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Original Article

Decline in dopamine agonists prescribing and characteristics of drugs prescribed during ambulatory office visits for restless legs syndrome: the National Ambulatory Medical Care Survey 2007–2015

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ABSTRACT

Objective: To examine prescribing of drugs treating or exacerbating restless legs syndrome (RLS) during U.S. physician office visits for RLS for the years 2007–2015; and to assess potential prescribing predictors of these drugs.

Methods: Using the National Ambulatory Medical Care Survey data, we conducted a retrospective cross-sectional study. We calculated weighted percentages of RLS-related office visits associated with RLS treatment drugs (alpha-2-delta ligands, dopamine agonists, and other drugs used for RLS) and exacerbating drugs. Using logistic regression, we examined the adjusted association between potential predictors and prescribing of major RLS treatment (dopamine agonists and alpha-2-delta ligands) and exacerbating drugs.

Results: A total of 456 RLS-related office visits were included for analysis, representing approximately 9.9 million visits. The weighted percentages of visits with dopamine agonists (excluding levodopa) decreased from 50% to 22% (RR 0.44; 95% CI 0.26, 0.77). A visit to a neurologist was associated with a 76% increase in prescribing of the major RLS treatment drugs compared with a visit to a family/general or internal medicine physician (RR 1.76; 95% CI 1.29, 2.42). RLS exacerbating drugs were listed in 28% (95% CI 21–36) of RLS-related visits, mostly for antidepressants (83%). Younger age groups (18–44 and 45–64) were predictors of RLS exacerbating drug prescribing, compared with the older age group (RR 2.46; RR 2.00, respectively).

Conclusion: Prescribing of dopamine agonists during RLS-related visits decreased during 2007–2015, but prescribing of RLS exacerbating drugs remained high. More investigation is necessary concerning whether clinicians assess the appropriateness of RLS exacerbating drugs for RLS patients before newly prescribing or continuing those drugs. Also, future research would need to investigate what factors contribute to the difference in the RLS treatment prescribing patterns between neurologists and family/general or internal medicine physicians.

1. Introduction

Several drugs have been approved by the Food and Drug Administration for the treatment of restless legs syndrome (RLS): ropinirole, pramipexole, rotigotine, and gabapentin enacarbil [1]. Despite the approval of several RLS drugs and the development of RLS treatment guidelines [2,3], little is known about how frequently RLS drugs are prescribed during physician office visits for RLS. It is plausible that the treatment guidelines and the evidence from clinical trials increased prescribers' preference for dopamine agonists and alpha-2-delta ligands over the years. However, it is not clear how concerns over augmentation associated with dopamine agonists might have counteracted the prescribing of dopamine agonists.

Furthermore, despite the fact that certain antihistamines, antiemetics, antidepressants, and antipsychotics are associated with the exacerbation of RLS [3,4], little is known about how frequent RLS exacerbating drugs are prescribed by clinicians treating RLS patients. As RLS is still an under-recognized and often mistreated disease [5,6], the level of awareness of RLS exacerbating drugs is not expected to be high among clinicians, which can potentially lead to

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unintentional prescribing and continuation of RLS exacerbating drugs while treating RLS patients [4].

To fill the knowledge gap regarding how clinicians prescribe RLS treatment and exacerbating drugs during office visits for RLS, a cross-sectional study was conducted using nationally representative survey data on U.S. physician office visits during the years 2007–2015. As a secondary objective, we examined the adjusted association between potential predictors and prescribing of major RLS treatment and exacerbating drugs.

2. Methods

2.1. Data and study sample

A cross-sectional study was conducted using the 2007–2015 National Ambulatory Medical Care Survey (NAMCS). The NAMCS is conducted annually and is comprised of nationally representative probability samples of non-federally employed office-based U.S. physicians. Prior to 2012, the samples were obtained via a multistage probability design [7]. In the first sampling stage, 112 geographical primary sampling units (PSUs) were sampled. In the second stage, non-federally employed office-based physicians were sampled within PSUs. In the last stage, patient visits were sampled within physician practices during a pre-specified period. Starting 2012, physicians were sampled in the first stage and visits were sampled in the second stage (a stratified two-stage sample) [8]. Each NAMCS visit record has a weight, known as patient visit weight [9]. Estimates generalizable to the U.S. physician office visits can be obtained after accounting for the sampling strategy and weights [10]. Incorrect estimates can be produced when weights are not applied [9]. To produce reliable estimates, at least 30 samples need to be used for estimation and a relative standard error (RSE) need to be less than 30%. A RSE is calculated by dividing the standard error by the estimate, and multiplying the number by 100 [9].

Survey data were collected via paper instruments prior to 2012 and an automated laptop-assisted data collection method was implemented starting in 2012 [11]. The survey gathered information on the patient and office visit characteristics [11]. For patient characteristics, the survey collected information on age, sex, race and ethnicity, pre-specified comorbidities, and payment methods. For office visit characteristics, the survey collected information on physician characteristics, patient's reason for visit, physician's diagnosis, and drugs, both prescription and over-the-counter (OTC) products, newly prescribed or continued during the visits. More details on the survey design and questionnaires can be found elsewhere [12]. Since the survey questionnaire allowed up to eight new or ongoing drugs to be recorded during 2007–2011, the first eight drugs were included for analysis to maintain consistency throughout the study period, as was done in other studies using the NAMCS [13,14]. RLS-related office visits were identified by using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9-CM) code of 333.94.

2.2. Medications

Major RLS treatment drugs were defined as alpha-2-delta ligands (pregabalin, gabapentin, and gabapentin enacarbil) and dopamine agonists (ropinirole, pramipexole, and rotigotine). We also separately measured prescribing of individual classes of RLS treatments: dopamine agonists (excluding levodopa), alpha-2-delta ligands, levodopa, iron, and opioids. Although benzodiazepines are not recommended therapy for RLS [2], we measured benzodiazepine prescribing as they are often prescribed for RLS patients. For dopamine agonists, ropinirole, pramipexole, and rotigotine were measured, but levodopa was not included. For alpha-2-delta-ligands, pregabalin, gabapentin, and gabapentin enacarbil were measured. We included both gabapentin and gabapentin enacarbil, because the survey data did not allow us to differentiate between these two drugs. For RLS exacerbating drug, first-generation antihistamines, dopamine antagonistic antiemetics, antidepressants (selective serotonin reuptake inhibitor (SSRI), serotonin norepinephrine reuptake inhibitor (SNRI), tricyclic antidepressants, and tetracyclic antidepressants), as well as antipsychotics were measured.

2.3. Statistical analysis

Weighted percentages of visits with a prescription for RLS treatment and RLS exacerbating drugs were calculated by dividing the weighted number of RLS-related visits listing those drugs by the weighted number of visits for RLS. The weighted percentages were calculated overall and by combined years (2007–2009, 2010–2012, and 2013–2015). The characteristics of the visits were examined with and without prescriptions for major RLS treatment drugs.

To assess potential predictors for major RLS treatment and exacerbating drug prescribing, logistic regression was used to estimate model-adjusted risk ratios and 95% confidence intervals (CIs), accounting for the clustered nature of the visits and sampling weights [15]. The models included age (18–44, 45–64, and 65 and older), sex, ethnicity/race (non-Hispanic white, and Hispanic or non-Hispanic other), and clinician specialty (general, family, internal medicine, neurology, and other specialties), and combined visit year (2007–2009, 2010–2012, and 2013–2015).

We used up to eight drug records for the primary analysis. To assess the impact of this restriction, a sensitivity analysis was conducted to investigate prescribing of major RLS treatment drugs using the 2014–2015 NAMCS data, which allows records of up to 30 drugs.

This study was conducted using SAS software, version 9.4 (Cary, NC) and SAS-callable SUDAAN statistical software version 11.0.1 (Research Triangle Institute, Research Triangle Park), to account for the complex survey design. This study was exempt by the Institutional Review Board at the University of Florida.

3. Results

A total of 456 samples of physician office visits with a diagnosis of RLS were identified during the years 2007–2015. When weighted to the U.S. population, the number represents approximately 9.9 million visits. The major RLS treatment drugs (ropinirole, pramipexole, rotigotine, pregabalin, gabapentin, and gabapentin enacarbil) were listed in 44% (weighted; 95% CI 35–54) of the visits. The characteristics of these visits overall and by the presence of prescription for the major RLS treatment drugs are available in Table 1. Overall, 36% (weighted; 95% CI 27–45) of the visits were associated with a prescription for the dopamine agonists (ropinirole, pramipexole, and rotigitoine), and 14% (weighted; 95% CI 9–18) of the visits were associated with a prescription for the alpha-2-delta ligands (gabapentin, gabapentin enacarbil, or pregabalin). The weighted percentages by combined years (2007–2009, 2010–2012, and 2013–2015) for major RLS treatment drugs, dopamine agonists (excluding levodopa), and alpha-2-delta ligands are available in Fig. 1. The weighted percentages of visits with major RLS treatment drugs were 54% (95% CI 41–69), 39% (95% CI 28–51), and 36% (95% CI 16–56) during 2007–2009, 2010–2012, and 2013–2015, respectively. The weighted percentages of visits with dopamine agonists (excluding levodopa) were 50% (95% CI 36–63), 32% (95% CI 20–44), and 22% (95% CI 8–36) during 2007–2009, 2010–2012, and 2013–2015, respectively. The

Table 1
Characteristics of office visits for restless legs syndrome.

	Major RLS Treatment Drug Prescribed	Major RLS Treatment Drug Not Prescribed	Overall
	N sample (%) N weighted to all ambulatory US visits (%)		
	254 (56)	202 (44)	456
	4,397,779 (44)	5,495,270 (56)	9,893,049
Age, years			
18–44	37 (15)	39 (19)	76 (17)
	655,650 (15)	308,566 (16)	1,564,216 (16)
45–65	118 (46)	87 (43)	205 (45)
	1,708,391 (39)	2,231,816 (41)	3,940,206 (40)
65 and over	99 (39)	76 (38)	175 (38)
	2,033,738 (46)	2,354,889 (43)	4,388,627 (44)
Gender			
Female	170 (67)	138 (68)	308 (68)
	2,920,471 (66)	3,757,645 (68)	6,678,116 (68)
Male	84 (33)	64 (32)	148 (32)
	1,477,308 (34)	1,737,625 (32)	3,214,933 (32)
Race/Ethnicity			
Non-Hispanic White	222 (87)	178 (88)	400 (88)
	3,664,552 (83)	3,961,105 (72)	7,625,657 (77)
Hispanic or Non-Hispanic Other	32 (13)	24 (12)	56 (12)
	733,227 (17)	1,534,166 (28)	2,267,392 (23)
Comorbidities			
Depression	62 (24)	41 (20)	103 (23)
	1,180,600 (27)	1,839,267 (33)	3,019,867 (31)
Hypertension	94 (37)	71 (35)	165 (36)
	1,984,706 (45)	2,558,965 (47)	4,543,671 (46)
Hyperlipidemia	54 (21)	45 (22)	99 (22)
	902,014 (21)	1,787,163 (33)	2,689,177 (27)
Specialty			
General or family practice and internal medicine	77 (30)	91 (45)	168 (37)
	2,272,388 (52)	3,888,164 (71)	6,160,553 (62)
Neurology	117 (46)	53 (26)	170 (37)
	1,146,759 (26)	665,165 (12)	1,811,924 (18)
Other Specialties	60 (24)	58 (29)	118 (26)
	978,631 (22)	941,941 (17)	1,920,572 (20)
Year			
2007–2009	83 (33)	56 (28)	139 (30)
	2,152,182 (55)	1,776,744 (45)	3,928,926 (40)
2010–2012	98 (39)	76 (37)	174 (38)
	1,226,251 (39)	1,912,537 (61)	3,138,788 (32)
2013–2015	73 (29)	70 (35)	143 (31)
	1,019,346 (36)	1,805,990 (64)	2,825,335 (28)

Abbreviation: RLS – restless legs syndrome.
Major restless legs syndrome (RLS) treatment drugs: dopamine agonists (ropinirole, pramipexole, rotigotine) and alpha-2-delta ligands (gabapentin, gabapentin enacarbil, pregabalin).

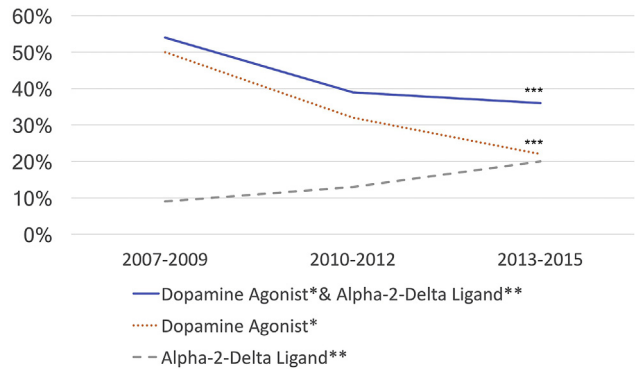

Fig. 1. Unadjusted Weighted Percentages of Office Visits with Major RLS Treatment Drugs by Year (%).
Abbreviation: RLS – restless legs syndrome.
*Dopamine agonists: ropinirole, pramipexole, rotigotine. **Alpha-2-delta ligands: gabapentin, gabapentin enacarbil, pregabalin. ***p-value <0.05 for comparison with year 2007–2009. Some visits were associated with both dopamine agonists (not excluding levodopa) and alpha-2-delta ligand.

weighted percentages of visits with alpha-2-delta ligands were 9% (95% CI 2–17), 13% (95% CI 7–20), and 20% (95% CI 6–33) during 2007–2009, 2010–2012, and 2013–2015, respectively.

The overall weighted percentages of visits with levodopa, iron, benzodiazepines, opioids, and RLS exacerbating drugs during 2007–2015 can be found in Fig. 2. Among the visits not associated with major RLS treatment drugs, 29% (weighted; 95% CI 20–38) were associated with non-major RLS treatment drugs (levodopa, iron, benzodiazepines, and opioids). The weighted percentages of visits associated with non-major RLS treatment drugs were 34% (95% CI 23–45), 30% (95% CI 19–42), and 32% (95% CI 11–52), during the years 2007–2009, 2010–2012, and 2013–2015, respectively.

Overall, RLS exacerbating drugs were listed in 28% (weighted; 95% CI 21–36) of visits. Among the visits associated with RLS exacerbating drugs, 83% (weighted; 95% CI 73–93) were associated with antidepressants. The weighted percentages of visits with RLS exacerbating drugs were 25% (95% CI 15–36), 33% (95% CI 21–44), and 30% (95% CI 12–47) during 2007–2009, 2010–2012, and 2013–2015, respectively. Among the RLS-related visits associated with the major RLS treatment drugs, 35% (weighted; 95% CI 26–45) of the visits were also associated with the RLS exacerbating drugs, and 29% (weighted; 95% CI 20–38) of the visits were associated with antidepressants.

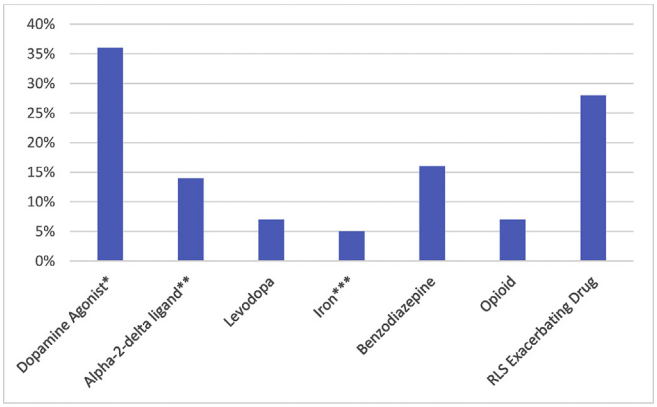

Fig. 2. Overall Unadjusted Weighted Percentages of Drugs Prescribed during Office Visits for RLS during 2007–2015 (%).
Abbreviation: RLS – restless legs syndrome.
*Dopamine agonists: ropinirole, pramipexole, rotigotine. **Alpha-2-delta ligands: gabapentin, gabapentin enacarbil, pregabalin. ***as the unweighted number of visits associated with iron was fewer than 30, the estimate is unreliable. The analysis captured both prescription and over-the-counter (OTC) iron products, but their prescription/OTC status could not be measured.

The weighted percentages of dopamine agonists, alpha-2-delta ligands, non-major treatment RLS drugs, RLS exacerbating drugs, and antidepressants by physician specialties are available in Supplementary Table 1. The names and weighted percentages of individual drugs identified as RLS exacerbating drugs are available in Supplementary Table 2.

In the analysis assessing the potential predictors of major RLS treatment drug prescribing, a visit to a neurologist was associated with a 76% increase in prescribing of the major RLS treatment drugs compared with a visit to a family/general or internal medician physician (adjusted RR 1.76; 95% CI 1.29, 2.42) (Table 2). Younger age groups (age 18–44 and 45–64) were associated with an increase in prescribing of the RLS exacerbating drugs, compared with an older age group (65 or older) (adjusted RR 2.09 95% CI (1.25, 3.50) and adjusted RR 1.82 95% CI (1.06, 3.10), respectively) (Table 2).

Table 2
Predictors of major RLS[a] treatment and RLS[a] exacerbating drugs.

	Use of Dopamine Agonists[b] or Alpha-2-delta ligand[c]	Use of RLS Exacerbating Drug
	Risk Ratio (95% confidence interval)	
Age, years		
18–44	0.79 (0.46, 1.34)	2.46 (1.33, 4.57)
45–64	0.89 (0.62, 1.26)	2.00 (1.05, 3.79)
65 and over	1.0	1.0
Gender		
Female	1.09 (0.77, 1.54)	1.03 (0.65, 1.65)
Male	1.0	1.0
Race/ethnicity		
Non-Hispanic White	1.0	1.0
Hispanic and Non-Hispanic Other	0.72 (0.38, 1.36)	1.08 (0.54, 2.17)
Specialty		
General/Family practice or internal medicine	1.0	1.0
Neurology	1.76 (1.29, 2.42)	1.00 (0.62, 1.62)
Other specialties	1.36 (0.86, 2.16)	1.33 (0.79, 2.26)
Year		
2007–2009	1.0	1.0
2010–2012	0.72 (0.49, 1.06)	1.24 (0.71, 2.18)
2013–2015	0.63 (0.40, 0.99)	1.43 (0.81, 2.50)

[a] RLS: restless legs syndrome.
[b] Dopamine agonists: ropinirole, pramipexole, rotigotine.
[c] Alpha-2-delta ligands: gabapentin, gabapentin enacarbil, pregabalin.

Visits during 2013–2015 were associated with a 37% reduction in prescribing of the major RLS treatment drugs, compared with the ones during 2007–2009 (adjusted RR 0.63; 95% CI 0.40, 0.99). Visits during 2013–2015 were associated with a 56% reduction in prescribing of dopamine agonists (ropinirole, pramipexole, rotigotine), compared with the ones during 2007–2009 (adjusted RR 0.44; 95% CI 0.26, 0.77). An increase in prescribing of alpha-2-delta ligands (gabapentin, gabapentin enacarbil, and pregabalin) during 2007–2015 was not statistically significant (adjusted RR 1.69; 95% CI 0.72, 3.95).

In the sensitivity analysis using the 2014–2015 NAMCS data which allowed records of up to 30 drugs, the raw number of major RLS treatment drugs increased from 36 to 39, changing the weighted percentage from 32% (95% CI 4–61) to 35% (95% CI 5–65).

4. Discussion

Using a representative sample of office visits to non-federally employed U.S. physicians, we conducted a cross-sectional study examining drugs continued or prescribed during ambulatory office visits for RLS. The weighted percentages of RLS-related visits associated with dopamine agonists (ropinirole, pramipexole, rotigotine) decreased by 56% during 2007–2015. Overall, one-fourth of RLS-related visits were associated with RLS exacerbating drugs, consisting mostly of antidepressants. Among the potential prescribing predictors assessed in the analysis, a visit to a neurologist was a predictor of major RLS treatment drug prescribing. Furthermore, younger age was a predictor of RLS exacerbating drug prescribing.

One of the reasons for the overall decrease in the percentages of visits associated with dopamine agonists (excluding levodopa) may be found from a concern over augmentation associated with dopamine agonists. Although alpha-2-delta ligands are unlikely to cause augmentation [16], alpha-2-ligand prescribing during 2013–2015 was not high enough to maintain the prescribing rate of major RLS treatment drugs found during 2007–2009. During the later years explored in the study, non-major RLS treatment drugs or non-pharmacological treatments could have been prescribed or recommended instead of dopamine-agonists. We assessed whether there was an increase in prescribing of non-major RLS treatment drugs, but the small sample size made it difficult to compare the percentages of non-major RLS treatment drug prescribing between the earlier and the later study years.

The current study found that a visit to a neurologist was a predictor of major RLS treatment drugs prescribing. Given that RLS has been under-recognized in the general population and even within medical communities, a concern has existed over misdiagnosis and mistreatment of RLS, especially by non-specialists [5,6]. Physicians' unfamiliarity with RLS and RLS treatment drugs could have contributed to the difference in the percentages of major RLS treatment drug prescribing found in this study. Conversely, it is plausible that RLS patients visiting neurologists had more severe RLS than those visiting non-neurologists, and, thus, they required treatment with the major RLS treatment drugs. More research is necessary to investigate what patient and clinician characteristics contributed to the difference in the percentages of major RLS treatment drug prescribing between neurologist and family/general or internal medicine physician visits.

To date, little information is available about how frequently RLS exacerbating drugs are prescribed for RLS patients. The current study found a high percentage of RLS-related visits associated with RLS exacerbating drugs, particularly in visits made by younger RLS patients. Antidepressants (selective serotonin reuptake inhibitor (SSRI), serotonin norepinephrine reuptake inhibitor (SNRI), tricyclic antidepressants, and tetracyclic antidepressants) were the most

frequently prescribed RLS exacerbating drugs. This may be attributable to the fact that depression is a common co-morbid condition of RLS [17–20]. Similarly, a French pharmacovigilance study reported that antidepressant were one of the most frequently reported drug classes among the RLS-related adverse drug reaction reports [21]. Due to the nature of the data used in this study, it was difficult to investigate whether the clinicians were aware that the antidepressants could cause or exacerbate RLS; or whether they evaluated the appropriateness of prescribing or continuing antidepressants for RLS patients.

Before concluding that the high percentage of antidepressant prescribing is an alarming issue, one needs to note that the effect of antidepressants to initiate or worsen RLS may vary across classes of antidepressants [22]. One study reported that, among patients treated with various antidepressants, the proportion of patients experiencing RLS symptom initiation and exacerbation was highest with mirtazapine (28%), but lower with other antidepressants (5–10%) [23]. In addition, given that concurrent treatment of depression and RLS is recommended in some cases of moderate to severe depression [17], visits associated with antidepressants in this study might have been made by RLS patients experiencing moderate to severe depression and therefore requiring therapy.

Several limitations exist within this study. First, the prescription data in the NAMCS were not validated against pharmacy dispensing records. Although there is a chance that patients did not fill prescriptions recorded in the questionnaire in the pharmacy, the questionnaire data still allows one to examine the prescribing trend during RLS-related visits. Second, the survey did not allow us to differentiate between gabapentin enacarbil and gabapentin. Because of that reason, both gabapentin and gabapentin enacarbil were included when measuring the major RLS treatment drugs and alpha-2-delta ligands. Third, because of a small number of samples, analyses by individual drug and by individual year were not possible. Instead, the analyses were conducted by drug class and by combining multiple years, which helped reduce the variability of the estimates. The small sample size also made it difficult to compare estimates between earlier and later years and across physician specialties for some of the outcome measures, such as prescribing of antidepressants. Fourth, as the validity of RLS diagnostic criteria has been unsatisfactory [24], there is a chance that some of the RLS diagnoses recorded in the questionnaires may have been misdiagnosed ("RLS mimics"). Fifth, as the analysis included up to eight drugs from each visit, underestimation of study outcomes may be a possibility. The result of the sensitivity analysis, which included up to 30 drugs, did not differ meaningfully from the original estimates. The impact of the restriction on the number of drugs used for analysis is not expected to be substantial for the entire study period.

These limitations notwithstanding, the results of our study provide information regarding the areas of RLS management that need to be further investigated to improve the quality of RLS patient care in ambulatory care settings. First, future research is necessary to investigate what contributes to the difference in the percentages of major RLS treatment drug prescribing between visits to neurologists and visits to family/general or internal medicine physicians. A difference in RLS severity between patients visiting family/general or internal medicine physicians and those visiting neurologists is one of the most likely contributing factors. However, it is important to note that RLS is a common condition, often under-recognized and mismanaged in primary care settings [5,6]. Therefore, it is necessary to assess whether unfamiliarity with RLS and RLS treatment guidelines in family/general or internal medicine physicians is a cause for the difference in the percentages of major RLS treatment drug prescribing between visits to neurologists and visits to family/general or internal medicine physicians. Furthermore, it is important to note that some internal medicine physicians specialize in sleep medicine, which could not be measured in this study. For future research, it would be of interest to investigate whether there is a difference in prescribing of major RLS treatment drugs between physicians with specialty training in sleep medicine and those without. Second, the percentage of RLS-related visits associated with RLS exacerbating drugs was high, particularly with antidepressants. Future study is necessary to investigate how often clinicians assess the appropriateness of antidepressants and other RLS exacerbating drugs prescribed or continued during RLS-related visits. Additionally, more research and treatment guidelines for RLS patients with depression are necessary to aid clinicians to make an evidence-based decision and use an appropriate class of antidepressants for depression.

5. Conclusion

Overall, the percentages of RLS-related visits associated with the prescription of dopamine agonists (excluding levodopa) declined during the years 2007–2015. Conversely, the percentage of RLS-related visit associated with RLS exacerbating drugs remained high, and mostly consisted of antidepressants. More investigation is necessary to determine whether clinicians evaluate the appropriateness of antidepressants and other RLS exacerbating drugs during physician office visits for RLS. In addition, there is a need to investigate what factors contribute to the difference in percentages of major RLS treatment drug prescribing between visits to neurologists and visits to family/general or internal medicine physicians.

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Conflict of interest

None.

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The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.10.028.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2018.11.011.

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