Progression of Parkinson's Disease and Unmet Needs in Mid- to Late-stage Patients

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Abstract

In early-stage Parkinson's disease (PD), dopaminergic treatment is highly effective in controlling motor symptoms. However, as the disease progresses, other symptoms and comorbidities need to be addressed, such as suboptimal motor control, emerging motor complications (e.g. nocturnal and early-morning akinesia/tremor, early wearing-off and dyskinesia), emerging levodopa-resistant motor symptoms, increasing non-motor symptoms and treatment of non-dopaminergic symptoms. Despite these unmet needs, no new therapies for PD have been introduced into routine clinical practice over the past 10 years. Safinamide is a new oral therapy that has both dopaminergic and non-dopaminergic mechanisms of action. In phase III clinical trials, safinamide has demonstrated significant clinical benefits in patients with mid- to late-stage PD experiencing motor fluctuations as an add-on therapy to levodopa and other PD medication versus those treated only on an optimised PD therapy. This includes improvements in daily ON time, improvements in motor function and beneficial effects on dyskinesia that have been studied in patients for up to 2 years. Safinamide is well tolerated, and it is a new and unique agent in the armamentarium of treatments for patients with mid- to late-stage PD experiencing motor fluctuations.

Keywords

Safinamide, mid- to late-stage PD, motor fluctuations, ON time, dyskinesia

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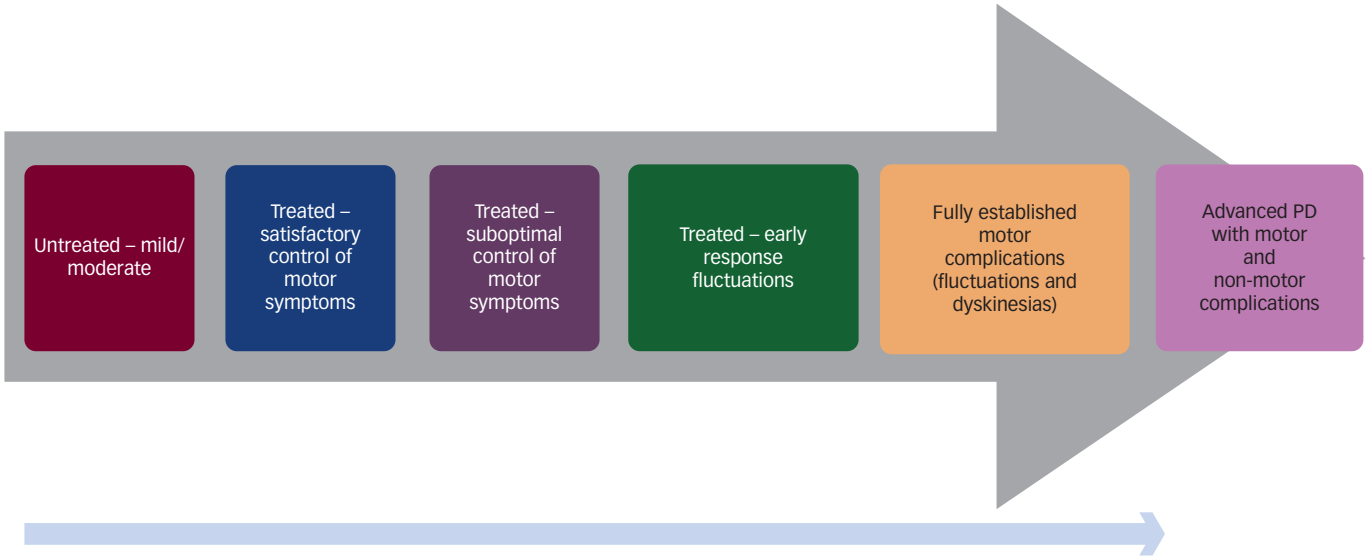
There have been tremendous advances in understanding the pathophysiology of Parkinson's disease (PD) over the past decades and the development of a range of treatments since the introduction of levodopa in the late 1960s. However, there are still significant unmet needs in the management of PD, particularly as the disease progresses, and no new classes of therapy have been introduced for more than a decade. This review focuses on the clinical development of safinamide, a new oral add-on therapy for mid- to late-stage PD that has both dopaminergic and non-dopaminergic mechanisms of action, and its potential use in practice as discussed at a satellite symposium held at the 1st European Academy of Neurology Congress, 22 June 2015, Berlin, Germany.

Disease Progression and Influence of Treatment on PD

In early-stage PD, dopaminergic treatment is highly effective in controlling motor symptoms, with coverage generally provided from 2 to 6 hours post-treatment with a single dose of levodopa. However, as the disease progresses through the mid- to late-stages, the therapeutic window narrows with significant OFF time and increased incidence of dyskinesia (see *Figure 1*). In a *post hoc* analysis of the STRIDE-PD study in *de novo* patients, both wearing-off and dyskinesia were associated with high-dose levodopa at the early stages of the disease. The risk of developing dyskinesia and wearing-off increased in a dose-dependent manner, with a threshold of 400 mg/day apparent above which the risk of dyskinesia and

Figure 1: Disease Progression and Influence of Treatment on PD



wearing-off was higher.[1] Wearing-off may occur earlier than physicians realise; in an Italian study by Stocchi et al., physicians typically identified wearing-off after 5 years of levodopa treatment whereas patients often reported wearing-off in the first 2 years of treatment.[2]

Current Treatment Challenges and Unmet Needs in Mid- to Late-stage PD

Through the course of the disease from the onset of motor symptoms, other problems need to be managed, such as suboptimal motor control, emerging motor complications (e.g. nocturnal and early-morning akinesia/ tremor, early wearing-off and dyskinesia), increasing non-motor symptoms and emerging levodopa-resistant motor symptoms.[3] The progressive nature of PD ultimately leads to visual hallucinations, falls, dementia and institutionalisation in the later stages.

Ideally, disease-modifying treatment to avoid some of these later motor and non-motor complications of PD would be the best adjunctive treatment to current therapy. Unfortunately, however, no treatments investigated in the last 10 years have demonstrated any neuroprotective or neurorescuing efficacy in PD.[4] While clinical trial methodology may have been part of the problem to date, our increasing understanding of the aetiology and pathogenesis of PD points to the possibility that a single drug with a specific mechanism of action may fail because several different pathogenic mechanisms are implicated, including oxidative stress, mitochondrial dysfunction, excitotoxicity and inflammation.[5]

At present, from mid-stage disease the focus of treatment generally shifts gradually towards achieving an optimal balance between managing the motor symptoms and minimising the motor response complications of fluctuations and dyskinesia that commonly occur as a result of chronic dopaminergic therapy (see *Figure 2*).[6] Various drug treatments, mainly adjunct therapies, are used for treating motor fluctuations associated with levodopa, including monoamine oxidase B (MAO-B) inhibitors, catechol O-methyltransferase (COMT) inhibitors and dopamine agonists (DAs). Although proven effective, these treatments have a range of limitations and there are limited clinical data on their long-term efficacy, which represents a pressing unmet need in mid- to late-stage patients.

Management of dyskinesia is an additional complication in mid- to late-stage PD with limited treatment options. Dyskinesia is classically thought to arise from an imbalance between dopaminergic and glutamatergic stimulation, resulting in receptor sensitivity changes and altered gene expression in the post-synaptic neuron.[7] This may explain why dyskinesia as an event, once it occurs, is difficult to control. Aside from titrating the dose of levodopa to try to avoid its occurrence, glutamatergic antagonists provide an additional approach. The only available agent of this type currently that exhibits an anti-dyskinetic effect is amantadine,[8–10] although it may be associated with a number of adverse effects, and new strategies for controlling dyskinesia are needed.

The Challenge of Achieving Full Control of Motor Symptoms in Mid- to Late-stage PD

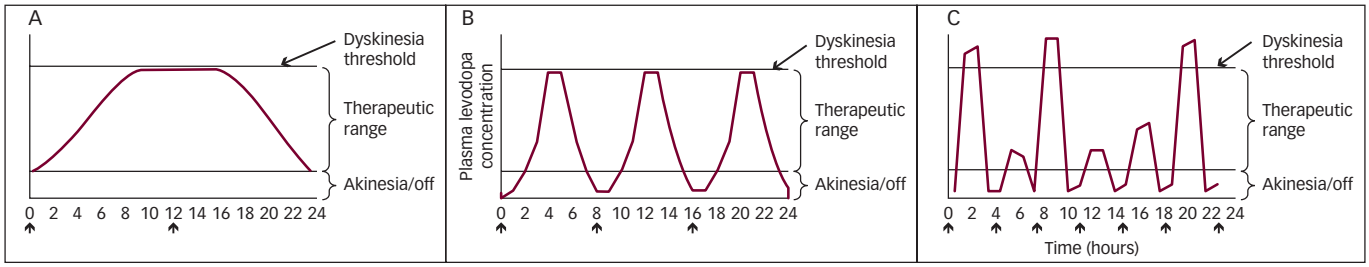
Gait disturbances, falls, fractures and dysphagia are major causes of death in patients with PD due to a lack of full motor symptom control, and represent important areas of unmet need. The first fall is a predictor of poor outcomes as well as other non-motor symptoms, including hypotension and fractures.[11] Patients with the postural instability gait difficulty (PIGD) clinical subtype, defined as those with more gait problems than tremor, have been shown to have reduced survival compared with the mixed subtype, and they are also at greater risk of developing dementia.[12]

Recent Data on the Management of Non-motor Symptoms

The management of non-motor symptoms represents an additional challenge in PD. In general, non-motor symptoms have been shown to contribute to poor quality of life and were found to be the strongest independent negative determinant of overall quality of life in one cross-sectional study.[13] Some evidence supports the efficacy of certain treatments for depression, dementia, psychosis, constipation and sialorrhoea; however, there is insufficient evidence for efficacious treatments for other important non-motor symptoms that certainly contribute to poor quality of life, such as orthostatic hypotension, neurogenic bladder disturbance, erectile dysfunction, fatigue, insomnia and excessive daytime sleepiness.[14]

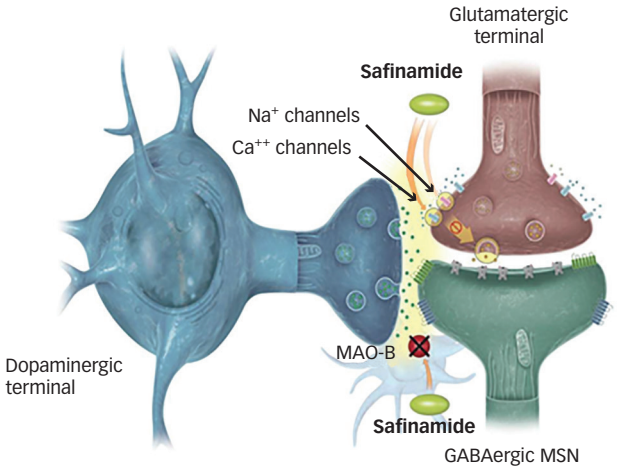
Pain, the most frequent non-motor symptom of PD, may be due to central and/or peripheral mechanisms.[15,16] Manifesting as arthralgic

Figure 2: Response to Levodopa and Disease Progression



A: Schematic graph to show the relationship between plasma levodopa levels and the clinical effects in early Parkinson's disease; B: Schematic graph showing dose responsive fluctuations in advancing Parkinson's disease; C: Schematic graph to show unpredictable fluctuations and dyskinesias unrelated to dose administrations ('yo-yoing') in advanced Parkinson's disease. Arrows indicate time of levodopa administration. Adapted from Thanvi and Lo, 2004.[6]

Figure 3: Sites of Action of Safinamide for the Treatment of Motor Symptoms in PD[22,23]



GABA = gamma-aminobutyric acid; MSN = medium spiny neurons; MAO-B = monoamine oxidase B; PD = Parkinson's disease.

pain, cramping pain, peripheral neuropathic pain and central pain, one may consider controlling pain at different levels with different treatments according to the origin of the problem.[17–19]

Neuropsychiatric symptoms associated with PD mainly relate to dysfunction of the reward circuitry, controlled by dopamine and also glutamate. There is now some evidence that glutamatergic modulation may reduce impulse control disorders, which are present in approximately 15 % of patients. One crossover study by Thomas et al. demonstrated a reduction in pathological gambling with the anti-glutamatergic agent amantadine.[20]

Dementia probably represents the latest stage of cognitive deterioration in PD. Data from several studies have shown that the prevalence of cognitive dysfunction in the very early stages of the disease is between 9 % and 20 %. At present it is not clear what proportion of PD patients with cognitive impairment will go on to develop dementia, but along with age it is considered a major risk factor for developing dementia. There are some data to show efficacy of the cholinesterase inhibitor rivastigmine in the treatment of PD-associated dementia, but insufficient evidence for donepezil and galantamine as well as for the N-methyl-D-aspartate (NMDA) receptor antagonist memantine; data for glutamatergic agents are currently lacking.

The Need for Targeting Non-dopaminergic Pathways in PD

It is now well established that non-dopaminergic neurotransmitter systems, including glutamatergic, gamma-aminobutyric acid (GABA) ergic, cholinergic, noradrenergic, serotonergic, opioidergic, histaminergic and adenosinergic systems, are affected in the pathogenesis of PD and represent multiple targets for the treatment of symptoms.[21]

Of particular interest is the glutamatergic pathway. The loss of dopamine neurones is believed to cause an increase in glutamatergic activity in the basal ganglia. Excessive glutamatergic signalling in PD contributes to the development of motor symptoms and – most notably – motor complications as well as levodopa-induced dyskinesias and the progression of neurodegeneration. It is therefore conceivable that in the future we may be able to target different neurotransmitter systems in order to treat different symptoms in patients with PD.

Counteracting the Dopaminergic/ Glutamatergic Imbalance in PD – Clinical Efficacy and Tolerability of Safinamide

Safinamide is a new oral therapy that has recently been approved by the European Medicines Agency (EMA) for the treatment of adult patients with mid- to late-stage fluctuating disease as add-on therapy to a stable dose of levodopa alone or in combination with other PD treatments. Safinamide is a unique molecule with a novel mechanism of action.[22] It is an α-aminoamide that has both dopaminergic and non-dopaminergic mechanisms of action, including inhibition of MAO-B, sodium (Na^+) channel blockade and modulation of stimulated release of glutamate (see *Figure 3*).[23–26]

Support for the non-dopaminergic effect of safinamide at clinically relevant doses comes from a phase II study in patients with refractory partial and/or generalised epilepsy.[27] In several central nervous system (CNS) disorders, including epilepsy, schizophrenia and PD, neuronal over-excitation due to membrane depolarisation leads to sodium channel opening. Profound depolarisation due to persistent sodium channel opening in turn opens voltage-dependent (Ca^+) channels, allowing the calcium entry that triggers overactive release of glutamate. Anticonvulsant activity is therefore considered evidence of functional sodium channel blockade *in vivo*. In this open-label, phase II, dose-escalation study to assess tolerability and drug–drug interactions in uncontrolled epilepsy patients, safinamide induced a statistically significant decrease in seizure frequency, starting from the initial dose of 50 mg and increasing at each incremental dose, even though the study was not designed or powered to provide proof of efficacy.[27] These findings observed at the recommended clinical doses

(50 and 100 mg) indicate that safinamide functionally inhibits Na^+ channels in patients and, through its primary state and use-dependent sodium channel blockade, may effectively prevent the neuronal over-excitation events that eventually result in overactive glutamate release.

Safinamide Clinical Development

The efficacy of safinamide as add-on treatment in mid- to late-stage PD patients with motor fluctuations currently receiving levodopa alone or in combination with other PD medications was evaluated in two phase III double-blind, placebo-controlled studies: Study 016/018 (safinamide 50 and 100 mg/day for 6 months with extension to 2 years)[28,29] and the SETTLE study (safinamide 50–100 mg/day for 6 months)[30] (see *Figure 4*). The primary efficacy parameter in these studies was the change from baseline to endpoint in 'ON time without dyskinesia and/or non-troublesome dyskinesia'.

Six-month Efficacy Data with Safinamide

The efficacy of safinamide after 6 months of treatment was evaluated in the two randomised, double-blind controlled trials Study 016 and SETTLE.[28,30]

In Study 016, patients were randomised to oral safinamide 100 mg/day (n=224), 50 mg/day (n=223) or placebo (n=222) for 24 weeks. The primary endpoint was the change in mean total daily ON time with no or non-troublesome dyskinesia (assessed using the Hauser patient diaries). Secondary endpoints included the change in mean total daily OFF time, Unified Parkinson's Disease Rating Scale (UPDRS) Part III (motor) scores and Clinical Global Impression-Change (CGI-C).[28] In the SETTLE study, safinamide in a dose range of 50–100 mg (n=274) was given orally once daily versus placebo (n=275) for 24 weeks as add-on therapy to a stable dose of levodopa in patients with PD and motor fluctuations. The primary endpoint was the change from baseline to week 24 in mean total daily ON time (ON time without dyskinesia plus ON time with non-troublesome dyskinesia). Secondary efficacy objectives included changes from baseline to week 24 in health-related quality of life (Parkinson's disease questionnaire-39 item version [PDQ-39] and EuroQol 5D [EQ-5D]), dyskinesia (Dyskinesia Rating Scale [DRS]), motor symptoms (UPDRS Section III during ON phase) and total daily OFF time, as measured by diary cards.[30]

In these two 6-month studies, safinamide significantly increased daily ON time without dyskinesia and/or with non-troublesome dyskinesia when used as add-on to levodopa as well as significantly reducing daily OFF time (see *Figure 5*).[28,30] In the SETTLE study at 6 months, the mean increase in ON time without dyskinesia and/or with non-troublesome dyskinesia versus baseline with safinamide 50–100 mg/day was +1.42 hours compared with +0.57 hours with placebo. This represents a mean difference versus placebo in ON time of +0.96 hours (p<0.001). In Study 016 at 6 months, the mean increase in ON time without dyskinesia and/or with non-troublesome dyskinesia versus baseline was +1.37 hours with safinamide 50 mg/day, +1.36 hours with safinamide 100 mg/day and +0.97 hours with placebo. The reduction in daily OFF time in the SETTLE study at 6 months versus baseline was –1.56 hours with safinamide 50–100 mg/day and –0.54 hours with placebo. This represents a mean difference versus placebo in OFF time of 1.03 hours (p<0.001). In Study 016 at 6 months, the mean reduction in OFF time versus baseline was –1.3 hours with safinamide 50 mg/day, –1.3 hours with safinamide 100 mg/day and –0.7 hours with placebo. In both of these studies, safinamide also reduced OFF time after the first morning dose of levodopa.[28,30]

Figure 4: Safinamide Clinical Registration Programme

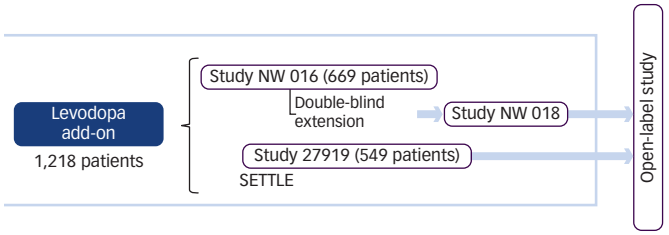


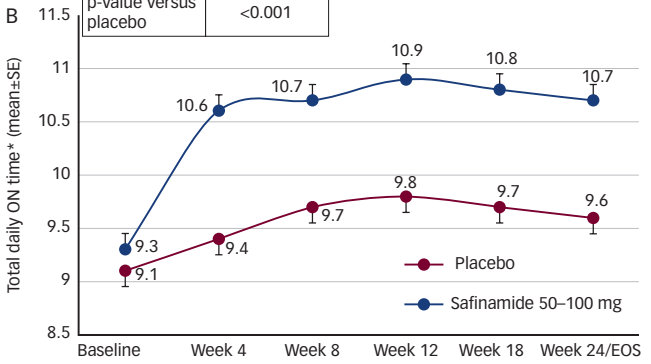
Figure 5: Study 016 Primary Efficacy Endpoint (ON Time) (A) and SETTLE Study (B)[28,30]

A

	Safinamide 50 mg	Safinamide 100 mg
LS mean	1.23	1.28
LS difference versus placebo	0.51	0.55
95 % CI of LS difference	(0.07, 0.94)	(0.12, 0.99)
p-value versus placebo	0.0223	0.0130

B

	Safinamide 50–100 mg/day
LS mean	1.52
LS difference versus placebo (95 % CI)	0.96 (0.56, 1.37)
p-value versus placebo	<0.001



*ON time = ON time without dyskinesia + ON time with minor dyskinesia

CI = confidence interval; EOS = end of study; LS = least squares.

Two-year Efficacy Data with Safinamide

The beneficial outcomes seen at 6 months with safinamide were sustained at 24 months based on results of Study 018.[29] Study 018 was a double-blind, placebo-controlled, 18-month extension to Study 016, aimed at assessing the long-term efficacy and safety of safinamide as add-on therapy to levodopa in patients with PD – 65.8 % of Study 016 patients completed the whole 2-year treatment period, and 80.9 % of Study 018 patients completed the 18-month extension period.[29] The primary efficacy endpoint was mean change from baseline (at Study 016 start) to endpoint of the total DRS score during ON time. Secondary efficacy endpoints included mean change from baseline to endpoint

Figure 6: Study 018 ON Time Over 2 years[29]

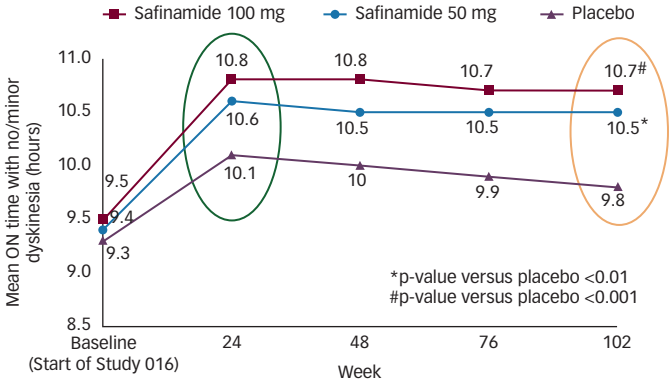
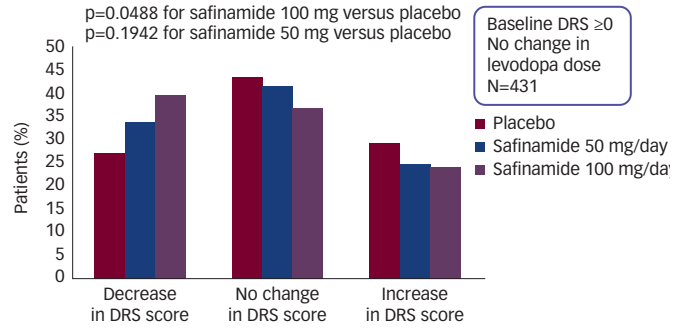


Figure 7: Proportions of Patients with Different Categorical Changes in DRS Score (Decrease, No Change, Increase) and No Change in Their Levodopa Dose (n=273) (*Post hoc* Analysis)[32]



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.

in diary ON time without troublesome dyskinesia (i.e. with no or only non-troublesome dyskinesia), UPDRS Part II (activities of daily living) scores, change in levodopa dose, UPDRS Part III (motor) scores, change in individual diary categories (ON with no dyskinesia, ON with non-troublesome dyskinesia, ON with troublesome dyskinesia, OFF, asleep) and Parkinson's Disease Questionnaire (PDQ)-39 subscale scores.[29]

At 24 months, the mean increase in ON time without dyskinesia or with non-troublesome dyskinesia versus baseline was +1.01 hours with safinamide 50 mg/day, +1.18 hours with safinamide 100 mg/day and +0.34 hours with placebo. The mean difference versus placebo in ON time without dyskinesia and/or with non-troublesome dyskinesia versus baseline was +0.67 hours with safinamide 50 mg/day (p<0.0031) and +0.83 hours with safinamide 100 mg/day (p=0.0002) (see *Figure 6*).[29] Safinamide also significantly reduced daily OFF time; –0.62 hours versus placebo (p=0.0011) with the 50 mg dose and –0.75 hours versus placebo with the 100 mg dose (p<0.0001), from a mean daily OFF time baseline of 5.2 hours.[29]

Safinamide has also been shown to significantly improve motor function even in patients already treated with a stable dose of levodopa as measured by the change in the UPDRS III score. In Study 018 after 24 months, safinamide 50 mg/day reduced the UPDRS III score from baseline by –1.05 points versus placebo and by –2.13 points in the 100 mg/day safinamide group (p≤0.001).[31]

These results at 2 years are particularly relevant in view of the lack of long-term clinical trial data supporting treatment with other adjunctive treatments in this patient population.

Impact of Safinamide on Controlling Dyskinesia

In Study 018, safinamide improved dyskinesias without the need to reduce levodopa dose in patients with moderate to severe dyskinesia. In the general treatment population, a worsening of dyskinesia rating scale (DRS) scores was observed with placebo and an improvement was observed with safinamide; this difference, however, was not statistically significant (p=0.21 with safinamide 50 mg/day and p=0.15 with safinamide 100 mg/day).[29]

However, a recent *post hoc* analysis of Study 018 evaluated the categorical changes in DRS scores at the end of study 018 after stratifying patients based on the presence or absence of dyskinesia (DRS score >0 or DRS score=0, respectively) at baseline, and by additional subgroups based on whether or not the levodopa dose had been changed during the entire treatment period of 24 months.[32] In this *post hoc* analysis, safinamide 100 mg/day administered as add-on to levodopa alone and other PD medications significantly improved the DRS score over 2 years of treatment compared with placebo. Statistically significant improvements in dyskinesia scores were seen also in patients with no changes in levodopa dose, suggesting that these improvements were not due to levodopa dose reductions (see *Figure 7*).[32] This finding is unlikely to be related to a reduced dopaminergic stimulation, as demonstrated by statistically significant effects of safinamide on motor fluctuations (ON and OFF times) over 2 years, as described earlier.

Tolerability of Safinamide

In clinical trials, safinamide was well tolerated with an adverse event and discontinuation rate similar to placebo.[28-30] No change in dose is required for patients with renal impairment and it can be used safely without any dietary tyramine restrictions.

The Role of Safinamide in Clinical Practice – Patient Selection

In light of the promising clinical trial data for safinamide, this novel agent appears to have several valuable applications in clinical practice for the control of symptoms in mid- to late-stage PD, some of which are highlighted by the following case profiles.

Patient Profile 1 – A Patient Not Well Controlled on an Optimised Levodopa Dosing Regimen

A retired 68-year-old male first presented with subjective symptoms of PD at the age of 65, involving some asymmetric right-side predominant stiffness and clumsiness of the arm and hand. He was initially treated with levodopa four times daily, titrated over a period of 3 months, which achieved satisfactory symptom control. He has now re-presented complaining of episodes, especially at meal times, during which he feels his symptom control is suboptimal; he reports experiencing best control after the first daily dose of levodopa in the morning. On examination during an episode of reduced symptom control, the patient exhibits typical signs of Parkinsonism, including facial immobility, monotony of speech, bilateral bradykinesia (slightly asymmetric) and reduced arm swing. On performing foot tapping, the rhythm is slow and amplitude decreased with subtle asymmetry. The patient's main problem during these recurring episodes is difficulty in standing up from a seated position and walking; the gait is very small stepped. Outside of these episodes,

the treatment appears still to be working well for many hours each day – foot tapping is performed with much improved speed and amplitude and he has no problem with standing up or walking. With reasonably stable function overall, the main goal with this patient is to improve his mobility during the periods when levodopa is losing its effectiveness.

Rationale for safinamide: In patients suboptimally controlled on a standardised levodopa dose regimen, there are a number of potential treatment strategies, including adjunctive treatment with either an MAO-B inhibitor, a COMT inhibitor, a DA or apomorphine rescue injections, although this approach is rarely used. In this situation the addition of a COMT inhibitor may be quite common. However, in a proportion of patients, particularly those with less-advanced disease, the addition of a COMT inhibitor to an optimised levodopa dose can lead to the emergence of dyskinesia.[33,34] Therefore, in these cases the addition of safinamide, with its favourable profile in terms of improving wearing-off symptoms without increasing dyskinesia, could be an effective approach.

Patient Profile 2 – A Patient with Long-standing Disease Now Experiencing Wearing-off and Emerging Dyskinesia

A female patient first presented with symptoms at age 28 years, although diagnosis was delayed for 10 years until age 38 due to the circumstances under which the symptoms first appeared: tremor of the left leg first occurred during an episode of severe nervous tension, which led to a psychogenic misdiagnosis; this left-sided symptom became an intermittent but chronic problem, and it took 10 years of evolution before a diagnosis of PD was made. That was 30 years ago, and the patient was started on low-dose (50 mg QID) levodopa, which eradicated her symptoms. She remained on levodopa monotherapy for many years with only a modest requirement to increase the dose; 15 years after initiation of levodopa, the first dyskinesias appeared, but they were only mild. Five years ago she started complaining of regularly waking after midnight with cramping and trembling of the left foot; she needed additional doses of levodopa (eventually rising to five daily) but still complains of poor sleep. She has leg tremor episodes during the day and now also right-sided hand tremor, together representing the phenomenon of crossed or inconsistent asymmetry. This case also illustrates how early-onset genetic PD is different from the classic sporadic onset.

Rationale for safinamide: This is a rare case of early-onset genetic PD that was very well controlled with levodopa over a long period of time. However, the patient is now experiencing wearing-off symptoms and the emergence of dyskinesia. This profile may be used to argue against the use of standard adjunctive therapies, such as DAs or COMT inhibitors. The dual mechanism of action of safinamide, together with promising long-term data on improvements in daily ON time when added-on to levodopa, as well as control of dyskinesia without the need to reduce levodopa dose, provides a strong rationale for the use of safinamide.

Patient Profile 3 – A Patient Receiving Levodopa Plus Rasagiline Now Experiencing Bothersome Dyskinesia

A 72-year-old male, previously a company executive, was diagnosed 3 years ago with PD manifesting as intermittent rest tremor. He was started on levodopa but began to experience wearing-off within 2 years; levodopa was increased from three to four doses and symptom control was regained for a further year. Subsequently, re-emergence of symptoms occurred with one or two episodes per day; he also complained of nocturnal immobility and mild chorea. Additional adjunctive therapy with rasagiline was prescribed for the re-emergence of wearing-off. This was effective for nocturnal mobility and wearing-off improved, but on-period dyskinesia became more troublesome – these were cranial–facial dyskinesias and were particularly bothersome to the patient because he still maintained a public profile.

Rationale for safinamide: This is a patient taking levodopa who is experiencing motor fluctuations and some dyskinesia. In a patient like this, amantadine might be considered to manage the dyskinesia although it does have a number of drug–drug interactions. Levodopa dose reduction may also be considered but at the risk of less well-controlled motor symptoms. A new alternative would be to switch from rasagiline to safinamide. In the long term, safinamide has been shown to significantly increase daily ON time without dyskinesia and/or troublesome dyskinesia when used as add-on to levodopa. A recent *post hoc* analysis has also indicated that safinamide improves DRS scores in patients with dyskinesia at baseline without changing their levodopa dose.

Patient Profile 4 – A Patient Starting with a Dopamine Agonist then Switched to Levodopa

A 58-year-old shop owner had first noticed right-hand tremor at age 55 and was diagnosed with PD 6 months later. At this stage his symptoms included hypomimia, mild hypophonia, intermittent right-hand rest tremor, reduced right-hand dexterity, reduced right-arm swing and slight dragging of the right leg. Initial treatment was DA monotherapy with a rotigotine patch (6 mg/day). Generally, his symptoms responded very well to rotigotine, with a reduction in UPDRS III score from 15 to 9, but he subsequently developed marked daytime sleepiness. He was switched to levodopa 100 mg three times a day and responded very well (UPDRS III score reduced to 7) and the sleepiness resolved. However, he now presents with loss of motor control, with recurring rest tremor episodes, increasing difficulties in handwriting and other right-handed manual tasks, and has difficulties turning in bed. His UPDRS III score has now gone back up to 13.

Safinamide rationale: In this patient, suboptimally controlled on levodopa 100 mg three times daily, a common treatment choice might be to increase the levodopa dose. However, there is considerable debate regarding optimal levodopa dosing, particularly regarding higher doses in earlier versus later disease. Data suggest that a low dosage of levodopa does seem to reduce the risk of developing early dyskinesias in the first years of the disease.[35] In this situation, safinamide offers a number of important benefits, including a significant improvement with safinamide 100 mg/day in motor function when used as an add-on to levodopa as shown by a 2.3-point reduction in UPDRS III score compared with placebo over 2 years of treatment.

Summary and Conclusions

As PD progresses, a wide range of factors, aside from controlling motor symptoms, need to be addressed. These include emerging motor complications (e.g. nocturnal and early-morning akinesia/tremor, early wearing-off and dyskinesia), emerging levodopa-resistant motor symptoms, increasing non-motor symptoms and treatment of non-dopaminergic symptoms. Despite these unmet needs, no new PD therapies have been introduced into clinical practice over the past decade. Safinamide is a new oral therapy that has both dopaminergic and non-dopaminergic mechanisms of action that include MAO-B inhibition, sodium channel blockade and calcium channel modulation, thus inhibiting excessive glutamate release. In phase III clinical trials, safinamide has demonstrated control of motor symptoms and motor

complications over a 6-month treatment period; uniquely, these benefits, including significant increases in total daily ON time without dyskinesia and/or with non-troublesome dyskinesia, reductions in total daily OFF time, improvements in early-morning akinesia and motor function (UPDRS III score reduction in patients treated with a stable dose of levodopa) as well as control of dyskinesia without the need to reduce levodopa dose, have been maintained in the long term over 2 years. Safinamide is administered at a dose of 50 or 100 mg/day once daily and is generally very well tolerated with no drug–drug interactions and can be used safely without any dietary tyramine restrictions. These favourable characteristics and clinical benefits make safinamide a valuable addition to the armamentarium of adjunctive treatments to levodopa for mid- to late-stage PD patients who are experiencing motor fluctuations and related complications. ■

SETTLE Study = SafinamidE Treatment as add-on To LEvodopa in idiopathic Parkinson's disease with motor fluctuations

STRIDE-PD = STalevo Reduction in Dyskinesia Evaluation-Parkinson Disease

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