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ADIS DRUG EVALUATION

Rasagiline: A Review of Its Use in the Treatment of Idiopathic Parkinson's Disease

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Abstract Rasagiline (Azilect®) is an oral, second-generation, selective, irreversible monoamine oxidase-B (MAO-B) inhibitor approved in the US for the treatment of Parkinson's disease. In randomized, controlled trials, oral rasagiline 1 mg once daily was superior to placebo in the symptomatic treatment of early Parkinson's disease, both as monotherapy or as an adjunct to dopamine agonists. Comparisons of early-start and delayed-start treatment suggested a disease-modifying effect for rasagiline, but the results were equivocal. Rasagiline 0.5 or 1 mg/day was also superior to placebo as adjunctive therapy to levodopa in Parkinson's disease patients with motor fluctuations. Rasagiline was generally well tolerated in clinical trials, displaying a placebo-like tolerability profile in several studies. Cost-utility studies predicted that rasagiline, either as monotherapy or adjunctive therapy, would be a cost-effective treatment option. Therefore, oral rasagiline is a valuable therapeutic option for use in all stages of Parkinson's disease.

Rasagiline in Parkinson's disease: a summary

An oral, second-generation, selective, irreversible monoamine oxidase-B (MAO-B) inhibitor
More potent MAO-B inhibition than with selegiline, and is not metabolized to amphetamines
Superior to placebo as monotherapy or as an adjunct to dopamine agonists in early Parkinson's disease
Superior to placebo as adjunctive therapy to levodopa in patients with motor fluctuations
Generally well tolerated and predicted to be cost effective or cost saving in modelled pharmacoeconomic analyses

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1 Introduction

Parkinson's disease is a progressive, degenerative neurological disorder characterized pathologically by the selective loss of dopaminergic neurons in the substantia nigra pars compacta and the intracellular accumulation of Lewy bodies [1–3]. The loss of dopamine-producing neurons leads to the characteristic motor symptoms (e.g. bradykinesia, hypokinesia, muscle rigidity, resting tremor and postural instability) of Parkinson's disease [1–3]. Patients also experience non-motor symptoms (e.g. autonomic dysfunction, orthostatic hypotension, dementia, depression, anxiety and sleep disturbances) [1–3]. While dopaminergic regions of the brain are the focus early in the disease process, non-dopaminergic regions of the brain are

involved later in the disease course [2]. The prevalence of Parkinson's disease increases with age; the disease affects ≈1 % of the population aged >60 years. While some Parkinson's disease cases are known to have an hereditary origin, most (90 %) are idiopathic [2].

There are no definitive disease-modifying or neuroprotective therapies available for Parkinson's disease [1, 2]. Initial therapy generally focuses on restoring striatal dopamine to control motor symptoms and the approved drug classes most commonly used for this purpose, in order of potency, are levodopa, dopamine agonists (e.g. pramipexole and ropinirole) and monoamine oxidase (MAO)-B inhibitors (e.g. selegiline and rasagiline) [1, 2].

MAO, which is classified as type A or B, breaks down biogenic amines, including neurotransmitters [4, 5]. Both MAO isoenzymes degrade dopamine, but display different specificities for other neurotransmitters and amines [4]. MAO-B is the predominant isoenzyme in the basal ganglia and is the isoenzyme mainly responsible for the breakdown of dopamine and phenethylamine, while MAO-A is responsible for the majority of the MAO activity in the intestinal tract [4]. Phenethylamine stimulates the release of dopamine from neurons and inhibits its reuptake. Therefore, selective inhibition of MAO-B results in an elevation of phenethylamine and dopamine levels in the brain without affecting processes dependent on MAO-A activity [4, 6, 7].

Rasagiline (Azilect®) is an oral, second-generation, selective, irreversible MAO-B inhibitor approved in the US for the treatment of Parkinson's disease [5]. Rasagiline is also approved in the EU [8]. It can be used as monotherapy in early disease or as an adjunct to other antiparkinsonian medications in early or more advanced disease [5]. This article provides a narrative review of the pharmacological properties of rasagiline, and its efficacy and tolerability in the treatment of patients with idiopathic Parkinson's disease.

2 Pharmacodynamic Properties

The pharmacological properties of oral rasagiline have been extensively reviewed previously [9–11]; therefore, only a brief overview is presented in this section.

Rasagiline (formerly termed TVP-1012) is the *R*-isomer of AGN1135, a member of the propargylamine family, and is a highly potent, irreversible inhibitor of MAO-B; the *S*-isomer of AGN1135 is >1,000-fold less active in inhibiting MAO-B [5, 12]. MAO-B inhibition results from the propargyl moiety of rasagiline covalently binding (irreversibly) to the flavin adenine dinucleotide moiety of the enzyme [13]. Recovery requires de novo synthesis of new MAO enzyme [13].

The MAO-A and MAO-B enzymes are located in the mitochondrial outer membrane and are responsible for catalyzing the oxidative deamination of neuroactive and vasoactive amines, including dopamine, noradrenaline, serotonin and tyramine [9, 13]. MAO is found throughout the body, particularly in nerve terminals, brain, intestinal mucosa and liver. MAO-A is found primarily in the intestinal tract and catecholaminergic neurons of the brain, and MAO-B is found mostly in serotonergic and histaminergic neurons, and astrocytes in the brain [9, 14]. The predominance of MAO-B in human basal ganglia and the fact that dopamine and phenethylamine are mainly oxidized by MAO-B in the human brain led to the use of MAO-B inhibitors in Parkinson's disease [12, 13]. Moreover, MAO-B levels, but not MAO-A levels, increase with age and may play a role in age-related neurological diseases, like Parkinson's disease, via other biological processes, such as an increase in oxidative stress; thus, further supporting the use of MAO-B inhibitors in Parkinson's disease [15].

At high doses (10 mg/kg), rasagiline inhibits both MAO-A and MAO-B, but at the therapeutic dosages used in Parkinson's disease (0.5–1 mg/day), rasagiline selectively inhibits MAO-B and does not potentiate the pressor response [i.e. ≥30 mmHg increase in systolic blood pressure (BP)] to oral tyramine (the 'cheese effect', since aged cheese typically contains high tyramine levels) that results from inhibiting MAO-A, which is particularly responsible for the catabolism of monoamines ingested in food [12, 13]. Therefore, restriction of dietary tyramine during therapy with rasagiline is not considered necessary, although the prescribing information still recommends that patients avoid foods with very high tyramine content [5]. Interestingly, a recent study found >70 % reduced MAO-A activity in plasma samples from patients with Parkinson's disease chronically treated with rasagiline or selegiline compared with healthy controls or patients not receiving MAO inhibitors [16].

Rasagiline inhibits MAO-B with a potency 5- to 10-fold higher than that of selegiline, the first MAO-B inhibitor to be marketed, and, unlike selegiline, is not metabolized to amphetamines and therefore does not display the sympathomimetic and neurological effects seen with selegiline [9, 13].

Rasagiline single oral doses of 1, 2, 5 and 10 mg in healthy volunteers produced approximately 35, 55, 79 and 99 % inhibition of platelet MAO-B activity at 1 h post-dose [17]. The inhibition was maintained for at least 48 h post-dose and MAO-B activity returned to baseline levels after 2 weeks [17]. Repeat administration of 2 mg/day for 10 days in volunteers inhibited platelet MAO-B activity by >90 % after 3 days and >99 % after 6 days. Maximal inhibition was then maintained for the remainder of the

study and MAO-B activity returned to baseline levels 2 weeks after the final dose [17].

Rasagiline demonstrated neuroprotective effects in a variety of in vitro and in vivo models of neurodegenerative disease, which appears to be dependent on the propargyl moiety and independent of MAO-B inhibition, since neuroprotection is also displayed by the *S*-isomer of AGN1135 [9, 12]. The principal metabolite of rasagiline, l-aminoindan, may also contribute to the neuroprotective effects of rasagiline [9, 12]. The exact mechanism of the neuroprotective effects is not fully understood, but rasagiline reduces oxidative stress, stabilizes mitochondrial membranes and prevents apoptosis [12, 18]. Rasagiline appears to intervene in the death signalling pathway in mitochondria and induces anti-apoptotic Bcl-2 and neurotrophic factors [19]. Rasagiline is also believed to have neurorestorative activity and has been shown to increase the proportion of tyrosine hydroxylase-immunopositive neurons in animal studies [13].

A thorough QT/QTc study in 250 healthy volunteers demonstrated that rasagiline at the approved dosage of 1 mg/day, as well as at supratherapeutic dosages of 2 and 6 mg/day, did not affect cardiac repolarization [20]. Following 10 days of therapy, the largest time-matched, baseline-adjusted mean differences in individual corrected QT interval between rasagiline 1, 2 and 6 mg/day and placebo were 4.4, 4.4 and 6.1 ms, respectively. For all doses, the two-sided 95 % confidence intervals were below the 10 ms regulatory threshold [20]. Rasagiline did not produce any clinically significant changes in heart rate or BP.

3 Pharmacokinetic Properties

3.1 Absorption and Distribution

Rasagiline in the 0.5–10 mg dose range displays linear pharmacokinetics [5, 21, 22]. Following oral administration, rasagiline is rapidly absorbed, attaining a peak plasma concentration (C_{max}) of 2.5 ng/mL at a time (t_{max}) of 0.5 h after a single 1 mg dose [17]. Rasagiline has an absolute bioavailability of approximately 36 % [5]. Repeat oral administration of rasagiline 0.5, 1 and 2 mg once daily for 12 weeks in patients with idiopathic Parkinson's disease produced C_{max} values of 4.2, 8.5 and 14.9 ng/mL, respectively, and area under the plasma concentration-time curve from time zero to up to 4 h after dosing (AUC_T) values of 6.4, 12.4 and 23.5 ng·h/mL, respectively [21]. The t_{max} for all three doses ranged from 0.5 to 0.7 h [21]. After repeat administration of rasagiline 2 mg once daily for 10 days in healthy volunteers, the AUC from time zero to 24 h (AUC_{24}) was 20 ng·h/mL [17].

The t_{max} of rasagiline is unaffected by food, but the C_{max} is reduced by ≈60 % and the AUC is reduced by ≈20 % when rasagiline is taken with a high-fat meal [5]. Since the exposure is not significantly affected by food, rasagiline can be taken with or without food [5].

Rasagiline is widely distributed in tissues, with a mean volume of distribution of 87 L at steady state [5]. At concentrations of 1–100 ng/mL, rasagiline is 88–94 % bound to plasma protein and 61–63 % bound to human albumin [5].

3.2 Metabolism and Elimination

Rasagiline undergoes hepatic metabolism by cytochrome P450 (CYP) isoenzymes, predominantly CYP1A2 [5]. The major metabolites of *N*-dealkylation and/or hydroxylation are l-aminoindan, 3-hydroxy-*N*-propargyl-l-aminoindan and 3-hydroxy-l-aminoindan; biotransformation is virtually complete [5]. These metabolites do not inhibit MAO-B, but the major metabolite 1-aminoindan has neuroprotective properties that may contribute to the overall neuroprotective activity of rasagiline [12, 23]. The major elimination pathway is urinary excretion of glucuronide conjugates of rasagiline and its metabolites. Approximately 62 % of the dose is excreted in urine and 7 % in the faeces over 7 days post-administration. Less than 1 % of rasagiline is excreted unchanged in the urine. The mean steady-state elimination half-life ($t_{½}$) of rasagiline is 3 h [5], although recovery of MAO-B activity, which requires de novo synthesis of new enzyme, is in the region of about 40 days [4].

3.3 Special Populations

Following the administration of rasagiline 1 mg/day for 7 days, the AUC and C_{max} were increased twofold and 1.4-fold, respectively, in patients with mild hepatic impairment (Child-Pugh score of 5–6) and sevenfold and twofold, respectively, in patients with moderate hepatic impairment (Child-Pugh score of 7–9) compared with healthy volunteers [5]. Therefore, a reduced dose of rasagiline should be used in patients with mild hepatic impairment (see Sect. 8) and the drug should not be used in patients with moderate or severe hepatic impairment [5].

The AUC of steady-state rasagiline (1 mg/day for 8 days) in subjects with moderate renal impairment was similar to that in healthy volunteers with normal renal function [5]. Therefore, dose adjustment is not necessary in those with mild or moderate renal impairment, but no data are available for patients with severe renal impairment. The AUC of the major metabolite l-aminoindan was increased 1.5-fold in those with moderate renal impairment compared with healthy subjects [5].

The pharmacokinetics of rasagiline are unaffected by gender and age in adults, although it has not been investigated in children and adolescents aged <18 years [5].

4 Drug Interactions

Concomitant administration of rasagiline with the CYP1A2 substrate theophylline in healthy volunteers did not affect the pharmacokinetics of either agent, while in vitro studies indicate that supratherapeutic concentrations of rasagiline do not inhibit CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 and CYP4A; therefore, it is unlikely that rasagiline would interact with substrates of these enzymes [5]. However, concomitant administration of rasagiline with the CYP1A2 inhibitor ciprofloxacin increased the AUC of rasagiline by 83 %, but did not affect the $t_{½}$ of rasagiline, indicating the need for rasagiline dose reduction when administered with CYP1A2 inhibitors [5]. Coadministration of rasagiline with levodopa/carbidopa in patients with Parkinson's disease did not affect the steady-state pharmacokinetics of rasagiline [5].

The concomitant use of an MAO inhibitor with an antidepressant (including tricyclic, tetracyclic or triazolopyridine antidepressants, selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors) may result in severe CNS toxicity associated with hyperpyrexia as part of the serotonin syndrome; occasionally this may be fatal [5]. Therefore, caution is required with the concomitant use of rasagiline and antidepressants from these classes, although the risk appears to be relatively low with this selective MAO-B inhibitor [4]. Concomitant use of rasagiline and some tricyclic antidepressants, trazodone or selective serotonin reuptake inhibitors was permitted in a small proportion of patients ($n = 256$) participating in the pivotal clinical trials of rasagiline without any reports of serotonin syndrome being noted [4, 24]. In addition, a retrospective cohort study did not identify any instances of serotonin syndrome in patients concomitantly taking rasagiline and antidepressants (see Sect. 6) [25].

Serotonin syndrome has also been reported with concomitant use of rasagiline and opioid analgesics such as meperidine (pethidine), tramadol, methadone and dextropropoxyphene; therefore, concomitant use of these drugs with rasagiline is contraindicated (Sect. 8) [5].

Concomitant use of rasagiline with the antitussive dextromethorphan has been reported to result in transient psychosis or bizarre behaviour; their combined use is contraindicated (Sect. 8) [5].

Concomitant use of rasagiline and other MAO inhibitors may lead to hypertensive crisis as a result of nonselective MAO inhibition; therefore, concomitant use of rasagiline with other MAO inhibitors [including St. John's wort (hypericum)] is contraindicated (Sect. 8) [5]. Higher than recommended dosages of rasagiline may result in reduced selectivity of the drug for MAO-B and an increased risk for hypertension [5]. While hypertensive reactions occur when sympathomimetics are used concomitantly with nonselective MAO inhibitors, these reactions are not expected with concomitant use of selective MAO-B inhibitors and sympathomimetics [5]. However, severe hypertension has been reported with concomitant use of rasagiline and sympathomimetic-containing ophthalmic drops. Therefore, caution is advised when using rasagiline concomitantly with sympathomimetic-containing products such as cold remedies, nasal, oral or ophthalmic decongestants [5].

Since tyramine is mainly metabolized by MAO-A in the intestines, the hypertensive reactions caused by high tyramine concentrations (via the release of noradrenaline from sympathetic neurons) observed with nonselective MAO inhibitor use in patients ingesting foods rich in tyramine (e.g. aged cheese), are not expected with the selective MAO-B inhibitor rasagiline. Tyramine challenge studies [26–28] and home BP monitoring in patients on unrestricted diets [29] have shown that, at the recommended therapeutic dosage of 0.5–1 mg/day, rasagiline is not associated with significant tyramine pressor responses, indicating that restrictions on dietary tyramine are unnecessary. However, there have been postmarketing reports of pressor responses to high dietary tyramine ingestion in patients taking rasagiline; therefore, it is recommended in the prescribing information that patients avoid tyramine-rich foods [5].

5 Therapeutic Efficacy

The therapeutic efficacy of oral rasagiline in the treatment of idiopathic Parkinson's disease has been assessed in five large ($n > 300$), pivotal, phase III or IV, randomized, double-blind, placebo-controlled, multicentre trials (see Table 1 for acronyms/definitions). The TEMPO [30, 31] and ADAGIO [32] trials assessed monotherapy with rasagiline in patients with early Parkinson's disease, the ANDANTE trial [33] assessed rasagiline as adjunctive therapy to a dopamine agonist in early Parkinson's disease, while the PRESTO [34] and LARGO [35] trials assessed rasagiline as adjunctive therapy to levodopa in patients with motor fluctuations. Four of these trials (TEMPO, ADAGIO, PRESTO and LARGO) have been reviewed in detail previously [9–11] and will only be briefly overviewed.

In addition to these large, pivotal, randomized, controlled trials, several other notable studies have assessed the efficacy of rasagiline as an adjunct to levodopa [36] or

Table 1 Acronyms and definitions for phase III/IV trials assessing rasagiline efficacy and/or tolerability in patients with Parkinson's disease

Acronym	Definition
ACTOR	ACceptabilité TOlérance Rasagiline
ADAGIO	Attenuation of Disease progression with Azilect GIven Once-daily
ANDANTE	Add oN to Dopamine AgoNists in the TrEatment of Parkinson's disease
LARGO	Lasting effect in Adjunct therapy with Rasagiline Given Once-daily
PRESTO	Parkinson's Rasagiline: Efficacy and Safety in the Treatment of 'Off'
STACCATO	Serotonin Toxicity Association with Concomitant Antidepressants and Rasagiline Treatment: Retrospective Study
TEMPO	TVP-1012 in Early Monotherapy for Parkinson's disease Outpatients

as both monotherapy and adjunctive therapy in community-based studies [37, 38].

5.1 Monotherapy in Early Parkinson's Disease

The TEMPO [30] and ADAGIO [32] trials each used a delayed-start design to evaluate potential disease-modifying effects of rasagiline monotherapy in patients with early Parkinson's disease (mean disease duration/group 0.36–1.13 years), as well as evaluating the symptomatic efficacy of rasagiline compared with placebo. Using the delayed-start design, a disease-modifying effect of the drug may be inferred as a possible explanation if the early-start group displays less disease progression than the delayed-start group. Enrolled patients in these trials displayed at least two of the three cardinal features of the disease (bradykinesia, resting tremor or rigidity) and had a disease severity of Hoehn and Yahr stage 3 or less [30, 32].

The TEMPO trial primarily assessed the symptomatic efficacy of rasagiline compared with placebo over 26 weeks [31]. The subsequent 26-week continuation phase used the delayed-start design to assess possible disease modification activity for rasagiline by comparing the change in total Unified Parkinson's Disease Rating Scale (UPDRS) score from baseline to week 52 [30]. Higher total UPDRS scores indicate more severe disease. Patients were randomized to treatment with rasagiline 1 mg/day ($n = 134$), rasagiline 2 mg/day ($n = 132$) or placebo ($n = 138$) for 26 weeks. Placebo recipients then switched to treatment with rasagiline 2 mg/day ($n = 130$) for 26 weeks (delayed-start group) while patients from the rasagiline 1 mg/day ($n = 122$) and 2 mg/day ($n = 119$) groups remained on their original treatment for an additional 26 weeks (early-start groups) [30, 31]. The primary efficacy endpoint in TEMPO was the change in total UPDRS score from baseline to week 26 (placebo-controlled phase) in the modified intent-to-treat (mITT) population (defined as all randomized patients who received at least one dose of study medication and had at least one post-baseline efficacy assessment) [30].

The ADAGIO trial primarily assessed the possible disease-modifying effects of rasagiline. Patients were randomized to rasagiline 1 mg/day ($n = 288$) or 2 mg/day ($n = 293$) for 72 weeks (early-start groups) or corresponding placebo for 36 weeks followed by rasagiline 1 mg/day ($n = 300$) or 2 mg/day ($n = 295$) for 36 weeks (delayed-start groups) [32]. ADAGIO used three hierarchical primary endpoints in the mITT population; that is, (1) superiority of early-start treatment versus placebo in the slope of the change in UPDRS score between weeks 12 and 36, (2) superiority of early-start treatment versus delayed-start treatment in the change in total UPDRS score from baseline to week 72 and (3) noninferiority of early-start treatment compared with delayed-start treatment with respect to the slope of the change from baseline in UPDRS score between weeks 48 and 72 [32]. All three endpoints had to be met to achieve a positive disease-modifying effect. The secondary endpoint of ADAGIO was the change from baseline to week 36 (placebo-controlled phase) in the total UPDRS score [32].

Rasagiline 1 or 2 mg/day was significantly ($p < 0.001$) more effective than placebo in preventing worsening of the total UPDRS score during the first half of both the TEMPO and ADAGIO studies (Table 2). During the first half of each study, the 1 and 2 mg/day dosages produced similar benefits with respect to placebo-corrected reductions in total UPDRS score [30, 32]. In a sub-study of patients in ADAGIO who had a baseline Parkinson's Fatigue Scale (PFS) score ($n = 1,076$; mean baseline PFS score of 2.20 units), placebo recipients had significantly greater deterioration in PFS score at week 36 (+0.17 units) than rasagiline 1 mg/day (+0.03 units; $p < 0.01$) or rasagiline 2 mg/day (−0.02 units; $p < 0.0001$) recipients [39].

In TEMPO, early-start rasagiline 2 mg/day, but not early-start rasagiline 1 mg/day ($p = 0.05$), was significantly ($p < 0.01$) more effective than delayed-start rasagiline 2 mg/day in limiting the adjusted mean change from baseline to 52 weeks in total UPDRS score (primary endpoint) (Table 2) [30]. Likewise, early-start rasagiline 2 mg/day, but not early-start 1 mg/day, for 1 year was superior

Table 2 Symptomatic efficacy and disease-modifying effects of monotherapy with oral rasagiline 1 or 2 mg once daily in the treatment of early Parkinson's disease. Results from the delayed-start TEMPO ($n = 371$) and ADAGIO ($n = 1,164$) trials

Study (duration)	Assessment	Treatment difference[a] (95 % CI)
TEMPO [30, 31] (26 + 26 weeks)	Change from BL to week 26 in total UPDRS score[b]	
	RAS 1 mg/day vs. PL	−4.20 (−5.66 to −2.73)***
	RAS 2 mg/day vs. PL	−3.56 (−5.04 to −2.08)***
	Change from BL to week 52 in total UPDRS score	
	Early-start RAS 1 mg/day vs. delayed-start RAS 2 mg/day	−1.82 (−3.64 to 0.01)
	Early-start RAS 2 mg/day vs. delayed-start RAS 2 mg/day	−2.29 (−4.11 to −0.48)**
ADAGIO [32] (36 + 36 weeks)	Rate of change in total UPDRS score/week for weeks 12–36[c]	
	RAS 1 mg/day vs. PL	−0.05 (0.08 to −0.01)**
	RAS 2 mg/day vs. PL	−0.07 (−0.11 to −0.04)***
	Change in total UPDRS score from BL to week 72[c]	
	Early-start RAS 1 mg/day vs. delayed-start RAS 1 mg/day	−1.68 (−3.15 to −0.21)*
	Early-start RAS 2 mg/day vs. delayed-start RAS 2 mg/day	0.36 (−0.99 to 1.70)
	Rate of change in total UPDRS score/week for weeks 48–72[c]	
	Early-start RAS 1 mg/day vs. delayed-start RAS 1 mg/day	0.00 (−0.04 to 0.04)[†]
	Early-start RAS 2 mg/day vs. delayed-start RAS 2 mg/day	0.03 (−0.01 to 0.06)[†]
	Change from BL to week 36 in total UPDRS score	
	RAS 1 mg/day vs. PL	−3.01 (−3.86 to −2.15)***
	RAS 2 mg/day vs. PL	−3.15 (−4.00 to −2.31)***

BL baseline, *PL* placebo, *RAS* rasagiline, *UPDRS* Unified Parkinson's Disease Rating Scale

* $p < 0.05$, ** $p \leq 0.01$, *** $p < 0.001$ for stated comparison; † Noninferiority achieved (upper limit of one-sided 95 % CI <0.15)

[a] Between-group comparisons of adjusted mean values for changes from BL using analysis of covariance

[b] Primary endpoint

[c] Co-primary hierarchical endpoints (all three required to be met to achieve a positive result for disease-modifying activity)

($p = 0.005$) to delayed-start rasagiline 2 mg/day with respect to UPDRS activities of daily living (ADL) subscale score. There were no significant between-group differences for the UPDRS motor and mental subscale scores, Hoehn and Yahr scale score or Schwab and England scale score [30].

Health-related quality of life (HR-QOL) was assessed in the TEMPO study using the 32-item Parkinson's Disease Quality of Life questionnaire (PDQUALIF) for which the score range was 0–128 with higher scores indicating worse HR-QOL; mean baseline scores in the rasagiline 1 and 2 mg/day and placebo groups were 27.1, 25.5 and 24.6, respectively [40]. In the first half of the TEMPO study ($n = 404$), the adjusted mean change from baseline to week 26 in PDQUALIF total score was significantly greater with rasagiline 1 (−0.36; $p = 0.01$) and 2 (−0.19; $p = 0.02$) mg/day than with placebo (+2.55) [40]. The differences between rasagiline and placebo were mainly due to significant differences in the self-image/sexuality subscore. However, at 1 year ($n = 266$), all three groups had worse PDQUALIF total scores than at baseline, with mean changes from baseline in the early-start rasagiline 1 and 2 mg/day and delayed-start 2 mg/day groups of +0.27, +2.28 and +0.54, respectively [40]. There were no significant between-group differences in change from baseline at 52 weeks.

After successfully completing the TEMPO study, patients ($n = 306$) entered an open-label extension in which they received rasagiline (initially 2 mg/day, but the dosage was later changed to 1 mg/day) plus other anti-parkinsonian medications, as necessary, for a mean overall treatment duration (double-blind plus open-label periods) of 3.5 (early-start patients) or 3.6 years (delayed-start patients) and a total observation period of 6.5 years [41]. At the end of the extension, the adjusted mean between-group difference in the change from baseline in total UPDRS score was 2.5 units ($p = 0.021$) in favour of the early-start group versus the delayed-start group. This represented a mean between-group difference of 16 % change from baseline ($p = 0.006$) [41].

In the ADAGIO study, the early-start rasagiline 1 mg/day dose met all three primary endpoints, suggesting a disease-modifying effect, but the early-start rasagiline 2 mg/day dose did not—there was no significant between-group difference (early-start vs. delayed-start) for change in total UPDRS score from baseline to week 72 (Table 2) [32].

5.2 Adjunctive Therapy

5.2.1 *Adjunct to Dopamine Agonists in Early Parkinson's Disease*

The phase IV ANDANTE trial assessed the efficacy of rasagiline 1 mg/day compared with placebo as add-on therapy for 18 weeks in patients with early Parkinson's disease who were not optimally controlled on dopamine agonist monotherapy [33]. Patients (328 enrolled and randomized) were required to have early idiopathic Parkinson's disease (Hoehn and Yahr stage 1–3) and to have received no more than 21 consecutive days of previous levodopa therapy and none in the previous 90 days. The mean age of enrolled patients was 62.6 years, 67.5 % were male, the mean duration of disease was 2.1 years and the mean total UPDRS score was 31.0 units. Eligible patients were on a stable dosage of ropinirole (≥6 mg/day) or pramipexole (≥1 mg/day) for at least 30 days (but not for more than 5 years) before entry and were not optimally controlled [33]. Concomitant therapy with amantadine and anticholinergics at stable dosages was permitted. The primary efficacy endpoint was the change from baseline to week 18 in the UPDRS total score [sum of parts I (mentation, behaviour and mood), II (ADL) and III (motor)] in the mITT population ($n = 321$). Secondary endpoints included changes from baseline in UPDRS motor subscale score, UPDRS ADL subscale score, Clinical Global Impression of Improvement (CGI-I) score, Clinical Global Impression of Severity (CGI-S) score and Patient Global Impression of Improvement (PGI-I) score.

After 18 weeks of adjunctive therapy, rasagiline 1 mg/day produced significantly greater improvement than placebo in UPDRS total score (primary endpoint) (Table 3) [33]. The least squares (LS) mean between-group difference (rasagiline minus placebo) was −2.4 units (95 % CI −4.3 to −0.5; $p = 0.012$). Rasagiline also improved the UPDRS motor subscale score significantly more than placebo, with a LS mean between-group difference of −1.8 units (95 % CI −3.1 to −0.5; $p = 0.007$), but there were no significant between-group differences for the UPDRS ADL subscale score, CGI-I score, CGI-S score or PGI-I score [33]. Within the UPDRS motor subscale, significantly greater improvements were observed with rasagiline than with placebo for bradykinesia ($p = 0.002$), tremor ($p = 0.005$) and postural instability/gait ($p = 0.031$), but not for rigidity. There were no significant differences between the groups in Scales for Outcomes in Parkinson's Disease-Cognition scores or the 39-item Parkinson's Disease Questionnaire (PDQ-39) [33].

5.2.2 *Adjunct to Levodopa in Patients with Motor Fluctuations*

The 18-week LARGO trial ($n = 687$ randomized) [35] and the 26-week PRESTO trial ($n = 472$ randomized) [34] each assessed the efficacy of oral rasagiline 0.5 and/or 1 mg/day as adjunctive therapy to levodopa in patients with idiopathic Parkinson's disease and experiencing motor fluctuations. The mean durations of Parkinson's disease were 8.7, 9.2 and 8.8 years in the rasagiline, entacapone and placebo groups, respectively, in the LARGO trial and 9.3, 8.8 and 9.7 years in the rasagiline 0.5 mg/day, rasagiline 1 mg/day and placebo groups, respectively, in the PRESTO trial. The LARGO trial also compared the efficacy of the catecholamine-*O*-methyltransferase (COMT) inhibitor entacapone [200 mg administered with each levodopa dose (mean 4.8 doses/day at baseline)] with that of placebo [35]. Patients had to be experiencing ≥1 h [35] or ≥2.5 h [34] of off-time (periods of poor or absent motor function) each day at baseline and be on an optimized stable dosage of levodopa administered ≥3 times daily, not including a bedtime dose, and ≤8 times daily. The primary endpoint in each trial was the change from baseline in mean total daily off-time as recorded in patients' 24-h diaries [34, 35].

Table 3 Efficacy of oral, once-daily rasagiline as adjunctive therapy to dopamine agonists (ropinirole or pramipexole) in patients with early idiopathic Parkinson's disease. Results of the 18-week, randomized, double-blind, placebo-controlled ANDANTE trial [33]

Treatment	No. of pts (mITT)	Mean score at week 18 [baseline value]			'Improved'[a] rating at week 18 (% of pts)	
		UPDRS total score[b]	UPDRS ADL subscale score	UPDRS motor subscale score	Site-rated CGI-I	Pt-rated CGI-I
RAS 1 mg/day	159	28.1* [32.1]	8.3 [8.6]	18.4** [22.2]	44.7	40.3
PL	162	28.9 [29.8]	8.3 [7.9]	19.1 [20.4]	39.5	40.1

ADL activities of daily living, *CGI-I* Clinician Global Impression of Improvement, *mITT* modified intent-to-treat, *PL* placebo, *pt(s)* patient(s), *RAS* rasagiline, *UPDRS* Unified Parkinson's Disease Rating Scale

* $p < 0.05$, ** $p < 0.01$ vs. PL

[a] Combined 'very much', 'much' and 'minimally' improved categories

[b] Primary efficacy endpoint

Table 4 Efficacy of oral, once-daily rasagiline as adjunctive therapy to levodopa in patients with idiopathic Parkinson's disease and motor fluctuations. Results of randomized, double-blind, placebo-controlled, multinational trials

Study (duration)	Adjunctive therapy	No. of pts (mITT)	Adjusted mean change from baseline in total daily off-time (h)[a] [baseline value]	Between group difference [adjunctive therapy vs. PL] (95 % CI)
LARGO [35] (18 weeks)	RAS 1 mg/day	222	−1.18 [5.58]	−0.78 (−1.18 to −0.39)***
	ENT 200 mg	218	−1.20 [5.60]	−0.80 (−1.20 to −0.41)***
	PL	218	−0.40 [5.55]	
PRESTO [34]	RAS 0.5 mg/day	164	−1.41 [6.0]	−0.49 (−0.91 to −0.08)*
(26 weeks)	RAS 1 mg/day	149	−1.85 [6.3]	−0.94 (−1.36 to −0.51)**
	PL	159	−0.91 [6.0]	

ENT entacapone, *mITT* modified intent-to-treat, *off-time* periods of the day with poor or absent motor function, *PL* placebo, *pts* patients, *RAS* rasagiline

* $p < 0.05$, ** $p < 0.001$, *** $p \leq 0.0001$ vs. PL

[a] Primary endpoint

In the LARGO study, both rasagiline 1 mg/day and entacapone were significantly ($p \leq 0.0001$) more effective than placebo in reducing from baseline the mean total daily off-time (Table 4) [35]. Both active drugs were significantly ($p < 0.001$ to $p < 0.0001$) more effective than placebo for a number of secondary endpoints including improvements in daily on-time (periods of improved motor function) without troublesome dyskinesia, responder rate, CGI-I score, total UPDRS score, UPDRS motor subscale score during on-time and UPDRS ADL subscale score during off-time [35].

A substudy of LARGO assessing motor function in the practically defined OFF state (the state prior to the first morning drug dose following a drug-free night; at least 12 h after the last dose of medication), found that the UPDRS motor OFF score change from baseline in the rasagiline group (−4.38 units), but not in the entacapone group (−1.95 units), was significantly ($p < 0.05$) improved over that in the placebo group (+1.27 units) indicating a longer duration of effect for rasagiline [42]. The equivalent change in UPDRS ADL OFF score was not significantly improved over that with placebo (−0.05 units) for either rasagiline (−1.89 units) or entacapone (−1.09 units) [42].

Both rasagiline 0.5 and 1 mg/day were significantly ($p < 0.05$ and $p < 0.001$, respectively) more effective than placebo in reducing mean total daily off-time in the PRESTO trial (Table 4) [34]. The major proportion of the observed total reduction in each group was achieved by week 6 and was sustained through to the end of the study at week 26. Both doses of rasagiline were significantly ($p < 0.01$ to $p \leq 0.001$) more effective than placebo for the secondary endpoints of CGI-I score, UPDRS ADL subscale score during off-time and UPDRS motor subscale score during on-time, but not for HR-QOL as assessed with the PDQUALIF scale [34]. Rasagiline 1 mg/day was also significantly more effective ($p < 0.05$ to $p < 0.01$) than placebo for the exploratory endpoints of change from baseline in daily on-time without dyskinesias, investigator-rated Schwab and England ADL score during off-time and the UPDRS scores for dyskinesia, rigidity, tremor and dyskinesia [34].

In a randomized, double-blind, placebo-controlled, multicentre study in Chinese patients ($n = 244$) treated with levodopa (mean of 515–521 mg/day) for a mean duration of 3.9–4.1 years, adjunctive rasagiline 1 mg/day for 12 weeks significantly ($p < 0.001$) reduced the motor fluctuation off-time while awake (co-primary endpoint) by 1.06 h more than placebo and significantly ($p < 0.001$) increased the on-time while awake (co-primary endpoint) by 0.87 h more than placebo [36]. Compared with placebo, adjunctive rasagiline significantly improved the symptoms of tremor ($p = 0.002$), rigidity ($p = 0.002$) and bradykinesia ($p = 0.005$), but not postural instability, at week 12 [36].

5.3 Community-Based Studies

A 12-week noncomparative study (named 'LEGATO') compared the time of onset of antiparkinsonian efficacy, using the UPDRS bradykinesia subscale score (primary endpoint), after the initiation of rasagiline therapy in patients who were (adjunctive therapy group; $n = 147$) or were not (monotherapy group; $n = 122$) taking other concomitant dopaminergic medications [37]. Rasagiline monotherapy consisted of 1 mg/day, while adjunctive therapy was initiated at 0.5 mg/day with the option to increase to 1 mg/day. The majority reduction (improvement) in bradykinesia score occurred similarly in the first 2 weeks in both the monotherapy and adjunctive therapy groups [approximately −2.3 units in each group (estimated from a graph)] after which time the improvements were generally sustained through to week 12. The improvement

at week 1 was −1.23 units in the monotherapy group and −1.35 units in the adjunctive therapy group [37]. Similar patterns of improvement were seen with investigator-rated and patient-rated CGI-I scores.

Another 4-week, noncomparative study assessed the early effect of rasagiline therapy (dosage not stated) on motor symptoms (UPDRS part III score) in therapy-naive patients ($n = 26$) or patients inadequately controlled on levodopa or dopamine agonists ($n = 76$) [38]. The mean change from baseline in UPDRS motor subscale score was significant at week 1 (−6.7 units; $p < 0.001$) and week 4 (−8.9 units; $p < 0.001$) with no significant difference between the monotherapy and adjunctive therapy groups. Similarly, the mean change from baseline in Hoehn and Yahr scale score was −0.40 at week 1 ($p < 0.0001$) and −0.67 at week 4 ($p < 0.0001$) [38].

A postmarketing surveillance (observational) study conducted in Germany assessed the efficacy of rasagiline 1 mg once daily as monotherapy ($n = 209$) or in combination with other antiparkinsonian medications ($n = 545$) for ≈4 months (mean of 118 days) using the UPDRS fluctuations subscale (4 items) score, the 13-item Columbia University Rating Scale (CURS) and assessments of daily off-time recorded in patient diaries [43]. Over the treatment period, there were significant ($p < 0.001$) reductions (improvements) from baseline in CURS total score in both the monotherapy (−4.1 points) and combination therapy groups (−4.6 points). In patients on combination therapy, rasagiline significantly ($p < 0.05$) reduced from baseline each of the UPDRS fluctuations subscale component scores and significantly ($p < 0.001$) reduced the median daily off-time from 120 min at baseline to 45 min at ≈4 months [43]. All 8 subscale scores of the PDQ-39 were significantly ($p < 0.001$) improved from baseline at the final evaluation in both the monotherapy and combination therapy groups, indicating marked improvement in patients' HR-QOL [43].

6 Tolerability

Data on the tolerability of approved dosages of oral rasagiline (1 or 0.5 mg/day) in the treatment of patients with idiopathic Parkinson's disease derive from the studies discussed in Sect. 5, as well as other studies assessing the safety and tolerability of rasagiline [25, 44–47].

In rasagiline monotherapy trials (TEMPO and ADAGIO), there were no significant differences between the rasagiline 1 mg/day group and the placebo group with respect to the incidence of any adverse events [30, 32].

In TEMPO, the most common adverse events with rasagiline 1 mg/day at the 1-year assessment were infection (13.1 % of patients), back pain (6.6 %), headache (4.9 %), unintentional injury (3.3 %), dizziness (3.3 %), nausea (3.3 %), arthralgia (2.5 %) and asthenia (2.5 %) [30]. Serious adverse events occurred in 4 of 122 patients (3.3 %) taking rasagiline 1 mg/day in each of the 6-month treatment periods (not further detailed) [30]. At the original 6-month assessment in TEMPO, there were 6 serious adverse events among 134 patients in the rasagiline 1 mg/day group and 4 among 138 patients in the placebo group; all serious adverse events were hospitalizations for a variety of reasons [31].

In ADAGIO, the most common adverse events with rasagiline 1 mg/day for 72 weeks (early start) were back pain (7.7 %), nasopharyngitis (5.1 %), arthralgia (5.1 %), headache (4.8 %), falls (4.8 %), nausea/vomiting (2.6 %), hypertension (2.6 %), orthostatic hypotension (1.8 %), musculoskeletal pain (1.8 %) and somnolence (1.5 %) [32].

There were five newly diagnosed neoplasms (one colon cancer, two squamous cell carcinoma of the skin, one basal cell carcinoma and one melanoma) in the rasagiline groups (1 or 2 mg/day group not stated) after treatment for 1 year in the TEMPO study [30] and one patient on rasagiline 1 mg/day with melanoma after treatment for 72 weeks in the ADAGIO study [32].

Rasagiline 1 mg/day was generally well tolerated as adjunctive therapy to dopamine agonists in the ANDANTE trial [33]. Most adverse events were mild or moderate in severity. Serious adverse events were experienced by 4.9 % of rasagiline 1 mg/day recipients ($n = 162$) and 3 % of placebo recipients ($n = 164$) [none were considered related to therapy], while 8 % of rasagiline recipients and 4.3 % of placebo recipients discontinued therapy as a result of an adverse event [33]. The most common treatment-emergent adverse events with rasagiline were dizziness (7.4 vs. 6.1 % with placebo), peripheral oedema (7.4 vs. 4.3 %), somnolence (6.8 vs. 6.7 %), nausea (6.2 vs. 4.3 %), headache (6.2 vs. 4.3 %), falls (5.6 vs. 1.2 %) and tremor (4.3 vs. 6.1 %) [33].

Rasagiline was also generally well tolerated as adjunctive therapy to levodopa in the LARGO and PRESTO studies [34, 35]. There were no significant differences between the rasagiline, entacapone and placebo groups in LARGO with respect to the incidence of adverse events, laboratory abnormalities or vital signs including BP and heart rate [35]. The most common adverse events with rasagiline 1 mg/day were dyskinesia (5 %), nausea (3 %), depression (3 %), dizziness (3 %), sleep disorder (3 %), postural hypotension (2 %), peripheral oedema (2 %), anxiety (2 %), dry mouth (2 %) and hallucinations (2 %). Numerically fewer rasagiline than placebo or entacapone recipients discontinued therapy overall (10 vs. 15 and 13 %, respectively) or as a result of adverse events (7 vs. 11 and 16 patients, respectively) [35]. Serious adverse

events occurred in 12 patients (5.2 %) on rasagiline compared with 17 patients (7.4 %) on placebo in the LARGO trial. The incidence of adverse events did not appear to be affected by patient age (<70 or ≥70 years).

In the PRESTO trial, the only adverse events occurring significantly more frequently with rasagiline 1 mg/day than with placebo were weight loss (9.4 vs. 2.5 %; $p = 0.02$), vomiting (6.7 vs. 1.3 %; $p = 0.03$) and anorexia (5.4 vs. 0.6; $p = 0.04$), while the incidence of balance difficulty was significantly higher with rasagiline 0.5 mg/day (but not 1 mg/day) than with placebo (5.5 vs. 0.6; $p = 0.03$) [34]. Dyskinesias were more common with rasagiline (0.5 and 1 mg/day recipients combined) than with placebo (18 vs. 10 %; $p = 0.03$). The incidence and nature of serious adverse events with rasagiline were similar to those with placebo. Newly diagnosed melanomas occurred in one patient on rasagiline 0.5 mg/day and two on rasagiline 1 mg/day (none on placebo). Rasagiline did not have adverse effects on BP or heart rate [34].

A combined analysis of the TEMPO and PRESTO trials found no difference in total adverse events between patients aged <70 years and those aged ≥70 years [48].

In the German postmarketing surveillance study, 2 % of rasagiline 1 mg/day monotherapy recipients and 8 % of those on combination therapy experienced adverse events, most commonly nausea, dizziness, headache and vomiting [43]. One percent of monotherapy recipients and 5 % of combination therapy patients withdrew because of lack of tolerability. The investigators rated the overall tolerability as good or very good in 97 % of monotherapy patients and 90 % of combination therapy patients. The tolerability of rasagiline did not appear to be affected by patient age (<70 or ≥70 years) [43].

A thorough QT/QTc study demonstrated that rasagiline 1 mg/day, as well as rasagiline at supratherapeutic dosages of 2 and 6 mg/day, did not affect cardiac repolarization (see Sect. 2) [20].

A meta-analysis of clinical trials and observational studies of rasagiline in the treatment of Parkinson's disease concluded that, despite a large number of adverse events reported with rasagiline, the incidences of adverse events with rasagiline did not differ significantly from those with placebo [45].

The tolerability of rasagiline 1 mg/day ($n = 53$) was directly compared with that of pramipexole 1.5 mg/day ($n = 56$) as monotherapy in patients with early Parkinson's disease in the 15-week, randomized, double-blind, multicentre ACTOR study (see Table 1 for definition) [46], focusing on clinically important adverse events (serious events, patient-rated moderate-to-severe events, or events leading to withdrawal or dose reduction). The incidence of clinically important adverse events with rasagiline (32.1 %) was noninferior (but not superior) to that with pramipexole (44.6 %) [treatment difference −12.6 %; 95 % CI −27.8 to 2.6 %] using a predefined noninferiority boundary of 10 %. Serious reactions consisted of serotonin syndrome in one patient taking rasagiline plus fluoxetine and ovarian cancer (considered unrelated to therapy) in one patient taking pramipexole [46]. Of physician-reported adverse events, nausea/vomiting and sleep disorders were significantly ($p < 0.05$) more frequent with pramipexole than rasagiline, while rash was significantly ($p < 0.05$) more frequent with rasagiline. Of patient-reported adverse events, digestive difficulties ($p < 0.05$) and nausea/vomiting ($p < 0.01$) were significantly more frequent with pramipexole, while conjunctivitis was significantly ($p < 0.01$) more frequent with rasagiline [46]. In the ACTOR trial, there were no significant differences between the treatments in clinical effectiveness, as measured by the PGI-I and CGI-I scales, or in HR-QOL, as assessed using the EuroQOL (EQ) five dimension questionnaire and the EQ visual analogue scale [46].

An indirect comparison of randomized, blinded, placebo-controlled trials of rasagiline, pramipexole and ropinirole in patients with early Parkinson's disease suggested that rasagiline may be associated with fewer adverse events and lower drop-out rates than ropinirole or pramipexole [47].

An analysis of the French PharmacoVigilance Database, comparing adverse drug reaction reports in which the suspected drug(s) included rasagiline ($n = 132$), selegiline ($n = 199$), ropinirole ($n = 432$) or levodopa ($n = 1{,}851$) found that rasagiline had numerically higher incidences than selegiline of renal adverse events (6 vs. 1 %), musculoskeletal adverse events (11 vs. 2 %), impulse control disorders (4 vs. 1 %) and headache (5 vs. 1 % for all other drugs), but numerically lower incidences of orthostatic hypotension (1 vs. 9 %), confusion, hallucination and agitation (specific incidences with rasagiline not given) [reported as an abstract] [44]. Rasagiline had numerically higher incidences than ropinirole of renal adverse events (6 vs. 3 %) and musculoskeletal adverse events (11 vs. 2 %), but numerically lower incidences of impulse control disorder (4 vs. 12 %) and somnolence (4 vs. 16 %) [44].

While concomitant use of rasagiline and antidepressants has been reported to result in potentially life-threatening serotonin syndrome in some patients [5], a multicentre, phase IV, retrospective cohort study (ClinicalTrials.gov identifier, NCT00955604) did not identify any instances of serotonin toxicity (reported as an abstract) [25]. This study, known as STACCATO (see Table 1 for definition), reviewed the case histories of patients receiving rasagiline with ($n = 471$) or without ($n = 511$) antidepressants, or patients receiving antidepressants with dopaminergic therapy not including rasagiline or selegiline ($n = 525$), who had at least one hospitalization or emergency room visit

[25]. The results of the STACCATO study are in accord with results from the clinical trial programme for rasagiline in which a small proportion of patients were permitted to take concomitant antidepressants without any adverse sequelae (see Sect. 4).

7 Pharmacoeconomic Considerations

Three fully published, modelled, cost-utility analyses have assessed the cost effectiveness of therapy with oral rasagiline 1 mg/day in patients with early [49, 50] or advanced [51] Parkinson's disease (see Table 5). All three studies used a Markov health-state transition model over a 2-year [51] or 5-year [49, 50] time horizon from a US managed care perspective [50], a UK healthcare payer perspective [49] or a societal perspective in Finland [51].

In the US analysis comparing rasagiline with approved dopamine agonists or levodopa as first-line therapy in patients with early Parkinson's disease, rasagiline was dominant (more effective and less costly) over pramipexole, extended-release ropinirole and levodopa, and, when compared with the least expensive agent, generic ropinirole, had an incremental cost-effectiveness ratio (ICER) [$US25,939 per quality-adjusted life-year (QALY) gained; 2010 values] that was well within the commonly accepted willingness-to-pay threshold of $US50,000/QALY (Table 5) [50]. The cost effectiveness of rasagiline was robust to variations in key parameters in one-way sensitivity analysis.

The UK analysis, which, like the US analysis, only considered direct costs, also found rasagiline to be dominant over pramipexole as first-line monotherapy in early Parkinson's disease (Table 5) [49]. In the base-case scenario of the model over a 5-year time horizon, initiating therapy with rasagiline 1 mg/day resulted in an 18 % reduction in direct medical costs and a gain of 0.19 QALYs compared with initiating therapy with pramipexole 2.5 mg/day. Dominance of rasagiline was maintained in sensitivity analyses which included varying the dosage of pramipexole from 1.5 to 3 mg/day and the utility values (QALYs) by −20 to +10 % [49].

Both rasagiline and entacapone as adjunctive therapy to levodopa dominated standard care (levodopa alone) in the cost-utility analysis conducted in Finland from a societal perspective, which included both direct and indirect costs (Table 5) [51]. Rasagiline was associated with a mean of 0.13 additional QALYs and a mean of 5.2 additional months with ≤25 % off-time/day compared with standard care over the 2-year time horizon. The respective values for

Table 5 Cost effectiveness of oral rasagiline 1 mg once daily in the treatment of Parkinson's disease. Results for base-case scenarios from fully published, modelled, cost-utility analyses

	Farkouh et al. [50]	Haycox et al. [49]	Hudry et al. [51]
Country	US	UK	Finland
Model	Markov	Markov	Markov
Year of costing	2010	2007	2004
Perspective	Managed care payer	Healthcare payer	Societal
Time horizon	5 years	5 years	2 years
Annual discounting (%)			
Outcomes	3	1.5	5
Costs	3	6	5
RAS clinical data source	TEMPO trial	TEMPO trial	LARGO trial
Disease state	Early PD	Early PD	Advanced PD
Modelled treatment	Monotherapy	Monotherapy	Adjunct to LD
Comparison(s)	RAS vs. ROP XL	RAS vs. PRA	RAS + LD vs. LD
	RAS vs. PRA		ENT + LD vs. LD
	RAS vs. LD		
	RAS vs. ROP		
Cost effectiveness[a]	RAS dominated ROP XL	RAS dominated PRA	RAS + LD dominated LD
	RAS dominated PRA		ENT + LD dominated LD
	RAS dominated LD		
	RAS ICER $US25,939/QALY gained vs. ROP		

ENT entacapone, *ICER* incremental cost-effectiveness ratio, *LD* levodopa, *PD* Parkinson's disease, *PRA* pramipexole, *QALY* quality-adjusted life-year, *RAS* rasagiline, *ROP* generic ropinirole, *ROP XL* extended-release ropinirole

[a] A dominant strategy is one that is more effective and less costly than the alternative

entacapone were 0.12 QALYs and 5.1 months. The total mean cost savings compared with standard care over 2 years were €930 for rasagiline and €830 for entacapone (2004 values) [51]. In a secondary analysis performed from a third-party payer perspective, which included only direct costs (about one-half of total costs), the ICER for rasagiline was €17,800/QALY gained and that for entacapone was €18,600/QALY gained compared with standard care [51]. Drug costs for each agent comprised approximately 30 % of total direct costs.

The cost-utility analyses of rasagiline therapy were generally well conducted, in that relevant costs were included, sources of data were clearly stated, clinical outcomes were relevant, appropriate discounting was applied and sensitivity analyses were conducted. However, as with all pharmacoeconomic analyses, there are study limitations. For example, even if the base-case results of cost-effectiveness analyses are robust to reasonable changes in key input variables in sensitivity analyses, they may not be applicable to other geographical regions because of differences in healthcare systems, unit costs and other factors. In addition, modelled analyses project longer-term costs and outcomes from shorter-term clinical trial data, typically using a variety of sources and extrapolating clinical trial results to the general population of interest. The selection of key studies and other data sources used to populate economic models, along with other factors such as the study perspective and specific costs included, can have an important impact on results of these analyses.

8 Dosage and Administration

Oral rasagiline (as the mesylate) is indicated in the US for use in all stages of Parkinson's disease, either as monotherapy or as an adjunct to other antiparkinsonian drugs [5]. The recommended dosage of rasagiline is 1 mg once daily in patients not taking levodopa and 0.5 mg once daily in patients taking levodopa, with or without other antiparkinsonian medications. In patients taking levodopa, the dose of rasagiline may be increased to 1 mg/day, if the 0.5 mg/day dose is tolerated and the clinical response is not sufficient. When rasagiline is used in patients taking levodopa, a reduction in the dose of levodopa may be considered, depending upon the clinical response. Owing to the risk of hypertension, the recommended dose of rasagiline should not be exceeded (see Sect. 4) [5].

Rasagiline is also approved in the EU as monotherapy or as adjunct therapy to levodopa in Parkinson's disease patients with end of dose fluctuations; 1 mg once daily is the recommended dose with or without levodopa [8].

Rasagiline is contraindicated in patients taking meperidine, tramadol, methadone, dextropropoxyphene, other MAO inhibitors, St. John's wort, cyclobenzaprine or dextromethorphan (see Sect. 4) [5]. In patients taking concomitant ciprofloxacin (see Sect. 4) or with mild hepatic impairment (see Sect. 4), the rasagiline dosage should not exceed 0.5 mg/day [5]. Rasagiline should not be used in patients with moderate or severe hepatic impairment.

Local prescribing information should be consulted for detailed information, including contraindications, precautions, drug interactions and use in special patient populations.

9 Place of Rasagiline in the Management of Parkinson's Disease

The choice of dopaminergic agent for the initial treatment of the motor symptoms of Parkinson's disease usually reflects a compromise between effectiveness and tolerability. Levodopa is the most effective symptomatic agent, but after some years of use is associated with disabling and difficult-to-treat motor complications, such as fluctuations, dyskinesias and dystonias [52]. Therefore, for patients requiring dopaminergic therapy, many physicians prefer to delay the introduction of levodopa therapy as long as possible, initially using dopamine agonists or MAO-B inhibitors instead, although all patients will eventually require levodopa [2]. MAO-B inhibitors provide more modest control of motor symptoms than levodopa or dopamine agonists [1], but may be used as monotherapy in patients with early Parkinson's disease and mild motor symptoms [2]. Since they have a different mechanism of action to other dopaminergic therapies, MAO-B inhibitors can be used as adjunctive therapy to dopamine agonists and levodopa, as well as other antiparkinsonian medications, in early and more advanced disease. Rasagiline has benefits over the first-generation MAO-B inhibitor selegiline, in that it is approximately tenfold more potent than selegiline in inhibiting MAO-B and is not metabolized to amphetamine derivatives, and thereby avoids the adverse cardiac and neurological effects seen with selegiline (Sect. 2).

In pivotal, randomized, double-blind, placebo-controlled, multicentre trials, monotherapy with rasagiline at the approved dosage of 1 mg/day for 36 weeks in patients with early Parkinson's disease significantly ($p < 0.001$) improved patients' symptoms compared with placebo, as measured by reductions in total UPDRS score (Sect. 5.1).

Each of the monotherapy studies assessed the effects of rasagiline on disease progression in early Parkinson's disease, but conflicting results have made interpretation of the

results difficult. The ADAGIO trial, using a delayed-start design, found that early-start rasagiline 1 mg/day was significantly more effective than delayed-start rasagiline 1 mg/day, suggesting that rasagiline had a disease-modifying effect. However, at the higher dosage of 2 mg/day, early-start rasagiline was not significantly more effective than delayed-start rasagiline, casting doubt on the results with rasagiline 1 mg/day. In the TEMPO trial, early-start rasagiline 2 mg/day was significantly more effective than delayed-start rasagiline 2 mg/day, again suggesting a disease-modifying effect, but early-start treatment with the approved dosage of rasagiline 1 mg/day, followed by rasagiline 2 mg/day, was not significantly more effective than delayed-start rasagiline 2 mg/day, suggesting a lack of disease-modifying effect with the approved dosage, although the statistical analysis was borderline significant ($p = 0.05$). Unfortunately, there was no 1 mg/day delayed-start treatment arm. Combined assessment of all patients in the extension of the TEMPO study found that the advantages seen in the early-start group over the delayed-start group at 1 year were sustained over several years of continued treatment with rasagiline (Sect. 5.1), indicating a need for further assessment of the drug's potential long-term disease-modifying effects.

Adjunctive rasagiline 1 mg/day for 18 weeks was superior to placebo in improving symptom scores, predominantly for motor symptoms, in patients with early Parkinson's disease who were not optimally controlled by dopamine agonists (pramipexole or ropinirole), with or without amantadine or anticholinergics (Sect. 5.2.1).

In patients with more advanced disease treated with levodopa and experiencing motor fluctuations, adjunctive therapy with rasagiline 0.5 or 1 mg/day for 18–26 weeks significantly reduced the daily off-time compared with placebo (Sect. 5.2.2). The differences between the rasagiline 0.5 and 1 mg/day treatment arms were stated to not be statistically significant "for most end points" [34].

The efficacy of rasagiline as both monotherapy or as adjunctive therapy to dopamine agonists or levodopa observed in randomized clinical trials have been confirmed in community-based and real-world studies (Sect. 5.3), including improvements in HR-QOL in a postmarketing surveillance study, which were not often seen in clinical trials.

Rasagiline, either as monotherapy or adjunctive therapy with dopamine agonists or levodopa, was generally well tolerated (Sect. 6). In monotherapy trials, the incidence of adverse events with rasagiline 1 mg/day did not differ significantly from that with placebo. In a direct monotherapy comparison in patients with early Parkinson's disease, the incidence of clinically important adverse events with rasagiline was noninferior to that with pramipexole, although rasagiline recipients had fewer gastrointestinal or sleep disorder symptoms.

The prescribing information warns of a risk for hypertension when rasagiline is used as an adjunct to levodopa, however, when given as adjunctive therapy to levodopa in controlled clinical trials, rasagiline 1 mg/day did not show any adverse effects on BP or heart rate.

Rasagiline was associated with a higher incidence of dyskinesias than placebo when used as an adjunct to levodopa in one trial; lowering the levodopa dose is expected to mitigate this effect [5].

Instances of newly diagnosed melanoma or other skin cancers were noted in some clinical trials of rasagiline. Patients with Parkinson's disease have a higher risk of melanoma than the general population, but it is not known whether this is related to the disease or other factors, such as drug therapy [5].

Despite a limited number of patients in the clinical trials of rasagiline taking concomitant antidepressants, there was only one reported incidence of serotonin syndrome (in the ACTOR trial) and the STACCATO study failed to find reports of the syndrome resulting from concomitant use of rasagiline and antidepressants. Overall, the risk of serotonin syndrome with concomitant use of these agents appears to be low. Nonetheless, concomitant use of rasagiline and antidepressants is not recommended in the prescribing information [5].

Rasagiline was predicted to be cost effective, both as monotherapy in early Parkinson's disease or as adjunctive therapy in patients with more advanced disease (Sect. 7). Analyses of patients receiving monotherapy predicted that rasagiline would be more effective and less costly than levodopa or branded dopamine agonists, and would be cost effective compared with low-cost generic ropinirole. However, cost-effectiveness comparisons with low-cost alternative MAO inhibitors, such as generic selegiline, would be of interest. Adjunctive therapy with rasagiline in patients treated with levodopa was predicted to be more effective and less costly than treatment with levodopa alone when considering both direct and indirect costs, and to also be cost effective when considering only direct costs.

In conclusion, rasagiline is an oral, second-generation, selective, irreversible MAO-B inhibitor that is effective in the symptomatic treatment of Parkinson's disease, both as monotherapy in early disease or as an adjunct to dopamine agonists or levodopa in early or advanced disease. Rasagiline was generally well tolerated, with several pivotal clinical trials showing rasagiline to have a tolerability profile similar to that of placebo. Rasagiline was predicted to be cost effective in the treatment of both early and advanced Parkinson's disease, most often dominating alternative therapies. Therefore, rasagiline is a valuable

therapeutic option for use in all stages of Parkinson's disease.

Data selection sources: Relevant medical literature (including published and unpublished data) on rasagiline was identified by searching databases including MEDLINE (from 1946) and EMBASE (from 1996) [searches last updated 24 September 2014], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Rasagiline, Parkinson's disease, Parkinson.
Study selection: Studies in patients with Parkinson's disease who received rasagiline. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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