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ORIGINAL RESEARCH

Restless Legs Syndrome Patients with Early Onset Disease or a Relevant Family History Associated with Pramipexole Ineffectiveness but Not Pregabalin

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Background: Restless legs syndrome (RLS) is a complex condition characterized by significant heterogeneity. Factors that affect medication efficacy remain unclear; different RLS subtypes may respond differently to various drugs.

Objective: To identify factors associated with the ineffectiveness of pramipexole and pregabalin in patients with various subtypes of RLS.

Methods: This retrospective nested case–control study enrolled 257 RLS patients prescribed pramipexole or pregabalin between March 2019 and April 2024 at the sleep center of Sir Run Run Shaw Hospital. All patients completed a semi-structured questionnaire, underwent polysomnography and laboratory evaluations, and participated in a telephone survey. To represent iron-storage status, one principal component score that included five indicators of peripheral iron metabolism was extracted by principal component analysis. Treatment effectiveness was assessed using the Clinical Global Impression-Improvement (CGI-I) scale, with scores of 1–3 indicating effective treatment and higher scores reflecting ineffective treatment. Multivariate logistic regression was employed to assess the risk factors (or RLS subtypes) of medication ineffectiveness.

Results: Of patients treated with pramipexole, 42.7% (70/164) reported poor outcomes. Early onset RLS (OR = 5.076; 95% CI, 1.836–14.033) and relevant family history (OR = 4.537; 95% CI, 1.556–13.437) increased pramipexole ineffectiveness risk. Among pregabalin users, 34.4% (32/93) reported ineffectiveness, which was associated with hemoglobin levels (OR = 1.039; 95% CI, 1.001–1.079).

Conclusion: These findings suggest that RLS patients with familial or early-onset characteristics may represent a distinct subtype that responds preferentially to α2δ ligands over dopamine agonists, supporting personalized treatment approaches based on clinical phenotyping.

Plain Language Summary: Restless legs syndrome (RLS) is a complex condition associated with significant heterogeneity. How can the best medications for RLS patients with different disease characteristics be chosen?

This study aimed to identify predictors of treatment response in restless legs syndrome (RLS) by evaluating clinical, polysomnography, and lab results to differentiate the effectiveness of pramipexole versus pregabalin. Key findings revealed that pramipexole ineffectiveness was associated with early-onset RLS and family history, while only low hemoglobin levels were linked to pregabalin ineffectiveness. A subtype of RLS—early-onset patients or patients with a family history—was identified as a risk factor for pramipexole ineffectiveness, but not for pregabalin ineffectiveness.

The above findings suggested that the disease subtype of RLS patients may be a critical factor that cannot be ignored when evaluating medication effectiveness. Prospective, randomized controlled trials are needed to evaluate the efficacy of pramipexole and pregabalin in these specific RLS subtypes.

Keywords: restless legs syndrome, family history, early onset, pregabalin, pramipexole

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Introduction

Restless legs syndrome (RLS) is a sleep-related movement disorder characterized by an irresistible urge to move the legs, particularly when attempting to fall asleep at night; this urge is relieved by movement and exhibits a distinct circadian rhythm.[1,2] Moderate-to-severe RLS significantly affects sleep, causes depression/anxiety, diminishes productivity, and increases the risk of cardiovascular diseases.[3] RLS is both complex and heterogeneous and exhibits different clinical manifestations in terms of onset time, relevant family history, periodic leg movements, iron deficiency status and other factors.[4] The pathogenesis is not well understood but may involve a brain iron deficiency, dopaminergic dysfunction, and/or disturbances in the adenosine and glutamatergic pathways.[4] Recent evidence suggests that the basic mechanisms of RLS might include not only the hypothalamus-spinal dopaminergic circuit (nucleus A11), but also a pathway including the basal ganglia and structures that are part of the limbic system.[5] Moreover, the genetically heterogeneous complex trait of RLS[6] may provide insights into the underlying mechanisms responsible for the diversity in pathogenesis and disease phenotypes.

The therapeutic landscape for RLS has undergone significant changes regarding the positioning of low-dose dopaminergic agonists and α2δ calcium channel ligands. Previously, clinical guidelines recommended both drug classes as first-line treatments for RLS.[7] However, according to the updated AASM treatment guideline for RLS (effective January 1, 2025), α2δ calcium channel ligands are now preferred over low-dose dopaminergic agonists for adult RLS management.[8] Consequently, pramipexole and pregabalin have emerged as the most commonly prescribed medications for RLS treatment in recent years. In general, these two drugs are effective for 1 year in 70–80% of RLS patients included in randomized controlled trials.[9] However, over the long term, dopaminergic drugs exhibit high incomplete response rates (42% to 45%) in real-world settings,[10,11] yet the underlying risk factors contributing to this low effectiveness have not been adequately investigated. Similarly, real-world data on pregabalin efficacy are exceedingly rare.

Further investigation is needed to determine whether clinical heterogeneity correlates with differential therapeutic responses to mechanistically distinct medications. Although RLS heterogeneity may potentially affect drug therapy efficacy, robust evidence remains lacking. Therefore, it is essential to identify patient subpopulations who respond optimally to different medications. This study addresses this knowledge gap by providing real-world evidence on medication efficacy while simultaneously identifying risk factors associated with treatment failure. Additionally, our findings help define specific RLS subtypes that may be related to clinical responses to pramipexole and pregabalin, thereby contributing to a more personalized therapeutic approach.

Methods

Study Setting and Design

The Institutional Review Board of Sir Run Run Shaw Hospital approved the study (permit number 20190226–9), and all clinical practices comply with the 1989 revision of the Helsinki Declaration. The study was registered in the Chinese Clinical Trial Registry as ChiCTR2000040784. Patients provided comprehensive informed consent when enrolled in the RLS database, which included consent for database inclusion, long-term follow-up, and authorization for use of clinical information in scientific research, data analysis, and publication. During telephone follow-up contacts, patients' continued consent for research participation was verbally re-confirmed and documented. The consent was recorded in our study database with the date of contact and the outcome of the consent verification process. Only patients who provided clear verbal agreement proceeded with the complete follow-up interview. Patients who declined participation (n=11) were excluded from the analysis, as detailed in the patient flow diagram (Figure 1). All patient information was de-identified and managed under strict confidentiality protocols.

We established an RLS clinical database in March 2019 at the Center for Sleep Medicine, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine. This database[12] contains comprehensive patient information including disease characteristics, indices of peripheral iron metabolism, polysomnography (PSG) reports, and clinical diagnoses and treatments. As of March 2024, a total of 522 RLS patients had been included in this database. For the current study, we conducted a nested case-control analysis using data from RLS patients treated with pramipexole and pregabalin who were followed up from December 2023 to April 2024.

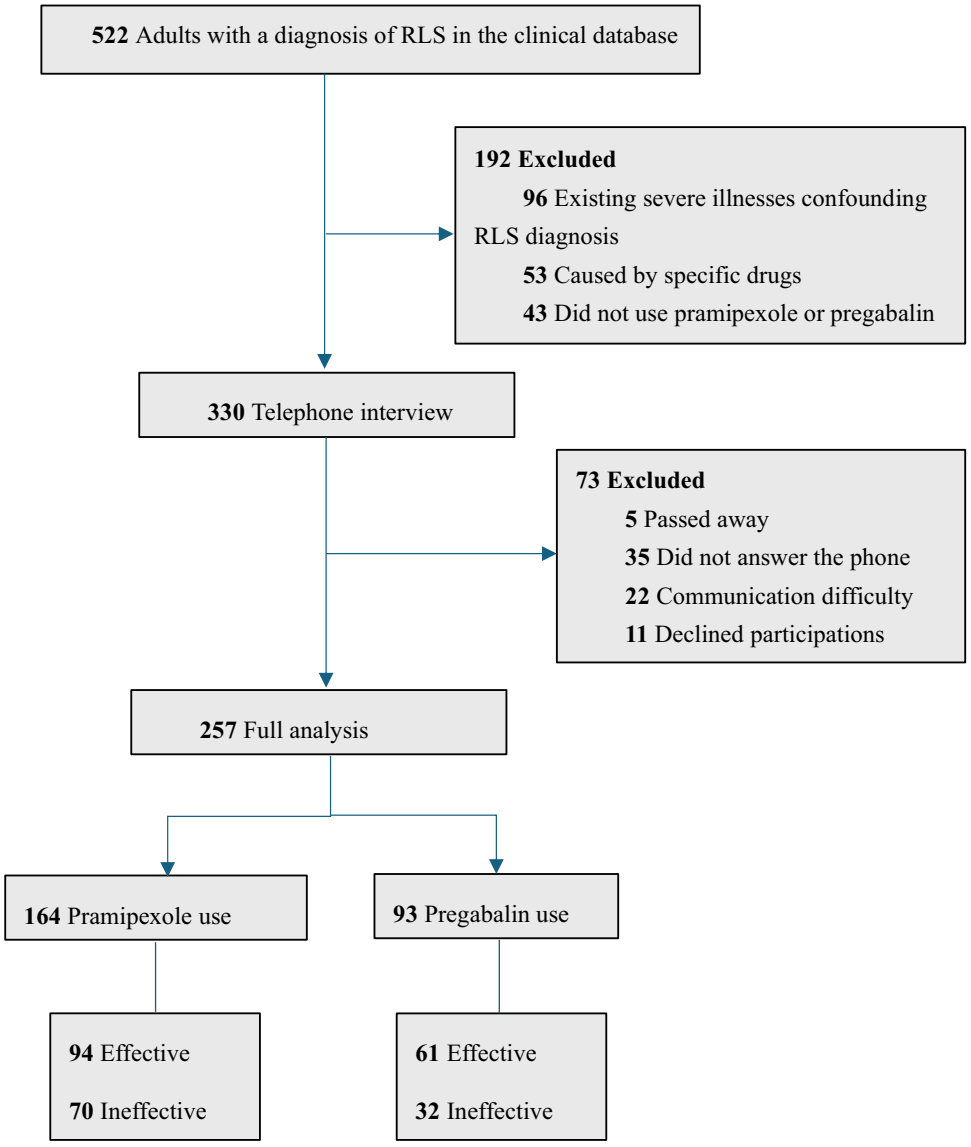

Figure 1 Flow diagram of cohort development and patient selection.
Abbreviations: RLS, restless legs syndrome.

Based on the therapeutic medications administered, patients were categorized into two treatment groups: pramipexole treatment and pregabalin treatment. Subsequently, within each treatment category, patients were further classified according to their Clinical Global Impressions (CGI) scores into two subgroups: treatment responders (effective treatment) and non-responders (ineffective treatment).[13] CGI-I scores of one to three indicated "effective" treatment; higher scores reflected "ineffective" treatment. The CGI-I questionnaire was administered by an experienced clinician who did not perform any other assessment at any patient visit and who was blinded to the patient-reported outcome measures.

Participants and Variables

All patients with RLS (not RLS mimics) were older than 18 years of age, and patients of both sexes were included. RLS diagnoses were based on the standard criteria of the International Restless Legs Syndrome Study Group (IRLSSG).[14]

The exclusion criteria were difficulty in determining current disease status (such as communication problems), any other severe illness that confounded RLS diagnosis (Parkinson's disease, bone metastases, severe lumbar disc herniation), and RLS symptoms caused by certain drugs (eg, antihistamines, dopamine antagonists, and some antidepressants).

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The IRLSSG developed and validated the widely used International Restless Legs Syndrome Study Group Severity Rating Scale (IRLS) in 2003.[15] IRLS was used with permission (License Number: 2510553) from Mapi Research Trust, Lyon, France (https://eprovide.mapi-trust.org). The IRLS uses ten questions to evaluate RLS severity[16] and the impact of RLS on sleep, mood, and daily activities (mild, IRLS score < 10; moderate, score of 10–20; severe, score > 20; very severe, score > 30), and was used in this study to evaluate RLS severity.

Data Sources/Measurements

A semi-structured questionnaire was administered by a neurologist with expertise in sleep medicine to gather data on medical history, comorbidities, current RLS medications, and disease characteristics (age at RLS onset, duration of RLS, and any family history of RLS).

After an overnight fast, antecubital venous blood samples were taken between 6:00 a.m. and 8:00 a.m. using standard operating procedures. Peripheral iron metabolism status was evaluated by measuring hemoglobin and C-reactive protein (CRP) levels; serum ferritin, iron, and transferrin concentrations; the unsaturated iron-binding capacity (UIBC) and the total iron-binding capacity (TIBC); and transferrin saturation (TSAT). Serum ferritin concentrations were determined using an electrochemiluminescence assay (Roche Diagnostics, Mannheim, Germany). Serum iron concentrations and transferrin saturation were measured using an Iron/UIBC Kit (Roche Diagnostics). Immunoturbidimetry was employed to determine the concentration of transferrin (kit catalog no. 332028; Shanghai Jiemen, Shanghai, China).

The Trackit 32-channel PSG monitor (Nihon Kohden Corporation, Tokyo, Japan) had an electrocardiogram, two electrooculogram, one chin electromyogram, and six electroencephalogram leads. A mouth thermistor, chest and abdominal bands, a nasal cannula/pressure transducer, and a pulse oximeter were used to gather data on respiration. Periodic limb movements (PLMs) and limb movements (LMs) were recorded using surface electromyogram electrodes on the bilateral anterior tibialis muscles. The American Academy of Sleep Medicine (version 2.4) criteria were employed[17] to measure sleep stage, respiratory events, microarousals, and LM parameters (LM events and PLMs). All data were reviewed by at least one sleep medicine specialist.

Quantitative Variables

There are two recognized epidemiological RLS subtypes: early onset (aged < 45 years) and late-onset RLS. The 45-year threshold was specifically established in familial RLS studies, where early-onset was defined as age 45 or younger versus late-onset as over age 45.[18] Additionally, this cut-off has been validated in previous research showing distinct clinical phenotypes between early and late-onset RLS.[4] So, a cut-off of 45 years was used to distinguish early and late-onset RLS in this study.

Principal component analysis was used to reduce the data dimensionality of the peripheral iron metabolism indicators. The factorability of six indicators of peripheral iron metabolism (serum ferritin, iron, and transferrin concentrations, UIBC and TIBC, and TSAT), and the CRP and hemoglobin levels, was initially investigated to establish correlations and identify important factors. When the serum ferritin, iron, and hemoglobin levels, UIBC, and TSAT were included in the analysis, the Kaiser–Meyer–Olkin sampling adequacy test statistic was 0.667, and the result of Bartlett's test of sphericity (reflecting correlations among indicators) was significant ($\chi 2 = 784.3$, $P < 0.001$), indicating that the data could be subjected to principal component analysis. The iron storage principal component (PC) explained 61.6% of the variance in peripheral iron metabolism. The five indicators included in the principal component analysis were normalized using the NormalizeData function with the default parameters. The principal component score (PCS) was calculated as follows: PCS = 0.332 * ferritin + 0.475 * iron + 0.530 * TSAT - 0.499 * UIBC + 0.367 * hemoglobin.

Statistical Methods

Demographic and disease data, clinical scores, and polysomnographic parameters are presented as means with standard deviations for normally distributed variables, medians with interquartile ranges for variables that are not normally distributed, and frequencies with percentages for categorical variables. Differences between the "effective" and "ineffective" groups were compared using the chi-squared test, the independent *t*-test, and non-parametric tests, as appropriate.

For multivariate analysis, binary logistic regression was performed to identify risk factors for ineffective medication. Clinically important variables (age, female, IRLS total score, medication duration, PLMS index, and iron storage status [Principal component score]) and all variables with *P*-values < 0.15 in between-group comparisons (relevant family history, early onset disease, RLS duration, rapid eye movement [REM] sleep latency, hemoglobin level, and drug dose) were included in the multivariate model (Model 1). As ferritin is not only a circulating iron-storage protein but also an acute-phase reactant, the CRP level was included to address potential confounding. Although the age at RLS onset differed significantly between the groups, this continuous variable was transformed into a categorical variable to avoid multicollinearity.

Considering the sample size requirements for multivariable regression analysis, we simplified our models based on Model 1 findings, study objectives, and clinical considerations. In Model 2, we included 6 variables for pramipexole (age, female sex, early-onset RLS, family history, medication duration, and current medication dose) and 4 variables for pregabalin (early-onset RLS, IRLS total score, hemoglobin, and current medication dose).

The peripheral iron metabolism data of six patients were incomplete. Missing fields were filled via multiple imputation, and the average of five imputation values was included in the analysis.

Results

Participants, Variables, and Exposures

In total, 257 patients with RLS were included (Figure 1). The median IRLS score was 21 (range: 16–27). The average age at the time of the telephone interview was 51.5 ± 13.4 years. Of all patients, 65.8% were women, and 13.2% had a family history of RLS. Of all patients, 164 and 93 were treated with pramipexole and pregabalin, respectively. The overall efficacy was 60.3% (155/257), while it was 57.3% (94/164) for pramipexole and 65.6% (61/93) for pregabalin.

This nested case–control study compared baseline characteristics (Table 1), medications (Table 2), and PSG parameters (Table 3) between groups for whom pramipexole and pregabalin were effective and ineffective.

Primary Analysis and Medication Efficacy

Patients for whom pramipexole was ineffective were more likely to have early onset RLS (χ^2 = 9.241, P = 0.002), a relevant family history (χ^2 = 14.414, P < 0.001), and medication discontinuation (χ^2 = 8.598, P = 0.003). Patients who did not respond to pregabalin had a higher hemoglobin level (z = –2.019, P = 0.043), took less medication (z = –2.419, P = 0.016), were medicated for a shorter period (z = –2.573, P = 0.010), were more likely to discontinue medication (χ^2 = 7.188, P = 0.007), and exhibited a shorter REM sleep latency (z = –2.370, P = 0.018). No other variable differed significantly between the two groups (all P > 0.05). All of the above variables were included in multivariate regression, with the exception of medication discontinuation because this might not be caused by drug ineffectiveness.

Early Onset RLS Was Associated with Ineffectiveness of Pramipexole but Not Pregabalin

The Statistical Methods section describes the variables subjected to multivariate analyses. Tables 4 and 5 show the logistic regression results for pramipexole and pregabalin, respectively. There were two regression models – one considered all crude comparisons and parameters of clinical significance, and the other was a simplified model.

Binary logistic regression indicated that pramipexole was five times more likely to be ineffective in early onset RLS patients (odds ratio [OR] = 5.076; 95% confidence interval [CI], 1.836–14.033). Patients with a relevant family history (OR = 4.573; 95% CI, 1.556–13.437) were at a 4.6-fold increased risk of treatment failure (compared to a response). Pramipexole ineffectiveness was dose-dependent (Table 4).

For pregabalin, multivariate logistic regression revealed that the hemoglobin level (adjusted OR [95% CI] for each g/L increment = 1.039 [1.001–1.079]) might be a risk factor for treatment ineffectiveness. Neither early onset RLS nor a family history was associated with treatment ineffectiveness (Table 5).

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Table 1 Baseline Characteristics of Restless Legs Syndrome Patients for Whom Pramipexole or Pregabalin Was Effective or Ineffective

Variables/Parameters	Pramipexole				Pregabalin			
	Effective (n = 94)	Ineffective (n = 70)	$\chi 2$/t/z value	*P*-value	Effective (n = 61)	Ineffective (n = 32)	χ^2/t/z value	*P* -value
Demographic characteristics								
Female, n (%)	63 (67.0)	40 (57.1)	1.676	0.253	46 (75.4)	20 (62.5)	1.698	0.232
Age (years), median (IQR)	53 (44, 67.6)	50 (41.75, 57)	−1.395	0.164	53 (45.5, 60.5)	54 (40.5, 62.25)	−0.218	0.827
BMI (kg/m^2), median (IQR)	23.42 (21.05, 24.9)	22.27 (20.44, 24.96)	−1.004	0.317	21.78 (19.96, 23.74)	22.11 (20.02, 23.44)	−0.125	0.900
Education (years), median (IQR)	9 (6, 12)	9 (6, 15)	−1.803	0.710	9 (6, 12)	8 (6, 12)	−0.013	0.990
Disease information								
Age at RLS onset (years), median (IQR)	43 (32, 51.25)	39 (26.75, 44.25)	−1.961	0.050	45 (34, 57)	48.5 (33.25, 57.75)	−0.316	0.752
Early onset of RLS[a], n (%)	54 (57.4)	56 (80)	9.241	0.002*	19 (31.1)	12 (37.5)	0.381	0.537
Duration of RLS (years), median (IQR)	9 (5, 17)	12 (7, 18.25)	−1.710	0.087	5 (2.75, 10)	4.5 (3, 6)	−0.556	0.578
Family history of RLS, n (%)	7 (7.4)	21 (30)	14.414	<0.001*	4 (6.6)	2 (6.3)	-	1.000
IRLS total score, median (IQR)	22 (16.5, 27.5)	22 (17, 27.25)	−0.309	0.758	20 (15, 26)	18.5 (14.25, 22.75)	−1.632	0.103
Peripheral iron metabolism assays								
Ferritin (μg/L), median (IQR)	122.3 (72.1, 216.6)	143.4 (47.6, 264.5)	−0.587	0.557	120.1 (50.8, 247.4)	186.5 (62.1, 371.6)	−0.768	0.442
Serum iron (μmol/L), mean ± SD	17.9 (14.5, 21.7)	16.7 (13.0, 21.8)	−1.049	0.295	16.8 (13.5, 20.9)	16.8 (11.2, 20.4)	−0.469	0.639
Transferrin saturation (%), mean ± SD	36.42 ± 12.46	34.42 ± 13.09	0.996	0.321	34.83 ± 12.19	34.33 ± 12.77	0.185	0.854
Unsaturated iron-binding capacity, (μmol/L), median (IQR)	31.1 (26.3, 36.9)	32.1 (26.8, 38.1)	−0.828	0.408	31.3 (24.9, 36.9)	30.9 (25.2, 40.1)	−0.109	0.913
Hemoglobin (g/L), median (IQR)	131.3 (120.0, 146.0)	136.0 (123.8, 144.3)	−1.112	0.266	127.0 (116.0, 139.0)	134.5 (129.0, 142.2)	−2.019	0.043*
Total iron-binding capacity (μmol/L), median (IQR)	50.1 (46.2, 55.3)	49.8 (46.1, 57.3)	−0.018	0.985	47.3 (44.6, 55.3)	48.8 (43.7, 54.9)	−0.020	0.984
Serum transferrin (g/L), median (IQR)	2.4 (2.2, 2.6)	2.4 (2.2, 2.7)	−0.426	0.670	2.4 (2.1, 2.7)	2.3 (2.1, 2.3)	−0.457	0.648
Principal component score[b], median (IQR)	0.155 (−0.983, 1.153)	0.089 (−1.08, 1.12)	−0.190	0.850	0.135 (−0.694, 1.102)	0.190 (−1.098, 1.274)	−0.332	0.740
C-reactive protein (g/L), median (IQR)	0.8 (0.4, 1.3)	0.9 (0.5, 1.5)	−1.326	0.185	0.6 (0.4, 1.0)	0.7 (0.4, 1.3)	−0.795	0.427

Notes: [a] Symptoms of RLS appeared before the age of 45 years. [b] In principal component analysis, the principal component score (PCS) was calculated using the following formula: PCS = 0.332 * ferritin+0.475 * iron+ 0.530 * TSAT-0.499 * UIBC + 0.367 * hemoglobin. * $P < 0.05$.

Abbreviations: BMI, body mass index; RLS, restless legs syndrome; IRLS, International Restless Legs Syndrome Study Group Severity Scale (IRLS); IQR, interquartile range; SD, standard deviation.

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Table 2 Pramipexole and Pregabalin Medication Details of Restless Legs Syndrome Patients for Whom the Drugs Were Effective or Ineffective

Variables/Parameters	Pramipexole				Pregabalin			
	Effective (n = 94)	Ineffective (n = 70)	$\chi 2$/t/z value	*P*-value	Effective (n = 61)	Ineffective (n = 32)	χ^2/t/z value	*P* -value
Initial dose (mg/24 h), median (IQR)	0.193 ± 0.102	0.200 ± 0.125	−0.406	0.685	127.9 ± 34.5	131.3 ± 33.0	−0.456	0.650
Maintenance dose (mg/24 h), median (IQR)	0.231 ± 0.159	0.254 ± 0.159	−0.884	0.378	130.3 ± 33.3	133.6 ± 31.55	−0.458	0.648
Dose unchanged, n (%)	58 (61.7)	46 (65.7)	3.037	0.233	52 (85.2)	26 (81.3)	0.755	0.805
Dose escalation, n (%)	21 (22.3)	19 (27.1)			2 (3.3)	2 (6.3)		
Dose reduction, n (%)	15 (16)	5 (7.1)			7 (11.5)	4 (12.5)		
Current medication dose (mg/24 h), median (IQR)	0.125 (0.000, 0.250)	0.000 (0.000, 0.250)	−1.641	0.101	0 (0, 112.5)	0 (0, 0)	−2.419	0.016*
Intermittently taking medications, n (%)	24 (25.5)	11 (15.7)	2.304	0.177	8 (13.1)	3 (9.4)	0.281	0.743
Medication duration (months), median (IQR)	14 (5, 27.5)	12 (3, 48)	−0.183	0.856	5 (3, 8)	3 (1, 4.25)	−2.573	0.010*
Medication discontinuation, n (%)	36 (38.3)	43 (61.4)	8.598	0.003*	37 (60.7)	28 (87.5)	7.188	0.007*
Switched from another DA to current therapy, n (%)	11 (11.7)	6 (8.6)	0.423	0.61	3 (4.9)	0 (0)	1.626	0.316
Occurrence of adverse effects, n (%)	5 (5.3)	5 (7.1)	0.233	0.745	6 (9.8)	2 (6.3)	0.343	0.710
Combined therapy, n (%)								
None, n (%)	48 (51.1)	38 (54.3)	3.294	0.689	38 (62.3)	21 (65.6)	1.490	0.914
Dopaminergic medication, n (%)	1 (1.1)	1 (1.4)			2 (3.3)	1 (3.1)		
$\alpha 2\delta$ calcium channel ligand, n (%)	10 (10.6)	3 (4.3)			1 (1.6)	1 (3.1)		
Oral iron supplementation, n (%)	26 (27.7)	21 (30)			14 (23)	5 (15.6)		
Benzodiazepines, n (%)	2 (2.1)	3 (4.3)			0 (0)	0 (0)		
Others[a], n (%)	7 (7.4)	4 (5.7)			6 (9.8)	4 (12.5)		

Notes: [a]Includes sedative and hypnotic drugs except benzodiazepines and traditional Chinese medicine preparations. * $P < 0.05$.
Abbreviations: IQR, interquartile range; DA, dopamine agonist.

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Table 3 Polysomnography Parameters of Restless Legs Syndrome Patients for Whom the Drugs Were Effective or Ineffective

Variables/Parameters	Pramipexole				Pregabalin			
	Effective (n = 94)	Ineffective (n = 70)	$\chi 2$/t/z value	*P*-value	Effective (n = 61)	Ineffective (n = 32)	χ^2/t/z value	*P* -value
Polysomnography parameters								
Total sleep time (minutes), median (IQR)	394.5 (312, 451.5)	407.5 (329.1, 447.9)	−0.347	0.730	385.5 (340.0, 459.5)	422.75 (295.25, 458.5)	−0.347	0.728
Sleep efficiency (%), median (IQR)	73.1 (59.28, 85.6)	72.85 (64.53, 82.7)	−0.071	0.944	72.91 (58.30, 84.11)	75.71 (62.18, 84.02)	−0.631	0.528
Wake time after sleep onset (minutes), median (IQR)	113.5 (55.25, 198.5)	122.75 (79.75, 170.63)	−0.070	0.945	128 (72.13, 195.88)	103.25 (54.13, 163.13)	−1.084	0.278
Sleep latency (minutes), median (IQR)	21.5 (9.25, 42)	16.75 (10, 41.25)	−0.249	0.804	15.5 (8, 43.25)	23 (9, 35.75)	−0.340	0.730
REM sleep latency (minutes), median (IQR)	102.5 (72, 165.5)	119.5 (78.63, 195.63)	−1.546	0.123	99.25 (71.38, 157)	65.25 (54.5, 108.13)	−2.370	0.018*
N1 (%), median (IQR)	6.8 (3.85, 11.8)	5.94 (3.375, 9.11)	−0.913	0.363	9.05 (4.6, 19.43)	9.15 (3.28, 13.1)	−1.383	0.167
N2 (%), mean ± SD	43.28 ± 14.95	50.63 ± 14.58	−3.143	0.535	43.84 ± 12.15	43.82 ± 15.57	0.003	0.139
N3 (%), mean ± SD	26.62 ± 13.52	23.38 ± 11.66	1.608	0.148	24.36 ± 11.56	26.48 ± 11.51	−0.838	0.847
REM (%), mean ± SD	19.15 ± 7.06	17.98 ± 7.09	1.043	0.876	18.59 ± 7.04	18.90 ± 8.06	−0.193	0.544
AHI, median (IQR)	3.83 (1.5, 11.73)	3.64 (1.98, 8.29)	−0.414	0.680	6.47 (1.84, 47.75)	4.56 (2.29, 7.84)	−1.420	0.155
PLMS index (/h), median (IQR)	7.54 (0.8, 30.66)	7.85 (1.03, 24.01)	−0.419	0.677	3.01 (0, 16.15)	1.19 (0, 12.47)	−1.180	0.238

Notes: * $P < 0.05$.

Abbreviations: IQR, interquartile range; REM, rapid eye movement; SD, standard deviation; AHI, apnea-hypopnea index; PLMS, periodic leg movements during sleep.

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Table 4 Multivariate Logistic Regression Analyses of Pramipexole Ineffectiveness

Independent Variables	Model 1[a]		Model 2[b]	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (years)	1.044 (0.998–1.096)	0.062	1.022 (0.986–1.060)	0.241
Female, n (%)	0.552 (0.216–1.408)	0.213	0.512 (0.236–1.114)	0.091
Early onset of RLS, n (%)	9.908 (2.575–38.125)	<0.001*	5.076 (1.836–14.033)	0.002*
Family history, n (%)	5.194 (1.693–15.936)	0.004	4.573 (1.556–13.437)	0.006*
Duration of RLS (years)	0.960 (0.905–1.019)	0.180	-	-
IRLS total score	1.014 (0.958–1.073)	0.642	-	-
PLMS index (/h)	0.998 (0.983–1.012)	0.745	-	-
Principal component score [c]	0.861 (0.637–1.164)	0.331	-	-
C-reactive protein (g/L)	0.969 (0.714–1.314)	0.838	-	-
Hemoglobin (g/L)	1.024 (0.992–1.057)	0.137	-	-
Medication duration (months)	1.006 (0.996–1.017)	0.228	1.003 (0.994–1.012)	0.556
Current medication dose (mg/24h)				
0 mg	Reference	0.002	Reference	0.003
0.125 mg	0.037 (0.007–0.207)	<0.001*	0.047 (0.009–0.243)	<0.001*
0.250 mg	0.415 (0.153–1.124)	0.084	0.437 (0.168–1.139)	0.090
>0.250 mg	0.372 (0.111–1.246)	0.109	0.358 (0.111–1.156)	0.086

Notes: [a] Model 1 included the results of the crude comparisons and parameters of clinical significance. The chi-squared value of model 1 was 52.366 ($P < 0.001$). Model 1 correctly classified 72.0% of all cases. In terms of medication ineffectiveness, the sensitivity was 64.3%, the specificity was 77.7%, the positive predictive value was 68.2%, and the negative predictive value was 74.5%. [b] Model 2 included six risk factors; the chi-squared value was 48.202 ($P < 0.001$), suggesting that this reduced model was adequate. Model 2 correctly classified 71.3% of all cases. In terms of medication ineffectiveness, the sensitivity was 62.9%, the specificity was 77.7%, the positive predictive value was 67.7%, and the negative predictive value was 73.7%. [c] In principal component analysis, the principal component score (PCS) was calculated as follows: PCS = 0.332 * ferritin + 0.475 * iron + 0.530 * TSAT - 0.499 * UIBC + 0.367 * hemoglobin. * $P < 0.05$.

Abbreviations: RLS, restless legs syndrome; IRLS, International Restless Legs Syndrome Study Group Severity Scale (IRLS); PLMS, periodic leg movements during sleep.

Table 5 Multivariate Logistic Regression Analyses of Pregabalin Ineffectiveness

Independent Variables	Model 1[a]		Model 2[b]	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (years)	1.027 (0.979–1.077)	0.273	-	-
Female, n (%)	0.593 (0.167–2.110)	0.420	-	-
Early onset of RLS, n (%)	1.021 (0.240–4.343)	0.977	0.858 (0.294–2.506)	0.780
Family history, n (%)	10.666 (0.252–452.235)	0.216	-	-
Duration of RLS (years)	0.985 (0.911–1.065)	0.709	-	-
IRLS total score	0.942 (0.872–1.017)	0.128	0.942 (0.879–1.010)	0.095
PLMS index (/h)	0.993 (0.952–1.035)	0.733	-	-
Principal component score [c]	0.743 (0.495–1.115)	0.151	-	-
C-reactive protein (g/L)	1.230 (0.901–1.681)	0.193	-	-
Hemoglobin (g/L)	1.059 (1.004–1.117)	0.034*	1.039 (1.001–1.079)	0.044*
Current medication dose (mg/24h)			-	-
0 mg	Reference	0.426	Reference	0.366
75 mg	0.222 (0.017–2.987)	0.256	0.177 (0.014–2.244)	0.181
150 mg	0.444 (0.085–2.322)	0.336	0.490 (0.105–2.278)	0.363

(*Continued*)

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Table 5 (Continued).

Independent Variables	Model 1[a]		Model 2[b]	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Medication duration (months)	0.924 (0.809–1.055)	0.242	0.961 (0.868–1.064)	0.445
REM sleep latency (minutes)	0.995 (0.988–1.001)	0.123	0.995 (0.988–1.001)	0.110

Notes: [a] Model 1 included the results of the crude comparisons and parameters of clinical significance. The chi-squared value was 28.169 and the *P*-value 0.014. Model 1 correctly classified 76.3% of all cases. In terms of medication ineffectiveness, the sensitivity was 59.4%, the specificity 85.2%, the positive predictive value 57.9%, and the negative predictive value 85.2%. [b] Model 2 used the four risk factors that remained after model simplification; the chi-squared value was 18.064 and the *P*-value 0.003, suggesting that the reduced model was indeed adequate. Model 2 correctly classified 75.3% of all cases. In terms of medication ineffectiveness, the sensitivity was 59.4%, the specificity 83.6%, the positive predictive value 65.5%, and the negative predictive value 79.7%. [c] On principal component analysis, the principal component score (PCS) was calculated as: PCS = 0.332 * ferritin +0.475 * iron+ 0.530 * TSAT-0.499 * UIBC + 0.367 * hemoglobin. * *P*-value less than 0.05.
Abbreviations: RLS, restless legs syndrome; IRLS, the International Restless Legs Syndrome Study Group Severity Scale; PLMS, periodic leg movements during sleep; REM, rapid eye movement.

Sensitivity and Subgroup Analyses

When variables that did not contribute significantly to model 1 were removed, the simplified model 2 provided similar results (Tables 4, 5; Figure 2).

Hemoglobin levels were the only contributor to pregabalin ineffectiveness, but when they were transformed into categorical variables—anemic status—according to the definition of anemia (hemoglobin level < 12 g/dL in women and < 13 g/dL in men), statistical significance was lost (data not shown).

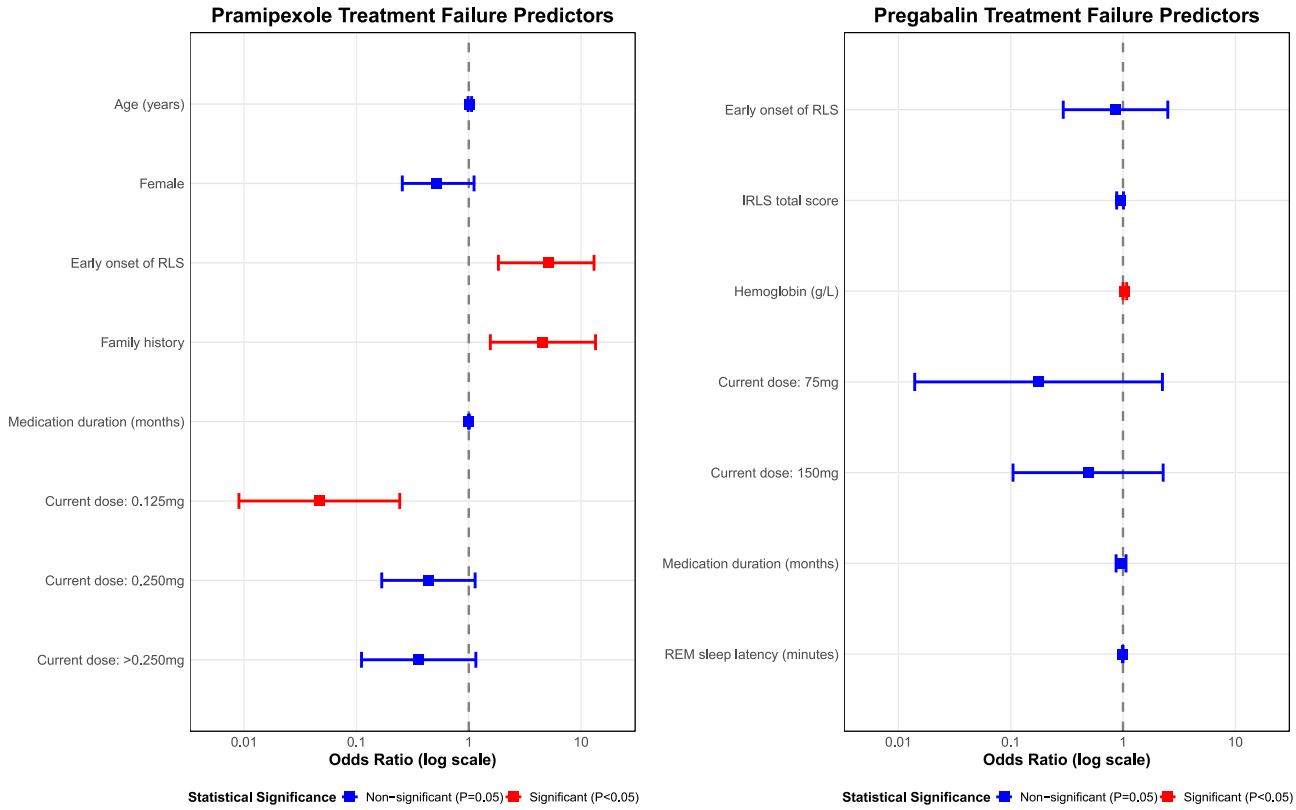

Figure 2 Forest plots showing multivariate logistic regression results for predictors of treatment ineffectiveness in restless legs syndrome patients. For pramipexole: Early onset RLS (OR=5.076), family history (OR=4.573), and current dose 0.125mg (OR=0.047) showed statistical significance. For pregabalin: Only hemoglobin level (OR=1.039) demonstrated statistical significance.
Abbreviations: RLS, restless legs syndrome; IRLS, International Restless Legs Syndrome Study Group Severity Scale; REM, rapid eye movement.

Discussion

The heterogeneity of RLS may influence drug efficacy. However, real-world assessments of factors influencing treatment effects are limited. After adjusting for confounders, we found that the factors influencing the efficacy of a dopaminergic agonist (pramipexole) and an α2δ calcium channel ligand (pregabalin) differed. The risk of pramipexole treatment failure was higher in patients with early onset RLS or a relevant family history; the clinical efficacy of pregabalin was not reduced in such patients.

The results suggested that early-onset RLS patients or those with a family history may represent an important disease subtype that could be more suitable for treatment with α2δ calcium channel ligands rather than dopamine agonists. The clinical manifestations and risk factors differ between early and late-onset patients. Early onset patients exhibited an autosomal dominant mode of RLS inheritance[19] and more frequently reported slow disease progression,[4] and this subtype was associated with more severe symptoms and higher PLMS indices,[20,21] Correspondingly, the late-onset RLS was related to serum ferritin level.[18] So, the PLMS index, age, and indicators of peripheral iron metabolism may confound the medication efficacy. Surprisingly, when these factors were entered into multivariate analyses none of them affected medication outcomes, which illustrated the early onset RLS or patients with a family history were the independent predictor for medication efficacy. Further studies are required to fully address the different clinical outcomes of pramipexole and pregabalin in this subtype of RLS patients.

Based on current evidence, the effectiveness of pregabalin in early onset RLS patients and those with a family history may be related to glutamatergic mechanisms. RLS is associated with altered glutamatergic neurotransmission caused by brain iron deficiency and hypoadenosinergic status.[4] Pregabalin binds to and blocks the action of the α2δ auxiliary subunits of neuron voltage-dependent calcium channels, reducing channel permeability and calcium cell influx[22] and ultimately inhibiting presynaptic glutamate release.[4,23] Importantly, Sergi Ferré et al demonstrated that glutamatergic mechanisms play a central role in the therapeutic effects of α2δ-ligands in RLS.[24] Furthermore, a recent genome-wide meta-analysis[6] identified 13 potential druggable candidates genes. Among them, GRIA1 and GRIA4, which encode subunits of AMPA-type glutamate ionotropic receptors (glutamate receptors 1 and 4) were identified. These findings provide genetic evidence of a link between RLS and glutamate receptor function. Clinical evidence also supports that RLS patients benefit from α2δ ligands such as pregabalin or gabapentin.[25] These converging lines of evidence suggest that genetic factors contributing to early onset RLS may involve glutamate receptor pathways, and α2δ ligands may exert therapeutic effects through modulation of glutamatergic neurotransmission. Of note, only hemoglobin levels were associated with pregabalin effectiveness in this study, but when these were transformed into categorical variables (anemia or not), statistical significance was lost (data not shown).

In contrast, pramipexole, a dopamine D2/3 receptor agonist, was less effective in early onset RLS patients and in those with a family history of RLS. RLS pathogenesis involves dopaminergic dysfunction caused by a genetic predisposition, brain iron deficiency, and/or external factors.[4] Presynaptic hyperdopaminergic status and a low post-synaptic D2 dopamine receptor level attenuate activity in the dopamine system.[26] While low-dose dopaminergic medication relieves RLS symptoms by increasing dopaminergic activity in the short term, long-term use can desensitize dopamine receptors, potentially exacerbating RLS symptoms.[27] Recent research has revealed that G protein-coupled receptor (GPCR) desensitization involves complex cellular mechanisms beyond the traditional steric hindrance model. Studies demonstrate that repeated agonist stimulation of dopamine D2/3 receptors can enhance epidermal growth factor receptor (EGFR) transactivation, which contributes to receptor desensitization through a series of cellular events.[28] This novel desensitization mechanism suggests that dopamine receptor desensitization occurs through intricate cellular processes that may vary depending on receptor subtypes and cellular environments.[27] The reduced efficacy of pramipexole in early onset RLS patients and those with family history observed in our study may be related to these complex desensitization mechanisms, though the specific relationship between genetic RLS subtypes and dopaminergic responsiveness requires further investigation to establish definitive mechanistic explanations.

Our findings regarding drug efficacy in early onset RLS patients differed from expectations based on traditional polysomnographic (PSG) parameters. Previous studies have shown that pregabalin increases N3 sleep and improves sleep quality more notably than pramipexole, which primarily targets PLMS.[29] Given that PLMS is more prevalent in younger

subjects,[20,21] one might anticipate greater responsiveness to pramipexole in this population. However, our results suggested a more complex relationship between patient characteristics and treatment response. Recent evidence indicates that RLS and periodic limb movements (PLM) may represent mechanistically distinct phenomena. Studies examining peripheral iron status[12] and proteomic insights into the pathophysiology of these conditions[30] have suggested that RLS and PLM operate through independent pathways. Additionally, clinical observations show that many individuals with PLM remain unaware of their leg movements unless informed by their bed partners, indicating that PLM reduction may not directly correlate with subjective symptom improvement in RLS patients. These findings suggest that traditional PSG parameters, particularly PLMS indices, may not serve as reliable predictors of clinical response in RLS treatment. The lack of association between PLMS and medication outcomes in our study aligned with emerging evidence that RLS symptom relief and PLM reduction represent distinct therapeutic endpoints that may respond differently to various treatment modalities.

This study had several limitations. First, the retrospective study design and telephone survey have inherent limitations including information bias, selection bias, and unmeasured confounders (patient compliance, lifestyle factors), which may overestimate predictor effects and limit generalizability to mild RLS patients. Future prospective multi-center studies with standardized protocols and biomarker incorporation are needed to validate our findings and establish definitive causal relationships. Second, treatment outcomes were assessed using the CGI-I rather than the IRLS score; although the IRLS is the optimal evaluation tool, the 10-item questionnaire was not suitable for telephone interviews. And potential inaccuracies in self-reported questionnaires, particularly among patients with lower educational attainment, may have introduced some bias. Third, considerable variation existed in the intervals between RLS diagnosis and follow-up calls (December 2023 to April 2024). Fourth, only single-night PSG data were available, precluding assessment of night-to-night variations in leg movements.

Conclusion

These findings suggest that patient phenotyping based on disease onset and family history may facilitate personalized RLS treatment selection. The differential predictor patterns between pramipexole and pregabalin support the clinical practice of individualized therapy approaches, potentially optimizing treatment outcomes through targeted medication selection. Further validation through prospective trials will strengthen the evidence base for precision medicine in RLS management.

Data Sharing Statement

The data that support the findings of this study are not openly accessible because they are sensitive, but they are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Sir Run Run Shaw Hospital (permit number 20190226–9) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Author Contributions

Miaofa Ying and Tiantian Wang are joint first authors. Conceptualization:Lisan Zhang, Miaofa Ying; Data curation: Miaofa Ying, Tiantian Wang; Formal analysis:Tiantian Wang, Ting Zhang, Ziyang Zhai,; Funding acquisition:Miaofa Ying; Investigation: Miaofa Ying, Tiantian Wang, Ting Zhang; Methodology: Lisan Zhang, Tiantian Wang; Project administration: Lisan Zhang; Resources: Lisan Zhang, Tiantian Wang, Ting Zhang, Ziyang Zhai; Supervision: Lisan Zhang; Validation: Tiantian Wang; Visualization: Tiantian Wang; Writing-original draft: Miaofa Ying, Ting Zhang, Ziyang Zhai; Writing-review & editing: Lisan Zhang, Tiantian Wang.

All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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