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# Treatment initiation and utilization patterns of pharmacotherapies for early-onset idiopathic restless legs syndrome

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ABSTRACT

*Objective/background:* Restless legs syndrome (RLS) is a complex condition associated with circadian rhythm that disrupts sleep and can cause multisystemic consequences. This study assesses pharmacotherapy treatment initiation, estimates annual treatment prevalence, and assesses treatment patterns for early-onset idiopathic RLS.

*Methods:* We used the MarketScan Commercial Claims Database from 2012 to 2019 to conduct a new user retrospective cohort study. Annual treatment prevalence was calculated from a cross-sectional sample. Newly diagnosed adults with early-onset (18–44 years) idiopathic RLS who initiated on and off-label gabapentinoids, dopamine agonists, or levodopa/carbidopa were included. Among monotherapy users who had one year of insurance enrollment, treatment patterns (single fill, continuous use of initiated therapy, switching, and add-on therapy) were examined and mean time on the initial treatment (as a measure of persistence) was calculated.

*Results:* In total, 6,
828 patients were initiated on monotherapy treatment for early-onset idiopathic RLS in which 4,638 met all inclusion criteria. In 2019, annual prevalence of monotherapy treatment of diagnosed patients for ropinirole was 171.3/1,000 patients; 85.0/1,000 patients for pramipexole; and 132.1/1,000 patients for gabapentin. Overall, 22.3% (n = 1,033) of patients maintained their initiated pharmacotherapy for the entire year. Rotigotine had the longest persistence (mean 185.4 [161.4 SD] days) but this user group was the smallest (n = 29). Gabapentin enacarbil, pregabalin, and rotigotine use was low (2.8% total).

*Conclusion:* Ropinirole, pramipexole, and gabapentin were initiated most often for early-onset idiopathic RLS. FDA-approved agents for RLS, including gabapentin enacarbil and rotigotine, were used less frequently. In general, persistence was low for all RLS study drugs examined.



## 1. Introduction

Restless legs syndrome (RLS, also known as Willis-Ekbom Disease) is a complex sensorimotor and sleep disorder associated with circadian rhythm. RLS can either cause or is comorbid with several chronic conditions including psychiatric, cardio-metabolic, and sleep-related conditions, with the latter often the most prevalent given RLS's cardinal feature of symptom manifestation at nighttime [1,2]. The most common sleep-related comorbidities are sleep deprivation and insomnia, which affect sleep quality and subsequent daytime functioning [3–5]. Early detection and long-term management of RLS is critical to improve prognosis and minimize or prevent poor outcomes. If untreated, RLS can cause lost days of productivity, debilitating quality of life, and can lead to onset of or worsening of psychiatric and medical comorbidities. RLS is comprised of both idiopathic (primary) and secondary RLS, with idiopathic RLS being distinct. Secondary RLS occurs due to an underlying medical condition (most commonly pregnancy, renal diseases, iron deficiency, and neuropathic pain) [2,6–8]. Idiopathic RLS is absent of these causes and tends to have a first-degree

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**Abbreviations**

| | |
|---|---|
| DA | dopamine agonists |
| FDA | U.S. Food and Drug Administration |
| ICD-9-CM/ICD-10-CM | International Classification of Diseases, Ninth and Tenth revision, Clinical Modification |
| RLS | restless legs syndrome |
| RCT | randomized controlled trial |

familial history. Early-onset typically occurs between the ages of 20–40 years although pediatric cases are not uncommon, while late-onset occurs after 45 years and older [3,9]. Prevalence of RLS in the general adult population is difficult to characterize, but clinically significant RLS (moderate to severe) is estimated to be between 1.6 and 2.5% overall in the United States (U.S.) [10,11]. Most epidemiological studies were conducted between 2000 and 2015, were cross-sectional, and used varying diagnostic methodologies, and thus these estimates may be either overestimated or underestimated [9]. Furthermore, because the literature has tended to focus on either RLS overall or on secondary RLS, there are few studies on early-onset idiopathic RLS. Assessment of early-onset RLS is important in establishing adequate treatment to control symptoms and to prevent worsening of health-related quality of life.

Both non-pharmacological and pharmacological treatments are key to RLS symptom management. Non-pharmacological treatment primarily consists of lifestyle modifications with an emphasis on moderate and routine exercise, moderation of caffeine intake, reduction in alcohol intake, and sleep hygiene practices [2,3]. Pharmacological treatment consists of dopamine agonists (DAs) and gabapentinoids (i.e., alpha-2-delta ligands at the GABA(A) receptor). DAs are first-line treatment, specifically ropinirole, pramipexole, and rotigotine, which are all approved by the U.S. Food and Drug Administration (FDA) for moderate-to-severe primary RLS. Other DAs formerly experimented with include carbidopa/levodopa, cabergoline, and pergolide [12–14]. Gabapentinoids are also first-line treatment, specifically gabapentin, gabapentin enacarbil, and pregabalin; however, only gabapentin enacarbil is FDA-approved while gabapentin and pregabalin are used off-label [15,16]. There is limited information available on prevalence and distribution of RLS treatments for early-onset idiopathic RLS patients and particularly since gabapentin enacarbil was approved in 2011 and rotigotine re-approved in 2012 (it was initially approved in 2008 but withdrawn due to inconsistent absorption of the patch formulation) [13]. Therefore, the objective of this study is to assess treatment initiation, estimate annual treatment prevalence, and assess treatment patterns of pharmacotherapies initiated among newly-diagnosed early-onset idiopathic RLS patients.

## 2. Materials and methods

### 2.1. Data source

IBM MarketScan® Commercial Claims and Encounters Databases were used [17]. The MarketScan claims database includes medical and pharmacy reimbursement claims incurred in inpatient and outpatient settings. These data are a nationally representative sample of privately insured beneficiaries up to 65 years of age from large employers and health plans in the U.S. MarketScan claims data provide detailed information on patient healthcare utilization with longitudinal follow-up across several years using an encrypted identifier. Clinical diagnosis and medical procedures are encoded using International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification codes (ICD-9-CM/ICD-10-CM). Pharmacy reimbursement claims are used for prescription medication ascertainment and include information on the date of dispensation and days' supply dispensed. The type of medication is encoded using National Drug Codes (NDC). Data from November 1, 2011 to December 31, 2019 were used to establish a study period of 2012–2019, when all comparator agents were available on the market. The MarketScan database is certified as de-identified data, and the present study was approved as exempt by the Institutional Review Board at the University of Florida (IRB approval number: IRB202101924).

### 2.2. Study design

This is a new-user retrospective cohort study and a cross-sectional sample of the cohort was used. A one-year lookback period and one-year follow-up period were anchored on an index date of first prescription fill within 60 days of RLS diagnosis. At least two outpatient RLS diagnoses 30 days apart, but less than 365 days apart were required. The earliest diagnosis date could be November 1, 2011, but the first prescription fill had to occur on January 1, 2012 or after. The one-year lookback period was used for exclusion assessment and washout of all RLS study drugs. Continuous insurance enrollment was required in the one-year lookback period. A schematic of the study design is presented in Fig. S1.

### 2.3. Study population

This study included enrollees who were adults ages 18–44 years, newly diagnosed with RLS and who initiated RLS study drugs within 60 days of first diagnosis. A new diagnosis was determined with the one-year lookback period. RLS diagnosis was determined by ICD-9/ICD-10-CM diagnosis codes in outpatient medical encounter claims. This study examined idiopathic RLS, which cannot be distinguished from secondary RLS with ICD-9/ICD-10-CM codes. Therefore, a presumptive idiopathic RLS definition was used based on literature and published studies to exclude possible secondarily acquired RLS [2,7,18,19]. Specifically, those with Parkinson's disease, pregnancy, renal disease, or iron deficiency in the pre-index period were excluded. A published algorithm for pregnancy was used [20]. Diagnoses for which gabapentinoids are approved were also excluded in the pre-index period because indications for prescribed medications are not available in the MarketScan database. Specifically, those with epilepsy or seizures, postherpetic neuralgia, fibromyalgia, and neuropathic pain were excluded. Neuropathic pain diagnoses were operationalized based on published literature [21].

The cross-sectional sample used for annual treatment prevalence was comprised of those who had newly diagnosed early-onset idiopathic RLS and filled one RLS study drug (monotherapy) within 60 days of diagnosis. The cohort included those with one year of continuous insurance enrollment after first prescription fill available. Only monotherapy users were included in the cohort as we considered those initiated on more than one medication a clinically different population. A new diagnosis was determined by absence of a RLS diagnosis in the one-year lookback period and one-year of continuous insurance enrollment prior to diagnosis. The study cohort was restricted to those diagnosed between January 11, 2011 and 12/31/2018 to allow for one-year of follow-up through 12/31/2019.

The inclusion criteria were: (1) adults ages 18–44 years; (2) a new RLS diagnosis with an additional diagnosis occurring 30 days apart but less than one year apart; (3) continuous insurance

enrollment for 365 days pre-index (index date is the date of first prescription fill); (4) new RLS prescription filled within 60 days of RLS diagnosis; and (5) continuous insurance enrollment for 60-days post-index (for cross-sectional sample) and 365 days post-index (for the cohort). A grace period for continuous insurance enrollment in both the pre-index and post-index periods was not allowed. The exclusion criteria were: (1) no diagnoses for gabapentinoid indications (≥1 condition) during the pre-index period and (2) no secondary RLS conditions (≥1 condition) during the pre-index period.

### 2.4. Exposures

The RLS study drugs examined were: current first-line DAs (pramipexole, ropinirole, and rotigotine), DAs recommended through 2012 (carbidopa/levodopa, cabergoline, and pergolide), gabapentinoids (gabapentin, gabapentin enacarbil, and pregabalin), and concomitance of more than one [13,16]. Current first-line DA medications and gabapentinoids are recommended for moderate-to-severe RLS by treatment guidelines [15,16]. Formerly used DA medications were included in consideration of the earlier years of the study period. Most notably, carbidopa/levodopa is now limited to intermittent use or for mild/infrequent RLS due to long-term risks of augmentation, which is a paradoxical worsening of RLS symptoms and severity over time associated with long-term dopaminergic treatment [12,22,23].

### 2.5. Treatment outcome measurements

Treatment initiation of RLS study drugs was used to estimate annual prevalence of treatment for initiated monotherapy. Annual prevalence of treatment was estimated using all early-onset idiopathic RLS patients initiated on monotherapy treatment with RLS study drugs as the numerator and all early-onset idiopathic RLs patients as the denominator, reported for each calendar year in the study period.

The one-year follow-up period was used to examine treatment patterns by following those initiated on monotherapy treatment who had one year of continuous insurance enrollment post-index available. Specifically, those initiated on first-line DAs, gabapentinoids, and carbidopa/levodopa were followed and those initiated on concomitant use of more than one were excluded. An initial analysis examined cabergoline and pergolide use, but these drugs were too rare and will not be reported further. A grace period of 14 days was allowed for permissible gaps between prescription fills in the main analysis and a grace period of 30 days was allowed for permissible gaps in a sensitivity analysis.

The treatment patterns examined were: those who filled initiated therapy once with no subsequent fill of any study drug (single fill), continuous use of initiated therapy with permissible gaps for 365 days, continuous use of initiated therapy with permissible gaps for less than 365 days, switching to a secondary medication, add-on therapy, and those who intermittently filled (at least one gap).

Mean time on initiated therapy was calculated as a measure of persistence, defined as the number of days from the index date to the end date of the last prescription fill (of initiated therapy), of which a subsequent prescription was not filled within 14 days (permissible gap) or the end of follow-up, whichever occurred first.

A switch was defined as a switch from initiated therapy to a second drug (a pharmacy claim for a second prescription) fewer than 14 days before completion date of initiated therapy; only the first switch from initiated therapy was examined. Add-on therapy was defined as addition of a second drug at least 14 days before completion of initiated therapy, combined with refills of the initiated and secondary drug. Those identified as either switch or add-on therapy may not have continued treatment for the entire study period (i.e., discontinued treatment <365 days).

For treatment pattern analysis, prescription fill dates were adjusted to account for early refills and stockpiling so that calculated gaps are true gaps in therapy and drug on hand. As a hypothetical example, a patient filled a prescription on 5/23/2014 with a 30-day supply and the end date of that supply is 6/22/2014. However, the patient filled their second prescription early on 6/16/2014, so the adjusted fill date of 6/22/2014 is used and the end date of that supply is 7/22/2014; the third prescription fill was on 7/26/2014 which represents a gap of 4 days. The documentation for the methodology used to adjust fill dates is available online [24].

Patient demographics and clinical characteristics (herein baseline characteristics) are described by: age (mean age and age groups), sex, geographic region (northeast, north central, south, west), insurance health plan type, number of unique prescription medications at time of treatment initiation (inclusive of the RLS prescription), prescription drug channel for the RLS prescription (retail or mail order), psychiatric comorbidities, and chronic condition comorbidities.

### 2.6. Statistical analysis

Annual prevalence of treatment was calculated as RLS pharmacotherapy users per 1,000 early-onset idiopathic RLS patients for each RLS study drug.

Treatment patterns were examined for the cohort of monotherapy users who had one year of continuous insurance enrollment available. Treatment patterns are summarized by frequencies and proportions for categorical variables. Means, standard deviations, and medians are used for the persistence measure (mean and median time on initiated therapy). Baseline characteristics are summarized by frequencies and proportions for categorical variables and by means and standard deviations for continuous variables. Treatment patterns and baseline characteristics are reported by RLS study drug initiated.

A sensitivity analysis of treatment patterns using a permissible gap of 30 days was performed. All statistical analyses were conducted using statistical software SAS®, version 9.4 (Cary, NC).

## 3. Results

### 3.1. Treatment initiation and annual prevalence of treatment

In total, there were 6,998 patients identified with newly diagnosed early-onset idiopathic RLS who received a RLS study drug within 60 days of diagnosis. Of those, 6,828 patients filled a monotherapy treatment for early-onset idiopathic RLS. A total of 4,638 patients met inclusion and exclusion criteria for the cohort (Fig. 1): 975 gabapentin users, 46 gabapentin enacarbil users, 54 pregabalin users, 2,124 ropinirole users, 1,303 pramipexole users, 29 rotigotine users, and 107 carbidopa/levodopa users. The demographics and clinical characteristics presented in Table 1 are reported by each study drug and for any RLS treatment overall.

Annual prevalence of treatment by calendar year for those initiated on monotherapy shows ropinirole is the most frequently prescribed drug across all study years, followed by pramipexole until 2016. In 2012, annual prevalence of monotherapy treatment was 201.2 per 1,000 patients for ropinirole; 152.6 per 1,000 patients for pramipexole; and 67.2 per 1,000 patients for gabapentin. After 2016, gabapentin became the second most prescribed drug through end of the study period. In 2019, annual prevalence of monotherapy treatment was 171.3 per 1,000 patients for ropinirole; 85.0 per 1,000 patients for pramipexole; and 132.1 per 1,000 patients for gabapentin. The remaining RLS study drugs collectively represent a

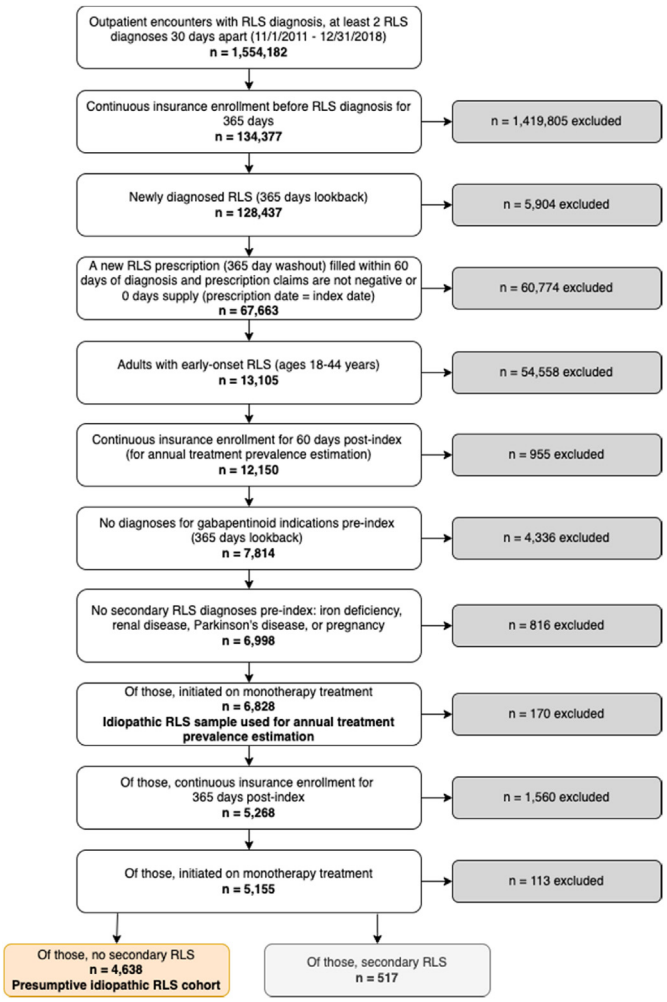


**Fig. 1.** Flow diagram of cohort sample selection.

small proportion. Annual prevalence of treatment by RLS study drug also shows ropinirole, pramipexole, and gabapentin are the most frequently prescribed. Ropinirole and pramipexole show a general decrease over time while gabapentin has increased over time. Annual prevalence of treatment for initiated monotherapy by calendar year is presented in Fig. S2 and by RLS study drug in Fig. S3.

### 3.2. Treatment patterns

For mean time on initiated therapy, persistence ranged from 138.6 (SD 143.5) days to 185.4 (SD 161.4) days with carbidopa/levodopa having the shortest mean persistence and rotigotine the longest mean persistence. The proportion of those who maintained continuous monotherapy treatment on the initiated therapy for the study period (365 days) was highest for pramipexole (23.4%) and lowest for pregabalin (11.1%). Among those who had continuous monotherapy of initiated study drug for less than 365 days, gabapentin enacarbil (19.6%) was the most frequent and rotigotine (3.4%) was the least frequent. Among those who received add-on therapy, the largest proportion was among the rotigotine users (13.8%) and the lowest proportion among ropinirole users (3.2%). Among those who switched from their initiated treatment, gabapentin enacarbil users (17.4%) had the largest proportion and pramipexole (3.5%) had the lowest proportion. Overall, the most frequent treatment pattern was those who had one or more permissible gaps in prescription fills, with the highest proportion among the carbidopa/levodopa users (50.4%) and the lowest proportion among gabapentin enacarbil users (37.0%). This group represents those who filled their initiated treatment intermittently, had add-on therapy outside of the permissible gap window, or switched to a secondary drug outside of the permissible gap window. Examples of the latter group include: (1) a patient was initiated on gabapentin, had a gap of 204 days, and then resumed filling gabapentin; (2) a patient was initiated on ropinirole, had a gap of 117 days, then filled gabapentin; and (3) a patient filled pramipexole for eight months but with more than one gap of 14 days between fills. Treatment patterns among monotherapy users following initiation are presented in Table 2 by RLS study drug and in Fig. 2.

### 3.3. Sensitivity analysis

For sensitivity analysis using a permissible gap of 30 days (Table S1), the proportion of the single fills was the same as the main analysis. Persistence (mean time on initiated therapy) ranged from 164.4 (SD 148.3) days to 212.4 (SD 172.1) days with gabapentin enacarbil having the shortest mean persistence and gabapentin the longest mean persistence, which differs from the main analysis. The second longest mean persistence was for pramipexole (209.5 days, SD 168.5), followed by rotigotine (208.9 days, SD 158.1), ropinirole (208.5 days, SD 167.9), pregabalin (190.0 days, SD 156.4), and carbidopa/levodopa (179.1 days, SD 163.7). All other results were consistent with the main analysis except for gabapentin enacarbil (26.1%) being the most frequent among those who maintained continuous monotherapy treatment (compared with pramipexole in the main analysis). Overall, the most frequent treatment pattern remained those who had one or more permissible gaps in prescription fills, except for gabapentin enacarbil users (10.9%) whose switches were the most common treatment pattern (compared with intermittent fills in the main analysis).

## 4. Discussion

In this study, we examined treatment initiation among patients with newly diagnosed early-onset idiopathic RLS and their treatment patterns during 365 days of follow-up. The mean age of patients is consistent with idiopathic RLS starting earlier in life in contrast to secondary RLS [9]. A recent French case-control study of primary RLS patients showed the mean age of RLS symptom onset was 34.2 (SD 16.4) years among those with moderate to severe RLS, which is close to the mean age of 36.6 years in this sample [25]. Most patients were in the 31–44 years age group, which aligns with early-onset RLS emerging between ages 20 and 40 years, although diagnosis typically occurs in a patient's fourth decade and later and thus it is likely that some patients with early-onset RLS were missed due to a lack of a formal diagnosis [3,26]. Complexities of the healthcare system and limited awareness of RLS among both physicians and patients may contribute to delayed diagnosis [23]. As expected, the proportion of females was higher than males, even after excluding pregnancy for secondary RLS [1,9]. At baseline, patients frequently had psychiatric, cardio-metabolic, and sleep-related comorbidities including anxiety, depression, hyperlipidemia, obesity, hypertension, insomnia, and OSA. The presence of psychiatric conditions and insomnia at baseline are concerning because RLS patients are at risk for long-term consequences including mental health problems, impaired cognition, decreased quality of life, and all-cause mortality [27]. A recent longitudinal cohort study found that RLS severity increased during the COVID-19 pandemic, which corresponded with significant increases in

**Table 1**
Key baseline demographics and clinical characteristics of patients with newly diagnosed, early-onset idiopathic RLS, by initiated monotherapy drug and overall.

| Pharmacotherapy Initiated | Gabapentin | Gabapentin enacarbil | Pregabalin | Ropinirole | Pramipexole | Rotigotine | Carbidopa/ levodopa | Any RLS treatment |
|---|---|---|---|---|---|---|---|---|
| Number of Users | 975 | 46 | 54 | 2,124 | 1,303 | 29 | 107 | 4,638 |
| Age | | | | | | | | |
| Mean (SD) age in years | 35.0 (7.5) | 37.4 (5.9) | 36.5 (7.9) | 36.9 (6.5) | 37.2 (6.3) | 36.8 (6.4) | 37.8 (5.3) | 36.6 (6.7) |
| 18–30, N (%) | 245 (25.1) | 6 (13.0) | 11 (20.4) | 347 (16.3) | 175 (13.4) | 6 (20.7) | 12 (11.2) | 802 (17.3) |
| 31–44, N (%) | 730 (74.9) | 40 (87.0) | 43 (79.6) | 1,777 (83.7) | 1,128 (86.6) | 23 (79.3) | 95 (88.8) | 3,836 (82.7) |
| Female, N (%) | 596 (61.1) | 30 (65.2) | 44 (81.5) | 1,316 (62.0) | 77 (59.1) | 17 (58.6) | 60 (56.1) | 2,833 (61.1) |
| Region, N (%) | | | | | | | | |
| Northeast | 95 (9.7) | 7 (15.2) | 8 (14.8) | 227 (10.7) | 134 (10.3) | 1 (3.5) | 6 (5.7) | 478 (10.3) |
| North Central | 253 (26.0) | 9 (19.6) | 14 (25.9) | 555 (26.1) | 323 (24.8) | 6 (20.7) | 32 (30.2) | 1,191 (25.7) |
| South | 444 (45.5) | 27 (58.7) | 29 (53.7) | 1,084 (51.0) | 612 (47.0) | 18 (62.1) | 51 (47.7) | 2,265 (48.8) |
| West | 177 (18.2) | 2 (4.4) | 3 (5.6) | 249 (11.7) | 228 (17.5) | 4 (13.8) | 18 (16.8) | 681 (14.7) |
| Unknown | 95 (9.7) | 7 (15.2) | 8 (14.8) | 227 (10.7) | 134 (10.3) | 1 (3.5) | 6 (5.7) | 478 (10.3) |
| Health Plan Type, N (%) | | | | | | | | |
| PPO | 588 (60.3) | 35 (76.1) | 34 (63.0) | 1,342 (63.2) | 800 (61.4) | 13 (46.4) | 60 (56.1) | 2,872 (61.9) |
| HMO | 127 (13.0) | 1 (2.2) | 4 (7.4) | 237 (11.2) | 157 (12.0) | 5 (17.9) | 14 (13.1) | 545 (11.8) |
| Non-Capitated POS, Comprehensive, or Other [1] | 232 (23.8) | 10 (21.7) | 14 (25.9) | 478 (22.5) | 306 (23.5) | 10 (34.4) | 28 (26.2) | 1,078 (23.2) |
| Missing | 28 (2.9) | – | 2 (3.7) | 67 (3.2) | 40 (3.1) | 1 (3.4) | 5 (4.7) | 143 (3.1) |
| Number of Unique Medications at Initiation [2], N (%) | | | | | | | | |
| 1-2 | 791 (81.1) | 40 (87.0) | 49 (90.7) | 1,701 (80.1) | 1,059 (81.3) | 27 (93.1) | 86 (80.4) | 3,753 (80.9) |
| 3-4 | 151 (15.5) | 5 (10.9) | 4 (7.4) | 343 (16.1) | 204 (15.6) | 2 (6.9) | 20 (18.7) | 729 (15.7) |
| ≥5 | 33 (3.4) | 1 (2.1) | 1 (1.9) | 80 (3.8) | 40 (3.1) | – | <1% | 156 (3.4) |
| Pharmacotherapy Initiated | Gabapentin | Gabapentin enacarbil | Pregabalin | Ropinirole | Pramipexole | Rotigotine | Carbidopa/ levodopa | Any RLS treatment |
| Prescription Drug Channel, N (%) Retail | 885 (90.8) | 44 (95.7) | 53 (98.1) | 1,948 (91.7) | 1,177 (90.3) | 29 (100) | 99 (92.5) | 4,235 (91.3) |
| Mail | 65 (6.7) | 2 (4.4) | – | 118 (5.6) | 87 (6.7) | – | 3 (2.8) | 275 (5.9) |
| Missing | 25 (2.6) | – | 1 (1.9) | 58 (2.7) | 39 (3.0) | – | 3 (2.8) | 128 (2.8) |
| Comorbidities | | | | | | | | |
| ADHD | 34 (3.5) | – | 2 (3.7) | 67 (3.2) | 44 (3.4) | 1 (3.5) | – | 148 (3.2) |
| Anxiety disorders | 108 (11.1) | 3 (6.5) | 4 (7.4) | 234 (11.0) | 154 (11.8) | 1 (3.5) | 19 (17.9) | 523 (11.3) |
| Depression | 27 (2.8) | 2 (4.4) | 2 (3.7) | 83 (3.9) | 48 (3.7) | 1 (3.5) | 3 (2.8) | 166 (3.6) |
| Hypertension (essential) | 83 (8.5) | 2 (4.4) | 5 (9.3) | 193 (9.1) | 130 (10.0) | 2 (6.9) | 10 (9.4) | 425 (9.2) |
| Hyperlipidemia | 35 (3.6) | 1 (2.2) | 2 (3.7) | 100 (4.7) | 54 (4.1) | – | 5 (4.7) | 197 (4.3) |
| Insomnia | 54 (5.5) | 3 (6.5) | 3 (5.6) | 203 (9.6) | 101 (7.8) | 1 (3.5) | 9 (8.5) | 374 (8.1) |
| Mood disorders [3] | 52 (5.3) | 3 (6.5) | 1 (1.9) | 100 (4.7) | 56 (4.3) | 3 (10.3) | 8 (7.6) | 223 (4.8) |
| Obesity | 19 (2.0) | 2 (4.4) | 2 (3.7) | 32 (1.5) | 21 (1.6) | 1 (3.5) | 2 (1.9) | 79 (1.7) |
| Obstructive sleep apnea | 38 (3.9) | 1 (2.2) | 1 (1.9) | 103 (4.8) | 50 (3.8) | – | 3 (2.8) | 196 (4.2) |

RLS = restless legs syndrome, PPO = preferred provider organization, HMO = health maintenance organization, POS = point-of-service plan, ADHD = attention deficit hyperactivity disorder. [1]Other includes non-capitated POS, exclusive provider organization (EPO), POS with capitation, consumer directed health plan (CDHP), and high-deductible health plan (HDHP); [2]Inclusive of RLS prescription; [3]including bipolar disorders.

sleep disturbances, depression, and anxiety [28]. However, it is important to note that the observed baseline comorbidities were assessed from the point of formal RLS diagnosis and patients may have had RLS for longer. Overall, health-related quality of life among RLS patients is lower than in the general population and is comparable to poor health-related quality of life associated with other chronic illnesses [4,5,9]. Furthermore, both DAs and gabapentinoids carry risks of serious psychiatric adverse effects, e.g., impulse control disorders for DAs and suicidal behavior and ideation for gabapentinoids, which can be more pronounced in patients who have pre-existing mental health comorbidities.

We found that the most frequently initiated pharmacotherapies for early-onset idiopathic RLS were ropinirole, pramipexole, and gabapentin, while the remaining study drugs were used minimally in comparison. Ropinirole and pramipexole maintained prescribing preference by far throughout the study period, although the annual treatment prevalence showed a slight decrease in the later years and an increase in gabapentin. This trend was expected given a recent shift in preference for gabapentinoids over DAs in light of the long-term risk of augmentation associated with chronic dopaminergic treatment [22]. Recent guidelines recommend starting initial treatment with non-dopaminergic therapies, i.e., gabapentinoids, in most cases [16]. The most recent guideline was released in 2016, which may explain why the annual treatment prevalence showed gabapentin moving up to the second most prescribed drug after 2016 through the end of the study period [16]. Augmentation remains a puzzling conundrum and early detection of RLS is critical in minimizing a patient's symptoms so that either dosage increases of DAs or switching from a gabapentinoid to a DA do not lead to augmentation, which is a common reason for long-term treatment discontinuation [15,23]. Additionally, managing symptoms early on (particularly with DAs) is imperative as there may be a reduced response to other treatments following long-term DA use. A randomized controlled trial (RCT) of idiopathic patients with moderate to severe RLS demonstrated reduced response to gabapentin enacarbil after long-term exposure to dopaminergic treatment [29]. This trial was conducted over only a two-week period, however, with a relatively small sample size (n = 45); thus longer studies are warranted [29]. Augmentation is the primary reason carbidopa/levodopa is no longer recommended,

**Table 2**
Treatment patterns among monotherapy users with early-onset idiopathic RLS for up to one year following treatment initiation (main analysis with permissible gap of 14 days).

| Pharmacotherapy Initiated | Gabapentin | Gabapentin enacarbil | Pregabalin | Ropinirole | Pramipexole | Rotigotine | Carbidopa/ levodopa |
|---|---|---|---|---|---|---|---|
| Number of Users | 975 | 46 | 54 | 2,124 | 1,303 | 29 | 107 |
| Mean (SD) time on initiated therapy in days | 176.9 (170.4) | 139.2 (143.1) | 166.2 (152.8) | 176.3 (164.1) | 179.5 (166.3) | 185.4 (161.4) | 138.6 (143.5) |
| Median time on initiated therapy in days | 90.0 | 68.5 | 90.0 | 90.0 | 90.0 | 120.0 | 72.0 |
| Proportion of those with a single fill of initiated therapy only (no subsequent fills of any RLS treatment) | 117 (12.0) | 6 (13.0) | 5 (9.3) | 327 (15.4) | 210 (16.1) | 4 (13.8) | 20 (18.7) |
| Proportion of continuous monotherapy of initiated therapy for 365 days | 216 (22.2) | 6 (13.0) | 6 (11.1) | 480 (22.6) | 307 (23.4) | 6 (20.7) | 12 (11.2) |
| Proportion of continuous monotherapy of initiated therapy for <365 days [a] | 104 (10.7) | 9 (19.6) | 10 (18.5) | 259 (12.2) | 159 (12.2) | 1 (3.4) | 12 (11.2) |
| Proportion of initiators who had an add-on therapy [b,c,d] | 34 (3.5) | – | 5 (9.3) | 68 (3.2) | 45 (3.5) | 4 (13.8) | 4 (3.7) |
| Proportion of initiators who switched to a subsequent therapy [c,d,e] | 49 (5.0) | 8 (17.4) | 4 (7.4) | 77 (3.6) | 45 (3.5) | 2 (6.9) | 5 (4.7) |
| Proportion of initiators who had at least 1 gap >14 days (intermittent fills) [f] | 455 (46.6) | 17 (37.0) | 24 (44.4) | 913 (43.0) | 537 (41.2) | 12 (41.4) | 54 (50.4) |

[a] Two or more fills of initiated therapy with permissible gaps in <365 days and no other drugs filled.
[b] Defined as addition of a second drug at least 14 days before completion of initiated therapy, combined with refill of initiated.
[c] Those with add-on therapy or switch may not have continued treatment for the entire study period (i.e., discontinued treatment <365 days).
[d] Patients with add-on therapy who did not have a second refill are included (n = 53).
[e] Defined as a switch from initiated therapy to a second drug (a pharmacy claim for a second prescription) fewer than 14 days before completion date of initiated therapy and only the first switch from initiated therapy is reported.
[f] This includes those who filled initiated therapy intermittently, switched to subsequent therapy(ies) outside of defined window, or had add-on therapy outside of defined window.

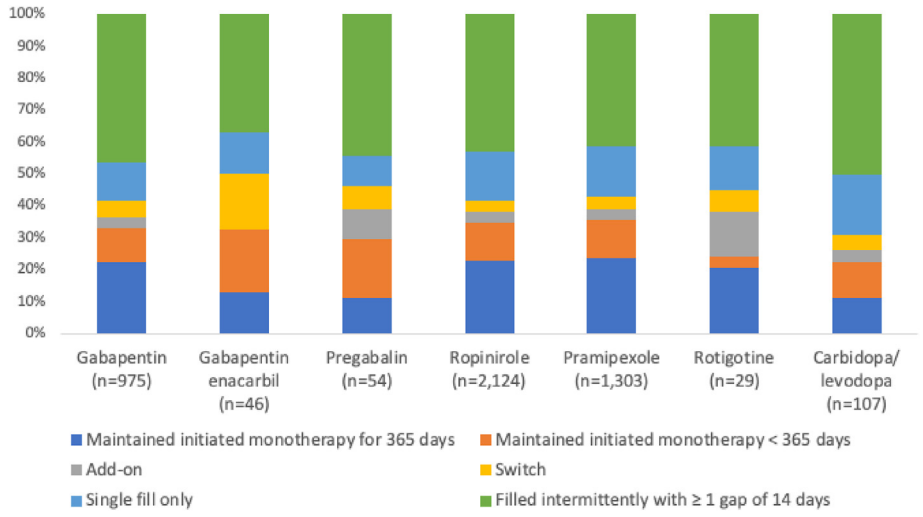


**Fig. 2.** Proportion of patients who initiated monotherapy treatment who maintained initiated therapy, switched to a second medication, added a second medication, had a single fill, or filled intermittently [*color should be used for figure*]. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

yet use of this drug was more frequent than newer FDA-approved drugs including gabapentin enacarbil and rotigotine. It is possible that those initiated on carbidopa/levodopa may have had intermittent symptoms and received it for as needed use.

In most years of the study period, carbidopa/levodopa prescriptions were more frequent than gabapentin enacarbil, rotigotine, and pregabalin, which suggests that providers may be unaware of its risk of augmentation. It is possible that affordability of available generics may be more of an influential factor for initiation rather than FDA-approved use (i.e., carbidopa/levodopa and gabapentin). Although gabapentin enacarbil and rotigotine are FDA-approved for idiopathic RLS, they are the most expensive of all the RLS study drugs and neither have generic formulations available, which could account in part for their limited use [30]. It is also possible that claims were not adjudicated through insurance if these medications were obtained as samples or through manufacturer vouchers. Furthermore, rotigotine has unique adverse effects specific to its patch formulation, including skin reactions [31]. Although pregabalin is recommended by current practice guidelines, it was also minimally initiated across all study years, perhaps due to its cost and/or step therapy requirements since it is in the same class as gabapentin, which is a cheaper alternative [30]. As of July 2019, a generic formulation of pregabalin was approved, and thus its use may increase over time due to decreased costs [32]. Moreover, there is an ongoing placebo-controlled RCT of pregabalin for idiopathic RLS in South Korea that should provide more evidence for its efficacy and safety (ClinicalTrials.gov Identifier: NCT04161027).

In the one year following treatment initiation, both persistence with initiated treatment and the proportion of those who maintained continuous monotherapy treatment throughout the study period were low. Out of the three drugs most frequently initiated (ropinirole, pramipexole, and gabapentin), only about one-fifth maintained continuous monotherapy treatment for the entire study period. When a longer grace period between refills was allowed in the sensitivity analysis, these three user groups only increased by a few percentage points. The low persistence is consistent with the literature. In a study by Kim and Hartzema

assessing adherence and persistence to ropinirole, pramipexole, and gabapentin among newly-diagnosed RLS patients between 2008 and 2014, the mean time to treatment discontinuation was 158 days for both ropinirole and pramipexole and 145 days for gabapentin [33]. This study included all RLS patients, whereas ours was restricted to early-onset idiopathic RLS, indicating that persistence and adherence were improved in our sample of RLS patients. It is encouraging that patients diagnosed with early-onset RLS may be able to continue trialing different pharmacotherapies to find the best treatment option before severity progresses. Nonetheless, out of the total sample, we identified nearly 15% of patients who had a single fill of their initiated therapy and then had no subsequent fills of any study drug for the remainder of the study period. It is possible that a proportion of these patients discontinued treatment early due to adverse events or they may have been incorrectly diagnosed with RLS and ended up having a differential diagnosis; however, we required two RLS diagnoses for study inclusion. It is also possible that some patients did not respond to the initiated therapy and did not follow up to try other options, a likely scenario for those who we identified as filling intermittently or inconsistently. Another explanation is that for some, a proportion did not have moderate to severe RLS and may have had minimal RLS symptoms that could be controlled non-pharmacologically. Although more recent studies have not been conducted to assess treatment patterns with all available comparator drugs, older studies of DA use found similar low levels of adherence and persistence to RLS pharmacotherapies [34,35]. In some cases, low persistence may be desirable if attributable to either improvement in symptoms or limited observed benefit of treatment.

While opioids have emerged as another treatment option, we did not examine them in this study given the emphasis on newly diagnosed, early-onset RLS. At this time, opioids are classified as second-line or third-line treatments and are typically reserved for more severe cases or treatment-resistant/refractory RLS [16]. Although there is some consensus on the benefits of low-dose opioids, given current restrictions on opioids and risks for adverse events, future experimental studies are needed to better weigh the risks and benefits of using this class for idiopathic RLS [23]. A National RLS Opioid Registry has been established which will provide future opportunities to evaluate opioid use for RLS [36]. In general, the evidence cites adverse effects as common reasons for early treatment discontinuation. This may be a factor in the current study given the younger age range of the early-onset patients, as the Kim and Hartzema study found that younger age was associated with lower adherence [33]. This is why we allowed up to 60 days for the first prescription fill in consideration of the younger age group. Overall, the consistency of the current findings with the previous literature suggests inadequate long-term efficacy of current treatments. Our findings suggest that more real-world evidence on the effectiveness of gabapentin enacarbil, pregabalin, and rotigotine are needed to determine if they are better treatment options. We recognize that monotherapy treatment may not be sufficient for all patients, and that add-on therapy may offer greater benefit. One prior study found improvement with pregabalin added to DAs among idiopathic patients who had inadequate responses to monotherapy treatment [37]. This study had a small sample size ($n = 32$) and short follow-up period (8 weeks), however, and thus future studies are needed to evaluate the long-term efficacy and safety of concomitant DA and gabapentinoid use.

There remains an incomplete understanding of the underlying causes and pathophysiology of RLS, which has impeded adequate clinical management as well as development of novel and specific pharmacotherapies. Growing evidence suggests that RLS may be a multi-pathway network disorder rather than a disorder purely attributable to dopaminergic function, suggesting that non-dopaminergic therapeutic targets warrant exploration [38]. Emerging evidence also indicates the possible involvement of hypoxia in RLS pathogenesis. This may partly explain not only the greater prevalence of RLS in regions with high altitude but also why diseases such as OSA and pulmonary hypertension tend to be co-morbid with RLS as lung diseases are associated with hypoxia [9,39–41]. Additionally, the roles of adenosine and glutamate warrant further exploration. Altered adenosine signaling may play a role in RLS via reduced iron stores in the central nervous system, which has in turn been linked to both hyperdopaminergic and hyperglutamatergic states [12]. The role of adenosine in RLS physiology has been recently explored with two RCTs of dipyridamole, a vasodilator that has shown to increase extracellular levels of adenosine in the brain [23,42,43]. Results from these trials appear to be positive, and indicate that continued efforts are being made to identify new pharmacological treatment options. Idiopathic RLS is often a chronic, lifetime disease and it remains currently incurable. The current available pharmacological options do not address the root causes of RLS pathophysiology.

### 4.1. Strengths and limitations

This study is not without limitations. First, pharmacy claims represent a surrogate measure of medication use but we are unable to determine whether the patient consumed the medication as directed. Second, there is potential for misclassification for those identified as idiopathic RLS and for those identified as monotherapy users. Although we operationalized idiopathic RLS based on published literature, conditions used for the presumptive idiopathic definition may have been too restrictive or may not have captured all cases of secondary RLS that did not have a diagnosis code available (e.g., iron deficiency anemia was new to ICD-10-CM codes and therefore, $n = 4$ patients with this condition were not excluded in our algorithm) [2,7,18,19]. Those with monotherapy use may also have filled a concomitant drug that was paid for out of pocket, as several of the study drugs are available through pharmacy discount programs (specifically ropinirole, pramipexole, and gabapentin). Reporting of gabapentin use is conservative as there could have been more gabapentin users given an affordable out-of-pocket cost and availability of generics. However, ropinirole is not used off-label whereas pramipexole has experimentally be used off-label for bipolar depression and major depressive disorder (RCTs conducted in 2004 and 2000, respectively). Third, there is potential for differential exposure misclassification among those prescribed gabapentin given its extensive off-label use for several conditions. We attempted to limit this by excluding on-label indications for gabapentin and gabapentinoids in the pre-index period. Fourth, the data used lack information on RLS severity and symptom frequency, and thus it is possible that there were patients included who did not have moderate to severe RLS for which routine pharmacological treatment is recommended. Finally, the MarketScan database represents privately insured beneficiaries, and the findings may not be generalizable to patients with other types of insurance, without insurance, or who reside outside of the U.S. However, claims-based studies provide a window into view real-world treatment management, and this study is important in raising awareness of the correlation of RLS with other commonly occurring chronic conditions and its contribution to patient outcomes.

The strengths of this study are that it is to our knowledge the first to explicitly examine pharmacotherapy initiation and treatment for early-onset idiopathic RLS, the data used are nationally representative, and all commonly used RLS medications were examined including two of the most recent FDA-approved drugs for primary RLS.

## 5. Conclusion

Ropinirole, pramipexole, and gabapentin were initiated most often for newly diagnosed early-onset idiopathic RLS. Mean time on therapy as a measure of persistence was low for all RLS study drugs examined. The results indicate that use of evidence-based first-line treatments was minimal (specifically gabapentin enacarbil, pregabalin, and rotigotine). This study demonstrates that available pharmacological RLS options are likely insufficient, and continued experimental research in RLS pathophysiology mechanisms, research in therapeutic development, and increased public awareness of RLS are urgently needed.

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The data are not available.

## CRediT authorship contribution statement

**Brianna Costales:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Writing – original draft, Visualization, Project administration, Funding acquisition. **Scott M. Vouri:** Writing – review & editing, Supervision. **Joshua D. Brown:** Writing – review & editing, Supervision. **Barry Setlow:** Writing – review & editing, Supervision. **Amie J. Goodin:** Writing – review & editing, Supervision.

## Declaration of competing interest

None.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2022.05.003.

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