Nature and Science of Sleep

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ORIGINAL RESEARCH

Exploring the Top 50 Drugs Associated with Restless Legs Syndrome Based on the FDA Data from 2004 to 2024

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Background: Drugs-associated restless legs syndrome(RLS) can significantly impact patients' quality of life. This study aims to identify the 50 most common drugs-associated with RLS in the FDA Adverse Event Reporting System (FAERS) database and track its epidemiological characteristics.

Methods: We extracted reports of adverse drug events related to restless legs syndrome from the FAERS database, covering the period from Q1 2004 to Q3 2024. We compiled a list of the 50 most frequently reported drugs based on RLS reports. Four risk signal detection methods were employed to assess whether valid signals were triggered by these drugs: Reporting Odds Ratio, Proportional Reporting Ratio, Multi-item Gamma Poisson Shrinker, and Information Component from the Bayesian Confidence Propagation Neural Network. Logistic regression evaluated risk factors, and the Weibull Shape Parameter (WSP) test analyzed time-to-onset (TTO).

Results: A total of 16,410 reports were linked to RLS, with sodium oxybate being the most common (648 cases, 3.9%). Nervous system medications comprised 31.3% of cases. Of the 50 drugs, 27 showed valid risk signals; only 6 were consistent with FDA labels. Risk factors included age under 44, weight over 64 kg, female gender, and 24 specific drugs. TTO analysis revealed that most drugs exhibited early onset patterns.

Conclusion: Our study highlights drugs potentially linked to drug-associated RLS emphasizing the need to consider these risks in clinical practice.

Keywords: restless legs syndrome, risk signal, FAERS, real-world data analysis, pharmacovigilance, drug-associated

Introduction

Restless legs syndrome (RLS; also known as Willis–Ekbom disease) is a common neuro-sensory disorder characterized by an intense urge to move the legs, particularly when at rest or before sleep. This condition worsens during the night and at rest, significantly impacting individuals' quality of life and mental health.[1] Over the years, RLS has been a common yet often undiagnosed condition, frequently underestimated. The prevalence of RLS among individuals aged 20 to 79 worldwide is approximately 7.12%, with a higher rate in women (8.27%) compared to men (5.98%). Most studies show that RLS prevalence increases with age, peaking around 60 years. Factors such as being female, older age, depression, and metabolic disorders (like diabetes and iron deficiency) increase the risk of developing RLS.[2]

The exact mechanisms underlying RLS remain unclear, although brain iron deficiency is widely recognized as a pathological mechanism.[3] However, an increasing body of research indicates that disruptions in dopamine levels, as well as changes in the glutamatergic and adenosinergic systems, are linked to the pathophysiology of RLS.[4–6] Genetic factors are also associated with RLS, as a significant proportion of patients report a family history of the condition. Twin studies have shown that identical twins exhibit a higher concordance rate for RLS compared to fraternal twins,[7] over the past few decades, several large genome-wide association studies have identified more than 20 risk loci, with MEIS1

Received: 24 December 2024
Accepted: 11 April 2025
Published: 15 May 2025

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confirmed as the strongest genetic risk factor for RLS.[8–10] However, the genetic architecture of RLS remains elusive due to factors such as population stratification, sample selection, and statistical analysis methods.

In addition to its primary associations with conditions such as renal failure (specifically end-stage renal disease necessitating hemodialysis), iron deficiency, and pregnancy, RLS may also be linked to the use of specific medications.[11] Medications can potentially trigger the onset of RLS or exacerbate symptoms in individuals already diagnosed with the condition. However, current research on the pathogenesis of drug-associated RLS is still in its preliminary stages and has not been fully elucidated. Recent evidence suggests that it may be associated with pharmacological effects on multiple receptor systems and neurotransmitter pathways.[12] Common classes of medications that can induce RLS include antipsychotics, antidepressants, and anticonvulsants.[13] Additionally, the development of drug-associated RLS is influenced by individual sensitivity, medication dosage, concurrent use of multiple drugs, and other risk factors such as age, smoking, and gastrointestinal disorders.[14]

The latest treatment guidelines recommend the use of α2δ ligand medications (gabapentin, gabapentin enacarbil, and pregabalin) for RLS in adults, rather than the dopamine agonists (pramipexole, ropinirole, and rotigotine) that have been widely used in clinical practice. Although dopaminergic therapy is initially highly effective, it can lead to acute adverse reactions (such as nausea, vomiting, and somnolence), as well as a worsening of symptoms over time with long-term use, known as augmentation.[15] Augmentation refers to the progressive exacerbation of the intensity and duration of RLS symptoms, which develops over a period of months to years following exposure to dopaminergic agents. This phenomenon is characterized by one or more of the following manifestations: an earlier onset of symptoms compared to the period before dopaminergic treatment (for example, shifting from nighttime to daytime), a decreased latency to symptom onset during sedentary activities, and/or the extension of symptoms to additional areas of the body.

To our knowledge, most existing literature on drug-associated RLS consists of case reports and reviews, with no comprehensive systematic studies evaluating the association between drugs and RLS in The Food and Drug Administration Adverse Event Reporting System (FAERS). Therefore, we conducted this study focusing on the pharmacological classification of drugs known to associated with RLS, while also aiming to identify high-risk medications for RLS that have not yet been clearly linked to the condition, thereby providing references for the safety of clinical drug use. FAERS is the largest adverse event reporting database globally, recording individual case safety reports (ICSRs), and has been utilized in numerous high-quality studies.[16,17] It provides extensive data to identify drug-related risk signals and offers critical information for regulatory decisions made by clinicians. This study encounters certain limitations. While limitations in the completeness of the ICSRs, the inability to establish a definitive causal relationship or differentiate between exacerbation or new onset RLS limit the analysis of FAERS, it provides extensive data to identify drug-related risk signals to identify a list of drugs associated with RLS that may be useful to clinicians.

Methods

Data Sources

Data from the first quarter of 2004 to the third quarter of 2024 was downloaded from FAERS (FAERS Quarterly Data Extract Files). Each file contains seven types of data: DEMO (patient demographics), REAC (all MedDRA terms encoded for events), DRUG (drug/biologic information), OUTC (patient outcomes), RPSR (report source), THER (start and end dates of drug therapy), and INDI (indications for drug use).

Identification of Target Data

In FAERS, adverse events (AEs) are standardized using the Preferred Terms (PT) from the MedDRA 25.0. We searched the PT column for "restless legs syndrome" (MedDRA code: 10058920) to identify drugs associated with RLS and downloaded all relevant reports. Following FDA guidelines, we removed duplicate data. If cases had the same CASEID, we retained the most recent report based on FDA_DT; if both CASEID and FDA_DT were identical, we kept the report with the larger PRIMARYID. After the initial removal of duplicates, some PRIMARYID duplicates were still found, leading to a secondary round of duplicate removal.

Statistical Analysis and Risk Signal Detection

In this study, we utilized R software (version 4.3.2, RStudio) for data processing and analysis. First, we conducted descriptive analyses to summarize the clinical characteristics of patients with drug-associated RLS, including gender, weight, age, and reporting country. Next, we listed the 50 most common drugs associated with reported RLS events and classified them according to the Anatomical Therapeutic Chemical (ATC) classification system (https://www.who.int/tools/atc-ddd-toolkit/atc-classification). To identify potential risk signals for RLS, we employed four methods: Reporting Odds Ratio (ROR),[18] Proportional Reporting Ratio (PRR),[19] Bayesian Confidence Propagation Neural Network (BCPNN),[20] and Empirical Bayesian Geometric Mean (EBGM).[19] All four methods were calculated based on a 2×2 contingency table, with specific calculation criteria detailed in Table 1. To minimize bias, reduce the false positive rate, and strengthen the detection threshold, we required that all four methods meet the criteria simultaneously to confirm a valid risk signal. This comprehensive approach enhanced the accuracy and reliability of risk signal detection, providing robust data support for subsequent drug safety assessments and regulatory decisions.

We extracted FAERS reports containing patient information (gender, age, weight) and analyzed only those with complete ICSRs. For drugs that generated valid signals and met the criterion a>40, we conducted univariate and multivariate logistic regression analyses using RStudio to identify the presence of risk factors associated with drug-associated RLS, p-value of < 0.05 was considered statistically significant.

In the final stage of this study, we analyzed the onset time of adverse reactions associated with drugs that generated significant risk signals. The time to onset (TTO) of adverse reactions was defined as the time interval between the date of the adverse event (EVENT_DT) and the date of drug use initiation (START_DT). To ensure the accuracy of calculations involving reports with date input errors (ie, where EVENT_DT precedes START_DT), we excluded entries with inaccurate dates and specific data omissions, we used the median, interquartile range, and Weibull shape parameter (WSP) tests to evaluate TTO. The Weibull distribution is characterized by two parameters: the scale parameter (α) and the shape parameter (β).[21] The scale parameter dictates the distribution's scale or width, whereas the shape parameter influences the configuration of the distribution curve. In the analysis of TTO, the shape parameter was employed to predict the hazard of AEs over time, classifying outcomes into early, random, or wear-out failure. A shape parameter and its 95% CI both less than 1 indicate a decreasing risk (early failure), values approximately equal to 1 with a CI encompassing 1 suggest a constant risk (random failure), and values greater than 1 with a CI exceeding 1 imply an increasing risk (wear-out failure).

Result

Basic Characteristics of RLS-Related ADE Reports

The entire research process is illustrated in Figure 1. Data from the FAERS database was retrieved, resulting in 53,463,446 adverse drug events (ADEs), of which 16,410 (0.03%) were associated with drug-associated RLS. As

Table 1 Four Major Algorithms Used for Risk Signal Detection

Algorithms	Equation	Criteria
ROR	ROR=ad/b/c 95% CI=$e^{\ln(ROR)\pm1.96(1/a+1/b+1/c+1/d)^{0.5}}$	Lower limit of 95% CI>1, a≥3
PRR	PRR=a(c+d)/c/(a+b) χ^2=[(ad-bc)^2](a+b+c+d)/[(a+b)(c+d)(a+c)(b+d)]	PRR≥2, χ^2≥4, a≥3
BCPNN	IC=$\log_2$a(a+b+c+d)(a+c)(a+b) 95% CI= E(IC) ± 2V(IC)^0.5	IC025>0
MGPS	EBGM=a(a+b+c+d)/(a+c)/(a+b) 95% CI=$e^{\ln(EBGM)\pm1.96(1/a+1/b+1/c+1/d)^{0.5}}$	EBGM05>2

Notes: a, number of reports containing both the target drug and target adverse drug reaction; b, number of reports containing other adverse drug reaction of the target drug; c, number of reports containing the target adverse drug reaction of other drugs; d, number of reports containing other drugs and other adverse drug reactions.
Abbreviations: 95% CI, 95% confidence interval; χ2, chi-squared; IC, information component; IC025, the lower limit of 95% CI of the IC; E(IC), the IC expectations; V(IC), the variance of IC; EBGM, empirical bayesian geometric mean; EBGM05, the lower limit of 95% CI of EBGM.

https://doi.org/10.2147/NSS.S513538

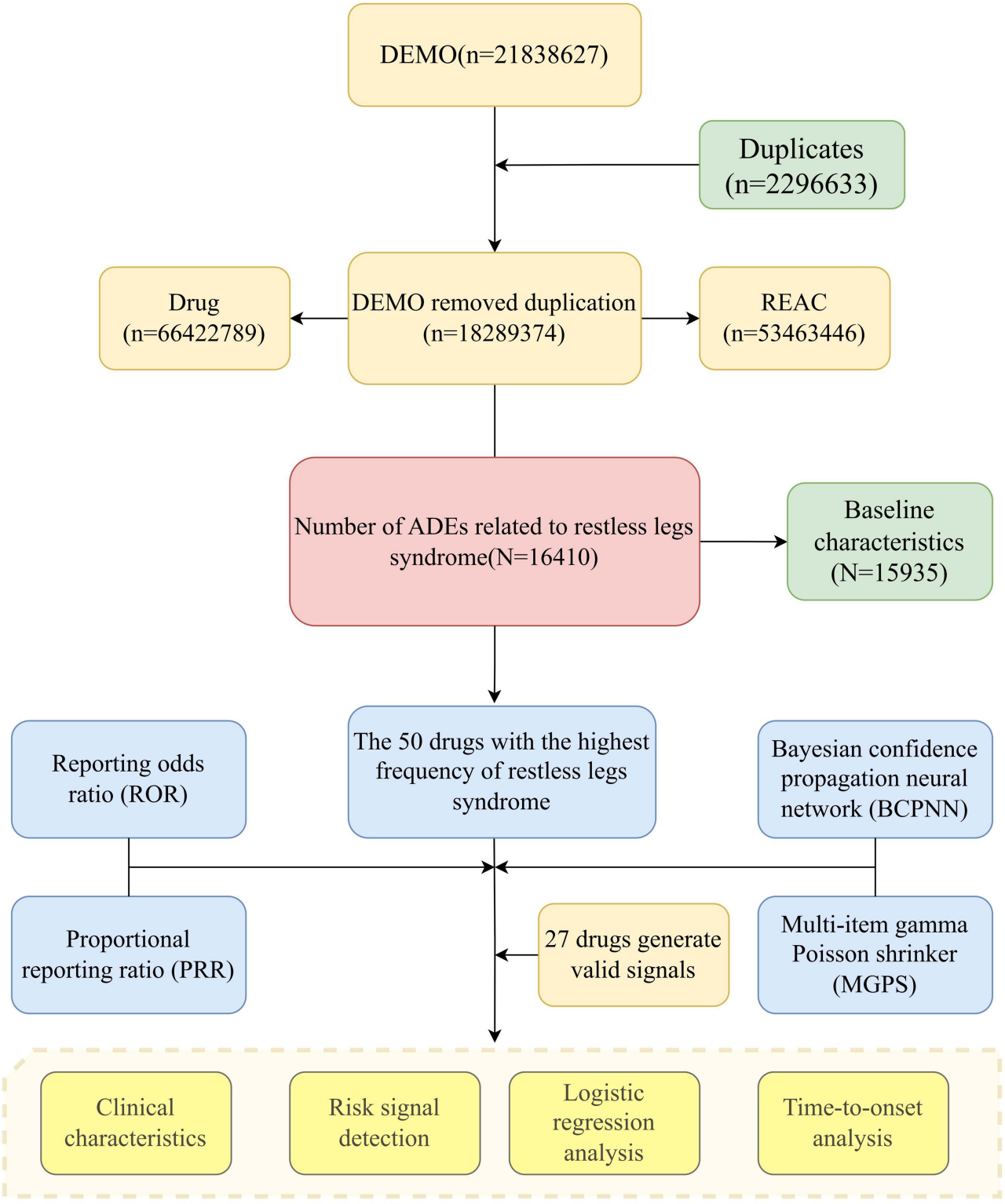


Figure 1 Flow chart for identification of RLS reports of suspected ADEs.

shown in Figure 2, the highest number of reports occurred in 2019, with 1212 cases, and there was an overall upward trend in reports from 2004 to 2024. A total of 15,935 patients were included in this study, the clinical characteristics of these patients are detailed in Table 2. Reports from females (9902 reports, 62.1%) were significantly higher than those

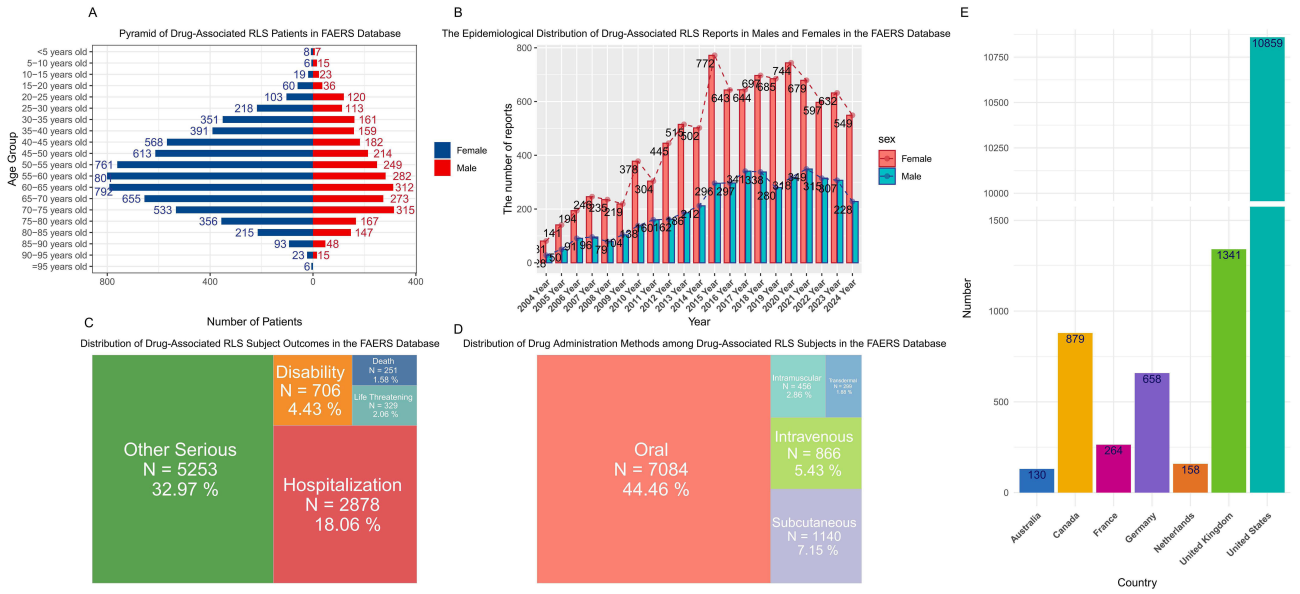


Figure 2 Distribution of baseline data for subjects with drug-associated RLS in the FAERS database.
Notes: (**A**) shows the age distribution pyramid chart of subjects with drug-associated RLS; (**B**) shows the distribution of subjects with drug-associated RLS by reporting year; (**C**) shows the distribution of adverse reaction outcomes for subjects with drug-associated RLS; (**D**) shows the distribution of medication intake methods for subjects with drug-associated RLS; (**E**) shows the distribution of reporting countries for subjects with drug-associated RLS.

from males (4375 reports, 27.5%), the most affected age group was individuals aged 41 and older (7470 reports, 46.9%). The majority of reports were submitted by consumers (8388 reports, 52.6%), with the United States being the primary reporting country (10,859 reports, 68.1%). Hospitalization was the most common clinical outcome (2878 reports, 18.1%).

Table 2 Clinical Characteristics of Patients with Drug-Associated RLS (From 2004Q1 to the 2024Q3)

Characteristics	Reports, n (%)
Sex	
Female	9902 (62.1%)
Male	4375 (27.5%)
Unknown	1658 (10.4%)
Weight(kg)	
<50	290 (1.8%)
50–100	4100 (25.7%)
>100	794 (5.0%)
Unknown	10751 (67.5%)
Age(years)	
<19	153 (1.0%)
19–41	1852 (11.6%)
41–65	4605 (28.9%)
≥65	2865 (18.0%)
Unknown	6460 (40.5%)
Reporter	
Consumer	8388 (52.6%)
Physician	2797 (17.6%)
Other health-professional	2795 (17.5%)
Lawyer	529 (3.3%)

(*Continued*)

https://doi.org/10.2147/NSS.S513538

Table 2 (Continued).

Characteristics	Reports, n (%)
Pharmacist	476 (3.0%)
Registered nurse	7 (0.0%)
Unknown	943 (5.9%)
Reported countries	
United States	10859 (68.1%)
United Kingdom	1341 (8.4%)
Canada	879 (5.5%)
Germany	658 (4.1%)
France	264 (1.7%)
Other	1934 (12.1%)
Outcomes	
Hospitalization	2878 (18.1%)
Other Serious	5204 (32.7%)
Disability	706 (4.4%)
Life Threatening	329 (2.1%)
Death	251 (1.6%)
Required Intervention to Prevent Permanent Impairment/Damage	35 (0.2%)
Congenital anomaly	14 (0.1%)
Unknown	6518 (40.9%)

The 50 Most Common Drugs

Based on the count of adverse drug reaction reports related to RLS, we identified the top 50 drugs (Figure 3), which had a total of 16,410 reports. Below is a categorical description of these drugs, with a particular focus on the ten most common ones, including their report counts and percentages: sodium oxybate (648 cases, 3.95%), metoclopramide (492 cases, 3.00%), pramipexole (360 cases, 2.19%), quetiapine fumarate (345 cases, 2.10%), mirtazapine (338 cases, 2.06%), aripiprazole (332 cases, 2.02%), pregabalin (320 cases, 1.95%), ropinirole (316 cases, 1.92%), adalimumab (313 cases, 1.91%), and alendronate sodium (255 cases, 1.55%). We categorized the drugs and found that those related to the nervous system constituted a significant proportion of RLS-related ADEs, with sodium oxybate (648 cases) and pramipexole (360 cases) being the most reported drugs in this category, In the category of alimentary tract and metabolism, metoclopramide (492 cases) had the highest number of reports, among antineoplastic and immunomodulating agents, adalimumab (313 cases) and interferon beta-1a (213 cases) were also reported frequently, in the musculoskeletal system category, burosumab (247 cases) and alendronate sodium (255 cases) had a relatively high number of reports, in the category of systemic hormonal preparations, excluding sex hormones and insulins, teriparatide (177 cases) was the most reported drug. Additionally, other categories such as the cardiovascular system, dermatologicals, and blood and blood-forming organs were also represented in RLS-related ADEs, but their counts were relatively low.

Risk Signal Detection

We employed four methods to calculate the signal values for the 50 most common drugs. According to the ROR criteria, Table 3 lists the top 50 drugs with the strongest risk signals. Out of the 50 drugs, 27 generated risk signals, with the top five results as follows: burosumab [ROR (95% CI): 61.16 (53.88, 69.43)], ropinirole [ROR (95% CI): 60.19 (53.80, 67.35)], pramipexole [ROR (95% CI): 44.29 (39.87, 49.20)], rotigotine [ROR (95% CI): 30.77 (26.88, 35.23)], and metoclopramide [ROR (95% CI): 26.73 (24.43, 29.25)]. Among the drugs evaluated that met all algorithm criteria, 27 were identified as producing valid risk signals, of the 27 drugs, only six FDA-approved drugs (such as burosumab, pramipexole, rotigotine, quetiapine fumarate, enzalutamide, and duloxetine) had labels that documented the expected RLS reactions. Notably, 21 of the 27 drugs did not indicate any RLS risk in their labels.

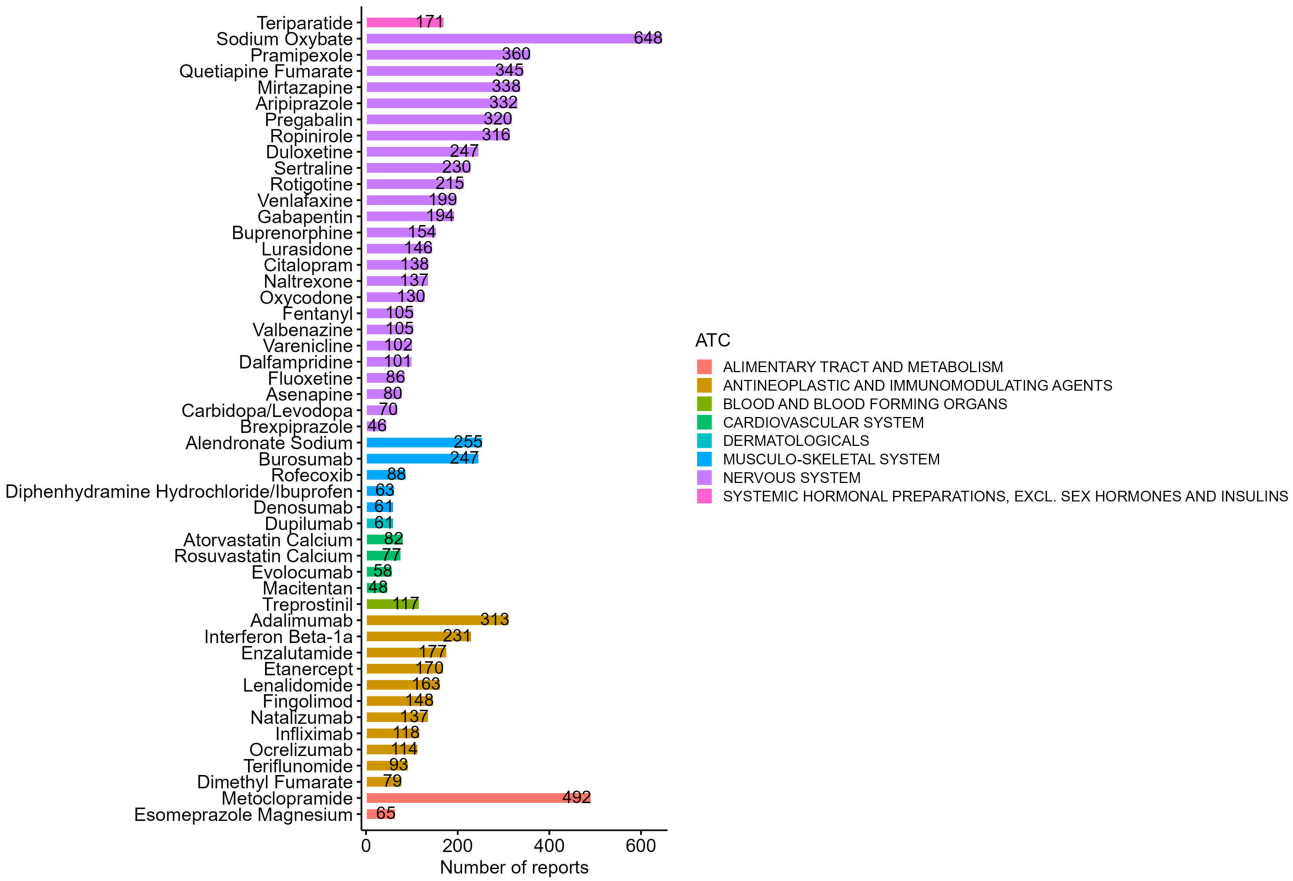


Figure 3 Top 50 drugs with the highest frequency of reported drug-associated RLS.

Regression Analysis

The correlation between patient gender, age, weight, and medication use with drug-associated RLS is shown in Figure 4. During the examination of these 27 drugs, it was found that ICSRs for burosumab and brexpiprazole were incomplete, resulting in their exclusion. Univariate and multivariate logistic regression analyses indicated that gender, age, weight,

Table 3 Risk Signal Scores for Drug-Associated RLS

Drug	a	ROR (95% CI)	PRR (χ^2)	EBGM (EBGM05)	IC (IC025)
Burosumab[#]	247	61.16 (53.88–69.43)*	60.07 (14,135.41)*	59.18 (53.22)*	5.89 (5.70)*
Ropinirole	316	60.19 (53.80–67.35)*	59.14 (17,718.31)*	58.02 (52.81)*	5.86 (5.69)*
Pramipexole[#]	360	44.29 (39.87–49.20)*	43.72 (14,702.04)*	42.78 (39.18)*	5.42 (5.26)*
Rotigotine[#]	215	30.77 (26.88–35.23)*	30.50 (6055.72)*	30.11 (26.89)*	4.91 (4.71)*
Metoclopramide	492	26.73 (24.43–29.25)*	26.53 (11,728.17)*	25.76 (23.89)*	4.69 (4.55)*
Diphenhydramine hydrochloride/ ibuprofen	63	24.60 (19.19–31.53)*	24.42 (1410.25)*	24.33 (19.77)*	4.60 (4.24)*
Asenapine	80	20.21 (16.21–25.19)*	20.09 (1444.54)*	20.00 (16.63)*	4.32 (4.00)*
Mirtazapine	338	17.44 (15.65–19.43)*	17.35 (5102.60)*	17.01 (15.54)*	4.09 (3.93)*
Lurasidone	146	11.88 (10.09–13.98)*	11.84 (1436.16)*	11.74 (10.24)*	3.55 (3.31)*
Sodium oxybate	648	9.18 (8.48–9.93)*	9.16 (4522.81)*	8.83 (8.27)*	3.14 (3.03)*

(*Continued*)

https://doi.org/10.2147/NSS.S513538

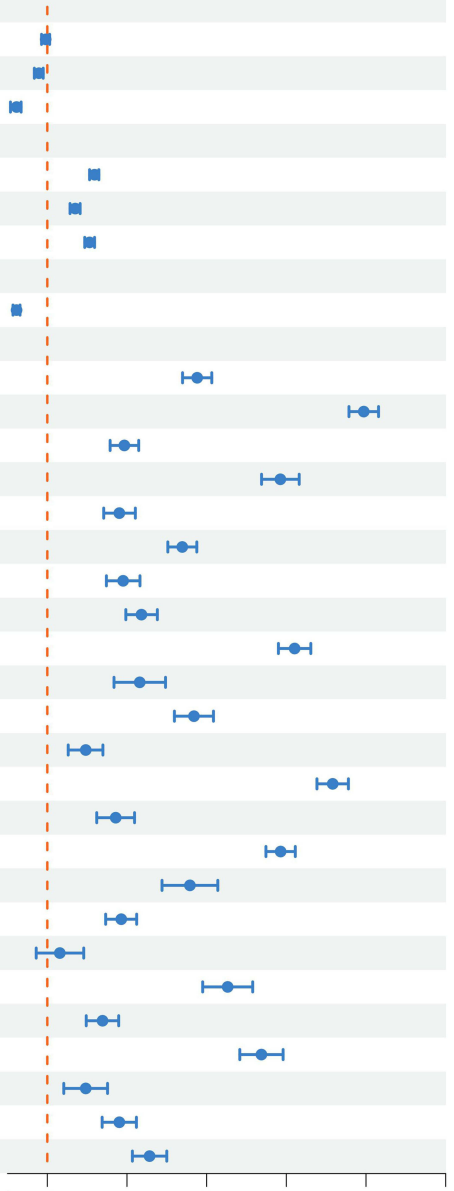
Table 3 (Continued).

Drug	a	ROR (95% CI)	PRR (χ^2)	EBGM (EBGM05)	IC (IC025)
Valbenazine	105	8.34 (6.88–10.10)*	8.32 (672.02)*	8.27 (7.04)*	3.05 (2.77)*
Quetiapine fumarate#	345	6.58 (5.91–7.32)*	6.57 (1595.00)*	6.45 (5.90)*	2.69 (2.53)*
Brexpiprazole	46	6.28 (4.70–8.38)*	6.27 (203.06)*	6.25 (4.91)*	2.64 (2.22)*
Aripiprazole	332	5.21 (4.67–5.80)*	5.20 (1103.77)*	5.11 (4.67)*	2.35 (2.19)*
Naltrexone	137	4.68 (3.95–5.53)*	4.67 (392.25)*	4.64 (4.03)*	2.21 (1.97)*
Enzalutamide#	177	4.44 (3.83–5.15)*	4.43 (465.74)*	4.40 (3.88)*	2.14 (1.92)*
Sertraline	230	4.26 (3.74–4.85)*	4.25 (564.03)*	4.21 (3.77)*	2.07 (1.88)*
Carbidopa/levodopa	70	3.42 (2.70–4.32)*	3.41 (119.07)*	3.40 (2.80)*	1.77 (1.42)*
Venlafaxine	199	3.27 (2.84–3.76)*	3.26 (308.88)*	3.24 (2.88)*	1.69 (1.49)*
Duloxetine#	247	3.25 (2.86–3.68)*	3.25 (378.21)*	3.21 (2.89)*	1.68 (1.50)*
Gabapentin	194	3.00 (2.61–3.46)*	3.00 (255.75)*	2.98 (2.64)*	1.57 (1.37)*
Fluoxetine	86	3.00 (2.43–3.71)*	3.00 (113.93)*	2.99 (2.50)*	1.58 (1.27)*
Buprenorphine	154	2.96 (2.52–3.47)*	2.96 (197.43)*	2.94 (2.57)*	1.55 (1.32)*
Alendronate sodium	255	2.92 (2.58–3.31)*	2.92 (317.59)*	2.89 (2.61)*	1.53 (1.35)*
Pregabalin	320	2.90 (2.60–3.24)*	2.90 (391.29)*	2.87 (2.61)*	1.52 (1.36)*
Citalopram	138	2.80 (2.37–3.32)*	2.80 (158.77)*	2.79 (2.42)*	1.48 (1.23)*
Rosuvastatin calcium	77	2.54 (2.03–3.18)*	2.54 (71.79)*	2.54 (2.10)*	1.34 (1.01)*
Ocrelizumab	114	2.31 (1.92–2.78)*	2.31 (84.06)*	2.30 (1.97)	1.20 (0.93)*
Fentanyl	105	2.23 (1.84–2.70)*	2.23 (70.52)*	2.22 (1.89)	1.15 (0.87)*
Teriflunomide	93	2.18 (1.78–2.67)*	2.18 (59.02)*	2.17 (1.83)	1.12 (0.82)*
Dalfampridine	101	1.97 (1.62–2.39)*	1.97 (47.86)	1.96 (1.67)	0.97 (0.69)*
Fingolimod	148	1.78 (1.51–2.09)*	1.78 (49.94)	1.77 (1.55)	0.82 (0.59)*
Atorvastatin calcium	82	1.72 (1.38–2.13)*	1.72 (24.38)	1.71 (1.43)	0.78 (0.46)*
Teriparatide	171	1.66 (1.43–1.93)*	1.66 (44.39)	1.65 (1.46)	0.73 (0.50)*
Varenicline	102	1.60 (1.32–1.95)*	1.60 (23.06)	1.60 (1.36)	0.68 (0.39)*
Interferon beta-1a	231	1.53 (1.35–1.74)*	1.53 (42.10)	1.52 (1.37)	0.61 (0.42)*
Treprostinil	117	1.33 (1.11–1.59)*	1.33 (9.49)	1.33 (1.14)	0.41 (0.14)*
Rofecoxib	88	1.26 (1.02–1.55)*	1.26 (4.61)	1.26 (1.05)	0.33 (0.02)*
Natalizumab	137	1.14 (0.96–1.35)	1.14 (2.26)	1.14 (0.99)	0.18 (−0.06)
Macitentan	48	0.94 (0.71–1.25)	0.94 (0.16)	0.94 (0.74)	−0.08 (−0.50)
Esomeprazole magnesium	65	0.91 (0.71–1.16)	0.91 (0.56)	0.91 (0.74)	−0.13 (−0.49)
Dimethyl fumarate	79	0.88 (0.71–1.10)	0.88 (1.27)	0.88 (0.73)	−0.18 (−0.51)
Lenalidomide	163	0.75 (0.64–0.88)	0.75 (13.19)	0.75 (0.66)	−0.41 (−0.63)
Oxycodone	130	0.72 (0.61–0.86)	0.72 (13.64)	0.73 (0.63)	−0.46 (−0.72)
Denosumab	61	0.66 (0.51–0.85)	0.66 (10.74)	0.66 (0.53)	−0.60 (−0.97)
Evolocumab	58	0.61 (0.48–0.80)	0.61 (13.94)	0.62 (0.50)	−0.70 (−1.07)
Adalimumab	313	0.53 (0.47–0.59)	0.53 (129.05)	0.54 (0.49)	−0.90 (−1.06)
Infliximab	118	0.52 (0.43–0.62)	0.52 (52.58)	0.52 (0.45)	−0.94 (−1.21)
Etanercept	170	0.41 (0.35–0.48)	0.41 (143.21)	0.42 (0.37)	−1.27 (−1.49)
Dupilumab	61	0.29 (0.23–0.38)	0.29 (103.32)	0.30 (0.24)	−1.76 (−2.12)

Notes: The asterisk (*) means statistically significant association, the adverse events are detected as signals. The number sign (#) indicates that the risk of restless legs syndrome was documented for the FDA-approved drugs labels. The forward slash sign (/) indicates that the drugs are in combination.
Abbreviations: CI, confidence interval; EBGM, the empirical Bayes geometric mean; EBGM05, the lower limit of 95% CI, of EBGM; IC, the information component; IC025, the lower limit of 95% CI, of the IC; PRR, the proportional reporting ratio; ROR, the reporting odds ratio.

and medication could be influencing factors for drug-associated RLS ($p < 0.05$), the ROC-AUC indicating the model's predictive accuracy was 0.72 (Figure 5). Specifically, compared to the age group under 44, the incidence risk decreased for those over 57, in contrast, higher weight groups had an increased risk compared to those under 64 kg, and males had a lower incidence risk than females. Regarding medication use, 24 drugs, excluding buprenorphine, were identified as

Variable	Factor	OR(95%CI)	P
Age	<44(reference)		
	44−57*	0.98(0.93,1.03)	0.391
	57−68*	0.9(0.85,0.95)	<0.001
	>68*	0.68(0.63,0.72)	<0.001
Weight	<64(reference)		
	64−77*	1.81(1.7,1.91)	<0.001
	77−93*	1.42(1.33,1.51)	<0.001
	>93*	1.7(1.6,1.81)	<0.001
Gender	Female(reference)		
	Male*	0.68(0.65,0.71)	<0.001
Drug	Rosuvastatin calcium(reference)		
	Sodium oxybate*	6.56(5.46,7.88)	<0.001
	Metoclopramide*	53.09(44.09,63.92)	<0.001
	Pregabalin*	2.63(2.2,3.15)	<0.001
	Ropinirole hydrochloride*	18.64(14.72,23.61)	<0.001
	Alendronate sodium*	2.47(2.03,3.02)	<0.001
	Quetiapine fumarate*	5.44(4.54,6.53)	<0.001
	Duloxetine*	2.59(2.1,3.2)	<0.001
	Aripiprazole*	3.26(2.68,3.98)	<0.001
	Rotigotine*	22.29(18.19,27.32)	<0.001
	Enzalutamide*	3.19(2.31,4.41)	<0.001
	Lurasidone*	6.3(4.93,8.05)	<0.001
	Sertraline*	1.62(1.3,2.01)	<0.001
	Pramipexole*	35.94(29.5,43.79)	<0.001
	Naltrexone*	2.36(1.86,2.99)	<0.001
	Mirtazapine*	18.7(15.55,22.48)	<0.001
	Valbenazine tosylate*	5.99(4.22,8.5)	<0.001
	Gabapentin*	2.53(2.08,3.07)	<0.001
	Buprenorphine	1.17(0.87,1.58)	0.288
	Asenapine maleate*	9.62(7.03,13.17)	<0.001
	Venlafaxine*	2(1.63,2.45)	<0.001
	Diphenhydramine hydrochloride/Ibuprofen*	14.69(11.2,19.29)	<0.001
	Fluoxetine*	1.62(1.23,2.13)	<0.001
	Citalopram*	2.47(1.99,3.06)	<0.001
	Carbidopa/Levodopa*	3.61(2.91,4.48)	<0.001



The asterisk (*) means statistically significant association.
The number sign (/) indicates that the drugs are in combination.

Figure 4 Results of the multi-factor logistic regression analysis.

independent risk factors for drug-associated RLS. Notably, the medications metoclopramide, pramipexole, rotigotine, mirtazapine, and ropinirole hydrochloride had odds ratios (OR) of 53.09 (95% CI: 44.09, 63.92), 35.94 (95% CI: 29.50, 43.79), 22.29 (95% CI: 18.19, 27.32), 18.70 (95% CI: 15.55, 22.48), and 18.64 (95% CI: 14.72, 23.61), with p-values all significantly less than 0.001.

Time-to-Onset Analysis

A TTO analysis was conducted on the 27 drugs that generated risk signals, excluding brexpiprazole, diphenhydramine hydrochloride/ibuprofen due to incomplete AE time data. The results are presented in Table 4. In the WSP analysis assessment, the shape parameters β for naltrexone and asenapine maleate were close to 1, with the 95% CI including 1,

https://doi.org/10.2147/NSS.S513538

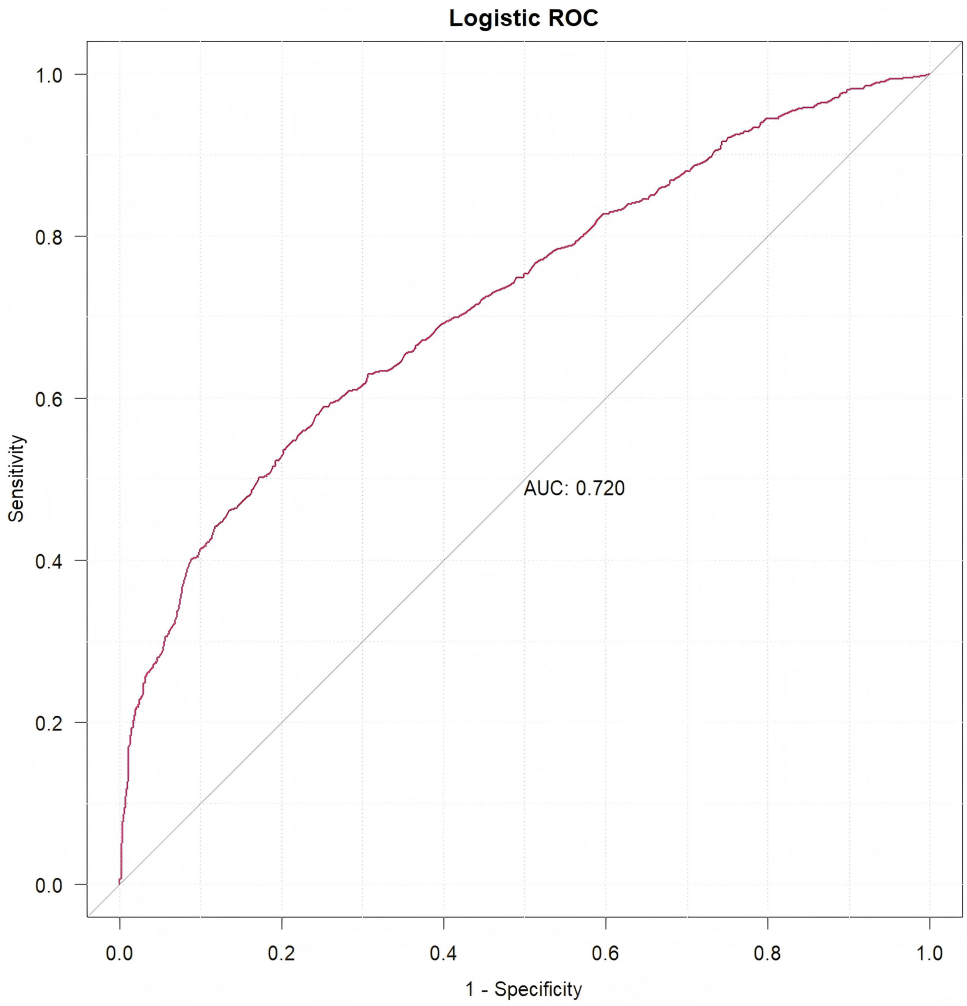


Figure 5 The ROC curves of drug-associated RLS risk factors.
Abbreviations: ROC, receiver operating characteristic; AUC, area under curve.

indicating a random failure type. For the remaining 23 drugs, all shape parameters β and their 95% CI upper limits were found to be < 1. This suggests that the incidence of drug-associated RLS decreases over time, indicating the presence of early failure types.

Table 4 Analysis of RLS Time-to-Onset for 25 Drugs Generating Risk Signals

Drug	a	TTO (Days)	Weibull Distribution		Failure Type
		Median (IQR)	Scale Parameter: α (95% CI)	Shape Parameter: β (95% CI)	
Sodium oxybate	648	60.5 (222.75)	162.17 (33.06,291.28)	0.44 (0.33,0.54)	Early failure
Metoclopramide	492	1467.5 (2378.25)	1548.89 (725.31,2372.48)	0.68 (0.48,0.88)	Early failure
Pregabalin	320	92 (335.5)	287.03 (47.17,526.89)	0.49 (0.35,0.63)	Early failure
Ropinirole hydrochloride	316	61 (354.5)	171.5 (60.06,282.94)	0.45 (0.35,0.54)	Early failure
Alendronate sodium	255	200 (654)	403.75 (274.16,533.35)	0.77 (0.63,0.91)	Early failure
Quetiapine fumarate	345	70 (601.5)	257.48 (108.40,406.57)	0.49 (0.39,0.59)	Early failure

(*Continued*)

Table 4 (Continued).

Drug	a	TTO (Days)	Weibull Distribution		Failure Type
		Median (IQR)	Scale Parameter: α (95% CI)	Shape Parameter: β (95% CI)	
Burosumab	247	225 (583.5)	327.37 (106.91,547.83)	0.64 (0.43,0.85)	Early failure
Duloxetine	247	104.5 (373)	219.20 (98.61,339.79)	0.58 (0.45,0.72)	Early failure
Aripiprazole	332	101.5 (452)	200.82 (75.33,326.31)	0.55 (0.41,0.70)	Early failure
Rotigotine	215	68 (649)	246.57 (−62.99,556.14)	0.40 (0.25,0.55)	Early failure
Enzalutamide	177	32 (68.75)	70.40 (36.41,104.40)	0.68 (0.52,0.84)	Early failure
Lurasidone	146	32.5 (217.75)	105.67 (−34.71,246.06)	0.49 (0.26,0.73)	Early failure
Sertraline	230	7 (251.25)	68.08 (23.23,112.93)	0.40 (0.33,0.48)	Early failure
Pramipexole	360	760 (1304.5)	1069.44 (580.19,1558.68)	0.77 (0.57,0.98)	Early failure
Naltrexone	137	2 (7)	7.10 (−0.21,14.41)	0.77 (0.35,1.18)	Random failure
Mirtazapine	338	6 (20)	25.12 (13.55,36.68)	0.45 (0.39,0.51)	Early failure
Valbenazine tosylate	105	26 (35)	35.52 (2.47,68.57)	0.62 (0.36,0.87)	Early failure
Gabapentin	194	2.5 (41.5)	31.85 (−5.65,69.36)	0.35 (0.25,0.44)	Early failure
Buprenorphine	154	240 (1044.5)	271.65 (−244.68,787.98)	0.41 (0.16,0.66)	Early failure
Asenapine maleate	80	2 (3)	3.48 (0.96,6.00)	1.28 (0.42,2.15)	Random failure
Venlafaxine	199	82.5 (319.25)	239.08 (118.58,359.58)	0.58 (0.46,0.70)	Early failure
Rosuvastatin calcium	77	11 (61)	34.53 (0.24,68.81)	0.63 (0.34,0.92)	Early failure
Fluoxetine	86	19 (233.75)	78.30 (−3.58,160.19)	0.41 (0.29,0.52)	Early failure
Citalopram	138	32 (109.5)	88.63 (14.56,162.70)	0.47 (0.35,0.60)	Early failure
Carbidopa/levodopa	70	83.5 (612.75)	149.25 (−62.82,361.32)	0.46 (0.23,0.69)	Early failure

Note: The forward slash sign (/) indicates that the drugs are in combination.

Discussion

This study is the first to use real-world data from the FAERS database to comprehensively assess the correlation between RLS and clinical drug use, summarizing patient clinical characteristics and identifying medications closely associated with RLS. The findings indicate that reported cases have been increasing annually since 2004, stabilizing after approximately 15 years. Furthermore, although RLS is generally considered a non-fatal condition, the incidence of severe outcomes, such as death and life-threatening events, was 1.6% and 2.1%, respectively, in the analyzed cases. Warranting attention, the observed increased risk of mortality may be attributed to potential suicidal and self-harming behaviors.[22] We observed significant gender and age differences in all drug-associated RLS cases reported to the FDA, with RLS being more common in females. Multivariate regression results indicate that female patients have a higher risk of onset compared to males, this phenomenon may be attributed to the elevated incidence rate of RLS observed in women. In this study, approximately 46.9% of drug-associated RLS cases occurred in individuals aged 41 and older. Although systematic studies investigating the characteristics of the drug-associated RLS population are lacking, a systematic review and modeling study indicated that globally, among patient with RLS aged 20–79, females account for 57.89%, the prevalence of RLS begins to increase after age 18, peaking around age 60,[2] which aligns with the characteristics observed in our study. Currently, the age-related risk of drug-associated RLS is unclear. Our study found that the risk of occurrence is lower in the >44 age group compared to those <44 (OR < 1), advanced age may serve as a protective factor against drug-associated RLS.

Regarding weight, individuals >64 kg exhibited a higher risk of onset compared to those <64 kg (OR > 1), higher weight may be a risk factor for drug-associated RLS. Given obesity is associated with OSA and OSA can exacerbate RLS,[23,24] it is possible that OSA may be a factor in increased prevalence of drug associated RLS with higher weight.[25] Certainly, further clinical trials are needed to elucidate potential confounding factors and to determine whether gender, age, and weight are risk factors for drug-associated RLS.

Preliminary evidence from case reports have documented drug-associated RLS associated with medications such as antidepressants, antipsychotics, anticonvulsants, opioid analgesics, antihistamines, and antiemetics.[2,26–30] Population-level studies remain scarce, a case-control study involving dialysis patients indicated that antidepressants, antipsychotics,

antihistamines, and antiemetics significantly increased the risk of developing RLS, with odds ratios ranging from 1.47 to 2.28 (all $p < 0.0001$),[31] but the evidence linking these medications to RLS remains limited, and there is a risk of false positives. Therefore, the limited generalizability of prior evidence, predominantly comprising case reports and single-population studies, underscores the critical need for our FAERS-based analytical framework.

In this study, we identified drugs associated with RLS that have been systematically reported in the FAERS database. Among the 50 most commonly reported drugs, those affecting the nervous system were the most prevalent (25/50), followed by antineoplastic and immunomodulating agents (11/50) and musculoskeletal system drugs (5/50). The following 27 drugs were identified as valid risk signals: burosumab, ropinirole hydrochloride, pregabalin, rotigotine, metoclopramide, diphenhydramine hydrochloride/ibuprofen, asenapine maleate, mirtazapine, lurasidone, sodium oxybate, valbenazine tosylate, quetiapine fumarate, brexpiprazole, aripiprazole, naltrexone, enzalutamide, sertraline, carbidopa/levodopa, venlafaxine, duloxetine, gabapentin, fluoxetine, buprenorphine, alendronate sodium, pregabalin, citalopram, and rosuvastatin calcium (Table 3), these 27 drugs were categorized primarily as antidepressants (mirtazapine, venlafaxine, duloxetine, fluoxetine, citalopram), followed by antipsychotics (asenapine, lurasidone, quetiapine fumarate, brexpiprazole, aripiprazole), antiparkinson agents (ropinirole, pramipexole, rotigotine, carbidopa/levodopa), antiepileptics (gabapentin, pregabalin), and other drug types (including antiemetics, analgesics, and monoclonal antibodies).

The relationship between antidepressants and RLS has been explored in numerous case reports, cross-sectional studies, and open-label trials, but the findings have been inconsistent.[32–34] Our study supports the notion that antidepressants are a risk factor for drug-associated RLS and are the most commonly reported drug category, noradrenergic and specific serotonergic antidepressants (NaSSAs), such as mirtazapine, as well as selective serotonin reuptake inhibitors (SSRIs) like fluoxetine and citalopram, and serotonin-norepinephrine reuptake inhibitors (SNRIs), including venlafaxine and duloxetine. Evidence from case reports and cross-sectional studies indicates that antidepressants may induce or exacerbate RLS,[33,35] which may be associated with the frequent occurrence of comorbid depression or a depressive state among patients with RLS. As demonstrated in a recent meta-analysis, the pooled prevalence of depression or depressive states among RLS patients reaches as high as 30.39% (95% CI: 20.55–42.43%).[36] Therefore, we recommend seeking medications with a lower risk profile, reducing dosages, or substituting drugs that may trigger or worsen RLS. Furthermore, the mechanisms by which antidepressants may lead to RLS remain unclear. A clinical study by Jhoo et al compared the availability of the serotonin transporter (SERT) between 16 untreated patient with RLS and 16 healthy controls, finding that the severity of RLS symptoms increased as the availability of SERT decreased. They further suggested that increased serotonergic transmission may be associated with the exacerbation of RLS symptoms.[37]

Among the antipsychotics we identified, the five drugs (asenapine, lurasidone, quetiapine fumarate, brexpiprazole, and aripiprazole) have numerous case reports, except for brexpiprazole,[38–41] quetiapine fumarate is the most frequently reported drug associated with RLS, the five drugs are classified as second-generation antipsychotics. The mechanisms of action of antipsychotic medications predominantly involve the inhibition of dopaminergic neurotransmission, in addition to engaging multiple other pathways. Dopaminergic inhibition might clarify the connection between antipsychotics and RLS, as shown in previous studies. Furthermore, a meta-analysis indicated that patients administered antipsychotic medications exhibited reduced iron levels. This finding implies, from an alternative standpoint, that antipsychotic drugs may contribute to the onset of RLS through their impact on iron metabolism.[42] There are case reports indicating that RLS induced by antipsychotic drugs can be resolved by changing the medication. For example, olanzapine-induced RLS completely resolved after changing olanzapine to aripiprazole, risperidone, and quetiapine.[43] Additionally, a genome-wide association study involving 190 schizophrenia patients further indicated that a haplotype of the MAP2K5 gene polymorphism may increase susceptibility to RLS symptoms induced by antipsychotics.[44] Given that the presence and exacerbation of drug-associated RLS symptoms may depend on the dosage of antipsychotics,[45] it is advisable to switch to drugs with a lower risk or to adjust the dosage for RLS induced by antipsychotics.

Among the four antiparkinson agents identified in this study, ropinirole, pramipexole, and rotigotine are all dopamine receptor agonists. Carbidopa/levodopa is a combination formulation, with levodopa serving as a precursor to dopamine, while carbidopa is a peripheral dopa decarboxylase inhibitor. Antiparkinson agents are also used to treat RLS due to their ability to enhance dopaminergic effects. A cross-sectional cohort study determined that the annual incidence of RLS

augmentation during the initial eight years of dopamine agonist therapy was 8%. Within this cohort, the risk of augmentation was most pronounced with levodopa, as compared to ropinirole and pramipexole, potentially attributable to levodopa's relatively shorter half-life,[1,46] patients receiving the long-acting dopamine agonist rotigotine may have a lower risk of augmentation (approximately 4% of patients).[47] This suggests that the concept of reduced dopaminergic function as the origin of RLS mechanisms is incomplete. The notion of a "hyper-dopaminergic" presynaptic state, defined by enhanced dopamine synthesis, release, and reduced uptake, resulting in elevated synaptic dopamine levels, is increasingly attracting scholarly attention. The augmentation of RLS symptoms may be attributable to prolonged dopaminergic therapy, which induces a hyperdopaminergic state. It is crucial to recognize that this state is frequently associated with a "hypo-dopaminergic" postsynaptic state, characterized by reduced D2/3 receptor availability.[48,49]

Among the antiepileptics identified as risk factors for drug-associated RLS, gabapentin and pregabalin are classified as α2δ calcium channel ligands, α2δ ligands are believed to reduce postsynaptic excitability and limit the release of several calcium-mediated neurotransmitters,[50] their efficacy in RLS may stem from their ability to counteract the excessive excitatory state associated with RLS. The latest international guidelines strongly recommend the use of α2δ calcium channel ligands for the treatment of adults with RLS, unless contraindicated.[15] In a 52-week randomized double-blind trial, the augmentation rate for pregabalin was significantly lower than that for pramipexole (2.1% vs 7.7%, P=0.001),[51] another single head-to-head study confirmed this conclusion.[52]

As a specific complication of long-term dopaminergic treatment, it is necessary to clarify the distinction between augmentation and other forms of symptom worsening. Augmentation refers specifically to the long-term iatrogenic increase in the intensity and duration of RLS symptoms that gradually occurs after months to years of dopaminergic therapy. This phenomenon is characterized by an earlier onset of symptoms (for example, shifting from nighttime to daytime), a shortened latency of symptoms during periods of inactivity, and the extension of symptoms to other parts of the body. In contrast, other forms of worsening, such as acute adverse reactions that are common at the beginning of treatment (nausea, vomiting, drowsiness), as well as worsening factors for RLS symptoms other than antidopaminergic medications (eg, alcohol, caffeine, antihistamines, serotonergic medications), and the natural progression of RLS symptoms that are unrelated to medication effects, do not exhibit these specific temporal or dose-dependent characteristics.[15] Recognizing this distinction is crucial, as augmentation often necessitates a reassessment of treatment strategies (eg, dosage adjustment or switching to other medications), while transient adverse reactions or disease progression may require different management approaches.

Sodium oxybate is the most frequently reported drug-associated RLS in this study, it is a sodium salt of gamma-hydroxybutyrate (GHB), acting on several neurotransmitters, including gamma-aminobutyric acid (GABA). GHB has a complex impact on the dopaminergic system, influencing dopamine release by bidirectionally acting on GABAergic neurons.[53] Glutamate is a crucial excitatory neurotransmitter in the central nervous system, and besides dopaminergic system, a hyperglutamatergic state is also involved in the development of RLS.[54] Surprisingly, GHB can modulate glutamate levels in the hippocampus in a concentration-dependent manner by acting on GHB receptors.[55]

Burosumab is the drug with the highest risk signal for adverse reactions in this study, which merits attention to some extent, it is approved for the treatment of patients with X-linked hypophosphatemia and tumor-induced osteomalacia, although there are no studies reporting that burosumab induces RLS, it is mentioned in its package insert. Future research should delve deeper into the connection between the two.

Among the remaining drugs, metoclopramide is a dopamine receptor antagonist, some case reports indicate that administration of metoclopramide can lead to transient RLS symptoms, which resolve after discontinuation of the medication.[30]

Buprenorphine and naltrexone are opioids used to treat patients with opioid use disorder, a survey of 129 patients with opioid use disorder found that, 13.2% of those receiving buprenorphine or naltrexone maintenance treatment exhibited RLS symptoms, occurring at least 5 to 15 times per month,[56,57] previous case-control studies have found that 51% of patients undergoing opioid withdrawal treatment have RLS, significantly higher than the 21.7% in the alcohol withdrawal group.[58] These studies suggest that opioid withdrawal may be more likely to trigger RLS. A prospective observational study further explored the incidence and clinical features of RLS during opioid withdrawal, as well as the intervention effects of buprenorphine and pregabalin.[59] The results showed that buprenorphine was ineffective in alleviating RLS,

while pregabalin had good effects. However, a retrospective cohort study indicated that buprenorphine significantly reduced RLS symptoms,[60] effectively eliminated patients' need for dopamine agonists, and improved sleep and other quality of life measures. This highlights the need for larger-scale, randomized controlled trials to comprehensively assess whether buprenorphine can serve as an alternative therapy for refractory RLS. RLS symptoms persisted even after opioid withdrawal symptoms subsided, suggesting that RLS may be an independent disease that may not be related to opioid withdrawal, or it could have preexisted. Some have proposed that endogenous and exogenous opioids protect against the loss of dopaminergic neurons, which may explain the potential association between opioid withdrawal and RLS.[61]

Enzalutamide inhibits androgen receptor activity, and most studies linking it to drug-associated RLS are case reports,[62–64] given that dopamine signaling is strongly regulated by androgens in various brain regions,[65] we hypothesize that androgen deficiency may lead to dopaminergic impairment.[66–68]

Diphenhydramine hydrochloride (commonly referred to as DPH) is a first-generation antagonist of the histamine H1 receptor, exhibiting notable anticholinergic properties. This drug category is frequently encountered among patients with RLS. Antihistamines are prevalent in over-the-counter (OTC) sleep aids, such as diphenhydramine and doxylamine, as well as in OTC cold medications. They are often combined with ibuprofen, which makes their presence even less obvious.[69] A case-control study conducted utilizing the US Renal Data System (USRDS) examined the relationship between the use of specific medications, including antihistamines, and the prevalence of RLS in patients with end-stage renal disease. The findings indicated that antihistamines were among the medication classes significantly correlated with an elevated likelihood of RLS diagnosis [OR(95% CI): 60.19 (1.79, 2.10), $p < 0.0001$].[31] An animal study offered an alternative perspective by investigating the relationship between antihistamines and RLS using histidine decarboxylase knockout mice.[70] While no significant alterations in sleep architecture were detected, these knockout mice demonstrated a decrease in tibialis anterior electromyographic (EMG) bursts during non-rapid eye movement (NREM) sleep compared to their wild-type counterparts. Crucially, these findings do not corroborate the hypothesis that inhibiting brain histamine signaling may facilitate RLS. Rather, the results indicate that limb movements during sleep, including those occurring at brief intervals, are indicative of subcortical arousal that necessitates intact brain histamine signaling.

Given the ubiquitous presence of diphenhydramine in OTC aids and combination cold medications, patients often encounter diphenhydramine without clinical supervision. Therefore, clinicians should exercise caution when recommending or prescribing OTC medications containing diphenhydramine, especially for patients with existing RLS or those at risk of developing RLS. The evidence provided in this article is one of the formal records documenting the relationship between diphenhydramine use and RLS, filling an important gap in clinical observations.

Valbenazine, alendronate sodium, and rosuvastatin calcium are also identified as potential risk factors for drug-associated RLS. However, the lack of discussion on their correlation with RLS in current medical literature, the level of evidence supporting these associations is considered low. Consequently, these factors will not be examined in detail in this discussion.

Additionally, we analyzed the TTO of drug-associated RLS. We observed that the median TTO for naltrexone was 2 days, making it the shortest among all the studied drugs. In contrast, the median TTO for metoclopramide was 1467.5 days, the longest among all analyzed drugs. Furthermore, of the 25 drugs, 18 had a median onset time of less than 100 days, indicating that drug-associated RLS onset occurs early in the course of treatment with these drugs. However, there is currently a lack of data analysis regarding the TTO of drug-associated RLS.

When exploring the association between drugs and RLS in the FAERS database, we encounter several limitations. (1) As a spontaneous reporting system, the integrity and accuracy of FAERS data are constrained by the voluntary nature of reporting, which may lead to underreporting, duplicate reports, and inaccuracies, ultimately affecting the reliability of the research findings. (2) The lack of information about healthy populations in the FAERS database prevents us from accurately calculating the incidence of drug-associated RLS, and we are unable to assess potential differences among various populations. (3) The correlation between RLS and medications is based on descriptions in the reports rather than rigorous causal assessments, making it difficult to ascertain whether these risk signals reflect true causal relationships. The occurrence of RLS may be influenced by underlying patient conditions, concomitant medications, or other unknown factors. (4) the FAERS database does not include

information on patients' health status prior to medication use and only contains data on drug indications. Therefore, we cannot determine whether patients had RLS before taking the medication, making it impossible to distinguish between drug-induced RLS and drug-exacerbated RLS. Finally, our findings require further validation through prospective studies and clinical trials to confirm the causal relationship between drugs and RLS. Despite these limitations, the FAERS database remains a crucial tool for monitoring drug safety and identifying potential risk signals.

Conclusion

This study utilized FAERS data to compile a comprehensive list of drugs potentially associated with RLS. We extracted reports from the FAERS database from the first quarter of 2004 to the third quarter of 2024, identifying 50 drugs most commonly associated with RLS and calculating their respective signal values. Notably, only six drugs (burosumab, pramipexole, rotigotine, quetiapine fumarate, enzalutamide, and duloxetine) listed RLS as an adverse effect in their prescribing information. Individuals under 44 years of age, weighing more than 64 kg, female individuals, or those who have taken one of 24 specific medications are at a higher risk of developing drug-associated RLS. Time-to-onset analysis revealed distinct patterns for the main associated drugs, with most exhibiting early onset of adverse reactions (within 100 days). Our list may assist clinicians in identifying alternative medications to consider when managing patients at risk for early RLS. All findings reported here require further validation through additional clinical studies and animal experiments.

Abbreviations

ADEs, adverse drug events; AUC, area under curve; BCPNN, Bayesian Confidence Propagation Neural Network; Cl, confidence interval; EBGM, Empirical Bayesian Geometric Mean; EMG, electromyographic; FAERS, Food and Drug Administration Adverse Event Reporting System; FDA, Food and Drug Administration; GHB, gamma-hydroxybutyrate; GABA, gamma-aminobutyric acid; ICSRs, individual case safety reports; IC, information component; IC025, the lower limit of 95% CI of the IC; MEIS1, myeloid ecotropic viral integration site 1; NREM, non-rapid eye movement; NaSSAs, noradrenergic and specific serotonergic antidepressants; OSA, obstructive sleep apnea; OTC, over-the-counter; PRR, Proportional Reporting Ratio; RLS, restless legs syndrome; ROC, receiver operating characteristic; ROR, Reporting Odds Ratio; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors; SERT, serotonin transporter; TTO, time-to-onset; V(IC), the variance of IC; USRDS, US Renal Data System; WSP, Weibull Shape Parameter.

Data Sharing Statement

The dataset generated during and analyzed during the current study is available from the corresponding author upon reasonable request.

Ethics Statement

The current study, which involved the analysis of anonymised data from the publicly available FAERS database, was determined to be exempt from institutional ethics approval. This exemption is in accordance with Article 32 of China's "Notice on the Issuance of Measures for the Ethical Review of Human Life Science and Medical Research" (2023), which allows for the waiver of ethical review for research using public, anonymised information data that does not harm human beings or involve sensitive personal information or commercial interests. Consequently, this study aligns with the exemption approval policy of the Ethics Committee of Henan University of Chinese Medicine and has been granted exemption approval.

Acknowledgments

This study was performed using the FAERS source that was provided by the FDA. The information, results, or interpretation of the current study do not represent any opinion of the FDA.

Author Contributions

Shiju Wei: Conceptualization, Data curation, Formal analysis, Software, Visualization, Writing–original draft. Xuhua Song: Conceptualization, Formal analysis, Methodology, Resources, Writing–original draft. Rui Chen: Formal analysis, Writing–original draft. Siyu Chen: Methodology, Project administration, Writing–original draft. Baoping Lu: Conceptualization, Funding acquisition, Supervision, Writing–review and editing.

All authors have agreed on the journal to which the article will be submitted. All authors reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage. All authors agree to take responsibility and be accountable for the contents of the article.

Funding

This study was supported by National famous traditional Chinese medicine Maudxi inheritance studio construction project (China Medical Office teaching Letter [2018] 119), Henan Province Chinese medicine scientific research special topic (2024ZY2156).

Disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the paper. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

1. Manconi M, Garcia-Borreguero D, Schormair B, et al. Restless legs syndrome. *Nat Rev Dis Primers*. 2021;7(1):80. doi:10.1038/s41572-021-00311-z
2. Song P, Wu J, Cao J, et al. The global and regional prevalence of restless legs syndrome among adults: a systematic review and modelling analysis. *J Glob Health*. 2024;14(7):4113. doi:10.7189/jogh.14.04113
3. Dauvilliers Y, Chenini S, Vialaret J, et al. Association between serum hepcidin level and restless legs syndrome. *Mov Disord*. 2018;33(4):618–627. doi:10.1002/mds.27287
4. Connor JR, Ponnuru P, Wang XS, Patton SM, Allen RP, Earley CJ. Profile of altered brain iron acquisition in restless legs syndrome. *Brain*. 2011;134(Pt 4):959–968. doi:10.1093/brain/awr012
5. Ferré S, Quiroz C, Guitart X, et al. Pivotal role of adenosine neurotransmission in restless legs syndrome. *Front Neurosci*. 2017;11(5):722. doi:10.3389/fnins.2017.00722
6. Khan FH, Ahlberg CD, Chow CA, Shah DR, Koo BB. Iron, dopamine, genetics, and hormones in the pathophysiology of restless legs syndrome. *J Neurol*. 2017;264(8):1634–1641. doi:10.1007/s00415-017-8431-1
7. Jiménez-Jiménez FJ, Alonso-Navarro H, García-Martín E, Agúndez JAG. Genetics of restless legs syndrome: An update. *Sleep Med Rev*. 2018;39(7):108–121. doi:10.1016/j.smrv.2017.08.002
8. Schormair B, Zhao C, Bell S, et al. Identification of novel risk loci for restless legs syndrome in genome-wide association studies in individuals of European ancestry: a meta-analysis. *Lancet Neurol*. 2017;16(11):898–907. doi:10.1016/S1474-4422(17)30327-7
9. Akçimen F, Sarayloo F, Liao C, et al. Transcriptome-wide association study for restless legs syndrome identifies new susceptibility genes. *Commun Biol*. 2020;3(1):373. doi:10.1038/s42003-020-1105-z
10. Schormair B, Zhao C, Bell S, et al. Genome-wide meta-analyses of restless legs syndrome yield insights into genetic architecture, disease biology and risk prediction. *Nat Genet*. 2024;56(6):1090–1099. doi:10.1038/s41588-024-01763-1
11. FCo P, Movement Disorders P-EH, Kassel ND, et al. Restless legs syndrome associated with major diseases: a systematic review and new concept. *Neurology*. 2016;86(14):1336–1343. doi:10.1212/WNL.0000000000002542
12. Ostroumova TM, Ostroumova OD, Filippova YA, Parfenov VA. Drug-induced restless legs syndrome. *Zh nevrol psikhiatr*. 2020;120(4):129–135. doi:10.17116/jnevro2020120041129
13. Patatanian E, Claborn MK. Drug-induced restless legs syndrome. *Ann Pharmacother*. 2018;52(7):662–672. doi:10.1177/1060028018760296
14. Allen RP. Controversies and challenges in defining the etiology and pathophysiology of restless legs syndrome. *Am J Med*. 2007;120(1 Suppl 1):S13–21. doi:10.1016/j.amjmed.2006.11.003
15. Winkelman JW, Berkowski JA, DelRosso LM, et al. Treatment of restless legs syndrome and periodic limb movement disorder: an American Academy of sleep medicine clinical practice guideline. *J Clin Sleep Med*. 2025;21(1):137–152. doi:10.5664/jcsm.11390
16. Kaur A, Wang S, Yu A, Elrafei T, Steinberg L, Kumar A. Real-world risk of anosmia with cancer directed systemic therapy: a pharmacovigilance assessment using FDA adverse events reporting system (FAERS) database. *J Clin Oncol*. 2021;39(15_suppl):e18790. doi:10.1200/JCO.2021.39.15_suppl.e18790
17. Xu P, Zheng Y, Li Z, Kuang Y, Tang K. Comparison of the checkpoint inhibitor pneumonitis incidence between immunotherapy alone or in combination with chemotherapy for lung cancer: An observational, retrospective pharmacovigilance study. *J Clin Oncol*. 2022;40(16_suppl):2655. doi:10.1200/JCO.2022.40.16_suppl.2655
18. van Puijenbroek EP, Bate A, Leufkens HG, Lindquist M, Orre R, Egberts AC. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. *Pharmacoepidem dr s*. 2002;11(1):3–10. doi:10.1002/pds.668

19. Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidem dr s*. 2001;10(6):483–486. doi:10.1002/pds.677
20. Bate A, Lindquist M, Edwards IR, et al. A Bayesian neural network method for adverse drug reaction signal generation. *Eur J Clin Pharmacol*. 1998;54(4):315–321. doi:10.1007/s002280050466
21. Kinoshita S, Hosomi K, Yokoyama S, Takada M. Time-to-onset analysis of amiodarone-associated thyroid dysfunction. *J Clin Pharm Ther*. 2020;45(1):65–71. doi:10.1111/jcpt.13024
22. Para KS, Chow CA, Nalamada K, et al. Suicidal thought and behavior in individuals with restless legs syndrome. *Sleep Med*. 2018;54:1–7. doi:10.1016/j.sleep.2018.09.019
23. Drager LF, Togeiro SM, Polotsky VY, Lorenzi-Filho G. Obstructive sleep apnea. *J Am Coll Cardiol*. 2013;62(7):569–576. doi:10.1016/j.jacc.2013.05.045
24. Lin S, Zhang H, Gao T, et al. The association between obesity and restless legs syndrome: a systemic review and meta-analysis of observational studies. *J Affect Disord*. 2018;235:384–391. doi:10.1016/j.jad.2018.04.042
25. Kim B, Kim TY, Choi EJ, Lee M, Kim W, Lee SA. Restless legs syndrome in patients with obstructive sleep apnea: association between apnea severity and symptoms of depression, insomnia, and daytime sleepiness. *Sleep Med*. 2024;117:40–45. doi:10.1016/j.sleep.2024.03.009
26. Saber WK, Almuallim AR, Algahtani R. Restless legs syndrome and the use of antipsychotic medication: An updated literature review. *Cureus*. 2022;14(8):e27821. doi:10.7759/cureus.27821
27. Korkmaz S, Aksu M. Topiramate induced restless legs syndrome case report. *Türk Uyku Tibbi Dergisi*. 2014;1(1):36–37.
28. Earley CJ, Allen RP. Restless legs syndrome augmentation associated with tramadol. *Sleep Med*. 2006;7(7):592–593. doi:10.1016/j.sleep.2006.05.011
29. Houston Methodist. Popular OTC antihistamines worsen restless legs syndrome. *React Wkly*. 2016;1599(1):6. doi:10.1007/s40278-016-16869-y
30. Aljunaid MA. An unusual case of an acute episode of restless leg syndrome following oral metoclopramide therapy. *Cureus*. 2024;16(2):e53754. doi:10.7759/cureus.53754
31. Bliwise DL, Zhang RH, Kutner NG. Medications associated with restless legs syndrome: a case-control study in the US renal data system (USRDS). *Sleep Med*. 2014;15(10):1241–1245. doi:10.1016/j.sleep.2014.05.011
32. C S, R A, H M, K D. Restless legs syndrome, periodic limb movements, and psychopharmacology. *Der Nervenarzt*. 2008;79(11):1263–4, 1266–72. doi:10.1007/s00115-008-2575-2
33. Kolla BP, Mansukhani MP, Bostwick JM. The influence of antidepressants on restless legs syndrome and periodic limb movements: a systematic review. *Sleep Med Rev*. 2018;38:131–140. doi:10.1016/j.smrv.2017.06.002
34. Rottach KG, Schaner BM, Kirch MH, et al. Restless legs syndrome as side effect of second generation antidepressants. *J Psychiatr Res*. 2008;43(1):70–75. doi:10.1016/j.jpsychires.2008.02.006
35. Ocak D, Kotan VO, Paltun SC, Mç A. Is restless legs syndrome related with depression/anxiety disorders or medications used in these disorders? A cross-sectional, clinic-based study. *Psychiatry Clin Psychopharmacol*. 2019;29(4):832–839. doi:10.1080/24750573.2019.1673943
36. Miyaguchi R, Masuda F, Sumi Y, et al. Prevalence of depression or depressive state in patients with restless legs syndrome: a systematic review and meta-analysis. *Sleep Med Rev*. 2024;77:101975. doi:10.1016/j.smrv.2024.101975
37. Jhoo JH, Yoon IY, Kim YK. Availability of brain serotonin transporters in patients with restless legs syndrome. *Neurology*. 2010;74(6):513–518. doi:10.1212/WNL.0b013e3181cef824
38. Oliveira C, Dehanov S, Vieira C, Maia T. P.158 restless legs syndrome induced by quetiapine: a case report and review of the literature. *Eur Neuropsychopharmacol*. 2019;29(Supl.6):S123–S124. doi:10.1016/j.euroneuro.2019.09.205
39. Kyung LE, Naomi S, Rebecca R. Aripiprazole, a novel option in the management of restless legs syndrome (rls) patients with augmentation and/or severe RLS symptoms: a report of 4 cases. *Nat Sci Sleep*. 2023;15:779–784. doi:10.2147/NSS.S421189
40. Ghori AK, Sajatovic M, Tampi RR. A Case of Emergent Restless Legs Syndrome With Lurasidone Therapy. *J Clin Psychopharm*. 2016;36(3):293–294. doi:10.1097/JCP.0000000000000496
41. McCall WV, Riley MA, Hodges C, McCloud L, Phillips M, Rosenquist PB. Asenapine-induced restless legs syndrome: differentiation from akathisia. *J Clin Sleep Med*. 2014;10(12):1341–1342. doi:10.5664/jcsm.4296
42. Schoretsanitis G, Nikolakopoulou A, Guinart D, Correll CU, Kane JM. Iron homeostasis alterations and risk for akathisia in patients treated with antipsychotics: a systematic review and meta-analysis of cross-sectional studies. *Eur neuropsychopharm*. 2020;35:1–11. doi:10.1016/j.euroneuro.2020.04.001
43. Aggarwal S, Dodd S, Berk M. Restless leg syndrome associated with olanzapine: a case series. *Curr drug saf*. 2010;5(2):129–131. doi:10.2174/157488610790936187
44. Seung-Gul K, Jin LY, Young-Min P, Leen K, Heon-Jeong L. Haplotype association of the MAP2K5 gene with antipsychotics-induced symptoms of restless legs syndrome among patients with schizophrenia. *Psychiatry Invest*. 2018;15(1):84–89. doi:10.4306/pi.2018.15.1.84
45. Zhao M, Geng T, Qiao L, et al. Olanzapine-induced restless legs syndrome. *J Clin Neurosci*. 2014;21(9):1622–1625. doi:10.1016/j.jocn.2014.01.007
46. Allen RP, Ondo WG, Ball E, et al. Restless legs syndrome (RLS) augmentation associated with dopamine agonist and levodopa usage in a community sample. *Sleep Med*. 2011;12(5):431–439. doi:10.1016/j.sleep.2011.03.003
47. Hening WA, Allen RP, Ondo WG, et al. Rotigotine improves restless legs syndrome: a 6-month randomized, double-blind, placebo-controlled trial in the United States. *Mov Disord*. 2010;25(11):1675–1683. doi:10.1002/mds.23157
48. Earley CJ, Connor J, Garcia-Borreguero D, et al. Altered brain iron homeostasis and dopaminergic function in restless legs syndrome (Willis–Ekbom Disease). *Sleep Med*. 2014;15(11):1288–1301. doi:10.1016/j.sleep.2014.05.009
49. Earley CJ, Uhl GR, Clemens S, Department of Neurology JHSoM, Baltimore, MD, USA. Electronic address: cearley@jhmi.edu. Research Service NMVHCS, Departments of Neurology, Neuroscience, Genetics M, et al. Connectome and molecular pharmacological differences in the dopaminergic system in restless legs syndrome (RLS): plastic changes and neuroadaptations that may contribute to augmentation. *Sleep Med*. 31;2017:71–77. doi:10.1016/j.sleep.2016.06.003
50. Pellitteri G, Versace S, Merlino G, Nilo A, Gigli GL, Valente M. A comprehensive update on the admet considerations for α2δ calcium channel ligand medications for treating restless legs syndrome. *Expert Opin Drug Metab Toxicol*. 2024;20(3):133–142. doi:10.1080/17425255.2024.2329738

51. Allen RP, Chen C, Garcia-Borreguero D, et al. Comparison of pregabalin with pramipexole for restless legs syndrome. *New Engl J Med*. 2014;370(7):621–631. doi:10.1056/NEJMoa1303646
52. Diego G-B, Jeffrey P, Sarah D, et al. Pregabalin versus pramipexole: effects on sleep disturbance in restless legs syndrome. *Sleep*. 2014;37(4):635–643. doi:10.5665/sleep.3558
53. Kamal RM, Van Noorden S, Ernst F, Dijkstra BA, Loonen AJ, De Jong CA. The neurobiological mechanisms of gamma-hydroxybutyrate dependence and withdrawal and their clinical relevance: a review. *Neuropsychobiology*. 2016;73(2):65–80. doi:10.1159/000443173
54. Beatriz A, Bertrand C, Jacques T, Yves D. Restless legs syndrome in narcolepsy: a side effect of sodium oxybate? *Sleep Med*. 2007;8(2):181–183. doi:10.1016/j.sleep.2006.06.003
55. Ferraro L, Tanganelli S, O'Connor WT, et al. gamma-Hydroxybutyrate modulation of glutamate levels in the hippocampus: an in vivo and in vitro study. *J Neurochem*. 2001;78(5):929–939. doi:10.1046/j.1471-4159.2001.00530.x
56. Benjamin W, Pearl CM, Wj W. Prevalence of current restless legs syndrome symptoms among patients treated with buprenorphine/naloxone for opioid use disorder. *Nat Sci Sleep*. 2023;15:851–859. doi:10.2147/NSS.S427403
57. Sieminski M, Zemojtel L. Acute drug-induced symptoms of restless legs syndrome in an emergency department. *J Clin Sleep Med*. 2019;15(5):779–780. doi:10.5664/jcsm.7774
58. Mackie SE, McHugh RK, McDermott K, Griffin ML, Winkelman JW, Weiss RD. Prevalence of restless legs syndrome during detoxification from alcohol and opioids. *J Subst Abuse Treat*. 2017;73:35–39. doi:10.1016/j.jsat.2016.10.001
59. Gupta R, Ali R, Ray R. Willis-Ekbom disease/restless legs syndrome in patients with opioid withdrawal. *Sleep Med*. 2018;45:39–43. doi:10.1016/j.sleep.2017.09.028
60. Berkowski J, Wang L, Mehra R. 0699 longitudinal assessment of buprenorphine effectiveness for severe restless legs syndrome and dopaminergic augmentation. *Sleep*. 2023;46(Supple1):A307–a308. doi:10.1093/sleep/zsad077.0699
61. Sun YM, Hoang T, Neubauer JA, Walters AS. Opioids protect against substantia nigra cell degeneration under conditions of iron deprivation: a mechanism of possible relevance to the restless legs syndrome (RLS) and Parkinson's disease. *J Neurol Sci*. 2011;304(1–2):93–101. doi:10.1016/j.jns.2011.02.003
62. Desax M-C, Hundsberger T, Rothermundt C, Omlin A, Gillessen S. Restless legs syndrome—an emerging potential side effect of enzalutamide: report of 2 cases. *Clin Genitourin Cancer*. 2015;13(5):e385–e386. doi:10.1016/j.clgc.2015.04.007
63. AVDdL G, Rá S, Jiménez A, González E. 5PSQ-067 Detection of adverse neuropsychiatric reactions associated with Abiraterone and enzalutamide treatments in the hospital. *Eur J Hosp Pharm*. 2019;26(S1):A232.
64. Guichard K, Ghorayeb I. Association of restless legs syndrome and Enzalutamide: one case report. *Sleep Med*. 2020;73(prepublish):15. doi:10.1016/j.sleep.2020.05.041
65. Seib DR, Tobiansky DJ, Meitzen J, Floresco SB, Soma KK. Neurosteroids and the mesocorticolimbic system. *Neurosci Biobehav Rev*. 2023;153:105356. doi:10.1016/j.neubiorev.2023.105356
66. Ferran J, Lm R, Nari K, et al. Testosterone boosts physical activity in male mice via dopaminergic pathways. *Sci Rep*. 2018;8(1):957. doi:10.1038/s41598-017-19104-0
67. Bispo JMM, Melo JEC, Gois AM. Testosterone propionate improves motor alterations and dopaminergic damage in the reserpine-induced progressive model of Parkinson's disease. *Brain Res Bull*. 2022;187:162–168. doi:10.1016/j.brainresbull.2022.06.018
68. Kritzer MF, Adler A, Locklear M. Androgen effects on mesoprefrontal dopamine systems in the adult male brain. *Neuroscience*. 2024;7(3):134–139.
69. Buchfuhrer MJ. Strategies for the treatment of restless legs syndrome. *Neurotherapeutics*. 2012;9(4):776–790. doi:10.1007/s13311-012-0139-4
70. Chiara B, Viviana LM, Sara A, et al. Tibialis anterior electromyographic bursts during sleep in histamine-deficient mice. *J Sleep Res*. 2020;30(4):e13255–e13255. doi:10.1111/jsr.13255

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