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Review

Optimized use of safinamide as an add-on therapy in Asian patients with Parkinson's disease: a narrative review and expert opinion

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***Abstract*:** Parkinson's disease (PD) imposes a large burden on Asian countries and threatens to grow rapidly as Asian populations age. PD phenotypes in Asian patients differ from those reported in the West, yet management generally follows a similar approach. Levodopa (L-dopa) is a mainstay of therapy and is typically followed by the addition of a catechol-*O*-methyltransferase inhibitor or a monoamine oxidase-B (MAO-B) inhibitor to address the wearing-off effect. There is little guidance on switching between MAO-B inhibitors or other adjunct therapies that consider the newer evidence for safinamide as an add-on PD therapy in Asian patients. Therefore, a group of PD experts in Asia evaluated the evidence supporting safinamide for the treatment of PD with a focus on integrating this treatment option into local clinical practice. A narrative review was conducted to identify supportive evidence for the formulation of summary statements on key topics. The efficacy and safety of safinamide added to L-dopa in Asian patients with PD are supported by both clinical trials and observational data, including two randomized trials enrolling exclusively Asian patients ($n = 406$; $n = 307$) and an Asian subpopulation analysis from another randomized trial ($n = 173$). Safinamide reduces wear-off duration and has beneficial effects on motor symptoms of PD, with good tolerability outcomes. Safinamide may also have beneficial effects on non-motor symptoms of PD such as urinary symptoms, apathy and sleep disturbances, and it is a suitable treatment for older patients. Overall, safinamide is an effective and well-tolerated treatment for the wear-off effect of L-dopa in Asian patients and, during long-term treatment, might reduce the risk of dyskinesia in patients without pre-existing dyskinesia. Additional research is needed to better understand the role of safinamide for patients with fluctuating pain, the dose–effect relationship of safinamide in Asian patients and the efficacy of safinamide in Asian patients with early-onset PD.

Plain language summary

A medical research summary on how use the drug safinamide in Asian patients with Parkinson's disease

Parkinson's disease is a growing problem in Asia as populations age. The treatment approach in Asia is similar to other parts of the world, even though Parkison's disease might affect Asian patients differently. A common treatment is Levodopa (L-dopa), often combined with other drugs to address 'wear-off' effects, which occur when L-dopa stops working before the next dose.

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This article focuses on safinamide, a drug used with L-dopa to manage Parkinson's disease. Asian neurologists reviewed studies to find the best ways to use safinamide in Asian patients. Research shows that safinamide helps reduce wear-off effects, improves movement, and eases some non-movement symptoms like bladder issues and sleep problems. Safinamide is well tolerated, works well for older patients, and may lower the risk of unwanted movements (dyskinesias) in long-term treatment.

The authors recommend safinamide as an option for managing Parkinson's disease in Asian patients. However, they call for more research on its effects on pain, the right doses, and how it works for younger patients with Parkinson's disease.

Keywords: Parkinson's disease, safinamide, switching

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Introduction

The burden of PD in Asia and its clinical characteristics

Parkinson's disease (PD) is a progressive neurodegenerative disease that manifests with a classic triad of motor symptoms: tremor, bradykinesia and rigidity.[1] These are accompanied by motor complications (e.g., dysphagia, increased risk of aspiration pneumonia and choking) and non-motor symptoms (e.g., pain, cognitive impairment, sleep disorders and depression).[1–3]

The age-standardized prevalence of PD in 2019 in East Asia (145.44 per 100,000) is similar to that of Europe and high-income North America (126.01 and 107.74 per 100,000, respectively), whereas Southeast Asia has a lower regional prevalence of 99.21 per 100,000.[4] National estimates of age-standardized PD prevalence in 2016 include 90 to <100 per 100,000 in China, Taiwan and Thailand, and 70 to <80 per 100,000 in Japan and South Korea.[5] Furthermore, Asia includes several countries with very large and ageing populations, driving an increase in PD prevalence. From 2005 to 2030, the number of people with PD is forecast to increase from 1.99 to 4.94 million in China; 320,000 to 690,000 in India and 90,000 to 250,000 in Indonesia.[6] In South Korea, from 2006 to 2018, the incidence of PD increased from 0.56 to 1.34 per 1000 person-years, and the prevalence in those aged ⩾50 years is 0.4%.[7] The ageing population of the region is likely to be the predominant cause of these increases, but improved diagnosis and knowledge of PD among healthcare professionals and the general public may also contribute.[8] Other factors that potentially contribute to the rise in prevalence include exposure to pesticides, air pollution and temperature extremes.[8–10] Genetic risk factors for PD mostly overlap between Asian and European populations, although several Asian-specific risk loci have been identified.[11]

Limited data are emerging that suggests that PD phenotypes vary by ethnicity. Limited data suggest that Asian patients with PD have differences compared with non-Asian populations in mortality risk, as well as in motor- and non-motor PD symptoms (Table 1).[12–29] Notably, Asian patients may be more likely to experience dyskinesia than non-Asian patients, potentially as a result of dopamine saturation, which has led to recommendations for lower dopaminergic drug dosages in this population.[12]

In addition to differences in PD phenotypes between Asia and other regions, additional challenges to management of PD in Asia include the limited availability of neurologists experienced in movement disorders and specialist nurses in some countries.[8] Due to geography, patients may have limited access to specialized treatment centres, and the latest treatment options may not be available outside larger cities.[8] The affordability and acceptability of device-aided therapies also pose a barrier in lower-income countries.[8]

Table 1. Differences in PD phenotypes between Asian and non-Asian populations.

Phenotype	Comparison in Asian patients vs other ethnicities with PD
Mortality risk	↔Unclear. Some studies show lower risk in Asian patients, but others show contrasting results.[16,20,26]
Freezing of gait	↑ Asian patients may be more susceptible.[28]
GI symptoms	↑ More common in Asian patients. Prevalence of GI symptoms is higher in Asian studies vs other regions.[12,14,18]
Depression, sadness or low mood	↑ More common in Asian patients. Depression is more commonly reported in Asian studies vs United States or United Kingdom studies.[12,14,15,18,23]
Daytime sleepiness	↓ Less common in Asian patients. A lower prevalence of daytime sleepiness is reported in studies in Asia vs North America and Europe.[12,13,17,19,21,22,24,25,27,29]
Dyskinesia	↑ More likely in Asian patients.[12]

Source: Adapted from Willis et al.,[26] Lo et al.,[20] Fernandez and Lapane,[16] Yu et al.,[28] Li et al.,[18] Cheon et al.,[14] Ben-Joseph et al.,[12] Duncan et al.,[15] Romenets et al.,[23] Lin et al.,[19] Setthawatcharawanich et al.,[24] Yu et al.,[27] Tan et al.,[25] Brodsky et al.,[13] Hobson et al.,[17] Ratti et al.,[22] Zhu et al.[29]
GI, gastrointestinal; PD, Parkinson's disease.

Pharmacological treatment of PD with L-dopa, COMT inhibitors and MAO-B inhibitors

The symptoms of PD are caused by the loss of dopamine-producing neurons in the substantia nigra, partly through the intracellular accumulation of aggregated α-synuclein (Lewy bodies).[1] The cornerstone of PD management is dopamine replacement therapy with oral precursor levodopa (L-dopa), usually in combination with agents (e.g., carbidopa) to inhibit peripheral metabolism.[1,30] Although effective as a first-line therapy for PD, L-dopa has a short half-life and can be subject to variable gastrointestinal absorption that causes fluctuations in treatment effectiveness both on a daily basis and over the longer term.[30–32]

Fluctuations in L-dopa's effectiveness, especially the wearing-off of drug effects over the course of a day, are problematic for patients' symptom control and often deteriorate over the course of the disease as patients develop reduced responsiveness to L-dopa.[30] Studies of this phenomenon refer to the duration of symptom control with medication as ON-time and the period without symptom control as OFF-time.[1]

Symptoms of wearing-off include tremor, gait changes and rigidity, and triggers associated with the phenomenon include stress and anxiety or depression.[33] Common non-motor symptoms of wearing-off reported in Chinese patients with PD include pain and aches; other non-motor symptoms may include fatigue, mood changes or restlessness.[34] In a study of 1385 Chinese patients with PD, the overall prevalence of wearing-off was 55.1%, increasing from 12.9% in patients with disease duration ⩽1 year to 76.2% in patients with 10–15 years of disease duration.[35] Recent data comparing subjective clinician-observed and subjective patient-reported measures of dyskinesia suggest that there are cultural differences in the perception of wearing-off in patients with PD.[36] Notably, the perception severity index of wearing-off in Chinese patients was higher than those of other languages, suggesting that these patients perceived their symptoms to be more severe than what clinicians' objective measurements indicated.[36]

Solutions to wearing-off include slower-release formulations of L-dopa (oral, intestinal gels, subcutaneous pumps) and add-on therapies of different classes (e.g., dopamine agonists, catechol-*O*-methyltransferase (COMT) inhibitors and monoamine oxidase-B (MAO-B) inhibitors) to enhance or prolong the duration of symptomatic effect of L-dopa.[1,37] The selective nature of the dopaminergic deficit in PD (substantia nigra but not ventral tegmental area), as well as the dynamics of the disease over time, places patients at risk of

complications from dopamine replacement therapy, including dyskinesia, gastrointestinal side effects, impulse control disorders (ICDs), somnolence, hallucinations, hypotension and others.[9,30,38,39]

COMT is expressed both peripherally and in the central nervous system. When functioning normally, COMT methylates L-dopa, preventing it from exerting its effects on motor function, and its methylation product competes with L-dopa for transport across the blood–brain barrier.[32] Three COMT inhibitors have been developed for the treatment of PD: entacapone, tolcapone and opicapone.[32] The effectiveness of COMT inhibitors in prolonging the duration of L-dopa's effects has been demonstrated in randomized clinical trials (RCTs), and reductions in daily OFF-time of approximately 1 h/day have been observed for members of this drug class.[31,32] A review of trial data on the impact of adding COMT inhibitors on L-dopa pharmacokinetics suggested that opicapone may be more efficacious than entacapone or tolcapone in terms of changes of L-dopa plasma concentrations.[40] Reported adverse events (AEs) associated with COMT inhibitors include dyskinesia, diarrhea and hepatotoxicity (for tolcapone).[31] The dosing of these agents varies in complexity from once daily with opicapone to thrice daily with tolcapone.[32]

MAO-B acts at the outer mitochondrial membrane in striatal glial cells to catalyse the oxidation of neurotransmitters, including dopamine, and three selective MAO-B inhibitors have been developed for the treatment of PD.[32] This class comprises selegiline and rasagiline, which are irreversible inhibitors of MAO-B, and safinamide, a reversible MAO-B inhibitor.[32] In addition to reversibility, safinamide is distinguished from other class members by having both a dopaminergic effect and an anti-glutamatergic effect, with animal model data showing it modulates excessive glutamate release, although the clinical relevance of the latter is unclear.[32,38] Clinical trials of safinamide have demonstrated modest benefits on PD motor symptoms with selegiline and rasagiline as monotherapy, and all three have shown beneficial effects on motor symptoms when added to L-dopa.[32] Nausea has been reported in clinical trials of all MAO-B inhibitors members, but other AEs vary among the class.[32] For example, insomnia has been associated with both rasagiline and selegiline, bradycardia and hypotension have been associated with selegiline, and light-headedness and headache have been reported in studies of rasagiline.[32] In studies of safinamide, dyskinesia and hallucinations have been reported as the main side effects.[32]

Understanding the clinical differences between MAO-B inhibitors is confounded by a lack of head-to-head studies.[41] Tolerability data suggest that there is an advantage for rasagiline over selegiline, possibly due to the latter's degradation to amphetamine and methamphetamine.[42] A network meta-analysis of 31 RCTs ($n=7142$) of MAO-B inhibitors as an adjunct to L-dopa concluded that safinamide was associated with a lower incidence of AEs compared with rasagiline, but it did not find any differences in efficacy among class members.[41] However, switching from rasagiline to safinamide has been shown to improve wear-off phenomena.[43] The relative safety of safinamide in the overall treatment landscape for L-dopa wear-off in patients with PD is illustrated by a network meta-analysis of 54 RCTs, including 11 drugs in the safety analysis and 12 drugs in the efficacy analysis.[44] When ranked by surface under the cumulative ranking curve, safinamide was among the three highest-ranked drugs for low risk of discontinuation due to AEs, low risk of orthostatic hypotension and low risk of hallucination; it was also highest ranked for overall AE profile.[44] This analysis concluded that of the agents assessed, safinamide, ropinirole and pramipexole were well-balanced drugs that satisfied both safety and efficacy outcomes.[44] A notable limitation of this analysis is that the studies included were too short to evaluate ICDs,[44] which are a known risk associated with ropinirole and pramipexole.[45]

Switching between MAO-B inhibitors may be needed to personalize therapy, improve symptom control, reduce wear-off phenomena and minimize adverse effects of therapy.[43,46,47] There are no formal guidelines on whether to switch between MAO-B inhibitors or to another class of adjunct therapy in L-dopa–treated patients who experience wearing-off phenomenon, and patterns of clinical practice for treating PD vary considerably by region.[48] A 2015 publication summarized expert perspectives on the diagnosis and management of wearing-off in Asian patients; however, safinamide was not available in Asia at the time of its publication.[34]

Methods

This narrative review and expert opinion summarizes the findings of a meeting of Asian neurologists who sought to review recent evidence supporting safinamide for the treatment of PD and explore how this treatment option may be better integrated into clinical practice for Asian patients. A committee of experts from South Korea, Taiwan and Thailand was selected based on criteria including long-term clinical experience and training in PD and movement disorders, and their research and publication history. The committee assessed data compiled from a targeted literature search summarizing clinical trials and real-world experience with safinamide. The PubMed database was queried for English-language publications (January 1, 2014–December 31, 2023) including the term "safinamide," which was further screened for relevance, language and to exclude publications describing preclinical research, animal studies, use of safinamide in indications other than PD and other off-topic results (Supplemental Figure S1). This yielded a core set of 29 publications, including two RCTs of safinamide in Asian populations, one RCT with an Asian population subanalysis, and three reviews/expert opinion publications discussing the adjunct therapies for wear-off in Asian patients with PD. Evidence was presented and discussed, and opinion summary statements were formulated during the meeting. The results are disclosed herein.

Efficacy and safety of safinamide in clinical trials: what clinicians need to know

Pivotal data showing the efficacy and safety of safinamide (primarily) in Asian patients can be found in three phase III RCTs: ME2125-3, XINDI and SETTLE.[49–51] In ME2125-3, Japanese patients with PD ($n = 406$) with wearing-off on L-dopa were randomized to add-on placebo, safinamide 50 mg/day or safinamide 100 mg/day for 24 weeks.[51] The change in baseline in mean daily ON-time with no or non-troublesome dyskinesias (primary endpoint) was 1.39 and 1.66 h compared with placebo in the 50 and 100 mg/day groups ($p = 0.0002$ and $p < 0.0001$, respectively, vs placebo).[51] A post hoc analysis of ME2125-3 found beneficial effects of safinamide on depression and pain, noting that safinamide may particularly benefit female patients and those with mild apathy.[52] Another post hoc analysis concluded that safinamide effectively improved wearing-off episodes without inducing marked dyskinesia, and it improved motor symptoms irrespective of dyskinesia presence or absence at baseline.[53]

In XINDI, a phase III multicentre study, the efficacy and safety of safinamide as an add-on to L-dopa was evaluated in Chinese patients ($n = 307$) with PD and motor fluctuations.[49] Patients were randomized to placebo or safinamide 50 mg/day and subsequently increased to 100 mg/day on day 15.[49] The primary endpoint was the change from baseline to week 16 in the mean daily OFF-time.[49] At week 16, mean daily OFF-time was 1.10 h shorter in the safinamide group ($p < 0.0001$ vs placebo); assessment of secondary endpoints found improvements in several subscales of the 39-item Parkinson's Disease Questionnaire (PDQ-39), including activities of daily living and emotional well-being.[49]

In the multicentre, international SETTLE study, the efficacy and safety of adding safinamide or placebo to the regimen of L-dopa–treated patients ($n = 549$, including 173 (32%) Asian patients) with motor fluctuations >1.5 h/day were assessed over 24 weeks.[50] The primary endpoint was the change in mean daily ON-time without troublesome dyskinesia from baseline at week 24.[50] Patients in the treatment group received 50 mg/day, increasing to 100 mg/day at day 14 if well tolerated.[50] Mean change in daily ON-time (primary endpoint) was +1.42 h (standard deviation (SD) 2.80; baseline, 9.30 (SD 2.41)) for safinamide, versus +0.57 h (SD 2.47; baseline 9.06, 9 (SD 2.50)) for placebo ($p < 0.001$, analysis of covariance).[50] A substudy of Asian patients in SETTLE revealed that safinamide as an L-dopa adjunct remains well-tolerated and effective, potentially especially so, in Asian patients.[54] Safinamide significantly increased daily ON-time in both Asian and Caucasian patients, and motor function (measured by the Unified Parkinson's Disease Rating Scale (UPDRS)) improved relative to placebo in Asian but not in Caucasian patients.[54] Furthermore, an analysis comparing the Chinese and non-Chinese populations of SETTLE and XINDI concluded that safinamide, compared with placebo, improved both primary (mean total daily OFF-time) and secondary endpoints in both populations to a similar magnitude.[55]

Safety assessments across ME2125-3, XINDI and SETTLE concluded that safinamide had a

favourable tolerability profile.[49–51,54] There are no RCTs comparing safinamide to an active comparator, but safinamide has been evaluated alongside other PD drugs in network meta-analyses. Sako and colleagues evaluated 12 PD drugs from four classes and concluded that safinamide (as well as several others) was a well-balanced anti-PD drug that satisfied both efficacy and tolerability outcomes.[44] Yan et al. included safinamide in a network meta-analysis comparing the adjunct use of MAO-B inhibitors with L-dopa monotherapy.[41] Combination therapy was more effective than L-dopa monotherapy as measured by the change in UPDRS III scores, with no significant differences within class members.[41] Overall, data from clinical studies show that adding safinamide is effective for reducing wearing-off phenomenon with an acceptable tolerability profile in Asian and non-Asian patients with PD treated with l-dopa.[49–51]

Effectiveness and safety of safinamide in real-world observational studies

Clinical trial data are complemented by real-world data showing the beneficial effects of safinamide on both motor and non-motor symptoms of PD. A retrospective cohort study of 20 patients in Italy investigated safinamide for motor fluctuations.[56] Statistically significant improvements were noted in motor symptom scores and in scores associated with fatigue, mood/cognition and sexual, urinary and cardiovascular function.[56] An observational prospective study of 32 patients with fluctuating PD concluded that 12 weeks of safinamide treatment was associated with improvements in executive function at the end of L-dopa dose effectiveness.[57] Pauletti et al. reported that after 24 weeks of treatment with safinamide, improvements were observed in fatigue, with >40% of patients being "fatigue-free" at the end of the study period.[58] A chart review including 46 patients with motor fluctuations treated with safinamide found that in addition to improvements in motor disability, safinamide-induced improvements in nocturnal sleep and diurnal sleepiness.[59]

In a prospective observational study in five centres in Spain, safinamide reduced scores on the Non-Motor Symptoms Scale by 38.5% over 6 months from baseline, including improvements in sleep/fatigue, mood/apathy and pain.[60] A single-centre observational study of 45 patients found that safinamide was associated with improved motor symptoms and decreased impairment of global non-motor symptoms at 6 months of follow-up.[61] Improvements in specific non-motor domains included pain, skin discolouration and oedema and sleep quality.[61] Similarly, the addition of safinamide was associated with significant improvements in pain (measured with King's Parkinson Disease Pain Scale) over a 6-month treatment period in a study of 27 patients with PD on stable doses of L-dopa.[62]

Data on safinamide's effects on apathy are conflicting; while some studies, including the ME2125-3 placebo-controlled RCT, have identified improvements in apathy associated with safinamide use,[52,60,63] a randomized placebo-controlled study that enrolled 30 patients did not find a significant effect of safinamide on apathy over 24 weeks of follow-up.[64]

Other studies suggest there are diverse non-motor benefits of safinamide, including improvements in urinary symptoms of PD, swallowing and sleep disturbances. A retrospective analysis of patients with PD treated with ($n = 32$) or without ($n = 78$) safinamide found that safinamide was associated with improvements in urinary symptoms at 1 month after initiation (compared with no improvement in the control group).[65] In a study of nine patients, analysis of swallowing using video fluoroscope imaging found that safinamide (mean treatment, 32 days) significantly improved some swallowing measures, including oral transit time and pharyngeal transit time.[2] A systematic review of 60 publications reporting the effects of MAO-B inhibitors on non-motor symptoms in PD concluded that although MAO-B inhibitors could have beneficial effects on depression, sleep disturbances, and pain, cognitive and olfactory dysfunction were unlikely to be improved.[66] MAO-B inhibitors' effects on fatigue, autonomic dysfunction, apathy and ICDs remain unclear.[66] The authors additionally noted that the studies tended to have small population sizes and varied designs, outcomes and lengths of follow-up.[66]

Commentary and recommendations on safinamide use

Expert opinion on the role of safinamide in Asian patients with PD is summarized as a set of opinion statements (Box 1); these are elaborated below. The decision to initiate safinamide should be individualized to the needs of the patient and

Box 1. Summary of expert opinion statements on safinamide in Asian patients with PD.

- Safinamide is effective in reducing OFF-time and might be effective in reducing the rate of dyskinesias in Asian patients with treated with L-dopa
- Safinamide is suitable for MAO-B inhibitor-naïve patients with PD who experience wearing-off phenomena on L-dopa
- Switching to safinamide may be a suitable approach for patients experiencing wearing-off effects with another MAO-B inhibitor
- Safinamide may be effective in improving some non-motor symptoms of PD
- Safinamide is a potential treatment option in older patients (>75 years)
- The combination use of safinamide and COMT inhibitors may be considered in carefully selected patients without dyskinesia and with appropriate monitoring
- Safinamide should be discontinued if patients experience intolerable AEs or do not experience symptomatic improvement

AE, adverse event; COMT, catechol-*O*-methyltransferase; MAO-B, monoamine oxidase-B; PD, Parkinson's disease.

should be made after consideration of comorbidities and the need to balance reductions in OFF-time and potential non-motor benefits against the risk of intolerable AEs.

Safinamide is effective in reducing OFF-time and might be effective in reducing the rate of dyskinesias in Asian patients with PD treated with L-dopa

Data from clinical studies show that safinamide, in addition to reducing OFF-time, has favorable effects on dyskinesias in Asian patients treated with L-dopa.[49–51] The subanalysis of SETTLE found that although the Asian patients in the study had a higher per-bodyweight dose of L-dopa than Caucasian patients (mean 13.09 mg/kg/day vs 10.41 mg/kg/day, respectively; $p = 0.0001$), the rate and severity of dyskinesias were lower in Asian versus in Caucasian patients (13.6%, predominantly 'mild' vs 15.3%, predominantly 'moderate', respectively).[54] These findings are notable because higher per-bodyweight doses of L-dopa are a known risk factor for dyskinesia.[67] This difference should be interpreted with caution as Asian patients in SETTLE were younger and had shorter disease duration than Caucasian patients[54]; however, the non-glutamatergic component of safinamide's mechanism of action is a potential explanation for the lower rate of dyskinesia in Asian patients.[68] In the XINDI study of Chinese patients with PD, the baseline dose of L-dopa was 8.0 mg/kg/day, and the dyskinesia rate was 11.9% versus 3.9% with placebo.[49] A significant improvement from baseline in ON-time without troublesome dyskinesia (1.07 h; $p = 0.0021$) was also noted.[49] A post hoc analysis of the long-term effects of safinamide on dyskinesia and efficacy outcomes in a 52-week phase III study in Japanese patients concluded that safinamide was associated with a short-term increase in dyskinesia but may not be associated with marked dyskinesia at 1-year follow-up in patients with pre-existing dyskinesia.[53] Safinamide was also associated with improved motor symptoms, irrespective of the presence of dyskinesia at baseline.[53]

Additional data on dyskinesia are available from studies and meta-analyses including both Asian and non-Asian patients. Study 018 was an 18-month placebo-controlled extension of a 6-month phase III study of safinamide in Indian and European patients.[69] At 24 months, an ad hoc subgroup analysis of patients with moderate-to-severe dyskinesia at baseline showed a decrease in dyskinesia (evaluated with the Dyskinesia Rating Scale) with safinamide 100 mg/day compared with placebo ($p = 0.0317$). A meta-analysis of 13 RCTs identified six studies that reported data on ON-time without troublesome dyskinesias (including SETTLE, XINDI, and ME2125-3).[70] Mean ON-time without dyskinesia was significantly improved versus placebo, with safinamide at both 100 and 50 mg/day doses and, although dyskinesia was a commonly reported AE with safinamide, it was always mild or moderate and did not require drug interruption.[70]

Adding safinamide may be preferable to adding entacapone in patients with dyskinesias; clinical experience among the experts suggested that the addition of entacapone was associated with a higher risk of AEs and dyskinesias than safinamide, an observation consistent with results of a meta-analysis of placebo-controlled RCTs.[71]

Notably, this meta-analysis, which included four trials of entacapone and two trials of safinamide, found that dopaminergic reactions occurred more frequently with entacapone than safinamide, despite a significant reduction in L-dopa doses with entacapone.[71] This meta-analysis also reported an advantage for safinamide compared with entacapone in terms of tolerability, particularly nausea, vomiting, shortness of breath, dizziness and diarrhea.[71]

Safinamide is suitable for MAO-B inhibitor-naïve patients with PD who experience wearing-off phenomena on L-dopa

When increasing L-dopa dose is undesirable, such as in patients with dyskinesia, add-on therapy (e.g., MAO-B inhibitors) may be the more appropriate choice. Local treatment guidelines in some countries (e.g., Taiwan) recognize the value of opting for combination therapy with MAO-B inhibitors and L-dopa rather than increasing L-dopa dosing, especially as the former may help to mitigate the development of dyskinesia.[72] Switching to longer-acting L-dopa formulations is an option but may only have a limited effect against wearing-off in patients with troublesome dyskinesia.[73] The approach to wearing-off should be individualized to the patient, according to the extent of wearing-off and especially the severity of dyskinesia in the patient.

Switching to safinamide may be a suitable approach for patients experiencing wearing-off effects with another MAO-B inhibitor

Switching to safinamide from another MAO-B inhibitor should be considered in patients whose wearing-off symptoms are not responding to the initial drug. It is especially important to consider a switch rather than discontinuation of add-on therapy if the patient is at risk of AEs from increasing the dose of L-dopa.

Clinical experience suggests that switching to safinamide from other MAO-B inhibitors can be performed safely. Switching is routine in clinical practice, with an Italian study of patients with PD treated with L-dopa and MAO-B inhibitors ($n = 1059$) finding that switches occurred in 18.0%, 11.0% and 4.3% of selegiline-, rasagiline- and safinamide-treated patients, respectively.[47] Package inserts recommend that at least 7 (Europe) or 14 days (United States) should elapse between the discontinuation of safinamide and the initiation of another MAO-B inhibitor, to minimize the risk of serotonin syndrome and hypertensive crisis.[74,75] Experience suggests that switching from rasagiline to safinamide is safe and is an opportunity to optimize therapy before considering advanced or second-line interventions.[43] Despite the recommendations for treatment breaks, more rapid switching is sometimes performed in clinical practice to minimize inconvenience for patients and avoid deterioration in symptom control.[76]

The safety of overnight switching from rasagiline to safinamide has been evaluated in a study of 20 patients treated with L-dopa and rasagiline.[76] Rasagiline was discontinued and safinamide was initiated and titrated to 100 mg/day after 2 weeks.[76] No cases of hypertensive crisis or serotonin syndrome were observed over the 6-week study period.[76]

Safinamide may be effective in improving some non-motor symptoms of PD

Patients with PD may experience a broad range of non-motor symptoms from the earliest stages of the disease; they may be dopaminergic or non-dopaminergic in origin and are profoundly detrimental to patients' quality of life.[77]

Data from an RCT substudy, as well as multiple observational studies, suggest that safinamide may have beneficial effects on depression and apathy,[52,60,63] fatigue,[56,58,60,63] sleep parameters[59–61] and urinary disturbances.[60,63,65] Expert opinion was that adding safinamide could improve pain, sleep, fatigue and apathy—an opinion that was generally aligned with consensus statements from Europe and Japan.[78,79]

Safinamide is a potential treatment option in older patients (>75 years)

East Asia has the largest trends among regions in the prevalence of PD, driven by population growth and aging,[4] Older patients are of particular concern in Asia, where the mean age of symptom onset is 60–69 years and PD incidence peaks at age 70–79 years.[80] In addition to being the strongest risk factor of PD, age also impacts disease severity, creating challenges for management. A study comparing 'young–old' (60–75 years) and 'old–old' patients with PD found that the latter had more

severe motor and non-motor phenotypes, global disability, higher prevalence of motor complications and heavier comorbidity burdens.[81]

Clinical experience among the experts suggested that initiating safinamide was an appropriate treatment option for older patients experiencing wearing-off effects of L-dopa. The panel preferred adding safinamide over adding dopamine agonists due to the latter's potential to induce or worsen psychosis, which is more prevalent in older patients, as well as their potential to cause drowsiness and cognitive impairment.[82]

In J-SILVER, a Japanese observational study with a mean patient age of 74.5 years ($n=24$), there was a statistically non-significant increase of 1.55 h in mean daily ON-time without dyskinesia 18 weeks after safinamide initiation and significant improvements in scores for bradykinesia ($p=0.029$), rigidity ($p=0.005$), axial symptoms ($p=0.047$) and postural instability gait difficulty ($p=0.018$).[83] A 1.55-h increase from baseline in ON-time without dyskinesia was reported but was not statistically significant ($p=0.22$).[83] Few patients in this study had dyskinesia at baseline, and duration and severity of dyskinesia did not worsen.[83] Notably, patients experienced improvements in pain as measured by an 11-point numerical rating scale (NRS, 0–10) or the King's Parkinson's Disease Pain Scale (KPPS).[83] Mean baseline total pain scores of 8.6 (KPPS) and 8.2 (NRS) were reduced by 2.6 ($p=0.25$) and 3.8 ($p=0.015$), respectively, and significant decreases in NRS scores from baseline were reported in OFF-time pain (−1.7; $p=0.012$) and nocturnal pain (−1.7; $p=0.021$).[83] Favourable changes from baseline were also reported for emotional well-being ($p=0.006$) and bodily discomfort ($p<0.001$) measured by the PDQ-39.[83]

A post hoc analysis of SYNAPSES, a 12-month observational study of safinamide in European patients with PD, found that the risk–benefit profile of safinamide was consistent between older patients (>75 years; mean, 79.7) and the overall population (mean, 68.4 years).[84,85] Non-motor symptom benefits of safinamide that may be of particular relevance to older patients include improvements in urinary symptoms and the potential for cognitive benefits,[60,63,65] although evidence for the latter is currently inconsistent. Rinaldi et al. did find benefits in attention and inhibition of cognitive interference 12 weeks after safinamide was added to L-dopa in a study of 32 fluctuating patients,[57] and Bianchi et al. reported a cognition benefit from safinamide in a study of 20 patients.[56] However, no evidence of a cognitive benefit from safinamide was found in a study by De Micco et al.[63] While the evidence for a cognitive benefit of safinamide remains uncertain, avoidance of agents with the potential to be cognitively impairing is a logical approach in the management of older patients.

The combination use of safinamide and COMT inhibitors may be considered in carefully selected patients without dyskinesia and with appropriate monitoring

Data to guide the combined use of safinamide and COMT inhibitors are scarce. Expert opinion was that this combination may help treat patients without dyskinesia, young patients with a predisposition to ICDs and sensitivity (or contraindication) to dopamine agonists or elderly patients who experience wearing-off phenomena despite treatment with COMT inhibitors alone. Patients treated with this combination would need to be closely monitored for the development of dyskinesia.

Safinamide should be discontinued if patients experience intolerable AEs or do not experience symptomatic improvement

The experts agreed that safinamide should be discontinued if patients do not experience improvements in their wearing-off or if they experience PD progression. A switch to long-acting L-dopa formulations could be a suitable alternative for such patients, but decisions should be made in accordance with best clinical judgement, the totality of the data and the needs of the individual patient. Other reasons for discontinuation include the development of intolerable AEs (e.g., dyskinesia), progression from moderate-to-severe hepatic impairment, development of daytime sleepiness or falling episodes or development of ICDs.[74]

Gaps in knowledge and opportunities for further research

The anti-glutamatergic activity of safinamide has been postulated to contribute to its beneficial effects on pain and motor symptoms and OFF-time reductions among a European expert group,[78] with which the panel generally agreed.

Additional benefits from safinamide's anti-glutamatergic activity are plausible, given that the anti-glutamatergic drug memantine has shown a limited ability to improve some aspects of PD-associated dementia.[86] Anti-glutamatergic activity is potentially beneficial for ICDs, although it is unclear whether sodium or calcium channel blockers acting on glutamatergic neurons have an effect on the mechanism underlying ICD in patients with PD. Multiple classes of anti-glutamatergic drugs have shown promising activity in experimental models of PD, but clinical evidence for them remains lacking.[87] Currently, only amantadine, with a 50-year history, is used in clinical practice for PD.[87,88]

Other opportunities for further research included understanding the role of safinamide for patients with fluctuating pain and the relationship between safinamide dose and orthostatic hypotension. A more detailed understanding of the efficacy and safety of safinamide and L-dopa in elderly patients would be valuable, including the possibility of using safinamide as monotherapy, given the desirability of simplifying treatment regimens in older patients.

Elucidation of the relationship between the dose of L-dopa and safinamide's effects would be helpful, especially considering the higher per-kilogram dose of L-dopa seen in Asian versus non-Asian patients in SETTLE.[54] Safinamide could be investigated specifically in Asian patients with early-onset disease who are at increased risk for dyskinesia; safinamide's effectiveness on dyskinesia could also be assessed in patients who are engaged in employment.

Other areas for further research include the effect of safinamide combined with dopamine agonists on the age of dyskinesia onset and disease duration, as well as the specific OFF-time symptoms that respond to safinamide treatment. Appropriate scales to assess the severity and duration of dyskinesia need to be identified, and there is room to optimize medication administration and adherence.

More broadly, there is a need for more data on how the efficacy and safety of other dopaminergic therapies may vary among patients of different ethnic backgrounds and the underlying mechanisms for these differences. A study of 51 Chinese PD patients has suggested that polymorphisms in the dopa-decarboxylase gene may affect motor response to L-dopa.[89] Polymorphisms in the CYP2C19 or CYP2B6 enzymes that metabolize selegiline lead to higher drug exposure and are found in 20% of Japanese people (compared with 5% in Caucasians), but the clinical implications of these data are unclear, and an analysis of a US Food and Drug Administration database did not identify ethnic differences in safety for any of the three approved MAO-B inhibitors.[90] A study of rasagiline pharmacokinetics and safety in Japanese and Caucasian subjects concluded that although rasagiline exposure may be higher in Japanese patients, the difference is unlikely to be clinically relevant.[91] Overall, interpreting these differences is challenging as genetic differences contribute not only to differences in drug metabolism among patients of different ethnic backgroup but also differences in bodyweight and differences in PD phenotypes.

Discussion

The narrative review and expert opinions summarized here are largely aligned with other expert opinion publications.[79] In a Delphi survey by Takeda et al., there was a high level of expert certainty regarding the benefits of safinamide on motor symptoms such as bradykinesia, rigidity, gait disorder and non-motor symptoms such as pain and depression/apathy; in the survey, there was moderate agreement that safinamide could improve dyskinesia, but the agreement was not enough to achieve consensus (⩾80% agreement).[79] A European Delphi consensus survey found an absolute (100% agreement) consensus and strong agreement on the ability of safinamide to increase ON-time without increasing dyskinesia (94%) and to increase quality of life for patients with PD (98%).[78]

The limitations of this work include the relatively small volume of evidence available on ethnic differences in response to safinamide and other dopaminergic agents, and a lack of evidence explaining these differences. The focus on data for safinamide limits the applicability of these findings to other members of the MAO-B inhibitor class. The opinions here reflect the clinical experience of the participating experts and may not be generalizable to other clinical settings.

Conclusion

Both real-world and RCT data support the safety and efficacy of safinamide in reducing OFF-time and improving motor symptoms in Asian patients with PD.[49–51,54,83] Safinamide also has beneficial effects on some non-motor symptoms of PD, notably apathy, fatigue, sleep and urinary symptoms.[52,56,58–61,63,65,83] The anti-glutamatergic effects of safinamide are thought to partly contribute to its beneficial effects, although further research is needed to distinguish between these two modes of action and how they translate into clinical benefits in patients with PD.

In summary, safinamide is likely to be an effective and well-tolerated option for add-on therapy in Asian patients with PD by reducing OFF-time and improving both motor and non-motor symptoms. It may be especially beneficial in Asian patients and older adults, given the potential for their increased sensitivity to L-dopa dosing and the potential for resultant dyskinesia and other AEs.

Declarations

Ethics approval and consent to participate

Not applicable: The meeting and manuscript involved the discussion and analysis of previously published and publicly available literature; no sensitive data were included. New research with human or animal subjects was not performed.

Consent for publication

Not applicable.

Author contributions

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Competing interests

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Availability of data and materials

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Supplemental material

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References

1. Poewe W, Seppi K, Tanner CM, et al. Parkinson disease. *Nat Rev Dis Primers* 2017; 3: 17013.
2. Hirano M, Samukawa M, Isono C, et al. The effects of safinamide on dysphagia in Parkinson's disease. *PLoS One* 2023; 18: e0286066.
3. Seppi K, Ray Chaudhuri K, Coelho M, et al. Update on treatments for nonmotor symptoms of Parkinson's disease: an evidence-based medicine review. *Mov Disord* 2019; 34: 180–198.
4. Ou Z, Pan J, Tang S, et al. Global trends in the incidence, prevalence, and years lived with disability of Parkinson's disease in 204 countries/territories from 1990 to 2019. *Front Public Health* 2021; 9: 776847.
5. GBD 2016 Parkinson's Disease Collaborators. Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2018; 17: 939–953.
6. Dorsey ER, Constantinescu R, Thompson JP, et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology* 2007; 68: 384–386.
7. Kang SH, Moon SJ, Kang M, et al. Incidence of Parkinson's disease and modifiable risk factors in Korean population: a longitudinal follow-up study of a nationwide cohort. *Front Aging Neurosci* 2023; 15: 1094778.
8. Bhidayasiri R, Sringean J, Van Le T, et al. Movement disorders in Indochina: resource challenges and future solutions. *J Neural Transm (Vienna)* 2023; 130: 875–889.
9. Mahmood A, Shah AA, Umair M, et al. Recalling the pathology of Parkinson's disease; lacking exact figure of prevalence and genetic evidence in Asia with an alarming outcome: a time to step-up. *Clin Genet* 2021; 100: 659–677.
10. Ben-Shlomo Y, Darweesh S, Llibre-Guerra J, et al. The epidemiology of Parkinson's disease. *Lancet* 2024; 403: 283–292.
11. Foo JN, Chew EGY, Chung SJ, et al. Identification of risk loci for Parkinson disease in Asians and comparison of risk between Asians and Europeans: a genome-wide association study. *JAMA Neurol* 2020; 77: 746–754.
12. Ben-Joseph A, Marshall CR, Lees AJ, et al. Ethnic variation in the manifestation of Parkinson's disease: a narrative review. *J Parkinsons Dis* 2020; 10: 31–45.
13. Brodsky MA, Godbold J, Roth T, et al. Sleepiness in Parkinson's disease: a controlled study. *Mov Disord* 2003; 18: 668–672.
14. Cheon SM, Ha MS, Park MJ, et al. Nonmotor symptoms of Parkinson's disease: prevalence and awareness of patients and families. *Parkinsonism Relat Disord* 2008; 14: 286–290.
15. Duncan GW, Khoo TK, Yarnall AJ, et al. Health-related quality of life in early Parkinson's disease: the impact of nonmotor symptoms. *Mov Disord* 2014; 29: 195–202.
16. Fernandez HH and Lapane KL. Predictors of mortality among nursing home residents with a diagnosis of Parkinson's disease. *Med Sci Monit* 2002; 8: CR241–CR246.
17. Hobson DE, Lang AE, Martin WR, et al. Excessive daytime sleepiness and sudden-onset sleep in Parkinson disease: a survey by the Canadian Movement Disorders Group. *JAMA* 2002; 287: 455–463.
18. Li HJ, Zhang MF, Chen MX, et al. Validation of the nonmotor symptoms questionnaire for Parkinson's disease: results from a Chinese pilot study. *Int J Neurosci* 2015; 125: 929–935.
19. Lin YY, Chen RS, Lu CS, et al. Sleep disturbances in Taiwanese patients with Parkinson's disease. *Brain Behav* 2017; 7: e00806.
20. Lo RY, Tanner CM, Albers KB, et al. Clinical features in early Parkinson disease and survival. *Arch Neurol* 2009; 66: 1353–1358.
21. Poryazova R, Benninger D, Waldvogel D, et al. Excessive daytime sleepiness in Parkinson's disease: characteristics and determinants. *Eur Neurol* 2010; 63: 129–135.
22. Ratti PL, Nègre-Pagès L, Pérez-Lloret S, et al. Subjective sleep dysfunction and insomnia symptoms in Parkinson's disease: insights from a cross-sectional evaluation of the French CoPark cohort. *Parkinsonism Relat Disord* 2015; 21: 1323–1329.
23. Romenets SR, Wolfson C, Galatas C, et al. Validation of the non-motor symptoms questionnaire (NMS-Quest). *Parkinsonism Relat Disord* 2012; 18: 54–58.
24. Setthawatcharawanich S, Limapichat K, Sathirapanya P, et al. Excessive daytime sleepiness and nighttime sleep quality in Thai patients with Parkinson's disease. *J Med Assoc Thai* 2014; 97: 1022–1027.
25. Tan EK, Lum SY, Fook-Chong SM, et al. Evaluation of somnolence in Parkinson's disease: comparison with age- and sex-matched controls. *Neurology* 2002; 58: 465–468.

26. Willis AW, Schootman M, Kung N, et al. Predictors of survival in patients with Parkinson disease. *Arch Neurol* 2012; 69: 601–607.
27. Yu RL, Tan CH and Wu RM. The impact of nocturnal disturbances on daily quality of life in patients with Parkinson's disease. *Neuropsychiatr Dis Treat* 2015; 11: 2005–2012.
28. Yu RL, Wu RM, Chan AY, et al. Cross-cultural differences of the non-motor symptoms studied by the traditional Chinese version of the International Parkinson and Movement Disorder Society–Unified Parkinson's Disease Rating Scale. *Mov Disord Clin Pract* 2017; 4: 68–77.
29. Zhu K, van Hilten JJ and Marinus J. Course and risk factors for excessive daytime sleepiness in Parkinson's disease. *Parkinsonism Relat Disord* 2016; 24: 34–40.
30. Lane EL. L-DOPA for Parkinson's disease: a bittersweet pill. *Eur J Neurosci* 2019; 49: 384–398.
31. Fabbri M, Barbosa R and Rascol O. Off-time treatment options for Parkinson's disease. *Neurol Ther* 2023; 12: 391–424.
32. Regensburger M, Ip CW, Kohl Z, et al. Clinical benefit of MAO-B and COMT inhibition in Parkinson's disease: practical considerations. *J Neural Transm (Vienna)* 2023; 130: 847–861.
33. Mantri S, Lepore M, Edison B, et al. The experience of OFF periods in Parkinson's disease: descriptions, triggers, and alleviating factors. *J Patient Cent Res Rev* 2021; 8: 232–238.
34. Bhidayasiri R, Hattori N, Jeon B, et al. Asian perspectives on the recognition and management of levodopa "wearing-off" in Parkinson's disease. *Expert Rev Neurother* 2015; 15: 1285–1297.
35. Wan Y, Yuan C, Hou X, et al. Wearing-off identification in Parkinson's disease: the shapd-woq study. *Front Neurol* 2020; 11: 116.
36. Kaasinen V, Luo S, Martinez-Martin P, et al. Cross-cultural differences in patient perceptions of dyskinesia in Parkinson's disease. *Mov Disord* 2023; 38: 688–692.
37. Fox SH, Katzenschlager R, Lim SY, et al. International Parkinson and movement disorder society evidence-based medicine review: update on treatments for the motor symptoms of Parkinson's disease. *Mov Disord* 2018; 33: 1248–1266.
38. Abbruzzese G, Barone P, Lopiano L, et al. The Current Evidence for the Use of Safinamide for the Treatment of Parkinson's Disease. *Drug Des Devel Ther* 2021; 15: 2507-2517.
39. O'Shea IM, Popal HS, Olson IR, et al. Distinct alterations in cerebellar connectivity with substantia nigra and ventral tegmental area in Parkinson's disease. *Sci Rep* 2022; 12: 3289.
40. Müller T. Clinical pharmacokinetics of levodopa and relevant add-on therapies for Parkinson's disease. *Expert Opin Drug Metab Toxicol*. Epub ahead of print November 2024. DOI: 10.1080/17425255.2024.2428831.
41. Yan R, Cai H, Cui Y, et al. Comparative efficacy and safety of monoamine oxidase type B inhibitors plus channel blockers and monoamine oxidase type B inhibitors as adjuvant therapy to levodopa in the treatment of Parkinson's disease: a network meta-analysis of randomized controlled trials. *Eur J Neurol* 2023; 30: 1118–1134.
42. Jost WH. A critical appraisal of MAO-B inhibitors in the treatment of Parkinson's disease. *J Neural Transm (Vienna)* 2022; 129: 723–736.
43. Sanchez Alonso P, De La Casa-Fages B, Alonso-Cánovas A, et al. Switching from rasagiline to safinamide as an add-on therapy regimen in patients with levodopa: a literature review. *Brain Sci* 2023; 13: 276.
44. Sako W, Kogo Y, Koebis M, et al. Comparative efficacy and safety of adjunctive drugs to levodopa for fluctuating Parkinson's disease—network meta-analysis. *NPJ Parkinsons Dis* 2023; 9: 143.
45. Carbone F and Djamshidian A. Impulse control disorders in Parkinson's disease: an overview of risk factors, pathogenesis and pharmacological management. *CNS Drugs* 2024; 38: 443–457.
46. Müller T, Hoffmann JA, Dimpfel W, et al. Switch from selegiline to rasagiline is beneficial in patients with Parkinson's disease. *J Neural Transm (Vienna)* 2013; 120: 761–765.
47. Ronconi G, Calabria S, Piccinni C, et al. Prescription pattern of monoamine oxidase B inhibitors combined with levodopa: a retrospective observational analysis of Italian Healthcare Administrative Databases. *Drugs Real World Outcomes* 2022; 9: 391–401.
48. Lim SY, Tan AH, Ahmad-Annuar A, et al. Parkinson's disease in the Western Pacific Region. *Lancet Neurol* 2019; 18: 865–879.
49. Wei Q, Tan Y, Xu P, et al. The XINDI study: a randomized phase III clinical trial evaluating the efficacy and safety of safinamide as add-on therapy to levodopa in Chinese patients with Parkinson's disease with motor fluctuations. *CNS Drugs* 2022; 36: 1217–1227.

50. Schapira AH, Fox SH, Hauser RA, et al. Assessment of safety and efficacy of safinamide as a levodopa adjunct in patients with Parkinson disease and motor fluctuations: a randomized clinical trial. *JAMA Neurol* 2017; 74: 216–224.

51. Hattori N, Tsuboi Y, Yamamoto A, et al. Efficacy and safety of safinamide as an add-on therapy to L-DOPA for patients with Parkinson's disease: a randomized, double-blind, placebo-controlled, phase II/III study. *Parkinsonism Relat Disord* 2020; 75: 17–23.

52. Hattori N, Kogo Y, Koebis M, et al. The effects of safinamide adjunct therapy on depression and apathy in patients with Parkinson's disease: post-hoc analysis of a Japanese phase 2/3 study. *Front Neurol* 2021; 12: 752632.

53. Hattori N, Kamei T, Ishida T, et al. Long-term effects of safinamide adjunct therapy on levodopa-induced dyskinesia in Parkinson's disease: post-hoc analysis of a Japanese phase III study. *J Neural Transm (Vienna)* 2022; 129: 1277–1287.

54. Bhidayasiri R, Ishida T, Kamei T, et al. Safinamide as an Adjunct to levodopa in Asian and Caucasian patients with Parkinson's disease and motor fluctuations: a post hoc analysis of the SETTLE study. *J Mov Disord* 2023; 16: 180–190.

55. Cattaneo C and Kulisevsky J. The effects of safinamide in Chinese and non-Chinese patients with Parkinson's disease. *Adv Ther* 2024; 41: 638–648.

56. Bianchi MLE, Riboldazzi G, Mauri M, et al. Efficacy of safinamide on non-motor symptoms in a cohort of patients affected by idiopathic Parkinson's disease. *Neurol Sci* 2019; 40: 275–279.

57. Rinaldi D, Sforza M, Assogna F, et al. Safinamide improves executive functions in fluctuating Parkinson's disease patients: an exploratory study. *J Neural Transm (Vienna)* 2021; 128: 273–277.

58. Pauletti C, Locuratolo N, Mannarelli D, et al. Fatigue in fluctuating Parkinson's disease patients: possible impact of safinamide. *J Neural Transm (Vienna)* 2023; 130: 915–923.

59. Liguori C, Stefani A, Ruffini R, et al. Safinamide effect on sleep disturbances and daytime sleepiness in motor fluctuating Parkinson's disease patients: a validated questionnaires-controlled study. *Parkinsonism Relat Disord* 2018; 57: 80–81.

60. Santos García D, Labandeira Guerra C, Yáñez Baña R, et al. Safinamide Improves non-motor symptoms burden in Parkinson's disease: an open-label prospective study. *Brain Sci* 2021; 11: 316.

61. De Masi C, Liguori C, Spanetta M, et al. Non-motor symptoms burden in motor-fluctuating patients with Parkinson's disease may be alleviated by safinamide: the VALE-SAFI study. *J Neural Transm (Vienna)* 2022; 129: 1331–1338.

62. Grigoriou S, Martínez-Martín P, Ray Chaudhuri K, et al. Effects of safinamide on pain in patients with fluctuating Parkinson's disease. *Brain Behav* 2021; 11: e2336.

63. De Micco R, Satolli S, Siciliano M, et al. Effects of safinamide on non-motor, cognitive, and behavioral symptoms in fluctuating Parkinson's disease patients: a prospective longitudinal study. *Neurol Sci* 2022; 43: 357–364.

64. Kulisevsky J, Martínez-Horta S, Campolongo A, et al. A randomized clinical trial to evaluate the effects of safinamide on apathetic non-demented patients with Parkinson's disease. *Front Neurol* 2022; 13: 866502.

65. Gómez-López A, Sánchez-Sánchez A, Natera-Villalba E, et al. SURINPARk: safinamide for urinary symptoms in Parkinson's disease. *Brain Sci* 2021; 11: 57.

66. Tsuboi T, Satake Y, Hiraga K, et al. Effects of MAO-B inhibitors on non-motor symptoms and quality of life in Parkinson's disease: a systematic review. *NPJ Parkinsons Dis* 2022; 8: 75.

67. Sharma JC, Ross IN, Rascol O, et al. Relationship between weight, levodopa and dyskinesia: the significance of levodopa dose per kilogram body weight. *Eur J Neurol* 2008; 15: 493–496.

68. Bhidayasiri R, Koebis M, Kamei T, et al. Sustained response in early responders to safinamide in patients with Parkinson's disease and motor fluctuations: a post hoc analysis of the SETTLE study. *Front Neurol* 2023; 14: 1147008.

69. Borgohain R, Szasz J, Stanzione P, et al. Two-year, randomized, controlled study of safinamide as add-on to levodopa in mid to late Parkinson's disease. *Mov Disord* 2014; 29: 1273–1280.

70. Kulisevsky J, Ferraz HB, Suppa A, et al. Effects of safinamide on motor and non-motor symptoms in patients with Parkinson's disease and motor fluctuations. *Eur Neurol*. Epub ahead of print September 2024. DOI: 10.1159/000541362.

71. Schnitker J and Müller T. Meta-analysis of placebo-controlled clinical trials of safinamide and entacapone as add-on therapy to levodopa in

the treatment of Parkinson's disease. *Eur Neurol Rev* 2015; 10: 15–22.

72. Treatment Guideline Subcommittee of Taiwan Movement Disorder Society. Evidence-based taiwan consensus recommendations for the treatment of Parkinson's disease. *Acta Neurol Taiwan* 2023; 32(3): 145–184.
73. Hauser RA, Zeitlin L, Fisher S, et al. Carbidopa and levodopa extended release capsules in patients with and without troublesome and non-troublesome dyskinesia. *J Parkinsons Dis* 2020; 10: 915–925.
74. Xadago (Safinamide) [US prescribing information]. Rockville, MD: MDD US Operations, LLC, 2021.
75. Xadago (Safinamide) [Summary of product characteristics]. Bresso, Italy: Zambon S.p.A, 2023.
76. Stocchi F, Vacca L, Grassini P, et al. Overnight switch from rasagiline to safinamide in Parkinson's disease patients with motor fluctuations: a tolerability and safety study. *Eur J Neurol* 2021; 28: 349–354.
77. LeWitt PA and Chaudhuri KR. Unmet needs in Parkinson disease: motor and non-motor. *Parkinsonism Relat Disord* 2020; 80(Suppl. 1): S7–S12.
78. Stocchi F, Antonini A, Berg D, et al. Safinamide in the treatment pathway of Parkinson's disease: a European Delphi consensus. *NPJ Parkinsons Dis* 2022; 8: 17.
79. Takeda A, Tsuboi Y, Nomoto M, et al. Collective expert perspectives on the use of safinamide as adjunctive therapy for Parkinson's disease: online-based Delphi survey. *Parkinsons Dis* 2022; 2022: 3203212.
80. Muangpaisan W, Hori H and Brayne C. Systematic review of the prevalence and incidence of Parkinson's disease in Asia. *J Epidemiol* 2009; 19: 281–293.
81. Virameteekul S, Phokaewvarangkul O and Bhidayasiri R. Profiling the most elderly Parkinson's disease patients: does age or disease duration matter? *PLoS One* 2021; 16: e0261302.
82. Latt MD, Lewis S, Zekry O, et al. Factors to consider in the selection of dopamine agonists for older persons with Parkinson's disease. *Drugs Aging* 2019; 36: 189–202.
83. Nishikawa N, Hatano T, Nishioka K, et al. Safinamide as adjunctive therapy to levodopa monotherapy for patients with Parkinson's disease with wearing-off: the Japanese observational J-SILVER study. *J Neurol Sci* 2024; 461: 123051.
84. Jost WH, Gluth I, Lück JC, et al. Real world data of a German Parkinson's disease population: effectiveness and safety of safinamide in routine clinical practice. *Curr Med Res Opin* 2023; 39: 1621–1628.
85. Abbruzzese G, Kulisevsky J, Bergmans B, et al. A European observational study to evaluate the safety and the effectiveness of safinamide in routine clinical practice: the SYNAPSES trial. *J Parkinsons Dis* 2021; 11: 187–198.
86. Wang HF, Yu JT, Tang SW, et al. Efficacy and safety of cholinesterase inhibitors and memantine in cognitive impairment in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies: systematic review with meta-analysis and trial sequential analysis. *J Neurol Neurosurg Psychiatry* 2015; 86: 135–143.
87. Carrillo-Mora P, Silva-Adaya D and Villasenor K. Glutamate in Parkinson's disease: role of antiglutamatergic drugs. *Basal Ganglia* 2013; 3: 147–157.
88. Crosby N, Deane KH and Clarke CE. Amantadine in Parkinson's disease. *Cochrane Database Syst Rev* 2003; 2003: CD003468.
89. Li L, Lin H, Hua P, et al. Polymorphism of the dopa-decarboxylase gene modifies the motor response to levodopa in Chinese patients with Parkinson's disease. *Front Neurol* 2020; 11: 520934.
90. Asano H, Tian YS, Hatabu A, et al. Safety comparisons among monoamine oxidase inhibitors against Parkinson's disease using FDA adverse event reporting system. *Sci Rep* 2023; 13: 19272.
91. Elgart A, Rabinovich-Guilatt L, Eyal E, et al. Pharmacokinetics and safety of single and multiple doses of rasagiline in healthy Japanese and caucasian subjects. *Basic Clin Pharmacol Toxicol* 2019; 124: 273–284.