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Rotigotine safety in real-world settings: a pharmacovigilance study using FAERS data

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Abstract

Background This pharmacovigilance study aims to assess adverse reactions to rotigotine based on spontaneous reports in the FDA Adverse Event Reporting System (FAERS) database, providing insights for clinical dosing.

Methods We conducted a retrospective analysis using FAERS data from Q2 2007 to Q2 2024, employing four disproportionality analysis methods: Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN), and Multinomial Gamma Poisson Shrinkage (MGPS). These methods were utilized to detect and evaluate adverse events (AEs) associated with rotigotine.

Results The dataset retrieved from the FAERS, encompassing 17,522,075 reports, a subset of 7,570 AE reports specifically implicated rotigotine. Upon analysis, 172 preferred terms (PTs) exhibited significant disproportionality and were consistently identified by the four employed algorithms. Particularly, product adhesion issue(*N* = 1,336, ROR 115,28 [108.94–121.98], PRR 108.46 [135850.43], EBGM 103.57 [98.79], IC (5.03) [5.03]) emerged as the predominant AE. Serious and unexpected AEs, such as drug ineffectiveness(*N* = 651, ROR 1.32 [1.22–1.43], PRR 1.31 [50.04], EBGM 1.31 [1.23], IC 0.39 [-1.27]), fall incidents(*N* = 361, ROR 2.93 [2.64–3.25], PRR 2.9 [451.76], EBGM 2.9 [2.66], IC 1.54 [-0.13]), and Parkinson's disease(*N* = 345, ROR 51.57 [46.31–57.42], PRR 50.79 [16476.71], EBGM 49.7 [45.43], IC 5.64 [3.97], were also recorded.The majority of these AEs were reported within the initial 30 days of therapy (*n* = 298, 22.1%), whereas a significant number were noted after 360 days of treatment (*n* = 507, 36.2%). The median time to the onset of AEs was 213 days.

Conclusion Our findings, which align with the established safety profile of rotigotine, reveal the presence of unexpected serious AEs and emphasize the importance of continued vigilance in post-marketing surveillance.

Keywords Rotigotine, Real-world analysis, Pharmacovigilance, Adverse drug event, FAERS

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Introduction

Willis-Ekbom disease, alternatively referred to as Restless Legs Syndrome (RLS), is a prevalent sensorimotor disorder characterized by a significant circadian rhythm [1]. Reports indicate that the prevalence rates in the United States and Europe range from 5 to 15% [2–4], whereas in Asian populations, the rates are comparatively lower, falling below 5% [5]. Moreover, with disease progression, it is reported that approximately 48% of the patients experience involvement of the arms [6]. Thus, once the condition is established, lifelong treatment becomes necessary [7]. During treatment, we would be wise to consider the use of long-acting drugs, such as rotigotine [8]. Rotigotine has a significantly stronger binding affinity for D2 and D3 receptors than endogenous dopamine, with 53-fold and 2600-fold greater affinity, respectively [9]. Meanwhile, the D1 receptor is crucial in the direct pathway; its activation enhances striatonigral pathway signal transduction, improving motor function. D2 and D3 receptors, mainly in the indirect pathway, are activated by rotigotine. This inhibits the overactive indirect pathway, reducing symptoms like bradykinesia, rigidity, and tremors [10, 11]. In Parkinson's disease (PD), D1, D2, and D3 receptors in the striatum (vital for fine-motor control) are targeted by rotigotine. By restoring dopaminergic stimulation, rotigotine alleviates fine-motor control disorders and improves motor symptoms [12].

Notably, in PD, the progressive loss of dopaminergic neurons in the substantia nigra pars compacta reduces dopaminergic neurotransmission in the basal ganglia, causing motor symptoms such as resting tremor, rigidity, bradykinesia, postural instability, and gait disturbances [12]. Rotigotine restores dopaminergic stimulation in relevant brain regions and effectively alleviates these motor symptoms. Randomized clinical trials have confirmed its efficacy in both early - and advanced - stage PD patients. For instance, Nir Giladi et al.'s study on early-stage PD showed that rotigotine treatment significantly improved Unified Parkinson's Disease Rating Scale (UPDRS) scores in a dose-dependent manner [13]. In RLS, though the etiology remains unclear, dopaminergic dysregulation is suspected. Rotigotine is effective in treating moderate to severe primary RLS. Randomized, double - blind, placebo-controlled studies, such as that of Claudia Trenkwalder et al., have demonstrated that rotigotine can significantly improve symptoms as evaluated by the International Restless Legs Study Group rating scale (IRLS) and Clinical Global Impression (CGI) scale [14]. Wolfgang Oertel et al.'s 5 - year open - label study further confirmed the long-term safety and efficacy of rotigotine in RLS. In this study, patients had overall improvements in IRLS total scores [15].

Dopaminergic agonists, including rotigotine, have long been a cornerstone in the therapeutic management of RLS and are extensively utilized in clinical settings. However, they have been associated with a range of side effects. For example, the most common is that the skin area where the patch is applied usually becomes sensitive. Other adverse reactions include dizziness, headache, sudden onset of sleepiness, insomnia, gastrointestinal disturbances, constipation, and orthostatic hypotension [15, 16]. Clinical trials furnish valuable insights, yet they present only a fragment of the overall scenario. Variations in patient responses in real-world settings stem from a multitude of individual health conditions and additional influencing factors [17]. Consequently, in-depth research is vital for gaining a thorough comprehension of rotigotine's impact across a spectrum of patient groups under real-world conditions. However, a large-scale safety analysis specifically tailored to post-marketing rotigotine data remains absent from the current body of research.

The FDA Adverse Event Reporting System database (FAERS) is a substantial database established to facilitate the FDA's drug safety monitoring program for FDA-approved medications in actual clinical practice [18]. In recent times, an increasing number of pharmacovigilance studies leveraging the FAERS database have been disseminated, highlighting the acknowledged reliability of this research methodology for assessing drug safety profiles [19, 20]. However, the FAERS database still has certain limitations, which does not affect its continued effectiveness as a method for analyzing large sample sizes [21].

In conclusion, recognizing the clinical benefits that may arise, our study's objective was to gather a thorough understanding of the post-marketing safety profile for rotigotine. The analysis of unforeseen adverse events (AEs) will provide medical professionals with a deeper insight into the potential reactions associated with rotigotine. Our research represents the inaugural use of the FAERS database to disclose the safety profile of post-marketing AEs related to rotigotine in a broad demographic. This notable accomplishment paves the way for future studies, and the identification of unexpected AEs will contribute to the refinement of therapeutic approaches.

Methods

Data source and collection

We performed a retrospective pharmacovigilance analysis leveraging the FAERS database to examine adverse event [22] reports for rotigotine from Q2 2007 to Q2 2024, encompassing the period post-FDA approval in May 2007. The FAERS database, which aggregates information from diverse sources such as demographic and administrative details (DEMO), adverse drug reactions (REAC), patient outcomes (OUTC), drug specifics (DRUG), therapy timelines (THER), reporting entity details (RPSR), and indications for use (INDI), was employed to categorize AEs in relation to individual

patient drug exposures [23]. The adverse events (AEs) were characterized as the adverse reactions that occurred in patients undergoing treatment with Rotigotine. To ensure consistency and standardization, AE reports were coded using preferred terms (PTs) sourced from the Standardized MedDRA Queries (SMQ) of the Medical Dictionary for Regulatory Activities (MedDRA Version 26.1). These codes are systematically arranged within a hierarchical framework that includes the system organ class (SOC), high-level group term (HLGT), and high-level term (HLT) [24]. Following the FDA-recommended deduplication approach, we selected specific fields from the Patient Personal Information Form (DEMO), namely the main number (PRIMARYID), case number (CASEID), and date and time (FDA_DT). We sorted the records in the order of CASEID, FDA_DT, and PRIMARYID. When multiple records had the same CASEID, we retained the report with the most recent FDA_DT value. This step was taken to ensure that our dataset was free from redundancy and reflected the most up-to-date information [21]; When no match was identified, we gave precedence to the record that bore the higher PRIMARYID [25]. Our study centered on rotigotine as the main suspected drug, leading to the detection of 7,570 adverse event [22] reports and the retrieval of 22,408 corresponding preferred terms (PTs) from the FAERS database. Figure 1 illustrates a comprehensive flowchart detailing the methodology employed in our investigation.

Statistical analysis

We utilized descriptive statistical methods to profile the reporting characteristics of adverse events (AEs) associated with rotigotine. The notion of disproportionality analysis pertains to evaluating the intensity of the association between a specific medication and an adverse event [22]. This is accomplished by scrutinizing the observed frequency ratios among groups exposed to the medication versus those unexposed, using a four-cell contingency table for comparative analysis as detailed in Supplementary Table 1. The Reporting Odds Ratio (ROR) algorithm it was used to determine positive signals. The criterion for including a risk signal related to the target drug was set as the number of cases with $N \geq 3$ and the lower limit of the 95% confidence interval 95% CI > 1. Regarding the Proportional Reporting Ratio (PRR) algorithm, positive signals were identified based on specific rules. A signal was considered positive when PRR ≥ 2,x2 ≥ 4, $N \geq 3$. For the Multinomial Gamma Poisson Shrinker (MGPS) algorithm, the generation of a positive signal was determined by the rule that EBGM05 > 2. Finally, with the Bayesian Confidence Propagation Neural Network (BCPNN) algorithm, positive signals were judged according to the rule that IC025 > 0. Supplementary Table 2 offers comprehensive information regarding the methodologies and threshold values employed in these disproportionality analyses. If an adverse event [22] exceeds the positivity threshold according to any of these methods, it is considered a potential adverse reaction [26]. A higher value indicates a stronger signal intensity and a more significant association between the medication under investigation and the adverse event [22]. In the sensitivity analysis, as rotigotine is often used with levodopa, we exclude reports with concurrent levodopa use by systematically searching for related terms. All analyses were performed using version 4.2.2 of the R software.

Results

Descriptive analysis

17,522,075 AE reports were extracted from the FAERS database between Q2 2007 and Q2 2024. Among these, 7,505 reports identified rotigotine as the primary suspected medication associated with the AEs. AE reports showed a gradual increase from 2007 to 2024, peaking in 2023 (Table 1). Demographic analysis revealed that the highest AE prevalence was observed in individuals aged 65–85 (32.3%), followed by those aged 18–65 (13.8%). The majority of reports originated from the United States (47.3%), with significant contributions from Germany (9.2%), Colombia (8.7%), Japan (6.2%), and Mexico (5.3%). Consumers submitted 61.5% of the reports. The most frequently reported indications were PD (50.9%) and RLS (18.6%), aligning with FDA-approved uses (Table 1).

Time to event onset

Among 1,347 reports detailing the timing of AEs, the median time to onset was 213 days (interquartile range: 41-592.5 days). The majority of AEs (22.1%) occurred within the first 30 days of therapy, while 36.2% were reported after 360 days of treatment(Fig. 2). The Weibull distribution analysis indicated a decreasing trend in AE occurrence over time, with a shape parameter (β) of 0.59 (95% CI: 0.53–0.66), suggesting early-stage adverse reactions (Table 2).

System organ class (SOC) level adverse event distribution

Rotigotine-related AEs were detected across all 27 system organ classes (SOCs). As presented in Table 3, the most pronounced signals emerged in general disorders and administration site conditions (N = 4,803, ROR 1.28 [1.24–1.32], PRR 1.22 [231.24], EBGM 1.22 [1.19], IC 0.29 [-1.38]), nervous system disorders (N = 3,407, ROR 1.94 [1.87–2.01], PRR 1.79 [1307.26], EBGM 1.79 [1.74], IC 0.84 [-0.82]), injury, poisoning and procedural Complications(N = 2,557, ROR 1.24 [1.19–1.29], PRR 1.21 [104.25], EBGM 1.21 [1.17], IC 0.28 [-1.39]), psychiatric disorders (N = 2302, ROR 1.89 [1.81–1.97], PRR 1.8 [865.62], EBGM 1.8 [1.73], IC 0.85 [-0.82]), and

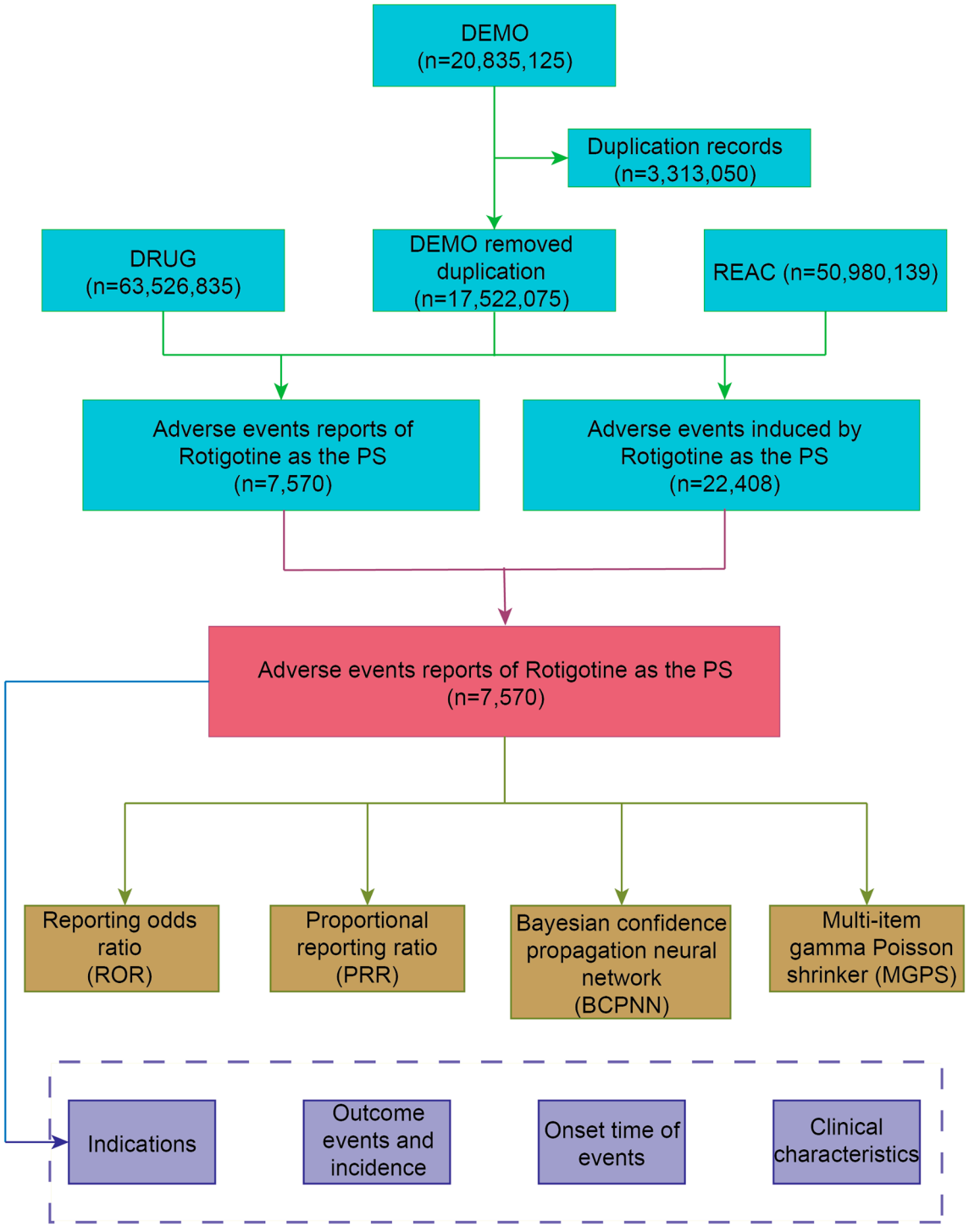

Fig. 1 The flow diagram of selecting Rotigotine-related AEs from FAERS database

product issues(N = 2,058, ROR 6.22 [5.94–6.51], PRR 5.74 [8166.52], EBGM 5.73 [5.51], IC 2.52 [0.85]). An ROR greater than 1, such as those in these three SOCs, indicates that the odds of reporting AEs in the rotigotine-exposed group are higher than in the non-exposed group. The fact that the entire 95% CI lies above 1 further validates the statistical significance of these associations. Notably, the ROR for product issues (6.22, 95% CI: 5.94–6.51) indicates a particularly robust association, with the lower limit (5.94) significantly higher than 1, highlighting a substantial risk. This suggests a likely causal link between rotigotine treatment and AEs in these organ

Table 1 Clinical characteristics of reports with rotigotine from the FAERS database

Characteristics	Case number	Proportion (%)
Number of events	7570	
Gender (%)		
Female	3325	43.9
Male	3180	42.0
Not specified	1065	14.1
Weight (kg)		
< 50	123	1.6
> 100	212	2.8
50~100	1346	17.8
Not specified	5889	77.8
Age(years)		
< 18	6	0.1
18~65	1042	13.8
65~85	2450	32.3
Not specified	3783	50
Reported Countries		
United States	3580	47.3
Mexico	401	5.3
Colombia	655	8.7
Germany	698	9.2
Japan	472	6.2
others	1809	23.9
Reporter		
Consumer	4658	61.5
Health Professional	201	2.7
Medical Doctor	1005	13.3
Pharmacist	574	7.6
Other health-professional	417	5.5
Lawyer	5	0.1
Not specified	710	9.3
Year of report		
2007	141	1.8
2008	608	8.0
2009	131	1.7
2010	111	1.4
2011	66	0.9
2012	107	1.4
2013	214	2.8
2014	156	2.0
2015	294	3.89
2016	421	5.6
2017	461	6.1
2018	355	4.7
2019	367	4.8
2020	869	11.5
2021	743	9.8
2022	841	11.1
2023	1222	16.1
2024	463	6.1
Outcomes		
Other serious outcome	1967	26.0
Hospitalization	1391	18.3
Death	2206	29.1
Disability	107	1.5
Required Intervention to Prevent Permanent Impairment	3	0.03
Life-Threatening	74	0.98
Not specified	2926	38.7
Indications		
Parkinson's disease	3852	50.9
Restless legs syndrome	1406	18.6
on-off phenomenon	20	0.3
Tremor	12	0.2
Neuropathy peripheral	8	0.1
Not specified	2272	30.2

systems. These findings thus pinpoint the primary organ systems significantly affected by rotigotine treatment, which can inform further research on its safety profile and clinical implications.

Preferred Term (PT) level distribution of adverse events

In this analysis, four computational algorithms were applied at the Preferred Term (PT) level to examine adverse drug reactions against established screening thresholds. This process identified 1888 PTs, with 172 PTs meeting all four algorithms (Fig. 3). Table 4 lists the top 30 most frequently reported PTs by volume, in descending order. Among these, positive signal reactions included product adhesion issues, drug ineffectiveness, death, off-label use, fall incidents, and various others. As per rotigotine's prescribing information, product adhesion issue ($N = 1{,}336$, ROR 115,28 [108.94–121.98], PRR 108.46 [135850.43], EBGM 103.57 [98.79], IC (5.03) [5.03]), dizziness ($N = 249$, ROR 1.35 [1.2–1.53], PRR 1.35 [22.84], EBGM 1.35 [1.22], IC 0.43 [-1.23]) were frequently reported. Notably, the product adhesion issue was the most prominent AE, consistent with rotigotine's prescribing information. Other significant AEs, such as drug ineffectiveness($N = 651$, ROR 1.32 [1.22–1.43], PRR 1.31 [50.04], EBGM 1.31 [1.23], IC 0.39 [-1.27]), fall incidents($N = 361$, ROR 2.93 [2.64–3.25], PRR 2.9 [451.76], EBGM 2.9 [2.66], IC 1.54 [-0.13]), and PD ($N = 345$, ROR 51.57 [46.31–57.42], PRR 50.79 [16476.71], EBGM 49.7 [45.43], IC 5.64 [3.97], were also identified. The product adhesion issue was the most prominent across all PTs. Figure 4 presents the top 20 PTs and their corresponding SOCs, with the PTs ranked in descending order according to the case number.

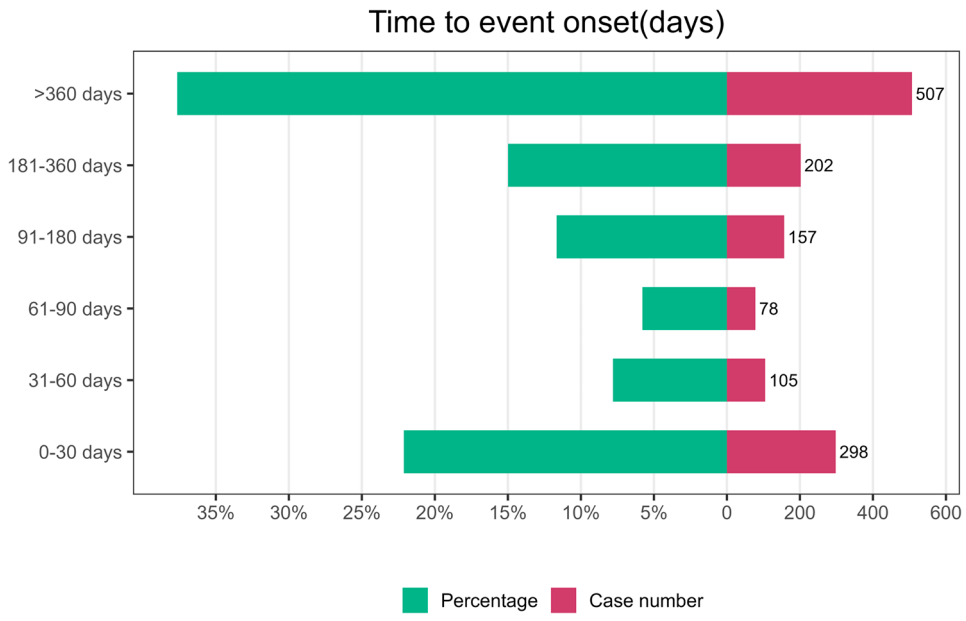

Fig. 2 Time to event onset

Table 2 Time to onset of Rotigotine-associated adverse events and Weibull distribution analysis

Drug	Time to onset (days)		Weibull distribution		
	Case reports	Median (IQR)	Scale parameter: α (95% CI)	Shape parameter: β (95%CI)	Type
Rotigotine	1347	213 (41–592.5)	214.31(161.95–266.68)	0.59(0.53–0.66)	Early failure

Abbreviations: CI, confidence interval; IQR, interquartile range

Sensitivity analysis

Rotigotine is commonly administered in conjunction with medications like levodopa. To isolate the safety signals uniquely associated with rotigotine, we employed the exclusion methodology. We systematically searched for any indication of concurrent levodopa use within the reports. This involved screening the text fields of all reports for keywords related to levodopa and other relevant terms. After applying this exclusion process, a total of 1,490 reports, which contained 15,268 AEs, were selected for in-depth analysis. Persistent AEs included product adhesion issue, application site erythema, and tremor, further supporting the safety signals identified in the primary analysis (Table 5).

Discussion

Although there have been numerous reports related to Rotigotine, there has been a lack of discussion on Rotigotine side effects based on large samples. Our investigation, which employed a substantial dataset, thoroughly evaluated the adverse events linked to rotigotine post its market introduction in 2007. This study, through the analysis of data from the FAERS, validated previously recognized adverse reactions included on the rotigotine drug label, including application site reaction, dizziness, insomnia, headache, and omnolence. Furthermore, adverse events not cited on the label, including drug Ineffective, death, PD, fall, Tremor. These results emphasize the importance of drug monitoring, especially at the beginning of treatment, which we should continue to monitor in order to effectively manage and reduce possible adverse reactions.

Previous clinical trials have extensively substantiated the common adverse reactions indicated on the rotigotine label. A previous double-blind, randomized, placebo-controlled trial by Antonini A et al. concluded that the most common treatment-emergent adverse events (TEAEs) in more than 5% of patients treated with rotigotine included nausea, somnolence, headache and application site reactions [27]. The identical conclusion was also arrived at in, the controlled trial led by Hening WA et al., the pharmacokinetic study carried out by Elshoff JP et al., and the PREFER study conducted by LeWitt PA et al. [28–30].Furthermore, the PREFER study, led by LeWitt PA et al., demonstrated that 3% of subjects in the placebo group reported itching at the application site, compared to 13% and 19% in the rotigotine treatment group [30]. Our findings are largely in line.

Within our study, numerous instances of product adhesion issue were observed. While this adverse reaction is noted as an expected occurrence within the product's labeling, the range of adverse effects it encompasses is excessively broad. In our study's findings, AEs at the PT level, including application site pruritus, application site

Table 3 The signal strength of AEs related to rotigotine at the SOC level in the FAERS database was detected by four algorithms

System organ class (SOC)	Case reports	ROR (95% CI)	PRR (χ^2)	EBGM (EBGM05)	BCPNN (IC025)
General Disorders And Administration Site Conditions*	4803	1.28 (1.24–1.32)	1.22 (231.24)	1.22 (1.19)	0.29 (-1.38)
Nervous System Disorders*	3407	1.94 (1.87–2.01)	1.79 (1307.26)	1.79 (1.74)	0.84 (-0.82)
Injury, Poisoning And Procedural Complications*	2557	1.24 (1.19–1.29)	1.21 (104.25)	1.21 (1.17)	0.28 (-1.39)
Psychiatric Disorders*	2302	1.89 (1.81–1.97)	1.8 (865.62)	1.8 (1.73)	0.85 (-0.82)
Product Issues*	2058	6.22 (5.94–6.51)	5.74 (8166.52)	5.73 (5.51)	2.52 (0.85)
Gastrointestinal Disorders	1082	0.54 (0.51–0.57)	0.56 (401.82)	0.56 (0.53)	-0.83 (-2.49)
Skin And Subcutaneous Tissue Disorders	942	0.77 (0.72–0.82)	0.78 (64.64)	0.78 (0.73)	-0.37 (-2.03)
Musculoskeletal And Connective Tissue Disorders	752	0.62 (0.57–0.66)	0.63 (173.68)	0.63 (0.59)	-0.67 (-2.33)
Infections And Infestations	630	0.52 (0.48–0.56)	0.53 (277.11)	0.53 (0.5)	-0.92 (-2.58)
Cardiac Disorders	547	0.94 (0.86–1.02)	0.94 (2.28)	0.94 (0.87)	-0.09 (-1.76)
Surgical And Medical Procedures*	525	1.74 (1.6–1.9)	1.73 (162.87)	1.73 (1.61)	0.79 (-0.88)
Investigations	518	0.36 (0.33–0.4)	0.38 (562.57)	0.38 (0.35)	-1.4 (-3.07)
Respiratory, Thoracic And Mediastinal Disorders	514	0.47 (0.43–0.51)	0.48 (304.48)	0.48 (0.45)	-1.06 (-2.73)
Vascular Disorders	316	0.65 (0.58–0.73)	0.66 (58.57)	0.66 (0.6)	-0.61 (-2.28)
Renal And Urinary Disorders	245	0.58 (0.51–0.66)	0.59 (71.77)	0.59 (0.53)	-0.76 (-2.43)
Metabolism And Nutrition Disorders	240	0.49 (0.43–0.56)	0.5 (124.46)	0.5 (0.45)	-1.01 (-2.67)
Eye Disorders	224	0.49 (0.43–0.56)	0.5 (115.8)	0.5 (0.45)	-1.01 (-2.67)
Social Circumstances	177	1.85 (1.6–2.15)	1.85 (68.89)	1.85 (68.89)	0.88 (-0.78)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	149	0.24 (0.2–0.28)	0.25 (354.76)	0.25 (0.21)	-2.02 (-3.69)
Hepatobiliary Disorders	74	0.36 (0.29–0.46)	0.37 (81.86)	0.37 (0.3)	-1.45 (-3.11)
Immune System Disorders	73	0.29 (0.23–0.36)	0.29 (127.7)	0.29 (0.24)	-1.78 (-3.45)
Blood And Lymphatic System Disorders	66	0.17 (0.13–0.22)	0.17 (262.73)	0.17 (0.14)	-2.52 (-4.19)
Reproductive System And Breast Disorders	63	0.34 (0.26–0.43)	0.34 (81.43)	0.34 (0.28)	-1.56 (-3.22)
Ear And Labyrinth Disorders	57	0.59 (0.45–0.76)	0.59 (16.54)	0.59 (0.47)	-0.77 (-2.43)
Pregnancy, Puerperium And Perinatal Conditions	17	0.18 (0.11–0.28)	0.18 (64.97)	0.18 (0.12)	-2.49 (-4.16)
Endocrine Disorders	11	0.19 (0.11–0.35)	0.19 (37.28)	0.19 (0.12)	-2.37 (-4.04)
Congenital, Familial And Genetic Disorders	5	0.07 (0.03–0.17)	0.07 (59.23)	0.07 (0.03)	-3.78 (-5.45)

Asterisks (*) indicate statistically significant signals. EBGM and IC are Bayesian-based metrics used to quantify the strength of associations between drugs and adverse events. EBGM represents the geometric mean of the posterior distribution of the reporting ratio, while IC measures the information gained from the association. Both metrics are accompanied by their 95% confidence intervals (EBGM05 and IC025), which indicate statistical significance. Abbreviations: ROR, reporting odds ratio; PRR, proportional reporting ratio; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of the 95% confidence interval of EBGM; BCPNN, bayesian confidence propagation neural network, the lower limit of the 95% confidence interval of the IC

erythema, and application site rash, accounted for a significant number of cases. The issue of product adhesion was the most prevalent among the cases in our research, and clinically, this category of adverse reactions remains one of the most common challenges faced by clinician. Rotigotine, as a topical agent, bypasses first-pass metabolism as well as the gastrointestinal tract, thus becoming a more favorable choice compared to other dopamine agonists (DAs), especially for those patients who seek the simplicity of a once-daily regimen or who have gastrointestinal problems such as dysphagia or gastroparesis [31, 32]. It is also this characteristic that has led to an increase in adverse reactions at the site of external application, such as: prpuritus, erythema, peripheral swelling, etc. In the research on the efficacy and safety of rotigotine for RLS, which was carried out in Japan by Yuichi Inoue and colleagues, application site reactions were reported in 42.1% of the patients in the 2 mg/24 h rotigotine group and 50.0% in the 3 mg/24 h group. Notably, one participant in the 2 mg/24 h rotigotine cohort presented with erythema, edema, papules, seropapules, and small vesicles at the application site by week 5 of the treatment [33]. Concurrently, in a German clinical trial assessing the efficacy and tolerability of rotigotine for treating RLS led by Karin Stiasny-Kolster et al., a total of 84 skin reactions were documented among 66 (9.6%) of the patients. The most frequently reported skin reactions included pruritus (23 cases), rash (15 cases), and allergic dermatitis (14 cases). A total of 45 (6.6%) patients ceased treatment because of these skin reactions [34]. As a result, there are reports showing that by altering the patch application site daily and ensuring the patch is removed gently, irritant effects can potentially be minimized [35].

The pathological feature of PD is the gradual loss of dopaminergic neurons within the substantia nigra pars compacta. This loss leads to a reduction in dopaminergic signaling within the basal ganglia, consequently leading to reduced dopaminergic input to the striatum [12,

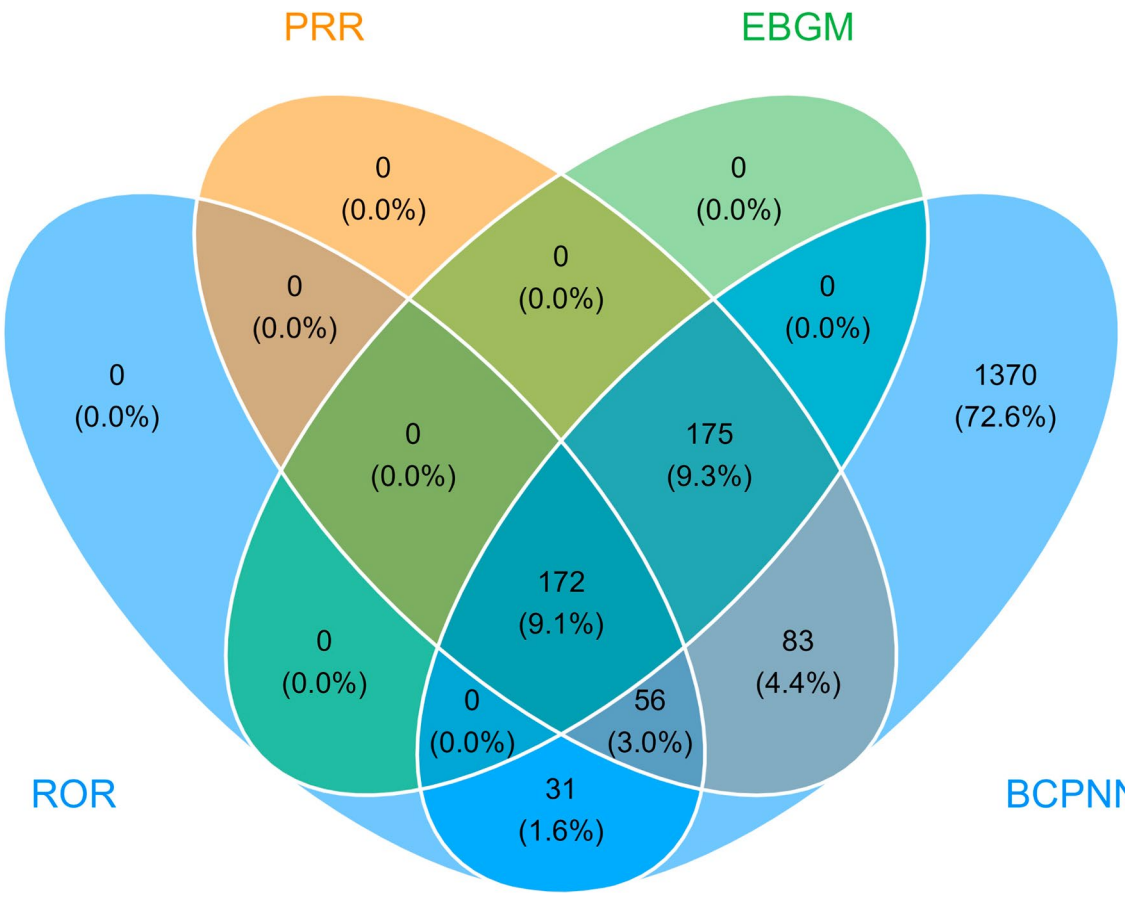

Fig. 3 Venn diagram for the screening of all PTs based on the results of the four algorithms

36]. In the progression of PD, the impairment and death of dopaminergic (DA) neurons are associated with a variety of biochemical elements, such as free radicals, mitochondrial dysfunction, abnormal protein aggregation, excitotoxicity, and inflammation [37]. Furthermore, mitochondrial impairment and the substantial generation of reactive oxygen species(ROS) are principal contributors to the demise of dopaminergic (DA) neurons [38]. Currently, the pathophysiological mechanism of RLS is still unclear. But there are reports indicating that the role of the dopaminergic system in the pathophysiology of RLS is evidenced by the prompt alleviation of symptoms following the administration of low doses of dopaminergic medications [39]. Dopaminergic agents might alleviate RLS symptoms due to their influence on neural networks rather than merely compensating for a dopaminergic insufficiency [40]. The fact that the dopaminergic agonists need to penetrate the blood-brain barrier to alleviate RLS symptoms suggests that dopamine's involvement is within the central nervous system, rather than the peripheral nervous system, which is implicated in the pathophysiology of RLS [41]. Nevertheless, the majority of preclinical and clinical data indicates an overactive, rather than an underactive, dopaminergic system characterized by hypersensitivity in corticostriatal pathways [42–44]. However, it is worth provoking us to think that this adverse reaction in PD may not be due to the drug. Therefore, the presence of "Parkinson's disease" as an adverse event requires careful interpretation. Rotigotine is used to treat PD, so it is crucial to distinguish between the progression of the primary disease and a potential drug - induced effect. In our dataset, it was not specified whether the administration of rotigotine was for primary or secondary RLS, and this lack of clarity adds to the complexity. Some patients with RLS may already be at a higher risk of developing PD, as there is a known association between the two disorders. A previous study in Brazil found a high incidence of PD - associated RLS, and other research has suggested that RLS in PD patients may be related to prolonged dopaminergic therapy rather than the disease itself [45, 46]. It is possible that some cases reported as PD as an adverse event of rotigotine could be the natural progression of an underlying, undiagnosed PD in patients initially presenting with RLS. On the other hand, although rare, there may be a paradoxical reaction to rotigotine that could potentially contribute to the manifestation of PD - like symptoms. However, more research is needed to confirm this hypothesis. In light

Table 4 The top 30 signal strength of adverse events of rotigotine ranked by the number of case reports at the PTs level in FAERS database

Preferred terms (PTs)	Case reports	ROR (95% CI)	PRR (χ^2)	EBGM (EBGM05)	BCPNN (IC025)
Product Adhesion Issue*	1336	115.28 (108.94–121.98)	108.46 (135850.43)	103.57 (98.79)	6.69 (5.03)
Drug Ineffective*	651	1.32 (1.22–1.43)	1.31 (50.04)	1.31 (1.23)	0.39 (-1.27)
Death*	529	1.67 (1.53–1.82)	1.65 (137.14)	1.65 (1.53)	0.72 (-0.94)
Off Label Use*	437	1.46 (1.33–1.6)	1.45 (62.01)	1.45 (1.34)	0.54 (-1.13)
Application Site Pruritus*	417	50.28 (45.59–55.46)	49.37 (19348.15)	48.34 (44.54)	5.6 (3.93)
Application Site Erythema*	409	41.5 (37.6–45.81)	40.77 (15592.76)	40.07 (36.89)	5.32 (3.66)
Device Adhesion Issue*	383	75.95 (68.54–84.16)	74.67 (26959.86)	72.33 (66.38)	6.18 (4.51)
Fall*	361	2.93 (2.64–3.25)	2.9 (451.76)	2.9 (2.66)	1.54 (-0.13)
Parkinson'S Disease*	345	51.57 (46.31–57.42)	50.79 (16476.71)	49.7 (45.43)	5.64 (3.97)
Overdose*	334	4.01 (3.59–4.46)	3.96 (740.61)	3.96 (3.61)	1.98 (0.32)
Tremor*	308	5.01 (4.48–5.61)	4.96 (974)	4.95 (4.51)	2.31 (0.64)
Dizziness*	249	1.35 (1.2–1.53)	1.35 (22.84)	1.35 (1.22)	0.43 (-1.23)
Insomnia*	245	2.46 (2.17–2.79)	2.45 (210.31)	2.45 (2.2)	1.29 (-0.38)
Hallucination*	233	8.7 (7.64–9.9)	8.62 (1564.37)	8.59 (7.71)	3.1 (1.44)
Nausea	224	0.77 (0.67–0.87)	0.77 (15.69)	0.77 (0.69)	-0.38 (-2.04)
Application Site Reaction*	215	98.76 (86.11–113.28)	97.82 (19756.77)	93.83 (83.66)	6.55 (4.89)
Restless Legs Syndrome*	210	30.74 (26.81–35.24)	30.46 (5905.93)	30.07 (26.82)	4.91 (3.24)
Somnolence*	199	2.69 (2.34–3.1)	2.68 (209.82)	2.68 (2.38)	1.42 (-0.25)
Application Site Rash*	191	35 (30.32–40.4)	34.71 (6159.97)	34.2 (30.33)	5.1 (3.43)
Gait Disturbance*	169	2.28 (1.96–2.65)	2.27 (120.64)	2.27 (2)	1.18 (-0.48)
Pneumonia*	164	1.39 (1.19–1.62)	1.38 (17.6)	1.38 (1.22)	0.47 (-1.2)
Wrong Technique In Product Usage Process*	160	2.15 (1.84–2.51)	2.14 (97.65)	2.14 (1.88)	1.1 (-0.57)
Anxiety*	159	1.47 (1.26–1.72)	1.47 (23.73)	1.47 (1.29)	0.55 (-1.11)
Fatigue	152	0.52 (0.44–0.61)	0.52 (66.3)	0.52 (0.46)	-0.93 (-2.6)
Vomiting	140	0.82 (0.69–0.97)	0.82 (5.59)	0.82 (0.71)	-0.29 (-1.95)
Pain	140	0.59 (0.5–0.69)	0.59 (40.4)	0.59 (0.51)	-0.76 (-2.43)
Intentional Product Misuse*	139	4.2 (3.56–4.97)	4.18 (336.66)	4.18 (3.63)	2.06 (0.4)
Asthenia	137	0.99 (0.83–1.17)	0.99 (0.03)	0.99 (0.86)	-0.02 (-1.69)
Pruritus	137	1.05 (0.89–1.24)	1.05 (0.35)	1.05 (0.91)	0.07 (-1.59)
Dysphagia*	128	3.7 (3.11–4.4)	3.68 (249.92)	3.68 (3.18)	1.88 (0.21)

Asterisks (*) indicate statistically significant signals. EBGM and IC are Bayesian-based metrics used to quantify the strength of associations between drugs and adverse events. EBGM represents the geometric mean of the posterior distribution of the reporting ratio, while IC measures the information gained from the association. Both metrics are accompanied by their 95% confidence intervals (EBGM05 and IC025), which indicate statistical significance. Abbreviations: ROR, reporting odds ratio; PRR, proportional reporting ratio; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of the 95% confidence interval of EBGM; BCPNN, bayesian confidence propagation neural network, the lower limit of the 95% confidence interval of the IC

of the above-mentioned complexities, when interpreting the data, it is essential to exercise extreme caution, particularly in the context of future updates and follow-ups within the FAERS database. In cases where PD is reported as an adverse event, a comprehensive clinical evaluation is necessary. This evaluation should include a detailed medical history, assessment of disease-specific biomarkers if available, and longitudinal follow-up to accurately determine whether it is disease progression or a drug-related reaction. Clinically, if a patient on rotigotine shows signs of PD, healthcare providers should not immediately attribute it to the drug. Instead, they should consider the patient's pre-existing risk factors, such as a family history of PD or other neurodegenerative disorders. Future research should focus on developing more specific criteria to differentiate between drug-induced Parkinson's-like symptoms and disease progression. This would not only improve the accuracy of data interpretation but also enhance the safety and effectiveness of rotigotine and similar medications in clinical practice.

Fall incidents were frequently reported, particularly in elderly patients. This may be attributed to rotigotine's side effects, such as dizziness and orthostatic hypotension, which are dose-dependent and more pronounced at higher doses [47, 48]. Additionally, the motor symptoms of PD, including postural instability and gait disturbances, may contribute to the risk of falls [49]. Moreover, tremors, which are also an adverse event associated with rotigotine, can further increase the risk of falls. Tremors can affect a patient's coordination and stability, making it difficult to maintain an upright posture. In addition, the underlying diseases themselves, such as RLS and PD, can cause balance problems.

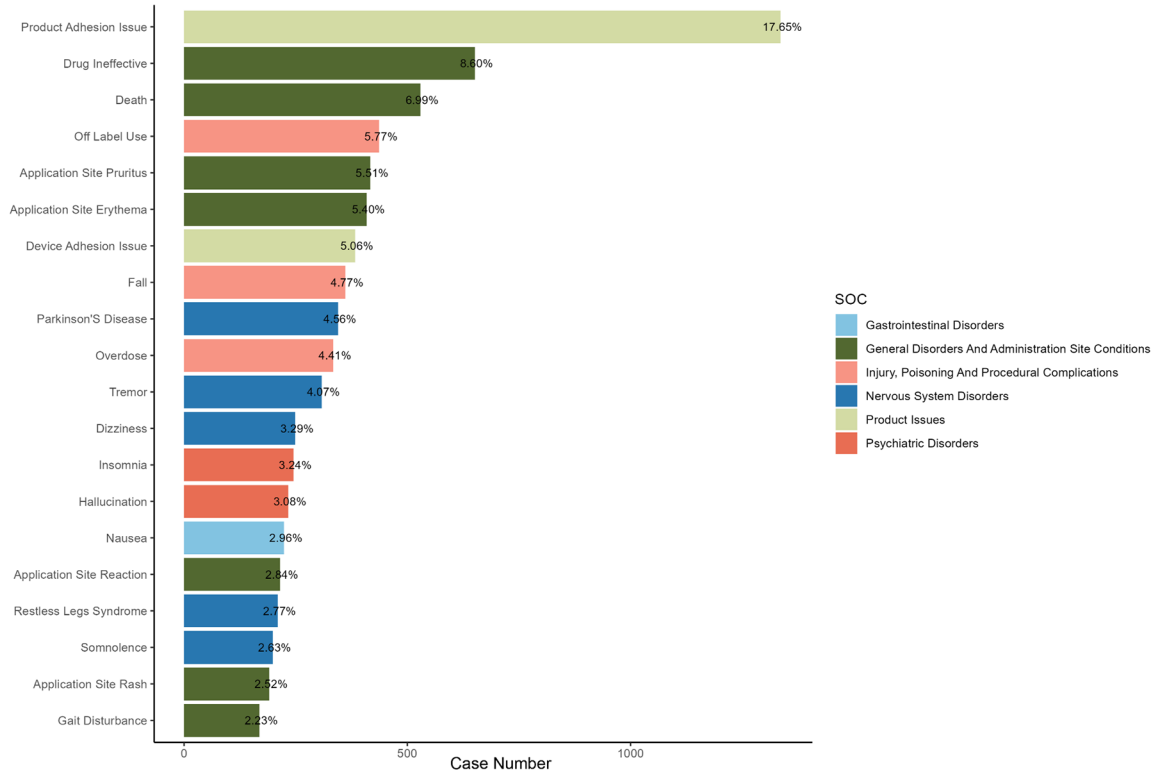

Fig. 4 Signal Strength of top20 AEs of Rotigotine at the PT Level in FAERS Database

Patients with RLS may experience involuntary leg movements that can disrupt their gait, and PD patients often have postural instability as a characteristic symptom. Rotigotine-related adverse events may exacerbate these existing balance-related problems, leading to more fall incidents.

Drug ineffectiveness was another significant AE identified in our study. Rotigotine is metabolized by various enzymes, and genetic variations in these enzymes can lead to differences in the rate of metabolism. Patients with slower metabolism may not achieve the optimal therapeutic concentration of rotigotine, resulting in drug ineffectiveness [50]. In some cases, the reported ineffectiveness may reflect the natural progression of the underlying disease rather than a failure of the drug itself. For example, in PD, the gradual loss of dopaminergic neurons may lead to reduced responsiveness to dopaminergic therapies over time [51]. Therefore, clinicians should consider these factors when interpreting reports of drug ineffectiveness and adjust treatment plans accordingly.)

Furthermore, in Table 1, we found that rotigotine is used not only for treating PD and RLS but also for conditions such as the on - off phenomenon and peripheral neuropathy. Although the proportions of these additional indications are not large, for safety reasons, further discussion is warranted.: The "on - off phenomenon" is a complex issue in PD treatment. In our dataset, though only 20 cases were linked to rotigotine, understanding its implications is vital. As a dopamine agonist, rotigotine may interact with the dopamine - regulation mechanisms in the "on - off" cycle. The "on - off phenomenon" often results from the progressive loss of dopaminergic neurons and dopamine level fluctuations and rotigotine can potentially modulate these through continuous dopaminergic stimulation.However, using rotigotine for the "on - off phenomenon" has risks. Its pharmacokinetics and pharmacodynamics are affected by factors like genetic variations in drug - metabolizing enzymes CYP enzyme polymorphisms, for instance, can alter rotigotine clearance, leading to sub - or supra - therapeutic levels and exacerbating "on - off" symptoms.Rotigotine may also interact with other Parkinson's medications. Levodopa, the gold - standard treatment, is associated with the "on - off phenomenon" When combined with rotigotine, it can either enhance treatment or cause adverse reactions. Antonini et al. [27] found that while rotigotine could improve motor symptoms, careful dosing was needed to avoid over - or under - stimulation. In the "on - off phenomenon," improper rotigotine dosing can cause dyskinesias during the "on" phase or worsen motor function during the "off" phase.

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Table 5 The top 30 most frequent adverse events for rotigotine excluding common medication co-usage at the PT level from FAERS data

Preferred terms (PTs)	Case reports	ROR (95% CI)	PRR (χ2)	EBGM (EBGM05)	BCPNN (IC025)
Product Adhesion Issue*	1264	160.34 (151.19–170.04)	147.15 (175675.65)	140.85 (134.1)	7.14 (5.47)
Drug Ineffective*	548	1.64 (1.5–1.78)	1.61 (130.25)	1.61 (1.5)	0.69 (-0.98)
Death*	473	2.17 (1.98–2.38)	2.14 (290.25)	2.14 (1.98)	1.1 (-0.57)
Application Site Erythema*	366	55.94 (50.39–62.11)	54.63 (18959.93)	53.75 (49.24)	5.75 (4.08)
Application Site Pruritus*	363	65.95 (59.37–73.26)	64.41 (22229.51)	63.18 (57.86)	5.98 (4.32)
Device Adhesion Issue*	362	103.72 (93.3–115.29)	101.28 (34871.71)	98.27 (89.94)	6.62 (4.95)
Off Label Use*	323	1.55 (1.39–1.73)	1.54 (62.36)	1.54 (1.41)	0.62 (-1.04)
Overdose*	306	5.39 (4.82–6.04)	5.31 (1071.41)	5.3 (4.82)	2.41 (0.74)
Parkinson'S Disease*	213	45.97 (40.12–52.67)	45.34 (9112.88)	44.73 (39.92)	5.48 (3.82)
Fall*	212	2.52 (2.2–2.89)	2.5 (191.58)	2.5 (2.23)	1.32 (-0.35)
Application Site Reaction*	191	132.75 (114.77–153.54)	131.1 (23711.11)	126.08 (111.63)	6.98 (5.31)
Tremor*	190	4.58 (3.97–5.28)	4.53 (523.69)	4.53 (4.02)	2.18 (0.51)
Restless Legs Syndrome*	189	40.9 (35.41–47.25)	40.41 (7177.46)	39.93 (35.39)	5.32 (3.65)
Application Site Rash*	180	48.55 (41.87–56.29)	47.99 (8163.67)	47.31 (41.8)	5.56 (3.9)
Insomnia*	175	2.6 (2.24–3.02)	2.58 (170.57)	2.58 (2.28)	1.37 (-0.3)
Nausea	171	0.86 (0.74–1.01)	0.87 (3.59)	0.87 (0.76)	-0.21 (-1.87)
Dizziness*	151	1.21 (1.03–1.42)	1.21 (5.44)	1.21 (1.06)	0.27 (-1.39)
Somnolence*	137	2.74 (2.32–3.25)	2.73 (150.25)	2.73 (2.37)	1.45 (-0.22)
Wrong Technique In Product Usage Process*	130	2.51 (2.12–2.99)	2.5 (117.48)	2.5 (2.16)	1.32 (-0.34)
Hallucination*	128	7.05 (5.92–8.39)	7 (657.71)	6.99 (6.04)	2.8 (1.14)
Pruritus*	116	1.3 (1.08–1.56)	1.3 (7.97)	1.3 (1.11)	0.38 (-1.29)
Rash*	114	1.07 (0.89–1.28)	1.07 (0.46)	1.07 (0.91)	0.09 (-1.58)
Pneumonia*	110	1.36 (1.13–1.64)	1.36 (10.43)	1.36 (1.16)	0.44 (-1.22)
Intentional Product Misuse*	109	4.74 (3.93–5.73)	4.71 (319.05)	4.71 (4.02)	2.24 (0.57)
Product Dose Omission Issue*	106	1.87 (1.54–2.26)	1.86 (42.52)	1.86 (1.59)	0.9 (-0.77)
Therapy Interrupted*	103	7.53 (6.2–9.14)	7.49 (578.03)	7.47 (6.35)	2.9 (1.24)
Product QualityIssue*	102	2.68 (2.21–3.26)	2.67 (106.8)	2.67 (2.27)	1.42 (-0.25)
Fatigue	97	0.48 (0.4–0.59)	0.49 (53.02)	0.49 (0.41)	-1.04 (-2.7)
Application Site Irritation*	87	28.44 (23.02–35.14)	28.28 (2270.62)	28.05 (23.5)	4.81 (3.14)
Gait Disturbance*	87	1.7 (1.38–2.1)	1.7 (25.2)	1.7 (1.43)	0.77 (-0.9)

Asterisks (*) indicate statistically significant signals. EBGM and IC are Bayesian-based metrics used to quantify the strength of associations between drugs and adverse events. EBGM represents the geometric mean of the posterior distribution of the reporting ratio, while IC measures the information gained from the association. Both metrics are accompanied by their 95% confidence intervals (EBGM05 and IC025), which indicate statistical significance. Abbreviations: ROR, reporting odds ratio; PRR, proportional reporting ratio; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of the 95% confidence interval of EBGM; BCPNN, bayesian confidence propagation neural network, the lower limit of the 95% confidence interval of the IC

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Furthermore, the relationship between rotigotine and peripheral neuropathy requires further study, especially considering only 8 cases in the dataset. The underlying mechanism remains unclear but may involve nerve conduction interference or reduced peripheral nerve blood flow. Dopamine agonists can affect the peripheral nervous system's microvasculature, with some causing vasoconstriction

and decreased nerve blood supply [53, 54]. In patients with pre - existing nerve - affecting conditions like diabetes, using rotigotine may be riskier [55]. Diabetic neuropathy is a common diabetes complication, and medications like rotigotine, which could worsen nerve damage, should be carefully considered. Rotigotine might also interfere with nerve repair or increase oxidative stress in nerve cells [56]. To clarify this relationship, more research, including large-scale observational and in-depth mechanistic studies, is needed. This will help optimize rotigotine's clinical use and improve patient outcomes.

However, we have several limitations in this study. Firstly, our research is based on the FAERS database, which is a voluntary reporting system for adverse events utilized by consumers, physicians, and pharmacists. Consequently, this data may be incomplete or imprecise, which could restrict the general applicability of our results. Secondly, the majority of reports in our study originated from the U.S., which may restrict the generalizability of our findings to other regions. Thirdly, ROR and PRR are merely measures of signal strength and do not indicate direct causal relationships [57]. Furthermore, it should be recognized that FAERS data cannot establish causality; it merely suggests potential associations [58]. Thus, we hold the view that a prospective, Long-term study of the potential adverse effects of rotigotine is necessary for enhanced accuracy.

Conclusion

In our study, we conducted a thorough analysis of the adverse effects of rotigotine in clinical settings using the FAERS database, with a focus on reports from the year 2007 onwards. By indicating a high-risk signal with a recognized Administration Site Conditions, Nervous System Disorders, Psychiatric Disorders necessitate vigilant monitoring during routine clinical practice. Implementing effective strategies can help mitigate post-treatment risks. At present, rotigotine demonstrates efficacy in the management of RLS, making it a valuable therapeutic alternative for individuals suffering from this condition. In the future, Research into the use of rotigotine in the treatment of restless legs syndrome may also be breaking new ground. Currently, it is essential to also focus on its adverse effects in order to better use in the clinic to the benefit of patients.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40360-025-00911-5.

Supplementary Material 1

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Author contributions
J.T: Conceptualization, Data curation, Methodology, Writing–original draft. C.Z: Data curation, Writing–original draft. Y.Q, H. Zand J.Z: Supervision, Writing–review and editing. S.X and J.H: Writing–review and editing.

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Data availability
No datasets were generated or analysed during the current study.

Ethical approval
was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Consent for publication
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Competing interests
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