NEURAL REGENERATION RESEARCH
www.nrronline.org

Review

Type-B monoamine oxidase inhibitors in neurological diseases: clinical applications based on preclinical findings

Marika Alborghetti[1], Edoardo Bianchini[1, 2], Lanfranco De Carolis[1], Silvia Galli[1], Francesco E. Pontieri[1, 2], Domiziana Rinaldi[1, 2, *]

https://doi.org/10.4103/1673-5374.375299

Date of submission: February 1, 2023

Date of decision: April 6, 2023

Date of acceptance: May 4, 2023

Date of web publication: May 31, 2023

From the Contents

Abstract

Type-B monoamine oxidase inhibitors, encompassing selegiline, rasagiline, and safinamide, are available to treat Parkinson's disease. These drugs ameliorate motor symptoms and improve motor fluctuation in the advanced stages of the disease. There is also evidence supporting the benefit of type-B monoamine oxidase inhibitors on non-motor symptoms of Parkinson's disease, such as mood deflection, cognitive impairment, sleep disturbances, and fatigue. Preclinical studies indicate that type-B monoamine oxidase inhibitors hold a strong neuroprotective potential in Parkinson's disease and other neurodegenerative diseases for reducing oxidative stress and stimulating the production and release of neurotrophic factors, particularly glial cell line-derived neurotrophic factor, which support dopaminergic neurons. Besides, safinamide may interfere with neurodegenerative mechanisms, counteracting excessive glutamate overdrive in basal ganglia motor circuit and reducing death from excitotoxicity. Due to the dual mechanism of action, the new generation of type-B monoamine oxidase inhibitors, including safinamide, is gaining interest in other neurological pathologies, and many supporting preclinical studies are now available. The potential fields of application concern epilepsy, Duchenne muscular dystrophy, multiple sclerosis, and above all, ischemic brain injury. The purpose of this review is to investigate the preclinical and clinical pharmacology of selegiline, rasagiline, and safinamide in Parkinson's disease and beyond, focusing on possible future therapeutic applications.

Key Words: glial cell line-derived neurotrophic factor (GDNF); glutamate; neurological disorders; neuroprotection; Parkinson's disease; preclinical studies; rasagiline; safinamide; selegiline; type-B monoamine oxidase (MAO_B) inhibitors

Introduction

Monoamine oxidases (MAOs) are flavin-dependent enzymes located in the outer mitochondrial membranes. Two different isoforms have been identified, MAO_A and MAO_B. MAO_A is localized in the gastroenteric cells, heart myocytes, platelets, and aminergic neurons, whereas MAO_B has been found in platelets and astrocytes. MAO_A and MAO_B participate in the catabolism of amine neurotransmitters, including dopamine (Bainbridge et al., 2008; Tripathi et al., 2018; Tan et al., 2022). In particular, MAO_A metabolizes amines in presynaptic neuronal terminals, whereas MAO_B is involved in the degradation of dopamine uptaken into astrocytes from the synaptic cleft. In clinical practice, MAO_A and MAO_B inhibitors are, respectively, helpful in treating neuropsychiatric disorders such as depression and Parkinson's disease (PD) (Carradori et al., 2018; Tan et al., 2022).

The symptomatic efficacy of MAO_B inhibitors in PD is mostly dependent on enzyme inhibition in the brain, which, in turn, increases the extracellular levels of dopamine (Alborghetti and Nicoletti, 2019). Three MAO_B inhibitors are available, selegiline, rasagiline, and safinamide. These drugs improve motor symptoms and reduce the severity and duration of motor fluctuations in PD patients undergoing levodopa (LD) treatment. Selegiline and rasagiline also display symptomatic efficacy as monotherapy in the early stage of the disease. Moreover, as discussed below, MAO_B inhibitors may be of benefit to some non-motor symptoms of PD (Alborghetti and Nicoletti, 2019; Armstrong and Okun, 2020). Therefore, MAO_B inhibitors could relieve symptoms and reduce LD dosage in patients with early or mild PD. In advanced PD, MAO_B inhibitors are useful add-ons to LD in patients experiencing motor fluctuations by reducing time spent OFF, increasing time ON, and significantly improving quality of life (Alborghetti and Nicoletti, 2019).

Despite the commonality of the primary mechanism of action, MAO_B inhibitors display peculiar differences that may be of interest to the clinical practice. Thus, selegiline and rasagiline are irreversible inhibitors forming a covalent bond within the active site of MAO_B. Conversely, safinamide is a reversible MAO_B inhibitor and, at the high daily dose (100 mg), inhibits voltage-sensitive sodium channels (VSSCs) and voltage-sensitive calcium channels (VSCCs), which, in turn, inhibit glutamate release (Blair and Dhillon, 2017; Alborghetti and Nicoletti, 2019; Tan et al., 2022). Beyond the primary mechanism of action, preclinical studies indicate additional consequences of MAO_B inhibitors that may represent a further therapeutic potential for these drugs in PD as well as other pathological conditions. Among anti-parkinsonian agents, MAO_B inhibitors have the most significant neuroprotective potential through inhibition of dopamine metabolism and stimulation of neurotrophic factors. In the case of high-dose safinamide, inhibition of glutamate neurotransmission. Preclinical studies suggest, indeed, additional therapeutic prospects of these drugs in PD as well as other neurological disorders characterized by either chronic progressive neurodegenerative damage or acute metabolic/oxidative stress (**Figure 1**). Given these premises, we sought interest in discussing the preclinical and clinical pharmacology of selegiline, rasagiline, and safinamide in PD and beyond, focusing on possible therapeutic advances. To this end, we focused on current preclinical evidence that may suggest the further therapeutic application of MAO_B inhibitors in PD as well as other neurological illnesses, with the aim of translationally expanding the use of these drugs.

Literature Search Strategy

A search was performed on the PubMed database for all studies according to the following keywords: "selegiline" OR "rasagiline" OR "safinamide" OR "MAOB" AND "neuroprotection" AND "Parkinson's disease" OR "neurological disorders" AND "basal ganglia" AND "glutamate" OR "NMDA receptor antagonists". Only articles in the English language published in the period between January 1978 and November 2022 were considered. We included preclinical studies as well as clinical trials and observational studies in humans. Two authors (MA and DR) examined each report independently with respect to methodologies, the relevance of the results, and potential implications. Discrepancies in the evaluation were discussed with the remaining Authors. Moreover, the search was enlarged to the references of the originally selected papers, and seminal studies were included with no age limit.

[1]Neurology Unit, NESMOS Department, Faculty of Medicine & Psychology, Sapienza—University of Rome, Sant'Andrea University Hospital, Rome, Italy; [2]Department of Clinical and Behavioral Neurology, IRCCS—Fondazione Santa Lucia, Rome, Italy

*Correspondence to: Domiziana Rinaldi, MD, domiziana.rinaldi@gmail.com or domiziana.rinaldi@uniroma1.it.

https://orcid.org/0000-0002-8011-087X (Domiziana Rinaldi)

How to cite this article: *Alborghetti M, Bianchini E, De Carolis L, Galli S, Pontieri FE, Rinaldi D (2024) Type-B monoamine oxidase inhibitors in neurological diseases: clinical applications based on preclinical findings. Neural Regen Res 19(1):16-21.*

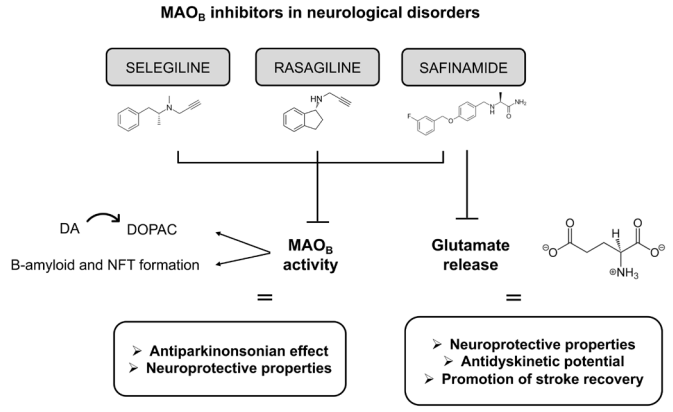

Figure 1 | **MAO$_B$ inhibitors in neurological disorders.**
DA: Dopamine; DOPAC: 3,4-dihydroxyphenylacetic acid; MAO$_B$: type B onoamine oxidase; NFT: neurofibrillary tangles.

MAO$_B$ Inhibitors for the Treatment of Parkinson's Disease

To date, LD remains the gold standard for the symptomatic treatment of motor symptoms of PD. LD is administered orally together with L-aromatic-amino-acid-decarboxylase inhibitors (carbidopa or benserazide) to reduce peripheral metabolism and allow adequate crossing of the blood-brain barrier (LeWitt, 2015). Despite L-aromatic-amino-acid-decarboxylase inhibition, the rather short plasma half-life of LD is a significant determinant for causing pulsatile stimulation of central dopaminergic receptors. Such phenomenon, together with progressive neuronal loss and maladaptive changes in the response of postsynaptic neurons, plays a relevant role in developing LD-related complications, such as motor (and non-motor) fluctuations and dyskinesia (Nutt, 2001; Fox et al., 2018). Therapeutic approaches for managing fluctuations include add-ons with direct dopamine agonists, catechol-O-methyltransferase inhibitors, or MAO$_B$ inhibitors (Fox et al., 2018; Alborghetti and Nicoletti, 2019; Gray et al., 2022). Conversely, amantadine is the only drug displaying anti-dyskinetic activity (Rascol et al., 2021).

Selegiline

Selegiline is an irreversible and selective MAO$_B$ inhibitor with a therapeutic indication in PD as monotherapy or in combination with LD, at daily doses of 5 or 10 mg (Knoll, 1989). It is rapidly absorbed from the gastroenteric tract, with peak plasma concentrations of about 2.7 ng/mL and a T_{max} value of 0.5 hours, and prompt crossing of the blood-brain barrier. Selegiline is metabolized in the liver, mostly through CYP2B6 and in the lower part by CYP2A6 and CYP3A4, in desmethylselegiline and methamphetamine, which are both pharmacologically active (Magyar, 2011; Alborghetti and Nicoletti, 2019). Selegiline is safe and well-tolerated in PD patients, with rare side effects being characterized by sexual dysfunction, sleep difficulty, and weight gain.

The beneficial antiparkinsonian effects of early monotherapy with selegiline were demonstrated in the DATATOP study (Shoulson, 1989), showing a significant delay in the need for add-on with LD. Moreover, findings from the SINDEPAR trail showed that selegiline 10 mg reduced the severity of parkinsonism, as measured by the Unified Parkinson's Disease Rating Scale (UPDRS) score when combined with either LD or bromocriptine (Stocchi and Olanow, 2003). In a head-to-head, real-life, retrospective study, Cereda and collaborators (Cereda et al., 2017) reported that long-term use of selegiline or rasagiline was associated with a reduction of LD requirement and LD-induced dyskinesia with respect to controls in moderate PD patients. In more advanced cases, an add-on with selegiline to LD treatment improved tremor, rigidity, and bradykinesia, significantly reducing the frequency and severity of motor fluctuations (Dashtipour et al., 2015; Tan et al., 2022).

Rasagiline

Rasagiline is an irreversible and selective MAO$_B$ inhibitor with a therapeutic indication in PD at the daily dose of 1 mg as monotherapy or add-on to LD in fluctuating subjects. Higher daily doses (10 mg), not used in humans, also inhibit MAO$_A$ activity. Rasagiline is readily absorbed following oral administration and has a bioavailability of about 35%, a peak plasma concentration of 2.5 ng/mL, and a Tmax value of 0.5 hours. The drug undergoes hepatic metabolism by CYP1A2, with a production of inactive metabolites (Chahine and Stern, 2011; Alborghetti and Nicoletti, 2019).

Several randomized clinical trials have shown the therapeutic efficacy of monotherapy with rasagiline in terms of motor symptoms and quality of life in early PD subjects (Parkinson Study Group, 2002, 2004; Hauser et al., 2009, 2016). Specifically, in placebo-controlled multicenter studies, TEMPO (TVP-1012 in Early Monotherapy for PD Outpatients) and ADAGIO (Attenuation of Disease Progression with Azilect Given Once-daily), rasagiline improved UPDRS part III score and quality of life to placebo over 36 weeks of treatment (Parkinson Study Group, 2002, 2004; Stocchi and ADAGIO investigators, 2014; Hauser et al., 2009, 2016).

Two other studies, LARGO (Lasting effect in Adjunct therapy with Rasagiline given Once-daily) and PRESTO (Parkinson's Rasagiline: Efficacy and Safety in the Treatment of 'Off') trials, demonstrated the efficacy of add-on with rasagiline to LD in reducing the "off" periods in fluctuating PD subjects (Rascol et al., 2005; Olanow et al., 2009). In particular, in the PRESTO study, rasagiline showed efficacy in the reduction of motor fluctuation in PD patients treated with LD and/or dopamine agonist or COMT inhibitors showing an increase in dyskinesia than placebo (Olanow et al., 2009).

Moreover, a recent retrospective case-control study showed that an add-on with either rasagiline or selegiline was associated with lower daily LD dose and lower frequency of LD-induced dyskinesia (Cereda et al., 2017). A further cohort study confirmed the reduction of daily LD dose following add-on with rasagiline (Rascol et al., 2005). In this double-blind, multicenter study, the Authors found a significant improvement in CGI score, daily living activities during off-time, and motor function during on-time in the rasagiline group compared to placebo.

Safinamide

Safinamide is the prototype of new-generation MAO$_B$ inhibitors. It is a selective, reversible MAO$_B$ inhibitor approved as an add-on to LD in PD patients experiencing fluctuations. Two dosages are available, 50 mg and 100 mg, which display similar inhibitory effects on MAO$_B$. At the daily dose of 100 mg, however, safinamide also blocks VSSCs and VSCCs, thus inhibiting glutamate transmission at overactive synapses (Blair and Dhillon, 2017; Schapira et al., 2017; Alborghetti and Nicoletti, 2019). Safinamide is readily absorbed after oral administration and shows a > 80% bioavailability with a T_{max} value of 1.8–2.8 hours, distribution volume of 150 L, plasma albumin binding of 92%, and elimination half-life of 21–24 hours. It is not metabolized by CYP450, thus avoiding significant drug interactions (Alborghetti and Nicoletti, 2019). The drug is metabolized by MAO$_A$ and amide hydrolases into pharmacologically inert acidic and N-dealkylated products.

Efficacy and safety profiles of safinamide were confirmed in a recent multicenter, observational, retrospective cohort study (SYNAPSES trial) (Abbruzzese et al., 2021) as well as in elderly people (Rinaldi et al., 2021a). Safinamide reduced "Off" time and improved "On" time without troublesome dyskinesia, as reported in two phase-III double-blind, randomized clinical trials (Borgohain et al., 2014a; Cattaneo et al., 2016). Interestingly, in a subgroup of patients with moderate-severe dyskinesia, treatment with a daily dose of 100 mg safinamide was accompanied by the reduction of the Dyskinesia Rating Scale score (Study 018) (Borgohain et al., 2014b). These latter, preliminary findings suggest that the anti-glutamatergic activity of high-dose safinamide may find clinical application for the management of LD-induced dyskinesia. This motor complication arises from maladaptive synaptic plasticity at synapses between corticostriatal fibers and GABAergic striatopallidal neurons of the direct pathway (Nutt, 2001; Alborghetti and Nicoletti, 2019), and, as mentioned previously, is poorly responsive to available treatments, amantadine being the unique drug with verified activity (Rascol et al., 2021).

MAO$_B$ inhibitors and non-motor symptoms of Parkinson's disease

Beyond motor symptoms of parkinsonism, people with PD frequently experience a number of non-motor symptoms (Schapira et al., 2017), which are often disabling and rather challenging to manage. Moreover, dopamine replacement therapy prescribed for the treatment of parkinsonism may exert rather controversial effects on some non-motor symptoms (Schapira et al., 2017; Armstrong and Okun, 2020).

As to MAO$_B$ inhibitors, selegiline displayed antidepressant effects (Knoll, 1989; Magyar, 2011, Ishikawa et al., 2019), possibly due to its amphetamine-like metabolic products. A transdermal patch of selegiline is marketed in some Countries for the treatment of depression (Thomas et al., 2015) and may represent an option in subjects affected by PD with comorbid depression.

The impact of rasagiline on depressive symptoms is somewhat controversial. In a double-blind, placebo-controlled trial, 1-month treatment with rasagiline showed significant efficacy (Olanow et al., 2009), whereas there was no difference between rasagiline and placebo in terms of depression outcome in the ACCORDO study (Parkinson Study Group, 2004). However, a sub-analysis of data from the ADAGIO trial showed the benefit of rasagiline on fatigue (Stocchi and Olanow, 2003; Stocchi and ADAGIO investigators, 2014). Eventually, both selegiline and rasagiline may ameliorate prefrontal executive functions in the early-moderate disease stage (Rinaldi et al., 2018, 2022), while in a more advanced stage, they appear to worsen prefrontal inhibitory control, possibly as the consequence of the excessive dopaminergic drive to prefrontal cortical regions (Rinaldi et al., 2018, 2022).

The dual mechanism of action of high-dose safinamide stimulated significant research on non-motor symptoms in PD. Indeed, simultaneous modulation of dopaminergic and glutamatergic neurotransmission appears extremely promising for several non-motor domains. Thus, safinamide improved painful cramps or spasms and allodynia in PD patients and allowed a 25% reduction in concomitant pain treatment use (Grigoriou et al., 2021). Other studies demonstrated that safinamide improves cognition and fatigue and is safe in elderly people (Bianchi et al., 2019; De Micco et al., 2022; Rinaldi et al., 2021a). Differently from other MAO$_B$ inhibitors, high-dose safinamide improved executive functions, including inhibitory control (Rinaldi et al., 2021b), an effect possibly secondary to the modulation of glutamatergic neurotransmission. Moreover, the results of a recent Spanish study showed that safinamide improves urinary symptoms, including urgency, incontinence, frequency of micturition, and nocturia (Gómez-López et al., 2021). Eventually,

treatment with safinamide was beneficial to sleep and daytime sleepiness in fluctuating PD patients (Santos García et al., 2022).

Additional Properties of MAO_B Inhibitors

Anti-oxidant and neurotrophic properties

Beyond the indirect stimulation of amine transmission, MAO_B inhibitors bear additional pharmacological effects that may be of interest in PD and other neurological disorders. Among all anti-parkinsonian drugs, MAO_B inhibitors hold the strongest neuroprotective potential, at least on the basis of preclinical studies, and administration of these drugs in the early stage of illness might be of benefit to disease progression (Riederer and Müller, 2017).

The etiology of PD and other synucleinopathies depends on multiple pathogenetic factors, including oxidative stress, mitochondrial dysfunction, alteration of the ubiquitin-proteasome protein degradation system, and neuroinflammation. In this context, MAO_B inhibitors may be of potential benefit as they reduce the production of reactive oxygen species, prevent mitochondrial damage, induce the expression of antiapoptotic proteins Bcl-2, downregulate the pro-apoptotic FAS and Bax protein families, and the production of neurotrophic factors. They also prevent aggregation and abnormal oligomerization of α-synuclein (see below).

The neuroprotective potential of MAO_B inhibitors has been investigated preclinically in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of parkinsonism. MPTP is a lipophilic compound that readily crosses the blood-brain barrier and is converted into its toxic metabolite 1-methy-4-phenylpyridinium (MPP^+) by MAO_B in the astrocytes. MPP^+ is then uptaken by dopaminergic terminals and interacts with complex I of the mitochondrial transport chain, thus producing oxygen-free radicals and leading to cell death. Consistently with this cascade, several reports indicate that MAO_B inhibitors protect nigral dopaminergic neurons against acute or subacute MPTP administration in mice and monkeys (Meredith and Rademacher, 2011; Zhao et al., 2013).

Several reports, however, suggest that the protective effect of MAO_B inhibitors on MPTP-induced dopaminergic cell damage may be, at least partially, independent of enzyme inhibition. Thus, MAO_B inhibitors showed rescuing properties on nigral dopaminergic cells also when injected after MPTP or after intracerebral infusion of MPP^+ (Wu et al., 2000; Szökő et al., 2018), and low-dose selegiline, ineffective on MAO_B activity *in vivo*, already protected against MPTP toxicity (Zhao et al., 2013). Moreover, the protective effects of pretreatment with selegiline on MPP^+ neuronal damage in the rat striatum were accompanied by increased superoxide dismutase and catalase activities (Vizuete et al., 1993). This observation is, indirectly, in line with microdialysis findings from Wu et al. (2000) showing that selegiline exerts stronger protective activity on MTPT or MPP^+ dopaminergic cell damage in the highly-metabolic-demanding nigrostriatal compared with the mesocorticlimbic neurons. Moreover, safinamide suppressed microglial activation and protected dopaminergic neurons from degeneration in the 6-hydroxydopamine model of parkinsonism (Sadeghian et al., 2016). In these experiments, safinamide 50 or 150 mg/mL was administered for seven days after injection of 6-hydroxydopamine into the medial forebrain bundle and caused a significant reduction of activated microglia MHC-II+ and the protection of dopaminergic neurons.

Taken together, all these findings suggest that mechanisms other than enzymatic inhibition may contribute to the neuroprotective potential of MAO_B inhibitors. Accordingly, treatment with selegiline was associated with the induction of neurotrophic factors such as glial cell line-derived neurotrophic factor and brain-derived neurotrophic factor, and anti-apoptotic genes in the subacute MPTP model of parkinsonism in mice (Zhao et al., 2013). *In vitro* and *in vivo* studies confirmed that both selegiline and rasagiline stimulate the synthesis and liberation of neurotrophic factors (Naoi et al., 2020). Among them, glial cell line-derived neurotrophic factor is considered a candidate target for disease-modifying therapy of PD since it promotes the survival and differentiation of dopaminergic neurons (Barker et al., 2020).

Furthermore, according to recent work, selegiline, and rasagiline also promote the expression of anti-apoptotic genes such as Bcl2 and genes coding for antioxidant enzymes. The induction of neuroprotective genes by MAO_B inhibitors was investigated in human glioblastoma U118MG cells. Interestingly, in MAO_B knockdown condition, mRNA levels of Bcl-2, brain-derived neurotrophic factor, and glial cell line-derived neurotrophic factor were higher compared to controls. These results indicate that MAO_B might function as a repressor of the constitutional expression of pro-survival genes, and selegiline and rasagiline might regulate different signal pathways to induce neuroprotective genes (Inaba-Hasegawa et al., 2017). The two MAO_B inhibitors also regulate the mitochondrial apoptosis system, sustain mitochondrial function, and suppress the oligomerization of alpha-synuclein in cellular and animal models (Naoi et al., 2020, 2022). In parkinsonian brains, apoptosis was demonstrated by the increase of active caspase-3 and decrease of Fas-associated protein with a death domain-immunoreactive DA neurons in the substantia nigra (Venderova and Park, 2012), and intrinsic apoptosis could be initiated by opening the mitochondrial permeability transition pore, leading to an increase in mitochondrial membrane permeability (Kroemer et al., 2007). Both rasagiline and selegiline prevented the mitochondrial permeability transition pore opening and the consequent apoptosis. In the pathophysiology of PD, there is probably a cross-talk between α-synuclein and MAOs. MAO_B expression is enhanced by α-synuclein, which may favor the loss of dopaminergic terminals. On the other hand, rasagiline and selegiline can bind to α-synuclein, change its conformation, turn it to non-fibril conformation, and reduce the aggregate accumulation (Braga et al., 2011; Kakish et al., 2015; Naoi et al., 2022).

Therefore, MAO_B inhibitors hold different molecular mechanisms of neuroprotection, involving mitochondrial homeostasis, pro-survival neurotrophic factors release, and prevention of toxic oligomerization and aggregation of α-synuclein.

The anti-glutamatergic activity of safinamide

High-dose safinamide inhibits depolarization-evoked glutamate and GABA release in the hippocampus, globus pallidus, subthalamic nucleus, and substantia nigra pars reticulata (Alborghetti and Nicoletti, 2019; Rinaldi et al., 2022). These effects are sustained by the blockade of VSSCs and VSCCs, reducing the excitatory overdrive in the basal ganglia motor circuitries in PD. Based on these pharmacological properties, safinamide was originally developed as an anti-epileptic drug and displayed a higher affinity for the batrachotoxin-sensitive site of VSCCs than riluzole, carbamazepine, phenytoin, and lamotrigine (Alborghetti and Nicoletti, 2019). Interestingly, zonisamide has a similar pharmacological profile to safinamide and these drugs are considered prototypes of a new generation of multi-active MAO_B inhibitors (Blair and Dhillon, 2017).

Preclinical studies confirm that excessive glutamatergic neurotransmission plays a fundamental role in several pathophysiological changes in the brain. As elegantly shown by Calabresi et al. (2022), several transmitter-receptor systems regulate synaptic plasticity in the striatum. In particular, long-term potentiation of excitatory synaptic transmission at corticostriatal synapses requires activation of D1 dopamine receptors, N-methyl-D-aspartate (NMDA) receptors, and metabotropic glutamate (mGlu) receptors, including mGlu1 and mGlu5 receptors. Thus, glutamate neurotransmission plays a crucial role in striatal long-term potentiation, and modulation of mGlu receptor activity represents a potential therapeutic target for basal ganglia circuitry dysfunction. Preclinical studies indicate that negative allosteric modulators of mGlu5 receptors (mavoglurant, dipraglurant, basimglurant) exert anti-dyskinetic effects in experimental animal models of PD (Ossowska et al., 2005; Samadi et al., 2008), findings confirmed by preliminary human studies (Rascol et al., 2014). Safinamide 100 mg reduces glutamate release but does not directly block glutamatergic receptors and is not considered an antidyskinetic drug. However, the second additional mechanism of action can reduce the excessive glutamatergic overdrive in the direct pathway underlying levodopa-induced dyskinesia. Morari et al. (2018) applied *in vivo* microdialysis to monitor the spontaneous and veratridine-induced glutamate and GABA release in naïve, awake rats. They demonstrated that safinamide at the maximum dosage inhibits the induced glutamate release in the hippocampus, in the subthalamic nucleus and substantia nigra pars compacta, but not in the dorsal striatum, and shows no effects on spontaneous glutamate release. Despite these negative findings, one cannot exclude that safinamide might counteract glutamatergic transmission in the striatum when a condition of excessive glutamatergic overdrive exists, as in PD.

Excessive glutamate transmission also has negative consequences on several non-motor symptoms of PD, belonging to the cognitive, neuropsychiatric, and sensory domains (Wang et al., 2020). In the early PD stage, cognitive impairment takes the features of the dysexecutive syndrome, whereas, in advanced stages, it may evolve into the condition of PD dementia with memory impairment, disorientation, and multiple deficits of cortical functions. Neuropsychiatric features, such as visual hallucinations, delusions, and psychosis, are also frequent. In such an advanced stage, multiple neurotransmitter/receptor systems contribute to cognitive impairment and neuropsychiatric features. Glutamate signaling regulates neuronal activity in the prefrontal cortex and modulates working memory and some neuropsychiatric signs. Memantine, a partial NMDA receptor antagonist, and amantadine, a low-affinity, non-competitive NMDA receptor antagonist, are frequently used to ameliorate attention and memory performances (Wesnes et al., 2015). Glutamate receptors are also widely expressed in the brain, spinal cord, and peripheral nerves involved in pain sensation and transmission, modulation of the glutamate system being an attractive target for pain therapies (Wozniak et al., 2012).

Eventually, pathological regulation of glutamate transmission is a major determinant of excitotoxicity and plays a role in both acute (Gasparini et al., 2013; Sciaccaluga et al., 2020) and chronic (Dong et al., 2009; Sciaccaluga et al., 2020) neuronal damage. Given the consequences of excessive glutamate transmission and the pathophysiological interactions between dopaminergic and glutamatergic pathways in the basal ganglia and cortical regions, the dual mechanism of action of high-dose safinamide is of particular interest for possible future studies.

Type-B Monoamine Oxidase Inhibitors and Parkinson's Disease: Translating Preclinical Findings into Clinical Practice

Therapeutic approaches able to reverse, block, or even slow down neuronal loss are still an unmet need for the management of neurodegenerative disorders, including PD. With this respect, preclinical studies provide clear evidence that the therapeutic potentials of MAO_B inhibitors in PD extend much beyond the consequences of their primary mechanism of action, i.e., inhibition of dopamine metabolism. In particular, the neurotrophic and

neuroprotective potentials of MAO_B inhibitors gained significant interest in the scientific and clinical communities. Despite this strong preclinical evidence, however, attempts to demonstrate a neuroprotective, or at least disease-modifying effects of MAO_B inhibitors in PD ended with negative results.

Back in the '90s, the results of the DATATOP trial (Shoulson, 1989) suggested a possible neuroprotective effect of selegiline 10 mg in early PD patients, based on the significant delay of the need for add-on with LD in selegiline-treated subjects with respect to a placebo-treated cohort. Later on, this effect was attributed to the symptomatic action of active metabolites of selegiline and the irreversible inhibition of MAO_B activity, which were found to last longer than the drug withdrawal period applied at the end of treatment. More than a decade after, the potential disease-modifying consequences of early treatment with rasagiline 1 mg were investigated in the TEMPO and ADAGIO trials using the "early *vs*. delayed start" design (Nayak and Henchcliffe, 2008; Hauser et al., 2009; Olanow et al., 2009). The such study design is of particular interest as it may contribute to identifying whether the early pharmacological intervention has a more pronounced chance of slowing down disease progression. Early treatment with rasagiline 1 mg, indeed, was associated with a more favorable outcome in terms of motor disability (UPDRS-III score at the end of the study), as if the early beginning of treatment in the early stage of the disease would reduce the progression of parkinsonism. These findings led to registering rasagiline as "disease-modifying treatment" for people with PD in the early stage. This enthusiastic interpretation was not confirmed, however, by long-term follow-up of participants and critical revaluation of the results. In particular, the minimal (< 2 points) difference in UPDRS-III score among groups, the low reliability of repeated administration of the outcome scale to the same subject, and the lack of effect of 2 mg rasagiline were considered significant biases to the original interpretation (Hauser et al., 2016).

Critical analysis of these trials is, in our opinion, fundamental for identifying and approaching difficulties and controversies in the attempt to translate findings from preclinical studies into clinical practice. The limitation of posing a correct clinical diagnosis early along the process of neurodegeneration in PD is, currently, a major limitation to neuroprotective or at least disease-modifying treatments. Unfortunately, attempts of validating instrumental markers of neurodegeneration, such as ^{123}I-fluopane scintigraphic scan, gave rather negative results (Cummings et al., 2011). Moreover, the application of such an approach as a screening tool on wide cohorts is ampered by economic burden. Furthermore, the current evidence of a long (even decades) premotor stage in PD further complicates attempts of early interventions. Hypothetically, the development and validation of algorithms combining familial/genetic features with premotor symptoms of PD and biological evidence of phosphorylated a-synuclein pathology in body fluids (Wang et al., 2012; Vivacqua et al., 2018) or peripheral biopsies (Delenclos et al., 2016; Campo et al., 2019) may help to identify subjects at high risk of being diagnosed with PD in the short future. These subjects might receive instrumental evidence of presymptomatic striatal dopamine denervation and become potentially eligible for enrollment in neuroprotective trials using safe and well-tolerated compounds. A further source of bias in clinical trials stems from the identification of correct outcome measures, scales measuring the progression of neural degeneration being lacking. Again, this problem should be faced by combining findings from available scales with biological/pharmacological data, including the request for symptomatic therapy. This is even more complicated if the case of differentiating disease-modifying from symptomatic effects of a drug (as in the instance of MAO_B inhibitors). Eventually, the long disease duration makes it difficult to get any conclusive finding within 3–5 years, but this latter observation does not support by itself any negative short-lasting finding. Future trials on PD subjects should face these difficulties with the aim of allowing promising advances.

Type-B Monoamine Oxidase Inhibitors and Other Neurological Disorders

MAO_B inhibitors also gained interest in managing neurodegenerative disorders other than PD. Several studies investigated the potential therapeutic application of selegiline and rasagiline in Alzheimer's disease (AD). AD is the most common age-related neurodegenerative disorder worldwide. As in the case of PD, the pathophysiology of AD is complex and not completely defined at present. Progression of the neurodegenerative process leads to loss of memory and cognitive functions, with difficulties in managing complex activities and problem-solving, and a significant negative impact on disability and quality of life of affected individuals and caregivers. Neurotransmitter deficiency, dyshomeostasis of biometals, and oxidative stress play a relevant role in disease progression. The hallmarks of the disease are β-amyloid deposits and intracellular neurofibrillary tangles constituted by hyperphosphorylated tau protein (Rajmohan and Reddy, 2017). Many researchers favor therapeutic approaches that target the formation, deposition, and clearance of β-amyloid. MAO activity contributes to the formation of amyloid plaques and neurofibrillary tangles and to damage of cholinergic neurons and pathways (Behl et al., 2021), and there is evidence of early and sustained alteration of MAO_A and MAO_B in the AD brain (Behl et al., 2018). In particular, biochemical investigation in the post-mortem AD brain showed variations in MAO_{A-B} levels detected in the cortex of AD early phases and sustained alteration throughout the development of AD (Kennedy et al., 2003). MAO_B enzymatic activity increases in brain tissue, cerebrospinal fluid, and platelets from AD patients over time. Thus MAO_B activity may be viewed as a disease biomarker in AD (Muck-Seler et al., 2009; Behl et al., 2021).

Monoamine activity may affect the cleavage of the amyloid precursor protein, leading to the clinical features of the neurodegenerative disorder. Overactivity of MAO_{A-B} catalyzes the cleavage of amyloid precursor protein by directly activating the β-secretase and γ-secretase activity, causing an aberrant amyloid plaque generation (Behl et al., 2021). Selegiline and other antiparkinsonian agents were able to inhibit β-amyloid fibrils formation from β-amyloid 1–40 and β-amyloid 1–42 as well as their extension *in vitro* (Ono et al., 2006). Furthermore, MAO_B inhibition might be of benefit by reducing the synthesis of hydrogen peroxide and oxidative stress radicals, which, in turn, contribute to disease development and progression (Bainbridge et al., 2008; Meredith and Rademacher, 2011; Zhao et al., 2013). Thus, selegiline can inhibit apoptosis induced by oxidative stress and cell death caused by glutathione depletion (Naoi et al., 2022). In animal models of aging, selegiline is also effective in delaying memory impairment (Knoll, 1989). In AD mice, the drug limits the impairment of synaptic plasticity and cognitive dysfunction by inhibiting GABA release from astrocytes (Jo et al., 2014). Short-term administration of selegiline improves cognitive impairment in AD, derived from GABA/MAO_B interactivity, and long-term administration attenuates abnormal GABA measured (Tábi et al., 2020).

Therefore, the neuroprotective properties of MAO_B inhibitors in AD may depend on promoting anti-oxidant and iron chelating activity, preventing oxidative stress and tau protein hyperphosphorylation, regulation of β-amyloid plaques formation, and improvement of cognitive deficits (Behl et al., 2021).

Duchenne muscular dystrophy (DMD) is a severe form of inherited muscular dystrophy, leading to death from heart and respiratory failure. Therapy of DMD is rather ineffective, although gene therapies have been recently introduced for patients with specific mutations (Fairclough et al., 2013). Mitochondrial dysfunction and oxidative stress play a concrete role, at least in disease progression, and increased expression and activity of muscular MAO_B have been found in murine models of muscular dystrophy, mdx for DMD, and Col6a1$^{-/-}$ mice for collagen VI-related myopathies (Menazza et al., 2010, 2012; Sorato et al., 2014). A study by Vitiello et al. (2018) evaluated the effects of safinamide on the skeletal muscles of mdx mice and cultured muscle cells from DMD patients, with good effects on myofiber damage, oxidative stress, and muscle functionality. By blocking skeletal muscle sodium channels, safinamide might represent a therapeutic option also in non-dystrophic myotonia because mutations in chloride and sodium channels occur, causing stiffness and prolonged muscle contraction (Cannon, 2015; Imbrici et al., 2016; Desaphy et al., 2020).

As mentioned earlier, safinamide was originally developed as an antiepileptic drug because of its ability to inhibit VSSCs and VSCCs. This mechanism is useful to limit the hyperexcitability of neuronal circuitries mediating seizure but may also be useful in other pathological instances. Thus, blockade of VSSCs can exert a protective action on white matter lesions in experimental models of demyelinating disorders and may position safinamide as a potentially protective agent in multiple sclerosis. Despite the original definition of multiple sclerosis as an immune-mediated, demyelinating disorder, evidence exists of long-term, degenerative damage producing axonal and neuronal degeneration over time (Haines et al., 2011), in turn determining permanent neurological disability. VSSCs blockers, such as phenytoin, carbamazepine, and lamotrigine, may limit axonal damage in experimental models of MS, the latter drug being also of benefit in preliminary trial on secondary progressive MS, despite questionable tolerability (Morsali et al., 2013). The high tolerability and safety profiles of high-dose safinamide in PD patients support its utilization in MS. With this respect, a study by Morsali et al. (2013) investigated the effects of safinamide and flecainide on axonal function and structure in two models of experimental autoimmune encephalomyelitis. Safinamide treatment was beneficial even when delayed to the onset of neurological symptoms. The authors concluded that the efficacy of safinamide on axonal survival likely depended on the reduction of microglial activation.

Epidemiologically, the most relevant perspective for using MAO_B inhibitors beyond PD refers to ischemic stroke. Stroke is a leading cause of death and disability in the United States and the European Community (Guzik and Bushnell, 2017). Despite the significant clinical benefit of pharmacological thrombolysis and thrombectomy in acute ischemic stroke, drug-induced neuroprotection and pharmacological strategies to improve post-stroke recovery are still unmet needs in stroke management. Profound neurorestorative processes occur in brain tissue following focal cerebral ischemia, and the post-acute phase is characterized by intense neuronal sprouting. Thus, the sprouting of pyramidal tract fibers that occurs after Wallerian degeneration is accompanied by the remodeling of trans-callosal projections that connect the cortical areas of the two hemispheres (Obi et al., 2018). Therefore, neural plasticity involves both the lesioned and contralateral hemispheres and may drive functional hemispheric imbalance, which may be targeted by therapeutic interventions. Modern strategies to stroke management should include functional- and structural-based approaches (Silasi and Murphy, 2014), including the effort to rebalance the activity of the two hemispheres through the modulation of glutamate neurotransmission. According to recent reports on animal models (Hermann and Chopp, 2012; Xu et al., 2020), drugs restraining glutamate neurotransmission may promote functional recovery even if administered days after transient or definite ischemic injury (Hermann et al., 2019; Salvalaggio et al., 2020). A recent work by Xu et al. (2020) demonstrates that safinamide has a protective effect in animal models of acute ischemic stroke and, *in vitro*, on endothelial cells and suggests that the drug may improve vascular integrity in cerebral ischemia. Indeed, safinamide might be a helpful treatment option for correcting abnormalities of brain connectivity secondary to focal ischemia

because of its complex mechanism of action. Thus, the drug combines the potential benefit of increased dopamine transmission (Obi et al., 2018; Talhada et al., 2021) and reduced free oxygen radical species genesis due to the inhibition of MAO_B with the inhibition of glutamate release. Despite the more straightforward mechanism of action, the administration of selegiline reduced oxidative stress, cell death, and cognitive impairment following transient global ischemia in rodents (Maia et al., 2004; Ahmari et al., 2020).

Conclusions

Robust preclinical evidence indicates that MAO_B inhibitors may benefit PD and other neurological disorders by means of mechanisms different from the conventional increase of dopamine neurotransmission. In particular, the antioxidant and potentially neuroprotective effects of these drugs and the stimulating action on the synthesis of neurotrophic factors and gene products affecting neuronal survival may represent the basis for the disease-modifying activity of these drugs. Moreover, the dual mechanism of action of the recent MAO_B inhibitors, safinamide, may add further symptomatic and non-symptomatic benefits by combining dopaminergic stimulation with inhibiting the consequences of an excessive glutamatergic drive. Future clinical studies must be designed considering several biases that may hamper the evaluation of the results.

Author contributions: *Review design: MA, EB, LDC, DR; data collection: MA, SG; manuscript draft: MA, EB, LDC; manuscript revision: FEP, DR. All authors approved the final version of the manuscript.*
Conflicts of interest: *None declared.*
Data availability statement: *Not applicable.*

References

Abbruzzese G, Kulisevsky J, Bergmans B, Gomez-Esteban JC, Kägi G, Raw J, Stefani A, Warnecke T, Jost WH, SYNAPSES Study Investigators Group (2021) A European observational study to evaluate the safety and the effectiveness of safinamide in routine clinical practice: The SYNAPSES trial. J Parkinsons Dis 11:187-198.
Ahmari M, Sharafi A, Mahmoudi J, Jafari-Anarkoli I, Gharbavi M, Hosseini MJ (2020) Selegiline (L-deprenyl) mitigated oxidative stress, cognitive abnormalities, and histopathological change in rats: alternative therapy in transient global ischemia. J Mol Neurosci 70:1639-1648.
Alborghetti M, Nicoletti F (2019) Different generations of type-B monoamine oxidase inhibitors in Parkinson's disease: from bench to bedside. Curr Neuropharmacol 17:861-873.
Armstrong MJ, Okun MS (2020) Diagnosis and treatment of Parkinson disease: a review. JAMA 323:548-560.
Bainbridge JL, Page RL 2nd, Ruscin JM (2008) Elucidating the mechanism of action and potential interactions of MAO-B inhibitors. Neurol Clin 26:S85-96, vi.
Barker RA, Björklund A, Gash DM, Whone A, Van Laar A, Kordower JH, Bankiewicz K, Kieburtz K, Saarma M, Booms S, Huttunen HJ, Kells AP, Fiandaca MS, Stoessl AJ, Eidelberg D, Federoff H, Voutilainen MH, Dexter DT, Eberling J, Brundin P, et al. (2020) GDNF and Parkinson's disease: where next? A summary from a recent workshop. J Parkinsons Dis 10:875-891.
Behl T, Kaur D, Sehgal A, Singh S, Sharma N, Zengin G, Andronie-Cioara FL, Toma MM, Bungau S, Bumbu AG (2021) Role of monoamine oxidase activity in Alzheimer's disease: an insight into the therapeutic potential of inhibitors. Molecules 26:3724.
Bianchi MLE, Riboldazzi G, Mauri M, Versino M (2019) Efficacy of safinamide on non-motor symptoms in a cohort of patients affected by idiopathic Parkinson's disease. Neurol Sci 40:275-279.
Blair HA, Dhillon S (2017) Safinamide: a review in Parkinson's disease. CNS Drugs 31:169-176.
Borgohain R, Szasz J, Stanzione P, Meshram C, Bhatt M, Chirilineau D, Stocchi F, Lucini V, Giuliani R, Forrest E, Rice P, Anand R, Study 016 Investigators (2014a) Randomized trial of safinamide add-on to levodopa in Parkinson's disease with motor fluctuations. Mov Disord 29:229-237.
Borgohain R, Szasz J, Stanzione P, Meshram C, Bhatt MH, Chirilineau D, Stocchi F, Lucini V, Giuliani R, Forrest E, Rice P, Anand R, Study 018 Investigators (2014b) Two-year, randomized, controlled study of safinamide as add-on to levodopa in mid to late Parkinson's disease. Mov Disord 29:1273-1280.
Campo F, Carletti R, Fusconi M, Pellicano C, Pontieri FE, Di Gioia CR, de Vincentiis M (2019) Alpha-synuclein in salivary gland as biomarker for Parkinson's disease. Rev Neurosci 30:455-462.
Cannon SC (2015) Channelopathies of skeletal muscle excitability. Compr Physiol 5:761-790.
Carradori S, Secci D, Petzer JP (2018) MAO inhibitors and their wider applications: a patent review. Expert Opin Ther Pat 28:211-226.
Cattaneo C, Sardina M, Bonizzoni E (2016) Safinamide as add-on therapy to levodopa in mid- to late-stage Parkinson's disease fluctuating patients: post hoc analyses of studies 016 and SETTLE. J Parkinsons Dis 6:165-173.
Cereda E, Cilia R, Canesi M, Tesei S, Mariani CB, Zecchinelli AL, Pezzoli G (2017) Efficacy of rasagiline and selegiline in Parkinson's disease: a head-to-head 3-year retrospective case-control study. J Neurol 264:1254-1263.
Chahine LM, Stern MB (2011) Rasagiline in Parkinson's disease. Int Rev Neurobiol 100:151-168.
Cummings JL, Henchcliffe C, Schaier S, Simuni T, Waxman A, Kemp P (2011) The role of dopaminergic imaging in patients with symptoms of dopaminergic system neurodegeneration. Brain 134:3146-3166.
Dashtipour K, Chen JJ, Kani C, Bahjri K, Ghamsary M (2015) Clinical outcomes in patients with Parkinson's disease treated with a monoamine oxidase type-B inhibitor: a cross-sectional, cohort study. Pharmacotherapy 35:681-686.
De Micco R, Satolli S, Siciliano M, De Mase A, Giordano A, Tedeschi G, Tessitore A (2022) Effects of safinamide on non-motor, cognitive, and behavioral symptoms in fluctuating Parkinson's disease patients: a prospective longitudinal study. Neurol Sci 43:357-364.
Desaphy JF, Farinato A, Altamura C, De Bellis M, Imbrici P, Tarantino N, Caccia C, Melloni E, Padoani G, Vailati S, Keywood C, Carratù MR, De Luca A, Conte D, Pierno S (2020) Safinamide's potential in treating nondystrophic myotonias: Inhibition of skeletal muscle voltage-gated sodium channels and skeletal muscle hyperexcitability in vitro and in vivo. Exp Neurol 328:113287.
Delenclos M, Jones DR, McLean PJ, Uitti RJ (2016) Biomarkers in Parkinson's disease: Advances and strategies. Parkinsonism Relat Disord 22 Suppl 1:S106-110.
Dong X, Wang Y, Qin Z (2009) Molecular mechanisms of excitotoxicity and their relevance to pathogenesis of neurodegenerative diseases. Acta Pharmacol Sin 30:379-387.
Fairclough RJ, Wood MJ, Davies KE (2013) Therapy for Duchenne muscular dystrophy: renewed optimism from genetic approaches. Nat Rev Genet 14:373-378.
Fox SH, Katzenschlager R, Lim SY, Barton B, de Bie RMA, Seppi K, Coelho M, Sampaio C, Movement Disorder Society Evidence-Based Medicine Committee (2018) International Parkinson and movement disorder society evidence-based medicine review: Update on treatments for the motor symptoms of Parkinson's disease. Mov Disord 33:1248-1266.
Gasparini F, Di Paolo T, Gomez-Mancilla B (2013) Metabotropic glutamate receptors for Parkinson's disease therapy. Parkinsons Dis 2013:196028.
Gómez-López A, Sánchez-Sánchez A, Natera-Villalba E, Ros-Castelló V, Beltrán-Corbellini Á, Fanjul-Arbós S, Pareés Moreno I, López-Sendon Moreno JL, Martínez Castrillo JC, Alonso-Canovas A (2021) SURINPARK: Safinamide for urinary symptoms in Parkinson's disease. Brain Sci 11:57.
Gray R, Patel S, Ives N, Rick C, Woolley R, Muzerengi S, Gray A, Jenkinson C, McIntosh E, Wheatley K, Williams A, Clarke CE, PD MED Collaborative Group (2022) Long-term effectiveness of adjuvant treatment with catechol-O-methyltransferase or monoamine oxidase B inhibitors compared with dopamine agonists among patients with Parkinson disease uncontrolled by levodopa therapy: the PD MED randomized clinical trial. JAMA Neurol 79:131-140.
Grigoriou S, Martínez-Martín P, Ray Chaudhuri K, Rukavina K, Leta V, Hausbrand D, Falkenburger B, Odin P, Reichmann H (2021) Effects of safinamide on pain in patients with fluctuating Parkinson's disease. Brain Behav 11:e2336.
Guzik A, Bushnell C (2017) Stroke epidemiology and risk factor management. Continuum (Minneap Minn) 23(1, Cerebrovascular Disease):15-39.
Haines JD, Inglese M, Casaccia P (2011) Axonal damage in multiple sclerosis. Mt Sinai J Med 78:231-243.
Hauser RA, Lew MF, Hurtig HI, Ondo WG, Wojcieszek J, Fitzer-Attas CJ, TEMPO Open-label Study Group (2009) Long-term outcome of early versus delayed rasagiline treatment in early Parkinson's disease. Mov Disord 24:564-573.
Hauser RA, Abler V, Eyal E, Eliaz RE (2016) Efficacy of rasagiline in early Parkinson's disease: a meta-analysis of data from the TEMPO and ADAGIO studies. Int J Neurosci 126:942-946.
Hermann DM, Chopp M (2012) Promoting brain remodelling and plasticity for stroke recovery: therapeutic promise and potential pitfalls of clinical translation. Lancet Neurol 11:369-380.
Hermann DM, Popa-Wagner A, Kleinschnitz C, Doeppner TR (2019) Animal models of ischemic stroke and their impact on drug discovery. Expert Opin Drug Discov 14:315-326.
Imbrici P, Altamura C, Camerino GM, Mangiatordi GF, Conte E, Maggi L, Brugnoni R, Musaraj K, Caloiero R, Alberga D, Marsano RM, Ricci G, Siciliano G, Nicolotti O, Mora M, Bernasconi P, Desaphy JF, Mantegazza R, Camerino DC (2016) Multidisciplinary study of a new ClC-1 mutation causing myotonia congenita: a paradigm to understand and treat ion channelopathies. FASEB J 30:3285-3295.
Inaba-Hasegawa K, Shamoto-Nagai M, Maruyama W, Naoi M (2017) Type B and A monoamine oxidase and their inhibitors regulate the gene expression of Bcl-2 and neurotrophic factors in human glioblastoma U118MG cells: different signal pathways for neuroprotection by selegiline and rasagiline. J Neural Transm (Vienna) 124:1055-1066.
Ishikawa T, Okano M, Minami A, Tsunekawa H, Satoyoshi H, Tsukamoto Y, Takahata K, Muraoka S (2019) Selegiline ameliorates depression-like behaviors in rodents and modulates hippocampal dopaminergic transmission and synaptic plasticity. Behav Brain Res 359:353-361.
Jo S, Yarishkin O, Hwang YJ, Chun YE, Park M, Woo DH, Bae JY, Kim T, Lee J, Chun H, Park HJ, Lee DY, Hong J, Kim HY, Oh SJ, Park SJ, Lee H, Yoon BE, Kim Y, Jeong Y, et al. (2014) GABA from reactive astrocytes impairs memory in mouse models of Alzheimer's disease. Nat Med 20:886-896.
Kennedy B, Ziegler M, Alford M, Hansen L, Thal L, Masliah E (2003) Early and persistent alterations in prefrontal cortex MAO A and B in Alzheimer's disease. J. Neural Transm 110:789-801.

Knoll J (1989) The pharmacology of selegiline ((-)deprenyl). New aspects. Acta Neurol Scand Suppl 126:83-91.
Kroemer G, Galluzzi L, Brenner C (2007) Mitochondrial membrane permeabilization in cell death. Physiol Rev 87:99-163.
LeWitt PA (2015) Levodopa therapy for Parkinson's disease: Pharmacokinetics and pharmacodynamics. Mov Disord 30:64-72.
Magyar K (2011) The pharmacology of selegiline. Int Rev Neurobiol 100:65–84.
Maia FD, Pitombeira BS, Aráujo DT, Cunha GM, Viana GS (2004) l-Deprenyl prevents lipid peroxidation and memory deficits produced by cerebral ischemia in rats. Cell Mol Neurobiol 24:87-100.
Menazza S, Blaauw B, Tiepolo T, Toniolo L, Braghetta P, Spolaore B, Reggiani C, Di Lisa F, Bonaldo P, Canton M (2010) Oxidative stress by monoamine oxidases is causally involved in myofiber damage in muscular dystrophy. Hum Mol Genet 19:4207-4215.
Meredith GE, Rademacher DJ (2011) MPTP mouse models of Parkinson's disease: an update. J Parkinsons Dis 1:19-33.
Morari M, Brugnoli A, Pisanò CA, Novello S, Caccia C, Melloni E, Padoani G, Vailati S, Sardina M (2018) Safinamide differentially modulates In Vivo glutamate and GABA release in the rat hippocampus and basal ganglia. J Pharmacol Exp Ther 364:198-206.
Morsali D, Bechtold D, Lee W, Chauhdry S, Palchaudhuri U, Hassoon P, Snell DM, Malpass K, Piers T, Pocock J, Roach A, Smith KJ (2013) Safinamide and flecainide protect axons and reduce microglial activation in models of multiple sclerosis. Brain 136:1067-1082.
Muck-Seler D, Presecki P, Mimica N, Mustapic M, Pivac N, Babic A, Nedic G, Folnegovic-Smalc V (2009) Platelet serotonin concentration and monoamine oxidase type B activity in female patients in early, middle and late phase of Alzheimer's disease. Prog Neuropsychopharmacol Biol Psychiatry 33:1226-1231.
Naoi M, Maruyama W, Shamoto-Nagai M (2020) Rasagiline and selegiline modulate mitochondrial homeostasis, intervene apoptosis system and mitigate α-synuclein cytotoxicity in disease-modifying therapy for Parkinson's disease. J Neural Transm (Vienna) 127:131-147.
Naoi M, Maruyama W, Shamoto-Nagai M (2022) Neuroprotective function of rasagiline and selegiline, inhibitors of type B monoamine oxidase, and role of monoamine oxidases in synucleinopathies. Int J Mol Sci 23:11059.
Nayak L, Henchcliffe C (2008) Rasagiline in treatment of Parkinson's disease. Neuropsychiatr Dis Treat 4:23-32.
Nutt JG (2001) Motor fluctuations and dyskinesia in Parkinson's disease. Parkinsonism Relat Disord 8:101-108.
Obi K, Amano I, Takatsuru Y (2018) Role of dopamine on functional recovery in the contralateral hemisphere after focal stroke in the somatosensory cortex. Brain Res 1678:146-152.
Olanow CW, Rascol O, Hauser R, Feigin PD, Jankovic J, Lang A, Langston W, Melamed E, Poewe W, Stocchi F, Tolosa E; ADAGIO Study Investigators (2009) A double-blind, delayed-start trial of rasagiline in Parkinson's disease. N Engl J Med 361:1268-1278.
Ono K, Hasegawa K, Naiki H, Yamada M (2006) Anti-Parkinsonian agents have anti-amyloidogenic activity for Alzheimer's beta-amyloid fibrils in vitro. Neurochem Int 48:275-285
Ossowska K, Konieczny J, Wolfarth S, Pilc A (2005) MTEP, a new selective antagonist of the metabotropic glutamate receptor subtype 5 (mGluR5), produces antiparkinsonian-like effects in rats. Neuropharmacology 49:447-455.
Parkinson Study Group (2002) A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study. Arch Neurol 59:1937-1943.
Parkinson Study Group (2004) A controlled, randomized, delayed-start study of rasagiline in early Parkinson disease. Arch Neurol 61:561-566.
Rajmohan R, Reddy PH (2017) Amyloid-beta and phosphorylated tau accumulations cause abnormalities at synapses of Alzheimer's disease neurons. J Alzheimers Dis 57:975-999.
Rascol O, Brooks DJ, Melamed E, Oertel W, Poewe W, Stocchi F, Tolosa E, LARGO study group (2005) Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily, study): a randomised, double-blind, parallel-group trial. Lancet 365:947-954.
Rascol O, Fox S, Gasparini F, Kenney C, Di Paolo T, Gomez-Mancilla B (2014) Use of metabotropic glutamate 5-receptor antagonists for treatment of levodopa-induced dyskinesias. Parkinsonism Relat Disord 20:947-956.
Rascol O, Fabbri M, Poewe W (2021) Amantadine in the treatment of Parkinson's disease and other movement disorders. Lancet Neurol 20:1048-1056.
Riederer P, Müller T (2017) Use of monoamine oxidase inhibitors in chronic neurodegeneration. Expert Opin Drug Metab Toxicol 13:233-240.
Rinaldi D, Assogna F, Sforza M, Tagliente S, Pontieri FE (2018) Rasagiline for dysexecutive symptoms during wearing-off in Parkinson's disease: a pilot study. Neurol Sci 39:141-143.
Rinaldi D, Bianchini E, Sforza M, Alborghetti M, Galli S, Salvetti M, Giovannelli M, Pontieri FE (2021a) The tolerability, safety and efficacy of safinamide in elderly Parkinson's disease patients: a retrospective study. Aging Clin Exp Res 33:1689-1692.
Rinaldi D, Sforza M, Assogna F, Savini C, Salvetti M, Caltagirone C, Spalletta G, Pontieri FE (2021b) Safinamide improves executive functions in fluctuating Parkinson's disease patients: an exploratory study. J Neural Transm (Vienna) 128:273-277.
Rinaldi D, Alborghetti M, Bianchini E, Sforza M, Galli S, Pontieri FE (2022) Monoamine-oxidase type B- Inhibitors and cognitive functions in Parkinson's disease: beyond the primary mechanism of action. Curr Neuropharmacol doi: 10.2174/1570159X20666220905102144.
Sadeghian M, Mullali G, Pocock JM, Piers T, Roach A, Smith KJ (2016) Neuroprotection by safinamide in the 6-hydroxydopamine model of Parkinson's disease. Neuropathol Appl Neurobiol 42:423-435.
Salvalaggio A, De Filippo De Grazia M, Zorzi M, Thiebaut de Schotten M, Corbetta M (2020) Post-stroke deficit prediction from lesion and indirect structural and functional disconnection. Brain 143:2173-2188.
Samadi P, Grégoire L, Morissette M, Calon F, Hadj Tahar A, Dridi M, Belanger N, Meltzer LT, Bédard PJ, Di Paolo T (2008) mGluR5 metabotropic glutamate receptors and dyskinesias in MPTP monkeys. Neurobiol Aging 29:1040-1051.
Santos García D, Cabo López I, Labandeira Guerra C, Yáñez Baña R, Cimas Hernando MI, Paz González JM, Alonso Losada MG, Gonzalez Palmás MJ, Cores Bartolomé C, Martínez Miró C (2022) Safinamide improves sleep and daytime sleepiness in Parkinson's disease: results from the SAFINONMOTOR study. Neurol Sci 43:2537-2544.
Schapira AH, Fox SH, Hauser RA, Jankovic J, Jost WH, Kenney C, Kulisevsky J, Pahwa R, Poewe W, Anand R (2017) Assessment of Safety and Efficacy of Safinamide as a Levodopa Adjunct in Patients With Parkinson Disease and Motor Fluctuations: A Randomized Clinical Trial. JAMA Neurol 74:216-224.
Sciaccaluga M, Mazzocchetti P, Bastioli G, Ghiglieri V, Cardinale A, Mosci P, Caccia C, Keywood C, Melloni E, Padoani G, Vailati S, Picconi B, Calabresi P, Tozzi A (2020) Effects of safinamide on the glutamatergic striatal network in experimental Parkinson's disease. Neuropharmacology 170:108024.
Shoulson I (1989) Deprenyl and tocopherol antioxidative therapy of parkinsonism (DATATOP). Parkinson Study Group. Acta Neurol Scand Suppl 126:171-175.
Silasi G, Murphy TH (2014) Stroke and the connectome: how connectivity guides therapeutic intervention. Neuron 83:1354-1368.
Sorato E, Menazza S, Zulian A, Sabatelli P, Gualandi F, Merlini L, Bonaldo P, Canton M, Bernardi P, Di Lisa F (2014) Monoamine oxidase inhibition prevents mitochondrial dysfunction and apoptosis in myoblasts from patients with collagen VI myopathies. Free Radic Biol Med 75:40-47.
Stocchi F; ADAGIO investigators (2014) Benefits of treatment with rasagiline for fatigue symptoms in patients with early Parkinson's disease. Eur J Neurol 21:357-360.
Stocchi F, Olanow CW (2003) Neuroprotection in Parkinson's disease: clinical trials. Ann Neurol 53 Suppl 3:S87-99.
Szökő É, Tábi T, Riederer P, Vécsei L, Magyar K (2018) Pharmacological aspects of the neuroprotective effects of irreversible MAO-B inhibitors, selegiline and rasagiline, in Parkinson's disease. J Neural Transm (Vienna) 125:1735-1749.
Tábi T, Vécsei L, Youdim MB, Riederer P, Szökő É (2020) Selegiline: a molecule with innovative potential. J Neural Transm (Vienna) 127:831-842.
Talhada D, Marklund N, Wieloch T, Kuric E, Ruscher K (2021) Plasticity-enhancing effects of levodopa treatment after stroke. Int J Mol Sci 22:10226.
Tan YY, Jenner P, Chen SD (2022) Monoamine oxidase-B inhibitors for the treatment of Parkinson's disease: past, present, and future. J Parkinsons Dis 12:477-493.
Thomas SJ, Shin M, McInnis MG, Bostwick JR (2015) Combination therapy with monoamine oxidase inhibitors and other antidepressants or stimulants: strategies for the management of treatment-resistant depression. Pharmacotherapy 35:433-449.
Tripathi AC, Upadhyay S, Paliwal S, Saraf SK (2018) Privileged scaffolds as MAO inhibitors: Retrospect and prospects. Eur J Med Chem 145:445-497.
Venderova K, Park DS (2012) Programmed cell death in Parkinson's disease. Cold Spring Harb Perspect Med. Aug 1;2(8):a009365.
Vitiello L, Marabita M, Sorato E, Nogara L, Forestan G, Mouly V, Salviati L, Acosta M, Blaauw B, Canton M (2018) Drug repurposing for duchenne muscular dystrophy: the monoamine oxidase B Inhibitor safinamide ameliorates the pathological phenotype in mdx mice and in myogenic cultures from DMD patients. Front Physiol 9:1087.
Vivacqua G, Mancinelli R, Belvisi D, Suppa A, Berardelli A (2018) Detection of α-synuclein in saliva: the importance of preanalytical assessment. Mov Disord. Jul;33(6):1029-1030.
Vizuete ML, Steffen V, Ayala A, Cano J, Machado A (1993) Protective effect of deprenyl against 1-methyl-4-phenylpyridinium neurotoxicity in rat striatum. Neurosci Lett 152:113-116.
Wang Y, Shi M, Chung KA, Zabetian CP, Leverenz JB, Berg D, Srulijes K, Trojanowski JQ, Lee VM, Siderowf AD, Hurtig H, Litvan I, Schiess MC, Peskind ER, Masuda M, Hasegawa M, Lin X, Pan C, Galasko D, Goldstein DS, Jensen PH, Yang H, Cain KC, Zhang J (2012) Phosphorylated α-synuclein in Parkinson's disease. Sci Transl Med. 4(121):121ra20.
Wang J, Wang F, Mai D, Qu S (2020) Molecular mechanisms of glutamate toxicity in Parkinson's disease. Front Neurosci 14:585584.
Wesnes KA, Aarsland D, Ballard C, Londos E (2015) Memantine improves attention and episodic memory in Parkinson's disease dementia and dementia with Lewy bodies. Int J Geriatr Psychiatry 30:46-54.
Wozniak KM, Rojas C, Wu Y, Slusher BS (2012) The role of glutamate signaling in pain processes and its regulation by GCP II inhibition. Curr Med Chem 19:1323-1334.
Wu RM, Chen RC, Chiueh CC (2000) Effect of MAO-B inhibitors on MPP+ toxicity in vivo. Ann N Y Acad Sci 899:255-261.
Xu T, Sun R, Wei G, Kong S (2020) The protective effect of safinamide in ischemic stroke mice and a brain endothelial cell line. Neurotox Res 38:733-740.
Zhao Q, Cai D, Bai Y (2013) Selegiline rescues gait deficits and the loss of dopaminergic neurons in a subacute MPTP mouse model of Parkinson's disease. Int J Mol Med 32:883-891.

C-Editors: Zhao M, Liu WJ, Li CH; T-Editor: Jia Y