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Safinamide effect on sleep architecture of motor fluctuating Parkinson's disease patients: A polysomnographic rasagiline-controlled study

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ABSTRACT

Introduction: Sleep problems commonly occur in Parkinson's disease (PD) and significantly affect patients' quality of life. A possible effect on subjective sleep disturbances of monoamine oxidase-B inhibitors (MAOB-Is) has been described.

Methods: This prospective, observational, single-centre study involved 45 fluctuating PD patients complaining sleep problems as documented by the PD Sleep Scale -2nd version (PDSS-2 $\geq$18) starting rasagiline 1 mg/daily or safinamide 100 mg/daily, according to common clinical practice, and maintaining antiparkinsonian therapy unchanged. Polysomnography (PSG), sleep questionnaires (PDSS-2, Epworth Sleepiness Scale - ESS), and motor function were evaluated at baseline (T0) and after 4 months of treatment (T1).

Results: Safinamide was prescribed in thirty patients and rasagiline in fifteen patients. Both drugs induced a significant improvement in Movement Disorder Society Unified PD Rating Scale III scores. Patients treated with rasagiline showed a significant increase in stage 1 (N1) Non-REM sleep compared to T0, with no significant effects on sleep scales. Patients treated with safinamide showed a significant increase in stage 3 of Non-REM sleep and sleep efficiency and a reduction in the rate of periodic limb movements, matching a significant reduction in PDSS-2 and ESS scales compared to T0.

Conclusion: This study showed that safinamide, in addition to having a significant effect on PD motor symptoms, like the other MAOB-Is, may exert a specific beneficial effect on subjective and objective sleep, probably driven by its dual mechanism of action, which involves both dopaminergic and glutamatergic neurotransmission.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the loss of dopaminergic neurons of Substantia Nigra pars compacta (SNpc) and widespread accumulation of α-synuclein containing Lewy Bodies (LBs). Along with the cardinal motor symptoms, namely bradykinesia, tremor, and rigidity [1], several non-motor symptoms (NMS), including pain, hyposmia, fatigue, and gastrointestinal disturbances, frequently accompany or even precede the clinical motor presentation by several years [1]. Among these NMS, sleep disturbances were the most common and can affect up to 90 % of patients with PD, with a detrimental impact on the overall quality of life and patients' and caregivers' burden of disease [1], further increased by motor fluctuations [2,3].

There is a strict relationship between the dopaminergic system and mechanisms underlying the sleep-wake cycle; accordingly, different dopaminergic drugs may interfere with sleep in PD patients [4]. In the last decades, clinical data showed that both dopamine-agonists and levodopa (LD) might be effective in treating some sleep problems in patients with PD, such as sleep fragmentation, insomnia, restless legs syndrome, and periodic limb movement disorder [5]. However, the same drugs may cause excessive daytime sleepiness or alter the sleep-wake cycle [6].

Recent evidence suggests a possible effect on sleep of monoamine oxidase-B inhibitors (MAOB-Is), including rasagiline, a second-generation irreversible MAOB-I, used in the management of PD motor

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symptoms as monotherapy or in add-on to dopaminergic drugs, and safinamide, a third-generation reversible MAOB-I, approved as adjunctive therapy in motor fluctuating PD patients [7,8]. However, most clinical studies focused on subjective sleep measures rather than objective assessment of sleep architecture [9–11].

Over the last years, polysomnography (PSG) emerged as a validated approach to studying sleep structure and defining the concept of sleep homeostasis in PD. In addition, PSG contributed to investigating the relationship between sleep structure and pharmacological treatment in patients with PD [12]. Considering previous studies reporting the beneficial effect of rasagiline on sleep architecture measured by PSG [13] and the greater effect of safinamide vs rasagiline on subjective sleep questionnaires in patients with PD [11], the primary objective of this observational study was evaluating the effect of 4-month treatment with safinamide *vs* rasagiline, as prescribed according to common clinical practice, on sleep and sleep disturbances, objectively measured by PSG and subjectively evaluated by the PD Sleep Scale-2nd version (PDSS-2) and the Epworth Sleepiness Scale (ESS), in mild to moderate motor fluctuating PD patients subjectively complaining sleep problems.

2. Materials and methods

2.1. Study population

This prospective, observational, single-centre study involved forty-five PD patients consecutively recruited from January 2022 until December 2023 showing sleep complaints as assessed by the PDSS-2 (cut-off score $\geq$18 [14]) evaluated at the PD Unit of Tor Vergata University Hospital (Rome, Italy). The main inclusion criteria were the diagnosis of idiopathic PD made by a movement disorder specialist (MP, TS, RC, AS) according to the 2015 MDS criteria [15] and the complaint of "poor sleep" as defined by the validated cut-off of 18 at the PDSS-2 [14]. Other inclusion criteria were: (1) Hoehn and Yahr (H&Y) stage between 1 and 3; (2) the presence of motor fluctuations; (3) ongoing and stable dose of antiparkinsonian treatment for at least four weeks before the baseline visit; (4) starting safinamide 100 mg/daily (titrated according to common clinical practice with the dose of 50 mg/day for 2 weeks) or rasagiline 1 mg/daily, according to standard clinical practice as an indication to improve motor symptoms, without modifying the remaining antiparkinsonian therapy.

Exclusion criteria were: (1) atypical or secondary parkinsonism; (2) PD-dementia with a Mini-Mental State Examination score <24; (3) concomitant neurological, psychiatric, or systemic disease possibly affecting sleep; (4) shift work or other conditions that cannot ensure a regular sleep-wake cycle; (5) previous diagnosis of sleep disorders and current treatment with drugs interfering with sleep, including benzodiazepines or Z-drugs for insomnia.

Apart from the introduction of the MAOB-I, participants did not change their medications during the study.

The study was approved by the local Ethics Committee and was conducted according to the Helsinki Declaration of 1975 (reference number 128.23). All the participants provided their signed informed consent.

2.2. Clinical assessments

In all patients, clinical assessments and the PSG recordings were performed on the same day: at baseline (T0), before starting treatment with rasagiline or safinamide, and after four months of treatment with the MAOB-I (T1).

Patients' PD severity was assessed according to the H&Y stage, and patients' motor impairment was quantified using the MDS-Unified Parkinson's Disease Rating Scale parts III and IV (UPDRS-III and UPDRS-IV) [15].

Patients' subjective sleep and daytime sleepiness complaints were assessed using the PDSS-2 [16] and the ESS [17] during the sleep medicine interview performed by a trained psychologist (MF).

Finally, at T0, the LD equivalent daily dose (LEDD) was calculated in all patients according to the conventional formula [18].

2.2.1. Polysomnographic recording

A trained sleep technician (GT) performed the PSG recordings in all patients to assess their nocturnal sleep at baseline (T0) and after four months of treatment with rasagiline or safinamide (T1), as previously reported (SOMNOscreen; SOMNOmedics GmbH) [19,20].

The montage consisted of two oculographic channels, three electromyographic channels (mental and anterior tibialis muscles), and eight electroencephalographic channels (F4, C4, O2, A2, F3, C3, O1, A1). Cardiorespiratory parameters were assessed by recording oronasal flow, thoracic and abdominal movements (plethysmography), pulse oximetry, and electrocardiography. Patients were instructed to maintain the usual sleep schedule and record it in a sleep diary during the week preceding the evaluation. All the PSG recordings were evaluated by experts in sleep medicine (CL, NM). The following standard PSG variables were included in the analysis: time in bed (TIB, time spent in bed between lights off and lights on), total sleep time (TST, the actual sleep time without sleep onset latency and awakenings), wakefulness after sleep onset (WASO), sleep efficiency (SE, the ratio of total sleep time to time in bed), sleep latency (SL); REM sleep latency (REML, the interval between sleep onset and the first epoch of REM), stage 1 of non-REM sleep (N1), stage 2 of non-REM sleep (N2), stage 3 of non-REM sleep (N3), REM sleep. Sleep stage percentages were calculated over the TST.

Finally, the PSG scorers identified apnoea/hypopnea events, oxygen desaturation index (ODI), PLMs, and the presence of REM sleep without atonia (RSWA), according to the international standard criteria of the American Academy of Sleep Medicine (AASM) [21].

2.3. Statistics

Continuous variables are expressed as mean and SD; categorical variables are presented as frequencies and percentages. Since the Kolmogorov-Smirnov test demonstrated a non-normal distribution of the variables, we used a nonparametric statistical analysis. The Mann-Whitney *U* Test was used to assess demographic and clinical differences between the rasagiline and safinamide groups at T0 and T1. The Wilcoxon test was used to compare the mean change in clinical parameters between T0 and T1 in each group. A Δ-score (T1-T0) of each clinical and PSG variable was calculated in each subject. Differences in Δ-values between groups were compared using the Mann-Whitney *U* Test. The Chi-square and Fisher tests were used to compare categorical variables between different groups. Finally, we used the PDSS-2 validated cut-off of 18 to differentiate poor sleepers (PDSS-2 total score $\geq$18) from good sleepers (PDSS-2 total score <18) in each group [14].

The statistical analyses were conducted using two-tailed tests. The false discovery rate (FDR) method was used to correct for multiple comparisons and control the increase of type I error. A significance level of $p < 0.05$ (FDR-corrected) was employed throughout the study. No statistical power calculation was conducted prior to the study. The sample size was based on the available data and our previous experience with this prospective study design. Statistical analyses were performed using SPSS 25.0 statistical software.

3. Results

3.1. Overall cohort features

A total of forty-five motor fluctuating PD patients (mean age 67.22 ± 8.39 years, males/females = 33/12) under stable antiparkinsonian therapy and with a PDSS-2 $\geq$18 were included in the study.

At T0, patients showed a medium MDS-UPDRS part III of 20.36 ± 5.78 and a medium MDS-UPDRS part IV of 2.22 ± 0.82. Rasagiline was prescribed in n = 15 patients, whereas safinamide in n = 30 patients,

according to common clinical practice, without following a randomized design.

3.2. Comparison analysis between patients treated with rasagiline and safinamide at T0

At T0, the two groups of patients were homogeneous in sex distribution and age and did not differ in terms of demographic and clinical data. No differences emerged in motor features and dopaminergic treatments (H&Y, MDS-UPDRS part III and IV, LEDD values)., as well as in in sleep scales (ESS and PDSS) between the two groups. Regarding PSG parameters, no differences were found between the two groups, including the rate of patients with RSWA. See Table 1.

3.3. Comparison analysis between patients treated with rasagiline and safinamide at T1 (see table 1)

At T1, we found no difference in MDS-UPDRS part III scores between groups, however, patients treated by safinamide had significantly lower MDS-UPDRS part IV scores than patients treated by rasagiline (0.13 ± 0.35 vs. 1.47 ± 1.19, u = 76.00, p < 0.001). Regarding sleep scales, patients treated by safinamide had lower PDSS-2 scales than those treated by rasagiline (19.77 ± 4.29 vs. 22.4 ± 4.73), although the difference did not reach statistical significance (u = 151.00, p = 0.0170). There were no differences in ESS scores at T1 between the two groups.

No differences in PSG parameters emerged between groups.

3.4. Comparison analysis in in patients treated by rasagiline between T0 and T1 (see table 1)

Compared to T0, patients treated with rasagiline showed significantly lower MDS-UPDRS part III scores (Z = −2.96, p = 0.017).

Regarding sleep scales, both PDSS-2 and ESS scores did not significantly improve comparing T1 to T0.

Regarding PSG parameters, patients showed a significant increase of N1 (Z = −2.38, p = 0.017). No further differences emerged.

3.5. Comparison analysis in patients treated by safinamide between T0 and T1 (see table 1)

Compared to T0, patients showed at T1 a significant reduction in MDS-UPDRS part III (Z = −4.52, p < 0.001) and part IV scores (Z = −4.58, p < 0.001), and displayed a significant decrease in PDSS-2 (Z = −4.30, p < 0.001) and in ESS scores (Z = −3.81, p < 0.001).

Fig. 1 shows the main differences between T0 and T1 in clinical scales in rasagiline- and safinamide-treated patients.

As for the PSG parameters, at T1 compared to T0, patients had a significant increase in SE (Z = −2.77, p = 0.023) and in N3 (p < 0.001), and a significant reduction in the rate of PLMs (Z = −3.84, p < 0.001).

Fig. 2 shows the main differences between T0 and T1 in PSG parameters in rasagiline- and safinamide-treated patients.

3.6. Δ-score comparison analyses (T1-T0) in patients treated by rasagiline and safinamide (see table 2)

The Mann-Whitney *U* Test showed a significant difference in ΔMDS-UPDRS-IV between groups (u = 187.00, p = 0.023) since the safinamide group showed a greater reduction from T0 to T1 compared to the rasagiline one. No difference was found in ΔMDS-UPDRS-III between groups.

Regarding sleep scales, patients treated with safinamide showed a greater ΔESS (u = 145.00, p = 0.022) compared to patients taking rasagiline.

As for PSG parameters, a significant difference emerged in the ΔSE (u = 108.00, p = 0.005), in ΔWASO (u = 126.00, p = 0022), ΔN1 (u = 211.00, p < 0.001), ΔN3 (u = 73.00, p < 0.001), and in ΔPLMs (u =

Table 1
The table shows in the upper part the main demographic and clinical features of the 45 patients with PD at baseline (T0) before starting rasagiline (n = 15) or safinamide (n = 30). The lower part shows the clinical scores and PSG parameters of the same patient groups at T0 and T1, after four months of treatment with MAO-I.

	Rasagiline (n = 15)			Safinamide (n = 30)		
						p-Value
Age	66.73 ± 9.76			67.47 ± 7.78		p = 0.962
Sex (M/F)	10/5			23/7		p = 0.603
H&Y	1.33 ± 0.49			1.40 ± 0.50		p = 0.754
LEDD	365.0 ± 94.32			373.50 ± 89.02		p = 0.824
	T0	**T1**	**p-Value**	**T0**	**T1**	**p-Value**
MDS-UPDRS-III	19.80 ± 5.59	18.4 ± 5.22	*p = 0.017	20.63 ± 5.94	18.63 ± 5.39	[a]p < 0.001
MDS-UPDRS-IV	2.33 ± 0.90	1.47 ± 1.19	p = 0.079	2.17 ± 0.79	0.133 ± 0.35	[a]p < 0.001
PDSS-2	24.13 ± 4.00	22.40 ± 4.73	p = 0.157	24.13 ± 3.93	19.77 ± 4.21	[a]p < 0.001
ESS	7.33 ± 4.48	7.13 ± 3.98	p = 0.754	8.03 ± 4.96	6.37 ± 4.07	[a]p < 0.001
TIB	432.86 ± 57.87	431.83 ± 43.67	p = 0.728	434.96 ± 71.84	429.71 ± 45.69	p = 0.906
TST	343.93 ± 83.39	338.60 ± 5.04	p = 0.289	343.56 ± 51.05	354.18 ± 48.46	p = 0.289
SE (%)	78.87 ± 12.66	77.95 ± 12.66	p = 0.233	79.87 ± 13.37	82.93 ± 10.91	[a]p = 0.023
WASO (min)	74.79 ± 53.61	81.07 ± 51.36	p = 0.299	77.14 ± 59.15	64.73 ± 50.02	p = 0.169
REML (min)	114.54 ± 67.84	111.87 ± 49.48	p = 0.953	114.34 ± 74.70	93.34 ± 45.85	p = 0.081
SL (min)	14.23 ± 10.92	12.17 ± 7.10	p = 0.520	14.43 ± 29.74	10.80 ± 10.86	p = 0.754
REM %	16.00 ± 6.59	16.47 ± 6.86	p = 0.289	15.81 ± 4.76	16.56 ± 4.65	p = 0.254
N1 %	10.82 ± 6.58	14.12 ± 11.13	*p = 0.017	10.66 ± 6.08	7.47 ± 4.91	p = 0.054
N2 %	54.51 ± 8.02	51.23 ± 9.04	p = 0.055	54.45 ± 8.01	53.57 ± 7.90	p = 0.244
N3 %	18.24 ± 10.37	18.18 ± 10.31	p = 0.289	18.73 ± 5.89	22.11 ± 6.57	[a]p < 0.001
AHI	14.30 ± 8.32	13.09 ± 10.31	p = 0.250	14.43 ± 9.05	14.32 ± 9.32	p = 0.289
ODI	13.38 ± 8.40	12.41 ± 8.32	p = 0.363	13.48 ± 9.24	13.33 ± 9.05	p = 0.289
PLMs	14.83 ± 9.92	14.22 ± 8.55	p = 0.688	13.89 ± 10.36	8.98 ± 5.24	[a]p < 0.001
RSWA (Y/N)	7/8	8/7	p = 0.793	13/17	11/19	p = 0.728
Poor sleepers (Y/N)	15/0	12/3	p = 0.236	30/0	19/11	[a]p < 0.001

H&Y, Hoehn and Yahr; *LEDD*, levodopa equivalent daily dose; *MDS-UPDRS,* Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; *PDSS-2,* Parkinson's Disease Sleep Scale-2*; ESS,* Epworth Sleepiness Scale*; TIB*, time spent in bed; *TST*, total sleep time; *SE*, sleep efficiency; *REML*, REM sleep latency; *SL*, sleep latency; *N1*, stage 1 of non-REM sleep; *N2*, stage 2 of non-REM sleep; *N3*, stage 3 of non-REM sleep; *AHI* apnea–hypopnea index; *ODI*, oxygen desaturation index; *PLMs*, periodic limb movements; *RSWA*, REM sleep without atonia. Age is expressed in years. LEDD is expressed as mg/day.

[a] Statistically significant test. NA, non-available.

Table 2
The table shows the differences in Δ score (T1-T0) of each clinical and PSG variable in the group of patients treated with rasagiline (n = 15) or safinamide (n = 30).

		Rasagiline (n = 15)	Safinamide (n = 30)	p-Value
Motor features	**ΔMDS-UPDRS III**	−1.40 ± 1.24	−2.00 ± 1.34	p = 0.361
	ΔMDS-UPDRS IV	−0.87 ± 1.36	−2.03 ± 0.81	[a]p = 0.023
Sleep scales	**ΔESS**	−0.20 ± 2.04	−1.67 ± 1.86	[a]p = 0.022
	ΔPDSS-2	−1.73 ± 3.08	−4.37 ± 4.11	p = 0.114
PSG parameters	**ΔTIB**	−1.03 ± 5.37	−5.24 ± 61.43	p = 0.953
	ΔTST	−5.33 ± 15.98	10.80 ± 43.21	p = 0.169
	ΔSE	−0.91 ± 2.50	3.06 ± 5.13	[a]p = 0.022
	ΔWASO	6.37 ± 18.12	−12.41 ± 40.42	p = 0.055
	ΔSL	−2.06 ± 7.17	−3.63 ± 22.07	p = 0.163
	ΔREML	−2.69 ± 24.13	−20.98 ± 57.49	p = 0.235
	ΔREM %	0.47 ± 1.64	0.75 ± 4.46	p = 0.361
	ΔN1 %	3.29 ± 5.72	−3.10 ± 5.28	[a]p < 0.001
	ΔN2 %	−3.28 ± 5.38	−0.87 ± 7.06	p = 0.802
	ΔN3 %	−0.05 ± 0.15	3.39 ± 4.03	[a]p < 0.001
	ΔAHI	−1.21 ± 2.75	−0.18 ± 0.67	p = 0.363
	ΔODI	−0.87 ± 3.11	−0.14 ± 0.59	p = 0.361
	ΔPLMs	−0.60 ± 2.50	−5.91 ± 6.44	[a]p = 0.022
	ΔRSWA	−0.067 ± 0.26	0.67 ± 0.37	p = 0.317
Poor sleepers	**ΔPoor sleepers**	−0.20 ± 0.41	−0.37 ± 0.49	p = 0.361

MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; *PDSS-2,* Parkinson's Disease Sleep Scale-2*; ESS,* Epworth Sleepiness Scale*; TIB*, time spent in bed; *TST*, total sleep time; *SE*, sleep efficiency; *WASO,* wakefulness after sleep onset; *SL*, sleep latency; *REML*, REM sleep latency; *N1*, stage 1 of non-REM sleep; *N2*, stage 2 of non-REM sleep; *N3*, stage 3 of non-REM sleep; *AHI* apnea–hypopnea index; *ODI*, oxygen desaturation index; *PLMs*, periodic limb movements; *RSWA*, REM sleep without atonia.
[a] Statistically significant test.

108.00, p = 0.022) between the two groups.

3.7. PDSS-2 "poor sleepers" and "good sleepers"

At T0, according to the study's inclusion criteria, all patients were poor sleepers (15/15 in the rasagiline group and 30/30 in the safinamide group, respectively).

Compared to T0, at T1, n = 3/15 patients (20 %) who received rasagiline (Fisher test: p = 0.236) and n = 11/30 (36.7 %) of those treated with safinamide (Fisher test: p < 0.001) became good sleepers.

At T1, no significant differences between the number of poor and good sleepers were found between the two groups.

4. Discussion

This study investigated the impact of two different MAOB-Is, rasagiline and safinamide, on sleep architecture and sleep disturbances in a cohort of motor fluctuating PD patients, combining PSG recordings with sleep clinical assessments. We found that both MAOB-Is significantly improved patients' motor function, but only safinamide exerted a marked positive effect on patients' sleep quality and architecture.

As expected, both patient groups receiving the MAOB-I as adjunctive therapy showed a significant improvement of motor symptoms, since both rasagiline and safinamide demonstrated comparable efficacy on patients' motor disability, as stated by rating the MDS-UPDRS-III, although safinamide revealed a superior effect compared to rasagiline, since it proved to be significantly influential on patients' motor fluctuations, as indicated by the significant reduction of MDS-UPDRS-IV scores. This latter observation aligns with previous clinical data reporting that safinamide may exert a significant reduction in daily OFF periods and motor fluctuations in LD-treated PD patients without increasing LD-induced-dyskinesias [22].

However, as the main finding of this study, safinamide proved to have a beneficial effect on patients' sleep, as assessed by both clinical scales and PSG recordings. Notably, after a four-month treatment period with safinamide 100 mg/daily, patients showed an overall improvement in nocturnal sleep macrostructure documented by PSG recordings, which was associated with the remarkable relief of subjective sleep complaints and diurnal sleepiness, as assessed by the sleep questionnaires. In contrast, patients treated with rasagiline showed only a non-significant improvement in the PDSS-2 scores, which did not match significant changes in sleep parameters at the follow-up PSG recordings.

The safinamide beneficial action on clinical scales investigating sleep, namely the PDSS-2 for night sleep disturbances and the ESS scale for daytime sleepiness, agrees with the results of a preliminary study by our group [15], confirmed by the subsequent SAFINMOTOR and VALE-SAFI studies [9].

A recent meta-analysis revealed that PD patients display significant reductions in total sleep time, sleep efficiency, slow wave sleep, and REM sleep, and a significant increase in N1, REM sleep latency, AHI, and

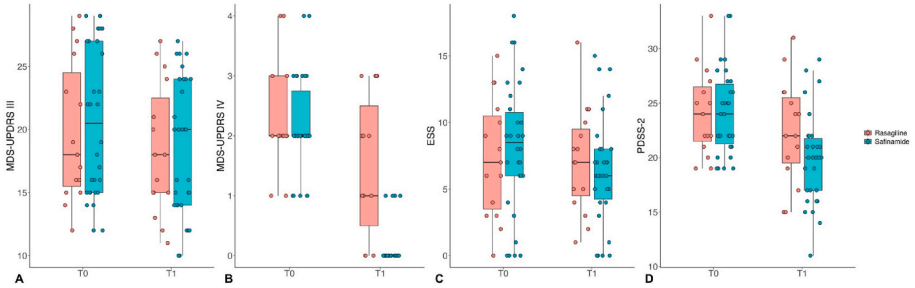

Fig. 1. The figure shows the main differences between T0 and T1 in clinical scales in both rasagiline- and safinamide-treated patients. MDS-UPDRS III, Movement Disorder Society – Unified Parkinson's Disease Rating Scale, motor section; MDS-UPDRS IV, Movement Disorder Society – Unified Parkinson's Disease Rating Scale, motor fluctuation section; ESS, Epworth Sleepiness Scale; PDSS-2, Parkinson's Disease Sleep Scale – 2nd version.

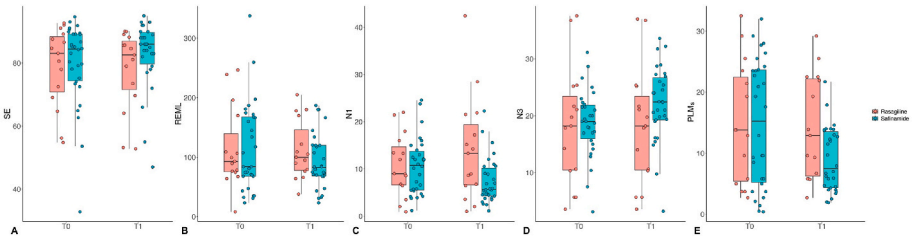

Fig. 2. The figure shows the main differences between T0 and T1 in PSG parameters in both rasagiline- and safinamide-treated patients. SE, sleep efficiency; REML, REM sleep latency; N1, stage 1 of Non-REM sleep; N3, stage 3 of Non-REM sleep; PLMs, periodic limb movements.

PLMs, with significant sleep fragmentation when compared to controls [23]. In this study, PSG recordings proved that several of these PD-related sleep disturbances improved after four-months of treatment with safinamide, documenting the effectiveness of safinamide in the improvement of sleep architecture, including overall increase in sleep efficiency associated with improvements in REM and Non-REM sleep. Indeed, safinamide increased N3 and improved sleep efficiency, indicating a global, more continuous nocturnal sleep. Moreover, we found that the drug decreased the rate of PLMs, matching previous findings of a beneficial effect of safinamide on PLMs in patients with PD and periodic limb movement disorder [10].

This improvement in sleep parameters was corroborated by the reduction of the PDSS-2 score below the cut-off defining "poor sleepers" at the follow-up visit, where almost 38 % of patients treated with safinamide improved to good sleepers compared to only 20 % of those treated with rasagiline.

Previous reports have shown a beneficial action of safinamide on RBD-related symptoms [24]. Here, we did not observe any significant changes in the rate of RSWA, but in the present study, RBD episodes were not counted, and REM sleep atonia index was not calculated.

Safinamide, unlike the irreversible and older MAOB-Is, has a more complex mechanism of action, not limited to the dopaminergic system. Notably, at 100 mg daily dose, safinamide acts as a glutamate release modulator through a use-dependent sodium and N-type calcium channel blockade. Experimental data described glutamate as an important wake-active neurotransmitter, proving that the release of glutamate from neurons of the supramammillary region produces sustained behavioral and EEG arousal, suggesting a pivotal role of these glutamatergic neurons in the sleep-wake rhythm [25]. Consistently, the block of glutamate release has been shown to exert positive effects on sleep, inducing a significant reduction of nocturnal wake and improving sleep quality and continuity [25]. Furthermore, thalamic glutamatergic hyperactivation, along with altered brain iron acquisition and dopaminergic dysfunction of mesolimbic and nigrostriatal pathways, underlie the occurrence of PLM in persons with PD [10].

Based on these data, we can suppose that the increase in slow wave sleep and the decrease in PLMs rate in motor fluctuating PD patients taking safinamide might be related to its specific mechanism of action, where the inhibition of the glutamatergic system might account for a beneficial reduction of the hyperactivation state, favoring the continuity of nocturnal sleep and the increase of N3 [11,26].

However, the beneficial action of safinamide on sleep might also reflect its stronger dopaminergic function compared to rasagiline. Indeed, it has been recently stated that rasagiline 1 mg corresponds to 100 mg of LD and safinamide 100 mg corresponds to 125 mg of LD, proposing that high doses of safinamide provide a greater dopaminergic boost compared to other MAOB-Is [27]. This mechanism might be significantly relevant in reducing PLMs, which strongly correlates with nigrostriatal dopaminergic degeneration, as confirmed by the beneficial effect exerted by dopaminergic drugs [5]. On the other hand, the reduction of PLMs, which are frequently associated with arousals that do not allow the maintenance of sleep [28], might, in turn, contribute to the increase in deep sleep and the reduction in diurnal somnolence in patients treated with safinamide.

Finally, considering the close relationship between sleep and motor disturbances in PD [29], as also postulated by the "sleep benefit" hypothesis [30], the improvement of sleep may also be related to the remarkable amelioration that safinamide seems to exert over rasagiline on patients' motor fluctuations.

Here, the specific effect of safinamide on sleep was further supported by the fact that rasagiline did not improve PSG sleep parameters and did not induce significant changes in either the ESS or the PDSS-2. The present study reported no significant effect of rasagiline on sleep and daytime sleepiness, which apparently contrasts with previous data [13]. However, our results agree with the findings of a recent double-blind placebo-controlled PSG study carried out in PD patients, documenting that rasagiline did not improve the PDSS-2 scores. It did not change sleep efficiency or sleep stages at the PSG, although the drug was able to reduce wakefulness after sleep onset and the arousal index [13].

This study has some limitations, primarily due to the naturalistic setting, where the two MAOB-I treatments were not randomly assigned but initiated according to the judgment of the clinician following clinical practice, possibly leading to selection bias; thus, the number of fluctuating PD patients starting safinamide as adjunct MAOB-I was higher than those starting rasagiline because this latter is commonly used as monotherapy in early PD patients. Another limitation is not having considered in the analyses potential confounding factors, such as age, disease duration, and other antiparkinsonian and non-PD related medications. Finally, other limitations comprise the relatively small number of patients included, the lack of a placebo-controlled group.

Despite its limitations, this study comparing rasagiline and safinamide as adjunctive therapies in motor fluctuating PD patients might indicate that safinamide, differently from the other MAOB-Is, may improve subjective sleep quality and architecture in patients due to its bimodal mechanism of action at the dosage of 100 mg daily, encompassing an anti-glutamatergic action in addition to a dopaminergic function.

More studies contemplating wider sizes of patients are needed to confirm these findings and further investigate the differential impact of safinamide on other motor and non-motor manifestations of PD.

Ethics approval

This study was conducted in accordance with the principles of the Helsinki Declaration. The local ethics committee approved the study.

Competing interests and funding

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Data availability statement

The datasets generated during analysis are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Roberta Bovenzi: Writing – original draft, Formal analysis, Data curation. **Matteo Conti:** Writing – original draft, Methodology, Formal analysis, Data curation. **Mariangela Pierantozzi:** Writing – review & editing, Visualization, Validation, Resources, Funding acquisition, Conceptualization. **Greta Testone:** Methodology, Investigation, Data curation. **Mariana Fernandes:** Methodology, Formal analysis, Data curation. **Natalia Manfredi:** Methodology, Investigation, Formal analysis, Data curation. **Tommaso Schirinzi:** Methodology, Formal analysis, Data curation. **Rocco Cerroni:** Methodology, Formal analysis, Data curation. **Nicola Biagio Mercuri:** Validation, Supervision, Funding acquisition. **Alessandro Stefani:** Validation, Supervision, Funding acquisition. **Claudio Liguori:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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