Rasagiline: defining the role of a novel therapy in the treatment of Parkinson's disease

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SUMMARY

Parkinson's disease (PD) is a therapy area with considerable unmet needs. The current key targets for PD treatment include the slowing of disease progression, improved control of motor fluctuations in advanced disease and the treatment of nonmotor symptoms. In view of such major requirements, it is important to consider how new drug treatments fit into the context of PD therapy, and the practical advantages that they may offer in the management of PD in clinical practice. Rasagiline is a novel, second-generation, irreversible, selective monoamine oxidase type B inhibitor that is indicated for the treatment of idiopathic PD, either as initial monotherapy or as adjunct therapy (with levodopa) for patients experiencing end-of-dose motor fluctuations. This review assesses the outcome from several large-scale clinical studies that have investigated the use of rasagiline in early and advanced PD patient populations and discusses the role of rasagiline within the current scope of PD therapy.

Keywords: Rasagiline; Parkinson's disease; motor fluctuations; MAOB inhibitor

INTRODUCTION

Accompanying the overall growth of the elderly population is an increasing prevalence of disorders, such as Parkinson's disease (PD), that predominantly affect this age group. As a result, the effective treatment of PD, as a chronic, neurodegenerative disease, is becoming increasingly significant – for patients, caregivers, healthcare providers and society as a whole.

The cardinal symptoms of PD (tremor, bradykinesia and rigidity) are produced by a loss of nigrostriatal dopaminergic neurones (1) and therefore, the majority of current treatments for PD are based around the supplement/replacement of dopamine in the brain. The mainstay of PD treatment for many years has been the dopamine precursor, levodopa, although current advances in the PD market are being driven by newer therapies such as dopamine agonists and COMT inhibitors. However, despite the available options for PD treatment, there are several key features of the disease that current therapies are unable to address, and which therefore form the focus for the development of this therapy area. Unmet needs include:

- Slowing disease progression – in the absence of a cure for PD, a therapy that could protect neurones against further degeneration and therefore slow or even halt disease progression would be a significant advance.
- Improving motor fluctuations/dyskinesias – although levodopa is currently the most effective treatment for the cardinal symptoms of PD, its long-term use is associated with the development of motor complications. The effectiveness of the drug begins to wear off at the end of doses, and fluctuations between periods of good (ON time) and poor (OFF time) motor control start to appear (1,2). In addition, prolonged use of dopamine replacement through levodopa can produce dyskinesias (1–3) – an effect that may be limited by lowering the dose of levodopa, but which may in turn increase the problem of motor fluctuations.
- Targeting nonmotor symptoms – the predominant pathology of PD (degeneration of dopamine neurones) has created an emphasis on treatments that target the motor symptoms of the disorder. However, there are many troubling PD symptoms that are not related to motor dysfunction, including fatigue, pain, sleep problems, cognition difficulties and depression (4).
- Providing simple treatments – patients with PD may experience a complicated treatment regimen, including drug titration, multiple daily dosing and combination therapies (for the treatment of PD symptoms, motor fluctuations, or unrelated medical conditions – common in an elderly population). A simplification of this regimen would be a valuable benefit to patients.

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MONOAMINE OXIDASE TYPE B INHIBITION

The clinical benefit of monoamine oxidase type B (MAO-B) inhibitors is thought to arise from an ability of these

medications to enhance the level of dopamine by decreasing the catabolism. Additionally, basic research suggests that MAO-B inhibitors may impart efficacy by inhibiting apoptosis (programmed cell death). There are two MAO-B inhibitors available today, selegiline and rasagiline.

Selegiline is an irreversible, relatively selective (its selectivity is lost at higher doses) MAO-B inhibitor. Selegiline possesses other pharmacological activities such as an effect on mitochondrial membrane potential activity, an antiapoptosis effect and reduction of oxidative stress which may play a role in its putative neuroprotective effect. When administered orally, selegiline has low bioavailability as a result of extensive hepatic first-pass metabolism. This metabolism produces high levels of amphetamine metabolites; L-methamphetamine and L-amphetamine account for more than three-fourths of the recovered metabolites from an oral dose of conventional selegiline. This can lead to clinical agitation or insomnia. Selegiline is used less frequently in PD because its neuroprotective effect remains unproven, it provides only minimal symptomatic control (even if the DATATOP trial showed statistically significative improvement after 3 months vs. placebo in *de novo* PD patients) and it is also not a particularly effective drug for treating motor fluctuations (5).

There is also an orally disintegrating tablet (ODT) of selegiline which is a rapidly dissolving formulation of selegiline. Selegiline ODT is being developed for use in PD patients experiencing off episodes while being treated with levodopa.

Selegiline ODT resulted to be effective treatment for wearing off episodes in patients with PD in the study performed vs. placebo. The innovative delivery system used in selegiline ODT has advantages over conventional oral selegiline. These advantages include rapid onset of action, avoidance of presystemic metabolism to provide higher drug levels and decreased plasma concentrations of amphetamine metabolites (6).

In this article, the new MAO-B inhibitor rasagiline is reviewed.

PHARMACOLOGY OF RASAGILINE

Rasagiline (*N*-propargyl-1(*R*)-aminoindan) is a potent, selective, irreversible MAO-B inhibitor (7,8). MAO-B is predominantly found in the brain (9), where it metabolises dopamine to an inactive compound (10). Consequently, MAO-B inhibitors have been developed to prolong the action of dopamine – whether endogenous or levodopa-derived – in the brain (10).

In this development, the selectivity and irreversible nature of rasagiline are both important factors. The type A isoform of MAO is found mainly in the gut, where it breaks down dietary amines, such as tyramine, which can have toxic potential if allowed to accumulate (11). At therapeutic levels, rasagiline shows a high level of specificity for MAO-B and therefore does not interfere with the action of MAO-A (8,12). This specificity for the B isoform has a positive impact on the drug's side-effect profile, as it avoids nonspecific inhibition of MAO-A, which could produce harmful side effects such as the tyramine reaction (the 'cheese effect') – a hypertensive crisis (9,13).

Because rasagiline is also an irreversible inhibitor, its duration of action is independent of the drug's half-life and is instead determined by the regeneration rate of MAO-B (14). This characteristic is potentially beneficial in PD, where rasagiline's prolonged effect may be able to limit the fluctuating responses that are characteristic of long-term drug treatment with levodopa (15,16). In addition, the extended action of irreversible MAO-B inhibitors also enables a simple, once-daily dosing strategy (14).

OTHER POTENTIAL EFFECTS

Preclinical investigations have shown that both rasagiline and its major metabolite, aminoindan (AI), exhibit neuroprotective properties. Rasagiline can increase the survival of dopaminergic neurones (17), protect against glutamate-induced neurotoxicity (18) and block neurotoxicity in the MPTP model of PD (19). The neuroprotective potential of AI is also demonstrated via its antiapoptotic activity (20). As rasagiline also induces neuroprotection in cell cultures lacking MAO-B (21), at least some of rasagiline's neuroprotective potential appears to be mediated by a mechanism other than MAO-B inhibition. Further to this, the S-enantiomer of rasagiline also demonstrates neuroprotective potential, while showing minimal MAO-B inhibitory activity (20,22,23).

There is insufficient evidence to prove that any current antiparkinsonian agent can contribute such neuroprotective/disease-modifying effects in the clinical setting (24). However, as this is a key target for PD therapies, a recent study included a delayed-start design to evaluate the effect of rasagiline on disease progression, and this produced some promising preliminary results (25).

Another important characteristic of rasagiline is that its metabolites do not appear to possess any detrimental characteristics and as discussed above, AI may even offer a therapeutic benefit (20,21,26). This is in contrast to the amphetamine metabolites of the MAO-B inhibitor selegiline, which have neurotoxic properties that may be related to safety concerns observed in the clinic (high blood pressure, increased heart rate and insomnia) (27–29).

RASAGILINE IN EARLY PD

The effect of initial rasagiline monotherapy on patients in the early stages of PD has been clinically evaluated in the

12-month TEMPO study (25,30). The initial placebo-controlled 6-month phase of this study was followed by a 6-month delayed-start phase that was designed to separate the symptomatic effects of rasagiline from any disease-modifying influence (25,30). The study has been continued further in an ongoing open-label extension for over 6 years now. Key results and conclusions from the TEMPO study are presented below.

Efficacy of Rasagiline as Monotherapy

The first 6-month phase of the randomised, double-blind TEMPO study included 404 patients with early PD (Hoehn and Yahr stage ≤ 3) who did not require dopaminergic therapy (30). The study assessed the effects of monotherapy with once-daily rasagiline 1 mg/day or 2 mg/day vs. matching placebo (30).

Primary analysis of the Unified Parkinson's Disease Rating Scale (UPDRS)-Total score revealed that both rasagiline-treated patient groups produced significant improvement over placebo (Figure 1), with an overall treatment effect of -4.20 for the rasagiline 1 mg/day group and -3.56 for the 2 mg/day group (30). This result was supported by a responder analysis, showing that there were significantly more responders (defined as <3 unit change in UPDRS-Total score) in the rasagiline 1 mg/day group (66%, $p < 0.01$) and 2 mg/day group (67%, $p = 0.001$) than in the placebo group (49%) (30).

More specific analysis, via the UPDRS subscales showed a significant benefit for patients receiving rasagiline (both treatment groups) in the measures of UPDRS-Motor and UPDRS-ADL (activities of daily living) (Figure 2) (30). The change observed in the UPDRS-Mental subscale was not significant (level of impairment was small), and no adverse changes in this subscale were seen.
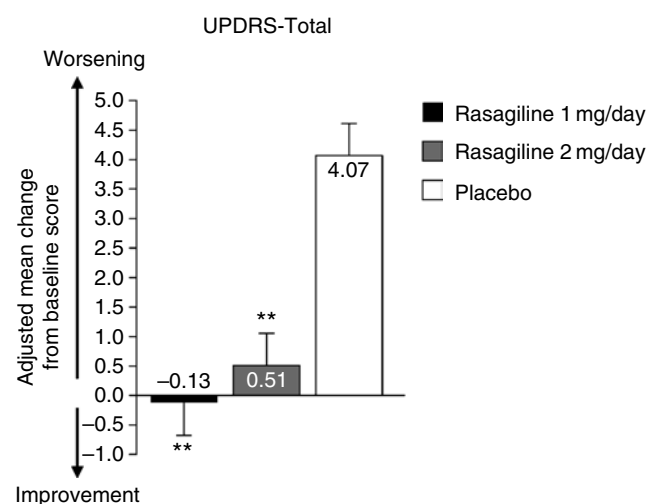

Figure 1 Rasagiline monotherapy in early Parkinson's disease (PD) (TEMPO study) – UPDRS-Total score, adjusted mean change (SE) from baseline to Week 26 (ITT, LOCF). **p < 0.001

In additional analyses, rasagiline patients experienced significant improvements vs. placebo in the measures of UPDRS-Bradykinesia (1 mg/day, $p < 0.001$; 2 mg/day, $p < 0.05$), UPDRS-Tremor (1 mg/day, $p < 0.01$) and quality of life (PD-QUALIF score; both groups, $p < 0.05$).

These results illustrate the efficacy of rasagiline monotherapy in early PD, including global benefits and specific effects on cardinal symptoms and quality of life. No advantages in efficacy were apparent for the rasagiline 2 mg/day dose over rasagiline 1 mg/day (30).

Disease-modifying Potential: Delayed-start Phase

As shown in Figure 3, three hundred eighty patients from the TEMPO placebo-controlled phase entered a 6-month phase of active treatment, where patients previously receiving placebo were switched to rasagiline 2 mg/day (25,30). The aim of this phase of the study was a comparison between those patients who received 12-month treatment with rasagiline and those patients, previously on placebo, who had a delayed start and received only 6-month treatment with rasagiline. This delayed-start technique is one of several study designs that have been employed to evaluate the disease-modifying potential of antiparkinsonian agents. The theory behind this particular design is that by the end of the full 12 months of study, the symptomatic effects of treatment will be balanced in all groups, leaving any observed differences attributed to disease-modifying effects (25).

Results showed that patients receiving 2 mg/day rasagiline for a 12-month period had a significant benefit over patients who had their treatment delayed by 6 months, as measured by UPDRS-Total score (-2.29 unit difference, $p = 0.01$) and UPDRS-ADL score (-0.96 unit difference, $p < 0.01$) (25). Once again, this was supported by a superior responder rate in the 12-month treatment group ($p < 0.05$) (25). Comparisons of other subscales (UPDRS-Motor and UPDRS-Mental) were not significant (25). Patients who received 1 mg/day rasagiline for 12 months also showed significant benefits over the 2 mg/day delayed-treatment group in UPDRS-Total score (-1.82 unit difference; $p = 0.05$) (25).

One potential disadvantage of this method of measuring disease modification is that symptomatic effects may be enhanced if treatment is started earlier in the disease course (25). However, taken as a preliminary indication, this delayed-start study may provide a promising indication of disease modification that certainly warrants further investigation.

Long-term Safety and Efficacy

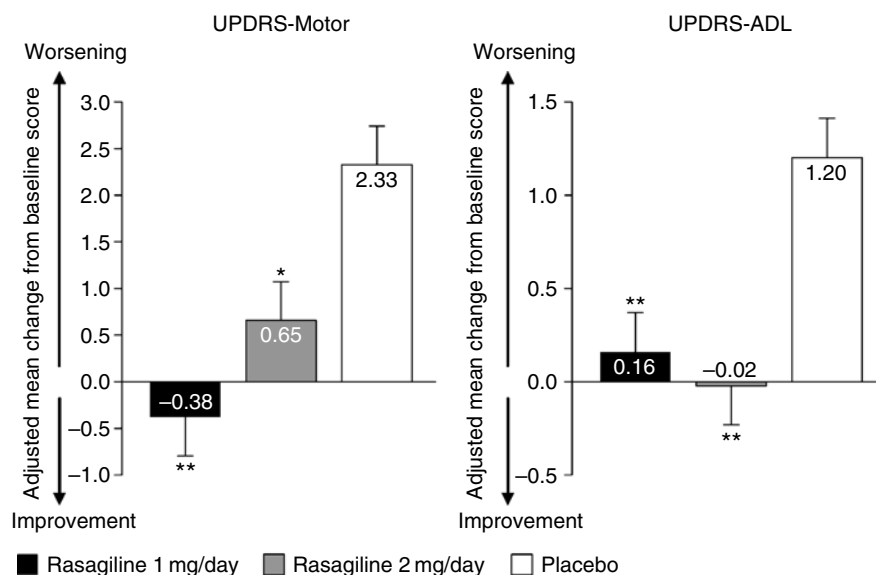The assessment of long-term therapy effects is an important aspect of any treatment for PD, as a chronic, progressive

Figure 2 Rasagiline monotherapy in early Parkinson's disease (PD) (TEMPO study) – UPDRS-Motor and UPDRS-ADL subscale scores, adjusted mean change (SE) from baseline to Week 26 (ITT, LOCF). *p < 0.01; **p < 0.001

condition. The results of the first two phases of the TEMPO study indicated that rasagiline monotherapy was efficacious, safe and well tolerated over a 12-month period (25,30). However, the TEMPO study has an additional extension period that has been ongoing for a period of >6 years, with all patients receiving once-daily treatment with open-label rasagiline 1 mg/day (Figure 3). Current indications are that the efficacy of rasagiline is maintained over this period, with no apparent concerns regarding safety or tolerability.

RASAGILINE IN ADVANCED PD

Motor fluctuations are a disabling complication of long-term dopaminergic treatment. Rasagiline is indicated for use in levodopa-treated patients with motor fluctuations, and its efficacy in this indication is supported by two large-scale clinical studies – LARGO and PRESTO (15,16).

Both of these studies were placebo-controlled and were run over a period of 26 weeks (PRESTO) and 18 weeks (LARGO) in levodopa-treated patient populations with advanced PD (Hoehn and Yahr stage <5) and motor fluctuations (15,16). PRESTO patients ($n = 472$) were randomised to receive rasagiline once-daily 0.5 mg/day, rasagiline 1 mg/day or placebo added to levodopa, and patients in LARGO ($n = 687$) received rasagiline 1 mg/day, entacapone (active comparator agent; 200 mg with each levodopa dose) or placebo added to levodopa (15,16).

Improvements in Daily OFF Time

The efficacy of rasagiline in these studies was assessed using change from baseline in total daily OFF time, as measured by 24-h patient diaries (15,16). As shown in Table 1, in each rasagiline-treated group, patients experienced a significant decrease in daily OFF time (of approximately 0.5–1 h)
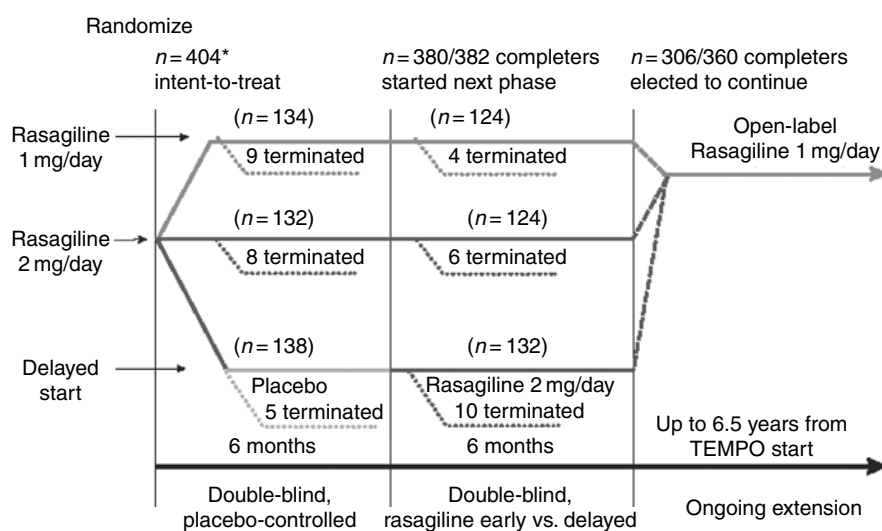

Figure 3 TEMPO study design

Table 1 PRESTO and LARGO studies: change in total daily OFF and ON time

Study group	Total daily OFF time – adjusted mean change from baseline		Total daily ON time – adjusted mean change from baseline	
	Difference from placebo (hour) (15,16)	p-value†	Difference from placebo (hour) (15,16)	p-value
Rasagiline 0.5 mg/day (PRESTO)	−0.49	<0.05	+0.40	0.0661
Rasagiline 1 mg/day (PRESTO)	−0.94	<0.001	+1.02	<0.0001
Rasagiline 1 mg/day (LARGO)	−0.78	<0.001	+0.82	<0.0001

compared to placebo, accompanied by a comparable increase in daily ON time (15,16). In each group, the majority of the increase in daily ON time was without troublesome dyskinesias (15,16). In the LARGO study, significantly more patients responded to treatment, by showing an improvement in mean daily OFF time of 1 h or more, in the rasagiline group (51%) as compared with the placebo group (32%, p < 0.001) (16).

Additional Efficacy Measures

Secondary and additional endpoint analyses from these studies showed that rasagiline was significantly more effective than placebo (PRESTO, p < 0.01; LARGO, p < 0.001) in terms of clinical global improvement (CGI) score (as assessed by the examiner), UPDRS-ADL (OFF) and UPDRS-Motor (ON) (15,16), whereas there was no statistically significant change in PDQUALIF.

The LARGO study confirmed rasagiline's efficacy as measured by individual UPDRS items of rigidity, tremor and bradykinesia (all scores showed significant improvement vs. placebo; p < 0.01). These observations were supported by one or both of the rasagiline groups in the PRESTO study (15). Further to these effects on typically dopa-responsive symptoms, the LARGO study showed that rasagiline also produced significant improvements in the UPDRS items of postural instability and gait disorder (PIGD), and freezing (p < 0.05 vs. placebo) – symptoms that are known to be less responsive to dopaminergic mechanisms (16). In addition to specific symptomatic effects, rasagiline produced significant improvements during the practically defined OFF state (i.e. before the first morning dose; p < 0.05 vs. placebo), which reflects a sustained effect on dopamine transmission (16).

Therefore, rasagiline has demonstrated substantial efficacy in treating advanced PD and motor fluctuations – providing patients with an increase in well-controlled ON time, as well as improving cardinal symptoms of the disease.

Distinguishing Properties of Rasagiline Therapy

Aside from the more general measures of efficacy, studies have also highlighted some more specific aspects of rasagiline

treatment that may be relevant in defining rasagiline's role as a therapy for PD.

Symptom Efficacy

The efficacy of rasagiline against the cardinal symptoms of PD has been discussed earlier in this article. However, as PD is a condition with many and varied symptoms, the importance of treating noncardinal, and even nonmotor, symptoms cannot be underestimated.

In PD, symptoms relating to gait are known to be poorly responsive to existing dopaminergic treatments. In patients with advanced PD, rasagiline has demonstrated a significant effect on the UPDRS subscores of PIGD and freezing (15,16). In addition, reports from a LARGO ancillary study on freezing of gait (FOG) indicate that rasagiline significantly reduces FOG in comparison with placebo and this effect may be independent of rasagiline's benefit in reducing OFF time (31).

Moreover, in all the studies, rasagiline showed an interesting effect on fatigue which deserves further investigations.

Concomitant Use With Other Drugs

Patients with PD, especially advanced disease, are often highly medicated in order to provide adequate symptom control. Therefore, in this clinical environment, it is obviously an advantage if a medication is able to work independently of concomitant therapies.

Studies of patients with advanced PD have demonstrated that rasagiline can be administered safely and effectively as an adjunct to levodopa (15,16). In addition, as measured by a reduction in OFF time, it can act to reduce the impact of motor fluctuations, which are a long-term complication of levodopa therapy (15,16).

In a post hoc assessment of the LARGO study, results were analysed according to concomitant usage of dopamine agonists (DAs) at baseline (16). This showed that the efficacy and safety of rasagiline were not influenced by ongoing treatment with DAs (16). These observations were supported by a subanalysis of the PRESTO study, which showed that the efficacy and tolerability of rasagiline continued to be observed

even when patients were already optimally treated with LD/DDI, DAs and/or COMT inhibitors (32).

Dosing Strategy

In addition to convenience alongside other commonly prescribed medications (see above), there are several properties of rasagiline's dosing schedule that make it appropriate for use in the PD patient population.

As stated earlier in this article, due to its irreversible inhibition of MAO-B, the clinical effect of rasagiline is not reliant on frequent dosing, and the drug is administered once daily, without titration (14). The extended action of rasagiline is also illustrated by clinical data, showing that its positive effect on motor function is still significant before the daily morning dose ('practically defined OFF' time) (16).

Additional factors, such as no requirement for dose alteration in the elderly and no requirement to be administered with regard to meals, are also favourable characteristics of the rasagiline dosing regimen. However, rasagiline should be used with caution in patients with hepatic dysfunction and in those taking drugs with CYP1A2 inhibitory effect (i.e. ciprofloxacin).

In the elderly population (>70), rasagiline is well tolerated with a safety profile similar to that for placebo (16).

However, an infrequent but increased occurrence of hallucinations was reported in elderly PD patients treated with rasagiline in combination with levodopa.

Comparison With Other Drugs

Currently, no clinical data are available on the use of rasagiline in direct comparison with other antiparkinsonian therapies. However, the LARGO study did include the COMT inhibitor, entacapone, as an active comparator agent. Although LARGO was not sufficiently powered to directly compare these two drugs, certain preliminary conclusions can be drawn. The effect of rasagiline on daily OFF time, CGI-examiner, and UPDRS subscales of ADL and Motor was of a similar magnitude to that observed in the entacapone group (16). It is interesting to note that although these motor effects were similar between the two treatment groups, rasagiline also produced significant effects in the measures of UPDRS-PIGD, UPDRS-Freezing and UPDRS-Motor during practically defined OFF, while entacapone showed a similar but nonsignificant trend (16).

Such distinguishing features may be expected in drugs with contrasting mechanisms of action, and further investigations to help define these effects would be valuable.

Neuroprotective Potential

Currently, no drug treatments are indicated as neuroprotective agents. Rasagiline does show enough potential to merit future investigations in this area, as it has demonstrated neuroprotective activity in preclinical studies (17–19,21) and has also produced signs of slowing functional decline in a preliminary investigation in a clinical setting (25). Any treatment that could provide neuroprotection in PD would represent a significant advance in therapy.

Side-effect Profile

In clinical studies, rasagiline is well tolerated, with a favourable side-effect profile. The discontinuation rate of patients receiving rasagiline in clinical studies was similar between rasagiline- and placebo-treated groups (15,16,30).

More specifically, clinical study revealed that the incidence of dopaminergic adverse events (AEs), such as nausea, hallucinations, depression and somnolence, was comparable between rasagiline and placebo groups (16). The most common side effects of rasagiline were hypotension and headache. Another dopaminergic AE, dyskinesia, is a frequent problem with long-term dopaminergic treatment of PD. In the rasagiline (1 mg/day)-treated group of the LARGO study, the incidence of dyskinesia as an AE was similar to that of placebo, and the UPDRS-dyskinesia score was not significantly different from that of placebo (16). In the PRESTO study, although the UPDRS-dyskinesia score was comparable to placebo in the patient group receiving rasagiline 0.5 mg/day, there was an increased occurrence of dyskinesia in patients receiving rasagiline 1 mg/day (p ≤ 0.05) (15). Combining the two rasagiline groups in the PRESTO study, the incidence of dyskinesia as an AE was also significantly above that of placebo (18 vs. 10%) (15). However, it should be noted that the PRESTO study design did not permit the adjustment of levodopa dosage, which could have potentially limited these dyskinesia effects (15). In both these studies, all rasagiline-treated patient groups experienced increased ON time without troublesome dyskinesias (15,16).

CONCLUSION

It is clear that rasagiline is an effective agent for the treatment of advanced PD, when used as an adjunct therapy to levodopa. The limiting of motor fluctuations and reducing the amount of time spent in OFF are important patient benefits and are recognised as such by prescribing physicians. In addition, rasagiline shows efficacy against cardinal symptoms of the disorder as well as gait-related symptoms such as PIGD and freezing, which are less well treated by currently available therapies. Efficacy has also been demonstrated in clinical study of early PD patients receiving initial rasagiline monotherapy, although it is unknown how this effect compares with that offered by other treatments at this stage in the disorder.

The simple dosing regimen of rasagiline alongside its maintained efficacy in combination with other antiparkinsonian therapies, and its good tolerability, also means that it is ideally placed for use in a highly medicated, elderly patient population.

There is no evidence so far that rasagiline has neuroprotective effects in humans; however, it shows enough potential to merit future investigations in the area.

In conclusion, rasagiline offers several distinguishing characteristics that position it as a valuable treatment choice for physicians managing patients with PD. Additional studies are warranted to further assess its disease-modifying potential.

ACKNOWLEDGEMENTS

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