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REVIEW ARTICLE

Different Generations of Type-B Monoamine Oxidase Inhibitors in Parkinson's Disease: From Bench to Bedside

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Abstract: Three inhibitors of type-B monoamine oxidase (MAO_B), selegiline, rasagiline, and safinamide, are used for the treatment of Parkinson's disease (PD). All three drugs improve motor signs of PD, and are effective in reducing motor fluctuations in patients undergoing long-term L-DOPA treatment. The effect of MAO_B inhibitors on non-motor symptoms is not uniform and may not be class-related. Selegiline and rasagiline are irreversible inhibitors forming a covalent bond within the active site of MAO_B. In contrast, safinamide is a reversible MAO_B inhibitor, and also inhibits voltage-sensitive sodium channels and glutamate release. Safinamide is the prototype of a new generation of multi-active MAO_B inhibitors, which includes the antiepileptic drug, zonisamide. Inhibition of MAO_B-mediated dopamine metabolism largely accounts for the antiparkinsonian effect of the three drugs. Dopamine metabolism by MAO_B generates reactive oxygen species, which contribute to nigro-striatal degeneration. Among all antiparkinsonian agents, MAO_B inhibitors are those with the greatest neuroprotective potential because of inhibition of dopamine metabolism, induction of neurotrophic factors, and, in the case of safinamide, inhibition of glutamate release. The recent development of new experimental animal models that more closely mimic the progressive neurodegeneration associated with PD will allow to test the hypothesis that MAO_B inhibitors may slow the progression of PD.

Keywords: Selegiline, rasagiline, safinamide, MAO_B, basal ganglia, Parkinson's disease, glutamate release.

1. INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder characterized by a progressive loss of dopaminergic neurons in the *substantia nigra pars compacta* (SNpc) resulting into dopamine (DA) denervation in the caudate nucleus and putamen. Neurons in other pigmented nuclei of the brainstem, as well as autonomic neurons in peripheral organs (*e.g*., heart and gut) also degenerate in PD [1]. The complex pathophysiology of neuronal degeneration is what makes PD a heterogeneous disorder. Intracellular inclusions called Lewy bodies containing aggregates of the protein, α-synuclein are found in most cases of sporadic PD, and mutations of α-synuclein are associated with rare monogenic cases of PD with autosomal dominant transmission [2]. However, there are cases of early-onset PD, such as those caused by parkin and PINK-1 mutations, in which Lewy bodies are absent [3, 4]. Abnormalities in the retromer pathway, which controls the clearance of α-synuclein and other membrane proteins, and defects in the mitochondrial quality control are considered as major cytopathological determinants in PD [5-8].

Striatal DA denervation is the cause of the hallmark motor symptoms of PD, *i.e*., rigidity, bradykinesia, resting tremor, and postural instability, which occur at the time of clinical diagnosis. Nonmotor signs, such as constipation, hyposmia, REM sleep disorders, depression, and cognitive impairment, may precede the clinical onset of PD by several years. L-3,5-dihydroxyphenylalanine (L-DOPA) combined with peripheral inhibitors of L-aromatic aminoacid decarboxylase (LAAD) is the gold standard treatment of PD, and a good motor response to L-DOPA is pathognomonic of the disorder. In the long-term, however, L-DOPA treatment becomes suboptimal beause of the occurrence of motor fluctuations (*e.g*., wearing-off and on-off phenomena) and dyskinesias (L-DOPA-induced dyskinesias or LIDs). This reflects changes in the pharmacokinetic and pharmacodynamic profile of L-DOPA within the context of a progressive dopaminergic denervation [9, 10]. In addition, L-DOPA does not halt or attenuate PD progression, and, might even be detrimental to SNpc dopaminergic neurons. The long-term L-DOPA syndrome gave impetus to the design of other antiparkinsonian drugs, which help to delay the onset of L-DOPA treatment, or could be given in association with L-DOPA to optimize motor response and/or mitigate LIDs (for example, by allowing a reduction in the daily dose of L-DOPA). These classes of drugs include DA receptor agonists, anticholinergic drugs, catechol-oxy-methyltransferase

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(COMT) inhibitors, the N-methyl-D-aspartate (NMDA) receptor antagonist, amantadine, and type-B monoamine oxidase (MAO_B) inhibitors [3,11]. Three MAO_B inhibitors with a different pharmacological profile are currently used in the treatment of PD: selegiline, rasagiline, and safinamide. The aim of the present review is to comparatively discuss the preclinical and clinical pharmacology of the three drugs, focusing on their efficacy in relieving motor and non-motor symptoms of PD, and motor complications associated with L-DOPA treatment. In addition, we will briefly discuss the potential of the three MAO_B inhibitors as disease-modifying drugs in PD.

2. METHODS

We searched for the following terms on Pubmed: selegiline, deprenyl, rasagiline, safinamide, MAO_B, neuroprotection and Parkinson's disease, basal ganglia motor circuit and glutamate, GDNF and Parkinson's disease, glutamate and basal ganglia, NMDA receptor antagonists and Parkinson's disease, mGlu5 receptor antagonists and Parkinson's disease, Parkinson's disease reviews (2015-2018).

3. COMPARATIVE PHARMACOLOGY OF DIFFERENT GENERATIONS OF MAO_B INHIBITORS

3.1. MAO_B and its Relevance to PD

MAOs are flavin-dependent enzymes bound to the outer mitochondrial membrane, with oxidase monoamines, like DA, noradrenaline, adrenaline, serotonin, and trace amines, reducing molecular oxygen to hydrogen peroxide. The two MAO isoforms, MAO_A and MAO_B, show a differential cellular localization in the CNS, with MAO_A being mainly localized in neurons and MAO_B in astrocytes. MAO_A, which metabolizes catecholamines and serotonin, is an established target for antidepressant medication, and both irreversible $MAO_{A/B}$ inhibitors and reversible MAO_A inhibitors (RIMA) have been developed for the treatment of unipolar depression. In contrast, MAO_B inhibitors have been developed for the treatment of PD because of their ability to inhibit DA metabolism [12, 17].

DA released from nigro-striatal fibers is taken up by both the high-affinity DA transporter (DAT) present in axon terminals, and the reverse organic cation transporter (OCT3) present in astrocytes. The latter transport provides the main source for the DA metabolized by MAO_B. DA oxidation by MAO_B generates radical oxygen species (ROS). This by-product of MAO_B activity might contribute to the pathophysiology of PD because of the high vulnerability of SNpc dopaminergic neurons to oxidative damage [3]. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which induces toxicological parkinsonism in mice and primates, is converted by MAO_B into the active metabolite, 1-methyl-4-phenylpyridinium (MPP^+). MPP^+ kills SNpc neurons by inhibiting complex I of the mitochondrial respiratory chain [18]. Because a number of pesticides and other environmental toxins are structurally similar to MPTP, MAO_B inhibition represents a potential strategy to limit the impact of the environment on the pathophysiology of PD [3].

3.2. Different Mode of MAO_B Inhibition by Selegiline, Rasagiline, and Safinamide

Selegiline (L-deprenyl) and rasagiline are irreversible MAO_B inhibitors. Crystallographic analysis showed that the active site of human MAO_B is formed by two cavities, named substrate and entrance cavity, respectively [19]. Rasagiline, for example, forms a covalent adduct with the N5 atom of the flavin cofactor within the active site cavity [20], thereby irreversibly inhibiting MAO_B. Selegiline also covalently binds to the flavin-protein complex within the active site of MAO_B [21]. Hence, full recovery of MAO_B activity requires several days or weeks after withdrawal of selegiline or rasagiline, a time necessary for a *de novo* synthesis of MAO_B. For example, PET studies with ^{14}C-L-deprenyl, which tracks brain MAO_B levels, demonstrate that about 40 days are required for near-to-full recovery of MAO_B in both normal subjects and patients affected by PD after selegiline withdrawal [22]. Similar recovery times were observed after rasagiline [23]. This long time of recovery should be taken into account when establishing the dose, duration of treatment, and pharmacodynamic or pharmacokinetic interactions with other drugs in PD patients treated with selegiline or rasagiline. In contrast, safinamide is a reversible MAO_B inhibitor. Full recovery of MAO_B activity is observed as early as 24 hours after a single i.p. injection of safinamide in the mouse brain, and within five days after a single oral administration of safinamide in human platelets [24, 25].

Potency and selectivity are two main issues when comparing different generations of MAO_B inhibitors in the treatment of PD. Rasagiline displays a high potency as MAO_B inhibitor, with an IC_{50} value of 4 and 14 nM in rat and human brain homogenates, respectively [26]. The IC_{50} value in the human brain is in the same range of the C_{max} value found after a single administration of 2 mg rasagiline in PD patients, taking into account that about 60% of the drug is bound to plasma albumin [27]. Selegiline displays a similar potency as rasagiline as a MAO_B inhibitor in rat and human brain homogenates, but is about 10-fold less potent than rasagiline on brain and liver MAO_B activity when administered systemically to rats [26]. Safinamide shows an IC_{50} value of 98 and 79 nM on MAO_B activity in extracts from rat and the human brain, respectively [24]. These values are in the same range of the C_{max} values in human volunteers after a single oral administration of safinamide at 2.5 mg/kg, or to steady-state plasma concentrations after a 6-day treatment with 1.25 mg/kg safinamide (approximately 3 and 1.1 μM, respectively) [28], considering that 88-90% of safinamide binds to plasma albumin [28]. The same *in vitro* measurements carried out in extracts of rat and human brain show a high selectivity of safinamide towards MAO_B with respect to MAO_A (IC_{50} values: 0.098 vs. 485 μM, and 0.079 vs. 80 μM in rat and the human brain, respectively) [24]. Rasagiline has a lower selectivity towards MAO_B vs. MAO_A (IC_{50} values: 0.004 vs. 0.412 μM and 0.014 vs. 0.7 μM in rat and the human brain, respectively) [26]. This results into a brain MAO_B/MAO_A selectivity ratio of about 1,000 for safinamide and about 50 for rasagiline, although values of 0.7 μM largely exceed the peak and steady-state plasma concen-

trations of rasagiline with the usual therapeutic doses in PD patients.

The possibility that MAO_A could be influenced by treatment with MAO_B inhibitors was examined in a series of clinical trials in which PD patients received long-term treatment with MAO_B inhibitors combined or not with L-DOPA *plus* LAAD inhibitors. The conclusion of a first study was that long-term treatment with irreversible MAO_B inhibitors could reduce MAO_A activity, as shown by measurements of enzymatic activity performed with the plasma collected from patients 4 hours after the last administration of either selegiline or rasagiline [30]. These findings were not replicated in another study in which peripheral MAO_A and MAO_B activities were measured in PD patients chronically treated with L-DOPA combined or not with 1 mg rasagiline or 50 or 100 mg safinamide [31]. No changes in MAO_A activity were found in any of the experimental groups, suggesting that at least in this study, rasagiline behaved as a selective inhibitor of MAO_B. The possibility that selectivity towards MAO_B is lost after long-term treatment with high doses of rasagiline or selegiline cannot be excluded and warrants further investigation because inhibition of MAO_A in PD patients might cause adverse effects (*e.g.*, sympathomimetic effects induced by dietary tyramine).

3.3. Safinamide: A New-generation Multi-active Drug that Inhibits Ion Channels and Glutamate Release

Safinamide was originally developed as an antiepileptic drug because of its ability to inhibit voltage-sensitive sodium channels (VSSCs) and voltage-sensitive calcium channels (VSCCs). Safinamide was shown to interact with the batrachotoxin-sensitive site of VSSCs with greater affinity as compared to riluzole and the antiepileptic drugs, phenytoin, carbamazepine, and lamotrigine [32]. In cultured hippocampal and cortical neurons, inhibition of VSSCs by safinamide was voltage-, use-, and frequency-dependent [32, 33], a characteristic shared by many antiepileptic drugs. Hence, the VSSC blockade by safinamide becomes prominent during repetitive neuronal firing. Safinamide also inhibits high-threshold N- and L-type VSCCs [32], with a preferential action on N-type channels. L-type VSCCs are largely expressed in the heart and blood vessels, where calcium entry enhances dromotropism and inotropism and causes vasoconstriction, respectively. However, inhibition of L-type VSCCs occurs at relatively high concentrations of safinamide, and this explains the lack of significant effects of the drug on blood pressure and heart function in patients affected by PD. Interestingly, the pharmacodynamic profile of safinamide is shared by zonisamide, an antiepileptic drug that inhibits both VSSCs, T-type VSCCs, and MAO_B [34-36]. Thus, safinamide and zonisamide can be considered as prototypes of a new generation of multi-active MAO_B inhibitors [35].

As a result of VSSC and VSCC blockade, safinamide inhibits depolarization-evoked glutamate release in cultured neurons and synaptosomal preparation [24, 32]. In a recent article, Morari *et al.* (2018) examined the effect of safinamide on glutamate and GABA release assessed by *in vivo* microdialysis in freely moving rats. Safinamide inhibited depolarization-evoked glutamate and GABA release in the hippocampus. In the globus pallidus (GP), subthalamic nucleus (STN), and substantia nigra pars reticulata (SNpr) safinamide selectively inhibited depolarization-evoked glutamate release, whereas the drug had no effect in the dorsal striatum, at least at the selected dose of 15 mg/kg. Measurements of free brain concentrations of safinamide suggested that the drug restrained neurotransmitter release by inhibiting VSSCs rather than VSCCs [33]. These findings are extremely interesting and suggest that safinamide may reduce the excitatory overdrive associated with PD in some stations of the basal ganglia motor circuit.

3.4. Comparative Pharmacokinetic Profiles of Selegiline, Rasagiline, and Safinamide

Selegiline, rasagiline, and safinamide show remarkable differences in their pharmacokinetic profiles in terms of absorption, distribution volume (V_D), metabolism, and elimination.

Selegiline is indicated for the treatment of PD at a daily dose of 10 mg, given either q.d. or b.i.d. At the oral dose of 10 mg, selegiline shows a bioavailability <10%, peak plasma concentrations of about 2.7 ng/ml, T_{max} values of 0.5 hours, V_D of 1854 liters, plasma albumin binding >90%, and elimination $t_{1/2}$ of 1.5 hours [37, 38]. The low bioavailability after oral administration reflects an extensive first-pass hepatic metabolism mediated by CYP2B6 and, to a lesser extent, by CYP2A6 and CYP3A4 [39]. Selegiline metabolism generates L-methamphetamine and desmethylselegiline, the latter also behaving as an irreversible MAO_B inhibitor [37]. Desmethylselegiline is in turn metabolized into L-amphetamine [37]. The generation of amphetamine metabolites confounds the pharmacodynamic profile of selegiline. CYP2B6 is highly polymorphic, with some genetic variants causing increases, and other reductions in enzymatic expression (CYP2B6*4/22, and CYP2B6*5/6/18, respectively). CYP2B6*6 shows a high frequency in Africans and Afro-Americans. Hence, it is more likely to find increased responses to selegiline in these ethnic groups. Drugs that could be associated with selegiline in the treatment of PD, such as the anticholinergic agent, orfenadrine, and the antidepressants, fluoxetine and paroxetine, are reversible inhibitors of CYP2B6. In addition, the thienopyridines, ticlopidine and clopidogrel, which are widely used to inhibit platelet aggregation, irreversibly inhibit CYP2B6 by forming a disulfide bond within the active core of the enzyme [40]. All these drugs may boost the activity of selegiline and increase the probability of dose-related adverse effects. Opposite effects might be produced by drugs that induce CYP2B6, such as phenobarbital and rifampicin.

At clinical oral doses of 1 or 2 mg (q.d.), rasagiline shows a bioavailability of about 35%, peak plasma concentrations of 2.5 and 4.9 ng/ml, respectively, T_{max} values of 0.5 and 1 hour, respectively, V_D of 87-243 liters, plasma albumin binding of 60%, and elimination $t_{1/2}$ of 1.5-3.5 hours [41-43]. Rasagiline undergoes hepatic metabolism by CYP1A2, with the production of inactive metabolites (1R-aminoindane; 3-hydroxy-N-propargyl-1-aminoindane; and 3-hydroxyaminoindane). Although several genetic variants of CYP1A2 have been found in humans (www.CYP.ki.se https://www.pharmvar.org/htdocs/archive/cyp1a2.htm), these variants are not considered clinically relevant. CYP1A2 is

induced by smoking and proton pump inhibitors (in particular, omeprazole, esomeprazole, and lansoprazole), and inhibited by fluoroquinolone antibiotics (*e.g.*, ciprofloxacin), the selective serotonin reuptake inhibitor (SSRI), fluvoxamine, and oral contraceptives [44-46]. None of these drugs should be associated with rasagiline. This concern is particularly relevant for the antidepressant, fluvoxamine, in light of the comorbidity between PD and depression [47]. Both rasagline and selegiline should be avoided in patients with liver failure.

At clinically effective doses (50 or 100 mg, q.d.) oral safinamide has a high bioavailability (80-92%) [48], and a linear pharmacokinetic profile, with a T_{max} value of 1.8-2.8 hours, a V_D of 150 liters, plasma albumin binding of 92%, and elimination $t_{1/2}$ of 21-24 hours [29]. C_{max} values and steady-state plasma concentrations after treatment with 1.25 mg/kg safinamide are about 1,050 and 450 ng/ml, respectively [28]. Full inhibition of MAO_B by safinamide is observed 2-3 hours after oral administration. Safinamide is not metabolized by cytochrome-P_{450}, and this avoids major pharmacokinetic interactions with other drugs. The main metabolites of safinamide (acidic and N-dealkylated metabolites) are generated by amide hydrolases and MAO_A, and are pharmacologically inert [48].

4. EFFICACY, SAFETY, AND TOLERABILITY OF MAO_B INHIBITORS IN THE TREATMENT OF PD

4.1. Effects of MAO_B Inhibitors on Motor Symptoms Associated with PD and their Impact on Motor Complications of L-DOPA Treatment

Motor symptoms associated with PD (rigidity, bradykinesia, resting tremor, postural abnormalities) reflect a defective network activity within the basal ganglia motor circuit, in which the neostriatum (caudate nucleus and putamen) represents the major input station. The neostriatum receives several inputs including glutamatergic fibers originating from the cerebral cortex, dopaminergic fibers originating from the SNpc, and serotonergic and noradrenergic fibers originating from brainstem nuclei. In humans, dopaminergic fibers are extremely long (axons can reach 4 meters of length) and make about two millions of synapses within the neostriatum. Medium spiny projecting neurons constitute the large majority (>90%) of striatal neurons. Large aspiny cholinergic interneurons and different population of GABAergic interneurons are also present in the neostriatum [49]. Striatal projection neurons use GABA as a neurotransmitter and give rise to the direct and indirect pathways of the basal ganglia motor circuit. Neurons of the direct pathway contain dynorphin and substance P and project to the internal globus pallidus (GPi) and SNpr, which constitute the output stations of the circuit and send inhibitory GABAergic projections to ventral motor thalamic nuclei (ventral anterior, ventromedial, and ventrolateral nuclei). Activation of the direct pathway by D1 dopamine receptors inhibits GPi and SNpr neurons, thereby stimulating ventral thalamic neurons projecting to the motor cortex. Striatal GABAergic projection neurons of the indirect pathway send axons to the external portion of the globus pallidus (GPe). GPe neurons send inhibitory GABAergic projections to the STN, which, in turn, send excitatory glutamatergic projections to the GPi and SNpr. Inhibition of striato-pallidal neurons of the indirect pathway mediated by D2 dopamine receptors restrains the activity of STN neurons, thereby reducing the excitatory drive to the GPi and SNpr and enhancing the activity of motor thalamic nuclei [49].

In PD, the progressive loss of striatal DA innervation results into a reduced activity of the direct pathway and an overactivity of the indirect pathway, which ultimately results into the hallmark motor signs of PD when striatal DA denervation exceeds 70-75% [3]. The glutamate released from cortico-striatal fibers stimulates both the direct and indirect pathways by activating ionotropic and metabotropic receptors postsynaptically localized on striatal projection neurons (Fig. **1**). An enhanced glutamate release at cortico-striatal and STN-GPi/SNpr synapses contributes to the pathophysiology of PD, and drugs that restrain the overactivity of glutamatergic fibers or block NMDA or mGlu5 receptors improve motor symptoms of PD [49].

L-DOPA restores an efficient dopaminergic control of the basal ganglia motor circuit in the first years of treatment when plasma concentrations of the drug always fall inside the therapeutic window. Afterwards, L-DOPA treatment is complicated by the occurrence of motor fluctuations (*e.g.*, early-morning off, wearing-off, delayed-on, no-on, and on-off phenomena) and LIDs. LIDs include tics, and choreiform, ballistic, and dystonic movements that more frequently occur at the time of peak concentrations of L-DOPA, but may be also present during the rising and declining phases of blood L-DOPA concentrations [50]. While changes in the pharmacokinetics of L-DOPA largely account for motor fluctuations, LIDs reflect mechanisms of maladaptive synaptic plasticity at the synapses between cortico-striatal fibers and striatal projection neurons of the direct pathway. Because activation of D1 receptors is critically involved in the induction and expression of LIDs, these adverse effects impose reductions in the daily dose and frequency of administration of L-DOPA, which may render the control of motor symptoms suboptimal [51].

By reducing brain DA metabolism, MAO_B inhibitors have a mild-to-moderate effect on motor symptoms on their own and reduce the time spent in the off phase when combined with L-DOPA in patients showing motor fluctuations. In addition, inhibition of MAO_B may allow a reduction of a daily dose of L-DOPA without compromising motor control in patients with LIDs. Inhibition of glutamate release by safinamide is an additional powerful mechanism that may highly contribute to improve motor symptoms (see below).

Selegiline was initially developed as a psychostimulant and antidepressant, and then used in the treatment of PD after the discovery that it behaves as an irreversible MAO_B inhibitor [52]. Selegiline is used at daily doses of 5 or 10 mg both in monotherapy and in combination with L-DOPA (a dose of 10 mg/die is indicated in patients with motor fluctuations). The antiparkinsonian effect of an early treatment with selegiline in monotherapy was demonstrated in the DATATOP trial [53], which is discussed in further detail below. In the Sinemet-Deprenyl-Parlodel (SINDEPAR) study, selegiline treatment improved UPDRS score in PD patients when combined with either L-DOPA/carbidopa or

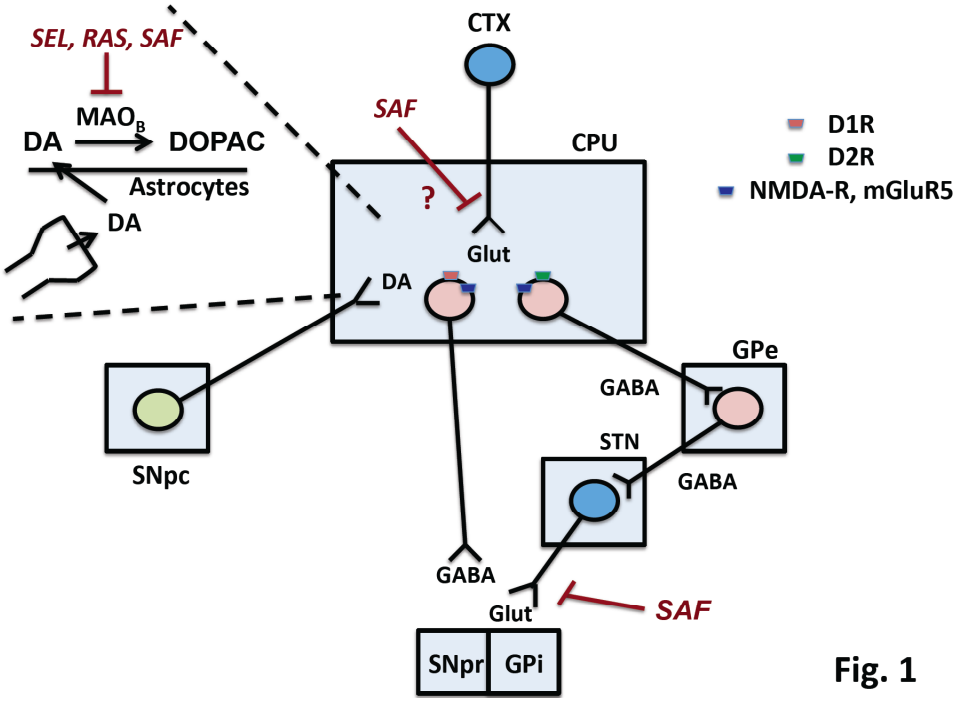

Fig. 1

Fig. (1). Mechanisms involved in the antiparkinsonian effect of selegiline (SEL), rasagiline (RAS), and safinamide (SAF). The Figure is a schematic drawing of the basal ganglia motor circuit, with dopaminergic neurons of the substantia nigra pars compacta (SNpc) projecting to the caudate nucleus and putamen (CPU). Striatal projection neurons of the direct and indirect pathway are stimulated and inhibited by D1 and D2 dopamine receptors (D1R, D2R), respectively. Both neurons express NMDA receptors (NMDA-R) and mGlu5 metabotroic glutamate receptors (mGluR5), which are activated by the glutamate released from cortico-striatal fibers (CTX = cerebral cortex). The external globus pallidus (GPe) and the subthatamic nucleus (STN) are the two stations of the indirect pathway. STN glutamatergic neurons send excitatory projections to the internal globus pallidus (GPi) and the substantia nigra pars reticulate (SNpr). Neurons of the direct patway send GABAergic projection to the GPi and SNpr. Dopamine (DA) released from nigro-striatal terminals is taken up by astrocytes, where it is transformed into DOPAC by MAO_B. Inhibition of MAO_B by SEL, RAS, and SAF enhances DA levels in the striatum. SAF can also inhibit glutamate release in the GP and SNpr. Inhibition of glutamate release in the striatum by SAF was not demonstrated by *in vivo* microdialysis experiments [33]. (*The color version of the figure is available in the electronic copy of the article*).

with the DA receptor agonist, bromocriptine [54]. The UPDRS (Unified Parkinson's Disease Rating Scale) is the most widely used scale in clinical studies of PD and is particularly helpful for the evaluation of the longitudinal course of the disease. In advanced PD, selegiline, added to pre-existing L-DOPA treatment, was able to improve tremor, rigidity, bradykinesia and dyskinesias, and was effective in reducing the frequency and severity of motor fluctuations [55].

Rasagiline has been approved as monotherapy for the early treatment of PD, and in association with L-DOPA in patients with motor fluctuations. The recommended daily dose is 1 mg. The therapeutic efficacy of rasagiline is largely discussed in two excellent reviews [15, 29]. Two clinical trials named TEMPO (TVP-1012 in Early Monotherapy for PD Outpatients) and ADAGIO (Attenuation of Disease Progression with Azilect Given Once-daily) showed the efficacy of rasagiline monotherapy in the early stages of PD as evaluated by UPDRS score and quality of life [56, 57]. A post-hoc analysis of the ADAGIO trial showed a good efficacy of rasagiline on tremor, bradykinesia, rigidity, and composite postural-instability-gait-difficulty, which was maintained for at least one year [58]. The efficacy of rasagiline in patients with advanced PD treated with L-DOPA and displaying motor fluctuations was examined in two clinical trials named LARGO (Lasting effect in Adjunct therapy with Rasagiline given Once-daily) and PRESTO (Parkinson's Rasagiline: Efficacy and Safety in the Treatment of 'Off'). In both trials, rasagiline was effective in reducing the time spent in the off phase [43, 59]. In the PRESTO trial, rasagiline was effective in reducing motor fluctuations regardless of the presence of other drugs combined with L-DOPA, such as DA receptor agonists or COMT inhibitors; however, rasagiline increased on-phase associated dyskinesias with respect to placebo [60]. A recent head-to-head 3-year retrospective case-control study evaluating the efficacy of selegiline and rasagiline in PD showed that treatment with either of the two MAO_B inhibitors was associated with a lower daily dose of L-DOPA and a lower frequency of LIDs [61]. A reduced risk of LIDs during treatment with selegiline and rasagiline was confirmed in another retrospective cross-sectional cohort studies comparing patients treated with either of the two MAO_B inhibitors for at least one year with patients who had never received MAO_B inhibitors [62]. We wish to highlight that neither selegiline nor rasagiline improves LIDs through a direct mechanism, but they allow to reduce the daily dose od L-DOPA without a major impairment of motor control. Reversible Pisa syndrome, a postural deformity characterized

by lateral trunk flexion, has been occasionally associated with rasagiline treatment in a patient affected by PD [63, 64]. Whether this rare complication is due to inhibition of DA metabolism or other mechanisms remains to be established.

Safinamide has been approved by FDA and EMA as an adjunctive therapy to L-DOPA and other antiparkinsonian drugs in patients affected by mid-advanced PD with motor fluctuations. A daily dose of 50 mg is required for reversible full inhibition of MAO_B activity. At the dose of 100 mg safinamide also inhibits glutamate release, an effect that may contribute to the efficacy of the drug on motor and non-motor symptoms and fluctuations. In principle, this mechanism could restrain dyskinesias that might result from the inhibition of DA metabolism.

As outlined above, LIDs are the phenotypic expression of a maladaptive form of activity-dependent synaptic plasticity at excitatory synapses between cortico-striatal fibers and striatal projection neurons of the direct pathway. Paolo Calabresi and his Associates have shown that long-term potentiation (LTP) of excitatory synaptic transmission at cortico-striatal synapses requires the activation of D1, NMDA, mGlu1 and mGlu5 receptors [65]. In the pathophysiology of LIDs, striatal LTP likely underlies the priming effect, *i.e.*, the re-occurrence of LIDs when L-DOPA is administered again after a period of withdrawal. In DA-denervated rats developing LIDs, striatal LTP becomes inflexible and cannot be depotentiated [66, 67]. In both animals and humans, LIDs are associated with an enhanced glutamate release in the neostriatum and SNpr [68]. Drugs that inhibit glutamate receptors, such as the NMDA receptor antagonist, amantandine, and a series of negative allosteric modulators of mGlu5 receptors (*e.g.*, mavoglurant and dipraglurant) show efficacy in reducing LIDs in experimental animals and PD patients [51]. Safinamide is not a direct glutamate receptor antagonist, and cannot be considered as an antidyskinetic drug. However, by inhibiting glutamate release, safinamide may reduce the excitatory overdrive of the direct pathway underlying with LIDs, and, at the same time, may improve motor symptoms by reducing excitation of the indirect pathway. The latter effect may allow the reduction of the daily dose of L-DOPA, with a favourable effect on LIDs. Morari *et al*. [33] have found that safinamide reduces the evoked release of glutamate in the SNpr and GP, but not in the dorsal striatum, of freely moving rats (see above). However, it cannot be excluded that safinamide can also restrain glutamatergic transmission in the neostriatum under conditions of excitatory overdrive, as occurs in PD. Thus, the overall impact of safinamide on LIDs would result from the combination of the reduced DA metabolism (which is expected to enhance LIDs), the inhibition of glutamate release (which is expected to reduce LIDs), and the antiparkinsonian effect (which allows to reduce the daily dose of L-DOPA with beneficial effects on LIDs) (Fig. **1**). In "parkinsonian" monkeys safinamide showed great efficacy in reducing LIDs, and, as opposed to amantadine, could also prolong the antiparkinsonian effects of L-DOPA [69].

The efficacy of safinamide in patients with mid-advanced stage PD and motor fluctuations under treatment with L-DOPA or other dopaminergic agents has been examined in two phase-III clinical studies (Study 016 and SETTLE trials) [12, 13, 70, 71]. In both trials, a 24-week treatment with safinamide improved on- without troublesome dyskinesias and reduced off-times after 2 or 4 weeks of treatment. Safinamide also improved the overall clinical status of the patients in both studies. Remarkably, in the 18-months extension of Study 016 ("Study 018") safinamide treatment significantly improved the DRS (dyskinesia rating scale) score in the subgroups of patients with moderate-to-severe dyskinesias [71]. This effect was seen with the daily dose of 100 mg, which should be effective in inhibiting glutamate release [72]. Interestingly, zonisamide, which shares with safinamide the ability to inhibit both VSSCs and MAO_B, has shown efficacy in improving motor fluctuations in PD patients in a double-blind randomized study [73].

4.2. Effects of MAO_B Inhibitors on Non-motor Symptoms Associated with PD

Non-motor symptoms are often considered as secondary symptoms in PD, but they critically affect the quality of life of patients, and are difficult to treat. PD is frequently associated with depression, fatigue, pain, and dysautonomic disorders such as orthostatic hypotension, constipation and genitourinary disorders. Several lines of evidence suggest that MAO_B inhibitors can be useful in the management of all these symptoms.

Depression is observed in a large proportion of PD patients (up to 50%) and is clinically different with respect to depression not associated with PD. Anxiety and pessimism predominate in PD patients, whereas the feeling of guilt, self-reproach, and suicidal tendencies are rarely observed. Mood changes are often associated with motor fluctuation in L-DOPA-treated patients, with a reduction of mood being observed in the off phase [74, 75]. Selegiline has been shown to produce antidepressant-like effects in experimental animals. For example, selegiline treatment partially reverses the deficit in effort-related choice behavior induced by tetrabenazide, a drugs that inhibit the vesicular monoamine transporter, VMAT-2 [76]. Selegiline also improves depression-like behavior in mice subjected to maternal separation, a model of stress-related disorders endowed with face, construct, and pharmacological validity [77]. Interestingly, selegiline was also found to improve depression-like behavior in mice with genetic deletion of CD157/BST1, which is a risk factor for PD [75]. Transdermal delivery of selegiline is FDA-approved for the treatment of depression and might represent a treatment option for PD patients with depressive symptoms [78]. To what extent the metabolites L-methamphetamine and L-amphetamine contribute to the overall antidepressant effect of selegiline remains to be determined.

The effect of rasagiline on depressive symptoms in PD patients is less clear. The effect of a 12-week treatment with rasagiline on depressive and cognitive symptoms in non-demented PD patients was evaluated in a double-blind, placebo-controlled, clinical trial [74]. At week 12, rasagiline did not differ from placebo in improving depressive symptoms, as assessed by the Beck Depression Inventory scale; however, a significant difference in favour of rasagiline was found after 4 weeks of treatment [74]. A sub-analysis of the

ADAGIO study showed a positive effect of rasagiline treatment on the fatigue [79], and rasagiline was also found to improve non-motor aspects of experiences of daily living [80].

The effect of safinamide (100 mg/die) on the emotional well-being domain of Parkinson's Disease Questionnaire (PDQ-39) and on GRID-HAMD score (a standardization of the Hamilton Depression Rating Scale) was evaluated in PD patients with motor fluctuation. Safinamide displayed a beneficial effect on mood, and this has been ascribed to the improvement in wearing-off and to the effect of the drug on glutamatergic transmission [81]. Interestingly, safinamide improved painful cramps or spasms and hot- and cold-allodynia in PD patients (items 37 and 39 of PDQ-39), and allowed to reduce the use of concomitant pain treatments by >25% [82, 83]. Sleep disorders, such as RBD (REM sleep behavioural disorder), nocturnal apnoeas, and restless leg syndrome (RLS), are frequently associated with PD [3]. Three-month treatment with safinamide (100 mg/die) added to L-DOPA has been shown to markedly improve RLS in two patients with motor fluctuations [84].

4.3. Safety and Tolerability Profile of MAOB Inhibitors

Class-related adverse effects of the three MAO_B inhibitors result from the enhancement of DAergic transmission in the CNS and in the periphery. In the case of selegiline, the formation of amphetamine-based metabolites might contribute to psychiatric, neurological, and cardiovascular effects.

Psychiatric adverse effects, such as delirium, hallucinations, and agitation, are more frequent with selegiline than with other antiparkinsonian drugs. Selegiline may also cause sedation or dyskinesias [85]. Cardiovascular adverse effects of selegiline include orthostatic hypotension, hypertension, atrial fibrillation, and other types of cardiac arrhythmias, as reported in the DATATOP study [86]. The risk of cardiovascular effects increases when selegiline is administered in combination with L-DOPA [87]. Amphetamine-based metabolites of selegiline may contribute to the psychiatric and cardiovascular adverse effects of the drug.

Data of TEMPO, LARGO and PRESTO trials (see below) indicate that rasagiline is well tolerated. In these trials, the adverse effects of rasagiline were classified as uncomfortable but not dangerous (*e.g.*, asthenia, nausea, arthralgia, back pain, and headache). Two post hoc analyses of TEMPO and PRESTO studies showed an increased risk of age-related depression, postural hypotension and hallucinations in patients treated with rasagiline. Combination of rasagiline with other dopaminergic therapies is in general well tolerated and does not cause a decline in mental function [88]. The possibility that high doses of rasagiline (and selegiline) inhibit MAO_A has been discussed above. However, tyramine-dietary restrictions are not recommended in patients treated with rasagiline; accordingly, tyramine challenge following a few weeks of rasagiline administration did not cause significant changes in blood pressure [88, 89]. In an open trial, a switch from selegiline (7.5 mg, daily) to rasagiline (1 mg, daily) improved motor behavior, motor complications, mood, and sleep in 30 patients affected by PD [90].

Safinamide treatment is well tolerated, and the reported adverse effects in clinical studies were mild-to-moderate and included gastro-intestinal effects, fever, hypertension, and back pain. The safety profile of the drug is excellent. Because of the potent and selective MAO_B inhibition dyskinesias may occur as a result of the enhanced DA levels in the neostriatum. However, this risk is mitigated by the inhibition of glutamate release (see below). In the 018 extension study (see above), the incidence of dyskinesias and other DA-related adverse effects was similar between safinamide and placebo [2, 29, 70, 91-93].

Because of the comorbidity between PD and depression, MAO_B inhibitors might be associated with SSRIs, serotonin and noradrenaline reuptake inhibitors (SNRIs), or other antidepressants that enhance serotonergic transmission. This association raises the potential concern of the serotonin syndrome, a rare but potentially fatal medical condition resulting from an excessive increase in central and peripheral serotonergic transmission. After reviewing the supporting evidence, Aboukarr and Giudice (2018) concluded that serotonin syndrome is infrequent and that combination of SSRIs and MAO_B inhibitors is well tolerated providing that the SSRI dose is kept low [94]. In support to this statement, the serotonin syndrome was not observed when rasagiline was combined with SSRIs or other serotonergic antidepressants [88, 95-97].

Concerns related to pharmacokinetic interactions with other drugs have been discussed above. Again, safinamide differs from selegiline and rasagiline because it is not metabolized by, and does not influence the activity of, cytochrome-P450.

5. MAO_B INHIBITORS AS POTENTIAL DISEASE-MODIFYING DRUGS IN PD

There are no treatments that halt the progression of PD perhaps because of the heterogeneity and redundance of the molecular events underlying the pathophysiology of neuronal death. However, among all classes of drugs that are currently used in the treatment of PD, MAO_B inhibitors have consistently shown the greatest neuroprotective potential, suggesting that an early use of these drugs might have a beneficial effect on the disease course (for an elegant review, see Riederer and Müller, 2017) [98]. The DATATOP trial (Deprenyl and Tocopherol Antioxidant Therapy of Parkinsonism) was the first large multicentre clinical study examining the effect of early treatment with selegiline in patients affected by PD. Selegiline (10 mg/day), but not tocopherol, delayed the onset of L-DOPA treatment, suggesting that the drug was able to slow the progression of neurological disability in patients affected by PD [53, 99]. However, data of the DATATOP trial were confounded by the long-lasting symptomatic effect of selegiline (at that time not recognized), taking into account that the half-life of MAO_B inhibition exceeded the duration of drug withdrawal in the study [100, 101]. Two subsequent clinical trials examined the protective and disease-modifying activity of rasagiline using the strategy of the "early vs. delayed start". In the TEMPO trial rasagiline showed a greater therapeutic effect when administered for 12 months rather than in the last 6 months [56]. In the ADAGIO trial, 1176 patients were treated daily with

rasagiline (1 or 2 mg) for 72 weeks or, alternatively, with placebo for the first 36 weeks followed by rasagiline in the remaining 36 weeks. The increase in UPDRS score at the end of the 72 weeks was smaller in the "early-rasagiline start" than in the "delayed-rasagiline start" group in patients treated with 1 mg of rasagiline [57]. In principle, these findings support the protective activity of rasagiline in PD. However, there are potential pitfalls that cannot be ignored. For example, the difference in the UPDRS score between the two groups treated with 1 mg rasagiline is very small (<2 points), the UPDRS scoring is not entirely objective (particularly when repeatedly applied to the same patient), and, more important, no changes between early and delayed starts were observed when rasagiline was administered at the dose of 2 mg/day [97]. It is the right time to perform comparative studies with selegiline, rasagiline, and safinamide on neuroprotection using more objective markers, such as longitudinal SPECT analysis of striatal dopaminergic terminals with ^{123}I-ioflupane (DaTSCAN) or fluid biomarkers, such as light-chain neurofilaments in the blood or CSF, or α-synuclein in the CSF [102].

Most of preclinical studies exploring the neuroprotective potential of MAO_B inhibitors were performed using the MPTP model in mice and monkeys. As highlighted above, the parkinsonian toxin, MPTP, crosses the blood-brain barrier and is then transformed into the active metabolite, MPP^+. MPP^+ is inwardly transported into dopaminergic nerve terminals, and then causes neurodegeneration by inhibiting the mitochondrial respiratory chain [18]. Of great relevance to the present review, conversion of MPTP into $MPDP^+$, and then to MPP^+, occurs in astrocytes and is catalyzed by MAO_B [103, 104]. A large body of evidence indicates that all MAO_B inhibitors, including zonisamide, protect SNpc neurons against damage caused by acute or subacute doses of MPTP in mice or monkeys [34, 105-116]. These models are extremely helpful for the screening of neuroprotective compounds although they do not mimic the slowly progressive degeneration of dopaminergic neurons occurring in PD. Interestingly, MAO_B inhibitors were also able to rescue SNpc neurons when administered after MPTP, and displayed neuroprotective activity against damage caused by i.c.v. or intracerebral injection of MPP^+ [114, 117-119]. This suggests that there are mechanisms other than inhibition of MPTP metabolism that contribute to neuroprotection by the three MAO_B inhibitors. Accordingly, selegiline was found to protect against MPTP toxicity at low doses that are unable to inhibit MAO_B *in vivo* [119]. Cell culture and *in vivo* studies demonstrate that selegiline and rasagiline enhance the production of neurotrophic factors, such as nerve growth factor (NGF), glial cell-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF) [119-125]. GDNF, in particular, supports the survival of SNpc dopaminergic neurons, and is considered as a potential target for disease-modifying drugs in PD [126-130]. Clinical studies with intraputaminal delivery of GDNF in PD have generated contrasting results [131], perhaps because exogenous GDNF has limited access to membrane receptors. By increasing endogenous production of GDNF MAO_B inhibitors could overcome this limitation thereby boosting the pro-survival activity of GDNF.

CONCLUSION

Although safinamide is not indicated in monotherapy for the early treatment of PD, it has great neuroprotective potential owing to its ability to inhibit both MAO_B activity and glutamate release. Again, PD is characterized by an increased excitatory drive in the basal ganglia motor circuit, and overactive excitatory fibers projecting from STN neurons to the SNpc might contribute to neuronal death through an excitotoxic mechanism. A role for glutamate in PD-associated neuronal death is suggested by the evidence that NMDA or mGlu5 receptor blockade is protective against neuronal damage caused by MPTP or its metabolite, MPP^+ [132-137]. It will be interesting to examine the disease-modifying activity of safinamide in animal models that recapitulate the slowly progressive damage of SNpc neurons that is typical of PD, such as chronic MPTP models [138] or genetic mouse models harboring PD-associated mutations (*e.g.*, LRRK2-G2019S) [139].

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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