Rasagiline for the management of Parkinson's disease

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Parkinson's disease is a neurodegenerative disorder manifested by a combination of motor and non-motor symptoms. Levodopa, a dopamine precursor, is the most efficacious drug available to control the symptoms of Parkinson's disease. Almost all other medications with symptomatic benefit for Parkinson's disease show their effect by facilitating the dopaminergic system, including dopamine agonists, catechol-*O*-methyltransferase inhibitors and monoamine oxidase-B inhibitors. Selegiline (Eldepryl®), selegiline orally disintegrating tablet (Zelapar®) and rasagiline (Azilect®) are monoamine oxidase-B inhibitors currently available in the USA. The novel monoamine oxidase-B inhibitor, rasagiline, is different from the first-generation monoamine oxidase-B inhibitor, selegiline, with a unique chemical structure and metabolite profile. A once-daily dose of rasagiline provides symptomatic therapy in patients with Parkinson's disease, and is safe and well tolerated in elderly patients as monotherapy or adjunct therapy. Rasagiline is distinguished from other agents currently used in Parkinson's disease by its potential neuroprotective effect. This effect has been demonstrated in various *in vitro* and *in vivo* studies. In addition, results of a controlled, randomized, delayed-start study of rasagiline in early Parkinson's disease showed slower progression of the disease with rasagiline compared with placebo, suggesting a neuroprotective effect of this agent. A second large, randomized, double-blind, placebo-controlled, delayed-start study is currently underway to verify previous results and confirm the potential disease-modifying activity of rasagiline.

Parkinson's disease (PD) is a neurodegenerative disorder manifested by a combination of motor and non-motor symptoms. It involves multiple neurotransmitter systems, including dopaminergic, cholinergic, noradrenergic, serotoninergic, GABAergic and glutamatergic systems, which demonstrates the complexity of this disease. The clinical criteria of PD include a triad of resting tremor, rigidity and bradykinesia. Postural instability usually occurs later in the course of the disease. There is no laboratory or radiological tool that specifically confirms a diagnosis of PD. The diagnosis is made by clinical judgment of an expert neurologist.

PD affects approximately 1 million people in the USA. The number of new cases per year in the USA is approximately 20 per 100,000 [1,2]. With improvements in the diagnosis of PD and increased life expectancy, the incidence and prevalence of the disease is expected to grow [3].

Despite the overall indolent course of PD, it may advance more rapidly during the preclinical stage and early years [4], which is why physicians are moving towards earlier treatment of the disease. There are several risk factors associated with a more rapid disease course, including older age of onset, associated comorbidities, presentation with rigidity and bradykinesia and decreased dopamine responsiveness [4–8]. There is no medication currently available to definitively stop or slow the progression of the disease. Symptomatic treatment is the only therapeutic approach to control clinical features of PD, while the underlying disease process may remain active.

Symptomatic therapy for PD dates back to the nineteenth century when anticholinergics became a target for pharmacotherapy [9]. Centrally acting anticholinergic drugs such as trihexyphenidyl and benztropine are useful for treating resting tremor, but are of less value in treating akinesia [3]. Anticholinergic drugs are typically reserved for younger patients, in whom tremor is the dominant clinical feature. Elderly or cognitively impaired PD patients are particularly sensitive to anticholinergics, as these drugs can impair executive function. As it became evident that the pathogenesis of the disease is correlated to dopamine deficiency secondary to neurodegeneration in the substantia nigra pars compacta [10], the main therapeutic strategy has been to replete this neurotransmitter. This therapeutic goal can be achieved by prescribing a precursor of dopamine, levodopa (L-dopa). This remains the gold standard and most effective symptomatic

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therapy for this disorder. L-dopa is converted to dopamine via the enzyme dopa decarboxylase and is eventually metabolized by monoamine oxidase (MAO) to dihydroxyphenylacetic acid and by catechol-*O*-methyltransferase (COMT) to 3-methoxytyramine. Both dihydroxyphenylacetic acid and 3-methoxytyramine can be further metabolized to homovanillic acid [11]. L-dopa is co-administered with an aromatic amino acid decarboxylase inhibitor, such as carbidopa or benserazide, to prevent peripheral conversion of L-dopa to dopamine. Adding an aromatic amino acid decarboxylase inhibitor minimizes the peripheral side effects of dopamine, including nausea and orthostasis, and leaves more L-dopa available for transporting to the brain [2,3,12]. A controlled-release formulation of L-dopa/carbidopa is also available in the USA. Chronic L-dopa administration is associated with significant motor complications, including dyskinesia (e.g., involuntary choreoathetoid movements) and motor fluctuations (e.g., wearing off, 'on–off' phenomena) that can limit its utility [3].

In the early 1970s, ergot-derived dopamine agonists (DAs) were first used to treat PD. DAs work by directly stimulating the postsynaptic dopamine receptors. While not as clinically effective as L-dopa, they improve symptoms of PD significantly, but cause fewer motor complications than L-dopa [3]. Dopamine agonists available now in the USA are apomorphine, bromocriptine, pramipexole, ropinirole and rotigotine. Non-ergot-derived DAs (pramipexole, ropinirole, rotigotine and apomorphine) act predominantly on D2 and D3 receptors and cause fewer side effects. The older ergot-derived DAs (e.g., bromocriptine) bind to D1 and D2 receptors and are partial agonists. Apomorphine is the only injectable formulation of medication readily available for patients with PD.

Another group of medications developed in 1990s are the COMT inhibitors. These medications inhibit the peripheral and/or central metabolism of L-dopa and extend the plasma half-life of L-dopa without increasing peak plasma concentration (C_{max}) or time to maximal concentration (T_{max}). Similar to aromatic amino acid decarboxylase inhibitors, these drugs do not have antiparkinsonian symptomatic effects when given alone, and are administered adjunctively with L-dopa. Co-administration of these agents with L-dopa and carbidopa increases the half-life of L-dopa from 1.3 to 2.4 h [13]. Tolcapone and entacapone are two COMT inhibitors currently available in the USA.

Amantadine has been used for the symptomatic therapy of PD for more than 25 years. It is an antiviral agent and an antagonist of NMDA receptors, but shows its symptomatic effect in PD most likely by increasing dopamine release and inhibiting its cellular reuptake [3].

Another group of medications currently available for symptomatic therapy in PD are MAO-B inhibitors. MAO, which catabolizes dopamine, became a target for pharmacotherapy during the mid-twentieth century. MAO-B inhibitors selectively inhibit the enzyme MAO-B and increase striatal dopamine levels [12,14]. Owing to their selectivity for MAO-B, they cause fewer drug interactions and are associated with a lower risk of serotonin syndrome and hypertensive crisis than the nonselective MAO inhibitors. In controlled clinical trials of early PD, MAO-B inhibitors have been shown to delay the development of disability that requires the addition of L-dopa and have demonstrated the potential to slow the decline of dopaminergic neuronal function [15]. In advanced stages of PD, MAO-B inhibitors prolong the symptomatic effect of L-dopa and allow reduction in L-dopa dose [16]. Selegiline was the first selective, irreversible MAO-B inhibitor, developed in 1962 and marketed in 1981 [17]. In addition to symptomatic benefit in PD, some evidence in animal models suggests possible neuroprotective effects with selegiline. Selegiline is metabolized to desmethylselegiline, levo-methamphetamine and levo-amphetamine; the latter two metabolites may explain some of its side effects, such as insomnia, euphoria, hallucinations and orthostatic hypotension [12,14]. There is also concern regarding amphetamine and methamphetamine metabolites and their potential long-term detrimental effect on neurons. Desmethylselegiline is most likely associated with the neuroprotective effects of selegiline seen in multiple *in vitro* and *in vivo* models [17].

A second-generation MAO-B inhibitor, rasagiline, was developed in 1987 and was approved by the European Medicines Agency (EMEA) and the Israeli Ministry of Health in 2005, and by the US FDA and Health Canada in 2006. The approved indications in these world markets are as monotherapy in early PD and as adjunctive therapy to L-dopa in patients with moderate to advanced PD. Several multinational Phase III double-blind, randomized, placebo-controlled, parallel-group studies showed safety, tolerability and efficacy of rasagiline in PD patients. Rasagiline is different from selegiline with regard to its unique chemical structure. Moreover, it is not a metabolized amphetamine derivative and, there-

fore, is not associated with the cardiovascular and nervous system side effects seen with selegiline. Rasagiline shows five-times more potent MAO-B inhibition than selegiline in animal models and cell cultures [18]. Whereas the selegiline metabolite, L-methamphetamine, has been shown to abolish the neuroprotective effect of the parent compound *in vitro* [19,20], both rasagiline and its main metabolite, aminoindan, have shown neuroprotective effects in various *in vivo* and *in vitro* models [19,21,22]. Rasagiline is dosed once daily and is safe and well tolerated in young and elderly patients [23,24]. It has a side-effect profile similar to placebo in early PD.

Chemistry

Rasagiline mesylate was developed in 1987 by Teva Pharmaceutical Industries Ltd (Petah Tikua, Israel) as a second-generation MAO-B inhibitor with an improved metabolite profile compared with selegiline (**Figure 1**). The chemical name of rasagiline is *N*-propargyl-1(*R*)-aminoindan. It is the *R*-isomer of the chiral parent compound AGN 1135, a nonamphetamine, secondary cyclic benzylamine propargylamine pharmacophore [25]. The relative molecular mass/weight is 267.34. Rasagiline is freely soluble in water or ethanol. Its melting range is 155–159°C, with specific optical rotation of 18.5–23°. Rasagiline contains a propargylamine structure, which may be responsible for its potential neuroprotective and antiapoptotic effects independent of MAO inhibition [22]. Its neuroprotective effect has been shown in numerous *in vitro* and *in vivo* studies [19,21,22].

The propargyl chain is an essential part of the molecule and binds covalently to form an irreversible bond with the flavin adenine dinucleotide moiety of the MAO enzyme. Structure–activity studies showed that maintaining a distance of no more than two carbon units between the aromatic ring and the *N*-propargyl terminal of the rasagiline pharmacophore is essential for conferring specificity for MAO-B [25]. The assay of rasagiline mesylate is determined by high-performance liquid chromatography for release and stability testing. Each tablet of rasagiline mesylate contains manitol USP/Ph.Eur., starch NF/Ph.Eur., pregelatinized starch NF/Ph.Eur., colloidal silicon dioxide NF/Ph.Eur., stearic acid NF/Ph.Eur. and talc USP/Ph.Eur.

Pharmacokinetics & pharmacodynamics

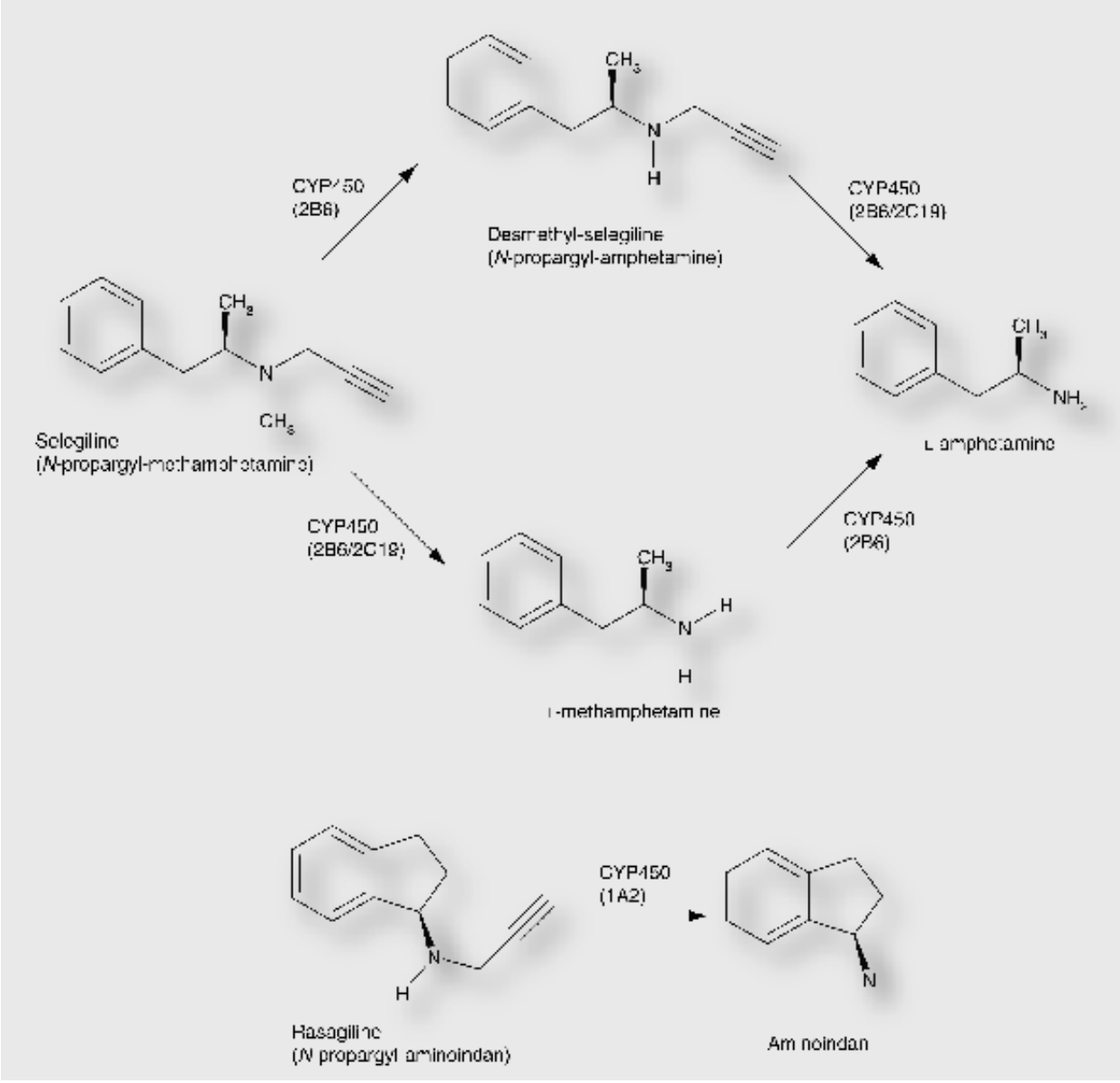
Preclinical pharmacology & toxicology

The high potency and selectivity of rasagiline in brain and peripheral tissues was shown in various *in vitro* and *in vivo* studies. The results of the *in vitro* studies are reproducible with *in vivo* models, indicating that rasagiline crosses the blood–brain barrier after oral or parenteral use. In a series of experiments, rasagiline selectivity for MAO-B inhibition (following repeated administration) is reflected in the high ED50 ratios (MAO-A):(MAO-B) ranging from 30 to 93 [26–28]. The main metabolite of rasagiline, 1-*R*-aminoindan (TVP-136), did not inhibit brain MAO-B *in vitro* and *ex vivo* [27]. Repeated administration of rasagiline causes more MAO inhibition than acute treatment, due to the cumulative effect of irreversible inhibition. Rasagiline was significantly more potent than selegiline *in vivo* in animal models. In the rat, a daily dose of rasagiline mesylate (0.05 mg/kg/day), which is a tenth of that of an equipotent dose of selegiline, was needed to inhibit over 90% of brain MAO-B activity with minor MAO-A inhibition [28]. *In vitro* and *in vivo* animal experiments demonstrated that the corresponding salts of the (*S*)-enantiomer of rasagiline exhibited very weak MAO inhibitory activity. In contrast to rasagiline, they had little or no selectivity for MAO-B compared with MAO-A [18,26,27,29].

As noted, *in vitro* and *in vivo* studies indicate that the primary pharmacodynamic action of rasagiline is selective inhibition of MAO-B. In the 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP) animal models of PD, rasagiline blocks MPTP-induced neurotoxicity [30,31]. Microdialysis in rats treated with rasagiline showed elevation in extracellular striatal dopamine levels [32]. The mechanism of chronic administration of rasagiline and its cumulative effect seems more complex than the mechanism observed after one dose of rasagiline and may involve its neuroprotective activity.

Studies on several types of neuronal cultures showed neuroprotective and neurotrophic effects of rasagiline [21,33]. The neuroprotective effect of rasagiline appears to be independent of its MAO inhibitory action, since some neuroprotective effects of rasagiline have been seen at low doses in cell lines and primary neurones that express only the MAO-A isoenzyme [20,34–38]. Moreover, the (*S*)-enantiomer of rasagiline, which lacks MAO-inhibitory activity, has also shown protective effects *in vitro* and *in vivo* [35,39–41]. It has been proposed that rasagiline protects neurons also by antiapoptotic effects [37]. This antiapoptotic effect of rasagiline is implemented by two different mechanisms; one is via interactions with the mitochondrial apoptotic cascade, and can also regulate the expression of anti-apoptotic and antioxidative proteins [37,42].

Figure 1. Chemistry of rasagiline and selegiline.



MAO-B is localized in the mitochondrial membranes of different structures, such as cerebral neurons, intestine and liver. Rasagiline specifically inhibits MAO type B, which is the main form of MAO in the brain, and reduces metabolic degradation of dopamine [25]. It is metabolized to its main metabolite, 1-[*R*]-aminoindan, but unlike selegiline does not yield amphetamine or methamphetamine metabolites [25]. Whether these metabolites of selegiline actually have toxic effects in PD patients remains a matter of debate [43,44].

In patients with PD, oral administration of rasagiline 1 mg/day results in near-complete inhibition (>90%) of MAO-B activity after the third daily dose [45]. Since there is a pressor effect with co-administration of MAO-A inhibitors and tyramine, the effect of tyramine interaction with rasagiline was assessed in several clinical studies. No significant potentiation of tyramine pressor response with co-ingestion of large amounts of tyramine was reported [46,47].

Clinical pharmacokinetics

The pharmacokinetics of rasagiline are linear with a dosage of 0.5–10 mg [48]. In a double-blind study in PD patients, the terminal half-life of rasagiline was reported to be approximately 1.34 h [45], but secondary to its irreversible effect

on MAO-B inhibition, there is no correlation between its clinical and pharmacological effect, and the symptomatic benefit of rasagiline may last beyond several half-lives. By studying positron emission tomography (PET) in patients with PD treated with MAO-B inhibitors, the recovery half-life of brain MAO-B was measured to be approximately 40 days [49].

Rasagiline is rapidly absorbed by the gastrointestinal tract, reaches C_{max} within 1 h and readily crosses the blood–brain barrier [45,50,51]. The pharmacokinetics of rasagiline were studied in a randomized, double-blind, placebo-controlled, three-way, single-dose study and a randomized, double-blind, placebo-controlled, repeated dose study by Thebault *et al.* [48]. At doses of 0.5 and 10 mg, rasagiline exhibits consistent dose linearity and proportionality for C_{max} and area under the concentration–time curve (AUC) values [48]. The T_{max} of rasagiline is not affected by food, although a high-fat meal reduces C_{max} and AUC by approximately 60 and 20%, respectively [25]. Therefore, rasagiline can be administered with or without food. The mean volume of distribution of rasagiline in patients with PD ranges from 182 to 243 l, and plasma protein binding ranges from 60 to 70% [25].

Rasagiline undergoes hepatic biotransformation and is dependent on CYP [25]. CYP1A2 is the major isoenzyme involved in its metabolism. Elimination of rasagiline primarily occurs in urine (62%) after glucuronide conjugation and only less than 1% is excreted unchanged. Rasagiline should not be used in patients with moderate to severe hepatic failure, since plasma concentration of rasagiline is increased significantly. For patients with renal insufficiency, dose adjustments have not been recommended.

Clinical efficacy

Phase II studies

In a 10-week, Phase II, double-blind, randomized, placebo-controlled study, the safety, tolerability and efficacy of rasagiline monotherapy was assessed in 56 patients with early PD not receiving L-dopa [52]. Patients (mean age of 61.5 years; 68% male; 91% Caucasian) were randomly assigned to rasagiline 1 mg (n = 15), 2 mg (n = 14) or 4 mg once-daily (n = 14), or placebo (n = 14). A 3-week dose-escalation period was followed by a 7-week maintenance phase. At week 10, the mean improvement from baseline in total Unified Parkinson's Disease Rating Scale (UPDRS) score were 9.9, 17.1, 17.8 and 2.8% in the rasagiline 1, 2 and 4 mg/day and placebo groups, respectively. Additionally, 28% of patients receiving rasagiline experienced an improvement in total UPDRS score of greater than 30% compared with none of the patients receiving placebo ($p < 0.05$). The frequency and types of adverse events reported by rasagiline-treated and placebo-treated patients were similar.

In a 12-week, Phase II, double-blind, randomized, placebo-controlled study, the safety, tolerability and clinical effect of rasagiline as adjunct therapy to L-dopa was assessed in patients with PD [45]. A total of 70 patients with PD (mean age: 57.4 years; mean disease duration: 5.7 years; 32 patients had motor fluctuations) received either placebo (n = 13) or rasagiline 0.5 mg/day (n = 21), 1 mg/day (n = 18), or 2 mg/day (n = 18). With all doses of rasagiline, a beneficial clinical effect, expressed as a decrease in total UPDRS score, was observed in fluctuating patients (23.0 vs 8.5% in the placebo group). The treatment effect was still evident 6 weeks after drug discontinuation (in all doses). Adverse events were no different than those of patients taking placebo. The study demonstrated that rasagiline has a good safety profile and a beneficial clinical effect in fluctuating patients with PD when given as an add-on to chronic L-dopa therapy.

Phase III studies

Three pivotal Phase III, double-blind, randomized, placebo-controlled studies took place in the USA, Canada and/or Europe, Israel and Argentina to evaluate the safety, tolerability and efficacy of rasagiline in patients with PD. In the Rasagiline (TVP-1012) in Early Monotherapy for Parkinson's Disease Outpatients (TEMPO) study, the safety and efficacy of rasagiline was evaluated in a multicenter, 26-week, parallel-group, randomized, double-blind, placebo-controlled clinical trial [53]. A total of 404 patients with early PD not requiring dopaminergic therapy were enrolled in the USA and Canada. All patients were evaluated at academically based movement disorder clinics. Subjects were randomized to receive rasagiline at a dosage of 1 or 2 mg once-daily, or matching placebo. In all, 328 participants completed 6 months without additional dopaminergic therapy. There were no significant differences in adverse events between the two groups of active treatment versus the placebo group. The symptomatic benefit of rasagiline was demonstrated in this study over a

6-month period by showing significant difference in the total UPDRS between the two treatment groups and placebo. This 26-week controlled study indicated that rasagiline was an effective therapy for patients with early PD. The 52-week delayed-start phase and potential neuroprotective/disease-modifying results of the TEMPO study are discussed below [54]. This is the first study to demonstrate an improvement in quality of life by an antiparkinsonian drug in early PD, as demonstrated by significant differences in Parkinson's Disease Quality of Life Questionnaire (PDQUALIF) scores with rasagiline compared with placebo [55].

The Parkinson's Rasagiline: Efficacy and Safety in the Treatment of OFF (PRESTO) study was a Phase III multicenter trial conducted in the USA and Canada. This was a 26-week randomized, placebo-controlled study to investigate the efficacy, safety and tolerability of rasagiline compared with placebo in L-dopa-treated PD patients with motor fluctuations [56]. A total of 472 patients with idiopathic PD who were optimally treated with L-dopa and experiencing motor fluctuations were enrolled. Patients were randomized to receive once-daily rasagiline 1 or 0.5 mg or matching placebo. The L-dopa dosage could decrease during the first 6 weeks based on the investigator's assessment, but the dosage was held constant for the rest of the study. Eligible patients had to have at least 2.5 h of 'off' time per day after receiving optimized dosing of L-dopa. The main outcome measure of this study was change from baseline in total daily off time measured by patients using home diaries. The PRESTO study showed that rasagiline treatment improved motor fluctuations, including decreased off time and improvement in PD symptoms, in L-dopa-treated patients.

Another Phase III pivotal study, conducted in Europe, Argentina and Israel, also investigated the efficacy and safety of rasagiline in L-dopa-treated PD patients with motor fluctuations [57]. The Lasting effect in Adjunct therapy with Rasagiline Given Once daily (LARGO) was a randomized, double-blind, parallel-group trial, with an active comparator treatment arm, conducted over 18-weeks at 74 hospitals and academic centers. A total of 687 PD patients were randomly assigned to oral rasagiline 1 mg, entacapone (the active comparator) or placebo. The primary measure of this study was the mean change in total daily off time as measured by patient diaries. The result of this study showed that rasagiline is a safe treatment that reduces mean daily off time and improves motor function in PD to a similar extent as entacapone.

In conclusion, the results of all Phase II–III studies demonstrated rasagiline as an effective and safe treatment to relieve PD symptoms in early, moderate and advanced disease.

Clinical safety & tolerability

The safety of rasagiline was confirmed in the three large clinical studies (TEMPO, PRESTO and LARGO) in PD patients. In the TEMPO study, no adverse events were reported to be significantly more frequent in patients originally assigned to rasagiline compared with those originally assigned to placebo. This was true over the entire 12 months of this trial (first 6 months double-blind, placebo-controlled and second 6 months blinded active-treatment phase) [53,54]. Rates of dopaminergic and psychiatric adverse events that are relatively frequent with other PD therapies (e.g., hallucinations, somnolence, confusion and edema) were similar across all treatment groups. The most commonly observed adverse effects during the active-treatment phase were infection, headache, dizziness and accidental injury. No adverse events were reported more frequently during the second 6 months of the trial.

In PRESTO, patients were monitored for safety and tolerability at baseline and at follow-up visits at 3, 6, 10, 14, 20 and 26 weeks [56]. Safety was assessed by the frequency and severity of reported adverse events, alterations in vital signs, laboratory findings and electrocardiograms (ECGs). Tolerability was measured based on the number of patients in each group who discontinued the trial. A total of 87% of patients receiving placebo, 91% of patients receiving rasagiline 0.5 mg/day and 95% of patients receiving rasagiline 1 mg/day showed some adverse effects. Gastrointestinal side effects, imbalance and dyskinesia were reported more often in patients with either dose of rasagiline compared with placebo. Gastrointestinal side effects appeared to be dose-related. Interestingly, it was significantly less common for patients on 0.5 mg rasagiline to suffer from depression compared with the placebo group ($p = 0.04$). Dyskinesias were reported as an adverse event in 10% of patients receiving placebo and 18% of patients receiving either dosage of rasagiline. The most frequent adverse effects (all three groups combined) were related to accidental injury, arthritis, stroke, melanoma, urinary tract infection and worsening of PD, with no significant differences among the three treatment groups.

In the LARGO study, patients were monitored for safety and tolerability at baseline and at weeks 3, 10 and 18 [57]. Safety was assessed by the frequency and severity of reported side effects, change in neurological examination, vital signs, laboratory parameters and ECGs. Tolerability was assessed based on rates of patients who discontinued early. There were no significant differences among patients treated with rasagiline, placebo or entacapone in dopaminergic adverse events. Postural hypotension, the most common cardiovascular-related dopaminergic adverse event, was reported in 2% of patients receiving rasagiline and entacapone. A total of 10% of patients receiving rasagiline discontinued before the study end, a smaller proportion than in the entacapone (13%) and placebo (15%) groups.

Rasagiline was equally tolerated in older and younger patients, with no evidence of increased hallucinations, daytime somnolence, nausea or leg edema.

No laboratory or ECG abnormalities have been attributed to rasagiline in Phase III clinical trials; therefore, there is no need to monitor any laboratory parameters in patients receiving rasagiline.

These Phase III clinical trials were performed with no dietary tyramine restriction. No serious tyramine reactions (hypertensive crisis) occurred during any of the Phase III studies. Two tyramine challenge studies in patients with PD receiving rasagiline have been reported [46,47]. Patients were challenged with oral tyramine HCl 75 mg in the TEMPO study, which evaluated rasagiline monotherapy in patients with early PD. In the PRESTO study, which evaluated rasagiline as adjunct therapy to L-dopa, patients were challenged with oral tyramine HCl 50 mg. In both studies, tyramine concentrations were far higher than would be achievable with a high-tyramine-content meal. In both studies, patients were followed up and monitored for changes in blood pressure and heart rate, and for ECG alterations. No clinically important tyramine interaction was observed in either study, despite challenge with tyramine concentrations far exceeding those likely with normal dietary consumption.

Conclusion & future perspective

Rasagiline has been available in the European Union and Israel since 2005, and in Canada and the USA since 2006, for the symptomatic therapy of patients with PD. Rasagiline open-label trials (TEMPO and PRESTO extension studies) have been ongoing for up to 8.5 years in many academic centers in the USA and Canada. The following are important clinical factors that should be considered when using rasagiline in clinical practice.

Rasagiline as a potential disease-modifying agent

To date, a large number of molecules (e.g., coenzyme Q10, creatine, pramipexole, rasagiline, ropinirole and selegiline) have been suggested as potential neuroprotective agents in PD based on preclinical animal models/research studies [58]. However, none of these agents have been definitively proven to be a disease-modifying agent in PD. Based on preclinical *in vitro* and *in vivo* studies, rasagiline is an agent that has shown potential for a neuroprotective effect [59]. Rasagiline has been shown to induce elevated gene expression of the neurotrophins, glial-cell-line-derived neurotrophic factor and brain-derived neurotrophic factor *in vitro*. Glial-cell-line-derived neurotrophic factor and brain-derived neurotrophic factor may protect dopaminergic neurons [60,61]. When rasagiline was given to mice post-MTPT-induced parkinsonism, neurorescue and restoration of nigrostriatal dopamine neurons were observed [62].

Preliminary clinical support for this effect of rasagiline can be seen in the delayed-start double-blind, placebo-controlled TEMPO study [54]. The patients in this trial who received rasagiline 1 or 2 mg/day in the first 6 months of the trial had significantly better total UPDRS scores at 12 months than patients with a delayed-start on rasagiline who received placebo for the first 6 months and rasagiline 2 mg/day for the next 6 months. Thus, the delayed-start group did not achieve the same level of improvement as the early-start group (patients who received rasagiline during the first 6 months of the trial). The fact that the differences in UPDRS remained almost constant by the end of the 12-month study suggests the possibility that rasagiline may provide more than a therapeutic or symptomatic benefit to patients with PD and provides evidence for possible disease modification or neuroprotection. To confirm these data and replicate the results of this delayed-start study, another larger trial with a delayed-start protocol, the ADAGIO study, is currently underway, with completion expected in 2008.

Rasagiline & dietary tyramine

Tyramine is found in certain foods and can act as a sympathomimetic amine. It has a pressor effect

that increases blood pressure by displacing norepinephrine from presynaptic storage vesicles if not properly metabolized after ingestion. Tyramine is metabolized by MAO-A in the gastrointestinal tract. Inhibiting MAO-A can increase a sympathomimetic reaction causing vasoconstriction, tachycardia, headache, hypertension, mydriasis and flushing. Tyramine content in foods varies, and ingesting large amounts of tyramine 10 min to 5 h prior to taking nonselective MAO inhibitors (mixed MAO-A and -B inhibitors) may lead to hypertensive crisis. This interaction of tyramine and MAO-A inhibitors is called the 'cheese effect', because aged cheeses are in the food group that is high in tyramine. Other foods that are high in tyramine include aged or smoked meats, sauerkraut, beer on tap and soy products. The rasagiline FDA labeling/package insert suggests that those taking rasagiline avoid foods that are high in tyramine. Rasagiline selectively inhibits MAO-B in preclinical models. At therapeutic doses of rasagiline, MAO-A should remain active in the gastrointestinal tract and, therefore, no 'cheese effect' is expected with simultaneous usage of rasagiline and foods rich in tyramine. All the pivotal Phase III trials with rasagiline in PD (i.e., TEMPO, PRESTO and LARGO) were performed without dietary tyramine restriction and no cheese effect was reported. Additionally, rasagiline–tyramine interaction studies have been performed in PD patients and no serious interactions were observed. In spite of the US labeling to avoid foods high in tyramine when taking rasagiline, no tyramine restrictions are being enforced in Canada and European Union countries, and no tyramine interaction has been confirmed to date.

Coadministration of rasagiline & antidepressants

Commonly used classes of antidepressants, such as selective serotonin-reuptake inhibitors and mixed serotonin/norepinephrine-reuptake inhibitors, can enhance serotonin and norepinephrine levels in the CNS. Thus, concerns exist regarding patients receiving MAO-B inhibitors and the above antidepressants and being at risk of developing serotonin toxicity. Since rasagiline selectively inhibits MAO-B, the risk appears to be lower than with the coadministration of antidepressants and nonselective MAO inhibitors. In clinical trials with rasagiline, no incidence of serotonin toxicity was associated with the use of rasagiline 0.5 or 1 mg with antidepressants [63]. Antidepressant doses used in these studies were those generally seen in clinical practice for elderly patients and those with Parkinson's disease. Rasagiline is not contraindicated with antidepressants (except mirtazapine), but the product insert labeling recommends not using these medications together. In reviewing rasagiline clinical trials, some patients received concomitant antidepressants such as citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, venlafaxine, amitriptyline, clomipramine, doxepin, nortriptyline, bupropion, mianserin, mirtazapine, nefazodone and trazodone. Some of the above medications were taken for just a few days (range: 1–3061 days); therefore, the data are not sufficient to exclude with certainty the possibility of serotonin toxicity for all of these agents.

Rasagiline behavioral effect

Antidepressant effects have been reported with oral selegiline in depressed patients with PD [64]. A high-dose selegiline transdermal system was approved in 2006 by the FDA for treatment of depression in adults. Further studies are warranted to assess the effect of rasagiline more specifically on depressive symptoms in patients with PD.

Rasagiline dosage: 0.5, 1 or 2 mg?

The TEMPO study in patients with early PD compared the efficacy of rasagiline 1 and 2 mg versus placebo [53]. At the end of the 6-month study, rasagiline 1 and 2 mg provided more benefits, as measured by total UPDRS scores, UPDRS motor subscale scores and PDQUALIF scores, compared with placebo, with little difference between the two rasagiline dose groups. Since there was no added benefit seen with the 2 mg/day dose versus the 1 mg/day dose, the recommended once-daily dosing for rasagiline in early PD is 1 mg once-daily, with no need to titrate up the dose.

In the PRESTO trial in patients with moderate-to-severe PD, at the end of the first 6 months of the study, patients treated with rasagiline showed 23 and 29% decreases in daily off time with 0.5 and 1 mg/day, respectively, compared with a 15% reduction in the placebo group [56]. UPDRS activities of daily living subscale scores during off time also showed more changes from the baseline with 1 mg/day. Although PRESTO was a fixed-dose trial, the recommendation for dosing with rasagiline in advanced PD as an adjunctive agent is to start with 0.5 mg dosed once-daily and to consider increasing to the maximum 1-mg daily dose if still needed to treat symptoms of wearing off. For patients who develop increasing dyskinesia upon rasagiline initiation, we suggest attempting to decrease the L-dopa dose.

In conclusion, MAO-B inhibitors are a valuable therapeutic option for patients with early or advanced PD. Features that differentiate rasagiline from selegiline include lack of amphetamine metabolites, more potent MAO-B inhibition, greater neuroprotective activity in experimental systems and more robust clinical data (**Table 1**). The favorable safety and tolerability profile of rasagiline, particularly in elderly patients, and its once-daily formulation, should also be considered as clinically significant features, especially with regards to improved drug adherence and improved outcomes in patients with PD.

Financial & competing interests disclosure

Dr Chen serves as a Teva Neuroscience consultant and on the Speaker's Bureau. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Table 1. Pharmacology, efficacy and safety of rasagiline and selegiline.

Rasagiline	Selegiline
Pharmacology	
Irreversible MAO-B inhibitor. Precise mechanisms of action are unknown, but one mechanism is thought to be related to MAO-B inhibitory activity, which increases striatal dopamine levels. Rasagiline undergoes almost complete transformation in the liver before excretion. Rasagiline metabolism proceeds through two main pathways: *N*-dealkylation and/or hydroxylation to yield 1-aminoindan, 3-hydroxy-*N*-propargyl-1-aminoindan and 3-hydroxy-1-aminoindan.	Mechanisms for the beneficial actions of selegiline adjunct therapy are not completely understood, but MAO-B inhibition is likely of primary importance. Selegiline is metabolized to L-methamphetamine and desmethylselegiline, and L-amphetamine, which are further metabolized to hydroxy metabolites. ODT selegiline produces a smaller fraction of the administered dose recoverable as metabolites than the conventional oral formulation of selegiline.
Efficacy	
Initial monotherapy in early PD	
The TEMPO study showed rasagiline once-daily was effective as measured by UPDRS scores vs placebo in patients treated in the initial 52-week multicenter, randomized, delayed-start study.	Not indicated for use as monotherapy.
Adjunctive therapy to L-dopa	**Adjunctive therapy**
The PRESTO and LARGO studies demonstrated the significant benefits of rasagiline as once-daily adjunctive therapy for reducing off time in patients with PD experiencing motor fluctuations despite optimal treatment with L-dopa and other dopaminergic medications.	Studies show modest decreases in symptoms, duration of wearing off' and motor fluctuations, L-dopa dose and disability. Other studies have shown minimal or no benefit from adjunctive selegiline treatment. Adjunctive therapy with ODT selegiline: results of one trial showed addition of ODT selegiline titrated to 2.5 mg/day to optimized L-dopa therapy significantly reduced total daily off time. Results of a second identical trial indicated no significant benefit of ODT selegiline treatment vs placebo in decreasing daily off time.
Safety	
Most common adverse effects (≥5%) when administered as 1 mg/day monotherapy	**Most common (≥3%) adverse effects with conventional selegiline monotherapy**
Headache (14%), arthralgia (7%), dyspepsia (7%), depression (5%), flu syndrome (5%)	Nausea (10%), dizziness (7%), abdominal pain (4%), confusion (3%), hallucinations (3%), dry mouth (3%)
Most common adverse effects when used as 1 mg/day adjunctive therapy	**Most common (≥5%) adverse events of ODT selegiline as adjunctive therapy at 1.25/2.5 mg/day**
Dyskinesia (18%), accidental injury (12%), nausea (12%), headache (11%), falls (11%), constipation (9%), weight loss (9%), postural hypotension (9%), arthralgia (8%), vomiting (7%), dry mouth (6%), rash (6%), somnolence (6%), abdominal pain (5%), anorexia (5%), diarrhea (5%), ecchymosis (5%), dyspepsia (5%) and paresthesia (5%)	Nausea (11%), dizziness (11%), pain (8%), rhinitis (7%), headache (7%), insomnia (7%), dyskinesia (6%), skin disorders (6%), back pain (5%), dyspepsia (5%) and stomatitis (5%)

LARGO: Lasting effect in Adjunct therapy with Rasagiline Given Once daily; MAO: Monoamine oxidase; ODT: Orally disintegrating tablet; PD: Parkinson's disease; PRESTO: Parkinson's Rasagiline: Efficacy and Safety in the Treatment of OFF; TEMPO: Rasagiline (TVP-1012) in Early Monotherapy for Parkinson's disease Outpatients; UPDRS: Unified Parkinson's Disease Rating Scale.
Adapted from [23].

Executive summary

- Rasagiline is an irreversible and selective inhibitor of monoamine oxidase type B.
- Unlike selegiline, which is metabolized to amphetamine derivatives, rasagiline is biotransformed to aminoindan, a non-amphetamine compound. Based on safety and tolerability data, rasagiline appears well tolerated with infrequent cardiovascular or psychiatric side effects.
- Rasagiline demonstrates efficacy as monotherapy in patients in early Parkinson's disease (PD) and is associated with improved quality of life.
- In patient with early PD (not yet requiring dopaminergic therapy), initiation of rasagiline earlier rather than later during the course of PD results in better measurable outcomes.
- Rasagiline is effective at reducing 'off' time when used as an adjunct to levodopa in patients with moderate-to-advanced disease and experiencing motor fluctuations.
- In the pivotal clinical trials, patients were not required to restrict tyramine at any time during rasagiline therapy, and tyramine restriction is not required in Canada, Israel or European countries in which rasagiline is marketed.
- Preliminary clinical data indicate that rasagiline can be administered safely with antidepressants, such as selective serotonin-reuptake inhibitors and tricyclic agents.
- Long-term clinical trials are required to further elucidate the presence of any neuroprotective or disease-modifying effect associated with rasagiline.

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