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RESEARCH ARTICLE

Sex-based disparities in dopamine agonist response in patients with restless legs syndrome

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Summary

This study aimed to investigate sex-related differences in the response to ropinirole and pramipexole in patients with restless legs syndrome (RLS). By analysing clinical parameters and polysomnographic (PSG) findings, we sought to elucidate the potential factors related to sex disparities modulating treatment responses and sleep quality in RLS. A total of 41 drug-free patients with RLS, aged ≥18 years, underwent two consecutive nocturnal PSG recordings, without medication at baseline; before the second night, 26 patients received an oral dose of 0.25 mg pramipexole whereas 15 received 0.5 mg ropinirole. After each PSG recording, patients self-evaluated the severity of their previous night symptoms by means of an ad hoc visual analogue scale (VAS). At baseline, sleep efficiency and percentage of Stage N2 tended to be higher in females while wakefulness after sleep onset was significantly higher in males. After treatment, total leg movements during sleep (LMS), periodic LMS (PLMS), and periodicity indexes were significantly lower in females than in males. The VAS score was lower after treatment in all patients, without differences between the two sexes. This study demonstrates a higher acute responsiveness of PLMS to dopamine agonists (pramipexole and ropinirole) in females than in males with RLS. These findings might be explained by differential sex-related expression of dopamine receptors, especially D_3, within the central nervous system. In addition, our findings provide translational hints toward a better tailored and sex-specific approach to the treatment of RLS associated with PLMS, with dopamine agonist possibly associated with a better outcome in females than in males.

KEYWORDS
dopamine agonists, isolated leg movements during sleep, periodic leg movements during sleep, restless legs syndrome, sex

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1 | INTRODUCTION

Restless legs syndrome (RLS) is a highly heterogeneous sensorimotor disorder, both in terms of clinical manifestations, onset, and evolution of symptoms (with sex- and age-related differences), and in terms of response to pharmacological treatment (DelRosso, Mogavero, & Ferri, 2021; Manconi et al., 2021). Epidemiological studies reveal a higher prevalence of RLS in females compared to males from adolescence onwards (DelRosso, Mogavero, Baroni, et al., 2021; Manconi et al., 2021). In males, periodic leg movements during sleep (PLMS) seem to prevail, present in 80% of patients with RLS (Manconi et al., 2021), with a peak particularly in old age (Ferri et al., 2020), although in females an increase in periodicity has been highlighted in conjunction with menopause, probably correlated with hormonal variations (Mogavero, DelRosso, et al., 2024).

The aetiopathogenesis of RLS remains elusive, with various biological mechanisms and neurotransmitter pathways implicated in its pathophysiology, including altered sleep homeostasis and disrupted neural plasticity, affecting not only the hypothalamus–spinal dopaminergic circuit (nucleus A11) but also the basal ganglia and other structures of the limbic system (Lanza et al., 2022; Manconi et al., 2021; Mogavero et al., 2021). These pathways not only modulate the clinical presentation and severity of RLS but also influence its response to pharmacological interventions.

Polysomnography (PSG) studies have provided valuable insights into the neurophysiological characteristics of sleep in patients with RLS. PSG demonstrates marked alterations in sleep architecture in patients with RLS, including a significant reduction in sleep efficiency, total sleep time, and Stage N2 and rapid eye movement (REM) sleep, as well as an increase in sleep latency, wakefulness after sleep onset (WASO), Stage N1, and number of awakenings (Geng et al., 2022). Such findings underscore the complex interplay between RLS pathology and sleep disturbances, necessitating tailored therapeutic approaches.

Therapeutic strategies for RLS aim to alleviate symptoms and improve sleep quality. Although they are not considered to be first-line treatment anymore, due to the frequent occurrence of augmentation (Silber et al., 2021), dopamine agonists, such as ropinirole and pramipexole, represent mainstays of RLS treatment. These agents target dopaminergic pathways implicated in RLS pathophysiology, effectively reducing PLMS and associated autonomic phenomena (Inoue et al., 2010; Manconi, Ferri, Zucconi, Clemens, et al., 2011; Manconi, Ferri, Zucconi, Oldani, et al., 2011). Additionally, $\alpha_2\delta$ ligands of calcium channels, now considered to be first-line treatments (Silber et al., 2021), have shown promise in ameliorating hyperarousability and hyperexcitability, as well as in enhancing deep sleep in patients with RLS (Garcia-Borreguero et al., 2002; Lanza et al., 2023; Winkelman & Jaros, 2018).

Despite the efficacy of these pharmacological interventions, sex-related differences in treatment response remain poorly understood. While RLS exhibits pronounced sex disparities in prevalence and clinical presentation, data regarding the impact of sex on therapeutic outcomes are limited (Manconi et al., 2021). Understanding sex-based variations in treatment response is essential for optimising RLS management and enhancing patient outcomes.

The present study aimed to investigate sex-related factors influencing the acute response to dopamine agonists, specifically ropinirole and pramipexole, in adult patients with RLS. By analysing both clinical parameters and PSG findings, especially PLMS known to be very little affected by the placebo effect (Fulda & Wetter, 2008), we sought to elucidate the potential implications of sex disparities on treatment efficacy and sleep quality in RLS management.

2 | METHODS

2.1 | Patients

We retrospectively recruited 41 consecutive, drug-free patients diagnosed with RLS (26 females and 15 males) with a mean (standard deviation [SD]) age of 59.7 (11.7) years, who provided their informed consent according to the Declaration of Helsinki.

The diagnosis of RLS was carried out according to the following five International Restless Legs Syndrome Study Group (IRLSSG) diagnostic criteria (Allen et al., 2014), through a semi-structured interview. Patients with a sleep disorder diagnosis other than RLS, any psychiatric diagnosis or use of antidepressants (Ferri et al., 2022; Ferri et al., 2023), neurodevelopmental delay, use of central nervous system drugs within the year prior to the study or use of any drug or medication for RLS for 3 weeks before the PSG recording were excluded. Also, patients with an apnea–hypopnea index >10 events/h of sleep were excluded. None of the patients had any additional significant medical or neurological disorder; therefore, none was taking other medications. The score at the IRLSSG rating scale (IRLS) (Walters et al., 2003) was also obtained.

Patients underwent two consecutive nocturnal PSG recordings. No medication was administered before the first night recording (baseline); before the second night recording, 26 patients (18 females and eight males) received a single oral dose of 0.25 mg pramipexole and 15 patients (eight females and seven males) received a single oral dose of 0.5 mg ropinirole at ~9.00 p.m. We selected these dosages as they typically serve as the initial doses when tapering therapy. There is a lack of data regarding the equivalent dosage between these two compounds in treating RLS. However, based on Parkinson's disease literature, the approximate equivalence ratio between pramipexole and ropinirole ranges from 1:2 to 1:4 (Linazasoro, 2008). Furthermore, these dosages are in line with the dosages suggested by the current treatment guidelines for RLS (Silber et al., 2021). No plasma levels were assessed because it has previously been reported that pharmacokinetics and pharmacodynamics of both pramipexole and ropinirole are not different between sexes (Contin et al., 2019; Kaye & Nicholls, 2000; Kompoliti et al., 2002). Bedtime was based on the usual individual bedtime and ranged between 9:30 and 11:00 p.m.

In the morning, after each PSG recording, all patients evaluated the severity of their previous night symptoms by means of a visual analogue scale (VAS) and reported eventual side-effects.

Patients provided informed consent to the study, which was approved by the Oasi Research Institute Ethics Committee.

2.2 | Polysomnographic recording and scoring

All the patients underwent a full-night PSG recording, which included electroencephalogram (at least three channels, one frontal, one central and one occipital, referred to the contralateral earlobe); electro-oculogram (two channels), electromyogram (EMG) of the submentalis muscle and of both tibialis anterior muscles, and electrocardiogram (one derivation). The EMG signals from the chin and both tibialis anterior muscles were band-pass filtered at 10–100 Hz, with a notch filter at 50 Hz. At the beginning of each recording session, the amplitude of the EMG signal from the two tibialis anterior muscles was assured to be <2 μV at rest.

Sleep stages were visually scored on 30-s epochs and all leg movements during sleep (LMS) were identified following standard criteria (Ferri et al., 2016), followed by the computation of a series of parameters including, in particular: (a) total LMS index, *n*/h; (b) PLMS index, *n*/h: LMS included in regular and non-interrupted sequences of at least four movements with onset-to-onset inter-movement interval (IMI) 10–90 s; (c) short-interval LMS (SILMS) index, *n*/h: LMS with preceding IMI <10 s; (d) isolated LMS (ISOLMS) index, *n*/h: LMS with IMI >90 s and LMS with IMI 10–90 s not meeting all the criteria for PLMS; (e) periodicity index: PLMS index/total LMS index ratio. Respiratory-related leg movements were not excluded from the counts because patients with an apnea–hypopnea index >10 events/h of sleep were excluded and not enrolled. In addition, there is no general agreement on the definition of the rules for the identification of these movements (Ferri et al., 2016) and respiratory-related LMS can be true PLMS (Manconi et al., 2014).

2.3 | Statistical analysis

Differences between the two groups were assessed by means of the Student's *t*-test, followed by the Bonferroni correction for multiple comparisons and supported by the Cohen's *d* effect size (Cohen, 1988). For the analysis of frequencies, the chi-square test was used. Correlations were assessed by multiple regression analysis. The commercially available Statistica software package (StatSoft, Inc., 2001. STATISTICA data analysis software system, version 6; www.statsoft.com) was used. Differences were considered significant for $p < 0.05$.

3 | RESULTS

Females were slightly younger than men, but the difference was not statistically significant (mean [SD] 58.0 [10.51] versus 62.6 [13.29] years, *t*-value −1.250, non-significant [NS]). Similarly, the IRLS score obtained from females and males was not significantly different (mean [SD] 25.1 [5.10] versus 24.1 [5.69], *t*-value 0.579, NS). We also checked for eventual differences at baseline between patients taking pramipexole and those taking ropinirole (Table 1) and found no significant differences in age, IRLS score, VAS score, and PLMS index. None of the patients reported side-effects after the treatment night.

3.1 | Sleep architecture

Table 2 shows the comparison of sleep architecture parameters obtained at baseline and during the treatment night in females and males. At baseline, we found only a small difference in the number of awakenings, which tended to be higher in males with a medium-to-large effect size; however, the difference was not significant after Bonferroni correction. For the treatment night, differences were found involving sleep efficiency and percentage of sleep Stage N2 (higher in females), which did not pass the Bonferroni correction but were characterised by a medium-to-large effect size. Conversely, WASO was significantly higher in males, with a significant *p* value after Bonferroni correction and a large effect size. The bottom part of the table reports the statistical comparison of the change in each parameter, expressed as a percentage of the baseline value. With this analysis we found a significant (not after Bonferroni correction but with a large effect size) difference of change in sleep Stage N2, smaller in males.

TABLE 1 Demographic and clinical features of patients.

Variable	Pramipexole ($n = 26$)	Ropinirole ($n = 15$)	Statistics
Sex, female/male, *n*	18/8	8/7	chi-square 1.04, NS
Age, years, mean (SD)	59.6 (10.04)	59.8 (14.45)	*t*-value −0.046, NS
IRLS score, mean (SD)	25.9 (5.64)	22.7 (4.05)	*t*-value 1.963, NS
PLMS index, *n*/h, mean (SD)	50.6 (49.67)	53.6 (46.17)	*t*-value −0.186, NS
VAS score at baseline, mean (SD)	7.4 (1.63)	7.1 (1.21)	*t*-value 0.690, NS
Comorbidities	None	None	–
Treatment	None	None	–

Abbreviations: IRLS, International Restless Legs Syndrome Study Group rating scale; NS, non-significant; PLMS, periodic leg movements during sleep; SD, standard deviation; VAS, visual analogue scale.

TABLE 2 Comparison of sleep architecture parameters obtained at baseline and during the treatment night in females and males; the comparison of the change of each parameter, expressed as a percentage of the baseline value is also reported.

Variable	Females ($n = 26$) Mean (SD)	Males ($n = 15$) Mean (SD)	Student's *t*-test		Effect size Cohen's *d*
			t-value	*p*	
Baseline					
Time in bed, min	518.0 (90.04)	492.8 (71.75)	0.925	NS	0.310
Sleep period time, min	482.5 (90.55)	454.1 (82.81)	0.995	NS	0.327
Total sleep time, min	358.4 (113.84)	332.2 (101.14)	0.739	NS	0.243
Sleep latency, min	26.1 (23.97)	24.3 (37.21)	0.190	NS	0.058
Stage R latency, min	137.4 (92.98)	103.9 (69.29)	1.210	NS	0.409
Stage shifts, *n*/h	10.9 (3.91)	13.4 (4.49)	−1.852	NS	−0.594
Awakenings, *n*/h	4.7 (2.62)	6.4 (1.90)	−2.103	0.042	−0.743
Sleep efficiency, %	68.4 (18.78)	67.0 (15.07)	0.253	NS	0.082
Stage W, %	26.8 (18.92)	27.5 (13.86)	−0.131	NS	−0.042
Stage N1, %	5.2 (5.45)	6.2 (4.92)	−0.613	NS	−0.193
Stage N2, %	39.6 (11.22)	41.1 (11.34)	−0.417	NS	−0.133
Stage N3, %	15.3 (8.53)	12.1 (8.23)	1.191	NS	0.382
Stage R, %	13.2 (7.84)	13.1 (7.30)	0.011	NS	0.013
Treatment					
Time in bed, min	515.2 (44.59)	515.3 (56.71)	−0.007	NS	−0.002
Sleep period time, min	481.8 (52.29)	486.5 (54.71)	−0.272	NS	−0.088
Total sleep time, min	413.6 (56.50)	370.9 (80.98)	1.983	NS	0.612
Sleep latency, min	20.6 (19.20)	17.7 (26.13)	0.412	NS	0.126
Stage R latency, min	137.9 (94.72)	110.1 (53.23)	1.042	NS	0.362
Stage shifts, *n*/h	13.2 (4.24)	15.4 (5.90)	−1.365	NS	−0.428
Awakenings, *n*/h	5.6 (2.62)	7.4 (3.82)	−1.873	NS	−0.550
Sleep efficiency, %	80.3 (8.13)	72.2 (14.21)	2.325	0.025	0.700
Stage W, %	14.1 (7.03)	24.2 (11.81)	−3.432	0.0014*	−1.039
Stage N1, %	4.5 (3.69)	5.6 (4.64)	−0.862	NS	−0.262
Stage N2, %	52.9 (9.95)	43.8 (12.66)	2.538	0.015	0.799
Stage N3, %	15.1 (7.13)	14.5 (9.37)	0.221	NS	0.072
Stage R, %	13.5 (7.15)	11.9 (4.22)	0.781	NS	0.273
Change					
Time in bed, %	5.9 (44.56)	6.4 (17.45)	−0.042	NS	−0.015
Sleep period time, %	6.7 (45.85)	10.0 (20.77)	−0.257	NS	−0.093
Total sleep time, %	42.6 (106.49)	16.6 (26.07)	0.926	NS	0.335
Sleep latency, %	224.9 (818.81)	233.6 (389.08)	−0.039	NS	−0.014
Stage R latency, %	−126.4 (746.01)	−43.2 (252.10)	−0.417	NS	−0.149
Stage shifts, %	30.1 (46.39)	19.1 (35.71)	0.791	NS	0.266
Awakenings, %	55.5 (103.09)	21.7 (62.65)	1.150	NS	0.396
Sleep efficiency, %	30.3 (55.61)	10.7 (21.61)	1.310	NS	0.465
Stage W, %	4.1 (154.13)	−0.1 (54.26)	0.103	NS	0.036
Stage N1, %	31.8 (103.09)	29.8 (93.82)	0.062	NS	0.020
Stage N2, %	40.6 (35.95)	11.8 (34.99)	2.495	0.017	0.812
Stage N3, %	−13.1 (42.93)	111.6 (333.94)	−1.781	NS	−0.524
Stage R, %	34.4 (138.33)	−2.8 (48.04)	0.968	NS	0.359

*Significant after Bonferroni correction.

Abbreviations: NS, non-significant; SD, standard deviation.

3.2 | Leg movement activity during sleep

Similarly to the previous table, Table 3 shows the same analysis performed for leg movement activity parameters obtained at baseline and during the treatment night in females and males. There was no significant difference at baseline for these parameters and effect sizes were small or medium. On the contrary, during the treatment night, total LMS, PLMS, and periodicity indexes were significantly (also after Bonferroni correction) lower in females than in males, accompanied by large effect sizes. Also the SILMS index tended to be lower in females, but the *p* value was not significant after Bonferroni correction, although the effect size almost reached the value of 0.8, considered large by Cohen (Cohen, 1988). The analysis of the changes, expressed as percentages of the baseline parameters, confirmed the significant differences found for the treatment night.

Finally, Figure 1 shows in a graphical way the distribution of inter-movement intervals obtained at baseline and during the treatment night in females and males.

3.3 | Visual analogue scale

The VAS score was very evidently lower after treatment in all patients; also, the score obtained in females and in males was not significantly different after both the baseline recording (mean [SD] 7.3 [1.49] versus 7.2 [1.40], *t*-value 0.306, NS) and the treatment night (mean [SD] 1.3 [1.45] versus 1.3 [1.49], *t*-value 0.000, NS); consequently, also the difference between the two nights was not different between females and males (mean [SD] −6.0 [1.97] versus −5.8 [1.64], *t*-value −0.242, NS).

TABLE 3 Comparison of leg movement activity parameters obtained at baseline and during the treatment night in females and males; the comparison of the change of each parameter, expressed as a percentage of the baseline value is also reported.

Variable	Females ($n = 26$) Mean (SD)	Males ($n = 15$) Mean (SD)	Student's *t*-test *t*-value	*p*	Effect size Cohen's *d*
Baseline					
Total LMS index, *n*/h	60.4 (54.85)	84.3 (65.23)	−1.253	NS	−0.396
PLMS index, *n*/h	43.2 (41.76)	66.4 (55.36)	−1.520	NS	−0.473
SILMS index, *n*/h	6.6 (10.71)	7.3 (9.42)	−0.201	NS	−0.066
ISOLMS index, *n*/h	10.5 (6.63)	10.5 (6.14)	−0.008	NS	−0.003
Periodicity Index	0.691 (0.141)	0.732 (0.183)	−0.791	NS	−0.247
PLMS duration, s	3.1 (0.93)	2.9 (0.85)	0.856	NS	0.281
SILMS duration, s	2.8 (0.75)	2.8 (0.93)	−0.102	NS	−0.032
ISOLMS duration, s	3.5 (1.01)	3.0 (0.91)	1.444	NS	0.476
Treatment					
Total LMS index, *n*/h	15.7 (10.24)	32.1 (23.03)	−3.149	0.0031*	−0.920
PLMS index, *n*/h	3.9 (5.59)	17.3 (21.61)	−3.014	0.0045*	−0.848
SILMS index, *n*/h	1.9 (2.25)	3.6 (2.37)	−2.282	0.028	−0.734
ISOLMS index, *n*/h	9.9 (4.17)	11.2 (5.61)	−0.849	NS	−0.264
Periodicity index	0.178 (0.176)	0.396 (0.266)	−3.159	0.003*	−0.966
PLMS duration, s	3.5 (1.55)	2.9 (0.95)	1.511	NS	0.536
SILMS duration, s	2.9 (1.21)	2.8 (1.02)	0.211	NS	0.071
ISOLMS duration, s	3.7 (0.90)	3.2 (0.90)	1.728	NS	0.560
Change					
Total LMS index, %	−63.9 (21.26)	−45.3 (40.77)	−1.924	NS	−0.571
PLMS index, %	−89.2 (14.68)	−66.0 (30.31)	−3.300	0.002*	−0.972
SILMS index, %	−49.6 (35.15)	53.1 (257.78)	−2.016	0.05	−0.558
ISOLMS index, %	11.3 (45.24)	24.0 (55.07)	−0.798	NS	−0.251
Periodicity Index	−73.6 (26.54)	−45.4 (32.24)	−3.027	0.0044*	−0.954
PLMS duration, %	−13.4 (81.70)	4.8 (36.44)	−0.812	NS	−0.287
SILMS duration, %	4.8 (54.75)	18.3 (99.25)	−0.564	NS	−0.168
ISOLMS duration, %	12.5 (33.61)	13.3 (41.52)	−0.068	NS	−0.021

*Significant after Bonferroni correction.

Abbreviations: ISOLMS, isolated leg movements during sleep; LMS, leg movements during sleep; NS, non-significant; PLMS, periodic leg movements during sleep; SD, standard deviation; SILMS, short-interval leg movements during sleep.

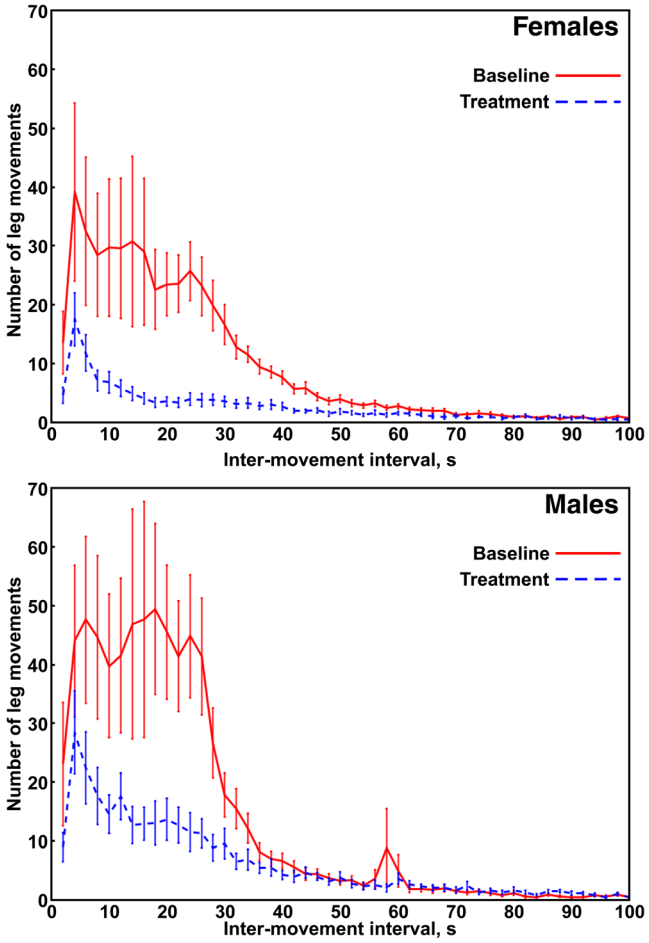

FIGURE 1 Distribution of inter-movement intervals obtained at baseline and during the treatment night in females and males.

4 | DISCUSSION

4.1 | Main findings

Pramipexole and ropinirole have long been recognised for their beneficial effects in the management of RLS. These dopamine agonists have demonstrated efficacy in alleviating symptoms such as uncomfortable sensations in the legs, restlessness, and disrupted sleep, thereby improving the quality of life for individuals with RLS (Ferri et al., 2010; Manconi et al., 2007; Manconi et al., 2021; Manconi, Ferri, Zucconi, Oldani, et al., 2011). Regarding PSG parameters, studies unanimously demonstrate efficacy in reducing PLMS, even at low dosage and both in acute and chronic settings, with no substantial differences between ropinirole and pramipexole (Manconi, Ferri, Zucconi, Clemens, et al., 2011; Manconi, Ferri, Zucconi, Oldani, et al., 2011); while there appear to be no alterations in sleep architecture, even in chronic usage and at maximum dosages permitted according to guidelines, except for a slight increase in Stage N2 highlighted in a few studies (Allen et al., 2004; Bliwise et al., 2005; Ferri et al., 2010; Saletu et al., 2002).

However, despite their effectiveness, they are now often considered second-line treatments in chronic persistent RLS due to the frequent development of augmentation, a phenomenon where symptoms worsen over time with continued use (Garcia-Borreguero et al., 2018; Silber et al., 2021). However, in refractory RLS the guidelines recommend, among the options, combined therapy (dopamine agonist plus $\alpha_2\delta$ ligand) (Silber et al., 2021). Augmentation can lead to increased severity and frequency of symptoms, diminishing the overall therapeutic benefit of these medications. As a result, healthcare providers are increasingly cautious in prescribing pramipexole and ropinirole as first-line options, opting for alternative treatments or combined therapies to mitigate the risk of augmentation and ensure optimal management of RLS symptoms. Sex differences in augmentation do not seem to have been reported (Liu et al., 2016); however, in light of the results of this study and the effects of dopamine agonists on sleep structure, previously described, the use of dopamine agonists in RLS may be a more suitable treatment option for females than for males, although a significantly better subjective clinical effect in females has yet to be demonstrated. Of foremost importance remains weighing the benefits and potential risks of augmentation and the fact that long-term use of dopamine agonists reduces the response to $\alpha_2\delta$ ligands of calcium channels (Garcia-Borreguero et al., 2019).

On the other hand, dopamine agonists are effective in modulating the increases in heart rate and blood pressure associated with PLMS (Manconi, Ferri, Zucconi, Clemens, et al., 2011; Rocchi et al., 2015), an important factor in cardiovascular risk prevention. There are no guidelines to treat PLMS in the absence of RLS symptoms; however, a recent meta-analysis has highlighted a greater risk of stroke associated with PLMS, regardless of the presence of RLS symptoms (Bassetti et al., 2020). One of the main findings of our study is a greater reduction in PLMS in females compared to males, due to the administration of dopamine agonists (Figure 1). Considering that pharmacokinetics and pharmacodynamics of both pramipexole and ropinirole are not different between sexes, as reported in the literature (Contin et al., 2019; Kaye & Nicholls, 2000; Kompoliti et al., 2002), there are other factors probably underlying these findings.

The fact that these drugs act mainly in females and that, as found in our previous study, there seems to be a greater impact of PLMS especially with menopause (Mogavero, DelRosso, et al., 2024), a period from which females are at greater cardiovascular risk (Mehta & Manson, 2024), their use could represent a valuable aid in preventing cardiac issues in females affected by RLS and PLMS. In addition, sex differences observed in the prevalence of PLMS have led to the hypothesis of a possible role of hormonal factors implicated in their (still unknown) pathogenesis (Mogavero, DelRosso, et al., 2024), and recent studies on the transcriptome in patients with RLS have confirmed with biological evidence an overexpression of the oestrogen signalling pathway (Mogavero, Salemi, et al., 2024). In this context, it is important to emphasise that oestradiol acutely and rapidly regulates dopamine release in females and dopamine re-uptake in males (Yoest et al., 2019), so the differences observed in the response to dopamine agonists between males and females in our study could be attributed

to hormonal differences between the two sexes, resulting in a different modulation of the dopaminergic system.

Dopamine agonists are known for their preferential action on dopamine D_3 receptors, which are implicated in the pathophysiology of RLS (Clemens & Ghorayeb, 2019). Although they are now considered as second-line treatments, by administering pramipexole and ropinirole acutely, researchers can elucidate the immediate effects of D_3 receptor activation on RLS symptoms and related biological processes. In addition, the immediate effects of low doses of pramipexole and ropinirole render them suitable for on-demand treatment and as a supportive tool for differential diagnosis in complex cases (Manconi, Ferri, Zucconi, Oldani, et al., 2011).

Emerging research suggests that there may be differences in the expression of dopamine D_3 receptors between females and males. While our understanding of these sex-specific variations is still evolving, preliminary studies indicate potential disparities in the density and distribution of D_3 receptors in the brain (Brown et al., 2012; Williams et al., 2021). These differences may contribute to variations in dopamine signalling and neurotransmission, potentially influencing various physiological and behavioural processes. For instance, alterations in D_3 receptor expression have been implicated in conditions such as substance abuse disorders, attention deficit hyperactivity disorder, depression and anxiety, schizophrenia, and Parkinson's disease, which often manifest differently between sexes (Bao & Swaab, 2010; Sokoloff & Le Foll, 2017) and are often associated with RLS (Manconi et al., 2021). Therefore, the administration of dopamine agonists in RLS comorbid with these pathologies could be particularly useful, especially in females. Further investigation into the complexity of D_3 receptor expression in females and males holds promise for elucidating the underlying mechanisms of sex differences in brain function and behaviour, with implications for personalised medicine approaches tailored to each sex.

The expression of dopamine D_3 receptors appears to vary between individuals, and whether they are more expressed in females compared to males is still an area of ongoing research and debate. While some studies suggest potential differences in D_3 receptor expression between sexes (Brown et al., 2012; Williams et al., 2021), the findings are not consistent across all research. Factors such as age, hormonal fluctuations, and genetic predispositions, as well as epigenetic factors, may also influence D_3 receptor expression. Therefore, it is essential to interpret the available evidence cautiously and await further research to draw definitive conclusions regarding the expression of D_3 receptors in females versus males.

Regarding alterations in sleep architecture, we did not find substantial variations induced by dopamine agonists, in agreement with previously described findings, although there appears to be an increase in Stage N2 in females compared to males and WASO significantly higher in males compared to females. These findings may be due to the greater reduction in PLMS in females compared to males, considering that these movements are mainly distributed in this N2 sleep stage (Ferri, 2012).

Finally, the VAS score did not show clinical differences between females and males, although objective PLMS data demonstrated significant differences between the sexes; this aspect supports the importance of using PSG in the management of RLS, although both international diagnostic criteria and treatment guidelines do not include it. It is undeniable that knowledge of the effects of therapies used in RLS on PSG parameters is important in order to restore and preserve the physiological architecture of sleep and its homeostasis. In addition, the evaluation of these parameters based on sex differences allows further stratification of patient types, with a targeted approach that may improve therapeutic response and reduce the risk of disease chronicity and onset of side-effects.

This seems to be the first study to have evaluated sex differences regarding a different PLMS response to pharmacological treatment in RLS, despite the marked differences between males and females found in this disorder (Kim et al., 2024; Manconi et al., 2021); this aspect has important clinical implications, in fact also recent research in other branches of medicine emphasises sex-related differences in the pharmacokinetics and pharmacodynamics of therapies used in arterial hypertension or myocardial ischaemia (Medzikovic et al., 2023; Tamargo et al., 2023), highlighting an important emerging topic in the field of Personalised and Precision Medicine and the need to consider this aspect in pharmacological guidelines. Therefore, it would be appropriate to evaluate a different sex-related approach also in RLS.

4.2 | Limitations

The primary limitation of this study is that we relied on a convenience sample of patients, lacking the opportunity to conduct a sample size analysis beforehand. Additionally, the absence of information on potential sex differences in response to dopamine agonist treatment in RLS further compounds this limitation. Nevertheless, it can be inferred that with our sample size consisting of 26 females and 15 males, we achieve a statistical power of 80% at an alpha level of 0.05 for comparisons featuring an effect size of 0.82 (large). Notably, our results also demonstrate effect sizes surpassing this threshold, thus affirming the robustness of our analysis.

Utilising two distinct dopamine agonists, namely pramipexole and ropinirole, could be perceived as an added constraint in this study. Nonetheless, we have previously documented a significant equivalence in the effects of these two compounds on sleep architecture, PLMS, and clinical outcomes among patients with RLS (Manconi, Ferri, Zucconi, Oldani, et al., 2011). Furthermore, it has been observed that the similarities in terms of efficacy and side-effects between pramipexole and ropinirole likely stem from their somewhat comparable pharmacokinetic and pharmacodynamic profiles (Manconi, Ferri, Zucconi, Oldani, et al., 2011). Both drugs act as preferential D_3 agonists, as evidenced by their inhibition constants (Ki) in nmol/L: pramipexole at 0.5 and ropinirole at 2.9 nmol/L. They share similarities in elimination half-life (pramipexole: 8–12 h; ropinirole: 6 h), oral bioavailability (pramipexole: >90%; ropinirole: 50%), protein binding (pramipexole: 15%; ropinirole: 20–40%), and clearance (pramipexole: 30 L/h; ropinirole: 47 L/h) (Kvernmo et al., 2008). This prior evidence validates the

amalgamation of these patient cohorts in the present study, also supported by an additional analysis we ran on leg movement parameters, separately for patients taking pramipexole or ropinirole, that showed substantially similar sex differences (supplementary Table S1).

Lastly, our findings pertain to the acute effects of pramipexole and ropinirole and should not be directly extrapolated to their long-term effects. Nonetheless, they offer valuable insights into the biological mechanisms underlying sex differences in RLS, which can inform treatment recommendations in future studies.

5 | CONCLUSIONS

In conclusion, our study results reveal sex differences in response to dopamine agonists among patients with RLS. These findings align with recent research emphasising sex disparities in the pharmacokinetics and pharmacodynamics of cardiovascular therapies, underscoring an important emerging aspect within the field of Personalised and Precision Medicine that warrants consideration in future pharmacological guidelines. The present findings offer translational insights toward a more precisely tailored and sex-specific approach to RLS treatment.

AUTHOR CONTRIBUTIONS

Maria P. Mogavero: Conceptualization; investigation; supervision; writing – original draft; writing – review and editing. **Elena Antelmi:** Writing – review and editing. **Giuseppe Lanza:** Writing – review and editing; writing – original draft. **Sara Marelli:** Writing – review and editing. **Alessandra Castelnuovo:** Writing – review and editing. **Michele Tinazzi:** Writing – review and editing. **Lourdes M. DelRosso:** Writing – review and editing. **Rosalia Silvestri:** Writing – review and editing. **Raffaele Ferri:** Methodology; formal analysis; data curation; supervision; writing – original draft; writing – review and editing; funding acquisition; visualization. **Luigi Ferini Strambi:** Supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

STUDY SUBJECTS OR COHORTS OVERLAP

Of note, a subset of the data presented in this study have been reported in previous studies (Manconi et al., 2007; Manconi, Ferri, Zucconi, Oldani, et al., 2011) assessing PLMS response to dopamine agonists.

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SUPPORTING INFORMATION

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