 37.9 MME (9.5 mg of methadone or 25.3 mg of oxycodone). The overall median total daily opioid dose was 30.0 MME. Among the subjects taking methadone, excluding 3 outliers, the mean total daily dose was 11.2 mg of methadone, or 44.8 MME (median 10 mg of methadone or 40.0 MME) (Table 2).

Factors that were independently associated with (p < 0.05) a baseline MME ≥50 (n = 104 or 21%) were: use of a prescribed opioid for a non-RLS comorbid pain condition (OR 3.18, 1.31–7.55), onset of RLS at an age younger than 20 (OR 1.98, 1.24–3.18), use of methadone (OR 1.93, 1.21–3.13), medium or high ORT score (OR 1.88, 1.13–3.11), and painful RLS (OR 1.71, 1.07–2.75). Male sex had a trend association (OR 1.52, 0.94–2.44). Use of current prescribed opioid <1 year prior to registry entry was associated with a lower probability of an MME ≥50 (OR 0.38, 0.20–0.69). Participants taking their current prescribed opioids for <1 year at baseline had a lower probability of an MME ≥50 (14/136; 10.3%) than those with durations of 1–3 years (36/131; 27.5%), 3–5 years (13/79; 16.5%), 5–10 years (16/70; 22.9%), and >10 years (24/82; 29.3%).

The median MME in the ORT high-risk group was nearly double that in the low-risk group (40.0 vs 24.0 MME) and the proportion

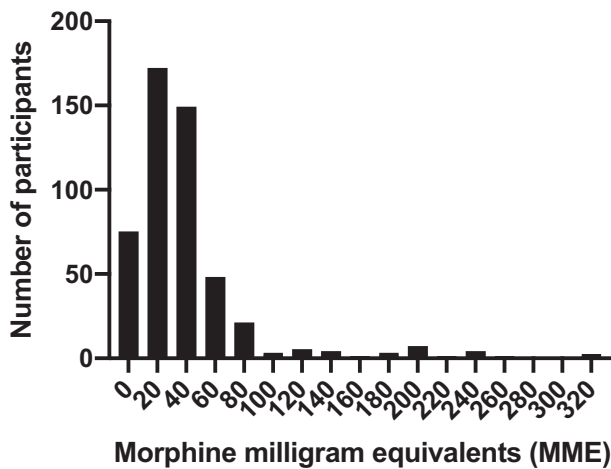


Figure 2. Distribution of total daily MME at baseline ( $n = 496$ ). Four high outliers (550, 600, 960, and 1,200) were not included.

of participants taking  $\geq 50$  MME per day was significantly higher in the ORT high-risk group (11/28; 39%) than in the low-risk group (68/380; 18%;  $p = 0.004$ ). The individual items of the ORT that contributed to this association were both history of psychiatric disease and childhood trauma (both  $p = 0.02$ ), with trend associations for family ( $p = 0.08$ ) and personal history of substance abuse ( $p = 0.11$ ).

MME did not correlate with symptoms of depression or anxiety.

#### Opioid duration and prior dose increase

At entry into the registry, nearly three-quarters of participants ( $n = 362$ ; 72%) had been taking a prescribed opioid for RLS for more than 1 year, and roughly one-third ( $n = 152$ ; 30%) for more than 5 years. To assess opioid dose changes during their RLS treatment prior to the registry entry, participants reported their “first stable dose,” which was the established dose 1–2 months after initiating prescribed opioid treatment. Among all participants, 29% reported that they had increased their total daily prescribed opioid dose by the time of registry entry ( $n = 145$ ), by a median of 10 MME or 50% of their original stable dose. Less than one-fifth ( $n = 88$ ; 18%) of all participants doubled their original stable dose, for a median increase of 20 MME; 7% tripled their original therapeutic dose ( $n = 35$ ), and 3% increased their dose by over 50 MME ( $n = 17$ ).

#### Opioid stigma

Roughly one-quarter (23.9%) of participants reported that they felt they had been discriminated against by health professionals due to their use of prescribed opioids for RLS, and 47.8% reported that they avoided telling others about their opioid treatment. Nearly all participants (95.8%) expressed worry about opioid regulations and their ability to continue receiving their opioid prescription.

#### RLS symptoms on opioid treatment

At baseline, registry participants had mild-moderate levels of overall RLS symptoms (mean IRLS score =  $13.2 \pm 9.8$ ); 23% of all participants reported no RLS symptoms at all in the past week ( $n = 114$ ). The average IRLS score was significantly lower for participants taking methadone ( $9.6 \pm 9.2$ ) than for participants taking

oxycodone ( $17.8 \pm 9.3$ ;  $p < 0.0001$ ). The IRLS score for participants taking only a prescribed opioid without other concomitant RLS medications ( $11.3 \pm 9.7$ ) was significantly lower than for participants taking an opioid and an  $\alpha\delta$  ligand ( $15.1 \pm 8.9$ ;  $p = 0.0013$ ) or a dopamine agonist ( $16.3 \pm 9.9$ ;  $p = 0.0004$ ).

The overall severity of past-week symptoms on the IRLS was in the mild range ( $n = 176$  or 35% of all subjects), though 17% reported them in the severe or very severe ranges ( $n = 83$ ). Under 10% of participants on methadone (18/228; 7.9%) had severe or very symptoms, compared to nearly a third on oxycodone (31/100; 31%). One-fourth of participants on dopamine agonists (32/125; 25.6%) reported severe or very severe symptoms, compared with 13.6% of participants not taking dopamine agonists (51/375). Nearly all participants taking opioids for RLS were satisfied with their RLS treatment response, with 94% of all participants reporting that the opioid treatment had “much” or “very much” improved their overall RLS severity ( $n = 468$ ).

Roughly one-third ( $n = 167$ ; 33%) of participants reported their RLS to be painful. Using adjectives from the McGill Pain Inventory [15], RLS pain was most commonly described as “aching” ( $n = 117$ ; 70% of participants who reported painful RLS), “tiring” ( $n = 94$ ; 56%), and “gnawing” ( $n = 83$ ; 50%). Painful RLS was more commonly reported in individuals over 80 years old than in those 80 or younger (54% of participants vs 32%;  $p = 0.0208$ ). Those with painful RLS were significantly more likely to have a baseline MME  $\geq 50$  (26.3% vs 17.8%;  $p = 0.03$ ) and have higher symptom rating scale scores (median IRLSSG scale score of 18.0 vs 11.0) than those with non-painful RLS.

Factors associated with a baseline IRLS score  $>15$  ( $n = 209$  or 42%) included: history of fibromyalgia (OR 3.91, 1.51–10.52), being on a prescribed opioid other than methadone (OR 2.43, 1.59–3.73), and reporting painful RLS symptoms (OR 1.72, 1.10–2.68).

#### Side effects of opioids

The most commonly reported side effect of prescribed opioids for RLS treatment is constipation ( $n = 260$ ; 52% of participants). Almost one-fourth of participants report drowsiness/fatigue as a side effect ( $n = 119$ ; 24%), but 43% of participants noted that they had lower levels of sleepiness after beginning prescribed opioids ( $n = 215$ ). Other common side effects were itching ( $n = 97$ ; 19%), sweating ( $n = 84$ ; 17%), change in appetite ( $n = 61$ ; 12%), and a lack of sexual interest ( $n = 57$ ; 11%). The following mood-related side effects were each endorsed by 5% of participants: anxiety ( $n = 31$ ), depression ( $n = 26$ ), apathy ( $n = 24$ ), and moodiness ( $n = 23$ ). Only 4% of participants endorsed “feelings of euphoria, warmth, intense relaxation, or giddiness” from the prescribed opioids ( $n = 19$ ).

Side effect profiles differed between the two most commonly prescribed opioids, methadone and oxycodone/OxyContin. The mean number of side effects experienced on methadone was 2.21 (median = 2) whereas the mean for participants on oxycodone was 1.84 (median = 1);  $p = 0.10$ . The most common side effects for patients on methadone were constipation (146/228; 64.0%), drowsiness/fatigue ( $n = 63$ ; 27.6%), sweating ( $n = 54$ ; 23.7%), itching ( $n = 47$ ; 20.6%), and changes in appetite ( $n = 29$ ; 12.7%) whereas the most common side effects for patients on oxycodone were constipation (58/122; 47.5%), itching ( $n = 33$ ; 27.0%), drowsiness/fatigue ( $n = 28$ ; 23.0%), changes in appetite ( $n = 15$ ; 12.3%), sweating ( $n = 14$ ; 11.5%), and lack of sexual interest ( $n = 14$ ; 11.5%).

## 1-year follow-up data

At the time of analysis, 448 participants had passed the 1-year anniversary of their baseline enrollment survey. Of these, a total of 421 participants completed the 1-year survey, and 1 additional participant missed the survey but remained in the study (Figure 1). A total of 16 other participants notified the study team that they discontinued opioid therapy. The most common reasons for opioid discontinuation were: side effects ( $n = 4$ ), clinician refusal to write the prescription ( $n = 4$ ), and switch to a non-opioid medication ( $n = 3$ ). When accounting for 10 other people who no longer participated in the registry (9 lost to follow-up and 1 withdrawn), the 1-year retention rate is 97.7% (422/432).

### Changes in RLS medications

Of 420 subjects who remained on prescribed opioid treatment and provided evaluable dosing information, 369 were on the same opioid medication as at baseline whereas 51 participants changed their opioid regimen: 37 switched to a new opioid (16 to methadone), 7 added an additional opioid, and 7 stopped using one of their two opioids. The most common reasons for switching were lack of efficacy (14/37; 38%) and side effects (11/37; 30%).

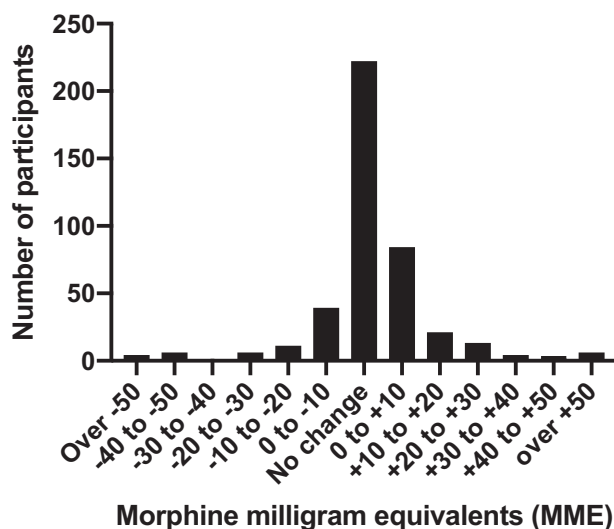


Figure 3. MME changes from baseline to 1-year ( $n = 420$ ).

Table 3. Independent associations with MME increase  $\geq 25$  at 1 year ( $n = 420$ )

Factor	Odds ratio	95% CI	P
Switched to methadone	15.68	[3.95, 64.45]	<b>&lt;0.0001</b>
Using opioid for comorbid pain condition	7.40	[1.81, 28.78]	<b>0.0039</b>
Sleeping difficulties at baseline (ISI > 10)	7.26	[1.91, 43.30]	<b>0.0099</b>
On opioid for under one year at baseline	5.59	[2.04, 16.60]	<b>0.0011</b>
Onset of RLS symptoms before age 20	3.16	[1.15, 9.40]	<b>0.0298</b>
Stopped or lowered dose of dopamine agonist or an $\alpha 2\delta$ ligand	3.07	[1.06, 8.44]	<b>0.0318</b>
Overall model evaluation			
Likelihood ratio test			<b>&lt;0.0001</b>
Goodness of fit test			
Hosmer–Lemeshow test			0.6164

Bold values denote statistical significance at the  $p < 0.05$  level.

Although there was no change in the proportion of participants taking dopamine agonists or  $\alpha 2\delta$  ligands at 1-year follow-up, some individuals added one of these agents whereas others discontinued them. Median dosages on both classes of medications did not change from baseline to 1 year.

### Changes in MME

At 1-year follow-up, both the median and modal change in MME was 0, with 52.9% of subjects on the same prescribed opioid dose as at baseline ( $n = 222$ ). Under one-third of participants ( $n = 131$ ; 31.2%) increased dose and 67 (16.0%) decreased their dose (Figure 3). Among those that increased their prescribed opioid dose, the median increase was 10 MME.

Independent associations with an MME increase  $\geq 25$  ( $n = 24$  or 5.7%) in the first year of prospective registry follow-up include: switching to methadone (OR 15.68, 3.95–64.45), prescribed opioid use for treating non-RLS comorbid pain (OR 7.40, 1.81–28.78), being on their current prescribed opioid for under 1 year at baseline (OR 5.59, 2.04–16.60), and stopping or lowering the dose of a dopamine agonist or an  $\alpha 2\delta$  ligand (OR 3.07, 1.06–8.44) (Table 3). Although participants who satisfied at least one of these four conditions represented just 40.5% of those who completed a 1-year survey and remained on prescribed opioid treatment (170/420), these individuals accounted for 91.7% of those who increased by  $\geq 25$  MME (22/24). From the opposite perspective, in the 250 registry participants who did not have one of these four attributes, only two (0.8%) increased MME  $\geq 25$  at 1-year follow up. Two additional associations with increases  $\geq 25$  MME were: sleep difficulties at baseline (ISI score >10; OR 7.26, 1.91–43.30) and onset of RLS symptoms before the age of 20 (OR 3.16, 1.15–9.40). Independent associations with an MME increase  $\geq 15$  were nearly identical to those noted above for MME  $\geq 25$ . Of note is that ORT score, male sex, and psychiatric illness were not associated with such larger opioid dose increases.

Table 4 summarizes dose changes within various groups of interest. Individuals who had been on their current prescribed opioids for under a year at entry into the registry saw particularly high rates of any dose increase (51/104; 49.0%), although these increases tended to be relatively small (52.9% were 10 MME or less). Increasing the duration of prescribed opioid use greater than 1-year prior to registry entry was not associated with a greater probability of dose increase in the first year of longitudinal follow-up: 1–3 years (31/115; 27.0%), 3–5 years (17/73; 23.3%), 5–10 years (17/61; 27.9%), and 10+ years (15/67; 22.4%).

Table 4. MME changes at 1 year

Factor	n	IRLS		MME						
		BL	BL dose	1-year dose	Decreased dose (%)	Same dose (%)	Increased dose (%)	Median increase	Increased $\geq 25$ (%)	
All who responded and remained on opioid treatment	420	13.0	30.0	30.0	16.0	52.9	31.2	10.0	5.7	
Did not add or remove opioid medications and used Methadone	369	12.4	30.0	30.0	12.7	59.3	27.9	10.0	4.1	
and used Oxycodone	178	9.4	40.0	40.0	9.0	64.0	27.0	10.0	5.1	
and used Hydrocodone	81	18.0	22.5	22.5	16.0	60.5	23.5	7.5	3.7	
	52	15.4	10.0	10.6	21.2	53.8	25.0	3.8	0.0	
Factors predicting dose increases of MME $\geq 25$										
(1) Sleeping difficulties at baseline (ISI > 10)	210	17.4	30.0	30.0	17.6	45.7	36.7	10.0	10.0	
(2) Onset of RLS symptoms under the age of 20	157	14.7	30.0	35.0	20.4	51.0	28.7	11.3	9.6	
(3) On current opioid(s) for under one year at baseline	104	13.1	20.0	25.0	14.4	36.5	49.0	10.0	14.4	
(4) Stopped or lowered dose of dopamine agonist or an $\alpha 2\delta$ ligand	59	17.6	20.0	29.3	13.6	28.8	57.6	13.0	16.9	
(5) Switched to methadone	16	18.9	15.0	40.0	18.8	0.0	81.3	25.0	43.8	
(6) Uses opioid(s) to treat comorbid pain condition	30	17.3	30.0	37.5	23.3	33.3	43.3	23.0	20.0	
Devoid of factors 3–6	250	11.8	30.0	30.0	15.6	64.0	20.4	7.5	0.8	
Other factors										
Painful RLS symptoms	136	16.9	30.0	30.0	16.9	49.3	33.8	10.0	7.4	
On dopamine agonist at 1-year	104	15.8	22.5	22.5	24.0	43.3	32.7	7.5	4.8	
On current opioid(s) for over one year at baseline	316	13.0	30.0	30.0	16.5	58.2	25.3	10.0	2.8	
Switched to opioid other than methadone	21	14.8	22.5	16.9	57.1	9.5	33.3	3.8	0.0	

### RLS symptoms

At 1-year follow-up, there were no changes from baseline in IRLS scores, sleep measures, mood measures, or other key study measures.

## Discussion

We report here the largest cross-sectional and longitudinal sample of patients using prescribed opioids for the treatment of RLS. In our registry, prescribed opioid doses are generally low, relatively stable over a median of 1–3 years prior to, and prospectively over 1 year following, registry enrollment, and are generally reported as efficacious for RLS symptoms in this refractory population.

The median daily dose of prescribed opioid doses in our registry was 30 MME, which is similar to previous studies of opioids for RLS [4, 7, 8]. The average daily dose was 27 MME for oxycodone controlled release in a large 1-year open-label trial in patients with refractory RLS [7], 37.5 mg in a small controlled clinical trial of oxycodone [23], and 62 MME and 40 MME in two small case series of patients prescribed methadone [4, 8]. Although the CDC does not define a “high” prescribed opioid dose, it recommends that clinicians carefully assess benefits and risks when administering doses of 50 MME or above [24]. Just one-fifth of our registry participants ( $n = 104$ ; 21%) are at or above this daily dose (Figure 2). Prescribed opioid doses used by registry participants for RLS are much lower than those

employed for methadone maintenance treatment of opioid use disorder (60–120 mg or 600–1,440 MME).

This is the first study to assess features associated with both prescribed opioid dose and the requirement for dose increases in the treatment of RLS. Such analyses may allow clinicians to better assess risks of this class of medication prospectively for individual patients. In our sample, early onset of RLS, use of methadone, and the presence of additional chronic non-RLS pain conditions predicted higher ( $\geq 50$  MME) baseline prescribed opioid doses whereas the duration of opioid use <1 year predicted lower opioid doses.

Methadone may be associated with higher doses for RLS treatment because it is used in participants with more severe initial symptoms, but it may also be an artifact of our use of a high conversion ratio for methadone to MME in our analyses. The CDC uses a conversion of 3 for methadone mg to MME; we used the CMS conversion of 4 which increases to 8 for methadone doses above 20 mg, 10 for doses >40 mg, and 12 for doses >60 mg. However, there is considerable controversy as to the optimal conversion ratio for methadone given its complex pharmacokinetics [25]. Registry participants on methadone also had substantially less severe RLS symptoms than those on other commonly used prescribed opioids; this may indicate that clinicians pursue better efficacy with this agent, at the cost of the higher dose, as they feel more comfortable with its tolerability, safety, and risk of abuse. Early-onset RLS may predict higher MME as it is more commonly severe than later-onset RLS [26, 27] and thus may require higher opioid doses for RLS symptomatic control.

Although the median dose change in the first year of longitudinal follow-up was 0 MME, prescribed opioid dose escalation did occur in roughly 30% of participants (131 of 420); on the other hand, 16% (67 of 420) of participants decreased their opioid dose (Figure 3). Dose increases were generally small with a median of 10 MME (equal to 2.5 mg of methadone or 7 mg of oxycodone). Consistent with our data, a previous longitudinal case series examining prescribed opioid dose increases demonstrated a median increase of 0 MME with an upper quartile increase of 15 MME in those taking methadone for 1 year after an initial (6-month) stable dose was achieved [4]. Another similar small case series of patients using methadone found a 2.5 mg median increase (MME of 10) in 2 years of follow-up [8].

The use of current prescribed opioid for <1 year prior to registry entry was associated with both low opioid dose at baseline and of larger ( $\geq 25$  MME) dose increases at 1 year of follow-up. Of note, there was no evidence (from our baseline data) that prescribed opioid dose continued to increase after the first year of use. This suggests that an optimal opioid dose for RLS treatment may not be reached until roughly 1 year after initiating these medications. This hypothesis will be assessed as a long-term follow-up of registry participants occurs.

The use of prescribed opioids for a comorbid non-RLS pain condition was also strongly associated with both higher baseline dose and larger dose increases at 1-year follow-up. In this group, it is unclear whether higher prescribed opioid doses and dose increases were necessitated by severe and increasing RLS symptoms or by the presence and worsening of comorbid non-RLS pain conditions. However, such patients should be carefully monitored to assess the appropriateness of higher doses and dose increases.

The benefits of polytherapy in RLS are not well established but this approach is commonly employed in practice [28], particularly in refractory RLS, as is apparent from our registry participants. If, as is commonly assumed, that multiple classes of medications contribute to therapeutic benefit, it is not surprising that discontinuing or reducing non-opioid medications was associated with larger increases in prescribed opioid doses.

A high rate of MME increase was observed among those who switched to a new prescribed opioid at 1-year: just 2 of the 37 participants who switched opioids saw no change in daily MME. The direction of the MME change seemed to be largely dependent on the prescribed opioids involved in the switch. For example, over 80% of those who switched to methadone saw an MME increase at 1-year (13 of 16; 81%), compared to just 33% of those who switched to another opioid (7 of 21). Of note, those who switched to methadone saw a significant decrease in IRLS scores (18.9 vs 10.8;  $p = 0.003$ ), whereas those who switched to other opioids did not see such a decrease (14.8 vs 16.0;  $p = \text{NS}$ ). Again, the increased MME in those switching to methadone may be an artifact of the conversion ratio we chose for this analysis.

Moderate severity RLS symptoms were present in registry participants on prescribed opioids, with a highly positive skewed distribution, as 23% had an IRLS score of 0 ( $n = 114$ ). In the absence of severity information prior to prescribed opioid use it is impossible to precisely assess the efficacy of opioids in our participants. However, 94% of patients reported being

much or very much better on prescribed opioids compared to prior treatment ( $n = 468$ ) and only 3% of our registry participants discontinued opioids in the first year of longitudinal follow-up ( $n = 16$ ). During the 1-year longitudinal follow-up, mean IRLS scores and sleep measures were virtually unchanged. The only long-term study to assess RLS severity in patients on prescribed opioids [7] found a slightly better efficacy than is present in our sample, though that trial explicitly excluded patients with augmentation and did not include the 20% of participants who dropped out prior to completion of the 1-year study. The lower severity scores with methadone compared to other prescribed opioids, even when looking solely at methadone users on doses <30 MME, may be due to the relatively long half-life of this medication, providing better suppression of daytime symptoms. Consistent with other data [29], painful RLS was also associated with particularly severe RLS symptoms.

Only a small percentage ( $n = 28$ ; 6%) of our registry participants had a high risk of opioid abuse based upon the ORT. Although those participants did have higher MME at registry enrollment, in the first year of follow-up they did not increase their prescribed opioid dose at a higher proportion or by a larger MME than participants with low-risk ORT score. High rates of psychiatric illness and suicidality are well established in patients with RLS [30–32]. Our baseline data demonstrating large reductions in active and passive suicidality following administration of low dose prescribed opioids speaks to the benefits of effective treatment of RLS. Future clinical trials should include suicidality as a treatment endpoint.

Stigma surrounding prescribed opioid use undeniably exists, and one-fourth of participants reported feeling discriminated against by healthcare professionals due to such prescriptions.

This study has certain limitations. The RLS opioid registry participants are not representative of the general population, being elderly, nearly all white, and well educated. Therefore, these results cannot be extrapolated to African American patients, Latinx patients, or those with lower educational levels. This homogeneity may be explained by the demographic distribution of RLS, recruitment sources for the registry, and/or physicians' opioid prescription biases, as risk of opioid abuse is relatively low in the elderly [33]. Additionally, the registry is comprised of patient volunteers and is not a consecutive series of patients enrolled by treating centers. Further, many of the participants were referred by clinicians at established RLS Quality Care Centers which may limit the generalizability of the data to those patients treated in academic and urban centers. Some baseline information was based on retrospective recollection (e.g. suicidality, initial stable opioid doses) and is thus subject to those limitations.

The low dose prescribed opioids have become a standard clinical treatment for treatment-refractory and augmented patients with RLS [28, 34]. However, in the relative absence of large-scale data that establishes their long-term safety and efficacy, it is difficult to assess the risks and benefits of these medications for RLS. This RLS opioid registry provides substantiation that, in refractory patients, prescribed opioids are generally used at low doses with good efficacy. Longitudinally over 1 year, roughly one-third of registry participants increased their prescribed opioid dose, though small dose increases were generally the rule, with larger dose increases ( $\geq 25$  MME) in a predictable



small group of sufferers with comorbid pain syndromes, those who only had been on their current opioid for <1 year, had switched opioids to methadone, or had discontinued other non-opioid RLS medications. Long-term follow-up of patients with RLS using prescribed opioids is indicated to better establish their safety and efficacy in this context.

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