


# Impact of Safinamide on Patient-Reported Outcomes in Parkinson's Disease

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**Introduction:** Parkinson's disease (PD) is a chronic and progressive neurodegenerative condition due to the degeneration of nigral dopaminergic cells. Both motor and non-motor symptoms (NMS) of PD produce a marked impairment in PD patients' quality of life (QoL), but contrary to motor features, NMS do not improve with dopamine replacement. Novel therapeutic interventions for PD have successfully controlled most motor manifestations of PD, but the management of NMS is still challenging. Since NMS have a negative impact on the QoL of PD patients, researchers are currently looking for drugs that can modulate the activity of neurotransmitter systems other than dopamine in the hope that can alleviate NMS in PD. Among the recently approved drugs for patients experiencing fluctuations in motor symptoms, safinamide stands out as an effective add-on therapy to levodopa. Safinamide is a monoamine oxidase type-B inhibitor (MAOB-I), with proven efficacy in reducing motor fluctuations. Its distinctive mechanism of action impacts dopaminergic pathways via MAOB inhibition and glutamatergic pathways by blocking sodium and calcium channels. Findings from Phase III clinical trials, meta-analysis, post-hoc analysis, and real-life experiences indicate that safinamide benefits motor symptoms such as tremor, bradykinesia, rigidity, and gait. Additionally, it shows promise for improving NMS like fatigue, pain, mood, and sleep disturbances in patients with PD.

**Areas Covered:** In this article, the authors explore the impact of safinamide on patient-reported outcomes in PD. A thorough search was conducted on PubMed focusing on studies published between 2018 and 2023 in English. The inclusion criteria encompassed clinical trials, randomized controlled trials, systematic reviews, meta-analyses, and reviews. The search strategy revolved around the implementation of MeSH terms related to safinamide and its impact on the quality of life in PD.

**Conclusion:** Our data strongly support the improving effect on QoL, reducing the disabling NMS reported in patients with PD.

**Keywords:** safinamide, Parkinson's disease, non-motor symptoms, monoamine oxidase inhibitors

## Introduction

Parkinson's disease (PD) is the second-most frequent neurodegenerative disorder after Alzheimer's disease. It is characterized by the progressive loss of the pigmented dopamine-producing neurons of the midbrain, leading to a marked decrease in the striatal dopamine content. The main cardinal features of PD include resting tremor, rigidity, and bradykinesia while balance and postural impairment usually appear later in the course of the disease. Protein deposits of aggregated forms of  $\alpha$ -synuclein in neuronal cytoplasm (Lewy bodies) and neuronal process (Lewy neurites) are the hallmarks of the disease. Interestingly, it has been suggested that misfolded  $\alpha$ -synuclein protein might spread either from peripheral structures (for instance, from the gastrointestinal tract) to the medulla and neocortex (body first phenotype) or from the amygdala to peripheral structures (brain first phenotype).<sup>1</sup> In both circumstances  $\alpha$ -synuclein deposits reach substantia nigra neurons, resulting in dopamine cell death, decreased striatal dopamine content, and ultimately the appearance of the PD symptoms.

NMS are very common in PD patients. Although they frequently develop prior to the occurrence of the motor manifestations of the disease, they are much more common in the advanced stages, particularly when motor fluctuations appear.<sup>2</sup> NMS in PD include neuropsychiatric features like anxiety, apathy, and depression, pain, fatigue, olfactory

impairment, autonomic dysfunction, and sleep and cognitive disturbances.<sup>3</sup> Increasing evidence is showing that in addition to the degeneration of nigrostriatal dopaminergic neurons, dysfunction of other neurotransmitter systems seems to be implicated in the pathophysiology of the disease, and they appear to massively contribute to the appearance of NMS. For instance, depression, anxiety, fatigue, sleep, and cognitive impairment have been ascribed to serotonin and cholinergic dysfunction.<sup>4</sup> This fact might account for the lack of response of NMS to dopamine replacement and targeting non-dopaminergic systems might be a good strategy to control NMS in PD. Thus, it is plausible that drugs acting on dopamine and non-dopamine systems might alleviate NMS. On the other hand, it is unknown the relevance of  $\alpha$ -synuclein protein deposits in structures outside the substantia nigra (both in the central and peripheral nervous system) in the development of the NMS, and it would be interesting to know if the use monoclonal anti- $\alpha$ -synuclein antibodies can be of value in the control of the NMS.

Numerous studies have reported the contribution of NMS to the deterioration of health-related-quality of life (HRQoL) which the World Health Organization defines as “the individual perception and evaluation by patients themselves of the impact caused on their lives by the disease and its consequences”.<sup>5</sup> In the last two decades, NMS have proven to be an essential part of the PD phenomenology and have been established as the major determinant of worse HRQoL. Contrary to initial reports that indicated that HRQoL and health care in PD were associated with motor symptoms severity and motor fluctuations, more recent evidence suggests a close relationship between NMS frequency and severity and HRQoL as a whole. The PRIAMO study (Barone et al, 2009) is the largest study (826 PD patients were enrolled) that investigated the relationship between NMS and HRQoL and found that apathy was associated with worse HRQoL, followed by cardiovascular symptoms, fatigue, attention/memory, and respiratory symptoms.<sup>5</sup> Subsequent studies identified the neuropsychiatric symptoms (apathy, depression) as the most important independent factor of HRQoL. In addition, longitudinal studies have demonstrated that the non-motor burden significantly progresses over time and considerably affects QoL.

More recently, Bock et al performed a cross-sectional analysis enrolling 23,058 PD patients and conducted a univariate and stepwise multivariate linear regression analysis of HRQoL. They found that patients with more moderate and severe depression, more severe motor symptoms, and higher burden of medical comorbidities had the most substantially decreased HRQoL.<sup>6</sup> Another study that included 689 PD patients from the cohort of Patients with Parkinson Disease in Spain (COPADIS) described that the NMS are closely associated with mobility, emotional well-being, and cognition. In addition, the most influential NMS were found to be fatigue, feeling sad, hyperhidrosis, impaired concentration, and daytime sleepiness. All these data clearly indicate that NMS have a negative impact on the HRQoL of PD patients and could lead to major functional impairment than motor symptoms by themselves.<sup>7</sup> Thus, improvement of NMS should be considered a major outcome variable in clinical trials. Most clinical trials in PD have been designed to assess the effect of a specific drug on controlling motor symptoms of the disease. However, numerous studies do not reflect the relevance of the motor improvement in HRQoL which is the most determinant feature for PD patients and caregivers' well-being. In addition, despite the large number of studies indicating that NMS are crucial determinants of PD HRQoL, NMS management remains challenging, and few randomized clinical trials have been focused on this issue. Thus, there is an urgent need for developing new drugs or strategies that can improve the NMS of PD since their presence is the major determinant of HRQoL in PD.

Here we review the impact of safinamide, a reversible MAO-B inhibitor, on patient-reported outcomes. Since modification in NMS seems to be the best determinant of patient-outcome we have focused on reviewing the effect of safinamide on HRQoL and NMS.

## Safinamide: General Characteristics

Safinamide is an orally administered  $\alpha$ -aminoamide derivative that combines potent, selective, and reversible inhibition of monoamine oxidase (MAO)-B with blockade of voltage-dependent Na<sup>+</sup> (VSCCs) and Ca<sup>2+</sup> (VSCCs) channels and inhibition of glutamate release, thus targeting both dopaminergic and glutaminergic systems. Consequently, safinamide is the prototype of new generation MAO-B inhibitors approved as an add-on to levodopa in PD patients experiencing motor fluctuations. Two doses of safinamide are available, 50 and 100 mg, which display a similar inhibitory effect on MAO-B activity. However, safinamide at doses of 100 mg also blocks VSSCs and VSCCs thus inhibiting glutamate transmission

at overactive synapses and reducing the excitatory overdrive in the basal ganglia motor circuits. Based on these properties, safinamide was initially developed as an antiepileptic drug. More recently, its anti-glutamatergic action has been associated with the reduction of the dyskinesia rating scale reported in a subgroup of PD patients with moderate-severe dyskinesia. These findings indicate that the anti-glutamatergic activity created by high doses of safinamide might be used for the management of levodopa-induced dyskinesia. In fact, safinamide might reduce the excessive glutamate release, created by dopamine depletion in the direct strio-pallidal pathway, which seems to underlie levodopa-induced dyskinesia. Interestingly, excessive glutamate transmission also negatively influences on several NMS of the disease, particularly cognitive, neuropsychiatric, and sensory features, and in these circumstances; in addition to motor improvement safinamide might exert a beneficial effect on these symptoms.<sup>8</sup>

The reversibility of safinamide represents an important advantage since the unspecific inhibition of MAO-B leads to un-metabolized dietary amines entering the bloodstream, where they produce noradrenaline release from peripheral adrenergic neurons, leading to a potentially fatal hypertensive response. Therefore, to avoid such effects, MAO-B selective inhibitors, such as safinamide, are essential for the treatment of PD.<sup>9</sup> Furthermore, MAO-B inhibition is also fully reversible, as it does not form irreversible covalent bonds with MAO-B, unlike rasagiline and selegiline.<sup>9</sup>

Safinamide is a small, water-soluble molecule that is rapidly absorbed with a half-life of approximately 21–24 hours, which allows for once-daily administration. Safinamide is not metabolized by CYP450, thus avoiding significant drug interactions. The drug is metabolized by MAO<sub>A</sub> and amine hydrolases into pharmacologically inert acidic and N-dealkylated products.<sup>8</sup>

Studies in animal PD models have demonstrated that brain levels of safinamide are higher than the corresponding plasma concentrations, indicating that there is a significant biotransformation of the drug. This is further supported by the very low concentrations of unchanged safinamide found in feces and urine. The drug exhibits a plasma protein binding of 92%, and only a small proportion is excreted unchanged.<sup>10</sup>

Safinamide has the potential for drug interactions and requires certain precautions. Concurrent use of specific opioids and antidepressants may increase the risk of developing serotonin syndrome. Safinamide should not be given to patients with uveitis and retinopathy due to the reported retinal degeneration in animal studies.<sup>11</sup>

The efficacy and safety profile of safinamide have been confirmed in a recent multicentric cohort study (SYNAPSES trial) and in elderly people.<sup>12</sup> Safinamide has demonstrated good tolerability in various randomized, controlled, and observational trials. Most adverse events are related to its dopaminergic activity and are common with other dopaminergic drugs.

## Methods

To gather relevant information, a thorough search was conducted on PubMed, focusing on studies published between 2018 and 2023 in English.

The search strategy revolved around the implementation of MeSH terms related to safinamide and its impact on the quality of life (QoL) in PD. For further insights, see [Table 1](#), which provides a comprehensive overview of the search strategy employed.

The inclusion criteria encompassed clinical trials, randomized controlled trials, systematic reviews, meta-analyses, and reviews. Detailed information about the studies is shown in [Table 2](#).

**Table 1** Details of the Search Strategies

Database	Search Terms	Filters	Results
PubMed	"Efficacy of Safinamide in quality of life in PD patients" and "Safinamide efficacy in non-motor symptoms"; MESH strategy was "Parkinson's disease" and "Safinamide".	2018–2023 (5 years) full-text, clinical trials, meta-analysis, randomized controlled trials, systematic reviews, reviews, English, humans.	31

**Abbreviation:** MESH, Medical Subject Headings.

**Table 2** Characteristics and Results of the Studies Included in This Review

Author	Year	Study Design	Treatment	Objectives	Follow-Up	Outcome	Test Used
Martí-Andrés et al	2019	Multicenter retrospective cohort study	Safinamide dose was 50 mg/day during the first month, and then increased to 100 mg/day as add-on therapy to $\pm$ COMT-DA, and L-dopa	Assess clinical effect of safinamide on motor and NMS of 213 PD patients using the CGI-C	2 months	Safinamide is an effective and safe drug add-on to levodopa drug for PD patients	CGI-C
Geroïn et al	2020	Prospective observational study	Safinamide starting with 50mg/day, and increasing up to 100mg as add-on to levodopa therapy	Effects of safinamide on pain in 13 patients with PD	Basal and 12 weeks after	Safinamide improved pain	UPDRS part II, III, and IV, PDQ-39, and CGI-C scales
Cattaneo et al	2020	Research report	Safinamide 100mg/day as add-on to levodopa and other anti-PD therapies	Effects of safinamide (352 patients) on daily OFF and ON time in the overall population and in subgroups; on PD symptoms severity and QoL. Data obtained from the 018 study	2 years	Safinamide demonstrates notable improvements in both QoL and activities of daily living, while also maintaining its efficacy over the long term.	UPDRS part II, III, and IV, and PDQ-39 scales
Abbruzzese et al	2021	Review	Safinamide (From 50 to 200 mg/day) as add-on to DA and levodopa	Efficacy and safety of Safinamide	PubMed search in September 2020	Safinamide has the potential to significantly enhance the QoL for patients.	UPDRS part II, III, IV, PDQ-39, CGI-C, and HAM-D scales
Grigoriou et al	2021	Observational, multicenter, open-label, pilot study	Safinamide 50 mg/day and up titrated to 100 mg/day in patients with previous levodopa treatment	Efficacy of safinamide on NMS and its burden in PD patients with motor fluctuations after 6 months of treatment	6 months	Safinamide may have a beneficial effect on pain	NMSS, KPPS, HADS, PDQ-8, PDSS-2, EQ-5D-3L, CGI-I, PGI-C, UPDRS part III and IV.
Sharaf et al	2022	Systematic review	Safinamide 50 mg and 100 mg/day in monotherapy and add on levodopa	Efficacy of Safinamide in the management of PD	Ten years review	Safinamide has benefits for motor and NMS	UPDRS part II, and III, PDQ-39 CGI-C, and HAM-D scales
Tsuboi et al	2022	Systematic review	Safinamide 50 and 100 mg as add-on therapy	Effects of MAO-BIs on NMS, and QoL in PD	Variable	MAO-BIs may potentially improve depression, sleep disturbances, and pain	UPDRS part II, III, IV, NMSS PDQ-39, PDSS-2, ESS, KPPS, SCOPA-AUC, MoCA, and HAM-D scales
De Masi et al	2022	Observational study	Safinamide 50 mg/day for two weeks and then increased to 100 mg/day as add-on to $\pm$ COMT, and $\pm$ DA	Explore the effect of safinamide treatment on NMS and QoL in motor-fluctuating PD patients	6 months	Beneficial effect of safinamide on motor and NMS, also improving QoL of PD patients	UPDRS part III and IV, NMSS, PDQ-39, PDFS-16, KPPS, ESS, PSQI and BDI-II

Hattori et al	2022	Post-hoc analysis	Safinamide doses of 50mg and 100mg, as add-on therapy to a stable dose of Levodopa	Impact of safinamide on depression and apathy when administered as add-on to levodopa in Japanese patients with PD	24 weeks	Safinamide could improve mild depression, pain during the OFF, and provide particular benefits for patients with PD who have mild apathy and female sex	PDQ-39, UPDRS part I, III, and IV
Pauletti et al	2023	Observational prospective study	Safinamide 50 mg/day for 15 days, then up titrated to 100 mg/day as add-on to levodopa	Impact of safinamide in fatigue improvement in 39 fluctuating PD patients	Basal and after 24 weeks	Over 40% of patients reported the complete absence of fatigue during the follow-up period	UPDRS part III, PDQ-39, FSS, and PFS-16 scales

**Abbreviations:** CGI-C, Clinical Global Impression of Change Scale; UPDRS, Unified Parkinson's Disease Rating Scale; PDQ-39, Parkinson's Disease Questionnaire; HAM-D, Hamilton Depression Rating Scale; NMSS, NMS Scale; KPSS, King's Pain Scale for Parkinson's Disease; HADS, Hospital Anxiety and Depression Scale; PDQ-8, Parkinson's Disease Quality of Life Questionnaire; PDSS, Parkinson's Disease Sleep Scale; EQ-5D-3L, EuroQol-5D 3 level version; PGI-C, Patient Global Impression of Change; ESS, Epworth Sleepiness Scale; SCOPA-AUT, Scales for Outcomes in Parkinson's disease-Autonomic dysfunction; MoCA, Montreal Cognitive Assessment; PSQI, Pittsburgh Sleep Quality Index; BDI-II, Beck Depression Inventory-II; FSS, Fatigue Severity Scale; PFS-16, Parkinson Fatigue Scale-16; DA, dopamine agonists; COMT-I, catechol-O-methyl transferase inhibitor.

## Safinamide and Motor Fluctuations

Most randomized controlled studies have consistently demonstrated that safinamide as an add-on therapy provides a substantial and maintained increase in the daily on time without troublesome dyskinesia in PD patients with motor fluctuations. In addition, in a retrospective analysis, Martí et al described an improvement in motor (80.4%) and NMS (32.5%) assessed by the CGI-C scale in PD patients after switching from rasagiline to safinamide, indicating that safinamide could elicit an additional motor benefit in PD patients treated with rasagiline and suboptimal motor control.<sup>13</sup>

A recent meta-analysis reported that safinamide as an add-on therapy to levodopa improved motor fluctuations in PD, with favorable tolerability and good adherence to treatment. The analysis assessed the impact of safinamide using three quantifiable measures: daily “on-time without troublesome dyskinesia”, daily “off-time”, and modifications in the UPDRS part III score. Notably, at 100 mg per day, safinamide elicited a significant improvement in all three parameters.<sup>14</sup> These findings provide additional evidence to support the effectiveness of safinamide in managing motor fluctuations in PD.<sup>15</sup> Considering the significant impact of motor fluctuations on patients’ QoL evaluation, safinamide seems to be a good strategy for treating PD patients in the early and advanced stages of the disease.

## Effect of Safinamide on Non-Motor Symptoms

NMS encompass a variety of conditions such as depression, psychosis, apathy, pain, sleep disorders, and urinary dysfunction.<sup>15</sup> These symptoms are considered inherent to the disease, but in some cases, can be exacerbated by dopaminergic treatment. They are not easily recognized in the clinical practice, particularly by general neurologist practitioners and their treatment is challenging.<sup>16</sup> Due to the NMS’s impact on the QoL of patients, most clinical trials include changes the NMS scale as a major primary clinical outcome.

One of the most commonly used scales for NMS in PD is the NMSS. It evaluates a wide range of NMS categorized into nine domains: cardiovascular (2 items), sleep/fatigue (4 items), mood/cognition (6 items), perceptual problems/hallucinations (3 items), attention/memory (3 items), gastrointestinal tract (3 items), urinary (3 items), sexual function (2 items), and miscellaneous (4 items).<sup>17</sup>

The observational VALE-SAFI study reported that safinamide produced a marked and sustained decrease in the NMS global score among PD patients, along with a significant decrease in the PDQ-39 global score, indicating an enhancement in PD patients’ overall QoL.<sup>18</sup> Furthermore, it was observed that safinamide, even at the dose of 50 mg/day and reinforced at 100 mg/day, exhibited improvements in specific NMS such as pain, sleep disorders, and mood, whether associated with or independent of motor fluctuations.<sup>19</sup>

## Effect of Safinamide on Quality of Life

Extensive investigation has assessed the effectiveness of safinamide in improving various aspects of QoL in patients with PD. The assessment of HRQoL in PD can be accomplished using the UPDRS part II scale and the PDQ-39 summary index score.<sup>20</sup> The PDQ-39 is a patient-reported outcome measure that specifically targets the disease and comprises 39 questions covering eight health dimensions: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily pain.<sup>21</sup> It is widely recognized as the most extensively utilized questionnaires for evaluating HRQoL in PD and provides valuable insights into the severity of NMS, which is known to have a negative impact on HRQoL. Additionally, PDQ39 questionnaires’ can be used to monitor the patient’s response to specific treatment and disease progression.<sup>20</sup>

In a meta-analysis, Abdelalem et al found that safinamide was superior to placebo in enhancing the QoL of PD patients. This improvement was demonstrated using different tools, including the UPDRS II scale, the PDQ-39 questionnaire, HAM-D, and the Mini-Mental State Examination (MMSE).<sup>14</sup>

Similarly, Giossi et al reported an increased PDQ-39 score in PD patients receiving 100 mg of safinamide.<sup>22</sup> Furthermore, Borgohain et al documented highlighting improvements in the PDQ-39 score and other QoL measures such as emotional well-being, communication, and physical comfort after adding 100 mg per day of safinamide compared to placebo.<sup>23</sup> In the study performed by Cattaneo et al involving 352 patients, the effect of safinamide added to levodopa on daily OFF and ON times was assessed. In this study, patients treated with safinamide showed a significant improvement in the PDQ39 summary index score with a −4.07 point score reduction, while the reduction in

the placebo group was  $-1.03$  points.<sup>20</sup> Finally, Martí-Andrés et al enrolled 213 patients diagnosed with PD and observed a significant improvement (76.4%) in the CGI-C score when evaluating the impact of safinamide on both motor symptoms and NMS as a whole. Regarding NMS, there were no statistically significant differences in CGI-C scores among the final doses of safinamide (determined through Fisher exact test,  $p = 0.139$ ); however, it is important to note that this study was conducted retrospectively. The authors concluded that safinamide is an effective and safe addition to levodopa therapy in PD, supporting patients' optimal adherence to treatment in real-world scenarios.<sup>13</sup>

## Effect of Safinamide on Neuropsychiatric Symptoms

Among neuropsychiatric manifestations, depression, anxiety, and cognitive decline are the more frequent and disabling NMS of the disease. They occur at every stage of the disease, but are more prevalent in advanced stages. Depression affects more than 80% of the patient population and, as reflected by numerous studies, has a highly negative impact on patients' QoL. Results from numerous clinical trials indicate that dopamine replacement elicits a marginal improvement in depression scores in PD patients. In addition, molecular neuroimaging techniques with Positron Emission Tomography (PET) have revealed that depression in PD is characterized by an upregulation of serotonergic receptors (SER) in specific structures of the brainstem and limbic system; which reflects a lower availability of serotonin in the synaptic cleft that may have some influence in the pathophysiology of this symptom in PD patients.<sup>24</sup> The MAO-B inhibitor rasagiline failed to improve depressive symptoms in PD patients without cognitive dysfunction, thus further supporting the notion that in PD, dopamine is not involved in depression and warranting the use of drugs acting on other neurotransmitter system to control depression in these patients.<sup>25</sup>

Interestingly, in addition to enhancing the striatal dopamine content, safinamide has the potential to modulate glutamate release from the cortico-striatal pathway, and hypothetically might contribute to alleviating depressive symptoms.<sup>26</sup> Furthermore, anxiety, another commonly observed NMS in PD with a significant impact on QoL, might share a similar pathophysiological mechanism as depression.

In a systematic review and meta-analysis, Abdelalem et al showed that safinamide was superior to placebo in improving the HAM-D scale, a score widely used for assessing depressive symptoms in most settings.<sup>14</sup> These results were, subsequently confirmed by Borgohain in a similar study, with safinamide superior to placebo in increasing HAM-D scores over a 24-week period.<sup>23</sup>

The 016 and 018 (extension study) studies showed the superiority of safinamide in comparison to placebo regarding the HAM-D scores and the emotional well-being subscore of the PDQ-39.<sup>27</sup> However, Borgohain et al reported that these benefits were evident with 100 mg of safinamide but not with lower doses.<sup>23</sup> Furthermore, a post hoc analysis of the 016 and 018 studies confirmed a clear effect of 100 mg of safinamide on depression.<sup>27</sup>

Hattori et al did a post-hoc analysis of data from II and III-phase clinical trials, and reported that safinamide exhibited significant improvement in patients with PD experiencing wearing-off symptoms, regardless of whether they received the 50 mg or 100 mg dose.<sup>28</sup> The initial study focused on evaluating changes in the UPDRS Part I item 3 score (depression) and item 4 (apathy), as well as the PDQ-39" emotional well-being.<sup>29</sup> Notably, reductions in depression were associated with changes in daily ON-time of at least 1 hour, the presence of pain during the OFF-time at baseline, and female sex.<sup>28</sup>

Several studies have described that cognitive dysfunction in PD is due to cholinergic neurotransmitter impairment.<sup>30</sup> This fact might account for the lack of cognitive improvement after imitating levodopa therapy and explain the cognitive benefit provided by cholinesterase inhibitors like rivastigmine. On the other hand, there is some evidence that has described improvement of frontal executive functions in PD patients with mild cognitive impairment under rasagiline therapy, but the rest of the cognitive domains remained unchanged. These results were explained by the increased frontal dopamine content created by rasagiline.

De Micco et al assessed the effect of 50 mg of safinamide on cognitive and behavioral symptoms over a 6-month period of treatment. Safinamide induced benefit was assessed by changes in the MoCA score range (0–30 points) and the PD Cognitive Rating Scale (PD-CRS) score range (0–134 points) that evaluate global cognitive functioning. However, the results of neuropsychological evaluations did not indicate any significant changes in global cognitive functioning or the five cognitive subdomains when comparing the follow-up period to the baseline assessment.<sup>16</sup>

Additionally, the results from the VALE-SAFI study in PD patients indicated that safinamide improves the irritability component accompanying the depressive episodes.<sup>18</sup>

## Effect of Safinamide on Pain

Pain is a frequent complaint among individuals with PD.<sup>26</sup> It is very frequently observed in fluctuating PD patients during OFF periods, and in these circumstances, it improves with strategies that provide more continuous dopamine stimulation (studied with levodopa and levodopa-carbidopa).<sup>31</sup> However, other central dopamine-independent mechanisms can be involved in the appearance of pain. Safinamide has been recognized for its analgesic properties, which are attributed to its dual modulation of dopaminergic and glutaminergic pathways.<sup>32</sup>

A comprehensive systematic review and meta-analysis have evaluated the analgesic benefit of several PD therapies, including safinamide, cannabinoids, COMT inhibitors, dopaminergic agonists, and others, and concluded that safinamide was superior to other treatments for relieving pain in PD.<sup>33</sup>

In a study conducted by Geroin et al involving 13 patients, safinamide significantly reduced pain as assessed by various measures, including the KPPS, Brief Pain Inventory (BPI) intensity and interference, and Numeric Rating Scale (NRS). A notable proportion of patients (7 out of 13) exhibited a responder status with an NRS improvement of more than 50%.<sup>34</sup>

Similar results were observed in the study by Grigoriou et al where a wide range of NMS, including pain, were assessed, and it was found that safinamide significantly reduced the KPPS score.<sup>35</sup> Pain improvement was also described in the post-hoc analysis of several clinical trials.<sup>20</sup>

In a large double-blind, placebo-controlled randomized controlled trial (RCT), advanced PD patients receiving safinamide 100 mg demonstrated significant amelioration of pain compared to placebo based on the PDQ-39 bodily discomfort subscore.<sup>23</sup> Additional open-label studies also reported positive outcomes based on the KPPS, indicating that safinamide 100 mg improves fluctuation-related pain.<sup>36</sup> All these data indicate that safinamide improves pain in PD patients, probably due to a central mechanism linked to the modulation of calcium channel activity induced by safinamide.

## Effect of Safinamide on Fatigue

Fatigue is characterized by a profound lack of energy and increased effort for performing common daily activities, it is one of the most common and disabling NMS of PD, and it is independent of others like apathy and sleep disorders.<sup>37</sup> Up to 37% of de novo PD patients and 50% of treated PD subjects suffer from fatigue. The severity of the disease, but not the degree of decreased striatal tracer uptake in the DAT-scan imaging, are associated with fatigue scores. Functional neuroimaging PET studies using the serotonin tracer 11C-DASB have reported decreased tracer binding in the striatum and limbic structures in PD patients with fatigue as compared with controls and no fatigue PD patients. However, both groups of PD patients exhibit similar decreased striatal uptake in the F-dopa PET, and dopamine replacement does not improve fatigue in PD patients.<sup>38</sup> All these data do not support the role of dopamine in the genesis of fatigue. However, a sub-analysis of the ADAGIO study that enrolled 1105 early PD patients demonstrated that the MAOB inhibitor rasagiline (1 and 2 mg) produced a lower deterioration of PFS scores than placebo. As motor scores and motor fluctuations also improved in the rasagiline treated arm, the effect on fatigue has been attributed to the better motor outcome of the rasagiline-treated patients.<sup>39</sup>

Pauletti et al assessed the benefit of safinamide as an add-on therapy for fatigue. They included 39 PD patients experiencing fatigue and motor fluctuations. The study found a significant improvement in fatigue scores after 24 weeks of safinamide treatment. Both FSS (pre:  $5.1 \pm 1.4$ , post:  $4.2 \pm 1.6$ ;  $p < 0.001$ ) and PFS-16 (pre:  $3.5 \pm 0.9$ , post:  $3.2 \pm 0.9$ ;  $p = 0.02$ ) were significantly reduced.<sup>40</sup> Furthermore, this study reported that the beneficial effect on fatigue was maintained for at least 6 months. Remarkably, over 40% of patients experienced a complete absence of fatigue at follow-up, suggesting that drugs like safinamide, which interact with multiple neurotransmission systems, have the potential to reduce this symptom and improve QoL. The multifactorial nature of PD-related fatigue suggests that dysfunction in the glutamatergic system may be a contributing factor to its development.<sup>40</sup>

Similar results found by De Micco et al who described a significant alleviation of fatigue when safinamide was added. The study demonstrated a large effect size, indicating the positive impact of safinamide on fatigue levels in PD patients.<sup>16</sup>

Additionally, the outcomes of the SAFINONMOTOR study supported the effectiveness of safinamide in improving fatigue scores in PD patients.<sup>41</sup> Consequently, safinamide holds promise as a potential treatment option for managing fatigue in individuals with PD.

## Effect of Safinamide on Sleep

Sleep disturbances are a prevalent and troubling NMS experienced by individuals with PD. These disturbances can manifest at any stage of the disease, but typically worsen as the disease progresses and exert an undesirable impact on the QoL of individuals with moderate and advanced stages of the disease.<sup>42</sup>

In the VALE SAFI study, De Masi et al examined sleep quality using the PSQI, a questionnaire consisting of 19 self-assessment questions that collectively form 7 component scores. These components include subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The study revealed a significant decrease in the global score of the PSQI from baseline to follow-up, indicating an improvement in sleep quality.<sup>18</sup>

SAFINONMOTOR was a groundbreaking prospective study designed to evaluate the impact of safinamide on sleep quality and daytime sleepiness, as well as on NMS. The study proved that after one month of safinamide treatment at a dosage of 50 mg/day, significantly improved both sleep and daytime sleepiness. However, no additional improvement was observed with a higher dosage (100 mg/day).<sup>43</sup>

Finally, Liguori et al, studied the effects of safinamide on patients' sleep quality and daytime sleepiness using the PDSS2, PSQI, and ESS. They showed a significant reduction in PDSS2 and ESS scores in patients treated by safinamide.<sup>44</sup>

## Effect of Safinamide on Autonomic Dysfunction

Autonomic dysfunction is manifested by excessive sweating, orthostatic hypotension, and urinary or sexual symptoms. It is particularly prevalent and more pronounced in advanced stages of the disease, although some authors consider that these symptoms could be the first manifestation of the disease, and can precede the motor manifestations of the disease.<sup>45</sup> The prevalence of these symptoms varies along the course of the disease, with a higher frequency in advanced stages (ranging from 24% to 96%).<sup>46</sup> Among these symptoms, nocturia is the most commonly reported in individuals with PD, and has a marked impact on sleep quality and daily functioning.<sup>45</sup>

In 2021, a small retrospective study examined the impact of safinamide on urological symptoms in PD patients and found that safinamide as an add-on therapy led to improvements in urological symptoms.<sup>47</sup>

In a small single-center, open-label, prospective study conducted on advanced PD patients, safinamide 50 mg demonstrated improvements in overall autonomic symptoms based on the SCOPA-AUT after 6 months.<sup>16</sup>

Similarly, a large single-center, open-label, retrospective study revealed that safinamide 100 mg reduced the urinary problems subscore of the SCOPA-AUT scale after 3 months.<sup>47</sup>

Furthermore, in a multicenter, open-label, prospective study focusing on PD patients with a high non-motor burden, safinamide 100 mg showed positive effects on autonomic symptoms as assessed by the subscore of the NMSS.<sup>36</sup>

## Conclusion

Data from the literature strongly indicate that, in addition to the improvement of motor fluctuations, safinamide markedly reduces the intensity of NMS particularly depression, apathy, and fatigue and to a lesser extent, sleep quality, which negatively influence the QoL in PD patients. The central dopaminergic and glutamatergic effects produced by safinamide might account for the alleviation of NMS in PD subjects. However, although some of the clinical benefits observed in PD patients taking safinamide have been attributed to its glutamatergic effect, more clinical research is required to confirm the usefulness of safinamide in the control of NMS and the mechanism underlying this effect. In summary, based on the data published in the literature safinamide might be the best option for PD with motor fluctuations and NMS. It remains unclear whether safinamide can be given to de novo PD patients with a high NMS burden.

## Disclosure

The authors report no conflicts of interest in this work.

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