



# Safinamide improves sleep and daytime sleepiness in Parkinson's disease: results from the SAFINONMOTOR study

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## Abstract

**Background and objective** Some studies observed a benefit of PD patients after treatment with safinamide in some non-motor symptoms. Our aim was to analyze the effectiveness of safinamide on sleep and daytime sleepiness in Parkinson's disease (PD) patients.

**Material and methods** SAFINONMOTOR is a prospective open-label single-arm study conducted in 5 centers from Spain. In this analysis, a secondary objective of the study, the score in the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS) at V1 (baseline) and V4 (6 months  $\pm$  1 month) were compared.

**Results** Fifty patients were included between May/2019 and February/2020 (age  $68.5 \pm 9.12$  years; 58% women;  $6.4 \pm 5.1$  years from diagnosis). At 6 months, 44 patients completed the follow-up (88%). The PSQI total score was reduced by 19.8% (from  $10.43 \pm 4.02$  at V1 to  $8.36 \pm 4.41$  at V4;  $p = 0.001$ ). By domains, improvement was observed in subjective sleep quality (PSQI-C1;  $-23.9\%$ ;  $p = 0.009$ ), sleep latency (PSQI-C2;  $-25\%$ ;  $p = 0.025$ ), sleep duration (PSQI-C3;  $-40\%$ ;  $p = 0.001$ ), and habitual sleep efficiency (PSQI-C4;  $-25.9\%$ ;  $p = 0.023$ ). A significant reduction ( $-24.7\%$ ) in the ESS total score from V1 to V4 was observed as well (from  $9.20 \pm 5.64$  to  $6.93 \pm 5.11$ ;  $p = 0.012$ ). Specifically, the improvement in daytime sleepiness was observed in sitting and reading ( $p = 0.024$ ) and sitting inactive in a public space ( $p = 0.027$ ). A total of 21 adverse events in 11 patients (22%) were reported, 5 of which were severe (not related to safinamide).

**Conclusion** Safinamide was well-tolerated and improved sleep and daytime sleepiness in PD patients at 6 months.

**Keywords** Effectiveness · Non-motor symptoms · Parkinson's disease · Safinamide · Sleep · Somnolence

## Abbreviations

ADLS	Schwab & England Activities of Daily Living Scale
BDI-II	Beck Depression Inventory-II
CGI	Clinical Global Impressions
ESS	Epworth Sleepiness Scale
FOGQ	Freezing Of Gait Questionnaire
H&Y	Hoehn & Yahr
KPPS	King's PD Pain Scale
NMS	Non-motor symptoms
NMSS	Non-Motor Symptoms Scale
PDQ-39SI	39-Item Parkinson's Disease Quality of Life Questionnaire Summary Index
PSQI	Pittsburgh Sleep Quality Index
UPDRS	Unified Parkinson's Disease Rating Scale
VAFS	Visual Analog Fatigue Scale
VAS-Pain	Visual Analog Scale-Pain

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## Introduction

Safinamide is a third-generation reversible I-MAOB approved as adjunctive therapy in fluctuating PD patients [1, 2]. In previous trials, safinamide has been demonstrated to improve both motor scores and duration of “on time,” and also to be safe and well-tolerated [3–5]. Furthermore, data from some studies suggest a possible benefit of PD patients after treatment with safinamide in some non-motor symptoms (NMS) such as pain, mood, or urinary symptoms [6–9]. Specifically, we observed very recently an improvement in the global NMS burden in 50 PD patients from the SAFINONMOTOR study (*an open-label study of the effectiveness of SAFInamide on NON-MOTOR symptoms in Parkinson’s disease patients*) [10]. However, there is a lack of evidence about the effect of safinamide on sleep and diurnal somnolence in PD patients. In a very recent report, Liguori et al. observed that safinamide may improve subjective sleep and daytime sleepiness in motor fluctuating PD patients [11]. Moreover, there is an ongoing phase IV trial about the effect of safinamide on sleep quality in patients with PD (NCT03968744; <https://clinicaltrials.gov/ct2/show/NCT03968744>).

In this analysis, a secondary objective of the SAFINONMOTOR study, we evaluated the change in sleep and daytime sleepiness between baseline and 6-month follow-up in PD patients treated with safinamide.

## Material and methods

SAFINONMOTOR is a mono-country (Spain), multicentre, observational (phase IV), prospective, open-label, follow-up study. Five neurology sites from Galicia (Spain) dealing with PD participated. Inclusion criteria were (1) diagnosis of Parkinson’s disease according to the UK Parkinson’s Disease Society Brain Bank criteria [12]; (2) to have the indication of receiving safinamide according to the neurologist criteria; (3) to have a total NMSS score at baseline  $\geq 40$ ; (4) no dementia criteria with a MMSE at baseline  $\geq 26$  [13]; (5) older than 30 years old; and (6) to wish to voluntarily participate and to sign a consent form. Exclusion criteria were (1) to be undergoing MAO-B inhibitor therapy (rasagiline or selegiline); (2) any other contraindication to be treated with safinamide according to product data; (3) incapacity to complete the questionnaires adequately; (4) other disabling concomitant neurological diseases (stroke, severe head trauma, neurodegenerative disease, etc.); (5) other severe and disabling concomitant non-neurological disease (oncological, autoimmune, etc.); (6) expected impossibility of long-term follow-up; and

(7) patient who was participating in a clinical trial and/or other types of study. All the neurologists who participated in the study were experts on PD/movement disorders.

The study visits included (1) V1 (baseline); (2) V2 (1 month  $\pm 7$  days); (3) V3 (3 months  $\pm 15$  days); and (4) V4 (6 months  $\pm 15$  days, end of the observational period). Subjects completed the Epworth Sleepiness Scale (ESS) [14] and the Pittsburgh Sleep Quality Index (PSQI) [15] in all visits. The ESS is a self-administered questionnaire with 8 questions. Respondents are asked to rate, on a 4-point scale (0–3), their usual chances of dozing off or falling asleep while engaged in eight different activities. Most people engage in those activities at least occasionally, although not necessarily every day. The ESS score (the sum of 8 item scores, 0–3) can range from 0 to 24. The higher the ESS score, the higher that person’s average sleep propensity in daily life, or their daytime sleepiness: 0–5, lower normal daytime sleepiness; 6–10, higher normal daytime sleepiness; 11–12, mild excessive daytime sleepiness; 13–15, moderate excessive daytime sleepiness; 16–24, severe excessive daytime sleepiness. The PSQI is a self-report questionnaire that assesses sleep quality over a 1-month time interval. The measure consists of 19 individual items, creating 7 components that produce one global score. Each item is weighted on a 0–3 interval scale. The global PSQI score is then calculated by totaling the seven component scores, providing an overall score ranging from 0 to 21, where lower scores denote a healthier sleep quality. The PSQI has a sensitivity of 89.6% and specificity of 86.5% for identifying cases with sleep disorder, using a cutoff score of 5 [15].

Information on sociodemographic aspects, factors related to PD, comorbidity, and treatment was collected. Moreover, other scales were administered by protocol in different visits of the study. Methodology about SAFINONMOTOR study can be consulted in <https://www.mdpi.com/2076-3425/11/3/316/htm> [10]. The analysis about the change in sleep quality and daytime sleepiness from V1 to V4 was a specifically proposed secondary objective in the protocol of the SAFINONMOTOR study.

Safinamide was administered as once-daily 50-mg pill for 1 month and switched to 100 mg/day at V2. However, in some cases (e.g., dyskinesia), the dose of 100 mg could be introduced earlier or the dose could be kept at 50 mg/day according to the criteria of the neurologist. Patients could be receiving any other antiparkinsonian drugs: levodopa, dopamine agonist, COMT inhibitor, amantadine, and/or anticholinergic. During follow-up, any other medications different from safinamide should not be modified (regimen, doses, etc.) except if the neurologist considered these changes absolutely necessary. All the changes including PD and not-PD related medications and levodopa equivalent daily dose (LEDD) [16] of levodopa were recorded.

## Data analysis

Data were processed using SPSS 20.0 for Windows. Continuous variables were expressed as the mean  $\pm$  SD or median and quartiles, depending on whether they were normally distributed. Relationships between variables were evaluated using the Student's *t*-test, the Mann–Whitney U test, Spearman's or Pearson's correlation coefficient as appropriate (distribution for variables was verified by one-sample Kolmogorov–Smirnov test). The change in score from V1 to V4 on ESS and PSQI were the principal efficacy outcome variables in this analysis. Analyses on efficacy variables were performed with the ITT data set (all subjects who receive at least 1 pill of safinamide and had a baseline and treatment observation for the primary efficacy outcome measure). A paired-sample *t*-test or Wilcoxon's rank sum test as appropriate was performed for testing the change from baseline. The frequency of patients with moderate-to-severe excessive daytime sleepiness (ESS total score  $\geq$  13) and with sleep disorder (PSQI total score  $>$  5) was compared between the baseline visit and the final visit using the McNemar test. Values of  $p < 0.05$  were considered significant.

The safety data set consists of all subjects for whom the study device was initiated. Safety analyses were assessed by adverse events (AEs). All AEs were coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent AEs by MedDRA system organ class and preferred term, by severity, and by relationship to study treatment as assessed by the investigator were provided for overall subjects.

## Standard protocol approvals, registrations, and patient consents

For this study, we received approval from the *Comité de Ética de la Investigación Clínica de Galicia* from Spain (2018–052; 28/FEB/2019). Written informed consents from all participants in this study were obtained before the start of the study. SAFINONMOTOR was classified by the AEMPS (*Agencia Española del Medicamento y Productos Sanitarios*) as a post-authorization prospective follow-up study with the code DSG-SAF-2018–01.

## Data availability

The protocol and the statistical analysis plan are available on request. De-identified participant data are not available for legal and ethical reasons.

## Results

A total of 50 patients were included between May/2019 and February/2020 (age  $68.5 \pm 9.12$  years; 58% females). Data about sociodemographic aspects, comorbidities, antiparkinsonian drugs, and other therapies are shown in Table 1.SM. The mean time from diagnosis of PD was  $6.4 \pm 5.1$  years. All patients except three were receiving levodopa, two patients were under levodopa/carbidopa infusion therapy, and none was with apomorphine or deep brain stimulation. At baseline (V1), 78% (39/50) of the patients presented with motor fluctuations and 30% (15/50) with dyskinesia. The mean UPDRS-III during the ON state was  $24.6 \pm 9.1$ . The mean LEDD was  $810.2 \pm 518.1$  (range from 100 to 2.350 mg).

At 6 months, 44 patients completed the follow-up (88%). Compared to baseline, a lower ESS total score was observed in 23 out of 44 patients (52.3%), the same score in 2 patients (4.5%), and a higher score in 19 patients (43.2%). In the case of the PSQI total score at V4, the percentages were 66.7%, 7.7%, and 25.6%, respectively. The ESS total score was reduced from V1 to V4 by 24.7% (from  $9.2 \pm 5.64$  at V1 to  $6.93 \pm 5.11$  at V4;  $p = 0.012$ ) (Table 1 and Fig. 1). Considering the different domains from the ESS, a significant change from V1 to V4 in ESS-domain 1 (sitting and reading) (from  $1.45 \pm 1.25$  to  $0.91 \pm 1.09$ ;  $p = 0.024$ ) and ESS-domain 3 (sitting, inactive in a public place; e.g., a theater or a meeting) (from  $0.69 \pm 1.06$  to  $0.41 \pm 0.81$ ;  $p = 0.027$ ) was observed. At the final follow-up visit, 15.9% of the patients presented moderate-to-excessive daytime sleepiness (ESS total score  $\geq$  13) compared to 32.7% at baseline ( $p = 0.016$ ).

With regard to the PSQI, it was reduced at V4 by 19.8% (from  $10.43 \pm 4.02$  at V1 to  $8.36 \pm 4.41$  at V2;  $p = 0.001$ ) (Table 1 and Fig. 2). By domains, a significance change from V1 to V4 was observed in PSQI-component 1 (subjective sleep quality) (from  $1.46 \pm 0.73$  to  $1.11 \pm 0.75$ ;  $p = 0.009$ ), PSQI-component 2 (sleep latency) (from  $1.24 \pm 1.15$  to  $0.93 \pm 1.12$ ;  $p = 0.025$ ), PSQI-component 3 (sleep latency) (from  $1.7 \pm 0.99$  to  $1.02 \pm 1.07$ ;  $p = 0.01$ ), and PSQI-component 4 (habitual sleep efficiency) (from  $1.85 \pm 1.23$  to  $1.37 \pm 1.15$ ;  $p = 0.023$ ). At 6 months, 23.8% of the patients presented without sleep disorder (PSQI total score  $>$  5) compared to 10.6% at V1 ( $p = 0.034$ ). Compared to the score at V1, the change at V2 and V3 for both ESS and PSQI scores was significant too but differences between the score from V2 and V3 to V4 (Fig. 1, Fig. 2, and Table 2) were not observed. Although average time (minutes) to fall asleep decreased from V1 ( $32.33 \pm 43.27$ ) to V4 ( $24.8 \pm 34.82$ ), it was not significant ( $p = 0.112$ ). However, significant difference ( $p = 0.008$ ) in terms of the mean number of hours sleeping in bed at V1 ( $5.8 \pm 1.62$ ) vs at V4 ( $6.53 \pm 1.92$ ) was observed.

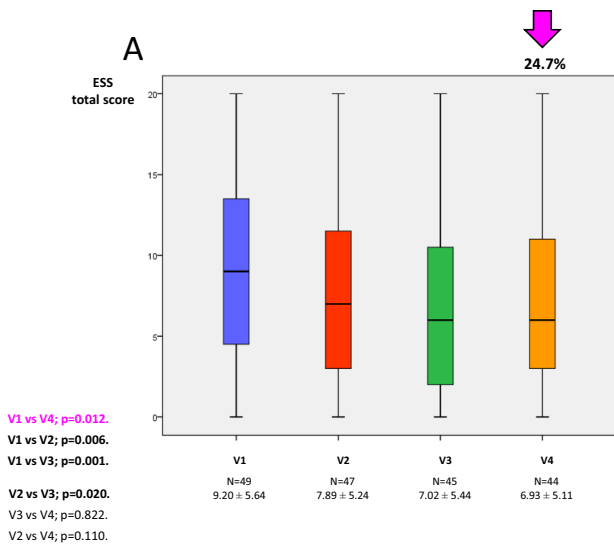
**Table 1** Change in the score of the ESS and PSQI and other scales of the study from V1 (baseline) to V4 (6 months ± 15 days)

	V1	N (V1)	V4	N (V4)	Δ V1–V4	p
Motor assessment						
H&Y-OFF	2.5 [2.3]	46	N. A			
H&Y-ON	2 [2.2.5]	49	N. A			
UPDRS-III-ON	24.63±9.12	48	20.21±9.81	39	–17.9%	0.009
UPDRS-IV	3.82±2.55	50	2.82±2.38	34	–25.4%	0.188
FOGQ	6.10±5.23	48	5.68±4.96	44	–6.9%	0.240
Non-motor assessment						
ESS	9.20±5.64	49	6.93±5.11	44	–24.7%	0.012
1. Sitting and reading	1.45±1.25	49	0.91±1.09	44	–37.2%	0.024
2. Watching TV	1.88±1.11	49	1.45±1.17	44	–22.8%	0.050
3. Sitting, inactive in a public place	0.69±1.06	49	0.41±0.81	44	–40.5%	0.027
4. As a passenger in a car for an hour without a break	0.92±1.25	49	0.64±1.05	44	–30.4%	0.080
5. Lying down to rest in the afternoon when it is possible	2.24±1.05	49	1.86±1.09	44	–16.9%	0.221
6. Sitting and talking to someone	0.27±0.56	49	0.18±0.44	44	–33.3%	0.340
7. Sitting quietly after a lunch without alcohol	1.51±1.26	49	1.23±1.11	44	–18.5%	0.306
8. In a car, while stopping for a few minutes	0.24±0.49	49	0.25±0.53	44	+4.2%	0.935
PSQI	10.43±4.02	47	8.36±4.41	42	–19.8%	0.001
1. Subjective sleep quality	1.46±0.73	50	1.11±0.75	44	–23.9%	0.009
2. Sleep latency	1.24±1.15	50	0.93±1.12	44	–25%	0.025
3. Sleep duration	1.7±0.99	50	1.02±1.07	44	–40%	0.001
4. Habitual sleep efficiency	1.85±1.23	48	1.37±1.15	42	–25.9%	0.023
5. Step disturbances	1.44±0.57	49	1.52±1.19	44	+5.5%	0.413
6. Use of sleeping medication	1.56±1.51	50	1.38±1.49	44	–11.5%	0.222
7. Daytime dysfunction	1.14±0.83	50	0.79±0.73	44	–30.7%	0.058
NMSS	97.48±43.70	50	59.91±35.49	44	–38.5%	<0.0001
BDI-II	15.88±10.46	50	10.18±6.76	44	–35.9%	<0.0001
KPPS	40.04±36.18	48	22.60±21.42	44	–43.6%	<0.0001
VAS-Pain	4.61±3.22	49	3.67±2.69	43	–20.4%	0.071
VAFS-Physical	4.18±2.84	49	3.64±2.55	44	–12.9%	0.293
VAFS-Mental	3.14±2.65	49	2.45±2.79	44	–21.9%	0.118
QOL and autonomy						
PDQ-39SI	30.07±17.61	49	21.24±13.48	44	–29.4%	<0.0001
ADLS	81.40±11.78	50	80.91±16.39	44	–0.6%	0.845

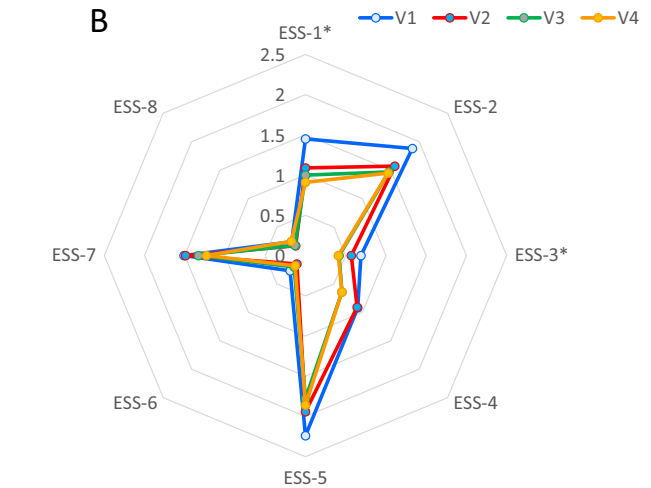
*P* values were computed using the Wilcoxon signed-rank test. The results represent mean ± SD or median (*p* 25, *p* 75). Domains of the NMSS and KPPS were expressed as a percentage to be able to establish comparisons on their severity between them. *ADLS*, Schwab & England Activities of Daily Living Scale; *BDI*, Beck Depression Inventory; *ESS*, Epworth Sleepiness Scale; *FOGQ*, Freezing Of Gait Questionnaire; *H&Y*, Hoehn & Yahr; *KPPS*, King's PD Pain Scale; *NMSS*, Non-Motor Symptoms Scale; *NPI*, Neuropsychiatric Inventory; *PDQ-39SI*, 39-item Parkinson's Disease Quality of Life Questionnaire Summary Index; *PSQI*, Pittsburgh Sleep Quality Index; *UPDRS*, Unified Parkinson's Disease Rating Scale; *VAFS*, Visual Analog Fatigue Scale; *VAS-Pain*, Visual Analog Scale-Pain

A significant reduction in the score of other scales used for the assessment of motor and NMS was observed (Table 1). A moderate correlation was observed between the change from V1 to V4 in the ESS total score and the PDQ-39SI score ( $r=0.352$ ;  $p=0.024$ ) but not between the PSQI total score and the PDQ-39SI score ( $r=0.260$ ;  $p=0.115$ ). With regard to mood, no significant correlation was observed between the changes detected in sleep (PSQI) and daytime sleepiness (ESS) and the change in mood (BDI-II) ( $r=0.230$  [ $p=0.229$ ] and  $r=0.241$

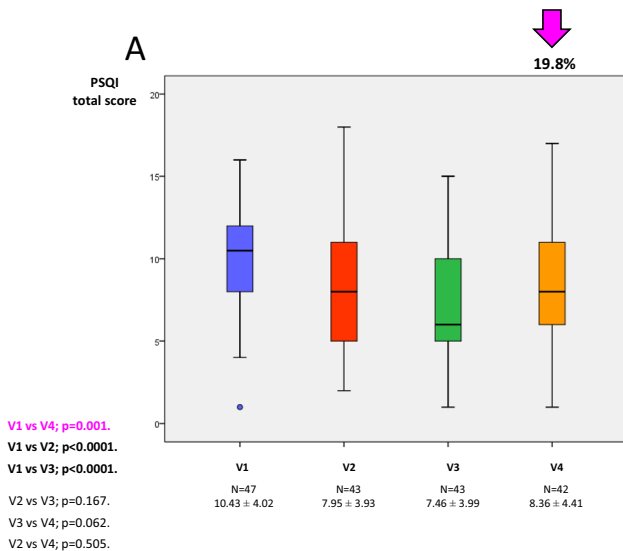
[ $p=0.184$ ], respectively). Patients with very severe NMSB burden at baseline (NMSS total score > 70;  $N=34$ ) presented a significant decrease in the PSQI total score at V4 (from  $11.27 \pm 3.66$  to  $8.2 \pm 4.52$ ;  $p < 0.0001$ ) but not those patients with severe NMS burden at baseline (NMSS total score 41–70;  $N=16$ ) (from  $8.42 \pm 4.23$  to  $8.69 \pm 4.3$ ;  $p=0.569$ ); the difference between both groups was significant ( $p=0.046$ ). However, differences between both groups with regard to the change from V1 to V4 in the ESS total score were not observed ( $p=0.203$ ).



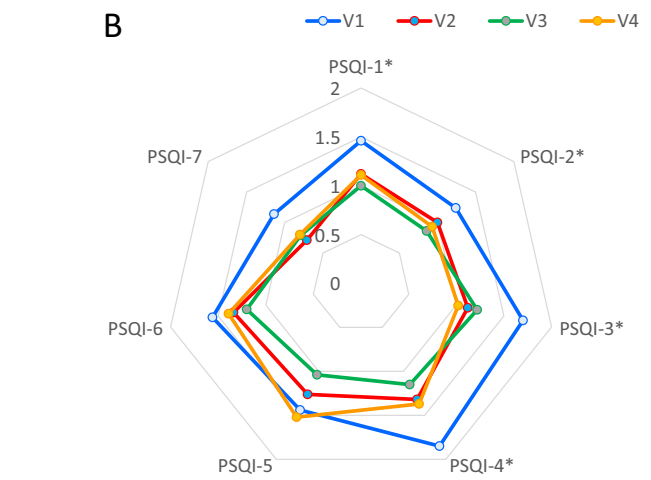
**Fig. 1** **A** ESS total score at V1 (baseline), V2 (1 months ± 7 days), V3 (3 months ± 15 days), and V4 (6 months ± 15 days). Compared to the score at V1, the change at V2, V3, and V4 was significant ( $p < 0.05$  for all analysis; V4 vs V1; V2 vs V1; V3 vs V1). **B** Mean score on each domain of the ESS scale at V1 (blue), V2 (red), V3 (green), and V4 (orange). The difference between V1 and V4 was significant for ESS-domain 1 (sitting and reading) ( $p=0.024$ ) and ESS-domain 3 (sitting, inactive in a public place, e.g., a theater or a meeting) ( $p=0.027$ ). Data are presented as box plots, with the box representing the median and the two middle quartiles (25–75%). *P* values were



computed using the Wilcoxon signed-rank test. Mild outliers (O) are data points that are more extreme than  $Q1 - 1.5 * IQR$  or  $Q3 + 1.5 * IQR$ . ESS, Epworth Sleepiness Scale; ESS-1, sitting and reading; ESS-2, watching TV; ESS-3, sitting, inactive in a public place (e.g., a theater or a meeting); ESS-4, as a passenger in a car for an hour without a break; ESS-5, lying down to rest in the afternoon when circumstances permit; ESS-6, sitting and talking to someone; ESS-7, sitting quietly after a lunch without alcohol; ESS-8, in a car, while stopping for a few minutes



**Fig. 2** **A** PSQI total score at V1 (baseline), V2 (1 months ± 7 days), V3 (3 months ± 15 days), and V4 (6 months ± 15 days). Compared to the score at V1, the change at V2, V3, and V4 was significant ( $p < 0.05$  for all analysis; V4 vs V1; V2 vs V1; V3 vs V1). **B** Mean score on each domain of the PSQI scale at V1 (blue), V2 (red), V3 (green), and V4 (orange). The difference between V1 and V4 was significant for PSQI-component 1 (subjective sleep quality) ( $p=0.009$ ), PSQI-component 2 (sleep latency) ( $p=0.025$ ), and PSQI-component 4 (habitual sleep efficiency) ( $p=0.023$ ). Data are presented as box



plots, with the box representing the median and the two middle quartiles (25–75%). *P* values were computed using the Wilcoxon signed-rank test. Mild outliers (O) are data points that are more extreme than  $Q1 - 1.5 * IQR$  or  $Q3 + 1.5 * IQR$ . PSQI, Pittsburgh Sleep Quality Index; PSQI-1, subjective sleep quality; PSQI-2, sleep latency; PSQI-3, sleep duration; PSQI-4, habitual sleep efficiency; PSQI-5, step disturbances; PSQI-6, use of sleeping medication; PSQI-7, daytime dysfunction



**Table 2** Change in the total ESS and PSQI total scores and its domains between the visits of the study: V1 ( $N=50$ ), V2 ( $N=47$ ), V3 ( $N=45$ ), V4 ( $N=44$ )

	V1	V2	V3	V4	$p^a$	$p^b$	$p^c$	$p^d$
ESS total score	9.20 ± 5.64	7.89 ± 5.23	7.02 ± 5.43	6.93 ± 5.11	0.012	0.001	0.087	0.110
1. Sitting and reading	1.45 ± 1.25	1.09 ± 1.12	1 ± 1.12	0.91 ± 1.09	0.024	0.030	0.021	0.215
2. Watching TV	1.88 ± 1.11	1.57 ± 1.11	1.47 ± 1.17	1.45 ± 1.17	0.050	0.011	0.015	0.489
3. Sitting, inactive in a public place	0.69 ± 1.06	0.57 ± 0.97	0.42 ± 0.78	0.41 ± 0.81	0.027	0.047	0.264	0.221
4. As a passenger in a car for an hour without a break	0.92 ± 1.25	0.91 ± 1.15	0.64 ± 1	0.64 ± 1.05	0.080	0.148	0.660	0.054
5. Lying down to rest in the afternoon when it is possible	2.24 ± 1.05	1.94 ± 1.15	1.78 ± 1.2	1.86 ± 1.09	0.221	0.014	0.058	0.568
6. Sitting and talking to someone	0.27 ± 0.56	0.15 ± 0.41	0.2 ± 0.5	0.18 ± 0.44	0.340	0.448	0.166	0.665
7. Sitting quietly after a lunch without alcohol	1.51 ± 1.26	1.49 ± 1.19	1.33 ± 1.2	1.23 ± 1.11	0.306	0.379	0.940	0.166
8. In a car, while stopping for a few minutes	0.24 ± 0.49	0.17 ± 0.48	0.18 ± 0.44	0.25 ± 0.53	0.935	0.609	0.609	0.492
PSQI total score	10.43 ± 4.02	7.95 ± 3.93	7.46 ± 3.99	8.36 ± 4.41	0.001	<0.0001	<0.0001	0.505
1. Subjective sleep quality	1.46 ± 0.73	1.12 ± 0.76	1 ± 0.67	1.11 ± 0.75	0.009	0.002	0.006	0.796
2. Sleep latency	1.24 ± 1.15	1 ± 1.01	0.86 ± 1.07	0.93 ± 1.12	0.025	0.070	0.420	0.450
3. Sleep duration	1.7 ± 0.99	1.12 ± 0.94	1.22 ± 1.08	1.02 ± 1.07	0.001	0.016	0.001	0.364
4. Habitual sleep efficiency	1.85 ± 1.23	1.32 ± 1.15	1.15 ± 1.24	1.37 ± 1.15	0.023	0.002	0.018	0.703
5. Step disturbances	1.44 ± 0.57	1.26 ± 0.57	1.04 ± 0.48	1.52 ± 1.19	0.413	0.001	0.071	0.114
6. Use of sleeping medication	1.56 ± 1.51	1.34 ± 1.49	1.2 ± 1.47	1.38 ± 1.49	0.222	0.020	0.149	0.746
7. Daytime dysfunction	1.14 ± 0.83	0.71 ± 0.83	0.79 ± 0.7	0.79 ± 0.73	0.058	0.047	0.016	0.440
Dose of safinamide (mg/day)	N.A	53.84 ± 13.49	96.15 ± 13.49	98.72 ± 8.00				

$P$  values were computed using the Wilcoxon signed-rank test. The results represent mean ± SD. Domains of the NMSS were expressed as a percentage to be able to establish comparisons on their severity between them;  $p^a$ , V4 vs V1;  $p^b$ , V3 vs V1;  $p^c$ , V2 vs V1;  $p^d$ , V4 vs V2. N.A., Not applicable; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index

A total of 21 adverse events in 16 patients (32%) were reported, 5 of which were severe (not related to safinamide) (Table 2.SM). Dyskinesias and nausea were the most frequent (6%). The reasons for withdrawing from the study of the 6 patients were 1 withdrawal of consent; 1 discontinuation of safinamide after deep brain stimulation procedure (it was recorded as SAE due to hospitalization process); 1 personal decision due to no effect; and 3 due to an adverse event (2 dizziness; 1 respiratory infection). Only one patient discontinued due to an adverse event related to safinamide (dizziness). All patients were receiving safinamide 50 mg/day at V2 except for 3 cases who were receiving 100 mg/day whereas all patients were receiving 100 mg/day at V3 and V4 except for 1 and 2 cases, respectively, who were receiving 50 mg/day. Only 3 patients were receiving rasagiline which was withdrawn with a washout period of at least 2 weeks before starting safinamide. At baseline, 32% of the patients were taking any antidepressant agent, 38% benzodiazepines, 4% antipsychotics, and 22% analgesics. During the follow-up, changes in treatment (other than receiving safinamide) were made in 7 patients, being only in 5 patients changes with drugs are related to PD symptoms (Table 3.SM).

## Discussion

The present study observed that sleep and daytime sleepiness improved in PD patients 6 months after starting with safinamide. Specifically, patients improved daytime sleepiness while sitting and reading, and subjective sleep quality, sleep latency, and habitual sleep efficiency. Moreover, patients improved their health-related quality of life (QoL) and a correlation between QoL improvement and daytime sleepiness improvement was observed.

Safinamide is an oral  $\alpha$ -aminoamide derivate marketed for the treatment of PD with both dopaminergic properties, namely highly selective and reversible inhibition of MAO-B, and non-dopaminergic properties, namely selective sodium channel blockade and calcium channel modulation, with consequent inhibition of excessive glutamate release [1, 2]. It has been suggested that this second action mechanism could explain at least in part the favorable effect of safinamide over some NMS such as pain, mood, or urinary symptoms [6–9]. However, it is not clear and other benefits could be related due to its dopaminergic action mechanism such as the improvement of executive

functions in fluctuating PD patients [17]. In line with this, we found that the improvement in the global NMS burden (NMSS total score) observed in 50 PD patients from the SAFINONMOTOR study 6 months after starting with safinamide with a mean dose of 99 mg/day did not significantly differ of the improvement observed at 1 month with a mean dose of 55 mg/day [10]. Furthermore, it is not clear whether the dopaminergic action of safinamide could be more potent than that of other MAO-B inhibitors such as rasagiline or if benefits could be related to its effect involving the glutamatergic system, or both [11, 18, 19]. A recent study [11] observed an improvement of nocturnal sleep, diurnal sleepiness, and daytime dysfunction in fluctuating PD patients treated with safinamide ( $N=46$ ), as assessed by sleep questionnaires, but not with rasagiline ( $N=15$ ). Although there are important methodological limitations in this study, such as the fact that it is a retrospective study in which the number of patients treated with rasagiline compared to safinamide was much lower and also a direct comparison between both groups was not made, it is the first study observing these findings and the authors speculate that their different influence on sleep may be due to a possible non-dopaminergic mechanism of action (i.e., involving the glutamatergic system). Our results are in line with Liguori et al.'s study [11]. However, to our best knowledge, SAFINONMOTOR is the first published prospective study designed for assessing the effect of safinamide on sleep and daytime sleepiness (a secondary objective specifically defined in the protocol). As other NMS [10], the improvement in both aspects was observed 1 month after starting with safinamide with 50 mg/day and a greater improvement with 100 mg/day was not observed. In Liguori et al.'s study, the dose of safinamide was not provided. Very recently and in line with our finding, Platinio et al. reported significant improvement on RBD (rapid eye movement) sleep behavior disorder symptoms in 30 patients in a randomized, longitudinal, cross-over pilot study with 50 mg/day of safinamide using video-polysomnography and the sleep behavior disorder questionnaire-Hong Kong-score (RBDQ-HS) [20]. Remarkably, mood improved with safinamide in patients from the SAFINONMOTOR study [10] as it happened in other studies [6, 8, 21], and a benefit of sleep and diurnal somnolence in relation to a possible antidepressant effect could be another explanation due to the relationship between mood and sleep disorders [22]. However, in our study, a correlation between the change observed in sleep and daytime sleepiness and the change in mood was not observed. Finally, it is important to emphasize that the patients selected in our study were subjects with a severe or very severe NMS burden and up to 50% with major depression, and that the benefit on sleep and daytime sleepiness was not general and it was observed in about half of the patients.

Our study has some important limitations. The most important is related to the study design itself and since there is not a comparative arm with placebo, the results should be interpreted with caution. Furthermore, the sample size is rather small, and for some variables, the information was not collected in all cases. The results are based on scales that collect the opinion of the patient and we did not include PSG recordings confirming subjective sleep improvement, so a bias due to the placebo effect cannot be ruled out. In fact, the improvement in mood could influence the perception of symptoms and the response in other scales [23]. Very interestingly, a phase 4 study for assessing the effect of safinamide on sleep quality in PD patients with polysomnography analysis (*A Prospective, Open Label, Single Arm, Clinical Study to Evaluate the Effect of Safinamide on Sleep Quality and Polysomnographic Parameters in Patients With Parkinson's Disease: the Safe Sleep Study*) is ongoing (NCT03968744; <https://clinicaltrials.gov/ct2/show/NCT03968744>). The effect that confinement due to COVID-19 [24] may have had on the last months of the follow-up in some of the patients is unknown. Of all the visits conducted, 4 visits (at V4) were by telephone due to the pandemic. Moreover and very importantly, patients included in this study had severe or very severe NMS burden and the results could be not extrapolated to patients with mild or moderate NMS burden. Finally, not all patients suffered from motor complications at baseline (78% motor fluctuations and 30% dyskinesia) and a small sample size could explain the lack of statistical significant reduction on the UPDRS-IV total score from baseline to the final follow-up visit (a trend of significance was observed;  $p=0.188$ ). On the other hand, this is the first study designed to assess the effect of safinamide on NMS burden in PD patients and the first one in which changes in some NMS such as pain; mood; or, in this case, sleep and daytime sleepiness have been exhaustively analyzed.

In conclusion, safinamide is well-tolerated and could improve sleep and daytime sleepiness in PD patients. Well-designed randomized double-blind studies with polysomnography analysis are necessary to analyze in detail the possible beneficial effect of safinamide on sleep disorders.

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**Author contribution** Santos García D: conception, organization, and execution of the project; statistical analysis; writing of the first

draft of the manuscript; recruitment and/or evaluation of participants. Cabo López I: review and critique; recruitment; and/or evaluation of participants. Labandeira Guerra C: review and critique; recruitment; and/or evaluation of participants. Yáñez Baña R: review and critique; recruitment; and/or evaluation of participants. Cimas Hernando MI: review and critique; recruitment; and/or evaluation of participants. Paz González JM: review and critique; recruitment; and/or evaluation of participants. Alonso Losada MG: review and critique; recruitment; and/or evaluation of participants. Gonzalez Palmás MJ: recruitment and/or evaluation of participants. Cores C: review and critique; collaboration in the manuscript redaction. Martínez Miró C: review and critique; organization; collaboration in the manuscript redaction.

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## Declarations

**Conflict of interest** Santos García D. has received honoraria for educational presentations and advice service by Abbvie, UCB Pharma, Lundbeck, KRKA, Zambon, Bial, Italfarmaco, and Teva. Cabo López I. has received honoraria for educational presentations and advice service by Abbvie and Zambon and Bial. Labandeira Guerra C. has received honoraria for educational presentations and advice service by Abbvie, Italfarmaco, Zambon, and Bial. Yáñez Baña R. has received honoraria for educational presentations by Teva, Bial, and Zambon. Cimas Hernando MI. has received honoraria for educational presentations and advice service by KRKA, Italfarmaco, Teva, Zambon, and Bial. Paz González JM. has received honoraria for educational presentations and/or advice service by UCB Pharma, Lundbeck, KRKA, and Zambon. Alonso Losada M. has received honoraria for educational presentations and advice service by Zambon and Bial. González Palmás MJ: None. Cores C. has received honoraria for educational presentations and advice service by Lundbeck and UCB Pharma. Martínez Miró C: None.

**Ethical approval** Approval from the Comité de Ética de la Investigación Clínica de Galicia from Spain (2018-052; 28/FEB/2019) was obtained for the present study.

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