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REVIEW ARTICLE

Clinical Pharmacokinetics and Pharmacodynamics of Safinamide

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Abstract The symptoms of Parkinson's disease (PD) reflect disruptions of a number of brain neurotransmitter systems of varying type and degree. Pharmacological agents with multiple neurochemical mechanisms of action are therefore promising candidates for countering these problems and providing comprehensive symptomatic relief for patients. The pharmacological profile of safinamide includes reversible monoamine oxidase B inhibition, blockage of voltage-dependent Na^+ channels, modulation of Ca^{2+} channels, and inhibition of glutamate release. Safinamide is administered once daily at oral doses of 50–100 mg; it is well-tolerated and safe. Clinical trials have found that it ameliorates motor symptoms when added to established levodopa or single dopamine receptor agonist therapy. The future role of safinamide in PD may be that it enables a reduction in the dosage of dopamine replacement therapies, thereby reducing the adverse effects associated with these treatments. The clinical convenience (once-daily administration), safety, and tolerability of safinamide are better than those of dopamine receptor agonists. The introduction of safinamide reflects a change of approach to drug development for anti-parkinsonian agents in that its broad spectrum of action corresponds to the multiple heterogeneous alterations of brain neurochemistry in PD, rather than being targeted at a single receptor type or neurochemical process. Safinamide is a promising new instrument for the effective symptomatic therapy of PD.

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Key Points

Safinamide inhibits monoamine oxidase B and reduces glutamate release.

This pharmacological profile suggests use of safinamide in Parkinson's disease.

Safinamide improved motor symptoms in patients with Parkinson's disease.

1 Introduction: Drug Therapy for Parkinson's Disease

1.1 Anticholinergic Agents

Anticholinergic drugs have been employed to treat the tremor of Parkinson's disease (PD), the second most common chronic neurodegenerative disorder, since the nineteenth century, longer than any other class of pharmacological agent used to manage this disorder. Their long-term use is associated with impaired short-term memory functioning [1].

1.2 Levodopa

The introduction of levodopa in the 1960s was a major advance in the drug therapy of PD. Levodopa is the amino acid precursor of the neurotransmitter dopamine; in contrast to dopamine, it crosses the blood–brain barrier into the central nervous system (CNS), where it is converted into

dopamine in presynaptic neuronal termini in the striatum. It thereby ameliorates the nigrostriatal dopaminergic deficiency that underlies the motor symptoms of PD by stimulating postsynaptic striatal dopamine receptors in a continuous fashion, improving the three main motor symptoms of PD: akinesia, rigidity, and tremor. As the half-life of levodopa is short, people with PD must take levodopa several times each day. In order to reduce the frequency of administration, levodopa has been combined with inhibitors of the major enzymes that metabolize levodopa, DOPA decarboxylase and catechol-*O*-methyltransferase (COMT) since the 1970s; more recently, retarded release formulations and infusion systems have been developed [1]. The primary objective of all of these strategies is to deliver dopamine to the target CNS regions in as continuous and consistent a manner as possible.

1.2.1 Inhibition of Glial Enzymes Reduces the Motor Complications of Levodopa Therapy

Despite these enhancements of levodopa administration, the rise and fall in plasma concentrations of the drug and therefore of dopamine in the synaptic cleft still contribute to the development of motor complications that reduce the longer-term quality of life for PD patients. In the course of long-term levodopa treatment, intervals of acceptable motor control ('ON'-time) are increasingly punctuated by periods in which motor symptoms are again manifest ('OFF'-time). Further, involuntary movements, predominantly of the limbs, also develop; these 'dyskinesias' occur more frequently during 'ON'-time, and in some patients are so severe that they limit quality of life. One strategy that has proved useful for ameliorating these motor complications is inhibition of dopamine metabolism by monoamine oxidase (MAO) and COMT in glial cells, producing more continuous and stable dopamine levels in the synaptic cleft [1].

1.3 Direct Stimulation or Indirect Modulation of Postsynaptic Dopaminergic Receptor Function

An alternative approach is direct stimulation of postsynaptic striatal receptors with dopamine receptor agonists. Their affinity for the dopamine receptor and metabolic half-life determine the efficacy of dopamine agonists [1]. Amantadine provides yet another option; initially employed as an antiviral compound, it also has a moderate effect on the motor symptoms of some PD patients. Amantadine blocks *N*-methyl-D-aspartate (NMDA) receptors, and this feature contributed to investigation of NMDA receptor blockade as a strategy for enhancing dopaminergic transmission in PD. Amantadine possesses other pharmacological properties, not all of which have been explored in detail, including direct dopamine-mimicking effects [2, 3]. A further approach is antagonism of adenosine A_{2A} receptors; for instance, the caffeine analog istradefylline, currently available for clinical use only in Japan, modulates downstream postsynaptic dopamine receptor function, thereby improving motor behavior in PD [4].

1.4 Principles of Drug Development and Therapy in PD

Drug development has traditionally focused on improving motor symptoms in PD, and the effects of drugs on non-motor symptoms have largely been neglected. There has been little advance since the most recent effective therapeutic principle, the introduction more than 10 years ago of retarded release formulations of dopamine agonists. Reasons for this relative standstill include an excessive focus on particular molecular structures: research concentrated on dopamine receptor subtypes and drugs with a mechanism of action. Furthermore, the results of some drug trials were disappointing because their designs did not take the heterogeneity of PD into account, but it has become clear that PD encompasses many subtypes, rather than being a unitary disease. As a result, drug therapy is complex, requiring cautious titration of multiple drugs, combined and adjusted to the disease process in an individual manner [5]. In addition, an optimized therapeutic regimen avoids physiological adaptation to PD. Unconscious learning processes may also aggravate certain symptoms of PD, such as rigid posture, reduced swinging of the arms, walking with small steps, and speaking in a low voice.

For these reasons, a pharmacological agent for PD with a broader spectrum of action has long been required. A promising candidate for this role is safinamide, recently approved in Europe for the treatment of PD, which may initiate a new era in drug development for PD. The aim of this review is to describe the pharmacokinetic and pharmacodynamic properties of safinamide and to provide an outlook on its potential for application in other diseases.

A PubMed search was undertaken for the term "safinamide" (census date: May 2016) and 89 relevant publications were identified. Three abstracts are also cited here, as they describe important trials of safinamide that have not yet been published as full articles.

2 The Pharmacologic Principle of Monoamine Oxidase (MAO) Inhibition and Safinamide

Glial cells contain two enzymes that metabolize biogenic amines: COMT and MAO. MAO, located in the outer mitochondrial membrane, occurs as two isozymes: A and B. MAO-A is predominantly found in the intestinal tract

and, in the CNS, presynaptic neurons; MAO-B is mainly located in the brain, generally in glial cells near dopaminergic synapses. MAO-B regulates the free concentrations of biogenic amines in the synaptic cleft [6, 7]. The oxidation of monoamine substrates by MAO-B also generates reactive oxygen species (ROS), the overflow of which contributes to the oxidative synthesis of neurotoxins such as salsolinol and 6-hydroxydopamine, recognized as accelerating chronic neurodegenerative processes. Findings from clinical and laboratory research suggest that a selective reduction of MAO-B activity slows chronic neurodegeneration, particularly via apoptosis, a natural cellular suicide program. Essential predisposing factors to such neurodegeneration include genetic damage, incorrect folding of proteins, and reduced neurotrophic cell survival factor synthesis.

MAO-B inhibitors may act to slow neurodegeneration through a number of mechanisms, including directly stabilizing mitochondrial membranes, inducing anti-apoptotic processes, preventing the opening of mitochondrial permeability transition pore complexes and mitochondrial swelling, lowering the mitochondrial membrane potential, and releasing cytochrome C, which suppresses various components of apoptosis, such as caspase activation and nuclear translocation of glyceraldehyde-3-phosphate-dehydrogenase [8, 9]. MAO-B inhibitors also increase gene transcription by activating the nuclear transcription factor system, which also promotes cellular survival [10].

Different modes of action characterize four different types of MAO inhibitor (MAOI). The first class are irreversible, non-selective inhibitors (such as tranylcypromine), the second are reversible, selective MAO-A inhibitors (moclobemide), and the third are irreversible, selective MAO-B inhibitors (selegiline, rasagiline) [7]. Specific inhibition of one MAO isoform activity is only possible within a certain concentration range of the inhibitor; that is, specificity of inhibition is lost at higher doses [6, 7]. The fourth class of inhibitor is represented by safinamide, the only reversible MAO-B inhibitor [7, 11].

2.1 Irreversible MAO-B Inhibitors Used in PD Therapy

Selegiline and rasagiline are relatively selective MAO-B inhibitors, but selectivity is lost and MAO-A is also inhibited at higher doses (selegiline >20 mg/day; rasagiline >2 mg/day). For this reason, a low risk of tyramine-associated hypertension (the 'cheese effect') is possible at higher doses. Selegiline and rasagiline may also increase the activity of catecholaminergic neurons by mechanisms other than MAO B inhibition, including stabilization of mitochondrial membrane potential and anti-apoptotic and antioxidant effects [12–14].

2.2 Safinamide: A Reversible MAO-B Inhibitor

Safinamide—(2*S*)-2-[[4-[(3-fluorophenyl)methoxy]phenyl] methylamino]propanamide]—is a small, water-soluble molecule, usually prepared as its methanesulfonate salt (Fig. 1). Safinamide has a relative broad spectrum of mechanisms of action, and its toxic potential in the CNS is low. It resembles selegiline and rasagiline in that it modulates dopaminergic neurotransmission by MAO-B inhibition, but its inhibition is reversible. In rats, safinamide is about 5000 times more selective for MAO-B than for MAO-A, and in humans it is 1000 times more selective for MAO-B; in comparison, selegiline is 127 times and rasagiline 103 times more selective for MAO-B than for MAO-A [12]. This selectivity explains why no cheese effect has been detected with safinamide [15, 16]. Safinamide also inhibits Na^+/Ca^{2+} channels, critical to the initial step in the final inhibition of glutamate release, meaning safinamide has NMDA receptor-antagonizing effects similar to those of amantadine (Fig. 2).

2.3 Safinamide in the Treatment of PD: Animal Models

The unique combination of inhibition of MAO-B and of glutamate release suggests that safinamide might provide symptomatic relief of motor impairment in PD patients; this supposition is supported by findings that it ameliorates disturbed motor behavior in animal models of PD [17, 18].

2.4 Safinamide and Neuroprotection

Safinamide has been reported to be neuroprotective in in vitro and in vivo models of PD and multiple sclerosis [19]. Safinamide blocked veratridine-induced neuronal death in vitro by inhibiting Na^+ and Ca^{2+} channels. It also reduced hippocampal neuronal loss in rats exposed to the glutamate analog kainic acid and protected hippocampal neurons from experimentally induced ischemia in gerbils [20, 21].

2.5 Pharmacokinetics of Safinamide

Safinamide is well-absorbed after oral administration. The maximum concentration (C_{max}) is reached in 2–4 h in

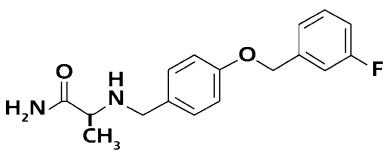

Fig. 1 Chemical structure of safinamide

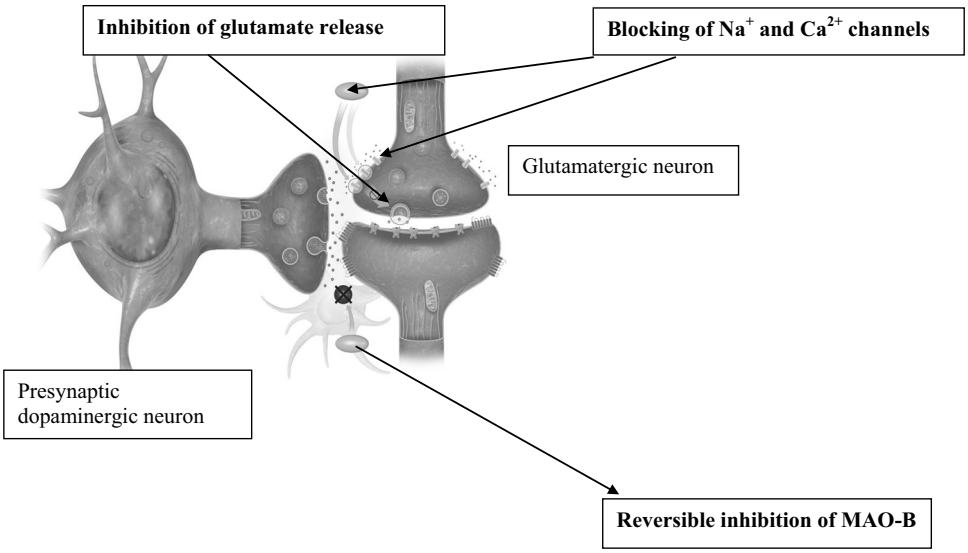

Fig. 2 Key pharmacological properties of safinamide. *MAO-B* monoamine oxidase B

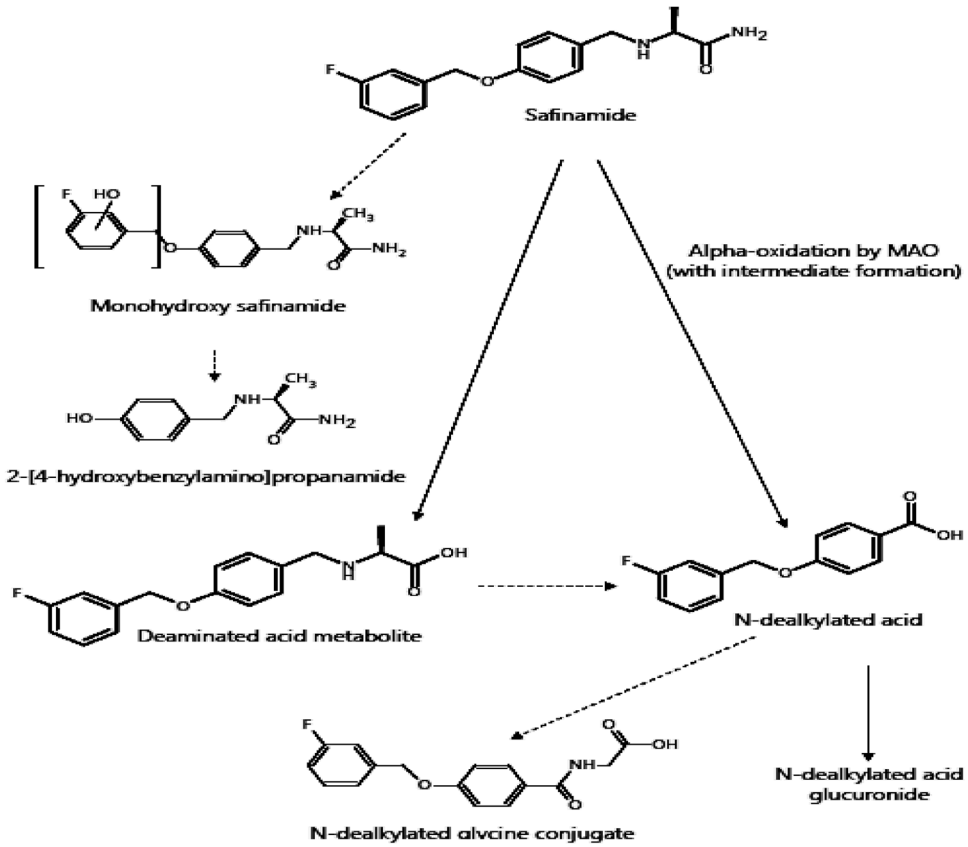

Fig. 3 Major metabolic pathways of safinamide (adapted and modified from Riederer et al. [1] and Metman et al. [2]). *MAO* monoamine oxidase

people who are fasting and its absolute bioavailability is 95 %. Safinamide reaches steady-state concentrations within a week; plasma protein binding is 88–90 %. The volume of distribution of safinamide is approximately 165 L, 2.5 times body volume, indicating extensive extravascular distribution of safinamide. The terminal elimination half-life is approximately 22 h (range 20–30 h) [19]; total clearance is 4.6 L/h [22].

Metabolism of safinamide is predominantly by amide hydrolytic oxidation; the major metabolite is safinamide acid. Other pathways include ether bond oxidation to *O*-debenzylated safinamide and oxidation of safinamide or

safinamide acid to *N*-dealkylated acid; these metabolites have no pharmacological activity. The β-glucuronide of the *N*-dealkylated acid and monohydroxy-safinamide have been found in urine [23, 24]; in addition, the glycine conjugate of the *N*-dealkylated acid and 2-[4-hydroxybenzylamino]propanamide were tentatively identified as minor urinary metabolites in urine [24, 25] (Fig. 3).

2.5.1 *Administration of Safinamide in Cases of Liver or Kidney Dysfunction*

Safinamide is administered once per day at a dose of 50 or 100 mg. Mild to moderate hepatic impairment increases plasma safinamide concentrations by 30–80 %; there is no need to adjust the dose in the case of mild hepatic impairment, but a reduction to 50 mg/day is recommended in cases of moderate impairment. Severe hepatic impairment is a contraindication for safinamide use. Renal impairment has no influence on safinamide concentrations.

2.5.2 *Pharmacokinetic Drug Interactions*

Systemic safinamide concentrations do not interfere with enzyme activities. No commercially available drug is known to have a clinical relevant drug interaction through the inhibition or induction of amidases involved in safinamide turnover.

The activity of the cytochrome P450 (CYP) systems is not affected by safinamide: CYPs 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A3/5 have been screened. The CYP1A2 substrate caffeine and the CYP3A4 inhibitor ketoconazole do not influence safinamide pharmacokinetics. Neither long-term levodopa nor dopamine agonist therapy influence safinamide clearance in PD patients [22, 23, 26]. Safinamide is not a substrate for breast cancer resistance protein (BRCP), the organic anion transporters (OAT) 1B1 or 1B3, or the organic anion-transporting polypeptide (OATP) 1A2 or 2A1. In the small intestine, BRCP is transiently inhibited by safinamide, thus clinically relevant interactions with BRCP substrates may occur if they reach C_{max} in under 2 h. The acid of safinamide is not a substrate of the organic cation transporter (OCT) 2 or OAT1; it is an OAT3 substrate, but clinically relevant interactions are unlikely. Safinamide does not inhibit OCT2 or multidrug and toxin extrusion protein (MATE) 1 or 2 K [23, 26].

2.5.3 *Pharmacodynamic Drug Interactions*

Serious adverse reactions are generally possible when pethidine or dextromethorphan are used together with MAOIs, and caution is recommended when combining MAOIs with sympathomimetic medicines. The use of safinamide with other MAOIs is contraindicated as the combination would elevate the risk of hypertensive crisis. Because safinamide is a selective and reversible MAOI, it can be cautiously used together with serotonin reuptake inhibitors, serotonin/norepinephrine reuptake inhibitors, and tricyclic and tetracyclic antidepressants, although the combination of MAOIs and antidepressant drugs should generally be used with caution because of the potential for serious adverse reactions.

2.6 Safety and Tolerability of Safinamide in Healthy Volunteers and PD Patients

Four clinical trials have investigated the pharmacokinetic and pharmacodynamic behavior and tolerability of safinamide at concentrations of 25–10,000 ng/mL. The first study was performed in eight Caucasian male healthy volunteers (age range 18–45 years) who received a single dose of safinamide 2.5, 5, or 10 mg/kg or placebo. The second trial was carried out in 16 Caucasian male healthy individuals (age range 18–45 years): four received a single dose of safinamide 25 μg/kg, four received safinamide 50 μg/kg, four volunteers took safinamide 75 μg/kg, and the remaining four received safinamide 150 μg/kg; the objective was to establish the ED_{50} (median effective dose) of MAO inhibition. Then for an interval of 7 days, volunteers 1–8 took safinamide 2.5 mg/kg once daily and the other eight received safinamide 5 mg/kg once daily. The third investigation included eight male healthy subjects (age range 18–45 years) who received safinamide 1.25 mg/kg once daily for 7 days. The fourth trial aimed to investigate the impact of a high fat content breakfast on the absorption of safinamide 900 μg/kg in comparison with the fasting state in six healthy male Caucasian individuals. The pharmacokinetics observed were linearly related to the administered dose (Figs. 4, 5). Accumulation was not clinically relevant, nor was there any interaction with food intake. Dosages of up to 200 mg/day were well-tolerated. High (150–200 mg/day) and low (50–100 mg/day) oral dosages of safinamide were also well-tolerated in PD patients during long-term intake [15, 19]. No serious adverse events related to safinamide have been reported.

2.7 Early Stages of PD

In the 009 Study, 172 PD patients were either untreated ($n = 67$) or had previously received only one dopamine agonist (apomorphine, one; bromocriptine, nine; cabergoline, eight; pergolide, 31; piribedil, four; pramipexole, 32; ropinirole, 16); two patients did not meet the inclusion criteria and two withdrew consent [27]. Fifty-six patients were randomly allocated to each treatment group; 49 completed the placebo arm, 52 the lower safinamide dosage group (0.5 mg/kg; equivalent to about 40 mg/day), and 49

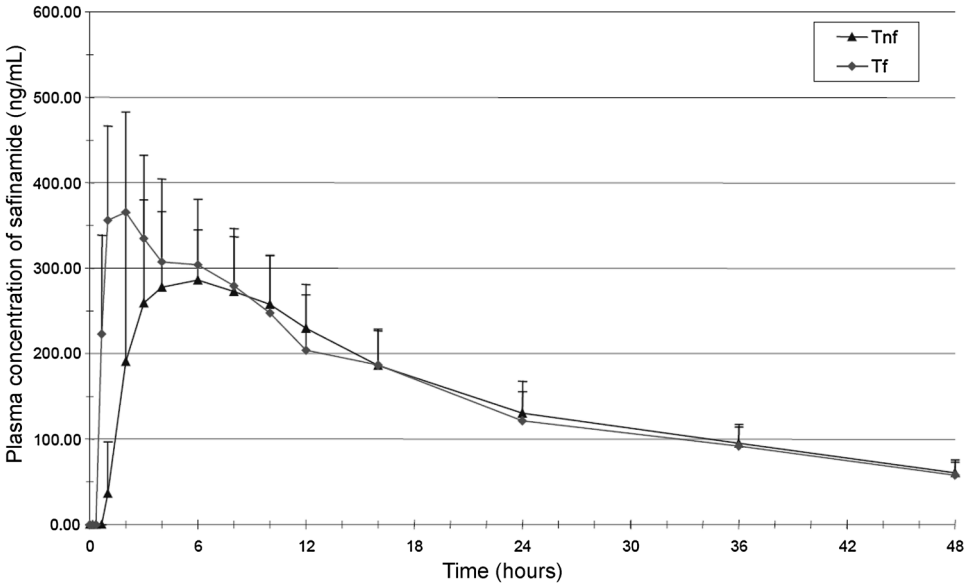

Fig. 4 Effect of food intake on the plasma concentration of safinamide (adapted and modified from Marzo et al. [19], Leuratti et al. [24], and Seithel-Keuth et al. [25]). *Tf* fasting, *Tnf* not fasting (following breakfast)

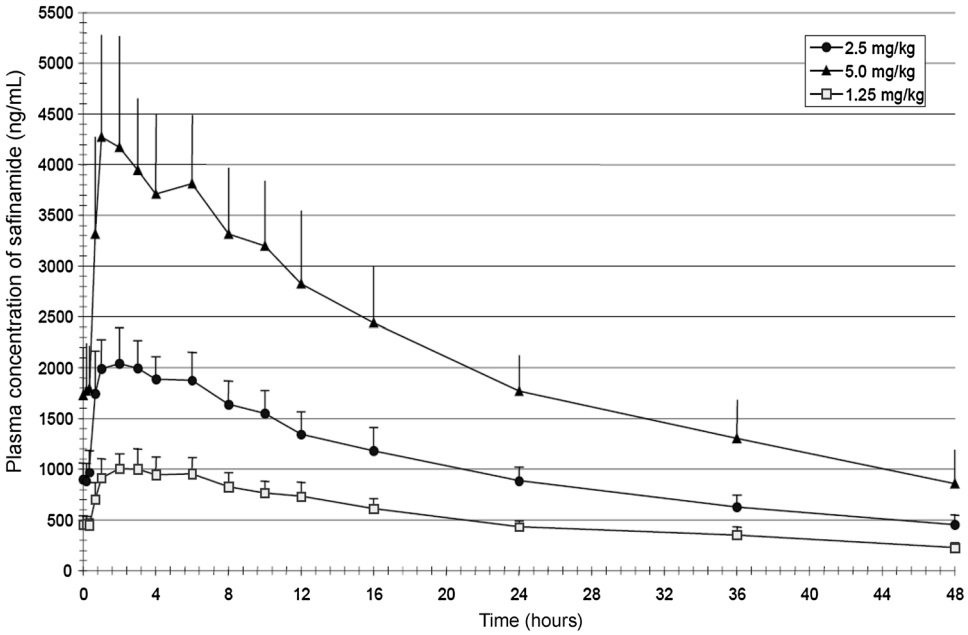

Fig. 5 Plasma concentrations of safinamide, according to dose (adapted and modified from Marzo et al. [19])

the higher dosage group (1 mg/kg; equivalent to about 90 mg/day). There were no significant between-group differences at baseline, and the withdrawal rates were similar. Safinamide treatment was associated with a significantly higher proportion of all patients with greater than 30 % improvement in Unified Parkinson's Disease Rating Scale (UPDRS) part III (motor examination) scores: 12 participants receiving placebo (21.4 %) improved compared with 17 receiving low-dose safinamide (30.9 %) and 21 receiving high-dose safinamide (37.5 %). The results for dopamine agonist-treated patients were similar: 20.6 % of placebo, 36.4 % of low-dose safinamide, and 47.1 % of high-dose safinamide recipients showed greater than 30 % improvement. On average, safinamide improved the UPDRS III score by 4.8 points in the higher-dose arm and by 3.9 points in the lower-dose arm compared with 1.4 points in the placebo group [27].

Study 015, a 6-month randomized, double-blind, placebo-controlled trial, aimed to check the positive outcomes of the 009 Study [28]. The major outcome examined was the effect of safinamide in 270 early PD patients (less than 5 years of disease duration) when added to a stable dopamine agonist therapy. The exclusion criteria were any type of motor complications, receiving more than one dopamine agonist or any other anti-PD medication in the 4 weeks prior to screening, and patients with dementia

or a cognitive dysfunction (Mini-Mental State Examination [MMSE] score <24, or a score of 3 on item 1 of the UPDRS part I [mental behavior] scale). Finally, patients with serious medical conditions or with mental or physical conditions that would preclude collection of safety or efficacy data were also excluded. Ninety participants were randomly allocated to each of the three treatment arms: A (safinamide 50–100 mg once daily), B (safinamide 150–200 mg once daily), or C (placebo). All patients continued to receive their usual dopamine agonist therapy. Improvement in the UPDRS III score was greater for the combined safinamide groups (A + B: mean improvement of 6.0 points [standard deviation (SD) 7.2]) than for the placebo group (C: 3.6 points [SD 7.1]; $P = 0.042$). UPDRS II (activities of daily living) scores were significantly lower in the low-dose safinamide group than in the placebo group (A: mean improvement of 2.2 points [SD 3.8]; C: 1.2 points [SD 3.5]; $P = 0.025$). High-dose safinamide was not superior to lower-dose safinamide with respect to UPDRS II outcomes, and there were also fewer premature discontinuations than in the other two groups. The authors concluded that once-daily administration of safinamide 50–100 mg was the most appropriate dosage for further studies [28].

A substudy of Study 015 assessed possible effects on cognition (38 patients from group A, 41 from group B, 44 from group C). A computerized test battery evaluated cognitive performance—working memory, executive function, and simple motor speed—at baseline and after 12 and 24 weeks. Both executive function and working memory improved in the groups receiving safinamide [28].

Study 015 participants were invited to participate in Study 017, a 52-week extension trial; 227 patients (84 %) enrolled, of whom 82 % completed the trial. The primary endpoint was time to intervention, defined by an increase in the dopamine agonist dosage, addition of another dopamine agonist, re-introduction of levodopa or any other PD drug, or discontinuation of safinamide because of lack of efficacy. Results for the two safinamide treatment arms did not differ from those of the placebo group in terms of this endpoint. Post hoc analysis indicated that patients receiving safinamide 50–100 mg required significantly fewer interventions (25 %) than patients receiving placebo (51 %; $P = 0.048$). After combining the data from Studies 015 and 017, post hoc analysis of UPDRS III scores found that this dose was also associated with significant improvement in UPDRS III scores over the 18-month treatment period. Quality of life, measured with the EuroQoL (EQ-5D), also improved [29].

The safinaMide add-On-To dopamine agonist in early Idiopathic ParkinsON's disease (MOTION) study (currently published only as an abstract) confirmed that treatment with safinamide 50 or 100 mg in combination with one dopamine agonist is well-tolerated and safe. A total of 607 of 679 patients completed the 24-week treatment period. In patients receiving dopamine agonist monotherapy, safinamide 100 mg once daily significantly improved UPDRS III scores (mean change −2.06 points [95 % confidence interval (CI) −2.35 to −0.06]; $P = 0.040$) when compared with placebo. However, 13 of the total intention-to-treat population ($n = 679$) did not meet the inclusion criterion of stable dopamine agonist monotherapy; when the results for these 13 patients were included in the analysis, the difference in the UPDRS score was no longer significant. The mean improvement in UPDRS III scores for PD patients receiving safinamide 50 mg once daily was not statistically significant (mean change −1.93 points [95 % CI −1.85 to 0.44]). Safinamide 100 mg significantly ($P = 0.0207$) improved quality-of-life scores compared with placebo (mean difference in EQ-5D vs. placebo: 0.039 points [95 % CI 0.011–0.068]); no significant difference to placebo was achieved, when safinamide was administered in a dosage of 50 mg once daily [30].

In summary, trials to date have indicated that that reversible MAO-B inhibition by safinamide as an adjunct to dopamine agonist therapy may provide a benefit for PD patients [31].

2.8 Addition of Safinamide to Levodopa/DOPA Decarboxylase PD Therapy

The 016 study was a 6-month randomized, double-blind, placebo-controlled trial that included 669 mid- to late-stage idiopathic PD patients with disease duration of more than 3 years. All patients were on a stable levodopa regimen and had motor fluctuations; the OFF time lasted at least 1.5 h daily. Concomitant stable therapy with a dopamine agonist and/or an anticholinergic drug was permitted. After inclusion, levodopa treatment was stabilized for 4 weeks, following which participants were allocated to one of the three treatment arms: safinamide 50 mg ($n = 223$) or 100 mg ($n = 224$) once daily as adjunct to levodopa therapy, or placebo ($n = 222$). Approximately 90 % of the patients in each arm completed the study (50 mg, 91 %; 100 mg, 87 %; placebo, 89 %). The primary endpoint was defined as the mean increase in total daily ON time (ON time without dyskinesia + ON time with minor dyskinesia), as assessed by patient diary over an 18-h period. The mean total daily ON time increased with both safinamide doses (mean 1.3 vs. 0.7 h for the placebo group; safinamide 50 mg vs. placebo: $P = 0.022$; safinamide 100 mg vs. placebo: $P = 0.013$). There was no increase in the ON time in patients with troublesome dyskinesia in any treatment arm. Accordingly, UPDRS part IV (complications of therapy) scores improved, but this amelioration was only significant in the safinamide 100 mg arm. There was also a

significant decrease in daily OFF time following the first morning levodopa dose when the effects of safinamide were compared with those of placebo. UPDRS III scores during ON time and the Clinical Global Impression of Severity of Disease score also improved more in the treatment arms than in the placebo arm [32].

More than 90 % of patients who completed the initial 24-week trial entered the 78-week placebo-controlled, double-blind extension 018 Study. The effect on dyskinesias was the primary endpoint (mean change from baseline in Dyskinesia Rating Scale [DRS] total score). The overall difference from baseline was not statistically significant, but post hoc analysis found that patients with moderate to severe dyskinesia at baseline (DRS total score >4; about 33 % of participants) significantly ($P = 0.032$) improved when treated with safinamide 100 mg once daily [33].

In the SafinamidE Treatment as add-on To LEvodopa in idiopathic PD patients (SETTLE) study, a phase III trial (which has only been published in abstract form to date), a total of 549 participants received safinamide 50 or 100 mg or placebo over 24 weeks; 484 participants finished the trial. Prior to randomization, treatment was optimized in the levodopa-treated patients who had motor fluctuations. Significantly greater ($P < 0.001$) reduction of OFF time (1.03 h [standard error (SE) 0.21]), increase of ON time (0.96 h [SE 0.19]) and improvement in UPDRS III scores (−1.82 [SE 0.61]) were achieved in the safinamide-treated participants than in the placebo arm [34].

3 Conclusions from the Clinical Study Program and Future Outlook

Clinical trials have provided evidence that safinamide improves impaired motor behavior in PD patients treated with levodopa, dopamine agonist monotherapy, or both. Safinamide was particularly efficacious in patients receiving levodopa. Levodopa therapy is complex because of its peripheral absorption, pharmacokinetic characteristics, short half-life, and delivery to the brain. Limitations associated with long-term treatment with levodopa include the development of motor complications. One potential role for safinamide is that it may allow a reduction in the dosage of levodopa, as shown for selegiline in the SELEDO trial (the name SELEDO is taken from selegiline plus levodopa), and of dopamine agonists [35]. The clinical convenience, safety, and tolerability of safinamide are better than those of dopamine receptor agonists, which must be taken several times a day; furthermore, their common long-term adverse effects include edema and nausea, particularly at higher doses. As required for its licensing as an anti-PD medication, clinical trials have generally focused on improvements in motor behavior in PD patients taking safinamide. However, comparisons with other compounds in terms of changes in ON or OFF time intervals play only a minor role in patient maintenance [36]. Effects on non-motor symptoms often provide clinically relevant, novel advantages in the real world of drug treatment for PD patients.

3.1 Safinamide and Non-Motor Features of PD

The pharmacology of safinamide suggests that it may also modulate the metabolism of other neurotransmitters, particularly of biogenic amines other than dopamine. As disturbed biogenic amine neurotransmission is thought to underlie the non-motor symptoms of PD, long-term application of safinamide may also exert positive effects on these aspects of the disorder. Features such as apathy or depression are particularly responsive to MAOIs, while vigilance improves in patients receiving NMDA receptor antagonists such as memantine and amantadine [37, 38]. Furthermore, levodopa and, to a lesser extent, dopamine receptor agonists increase sleepiness in some patients, and lowering the dosage of these drugs should diminish this effect. Therefore, safinamide might be expected to reduce sleepiness, apathy, and depression and to improve vigilance in people with PD, a hypothesis that warrants exploration. Beneficial effects on cognition have also been reported during treatment with safinamide, perhaps as a consequence of improved vigilance. PD patients report an average of eight non-motor symptoms, and their frequency and severity increase with increased disease duration [39]. The outcomes of pilot trials indicate that the beneficial effects of inhibiting glial COMT on biogenic amine levels in the synaptic cleft resemble those of MAO inhibition [40–42]. Small clinical studies have found improved cognitive performance and cortical information processing following central COMT inhibition. Increased CNS dopamine levels secondary to central COMT inhibition are associated with improved cognition, selectively reducing apathy and motivation in particular [43–45]. The effects of central COMT and MAO inhibition on biogenic amine levels are perhaps comparatively more restricted to the prefrontal lobe than those of stimulants such as amphetamine, which enhance dopaminergic, norepinephrine and serotonergic transmission across the brain, for which reason such psychostimulants possess a greater potential for abuse and tolerance [40].

3.2 *N*-Methyl-D-Aspartate Receptor Modulation

Amantadine, memantine, rasagiline, and safinamide modulate glutamatergic transmission in a similar fashion [46–48], and all improve OFF phenomena and reduce the severity of dyskinesia [49, 50]. Demonstrating

symptomatic or preventive anti-dyskinetic effects in PD is difficult as the degree of dyskinesia can vary from day to day; furthermore, a variety of environmental and psychological stressors can significantly aggravate dyskinesia and other involuntary movements, confounding interpretation of standardized assessment tools used in clinical trials. The reliable evaluation of an anti-dyskinetic effect is best undertaken in small, well-designed studies by experienced investigators using standardized levodopa dosages known to provoke dyskinesia.

Dyskinesia more commonly occurs during therapy with levodopa than with dopamine receptor agonists. In clinical practice, the dopamine-substituting properties of safinamide may aggravate dyskinesia, meaning a cautious, concomitant reduction of the oral levodopa dosage is advisable when adding safinamide to an anti-parkinsonian drug regimen. Variable but mild dyskinesia is often accepted more by patients than their physicians; PD patients are generally more concerned regarding their OFF states, whereas the attention of caregivers is captured more by dyskinesia [51]. Alternative symptomatic drug treatment for severe dyskinesia may be available in the foreseeable future; for instance, retarded release formulations of amantadine have been reported to have a distinct benefit in reducing dyskinesia [3].

3.3 Safinamide: Not Just Another MAO-B Inhibitor

Health authorities and insurers classify selegiline, rasagiline, and safinamide as similar agents on the basis of their MAO-B-inhibiting properties, particularly in terms of pricing; however, there are important differences between them. Firstly, selegiline is metabolized to desmethylselegiline and amphetamine derivatives and rasagiline to aminoindane, each of which is pharmacologically active; safinamide, in contrast, is primarily converted to inactive dealkylated derivatives (Fig. 3). Secondly, the mean elimination half-life of selegiline is 1.5 h, and that of rasagiline is 1.0 h in controls and 1.3 h in patients. If selegiline is administered to PD patients at a daily dose of 10 mg, however, its half-life is 6 h [52]. As described earlier, the half-life of safinamide is, in contrast, 22 h.

Thirdly, irreversible 'selective' MAO-B inhibitors also reduce MAO-A activity in a dose-dependent fashion. Recovery of enzyme activity after blockade by an irreversible MAO-B inhibitor requires de novo enzyme generation, and it is generally several weeks before levels are fully restored. Once MAO-B is totally blocked, a cumulative effect results in MAO-A inhibition. The beneficial effect of rasagiline on the in vitro synthesis of the neuronal survival-enhancing Bcl-2 and neurotrophic factors is, for instance, mediated by MAO-A inhibition; selegiline and rasagiline each increase the messenger RNA, protein, and catalytic activity of MAO-A in SH-SY5Y cells [52]. The two irreversible MAO-B inhibitors correspondingly exhibit MAO-A-inhibiting properties during long-term administration to PD patients. There are currently no data on whether the same effects occur during long-term administration of safinamide, but the question warrants investigation in PD patients [6, 53].

In summary, these pharmacological differences allow the conclusion that safinamide is not just another MAO-B inhibitor, but rather possesses a unique and novel combination of modes of action that may prove valuable in the treatment of PD.

3.4 Safinamide for Restless Legs Syndrome and Pain Syndromes

By enhancing dopaminergic transmission and blocking Na^+/Ca^{2+} channels, safinamide may be useful for treating pain syndromes. Safinamide has similar anticonvulsant effects to drugs such as pregabalin and gabapentin, which also alleviate the symptoms of restless legs syndrome [54]. Thus, treating restless legs syndrome patients with safinamide has been suggested. A benefit for PD patients with pain syndromes was also detected in a post hoc analysis [55, 56].

4 Conclusion

Safinamide provides symptomatic relief of the motor symptoms of PD. Its combination of a variety of pharmacological mechanisms is advantageous in light of the alterations in multiple neurotransmitter systems in the brain of PD patients. The pharmacology of this compound means that it has a combination of effects similar to those of amantadine and antidepressants, including stabilization of mood, reduction of apathy, and improved vigilance. Thus, safinamide may assist PD patients to better tolerate the motor and non-motor features of periods of OFF time that characterize long-term dopamine replacement therapy. Safinamide elevates the CNS levels of biogenic amines, and may thus produce dyskinesia and psychosis. The onset of either of these problems will make reduction of the concomitant levodopa or dopamine agonist dosage necessary.

In general, treatment for long-term neurodegenerative disorders such as PD must be individually tailored from several components according to the needs of the patient. In clinical practice, each patient, their caregiver, and their treating physician will ultimately determine together the value of any component of this therapeutic package, including safinamide, for themselves.

Compliance with Ethical Standards

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