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REVIEW

Use of safinamide for treatment of Parkinson disease: real-world data from Spain

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Abstract

Safinamide is a monoamine oxidase B inhibitor that was approved in Europe in February 2015 to complement a stable dose of levodopa in monotherapy or in combination with other antiparkinsonian agents in adults affected by mid-stage or advanced Parkinson disease (PD) with fluctuations. It is characterized by a dual mechanism of action (dopaminergic and non-dopaminergic), thus enabling an innovative approach in the management of motor and non-motor symptoms. The safety and efficacy profile of safinamide was previously shown in placebo-controlled randomized clinical trials, which demonstrated that ON time could be increased without the onset of dyskinesia and that OFF time could be decreased, with an improvement in PD. However, the strict inclusion and exclusion criteria in these studies meant that not all patients seen in daily clinical practice were represented, hence the importance of observational studies that evaluate the drug in these situations. The objective of the present article was to collect and review reports from Spanish authors presented at national and international conferences on the use of safinamide in patients with PD. We reviewed a total of 36 reports covering around 2000 patients with PD. The reports confirm the safety and efficacy results obtained in clinical trials, showing a significant improvement in motor and non-motor fluctuations and enabling the dose of levodopa to be reduced, thus decreasing the likelihood of motor complications.

Keywords: clinical practice, fluctuations, observational studies, monoamine oxidase B inhibitors, safinamide, Parkinson disease.

Citation

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Introduction

Parkinson disease (PD) is characterized by progressive degeneration of nigrostriatal dopaminergic neurons, which leads to the dopamine deficiency that is responsible for the motor symptoms typical of the disease.[1] PD is also associated with various non-motor symptoms that increase the associated clinical and cost burden. Furthermore, in mid–advanced-stage PD, the combination of motor and non-motor symptoms usually leads to marked functional disability, with the result that treatment must be tailored.[2,3]

Levodopa is currently the most effective treatment for PD.[4] However, the advance of the degenerative process and the lack of continuous dopaminergic stimulation lead to increased dosing requirements. These, in turn, lead to complications, such as motor and non-motor fluctuations, that negatively affect the quality of life of patients.[5–8] While several strategies have been applied to manage or even delay the onset of these complications, this objective has not been reached in the long term. Moreover, symptoms become increasingly difficult to control as the disease progresses.[9–14]

One common strategy for managing complications is combining levodopa with drugs that increase dopamine availability in the striatum such as dopaminergic agonists, catechol-O-methyltransferase inhibitors (entacapone, tolcapone and opicapone), monoamine oxidase B (MAO-B) inhibitors (rasagiline and selegiline) and dual-action agents (safinamide).[15]

Safinamide is a MAO-B inhibitor with a dual mechanism of action involving selective and reversible inhibition of MAO-B (dopaminergic) and modulation of abnormal glutamate release via blockade of presynaptic voltage-gated sodium and calcium channels (non-dopaminergic). This dual mechanism enables an innovative

approach to the management of motor and non-motor symptoms and motor complications.[16–21] Pivotal studies in patients with PD have shown safinamide to be an efficacious, safe and well-tolerated agent for reducing motor and non-motor fluctuations.[16,17] Safinamide also makes it possible to decrease the dose of other dopaminergic drugs, in turn reducing the likelihood of adverse events (AEs) such as impulse control disorder.[19]

Randomized clinical trials (RCTs) are the gold standard for evaluating the safety and efficacy profile of new treatments. However, their strict inclusion and exclusion criteria mean that the patients included are not generally representative of the individuals seen in daily clinical practice.[22,23] Hence, studies that complement RCTs by evaluating the drug in real-world practice are of importance.

The most relevant real-world study on safinamide is SYNAPSES, which included 1610 patients with PD treated over the duration of 1 year.[24] The results confirmed the efficacy, safety and tolerability of safinamide as an add-on treatment in PD. The improvement in motor complications was clinically relevant, and results for the Unified Parkinson's Disease Rating Scale (UPDRS) were maintained in the long term. The results were subsequently confirmed in a post hoc analysis conducted in Spanish patients.[25,26]

The objective of the present study was to collect and review reports from Spanish authors presented at national and international conferences on the use of safinamide in patients with PD. Most reports addressed the drug's use in daily clinical practice.

Review

Characteristics of real-world studies with safinamide in Spain

We reviewed 36 reports presented between 2018 and 2023 at national and international conferences covering around 2000 patients (Table 1). While the range for the number of patients from the different studies was very broad (3–511 patients), most (67%) included at least 30 patients. Sixteen studies were retrospective and 20 were prospective. Follow-up ranged from 1 to 40 months, although in most cases it ranged from 3 to 6 months. Mean age was 52–84 years, with a similar percentage for each sex. Mean disease duration was 2–14 years. Most patients were in stages 2 and 3 of the Hoehn and Yahr (H&Y) scale. The daily levodopa equivalent daily dose (LEDD) varied considerably, from 300 to 1391 mg.

Effectiveness of safinamide

Effectiveness of safinamide for treatment of motor symptoms

Most real-world studies support the results of the pivotal studies, highlighting not only an improvement in motor fluctuations[25,27–31] but also in motor symptoms measured using the scales UPDRS-III[19,25,27,28,32–37] and Clinical Global Impression (CGI).[27,34,38–40] Even the change from rasagiline to safinamide was shown to be safe and effective, with improvements in motor fluctuations, motor symptoms and perception of severity by patients after switching.[28]

Morales-Casado et al.[28] evaluated the effectiveness and safety of safinamide in 93 patients with PD, at both 50 mg/day and 100 mg/day, and in those who switched from rasagiline to safinamide. The UPDRS-III score for the whole study population decreased by 18% at 6 months; in those who switched from rasagiline to safinamide, it decreased by 10.3% (Figure 1).

Dopaminergic treatment is useful, although some symptoms respond poorly, including axial problems such as freezing of gait (FOG); safinamide could prove useful in affected patients. In their prospective study, Machío Castelló et al.[37] evaluated patients with PD characterized by motor fluctuations and FOG before and 1 month after receiving safinamide. Despite the severity of the disease, FOG improved in 34.1% of patients. The authors concluded that, in addition to its known clinical indications, safinamide has a specific effect on axial symptoms, even in patients with advanced disease, thus underlining its usefulness for treating a wide range of symptoms, especially those that are disabling and refractory.

Atypical PD symptoms include infrequent findings such as early dementia, frequent falls, prominent dysautonomia and ataxia. Standard dopaminergic therapy is often inefficacious. In fact, the medications approved for PD are commonly used off-label to treat the symptoms of these atypical parkinsonian syndromes. According to data from a small retrospective case series (n=5) reported by Machío Castelló et al.,[41] the clinical response to safinamide 50 mg/day was positive in all patients with atypical PD. Both FOG and other motor symptoms improved in all cases, and none of the patients experienced adverse effects or exacerbation of symptoms.

Effectiveness of safinamide in non-motor symptoms

Improvements in motor symptoms with safinamide may positively affect mental status, although the non-dopaminergic mechanism of this MAO-B inhibitor may also account for this effect. As with motor symptoms, real-world studies once again confirm the results of the pivotal studies for improvement in non-motor symptoms such as depression,[27,32,42] mood, apathy,[42,43] sleep,[29,44–47] pain[29,46–48]

Table 1. Characteristics of studies and of patients included in real-world studies with safinamide in Spain.

Year[ref]	Design	Sample size	Men/ Women	Mean age, years	Disease	Disease duration, years	Follow-up	Other characteristics and concomitant treatments	Study objective
2018[32]	Prospective	32	12/7	63	PD	9.8	105 days	Depression 73% BDI 13 BDI severity 1 UPDRS-III 20	Effect on mood
2018[63]	Prospective	5	2/3	52–71	RLS		3 months	RLSRS 14–28	Efficacy in RLS
2018[37]	Prospective	52	35/17	69	Advanced PD	11	1 month	MF and FOG	Efficacy in MF and FOG
2018[50]	Prospective	3	2/1	80	PD	12	3 visits	Disabling dyskinesia Visual hallucinations Delirium LED 575 mg H&Y 3.7 UPDRS-III 33	Efficacy in patients with pharmacological psychosis
2018[58]	Prospective	19	12/7	69	PD	10	12 weeks	MF H&Y 2.6 LED 974 mg	Interaction between SAF and opicapone
2018[41]	Retrospective	5	2/3	65	Atypical PD	7	1 month	MF and FOG	Effect in atypical PD
2018[54]	Retrospective	58	35/23	74.3	PD	8.3 months	–	75% with concomitant treatment	Review of clinical practice (2 years)
2018[30]	Retrospective	214	117/97	67	PD	8.3	5.6 months	Mild cognitive impairment 10.1% Dementia 1.2% LEDD 720.3 mg H&Y 2.5 Rasagiline 53.7% Amantadine 19.2%	Efficacy and safety in advanced PD

(*Continued*)

Table 1. (*Continued*)

Year[ref]	Design	Sample size	Men/ Women	Mean age, years	Disease	Disease duration, years	Follow-up	Other characteristics and concomitant treatments	Study objective
2019[31]	Prospective	169	87/82	72.6	PD	11.8	24 months	Dyskinesia 53% Fluctuations 73% Cognitive impairment 19% LEDD 936.9 mg COMTi 32% Dopa ago 49% Amantadine 18% Antidepressants 36% Rasagiline 58%	Long-term efficacy and tolerability in polymedicated patients with PD
2019[40]	Retrospective	52	27/25	83.7	PD	10.2	56.6 weeks	Cognitive impairment 53.4% Mild cognitive impairment 17.8% Dementia 35.6% LED 1015.37 mg	Safety in elderly patients and in dementia
2019[38]	Retrospective	50	35/15	67.5	Non-advanced PD	2-4	3–36 months	H&Y 2 Levodopa 300–500 mg	Reduced dose of levodopa
2019[49]	Prospective	32 with SAF 78 without SAF	20/12 45/33	74 72	PD without dementia	8.2 6.4	1 month	H&Y 2.1 and 1.9 SCOPA 9.1 and 7.2 Urological drugs 19% and 26% Levodopa 100% and 78% Dopa ago 50% and 40% Rasagiline 31% and 53%	Effect on urinary symptoms
2019[57]	Prospective	15	11/4	68.7	PD		3 and 6 months	Recent diagnosis	Efficacy of SAF in monotherapy
2019[55]	Retrospective	6 with SAF 14 without SAF	3/3	70.7	Advanced PD		6 months	Levodopa-carbidopa intestinal gel Levodopa 1370 mg Levodopa 1391 mg	Modification of dose of levodopa
2019[60]	Retrospective	30	16/14		Advanced PD	11.3		MF FOG H&Y 3	Efficacy and safety in patients >70 years

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Table 1. (*Continued*)

Year[ref]	Design	Sample size	Men/ Women	Mean age, years	Disease	Disease duration, years	Follow-up	Other characteristics and concomitant treatments	Study objective
2020[59]	Retrospective	26	10/16	70	Atypical PD	6.6	8±9 months	Corticobasal syndrome 53.8% Multiple system atrophy 42.3% Progressive supranuclear palsy 3.9%	Efficacy in atypical PD
2020[39]	Retrospective	18	11/7	72.5	Advanced PD	13.5		H&Y 3 Dementia 16.7% Impulse control disorder 5.6% Deep brain stimulation 22.2%	Efficacy and safety in advanced PD
2020[61]	Retrospective	53		75.09	PD		7.67±6.77 months		Safety in older population
2021[27]	Prospective	82 total 38 SAF mono 44 SAF plus antidepressant	37/45 21/17 16/28	68.33 70.13 66.77	PD	7.84 9.39	3 months	HAMD-17 19.49 LEDD 810.26 mg	Effect on motor symptoms according to UPDRS
2021[45]	Prospective	50	21/29	68.5	PD	6.4	6 months		Effect on sleep
2021[42]	Prospective	50	21/29	68.5	PD	6.4	6 months		Effect on mood
2021[48]	Prospective	50	21/29	68.5	PD	6.4	6 months		Effect on pain
2021[51]	Prospective	50	21/29	68.5	PD	6.4	6 months		Identify factors that are protective of quality of life
2021[34]	Retrospective	111 total 46 <70 years 55 ≥70 years		61.7 77.6	Fluctuating PD	9.5 10.1		Levodopa 485 mg and 627 mg Dopa ago 63% and 55% Dementia 7% and 22%	Efficacy in fluctuating PD
2021[52]	Retrospective	18	7/11	72.28	PD	4.72	8.3 months	LED 484.17 mg H&Y 2 PDQ-39 31.22	Changes in PDQ-39
2021[33]	Prospective	20	13/7	71.8	PD	8.9		LEDD 566 mg H&Y 2.6 UDPRS-III 30.2	Efficacy in non-motor symptoms and quality of life

(*Continued*)

Table 1. (*Continued*)

Year[ref]	Design	Sample size	Men/ Women	Mean age, years	Disease	Disease duration, years	Follow-up	Other characteristics and concomitant treatments	Study objective
2022[53]	Prospective	75	50/25	68.7	Nonadvanced PD	2-4	3–36 months	H&Y 2 LEDD 300-400	Efficacy in non-advanced PD
2022[43]	Prospective Randomized	14 SAF 13 placebo	5/9 4/9	66.7 72.3	PD without dementia	57.8 months 47.8 months	24 weeks	LEDD 543 mg and 631 mg H&Y 2.1 and 2.1 PDQ-39 25.4 and 27.5 UPDRS-III 29.9 and 29.9 NPI apathy 4.5 and 3.8	Efficacy in apathetic PD without dementia
2022[35]	Retrospective	82	37/45	68.33	PD	8.67	3 months	HAMD-17 19.49 UPDRS-III 22.91 LEDD 810.26 mg Pain 12.2%	Effect of factors on efficacy of SAF
2022[28]	Prospective	93	44/49	67.8	PD		6 months	UPDRS-III 24.72	Efficacy of switching from rasagiline to SAF
2023[25]	Prospective	511	289/222	68	PD		12 months	Levodopa 97.3% Dopa ago 58.5% Antidepressants 35.8% COMTi 28.8% Amantadine 11.4%	Efficacy in improvement in motor symptoms in Spanish patients
2023[26]	Prospective	511	289/222	68	PD		12 months	Levodopa 97.3% Dopa ago 58.5% Antidepressants 35.8% COMTi 28.8% Amantadine 11.4%	Safety in Spanish patients
2023[62]	Retrospective	200		71.4	PD		40.6 months	Rasagiline 54% No previous exposure 46%	Safety of SAF and switch from rasagiline to SAF
2023[68]	Retrospective	60 SAF 29 opicapone	33/27 17/12	73 65	Fluctuating PD	7 6	15 weeks 13 weeks	H&Y >2: 47% and 28% LEDD 655 mg and 650 mg Dyskinesia 27% and 35%	Adherence and effect of SAF and opicapone on dyskinesia in a patient with fluctuating PD

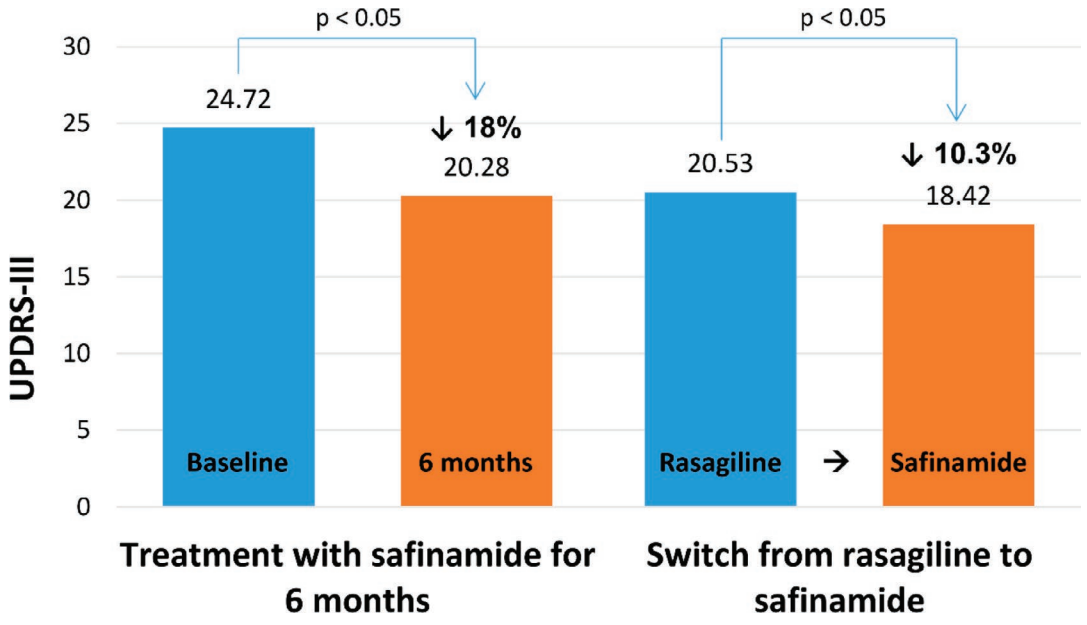
(*Continued*)

Table 1. (*Continued*)

Year[ref]	Design	Sample size	Men/ Women	Mean age, years	Disease	Disease duration, years	Follow-up	Other characteristics and concomitant treatments	Study objective
2023[56]	Retrospective	180		72.34	PD		14.57 months	UPDRS-III 11.64 H&Y ≤2: 91% Dopa ago 74.78 mg LEDD 364.9 mg	Effectiveness and rate of discontinuation of SAF
2023[69]	Prospective	9			PD		6 months		Effect of SAF as add-on therapy in PD

BDI, Beck Depression Inventory; COMTi, catechol-O-methyltransferase inhibitors; Dopa ago, dopaminergic agonist; FOG, freezing of gait; HAMD-17, Hamilton Depression Rating Scale; H&Y, Hoehn and Yahr; LED, levodopa equivalent dose; LEDD, levodopa equivalent daily dose; MF, motor fluctuations; NPI, Apathy item of Neuropsychiatric Inventory; PD, Parkinson disease; PDQ-39, Parkinson's Disease Questionnaire; RLS, restless leg syndrome; RLSRS, Restless Legs Syndrome Rating Scale; SAF, safinamide; UPDRS, Unified Parkinson's Disease Rating Scale.

Figure 1. Impact of safinamide according to UPDRS-III.[28]



UPDRS, Unified Parkinson's Disease Rating Scale.

and urinary symptoms.[29,46,47,49] Table 2 shows the main non-motor symptoms, and the percentage reduction reached with safinamide for each of the scales used. In all cases, the effect of safinamide seems to be mediated by dopaminergic action, although it may also be due to inhibition of glutamate release, leading to a positive effect in attention, sleep and motor symptoms.[33,49]

Depression, mood and apathy

Several studies have shown that safinamide significantly improves depression, mood and apathy in patients with PD. This improvement can be observed with multiple scales (Table 2), such as the Beck Depression Inventory (BDI),[32] mood and apathy domains of the Non-Motor Symptoms Scale (NMSS), the emotional well-being domain of the Parkinson's Disease Questionnaire on quality of life (PDQ-39),[42] the Starkstein Apathy Scale (AP) and the apathy item of the Neuropsychiatric Inventory (NPI).[43] Interestingly, while improvements recorded in the AP and NPI scales were not statistically significant with respect to placebo-treated patients, the greatest change was recorded between 12 and 24 weeks, thus highlighting the delayed positive effect of safinamide.[43] Therefore, longer studies are necessary to more carefully determine the effect of safinamide on apathy in PD.

Sleep

Liguori et al.[44] observed that safinamide leads to a subjective improvement in sleep and daytime sleepiness in patients with fluctuating PD. Similar findings were reported by Cabo López et al.[45] in a sub-analysis of the SAFINONMOTOR study, which concluded that safinamide improved sleep and daytime sleepiness in patients with PD after 6 months of treatment. The Pittsburgh Sleep Quality Index (PSQI) fell by 19.1%, especially in the domains sleep quality, sleep latency, sleep duration and sleep efficiency (Table 2). A significant reduction (24.7%) was also observed in the Epworth Sleepiness Scale, with the most notable improvement being in daytime sleepiness while sitting or reading, watching television, and sitting still in a public place.

Pain

In another sub-analysis of the SAFINONMOTOR study, Yáñez Baña et al.[48] concluded that after 6 months of treatment with safinamide, the score on the King's Parkinson's Disease Pain Scale (KPPS) fell significantly (43.6%), especially in the domains musculoskeletal pain, fluctuation-related pain, discoloration, oedema/swelling and radicular pain. There was also a significant reduction in the Visual Analogue Scale for Pain (VAS-PAIN) (20.4%) (Table 2).

Urinary symptoms

Urinary symptoms are common and disabling and do not respond well to treatment. However, according to the SURINPARK study by Gómez López et al.,[49] in which patients with PD without dementia were evaluated using the Scales for Outcomes in Parkinson's disease–Autonomic Dysfunction (SCOPA-AUT), safinamide 100 mg/day significantly improved urinary symptoms compared with the group that did not receive the medication (Table 2).

Psychotic symptoms and hallucinations

Patients with PD may present psychotic symptoms and visual hallucinations associated with the pro-

Table 2. Effectiveness of safinamide against non-motor symptoms.

Non-motor symptoms	Scale[ref]	% reduction
Depression	BDI[32]	18.5%
	BDI-II[42]	35.9%
Mood and apathy	NMSS (mood and apathy domain)[42]	57.9%
Sleep	PSQI[45]	19.1%
	PSQI sleep quality[45]	23.9%
	PSQI sleep latency[45]	25.0%
	PSQI sleep duration[45]	40.0%
	PSQI sleep efficiency[45]	25.9%
	ESS[45]	24.7%
	NMSS (sleep domain)[29]	35.8
Pain	KPPS[48]	43.6%
	KPPS musculoskeletal pain[48]	35.9%
	KPPS fluctuation-related pain[48]	51.7%
	KPPS discoloration; swelling/oedema[48]	50.4%
	KPPS radicular pain[48]	40.1%
	VAS-PAIN[48]	20.4%
	NMSS (pain domain)[29]	43%
Urinary symptoms	SCOPA-AUT[49]	27.5%
	NMSS (urinary symptoms domain)[29]	28.3%
Social well-being and quality of life	NMSQ[33]	9.0%
	PDQ-39 (social well-being domain)[42]	40.6%
	PDQ-39 (writing clearly)	21.1%
	PDQ-39 (muscle cramps or painful spasms)	30.4%
	PDQ-39 (discomfort or pain in joints or body)	32.0%

BDI, Beck Depression Inventory; ESS, Epworth Sleepiness Scale; KPPS, King's Parkinson's Disease Pain Scale; NMSQ, Non-Motor Symptoms Questionnaire; NMSS, Non-Motor Symptoms Scale; PDQ-39, Parkinson's Disease Questionnaire (quality of life); PSQI, Pittsburgh Sleep Quality Index; SCOPA-AUT, Scale for Outcomes in Parkinson's disease for Autonomic Symptoms; VAS-PAIN, Visual Analogue Scale for pain.

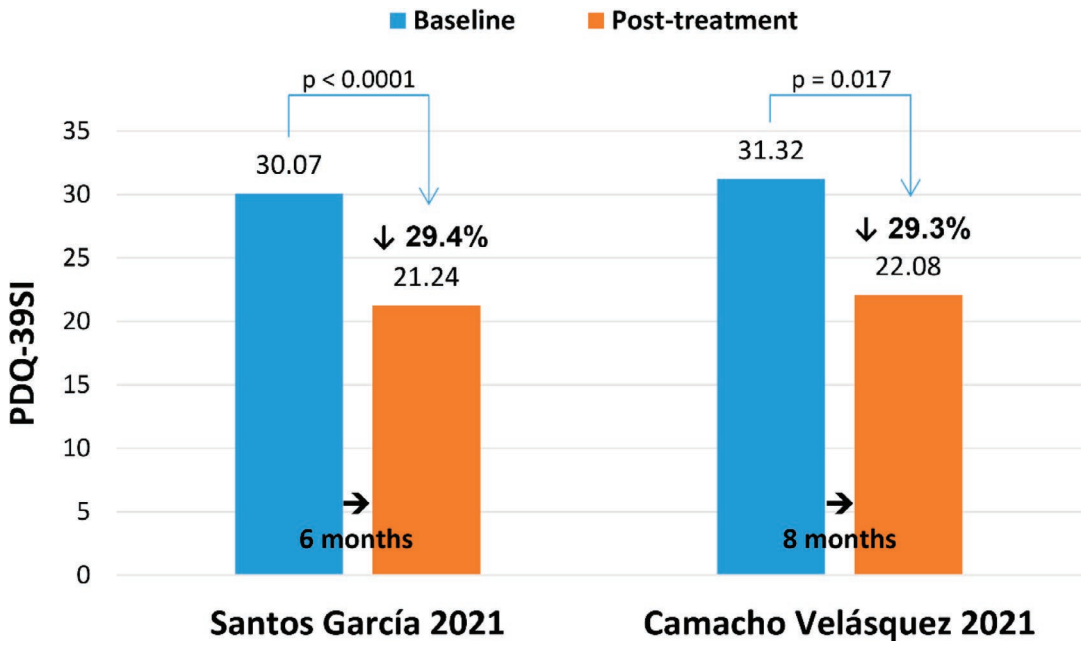
gression of PD and dopaminergic treatment. In their observational study, Rodríguez Sanz et al.[50] evaluated the safety and effectiveness of safinamide in patients aged >70 years with a >10-year history of PD who did not fulfil the criteria for dementia and who had developed disabling dyskinesia, visual hallucinations and delirium associated with dopaminergic treatment. Safinamide 100 mg/day was shown to be safe and improved disabling dyskinesia without triggering psychotic symptoms (no reappearance of hallucinations or visual delirium).

Impact of treatment on quality of life

Both motor symptoms and non-motor symptoms have a major impact on the quality of life of patients with PD. Several studies have identified factors that predict improvements in quality of life.

Santos García et al.[51] found that the quality of life of patients with PD improved significantly after 6 months of treatment with safinamide (50 mg/day for the first month, followed by 100 mg/day with evaluations at 3 and 6 months) (Figure 2). The domains that improved were mobility, autonomy in activities of daily living, emotional well-being, stigma and bodily pain/discomfort. Improvement in motor symptoms (reduced UPDRS-III score), non-motor symptoms (reduced NMSS score) and mood (reduced BDI-II score) were independently associated with improvements in quality of life at 6 months, that is, the improvements recorded on these

Figure 2. Impact of safinamide on quality of life in patients with Parkinson disease.[51,52]



PDQ-39SI, 39-item PD questionnaire summary index.

three scales accounted for 75% of the improvement in quality of life according to the PDQ-39 score.

Camacho Velásquez et al.[52] recorded a slight reduction in the H&Y score from 2 to 1.71 (p=0.056) and a statistically significant reduction in the PDQ-39 scale of 29.3% (p=0.017) (Figure 2), as well as in the different subcategories, in patients with PD who received safinamide 100 mg/day as add-on therapy.

In their study of a small sample of patients with PD (n=20), Giraldo et al.[33] analysed the use of safinamide for non-motor symptoms and quality of life after 3 months of treatment, finding a significant reduction in the Non-Motor Symptoms Questionnaire (NMSQ) score (9%), with specific improvements in sleep, fatigue and urinary symptoms. They also reported an improvement in problems writing clearly, muscle cramps and painful spasms and in joint and bodily pain and discomfort (Table 2).

Levodopa: dose modifications

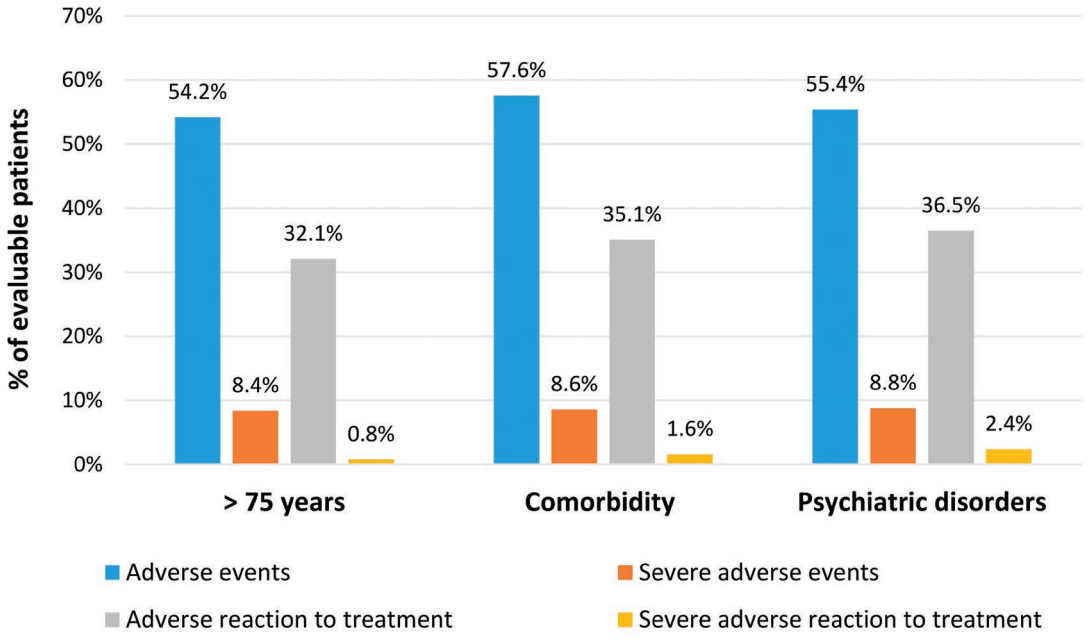
Most studies on modifications to the dose of levodopa or the LEDD after administration of safinamide report statistically significant dose reductions.[50,52,53] After reviewing the clinical records of patients with PD who started safinamide in daily clinical practice, Borrué-Fernández[54] found that, in 68% of patients, it was not necessary to adjust the dose of levodopa during the 2-year observation period.

In a study with a >8-month follow-up, Camacho Velásquez et al.[52] found that safinamide 100 mg/day made it possible to significantly reduce the LEDD (p=0.002). Similarly, in two studies by de la Fuente Cañete,[38,53] who evaluated the effectiveness of safinamide in early-stage or non-advanced PD over 36 months, the levodopa dose was reduced from 400 to 300 mg/day, with stabilization of motor and non-motor symptoms. Elsewhere, González-Pinto et al.[55] studied patients with advanced PD who had received levodopa-carbidopa intestinal gel (LCIG) for ≥6 months and found that levodopa could be reduced by 3.4% to 21.40%.

Safety and tolerability of safinamide

Most studies performed in daily clinical practice found safinamide to be safe and tolerable. The few AEs reported were mild and resolved by reducing the dose. However, some patients had to suspend treatment owing to adverse effects or lack of efficacy, although the frequency of these events was low (7.8% after 15 months of treatment).[56] This favourable safety profile was observed at 50 mg/day,[28] 100 mg/day[50] and at >100 mg/day,[39] even in polymedicated elderly patients,[31,50,54] thus confirming the findings of the SYNAPSES study.[24,26] Figure 3 shows the percentage of AEs by age, comorbidity and psychiatric status of Spanish patients treated with safinamide for 12 months.[26] The favourable safety profile of safinamide has been demonstrated in monotherapy[57] and in combination with other drugs such as opicapone.[58] Similarly,

Figure 3. Percentage of patients who reported at least 1 adverse event or adverse reaction to treatment after 12 months of treatment with safinamide.[26]



no relevant AEs were reported in patients who switched from rasagiline to safinamide.[28]

Dyskinesia was one of the most frequent AEs. This was reported at 100 mg/day and was resolved by reducing the dose to 50 mg/day. Transient sleepiness was also reported in 31% of patients.[54] According to the records of patients with PD treated with safinamide, 8 (30.8%) patients experienced mild AEs (sleepiness, confusion, malaise and headache), and it was necessary to discontinue treatment in one case.[59] No neuropsychiatric adverse effects have been observed in patients previously diagnosed with mild cognitive impairment.[54]

In one of the most extensive studies on the safety and tolerability of safinamide (52 patients with 56.6 weeks of follow-up), Labandeira et al.[40] recorded AEs in 7 (13.5%) patients: 1 was considered mild and only 1 was severe (worsening of FOG). The most common AEs were hallucinations and agitation, problematic dyskinesia, unstable gait and recurrent syncope (Table 3). Eight patients discontinued safinamide because of AEs (six cases) and absence of improvement (two cases). Three patients died during follow-up, although their deaths were not treatment related. Twenty patients had previously experienced AEs with other PD treatments but not with safinamide. All the patients who experienced an AE with safinamide also reported previous AEs with other dopaminergic drugs. Among the patients with cognitive impairment (n=24; median age, 84 years; 11-year disease progression), five reported AEs and had to discontinue treatment (three psychiatric, one recurrent syncope (resolved after discontinuation), and one worsening of gait and dyskinesia). The authors concluded that safinamide had a good safety and tolerability profile in older patients and patients with dementia, thus making it a key option for adding to levodopa.

Table 3. Frequency of adverse events related to treatment with safinamide.

Adverse event	Labandeira et al.[40] n=52
Hallucinations and agitation	7.6%
Problematic dyskinesia	5.7%
Unstable gait	3.8%
Recurrent syncope	1.9%

According to Ruíz-López et al.,[60] safinamide demonstrated a favourable tolerability profile in patients over 70 years of age with PD: 26 (86.6%) patients did not experience AEs, and 7 (23.3%) had to interrupt treatment (3 owing to hallucinations and cognitive impairment, the remainder because of gastrointestinal problems). These findings were confirmed in the study by Hernández Martínez[61] in patients aged >70 years, in whom the safety profile was similar to that reported in the pivotal studies, with a population aged 15 years younger.[16,18]

In another of the more extensive studies (200 patients with PD and a mean age of 71.4 years), Carmona-Abellán et al.[62] evaluated the safety of switching from rasagiline to safinamide. The switch was gradual in 78% of patients and direct in the remaining 22%. After a median follow-up of 40.6 months, 68% of patients continued treatment, and the most frequent AEs were hallucinations and dizziness. The authors concluded that switching directly from rasagiline to safinamide was safe in older patients.

Safinamide in specific populations

Patients with restless leg syndrome

Restless leg syndrome (RLS) is a common sensorimotor disorder characterized by the need to move and associated with uncomfortable sensations in the legs.[63] Refractory RLS is characterized by an absence of response to dopaminergic agonists or to α2δ ligands owing to inadequate efficacy or onset of AEs. González Hernández et al.[63] evaluated the effectiveness and tolerability of safinamide in patients with refractory RLS who had previously received dopaminergic agonists or α2δ ligands. The authors applied the Restless Leg Syndrome Rating Scale (RLSRS) at visit 1 (inclusion) and visit 3 (3 months after inclusion). Visit 2 was scheduled for 4 weeks after inclusion to evaluate whether safinamide 50 mg/day was effective. The initial RLSRS score was between 14 and 28, but this fell by 9 points after therapy with safinamide, revealing a greater effect in patients with mild disease. The study concluded that safinamide was effective and well tolerated in patients with refractory RLS, not only because of the mechanism of action of the dopaminergic agonist but also because of its indirect effect on glutamate release. Treatment with safinamide could be more effective when administered early.

Patients receiving advanced therapies

Rodríguez Jorge et al.[39] evaluated the effect of treatment with safinamide (>100 mg/day for 3.5 months) in 18 patients who had been treated with deep brain stimulation. Their results showed that the increase in the dose of safinamide from 100 mg/day to >100 mg/day significantly improved the UPDRS-IV score (from 7.8 to 6.2; p=0.007), mainly owing to a reduction in OFF time (2.0 *versus* 1.3; p=0.013). Moreover, nine patients had a CGI of improvement (GCI-13) ≥4. In general, dyskinesia did not worsen, although, in three (20%) patients, it caused treatment to be interrupted. Safinamide 200 mg/day was discontinued in only one patient, who started therapy with LCIG.

Borrué-Fernández[54] and Martín de la Morena et al.[64] evaluated the use of safinamide in patients with PD receiving concomitant treatments such as apomorphine infusion pump therapy and LCIG. The results showed that safinamide was efficacious and safe as an adjunctive treatment, especially for the control of non-motor symptoms. González-Pinto et al.[55] evaluated safinamide as add-on therapy to LCIG in patients with advanced PD. The authors found that the drug was safe, leading to a 7.65% reduction in the LEDD and enabling oral levodopa to be maintained. Vinagre-Aragón et al.[31] also evaluated the efficacy and tolerability of long-term safinamide in patients with PD (14% of whom were receiving advanced therapy, namely apomorphine, deep brain stimulation or LCIG). The authors reported that 30% of patients had to adjust treatment despite the advanced therapies.

Patients on monotherapy

In their exploratory study, González Hernández et al.[57] included 15 recently diagnosed treatment-naive patients to analyse the effectiveness of safinamide in monotherapy off-label. The patients were evaluated at 3 and 6 months after initiating safinamide. At 3 months (n=14), the UPDRS-III score had fallen by 1.4 points over baseline; at 6 months (n=12 with 100 mg/day and n=2 with 50 mg/day), it had fallen by 1.6 points. These results pave the way for more exploratory studies on the potential usefulness of safinamide as a therapeutic option in monotherapy.

Discussion

The collection of real-world data is crucial for complementing insights from RCTs, as it reflects the use and performance of medications in routine clinical practice across diverse patient populations. The presented review summarizes findings from 36 Spanish real-world reports, encompassing approximately 2000 patients with PD, consistently confirming the safety and efficacy of safinamide observed in pivotal clinical trials. This aligns well with several published reports, including the European SYNAPSES trial,[24] which investigated safinamide in real-life conditions across six European countries, including Spain, confirming its good safety profile and clinically significant improvements in motor complications and UPDRS scores. The Belgian[65] and Spanish (Martí-Andrés et al.[66] and Planas-Ballvé et al.[67]) cohorts further reinforce these observations, providing specific regional perspectives.

Regarding efficacy, all studies demonstrate safinamide's positive impact on motor symptoms. The SYNAPSES trial reported clinically significant improvements in UPDRS total and motor scores in at least 40% of patients, while the Belgian cohort found improvements in 35% of motor and 27% of total UPDRS scores.[24,65] Martí-Andrés et al., using the CGI scale, noted improvement in motor symptoms in 76.4% of patients.[66] The present review highlights an 18% decrease in UPDRS-III score overall and a 10.3%

decrease in patients who switched from rasagiline to safinamide. Planas-Ballvé et al. showed a stable UPDRS-III score over a median follow-up of 40 months, implying long-term symptom control in a cohort predominantly in earlier disease stages.[67] Furthermore, motor fluctuations, particularly wearing-off, consistently improved across studies, with the Belgian cohort reporting a 50% reduction in patients with wearing-off at baseline after 1 year, and the SYNAPSES trial observing a 40–50% reduction in motor fluctuations overall.[24,65] Beyond motor control, improvements in non-motor symptoms, like depression, mood, sleep, pain and urinary symptoms, were also consistently reported in all studies.

The safety and tolerability profile of safinamide is consistently reported as favourable. The SYNAPSES trial indicated that 45.8% of patients experienced AEs and 27.7% had adverse drug reactions, with most being mild or moderate and resolving completely.[24] The Belgian cohort reported an adverse drug reaction rate of 36.3%,[65] and Martí-Andrés et al. observed AEs in 24.7% of patients, primarily mild.[66] The most frequently reported AE across multiple sources was dyskinesia. Interestingly, Martí-Andrés et al. noted that dyskinesia often involved the aggravation of pre-existing movements rather than de novo induction.[66] Discontinuation rates varied, with SYNAPSES reporting 21.6% total discontinuation (10.3% due to AEs), the Belgian cohort showing 28.6% permanent discontinuation, and Martí-Andrés et al. at 16.4% (11.2% AE related).[24,65,66] Notably, Planas-Ballvé et al. reported a significantly lower overall discontinuation rate of 7.8% over a longer follow-up period, with only 4% due to AEs.[67] This lower rate might be attributed to its patient cohort being predominantly in earlier disease stages compared with the broader SYNAPSES study.

In terms of levodopa dose management, the present review and Martí-Andrés et al. suggested that safinamide allowed for levodopa dose reduction or maintenance.[66] However, Planas-Ballvé et al. noted a statistically significant increase in overall LEDD but stable dopamine agonist LEDD, suggesting a potential levodopa-sparing effect for dopamine agonists over a longer period.[67]

Real-world studies also provided valuable insights into special populations. The present review, the SYNAPSE trial and the Belgian cohort consistently showed that safinamide maintained a good safety profile in older patients and those with relevant comorbidities or psychiatric conditions, with any slight increase in serious AEs in these groups being attributed to their general health status rather than a specific safinamide contraindication.[24,65] Furthermore, the present review, the Belgian cohort[65] and Martí-Andrés et al.[66] indicated that switching from rasagiline to safinamide was safe and could offer additional clinical benefits, particularly in managing motor fluctuations. The findings by Planas-Ballvé et al., showing a significant improvement in UPDRS-III in a small monotherapy subgroup, support the potential role of safinamide in early, non-fluctuating PD patients,[67] which the present review also highlights as an area for further exploratory studies.

Conclusions

Data from real-world studies in Spain on more than 2000 patients with PD treated with safinamide confirm the efficacy and safety of this agent, as reported in RCTs, even in older patients taking concomitant treatment and with cognitive impairment or atypical parkinsonian syndromes. Safinamide significantly improved motor and non-motor symptoms, making it possible to reduce or not increase the necessary dose of levodopa, or the LEDD, thus preventing secondary motor complications.

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