Safinamide – A Unique Treatment Targeting Both Dopaminergic and Non-Dopaminergic Systems

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Dopaminergic replacement therapies are prescribed widely to improve motor problems in Parkinson's disease (PD). However, as the disease progresses, the response to levodopa (l-dopa) doses becomes shorter and patients experience symptom recurrence at the end of the dose effect. These so-called OFF periods may become refractory to treatment, and may become associated with disabling motor fluctuations or dyskinesias. In addition to dopamine, glutamate excitotoxicity, resulting from disturbance of the homeostatic balance of neurotransmitters and elevated extracellular levels of glutamate, is potentially an important therapeutic target. Safinamide has been investigated in phase III clinical trials as adjunct therapy to l-dopa in mid- to late-stage fluctuating PD. Adding safinamide to l-dopa increases the time patients' symptoms are controlled – so-called ON time, without increasing troublesome dyskinesia. Although safinamide has dopaminergic actions, recent data have suggested that the long-term effects of safinamide on dyskinesia are related to safinamide state- and use-dependent inhibition of sodium channels and stimulated glutamate release, rather than reduced dopaminergic stimulation. Safinamide's unique dual mechanism of action makes it a valuable treatment option for fluctuating PD patients.

Keywords

Dopamine, glutamate, Parkinson's disease, safinamide

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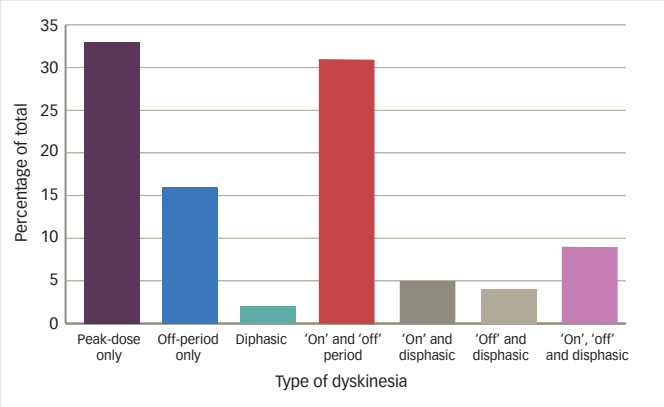
Parkinson's disease (PD) is a progressive neurodegenerative disorder, with a prevalence that increases with age: 41 in 100,000 in the age group 40–49, rising to 1,903 in 100,000 in those aged over 80 years.[1] PD is characterised by striatal dopamine deficiency resulting from progressive degeneration of dopaminergic cells in the pars compacta of the substantia nigra, the brain region responsible for motor control.[2] Symptoms of PD include bradykinesia, rigidity, tremor, gait and postural abnormalities, and speech difficulty,[3] as well as non-motor symptoms including cognitive dysfunction, mood disorders, sleep disturbance and pain.[4]

Although PD is incurable, symptoms can be alleviated using dopaminergic therapies including the dopamine precursor levodopa (l-dopa), dopamine agonists and monoamine oxidase (MAO)-B inhibitors that block dopamine degradation, thereby helping restore dopamine levels in the brain.[5,6] L-dopa is currently the standard treatment for motor symptoms in PD, but its long-term use has important limitations.[5] As the disease progresses, the response to l-dopa doses becomes shorter and patients motor fluctuations, which involve periods of being ON, during which the patient experiences a positive response to medication, and being OFF, during which the patient experiences a re-emergence of the symptoms suppressed during the ON state.[7,8] Furthermore, symptoms of PD, including gait and tremor, gradually become resistant to l-dopa.[8] Other limitations of the use of l-dopa include the fact that it does not prevent PD progression,[9] and many non-motor symptoms do not respond well to l-dopa.[9]

As well as motor fluctuations, abnormal involuntary movements, known as l-dopa-induced dyskinesia (LID), develop with prolonged use of l-dopa; these may occur at peak effect of l-dopa, at the beginning and end of dose, or between doses (see *Figure 1*).[8,10–12] These movements usually involve the face and the side of the body that is initially affected by the disease, but they commonly progress and affect the neck, upper and lower limbs, and body axis. Chorea and dystonia are the most frequent forms of LIDs, but ballismus and myoclonus can also appear.[13,14] Around 40% of patients experience motor fluctuations and LID after 4-6 years of treatment with l-dopa,[14] and 60% to 100% may experience LID after 10 years.[15,16]

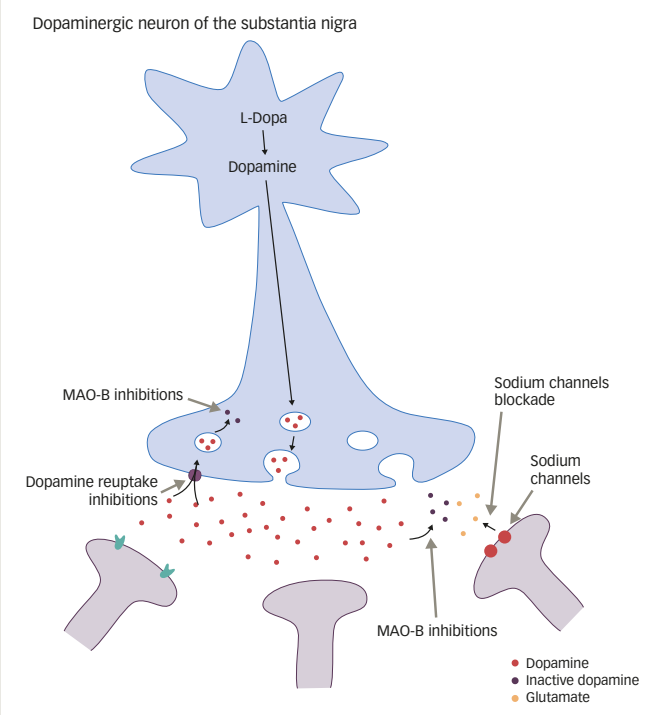
Motor fluctuations are the result of alterations of the functional organisation of the basal ganglia circuitry following long-term exposure to l-dopa. Progressive degeneration of the nigro-striatal dopaminergic pathway reduces the ability of nerve terminals to store and release dopamine.[17] As a result of this loss of storage capacity, l-dopa induces a more pulsatile stimulation of postsynaptic dopamine receptors, consistent with l-dopa's short (90-minute) half-life and its rapid cycling pharmacokinetics. This pulsatile stimulation causes functional changes within the basal ganglia, leading to involuntary movements and altered neural activity in the basal ganglia, thalamus cerebral cortex.[17]

Figure 1: Estimated frequency of different types of levodopa-induced dyskinesia



Source: Aquino, 2015[8]

Figure 2: Dual mechanism of action of safinamide



L-dopa = levodopa; MAO-B = monoamine oxidase-B

Several risk factors are associated with the development of LID, including increased body weight,[18] age of onset and severity of PD,[19] higher dose and longer duration of l-dopa therapy.[8,19] Dyskinesias are associated with substantially decreased quality of life (QoL) for both patients and caregivers, and create an additional burden on healthcare systems as they require increased monitoring and complex medical management.[8,20] Moreover, as LIDs worsen, they lead to increased risk of injury, exhaustion and fatigue.[8]

Patients with motor fluctuations often require add-on therapies, many of which improve motor fluctuations, but exacerbate dyskinesia.[21] The current recommended treatment for dyskinesia is the non-selective N-methyl-D-aspartate (NMDA) receptor antagonist amantadine,[22] but its effects are modest and short in duration. Moreover, it is associated with poor tolerance and adverse effects including hallucinations, leg oedema and livedo reticularis, requiring careful monitoring.[2,23] Clozapine, a high-affinity serotoninergic agonist used to treat psychosis in PD, has also been found to reduce LID[24] but it is associated with severe adverse effects,[25,26] that limit its use in this indication. Non-oral treatment includes continuous subcutaneous apomorphine infusion,[27] levodopa-carbidopa intestinal gel[28] and transdermal rotigotine therapy.[29] Deep-brain stimulation may help improve motor fluctuations and dyskinesia in advanced PD.[30]

In a 2009 survey, better treatments for motor symptoms were emphasised as a major unmet need in PD therapy.[31] Fluctuating response to treatment is the most troublesome motor symptom reported by PD patients.[32] There is therefore an unmet need for additional therapeutic options in fluctuating PD patients.

Pathophysiological mechanisms underlying dyskinesias in Parkinson's disease

While the pathogenesis of motor fluctuations has not been fully elucidated, *in vitro* studies suggest that other neurotransmitters in the brain, including glutamate, adenosine and serotonin are involved in the control of motor symptoms and the development of dyskinesia.[11] Glutamate plays a key role in the pathophysiology of PD. The dendritic spines of striatal medium-sized gamma-aminobutyric acid (GABA)-ergic neurons exhibit both dopamine and N-methyl-D-aspartate (NMDA) receptors and receive both cortical–striatal glutamatergic projections and nigrostriatal dopaminergic fibres.[33] Excessive oxidative stress in the substantia nigra pars compacta results in a reduction in the capacity of nigral neurons to cope with metabolic demands and the development of susceptibility to the effects of glutamate. Under conditions of impaired cellular energy metabolism, glutamate acts as a neurotoxin, causing degeneration of nigral neurons followed by striatal dopaminergic denervation.[33] This leads to a pathophysiological cascade of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MTMP)-induced neuronal cell death.[34] The loss of dopamine neurons is believed to cause an increase in glutamatergic activity in the basal ganglia.[35] This activates the striatopallidal pathway, inhibiting outputs of the basal ganglia and resulting in dyskinesia.[36] Glutamate excitotoxicity is therefore potentially an important therapeutic target.[37] Targeting non-dopaminergic systems provides complementary approach that may improve and control motor complications, while maintaining the efficacy of l-dopa.[38]

The use of safinamide in Parkinson's disease

Safinamide (Xadago®, Zambon, Bresso, Italy) is a novel α-aminoamide with a unique multi-modal mechanism of action distinct from that of amantadine.[39] It has antiparkinsonian, anticonvulsant and neuroprotective properties. Safinamide offers a unique approach to the management of motor symptoms and motor fluctuation/dyskinesia due to its unique dual mechanism of action (see *Figure 2*). Safinamide has dopaminergic mechanisms of action, including selective and reversible MAO-B and dopamine reuptake inhibition, which are largely responsible for its effects on motor symptoms.[39–41] However, it also has non-dopaminergic mechanisms of action. It suppresses repetitive firing by use- and state-dependent sodium channel blockade that in turn decreases calcium channel opening, and reduces excessive release from synaptic terminals of glutamate.[42] In this glutamatergic mechanism of action, safinamide differs from amantadine and memantine; it has an indirect effect on glutamate release through sodium channels blockade, whereas amantadine and memantine have a direct effect due to NMDA receptor antagonism.[39,43,44] It must be stressed that safinamide has a multimodal action and is not a pure antidyskinetic drug. In addition, safinamide has no effect on l-type calcium channels, and therefore does not affect blood pressure or heart rate.[45]

Table 1: Summary of clinical trials to date investigating the use of safinamide in Parkinson's disease as add-on to levodopa

Study name	Patient population	Study design	Efficacy findings	Safety findings
Study 016[49]	6-month (24-week) trial, n=669, PD fluctuating patients, receiving a stable dose of levodopa (alone or with other anti-parkinson drugs)	Patients received placebo, safinamide 50 or 100 mg/day as add-on to levodopa	At week 24, improvements in ON time with no/non-troublesome dyskinesia and OFF time were significantly higher in safinamide 50 and 100 mg/day groups versus. placebo, starting from week 4 onward, as well as improvements in UPDRS III motor scores	There were no significant differences among groups in the incidence of SAEs, TEAEs or AEs causing discontinuation. Most common AEs (≥5% in one group or more) were non-troublesome dyskinesia, back pain, worsening of PD, cataract and headache
Study 018[50]	18-month extension of study 016, n=544	Patients continued on randomised placebo, 50, or 100 mg/day safinamide	Change in DRS was not significantly different in safinamide vs. placebo groups. Ad hoc subgroup analysis of moderate to severe dyskinetic patients at baseline (36% of patients) showed a statistically significant decrease with safinamide 100 mg/day vs. placebo. Improvements in ON and OFF time, motor function, activities of daily living and QoL at 6 months remained significant at 24 months	SAEs, TEAEs and discontinuation rates were similar with safinamide and placebo
SETTLE[52]	6-month (24-week) trial, n=552, PD fluctuating patients, receiving a stable dose of levodopa (alone or with other anti-Parkinson drugs)	Patients started treatment with safinamide 50 mg/day and could increase the dose to 100 mg/day after 2 weeks. Patients received placebo or safinamide as add-on to levodopa	At 24 weeks, significantly more patients in the safinamide group vs placebo group had an improvement in both ON time with no/non-troublesome dyskinesia, OFF time and in the UPDRS III motor score	TEAEs, discontinuation rate and SAEs were similar across treatments. The most frequent treatment-related AEs (≥5% in one group or more) were back pain, non-troublesome dyskinesia, falls, headache, nausea, and urinary tract infections

AE = adverse effect; DRS = Dyskinesia Rating Scale; PD = Parkinson's disease; QoL = quality of life; SAE = serious adverse effect; TEAE = treatment-emergent adverse effect; UPDRS = unified Parkinson's disease rating scale.

Studies investigating safinamide's anticonvulsant properties in rat brain membranes showed that safinamide has high affinity for binding site 2 of the sodium channel receptor and exerts its actions through the inhibition of sodium and calcium channels, stabilising neuronal membrane excitability and inhibiting transmitter release.[46] A higher number of sodium channels are therefore kept in the inactivated state. In another animal study, the sodium channel opener, veratridine, was administered for 30 minutes to induce a rapid and transient increased glutamate release in the rat hippocampus. Safinamide inhibited glutamate release without affecting basal glutamate release.[47]

This non-dopaminergic mechanism of action of safinamide might be important in terms of the effects of the drug on motor complications. In a study of a primate model, both safinamide and amantadine reduced LID but only safinamide increased the duration of response of l-dopa.[48] These effects cannot be accounted only for by MAO-B inhibition, since the latter is associated with worsening rather than improvement of LID. The authors concluded that this finding might be related to a reduction in cortical and/or thalamic excitatory inputs resulting from reduced presynaptic glutamate release due to the blockade of voltage-gated sodium channels.

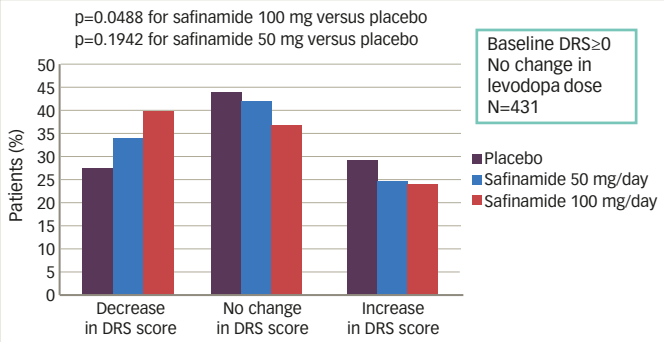
Safinamide has emerged as a useful add-on therapy for l-dopa following the findings of three phase III multicentre, randomised, double-blind, placebo-controlled, parallel-group trials of patients with mid-to late-stage PD and motor fluctuations: trials 016, 018 and SETTLE (Safinamide in Idiopathic Parkinson's Disease With Motor Fluctuations, as add-on to Levodopa).[49–51] In all studies, treatment with safinamide at daily doses of 50–100 mg (studies 016 and 018) or 100 mg (SETTLE) for 24 weeks (studies 016 and SETTLE) or 2 years (study 018) as add-on to l-dopa (alone or with other anti-parkinson drugs) increased daily ON time without dyskinesia, as assessed by Hauser patient diaries (see *Table 1*).[51] The dose of l-dopa remained stable in the majority of patients.

In study 016 (n=669), there were significant differences in the mean change in ON time without dyskinesia versus placebo in both the safinamide 50 mg (0.51 hours; 95% confidence interval [CI] 0.07–0.94; p=0.0223) and the safinamide 100 mg (0.55 hours; 95 % CI 0.12–0.99; p=0.0130) groups. Both safinamide doses did not increase troublesome dyskinesia despite the significant increase in ON time. There were also significant improvements in OFF time and Unified Parkinson's Disease Rating Scale (UPDRS)-III (motor) scores. In the 100 mg dosage group there were significant increases in UPDRS-II (activities of daily living) scores, Parkinson's Disease Questionnaire (PDQ-39) total score (p=0.0360) and subscale scores for emotional wellbeing (p=0.0116), communication (p=0.0361), and bodily discomfort. Differences from placebo in ON and OFF time were significant for both doses (p=0.0159) from the first post-baseline evaluation (week 4) onward.[49]

Of the patients enrolled in study 016, 81% (n=544) continued into an 18-month extension study (study 018).[50] Inclusion criteria for continuation were compliance with treatment and willingness to continue, or discontinuation but completion of the scheduled efficacy evaluations at weeks 12 and 24. Patients were excluded if they had experienced clinically significant adverse events (AEs) or shown clinically significant deterioration in motor symptoms during study 016. The primary endpoint was the change from baseline in Dyskinesia Rating Scale (DRS) total score during ON time over 24 months. The improvements in ON time without dyskinesia seen at six months in study 016 were maintained up to two years in study 018, as well as the improvements in OFF time and in motor scores. Although there was no overall difference in dyskinesias between patients and controls, improvement in dyskinesia compared with placebo (p=0.0317) was seen in patients at least moderately dyskinetic (36% of patients) at baseline.[50]

In the SETTLE study (n=552), as early as week 2 (first post-baseline assessment), a significant increase in median ON time without dyskinesia

Figure 3: Proportions of patients with different categorical changes in dyskinesia rating scale score (decrease, no change, increase) and no change in their levodopa dose (post-hoc analysis)



Variable	Placebo	Safinamide 50 mg	Safinamide 100 mg
Decrease	27.2 % (37/136)	33.8 % (50/148)	39.5 % (58/147)
No change	43.4 % (59/136)	41.9 % (62/148)	36.7 % (54/147)
Increase	29.4 % (40/136)	24.3 % (36/148)	23.8 % (35/147)

DRS = Dyskinesia Rating Scale. Reproduced with permission from Cattaneo, 2015[54]

and OFF time of one hour was observed for safinamide (50 mg/day) compared with 30 minutes for placebo.[51] At week 24, the change from baseline to 24 weeks in daily ON time with no/non-troublesome dyskinesia was significantly different for safinamide 100 mg/day versus placebo (0.96 hours; 95% CI 0.56–1.37; p<0.001). Safinamide also significantly improved UPDRS-III score, Clinical Global Impression of Severity (CGI-S), Clinical Global Impression of Change (CGI-C), the 39-item PDQ-39, and OFF time following the first morning l-dopa dose (i.e., latency to ON) compared to placebo. In addition, a significantly higher proportion of patients achieved improvements of at least one hour in motor fluctuations and a percentage of improvement of 30% and more in motor symptoms, a clinically meaningful benefit.[52]

Safinamide was well tolerated in these studies. Common adverse effects (reported in ≥5% of patients) included worsening of PD, cataract, back pain, pyrexia and hypertension.[49,52] In study 016, dose reduction was required for 10 patients (4%) in the 100 mg/day group, seven (3%) in the 50 mg/day group, and nine (4%) in the placebo group. Completion rates were high (87%–90%), and there were no significant between-group differences for incidences of treatment-emergent AEs (TEAEs) or TEAEs leading to discontinuation. Although dyskinesia was reported as a TEAE in a minority of patients, this was generally mild or moderate.[49] This seems an incongruous finding, since patient-recorded ON time showed that safinamide significantly improved ON time with no or non-troublesome dyskinesia, and may be due to differences in data collection. Patients recorded ON time in their diaries every 30 minutes over an 18-hour period for five consecutive days preceding each visit. By contrast, AEs were reported at study visits and may reflect whether a patient is experiencing any dyskinesia at that moment, regardless of its impact on functioning.

As a result of these data, safinamide received European Medicines Agency approval in 2015, (dosage 50–100 mg/day) for the treatment of mid- to late-stage fluctuating PD, as an add-on to l-dopa, alone or in combination with other PD medications.[53]

A post-hoc analysis of studies 016 and 018 aimed to characterise further the effects of safinamide on dyskinesia in mid- to late-stage PD patients.[54] While the effects of the 50 mg/day dosage of safinamide in study 016 may be attributable to MAO-B inhibition, the superiority of the effects at 100 mg/day suggest that other mechanisms may be involved, as a dose of 50 mg/day is sufficient to achieve complete MAO-B inhibition. It was therefore postulated that the antidyskinetic effects of the higher dose could be attributed to non-dopaminergic mechanisms. Patients were therefore stratified by the presence or absence of dyskinesia at baseline score >0 or DRS score = 0, respectively), and by whether or not the dose of l-dopa had been altered during the 24-month treatment period. Safinamide 100 mg/day significantly improved the DRS versus placebo in the subgroup of patients with or without changes in l-dopa dose. In patients with baseline dyskinesia, improvements were also significant in patients without changes in l-dopa dose (see *Figure 3*), suggesting that these improvements did not result from reduced dosage of l-dopa, but from the action of safinamide 100 mg on glutamatergic neurotransmission. The authors concluded that the higher dose is needed to optimise the dopaminergic and non-dopaminergic effects of safinamide.[54]

A post-hoc analysis of pooled data from studies 016 and SETTLE found that safinamide 100 mg significantly increased mean ON time with no or non-troublesome dyskinesia by 1.42h (95% CI: 1.21 to 1.64) versus 0.58 hour (0.37 to 0.80) with placebo (p<0.0001) and reduced mean OFF time by -1.49 hour (-1.68 to -1.30) versus -0.63 hour (-0.82 to -0.44) with placebo; p<0.0001). Significant changes compared with placebo in ON and OFF time were observed whether safinamide used as first or later adjunct therapy in l-dopa treated patients, and regardless of whether patients were receiving concomitant dopamine agonists, catechol-O-methyltransferase inhibitors or amantadine.[55] These findings suggest that safinamide may be considered either as a first adjunct therapy in PD patients who are not sufficiently controlled on l-dopa, and as an add-on therapy in patients taking l-dopa and other concomitant dopaminergic medications.

There is a need for further studies to explore the effect of safinamide on LID, as it is an important finding. Patients consider ON time with no or non-troublesome dyskinesia as 'good' ON time and it correlates with patients' perceived duration of a good response throughout the day.[49] By contrast, the MAO inhibitor rasagiline has shown to increase ON time with troublesome dyskinesia, suggesting that targeting the dopaminergic pathway alone is effective in controlling motor fluctuations but not motor complications.[42] In the phase III PRESTO study, the difference between the rasagiline dose of 1.0 mg/day and placebo in the ON time with dyskinesia was in favour of placebo: 0.37 h (p=0.048).[56]

Summary and concluding remarks

PD is a complex condition and recent advances have elucidated the pathogenic processes underlying its symptoms. Numerous non-dopaminergic neurotransmitters are involved in the control of motor symptoms and the development of motor fluctuations and dyskinesias following long-term l-dopa therapy. In particular, glutamate plays a key role in the pathophysiology of PD and represents a valuable therapeutic target.

Unlike other drugs that can improve motor function, long-term studies have shown that safinamide does not lead to an overall worsening of dyskinesia. Recent data suggest that this may be a consequence of its a unique dual mechanism of action, combining reversible MAO-B inhibition with blockage of voltage-dependent sodium channels, modulation of calcium channels and inhibition of abnormal glutamate release. The inhibition of sodium and calcium channels by safinamide is an important clinical finding and warrants further investigation. In phase III clinical studies, safinamide has been shown to significantly increase ON time with no/non-troublesome dyskinesias and decrease OFF time, as well as having beneficial effects on motor symptoms and QoL. Safinamide has

been investigated in long-term (24-month) studies, and has shown a very good safety profile, as well as long-term efficacy.

In conclusion, safinamide is a unique therapy that combines non-dopaminergic and dopaminergic mechanisms of action, modulating altered dopaminergic and glutamatergic neurotransmission. There is a need for more clinical trial data to assess the effect of safinamide in dyskinesias. However, clinical trial findings to date suggest that safinamide represents an important therapeutic option for fluctuating PD patients. ❑

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