

# Expert Opinion

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## An expert opinion on safinamide in Parkinson's disease

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**Background:** Dopamine replacement therapies (levodopa, dopamine receptor agonists, anticholinergics, monoamine oxidase B inhibitors, and catechol-O-methyltransferase inhibitors) remain the cornerstones of therapeutic interventions for Parkinson's disease (PD). Despite the treatment options for PD symptoms, a cure remains elusive. An optimal treatment would be one that combined relief in both motor and nonmotor symptoms with neuroprotective properties. Safinamide is an investigational drug for PD currently in development as add-on therapy to both dopamine agonists and levodopa. Safinamide is a unique molecule with a novel mode of action, targeting both dopaminergic and glutaminergic systems, and potentially provides motor symptom control. Preliminary results from experimental models suggest potential neuroprotective effects. Studies on the potential effects on nonmotor symptoms are ongoing. **Objective:** To review the mechanism of action and pharmacokinetics, and to evaluate the available clinical safety and efficacy results of safinamide. **Methods:** A search of the electronic database MEDLINE (PubMed, no time limits) was performed on 14 December 2007. The full text of all citations was obtained for review. Furthermore, two abstracts on safinamide published as proceedings of a European conference were reviewed. **Results/conclusion:** Safinamide is a promising investigational drug for PD with a novel mode of action. Early reports confirm the potential efficacy of safinamide in PD. Further studies on potential effects on cognition and neuroprotection are needed.

**Keywords:** glutamate, monoamine oxidase B, motor fluctuations, neuroprotection, Parkinson's disease, safinamide

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### 1. Introduction

#### 1.1 Parkinson's disease: epidemiology, presentation and pathophysiology

Idiopathic Parkinson's disease (PD) is an adult-onset neurodegenerative disorder that is prevalent worldwide. Incidence increases sharply with age, with approximately 1 in 200 people over 70 years of age suffering from the disease [1].

PD is clinically characterised by resting tremor, bradykinesia, rigidity and gait disturbances. Progressive clinical impairment occurs, usually over a 10- to 15-year period, reflecting the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta, resulting in a significant loss of dopamine (DA) in the striatum. DA replacement therapy, able to improve motor symptoms of PD, remains the backbone of antiparkinson therapy [2]. However, as PD progresses, further symptoms appear that either do not respond to dopaminergic replacement therapy or are related to levodopa treatment. Disabling dyskinesias and motor fluctuations are often referred to as DA-related symptoms of PD, even though these complications are likely to be a consequence of underlying nigrostriatal degeneration, revealed by exposure to dopaminergic treatment [3-5].

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## 1.2 Overview of the market

Satisfactory approaches to relieve late symptoms and to slow the progression of the disease (i.e., by protecting dopaminergic neurons from premature death) have not yet been developed. Although promising results have been experimentally obtained with several classes of drugs [6,7], the challenge remains to show a clinical proof of arrest or delay neuron loss in PD.

Current symptomatic treatment relies on levodopa, DA agonists, monoamine oxidase B (MAO-B) inhibitors, and catechol-*O*-methyltransferase (COMT) inhibitors that compensate for the deficit in the nigrostriatal dopaminergic input pathways, but it is now accepted that several other factors contribute to disease progression. These include oxidative stress with free-radical production [8], neuroinflammation [9], alterations in the ubiquitin-proteasome system leading to apoptosis [10], mitochondrial dysfunctions [11], and glutamate-mediated excitotoxicity [12].

Although efficacious, long-term levodopa treatment can elicit a number of debilitating side effects, such as dyskinesias and motor fluctuations. These side effects are exacerbated by dose and duration of levodopa treatment; thus treatment options that delay and minimise the need for levodopa are desirable [13,14].

Catechol-*O*-methyltransferase inhibitors can be added to levodopa/carbidopa treatment. These drugs prevent the conversion of levodopa to 3-*O*-methyldopa in the gut by COMT, thus increasing the levels of unmetabolised levodopa reaching the substantia nigra. However, COMT inhibitors can induce dyskinesia in susceptible patients [14].

Monotherapy with DA agonists has proven effective in the treatment of early PD and, as such, can permit a significant delay in the need to prescribe levodopa. In patients treated initially with DA agonists such as ropinirole or pramipexole, the dopamine transporter decrement or reduction [15,16] of F-18-dopa uptake in the striatum was less severe than in patients treated initially with levodopa [17]. However, recent concerns arise from the use of DA agonists, since ergolinic DA agonists potentially induce endocarditic vegetations [18,19] and all DA agonists, including non-ergolinic DA agonists such as pramipexole and ropinirole, can induce sleep attacks and oedema of the lower extremities and lead to compulsive disorders [20-23].

Another approach in PD treatment is the use of inhibitors of MAO-B, one of the key enzymes responsible for the metabolism of dopamine in the brain. MAO-B inhibitors increase levels of dopamine at the synapses and improve PD motor symptoms. There is also evidence of neuroprotective properties with some MAO-B inhibitors [24].

The first MAO-B inhibitor to be widely used for PD was selegiline, which irreversibly binds to MAO-B. Selegiline has been demonstrated to improve overall symptom control compared with placebo but effects on dyskinesias are equivocal, with dyskinesias being worsened in one study and unaffected in another trial [25-27]. There are some drawbacks to selegiline: at high doses selegiline loses its selectivity, also inhibiting MAO-A [24]; the bioavailability is

low; the drug shows extensive first-pass hepatic metabolism [28]; and it is structurally related to amphetamine so that it is metabolised to methamphetamine-based compounds, implicated in cardiovascular toxicity, including hypertension [24].

Rasagiline is an irreversible MAO-B inhibitor that is more selective than selegiline [29]. It has recently received approval in Europe (2005) and the United States (2006) for the treatment of PD. It is not structurally related to amphetamine and therefore does not exhibit the side effects associated with selegiline. The efficacy of rasagiline has been demonstrated as an adjunct to levodopa and as monotherapy for early-stage PD [27,30-32]. Despite the well-documented 'selectivity' of rasagiline for MAO-B, the manufacturer recommends virtually all dietary and drug restrictions required for nonselective MAO inhibitors [29].

Another drug used in the treatment of PD is amantadine, which shows its greatest effect on the treatment of dyskinesia [33-38]. Recent evidence suggests that it may also have neuroprotective properties through its ability to block *N*-methyl-*D*-aspartate receptors, which have been implicated in neurodegeneration by mediating excitotoxicity in the basal ganglia [39]. Adverse effects associated with amantadine include altered mental status, lower-extremity oedema and livedo reticularis [14,38].

Anticholinergics can produce benefits in the treatment of PD-related tremor in combination with levodopa. However, they are associated with certain adverse effects, including dry mouth and cognitive impairment, limiting their use [14,40].

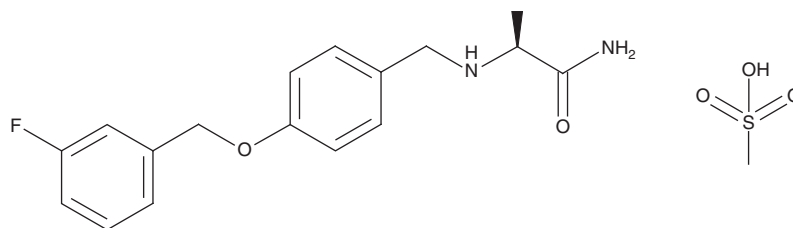
## 1.3 Drugs under development

Newer compounds in late clinical development are fipamezole (an  $\alpha$ -2 receptor antagonist), talampanel (an AMPA-kainate receptor antagonist), istradefylline and BIIBO14 (adenosine receptor A2a antagonists), pardoprunox (a non-ergolinic DA agonist), methylphenidate (a mild CNS stimulant), NS 2330 (tesofensine, a monoamine reuptake inhibitor) and atomoxetine HCl (a noradrenaline reuptake selective inhibitor). Isradipine (a calcium channel blocker) has recently been used in PD. These molecules are theoretically targeted to address motor fluctuations and dyskinesias and to provide neuroprotection.

## 2. Safinamide

### 2.1 Introduction to the compound and chemistry

Safinamide, (*S*)-(+)-2-[4-(3-fluorobenzoyloxybenzylamino)propanamide]methanesulfonate (1:1 salt) (Figure 1), is an orally available derivative of the chemical class of  $\alpha$ -aminoamides, with multiple mechanisms of action and experimental evidence of symptomatic and neuroprotective potential [41]. Its potency, broad spectrum of activity, and safety profile led to safinamide being investigated for the treatment of epilepsy and PD. Safinamide inhibits MAO-B and DA reuptake [42], resulting in relief of PD symptoms. In addition, safinamide blocks voltage-dependent sodium channels, modulates calcium channels and inhibits glutamate release induced by abnormal



**Figure 1. Chemical structure of safinamide.**

neuronal activity, all of which may provide improvements in cognition and neuroprotective properties [43,44].

### 2.1.1 Dopamine modulation

MAO catalyses the major inactivation pathway for the catecholamine neurotransmitters, including DA. Two distinct isoforms of MAO have been identified: MAO-A and MAO-B. MAO-A preferentially deaminates noradrenaline and serotonin while MAO-B shows affinity for dopamine and phenylethylamine. Monoamines (e.g., DA) are substrates of both isoforms; however, in humans, more than 80% of DA is metabolised by MAO-B. While reversible inhibitors of MAO-A have been indicated in the treatment of depression, the selective inhibition of MAO-B has a therapeutic role in the treatment of PD [24,45].

Unspecific inhibition of MAO results in unmetabolised dietary amines entering the circulatory system, where they induce noradrenaline release from peripheral adrenergic neurons, resulting in a severe and potentially fatal hypertensive response. To avoid this 'cheese effect', MAO-B inhibitors with high selectivity have been called for [24].

Safinamide is a DA modulator that exhibits potent, highly selective and reversible MAO-B inhibition (full inhibition in human platelets at 0.6 mg/kg orally) [46]; its selectivity for MAO-B is superior to selegiline and rasagiline. In binding studies in rat brain mitochondria *in vitro*, safinamide demonstrated 5000 times greater selectivity for MAO-B than for MAO-A (based on  $IC_{50}$  values in a radioenzymatic assay) compared with 127 times and 103 times greater selectivity for MAO-B over MAO-A with selegiline and rasagiline, respectively [46-48]. This level of selectivity may omit the need for any dietary restrictions with safinamide use (i.e., to avoid the 'cheese effect'), although this remains to be verified [49].

In addition to its selectivity, MAO-B inhibition by safinamide is fully reversible: safinamide does not form the irreversible covalent bonds with MAO-B that are associated with selegiline and rasagiline [50]. This is an important advantage for patients who experience adverse events that need to be treated with other drugs, as the reversibility of safinamide avoids potential drug interactions [49].

### 2.1.2 Sodium channel inhibition

Safinamide has demonstrated in rat cortical membranes high affinity for the sodium channel binding site II. Safinamide

inhibits the fast sodium currents in a concentration- and state-dependent manner. At depolarised membrane potentials, when a large number of channels are in the inactivated state, mimicking neuronal pathologic conditions, safinamide is three times more potent ( $IC_{50} = 33 \mu M$ ) than at resting potential ( $IC_{50} = 96 \mu M$ ), suggesting a preferential interaction with the inactivated state of the channel [46]. Therefore, in the presence of safinamide, a much higher proportion of sodium channels is kept in the inactivated state and prevented from activating. In addition, the blockade of sodium currents by safinamide is use-dependent, meaning that an enhancement of the blockade occurs during high-frequency stimulation when many channels are in the inactivated state. This effect results in depression of neuronal activity at high-frequency firing and ineffectiveness at a normal firing rate. This effect also suggests that safinamide selectively depresses abnormal activity, leaving physiologic activity unaffected and thus avoiding CNS depressant effects [46].

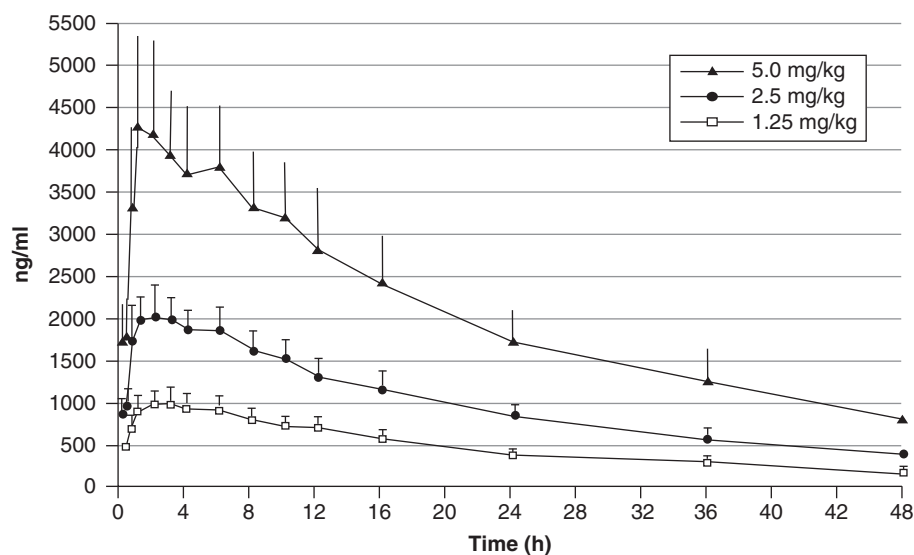
Safinamide inhibits the action potential firing in cortical neurons, slowing recovery from the inactivation state and thus reducing channel availability for subsequent sodium spikes [46].

### 2.1.3 Calcium channel modulation

In rat cortical neurons, safinamide also inhibited N-type calcium currents ( $IC_{50} = 23 \mu M$ ) [46], suggesting that it might participate in the inhibition of neurotransmitter presynaptic release (e.g., excitatory amino acids), mostly influenced by the activation of N-type calcium channels. *In vivo*, L-type calcium channels are not affected by safinamide, as demonstrated by the lack of effects by safinamide (up to 50 mg/kg intraperitoneally in the pithed rat) on blood pressure and heart rate or on the pressor response to noradrenaline [46].

### 2.1.4 Glutamate release inhibition

In rat hippocampal synaptosomes, safinamide inhibits glutamate release induced by depolarising conditions ( $IC_{50} = 9 \mu M$ ). At high potassium concentrations, the release of the neurotransmitter is calcium-mediated. Therefore safinamide, by blocking the N-type calcium mobilisation, inhibits glutamate release, one of the most relevant excitotoxic inputs leading to neuronal death [46].



**Figure 2. Plasma levels of safinamide at steady state in healthy volunteers at oral doses of 1.25, 2.5 and 5.0 mg/kg for 7 days.**

Note the linearity and proportionality of the curves within the three doses.

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## 2.2 Neuroprotection

It is possible that MAO-B inhibition prevents formation of toxins or free radicals formed by oxidative processes. This is demonstrated with all three drugs, selegiline, rasagiline and safinamide, by using the *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model. MPTP is a neurotoxin that is metabolised by MAO-B to the active toxin MPP<sup>+</sup>, which causes PD-like symptoms in humans and is selectively toxic to dopaminergic neurons in the substantia nigra in animals. The three drugs prevented MPTP from being oxidised to MPP<sup>+</sup> [46] and therefore obviously prevented the neurotoxic effect of MPP<sup>+</sup>.

In clinical trials, results of the Deprenyl And Tocopherol Antioxidative Therapy Of Parkinsonism (DATATOP) study [51] assessing the potential neuroprotective properties of selegiline were disappointing, whereas, according to the results of the TVP-1012 in Early Monotherapy for Parkinson's disease Outpatients (TEMPO) trial [30], rasagiline seems to be more promising, although the significant improvement of the Unified Parkinson's Disease Rating Scale (UPDRS) total score is not clinically relevant.

Neuroprotective properties of safinamide, independent of MAO-B inhibition, have been investigated in models *in vitro* and *in vivo*. These include prevention of *in vitro* veratridine-induced neuronal cell death through sodium and calcium channel inhibition, protection of hippocampal neuronal loss induced by the glutamate analogue kainic acid in rats, and a neuro-rescuing effect on ischaemia-induced hippocampal neuronal death in gerbils [46].

## 2.3 Pharmacokinetics and metabolism

Preclinical pharmacokinetic studies have been performed in mice, rats and monkeys [46]. Safinamide has a high oral

bioavailability (80 – 92%), is rapidly absorbed and after reaching peak levels in plasma within 0.5 – 2 h declines, with a terminal half-life of about 3, 7 and 13 h in mice, rats and monkeys, respectively. Brain levels of safinamide are always higher than the corresponding plasma concentrations, with a brain:plasma ratio of 16, 16 and 9 in mice, rats and monkeys, respectively. At current pharmacological doses, the brain levels of safinamide are expected to be in the high micromolar range.

Assuming for humans the same brain:plasma ratio as for monkeys (i.e., 9), plasma levels of 5 – 6  $\mu$ M, which are seen in humans at steady state after 7 days of an oral dose of 150 mg, should correspond to brain levels of 40 – 50  $\mu$ M [46].

Pharmacokinetic studies conducted in 97 healthy volunteers enrolled in Phase I studies showed that safinamide absorption is rapid (passive diffusion) after single or multiple oral dosing under fasting conditions, reaching  $T_{max}$  in 1.8 – 2.8 h [C Caccia, pers. commun.]. Food intake delays the absorption of the drug ( $T_{max} = \sim 5$  h), without affecting its extent. The elimination half-life is in the range of 21 – 24 h, allowing once-daily administration. The  $AUC_{\infty}$  acute or  $AUC_{ss}\tau$  steady-state and  $C_{max}$  increased linearly in a dose-proportional manner (dose-linearity and dose-proportionality were both demonstrated for safinamide), both indicative of first-order kinetics (Figure 2) [52].

The apparent oral volume of distribution of the unchanged drug is approximately 150 l, indicative of extensive extravascular distribution, in agreement with the high lipophilicity of the safinamide base, and a plasma protein binding (92%) apparently lower than the extravascular tissue binding [52].

Safinamide appears to be extensively biotransformed. Unchanged safinamide in urine and faeces respectively accounted for 7 – 10% and 1.5% of the administered dose,

**Table 1. UPDRS-III scores and standard deviations at baseline and study end in the intention-to-treat cohort and a subset of patients taking one DA agonist.** Responders were defined as patients improving  $\geq 30\%$  in their UPDRS-III scores.

Parameter	ITT cohort (n = 167)			DA agonist-treated subset (n = 101)		
	Placebo, n = 56	Safinamide 0.5 mg/kg, n = 55	Safinamide 1.0 mg/kg, n = 56	Placebo, n = 34	Safinamide 0.5 mg/kg, n = 33	Safinamide 1.0 mg/kg, n = 34
UPDRS-III mean $\pm$ SD baseline	17.3 $\pm$ 7.8	16.4 $\pm$ 7.7	16.5 $\pm$ 7.4	17.1 $\pm$ 8.6	17.6 $\pm$ 7.5	16.9 $\pm$ 7.4
UPDRS-III mean $\pm$ SD final	16.7 $\pm$ 8.9	13.8 $\pm$ 7.8	13.2 $\pm$ 7.1	15.7 $\pm$ 7.7	13.6 $\pm$ 7.3	12.2 $\pm$ 6.5
Baseline to final difference (%)	-0.6 (3.4)	-2.6 (15)	-3.3 (20)*	-1.4 (8)	-4.0 (22)	-4.7 (27)*
Responders (rate of responders in the same groups)	12 (21.4)	17 (30.9)	21 (37.5) <sup>‡</sup>	7 (20.6)	12 (36.4)	16 (47.1) <sup>§</sup>

\*p < 0.05 by Dunnett test after analysis of covariance.

<sup>‡</sup>p = 0.016 by logistic regression analysis.

<sup>§</sup>p = 0.024 by logistic regression analysis.

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SD: Standard deviation; ITT: Intention-to-treat.

indicative of practically complete absorption of the drug and very little biliary excretion.

Pharmacokinetic data showed no relevant accumulation with safinamide at steady state. From data obtained from *in vitro* experiments, no relevant interactions were found in oxidative metabolic pathways controlled by CYP2C9, CYP2C19, CYP2D6, CYD2E1 and CYP3A4 [52].

Studies on healthy volunteers, which focused on single ascending oral doses of the drug (2.5 mg/kg – 10.0 mg/kg) or on repeated oral doses, confirmed the linear kinetics of safinamide [53,54].

After a single oral administration of safinamide, the main components observed in plasma were the unchanged drug and two metabolites, the ‘safinamide acid’ (NW-1153) and the *N*-dealkylated acid (NW-1689). In urine, the main metabolites were the safinamide acid and the glucuronide of the *N*-dealkylated acid. Based on plasma and urine data, the main Phase I enzymes involved in human safinamide metabolism are amide hydrolases and MAO-A. The main Phase II enzyme involved is a glucuronyltransferase.

## 2.4 Clinical efficacy of safinamide

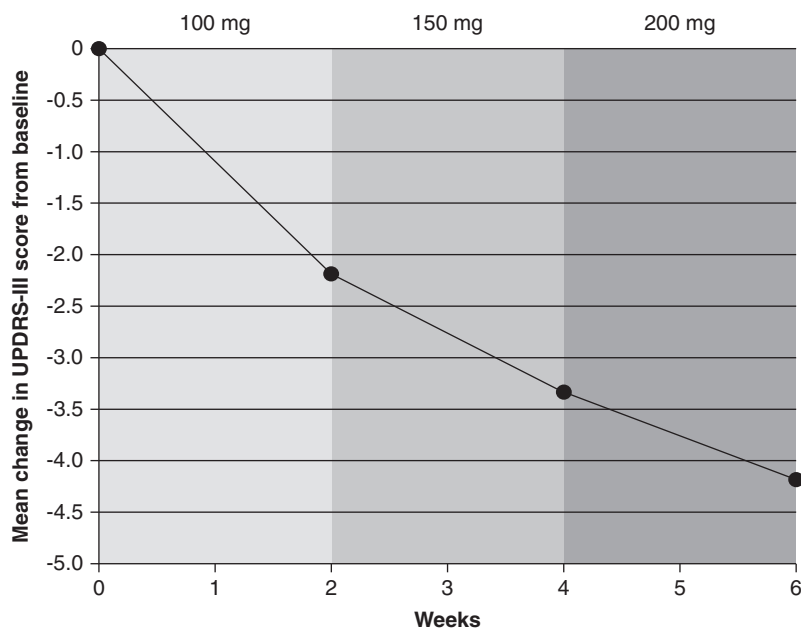
Two published studies show the efficacy of safinamide in patients with PD [55,56].

A three-month, placebo-controlled study was conducted on 172 patients with early PD to investigate the effects of safinamide on motor function [55]. The average age of participants was approximately 59 years, 64% were male and the mean duration of PD was approximately 30 months. Around 50% of patients had a Hoehn and Yahr stage of 2, and the mean UPDRS-III score at baseline was approximately 17. There were no systematic or statistically significant differences

for all three treatment groups for any demographic or disease severity variable. Patients were required to follow a tyramine-restricted diet. Patients were randomised to receive placebo, low-dose safinamide (0.5 mg/kg) or high-dose safinamide (1 mg/kg) (5 capsules to be taken daily, fasted, at 8 a.m.). The high dose was calculated as the dose that would mediate blockage of glutamate release and ion channels, while the low dose was calculated to provide complete MAO-B inhibition. Responders were defined as those patients with  $\geq 30\%$  improvement in UPDRS-III scores at the end of the study versus baseline. At the end of the study, 37.5% of patients receiving high-dose safinamide (median dose 70 mg/day) responded to treatment compared with 21.4% of the placebo-treated patients (p = 0.02), with a mean motor score decrease of 3.3 (p < 0.05 compared with baseline) (Table 1) [55].

Safinamide was also administered in this study as adjunctive therapy to a subgroup of patients (n = 101) who were already on a stable, single dose of DA agonist (apomorphine, n = 1; bromocriptine, n = 9; cabergoline, n = 8; pergolide, n = 31; piribedil, n = 4; pramipexole, n = 32; ropinirole, n = 16). Patients receiving safinamide (1 mg/kg) as adjunctive therapy showed a significant increase in response compared with placebo (47.1% vs 20.6%, p = 0.02), with a mean motor score decrease of 4.7 (p < 0.05, Table 1) [55].

The study demonstrated a robust symptomatic effect with the higher dose of safinamide. The study was well designed, being focused on a specific cut-off of 30% that was based on the known placebo effect observed in PD [57]. The placebo effect in the study, however, was higher than usually observed, as some 20% of patients on placebo were found to be responders.



**Figure 3. Mean changes of UPDRS-III (motor function) score (point variations on the ordinate) in patients after addition of increasing doses of safinamide to DA agonists.** Patients ( $n = 14$ ) were on a stable dose of a single DA agonist, and every 2 weeks the initial safinamide dose of 100 mg/day was increased, to 150 and 200 mg/day. Reproduced with permission from [56].

An unexpected finding was the superior benefit of safinamide when added to a single DA agonist. The authors concluded that the ability of safinamide to block ion channels and inhibit glutamate release was adding to the symptomatic effect of MAO-B inhibition on motor function [55].

The other reported study investigating efficacy of safinamide was an open-label pilot study, in which doses of 100, 150 and 200 mg/day were progressively administered to patients ( $n = 14$ ) on a stable dose of DA agonist over 6 consecutive weeks [56]. A progressive improvement in motor performance was observed at the end of the study, with a 4.2-point decrease in UPDRS-III score, changing from a mean baseline score of 18.0 (in 'on' conditions) to a mean score at week 6 of 13.8 ( $p < 0.001$ , Figure 3) [56]. Significant changes from baseline were observed already at week 2 ( $p = 0.02$ ) and at week 4 ( $p < 0.001$ ).

A different group of patients ( $n = 11$ ), not overlapping with the 14-patient group, received safinamide at the same dose as adjunctive treatment to levodopa. A significant decrease was observed in UPDRS-IV score. At 100 mg/day there was a 1.2-point decrease (from a mean score of 5.1 to 3.9;  $p = 0.008$ ) and at 150 mg/day a 3.0-point decrease (mean score 3.0;  $p < 0.001$ ) but no further improvement was seen with 200 mg/day (mean score 2.9;  $p < 0.001$ ) (Figure 4) [56]. The addition of safinamide to levodopa produced a significant progressive augmentation of the levodopa serum AUC (measured using HPLC coupled with an electrochemical detector), ranging from 56% at the 100 mg/day

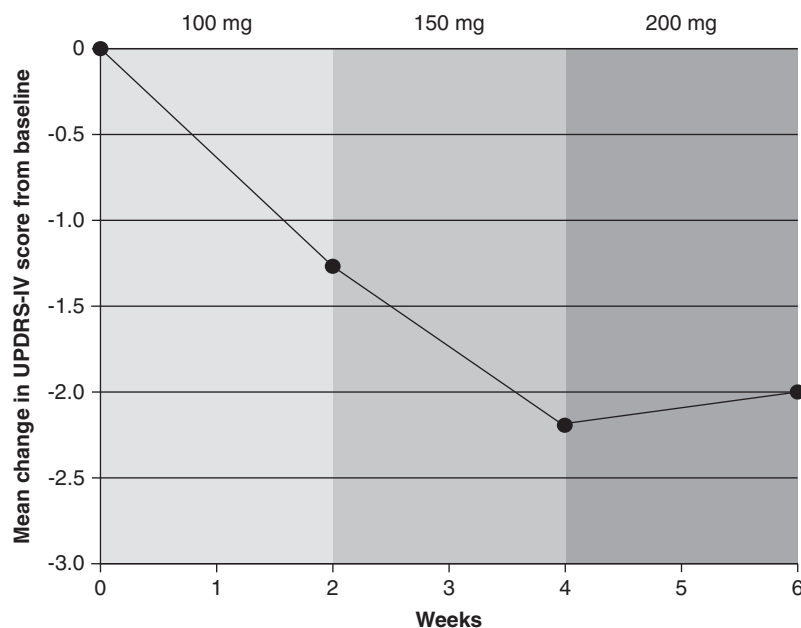
dose to 88% with 200 mg/day. Two patients had their levodopa dose reduced by a third [56].

Several conclusions were drawn from this study. MAO-B inhibition was close to 100% at all doses (evaluated in platelet-rich plasma by a radioenzyme assay using [ $^{14}\text{C}$ ]-PEA (phenylethylamine) as a selective substrate), and the moderate increase in DA levels (measured using HPLC as described by Blandini *et al.* [58] with slight modifications) of 30% over baseline remained constant at all dose levels. However, symptom improvement was observed at each increment of the safinamide dose, which suggested that, as hypothesised, safinamide has other symptom-relieving effects.

To eliminate the possibility that safinamide raised peripheral levodopa levels by inhibiting the main metabolising enzymes dopadecarboxylase and COMT, a separate study demonstrated that safinamide had no inhibitory activity on COMT [C Caccia, pers. Commun.]. This suggested that safinamide itself raised levodopa levels by the putative inhibition of DA reuptake in addition to the consequences of MAO-B inhibition.

## 2.5 Safety and tolerability

To describe the pharmacokinetics, pharmacodynamics and tolerability of safinamide, four clinical trials on healthy male volunteers were performed using a concentration range of 25 – 10,000  $\mu\text{g/ml}$ . Safinamide was administered in single (up to 10 mg/kg/day) or repeated doses (5 mg/kg/day) to steady state and included a food-interaction trial. Tolerability in all four trials proved to be good [52].



**Figure 4. UPDRS-IV scores in patients after addition of increasing doses of safinamide to levodopa.** Patients were on a stable dose of levodopa, and every 2 weeks the initial safinamide dose of 100 mg/day was increased, to 150 and 200 mg/day. Reproduced with permission from [56].

In the placebo-controlled patient study [55], safinamide was not associated with any tolerability issues. The adverse events experienced with 0.5 mg/kg and 1 mg/kg were lower than those reported for the placebo group. By body system, the most common events experienced in the safinamide arms were nervous system disorders (11 and 7% of subjects in the low- and high-dose arms, respectively), gastrointestinal disorders (5 and 11%), infections and infestations (7 and 7%), skin and subcutaneous tissue disorders (7 and 4%), general disorders and administration-site conditions (2 and 5%) and cardiac disorders (5 and 0%). In the open-label pilot study, doses up to 200 mg/day were well tolerated, with no serious or clinically significant adverse events [56].

### 2.6 Further trials

The results of a completed Phase III trial of safinamide as adjunctive therapy to DA agonists are to be published, and a trial as adjunctive therapy to levodopa is ongoing. Further trials of the lower dose range (50 – 100 mg/day) of safinamide as an adjunct to DA agonists and levodopa are planned, and a comprehensive cognition study is anticipated.

### 3. Conclusion

Safinamide appears to have a multimodal mechanism of action. It increases levels of available DA through highly selective and reversible MAO-B inhibition. However, safinamide also has an important and novel mode of action that results in blockade of sodium channels and modulation of calcium channels, which inhibits glutamate release and

therefore may provide a level of cognitive improvement and neuroprotection.

Clinical trials have demonstrated that already a low dose of safinamide provides full MAO-B inhibition [56], suggesting that the observed dose-dependent biochemical and symptomatic effects may be related to the drug's additional mechanisms of action. All studies have demonstrated good tolerability.

Ongoing trials of safinamide will examine its efficacy and tolerability as an adjunct to DA agonists and levodopa and other possible effects on nonmotor symptoms, such as cognition.

### 4. Expert opinion

Safinamide is a promising new drug for the treatment of PD. Compared with other available treatments, safinamide reaches extraordinarily high CNS concentrations [46], and its selective effect on MAO-B could explain its symptomatic effect on PD symptoms. Moreover, its reversible bond to MAO-B offers an option to easily control possible side effects.

In our personal experience with study protocols of safinamide, we had the chance to follow 53 patients randomised to safinamide or placebo treatment for as long as 5 years. Despite blinding, we could observe a clear separation between patients. Some patients experienced powerful improvements in motor performance, which were higher than the 30% cut-off set to account for a placebo effect, and confirmed by standardised assessments (low inter-rater variability).

## Safinamide

Similarly, drug withdrawal resulted in evident worsening of motor symptoms.

Although we could not unblind the data during the study, the extent of the effect was surprising, as we had never observed such a clear separation between patients admitted to blinded protocols during our investigation of other drugs (including new DA agonists, antiglutamatergic drugs, A2a antagonists, and MAO-B inhibitors).

As safinamide has no direct dopaminomimetic activity, we hypothesise that its symptomatic effect is mostly dependent on the high concentration that this drug reaches in the CNS (with a brain:plasma ratio of 9:1 in primates) and on its powerful MAO-B inhibiting effect.

Homeostatic interactions between DA and glutamate are central to the normal physiology of the basal ganglia. In PD, this relationship is altered, resulting in upregulation of corticostriatal glutamatergic function in levodopa-induced dyskinesias [59]. Any drug that can counteract such unbalance in glutamate function is potentially useful in controlling dyskinesias [60].

Several antiglutamatergic drugs, such as amantadine, budipine, and memantine, can improve dyskinesia in PD patients [35,36,61]. In studies *in vitro*, safinamide demonstrates strong antiglutamatergic activity when the release of glutamate is excessive and seems promising as antidyskinetic treatment. Yet the only available study describing safinamide's effects in levodopa-treated patients reported that levodopa doses were reduced when safinamide was added to levodopa [56], which resulted in reductions in dyskinesias accompanied by UPDRS motor improvements. Thus, motor improvements could result from the symptomatic effect of safinamide, while dyskinesia reduction could result from levodopa reduction.

It is not appropriate, however, to compare these results with those observed following amantadine adjunctive therapy

in dyskinetic patients, who experienced reduction of dyskinesias when levodopa levels were left unchanged [38]. The main disadvantage with amantadine is tachyphylaxis, as antidyskinetic effects almost disappeared during a 12-month observation period [38].

In order to understand whether the antiglutamatergic effect of safinamide might reduce dyskinesias, further studies should be conducted, replicating the design used with amantadine. In our opinion we must, however, argue that the antidyskinetic effects of amantadine are far from being clearly understood based on pharmacologic properties, as more recent hypotheses suggest that effects on dyskinesias might be linked to adenosine A2a antagonistic properties [62] rather than to the hypothesised antiglutamatergic effect.

Overall, safinamide shows promising effects (based on UPDRS motor scores), which we believe are most likely due to its high CNS bioavailability and high MAO-B selectivity. Preliminary studies have demonstrated its efficacy and safety. Safinamide has a unique and diverse pharmacologic profile and hence appears to be a promising new agent in the treatment of PD.

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## Declaration of interest

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M Onofrj has received a salary from Newron to participate in two meetings on safinamide.

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