National PBM Drug Monograph

Rasagiline (Azilect®)

June 2007

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

The purpose of VACO PBM-SHG drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:

Rasagiline is an MAO type B inhibitor which is approved for monotherapy and adjunct therapy in the treatment of Parkinson's disease.

The TEMPO trial assessed the efficacy of monotherapy with rasagiline in patients who had symptoms of Parkinson disease, however had not required any dopaminergic therapy such as levodopa, dopamine agonist, selegiline or amantadine. Compared with patients on placebo, the condition of patients on rasagiline showed significantly less worsening on a rating scale that measures the ability to perform mental and motor tasks as well as daily living activities

The PRESTO study also assessed the effectiveness of rasagiline as adjunctive therapy for Parkinson disease. Rasagiline demonstrated improvement in motor fluctuations and Parkinson disease symptoms in levodopa-treated Parkinson disease patients

Additionally, the LARGO study assessed the effectiveness of rasagiline as adjunct therapy to levodopa in comparison with entacapone. Once daily dosing of rasagiline demonstrated a reduction in daily "off" time and improved symptoms of Parkinson disease in levodopa treated patient with motor fluctuations. The effect seen with rasagiline 1mg daily was similar to the group that received entacapone.

The adverse event profile of rasagiline is similar to that seen with dopamine excess; in patients on concurrent levodopa therapy these effects may be decreased with a decrease of the levodopa dose.

There is incomplete information regarding the selectivity of rasagiline in regards to MAO function. Drug interactions with agents metabolized by this system; SSRI, triptans, dobutamine, are not known. There have been some Phase III trials that allowed concomitant SSRI therapy with no documented increase in adverse events.

There is a theoretical risk of hypertensive crisis in patients receiving rasagiline who also consume tyramine-rich foods, beverages (such as cheese and red wine) or dietary supplements or amines contained in many cough/cold medications. In clinical trials of 1 mg or less this adverse event has not been documented.

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating for possible addition of rasagiline to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics[1-3]

The exact mechanism of action for rasagiline is unknown. The mechanism is believed to be related to its MAO-B inhibitory activity[3], which causes an increase in extracellular levels of dopamine in the striatum.

The elevated dopamine level and subsequent increased dopaminergic activity are likely to mediate rasagiline's beneficial effects seen in models of dopaminergic motor dysfunction. However, there have not been adequate studies to establish whether rasagiline is selective for MAO type B (MAO-B) in humans.

Rasagiline is rapidly absorbed, reaching peak plasma concentration (Cmax) in approximately 1 hour. The absolute bioavailability of rasagiline is about 36%. Rasagiline can be administered with or without food. Rasagiline undergoes almost complete biotransformation in the liver prior to excretion. This metabolism proceeds through two main pathways: N-dealkylation and/or hydroxylation to yield four metabolites. The oxidative pathway is catalyzed by the cytochrome P-450 system, mainly the 1A2 isoenzyme.

FDA Approved Indication(s) and Off-label Uses [1]

Rasagiline (Azilect®) was approved on May 17, 2006 for use as monotherapy in early Parkinson's disease (PD), and as an addition to levodopa in more advanced patients.

Current VA National Formulary Alternatives

The current VANF lists selegiline tablets as a formulary agent.

Dosage and Administration[1]

For monotherapy, the recommended dose for the treatment of Parkinson's disease patients is 1 mg of rasagiline administered once daily.

For adjunctive therapy, the recommended initial dose is 0.5 mg of rasagiline administered once daily. If a sufficient clinical response is not achieved, the dose may be increased to 1 mg administered once daily.

Hepatic Insufficiency and Impairment[1]

Following repetitive administration (7 days) of rasagiline (1 mg/ day) in subjects with mild hepatic impairment (Child-Pugh score 5-6), AUC and C_{max} were increased by 2 fold and 1.4 fold, respectively, compared to healthy subjects. In subjects with moderate hepatic impairment (Child-Pugh score 7-9), AUC and C_{max} were increased by 7 fold and 2 fold, respectively, compared to healthy subjects. Therefore, rasagiline should not be used in patients with moderate or severe hepatic impairment. Patients with mild hepatic impairment should use 0.5 mg daily.

Renal Insufficiency and Impairment[1]

Conclusive data are not available for renally impaired patients. Since unconjugated rasagiline is not excreted by the kidney, rasagiline can be given at usual doses in patients with mild renal impairment.

Geriatrics

Rasagiline has been extensively studied in elderly subjects, as PD's prevalence increases with increasing age. The mean age of subjects in the majority of the rasagiline studies was between 61 and 64 years, and approximately half of patients in clinical trials were 65 years and over. Age has little influence on rasagiline pharmacokinetics. Thus, it can be administered at the recommended dose in the elderly. Additionally, Goetz et al. evaluated age effects on adverse events from the TEMPO and PRESTO trials and found no statistical interaction between age and rasagaline exposure, suggesting that it does not require special safety precautions in the elderly. [4]

Efficacy

Efficacy Measures

There is no uniformly agreed upon outcome variable for measuring disease progression. However, most researchers use The Unified Parkinson's Disease Rating Scale (UPDRS), a rating tool designed to follow

the longitudinal course of Parkinson's disease and assess response to therapy. This scale can also be used to help determine when patients' symptoms are problematic enough to require pharmacologic treatment. The entire scale can be viewed at http://www.wemove.org/par_rs.html and has been in use since 1987. A total of 199 points are possible with 0 representing no disability and 199 representing total disability. The scale is divided into six sections as follows:

I. Mentation, Behavior and Mood

II. Activities of daily living (ADLs) taking both "on" and "off" symptoms into account

III. Motor Examination

IV. Complications of Therapy (In the past week) Complications are divided into:

   a. dyskinesias,

   b. clinical fluctuations

   c. Other complications

V. Modified Hoehn and Yahr Staging

VI. Schwab and England Activities of Daily Living Scale

The last two sections of UPDRS are qualitative rating scales that were in use prior to UPDRS and have been incorporated into the UPDRS. They are described at the aforementioned website. UPDRS is an attempt to quantitate response to therapy and disease progression.

Summary of efficacy findings [4-13]

Rasagiline has been studied both as monotherapy in patients with early PD, adjunct therapy for PD and for patients who are experiencing motor fluctuations. These studies were all randomized, blinded and used either placebo control or active control. Descriptions of these trials can be found in **Table 1**. These trials demonstrated rasagiline to be superior to placebo and via the use of an active comparator, entacapone, rasagiline appears to confer equivalent benefit to current adjunct therapy. Additionally, subanalyses of data from PRESTO, LARGO and TEMPO demonstrated no significant age effect on efficacy.

The effect of rasagiline on quality of life measures (QOL) was analyzed in a subpopulation of the TEMPO study.[5,6,14] The difference seen in these subsets appears to have been driven by changes in the scores of self image/sexuality and social role domains. There was not a significant difference in the measures related to movement, dyskinesias or activities of daily living. These results suggest that rasagiline may improve QOL in areas other than motor control.

In animal trials, potential neuroprotective properties of rasagiline and its major metabolite have been demonstrated. [15-17] These trials have shown rasagiline to be of benefit in a variety o f neurodegenerative disorders seen in aging patients. These properties have also been demonstrated in vitro. Human trials are necessary to document equivalent efficacy in patients.

Adverse Events (Safety Data)

Rasagiline has a theoretical risk of hypertensive crisis if patients also consume tyramine-rich foods, beverages (such as cheese and red wine) or dietary supplements or amines contained in many cough/cold medications. Therefore, current recommendations include

that patients will need to avoid these sources of tyramine and amines when taking rasagiline. Several clinical trials have demonstrated that the risk of tyramine response is low. As with most other medications for Parkinson's, rasagiline has the potential to cause involuntary movements (dyskinesias), hallucinations and lowered blood pressure. [18-20]

During development, melanoma was diagnosed in a small number of patients treated with rasagiline. [21,22] Although the FDA has concluded that the available data do not establish that rasagiline is associated with an increased risk for melanoma, it appears that compared to the general population, patients with Parkinson's disease have an increased risk for this form of skin cancer. In order to address the question of whether or not rasagiline itself increases such risk, the drug's manufacturer will perform a Phase 4 (postmarketing) study. The product labeling will recommend that patients undergo periodic dermatologic examinations. Tables outlining adverse effects and incidence among placebo, drug, and comparator agents are preferred method of presenting the data in this section. Other relevant comments regarding safety (i.e. pregnancy, lactation issues) should also be addressed in paragraph form under Precautions.

Table 2: Treatment emergent adverse events with rasagiline monotherapy*

Placebo-Controlled Studies Without Levodopa Treatment	Rasagiline 1 mg (N=149)	Placebo (N=151)
	% of Patients	% of Patients
Headache	14	12
Arthralgia	7	4
Dyspepsia	7	4
Depression	5	2
Fall	5	3
Flu syndrome	5	1
Conjunctivitis	3	1
Fever	3	1
Gastroenteritis	3	1
Rhinitis	3	1
Arthritis	2	1
Ecchymosis	2	0
Malaise	2	0
Neck Pain	2	0
Paresthesia	2	1
Vertigo	2	1

*Incidence ≥ 2% in rasagiline 1 mg group and numerically more frequent than in placebo group

Tolerability

The use of rasagiline in monotherapy has demonstrated an adverse event profile similar to placebo. When used as adjunct therapy with levodopa/carbidopa, rasagiline displays an adverse event profile consistent with dopamine excess.

Precautions/Contraindications[1, 24, 25]

Precautions

Rasagiline treatment at any dose may be associated with a hypertensive crisis if the patient ingests tyramine-rich foods, beverages, or dietary supplements or amines (from over-the-counter medications). Hypertensive crisis, which in some cases may be fatal, consists of marked systemic blood pressure elevation and requires immediate treatment/ hospitalization.

Patients receiving rasagiline should be instructed about the tyramine content of foods and beverages and amine containing medications that should be avoided. Sympathomimetic amines found in over-the-counter medicines to be avoided include pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine. It is also necessary to maintain this dietary tyramine restriction

Contraindications

Rasagiline is contraindicated with meperidine (Demerol®). Serious reactions such as coma, severe hypertension or hypotension, severe respiratory depression, convulsions, malignant hyperpyrexia, excitation, peripheral vascular collapse and death have been associated with concomitant use of meperidine and MAO inhibitors including selective MAO-B inhibitors. A minimum of 14 days must elapse between discontinuation of rasagiline and initiation of treatment with meperidine. Due to seriousness of reports, other analgesic agents such as tramadol, methadone, and propoxyphene should not be used with rasagiline.

Rasagiline should not be used with dextromethorphan. The combination of MAO inhibitors and dextromethorphan has been reported to cause brief episodes of psychosis or bizarre behavior. Rasagiline is also contraindicated for use with St. John's wort, mirtazapine (a tetracyclic antidepressant), and cyclobenzaprine (a tricyclic muscle relaxant).

Like other MAOI's, rasagiline is contraindicated for use with sympathomimetic amines (amphetamines, cold products, pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine). Severe hypertensive reactions have followed the administrations of sympathomimetics and non-selective MAO inhibitors. Rasagiline should not be administered along with other MAO inhibitors because of the increased risk of non-selective MAO inhibition that may lead to a hypertensive crisis. At least 14 days should elapse between discontinuation of rasagiline and initiation of treatment with MAO inhibitors. As with other MAOI's, rasagiline is contraindicated in patients with pheochromocytoma.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for generic name **rasagiline**

razadyne, raloxifene hydrochloride, selegiline hydrochloride, repaglinide, ranitidine and rapamune

LA/SA for trade name **Azilect®**

Adalat CC®, Azelex®, Acilac® and Anzemet®. The Institute for Safe Medication Practices has issued a high alert for potential confusion with Aricept®.

Drug Interactions [1, 24, 25]

Metabolism studies have shown that the CYP1A2 enzyme was a major enzyme responsible for the metabolism of rasagiline. Therefore, there is potential for inhibitors of this enzyme to alter the clearance of rasagiline such as ciprofloxacin.

Data from population pharmacokinetic studies comparing rasagiline clearance in the presence and absence of levodopa have given conflicting results. Although there may be some increase in rasagiline blood levels in the presence of levodopa, the effect is modest and rasagiline dosing need not be modified in the presence of levodopa.

Rasagiline should not be used in patients receiving meperidine, tramadol, methadone or propoxyphene due to a potential risk of respiratory depression, severe hypo/hypertension, vascular collapse and death. Therapy should be withdrawn for a minimum of 14 days before initiation of the pain control agents.

Acquisition Costs

Drug	Dose	Cost	Monthly Cost (estimated)
Rasagiline (Azilect®)	0.5mg	$5.07/tablet	$152.10 0.5mg daily
Rasagiline (Azilect®)	1.0mg	$5.07/tablet	$152.10 1mg daily
Selegiline (Eldepryl®)	5mg	$0.12 – $0.30/tablet depending on contract	$9.60 5mg BID
Entacapone (Comtan®)	200mg	$1.33/tablet	$39.90-119.70 200mg- 600 mg daily
Ropinirole (ReQuip)	3mg	$1.50/tablet	$135 3mg TID
Pramipexole (Mirapex)	0.5mg, 1.5mg	$1.48/tablet	$133.20 0.5mg TID – 1.5mg TID

Based on FSS pricing as of 4-24-07

Pharmacoeconomic Analysis

To date no pharmacoeconomic analysis for rasagiline has been completed.

Conclusions

Rasagiline was approved in May 2006 and has been demonstrated to be safe and effective in improving symptoms of Parkinson disease. However, there are no current head to head comparisons of rasagiline and dopamine agonists or selegiline. While rasagiline has demonstrated effectiveness in the TEMPO and

PRESTO studies as monotherapy, it has also shown to be comparative to other Parkinson disease medications as adjunct therapy.

Rasagiline offers an advantage over selegiline in that it is not metabolized to amphetamine derivatives. Additionally, rasagiline does not demonstrate orthostatic hypotension. As a class the MAO-B inhibitors as are an alternative to levodopa in the initial treatment of PD. However this class may be better tolerated but less effective than dopamine agonists.

The current practice parameter of the American Academy of Neurology gives a level A recommendation to the use of rasagiline in the treatment of motor fluctuations and dyskinesias, with other agents entacapone, dopamine agonists and selegiline have level A, B, C recommendations, respectively.

The potential neuroprotective effect of rasagiline is important. These preliminary results need to be validated with human trials. This effect may provide benefit in PD patients but also in patients with Alzheimer's Disease.

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Table 1 Trial summary for rasagiline

Study	# and Type of Subjects	Treatment	Time	Design	Endpoints	Results/Comments
TEMPO[40, 47, 65]	404, subjects with early PD, no other antiparkinson medication allowed	R 1 mg for 1 year (n=134) R 2 mg for 1 year (n=132) Placebo for 6 mos. then R 2 mg for 6 mos. (n=138)	52 weeks	R, DB, PC and AC, MC	1) Δ in UPDRS score (baseline to wk 26) 2) Δ in UPDRS score for delayed group vs early groups (baseline to 1 year) 4) Δ in motor, and ADL subscores for PC phase 5) Δ in quality of life	**Initial 26 Week Double-Blind Phase** • Both rasagiline groups showed benefits relative to placebo in change in total UPDRS score from baseline ($p<0.001$ for each comparison). • Rasagiline demonstrated benefits relative to placebo for the UPDRS motor subscale and the activity of daily living (ADL) subscale. • Rasagilinr 1 mg was associated with reductions in the symptoms of tremor and bradykinesia, compared with placebo. • Both rasagiline doses were associated with significant ($p\leq0.019$) improvements in quality of life. **Delayed Start, Active-Controlled Phase** • Early treatment with R 1mg compared with the same treatment started 6 months later, was associated with significantly less progression of: Parkinson's symptoms, impairment in activities of daily living. • Early treatment R 2mg was associated with a trend toward less progression of Parkinson's symptoms, compared with delayed treatment with R 2 mg. • R treatment over 1-year was safe with rates of adverse events similar to placebo.
PRESTO[49, 67, 68]	472, subjects with moderate-to-advanced PD, all subjects on levodopa and experiencing motor fluctuations	R 0.5 mg (n=164) R 1 mg (n=149) Placebo (n=159)	26 weeks	R, DB, PC, MC	1) Δ in mean total daily "OFF" time from baseline 2) Clinical Global Improvement (CGI), Δ in ADL subscore during "OFF", Δ in Motor subscore during "ON" and Δ in QOL 3) Δ in tremor, bradykinesia, rigidity and postural instability/gait disorder (PIGD)	• R 1 mg treatment sig reduced "OFF" time by approximately 1.9 hour compared to a 0.9 hour reduction with placebo treatment. • R increased total daily "ON" time, relative to placebo. • Compared with placebo, treatment with R 0.5 mg and 1 mg sig improved the CGI score. • Both R doses were associated with improvements compared with placebo in: ADL sub-score of the UPDRS during "OFF," motor sub-score of the UPDRS during "ON". There was no Δ in QoL • Compared with placebo, R 1 mg reduced the symptoms of tremor, rigidity and bradykinesia; while R 0.5 mg sig reduced the symptoms of postural instability/gait and tremor.
LARGO[64, 71]	687, subjects with late PD, all subjects on levodopa and experiencing	R 1 mg (n=231) Entacapone 200mg (n=227)	18 weeks	R, DB, PC, MC	1) Δ in mean total daily "OFF" time (baseline to wk 18) 2) Δ in clinical global improvement (CGI), ADL subscore and motor subscore	• R sig reduced total daily "OFF" time by almost 1 hour relative to placebo. This was not associated with an increase in dyskensias • R 1 mg sig improved CGI score compared with placebo. • Relative to placebo, R was associated with significant improvements in the Motor sub-score of the UPDRS during

	motor fluctuations	Placebo (n=229)			during "ON" (baseline to wk 18) 3) Δ in tremor, bradykinesia, rigidity, postural instability/gait disorder (PIGD) and freezing of gate (FOG)	"ON" and the ADL sub-score during "OFF". • Daily levodopa dose sig reduced in R group vs placebo group. • Rates of adverse events were similar between active treatment groups and placebo with no sig differences in rates of discontinuation.
Stern et al.[73]	56, subjects with early PD, no other antiparkinson medication allowed	R 1 mg (n=15) R 2 mg (n=14) R 4mg (n=14) Placebo (n=13)	10 weeks	R, DB, PC, MC	1) Preliminary efficacy as measured by Δ in total UPDRS from baseline 2) % of subjects with a ≥ 30% improvement in total UPDRS	1) R sig. reduced total UPDRS score vs. placebo, p<0.05 2) 12/43 (28%) of patients receiving R had an improvement of > 30%, no subjects in the placebo had a >30% improvement, p<0.05
Rabey et al.[74]	70, subjects with late PD, all subjects on levodopa and roughly half experiencing motor fluctuations	R 0.5 mg (N=21) R 1 mg (N=18) R 2 mg (N=18) Placebo (N=13)	12 weeks	R, DB, PC, MC	1) Δ in total UPDRS from baseline to week 12. 2) % of subjects with a ≥ 30% improvement in total UPDRS	1) NS different between treatment groups 2) 38/70 (54%) of patient receiving R had an improvement of > 30%, NS different than placebo.
Goetz et al.[42]	876 (404 from TEMPO and 472 from PRESTO	As per TEMPO and PRESTO	26 weeks	Post-hoc analysis	Comparison of placebo and R in younger (<70 yrs) and elderly patients (≥70 yrs)	Regardless of age, the occurrence of total AEs was similar among pts receiving R or placebo as initial monotherapy (TEMPO), p=0.46). In PRESTO, no difference was noted for age in incidence of total AEs, although more pts receiving R than placebo experienced more total AEs. In both trials, irrespective of treatment, serious AEs occurred more frequently in older pts than younger pts.

References:

1. Azilect Package Insert. Kansas City, MO: Teva Neuroscience, Inc.; May 2006.
2. Chen JJ, Swope DM. Clinical pharmacology of rasagiline: a novel, second-generation propargylamine for the treatment of Parkinson disease. *J Clin Pharmacol.* Aug 2005;45(8):878-894.
3. Finberg JP, Lamensdorf I, Commissiong JW, Youdim MB. Pharmacology and neuroprotective properties of rasagiline. *J Neural Transm Suppl.* 1996;48:95-101.
4. Goetz CG, Schwid SR, Eberly SW, Oakes D, Shoulson I. Safety of rasagiline in elderly patients with Parkinson disease. *Neurology.* May 9 2006;66(9):1427-1429.
5. Parkinson Study Group. A controlled, randomized, delayed-start study of rasagiline in early parkinson's disease. *Archives of Neurology.* 2004;61:561-566.
6. Parkinson Study Group. A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study. *Arch Neurol.* Dec 2002;59(12):1937-1943.
7. Siderowf A, Parkinson Study Group. Earlier treatment with rasagiline may attenuate (UPDRS) progression of PD. *Movement Disorders.* September 30, 2001;16(3):981.
8. Parkinson Study Group. A randomized placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson disease and motor fluctuations: the PRESTO study. *Arch Neurol.* Feb 2005;62(2):241-248.
9. Stern M, Parkinson Study Group. A controlled trial of rasagiline in parkinson's disease patients with levodopa-related motor fluctuations (PRESTO Study). *Annals of Neurology.* 2003;54(Supplement 7):S27.
10. Rascol O, Brooks DJ, Melamed E, et al. Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily, study): a randomised, double-blind, parallel-group trial. *Lancet.* Mar 12-18 2005;365(9463):947-954.
11. Rascol O, Brooks D, Melamed E, et al. A comparative randomized study of rasagiline versus placebo or entacapone as adjunct to levodopa in Parkinson's disease patients with motor fluctuations (The LARGO Study). Paper presented at: 7th Congress of the European Federation of Neurological Societies; August 30-September 2, 2003; Helsinki, Finland.
12. Stern MB, Marek K, Friedman J, et al. Double-blind, randomized, controlled trial of rasagiline as monotherapy in early Parkinson's disease patients. *Movement Disorders.* May, 2004;19(9):916-923.
13. Rabey JM, Sagi I, Huberman M, et al. Rasagiline mesylate, a new MAO-B inhibitor for the treatment of Parkinson's disease: a double-blind study as adjunctive therapy to levodopa. *Clin Neuropharmacol.* Nov-Dec 2000;23(6):324-330.
14. Biglan KM, Schwid S, Eberly S, et al. Rasagiline improves quality of life in patients with early Parkinson's disease. *Mov Disord.* May 2006;21(5):616-623.
15. Abu-Raya S, Blaugrund E, Trembovler V, Lazarovici P. Rasagiline, a novel monoamine oxidase-B inhibitor with neuroprotective effects under ischemic conditions in PC12 cells. *Drug Development Research.* 2000;50:285-290.

16. Suchowersky O, Gronseth G, Perlmutter J, Reich S, Zesiewicz T, Weiner WJ. Practice Parameter: neuroprotective strategies and alternative therapies for Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* Apr 11 2006;66(7):976-982.
17. Abu-Raya S, Blaugrund E, Trembovler V, Shilderman-Bloch E, Shohami E, Lazarovici P. Rasagiline, a monoamine oxidase-B inhibitor, protects NGF-differentiated PC12 cells against oxygen-glucose deprivation. *J Neurosci Res.* Nov 1 1999;58(3):456-463.
18. Shulman K, Walker S. A reevaluation of dietary restrictions for irreversible monoamine oxidase inhibitors. *Psychiatric Annals.* 2001;31(6):378-384.
19. Parkinson Study Group. Safety of rasagiline in combination with serotonin reuptake inhibitors. Paper presented at: 57th Annual Meeting of the Academy of Neurology; April 9-16, 2005; Miami Beach, FLA.
20. White B, DeMarcaida A, Salzman P, Schwid S, Shoulson I. Rasagiline does not affect blood pressure in Parkinson's disease patients following meals unrestricted in dietary tyramine content: Results from over 25,000 trans-telephonic blood pressure measurements in 443 patients. *Neurology.* 2006;66 (Suppl 2):A314-315.
21. Olsen JH, Friis S, Frederiksen K, McLaughlin JK, Mellemkjaer L, Moller H. Atypical cancer pattern in patients with Parkinson's disease. *Br J Cancer.* Jan 17 2005;92(1):201-205.
22. Moller H, Mellemkjaer L, McLaughlin JK, Olsen JH. Occurrence of different cancers in patients with Parkinson's disease. *Bmj.* Jun 10 1995;310(6993):1500-1501.
23. Pahwa R, Factor SA, Lyons KE, et al. Practice Parameter: treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* Apr 11 2006;66(7):983-995.
24. Guay DRP. Rasagiline (TVP-1012): A New Selective Monoamine Oxidase Inhibitor for Parkinson's Disease. Am J of Geriatric Pharmacotherapy 2006,4:330-346.

25. Chen JJ, Ly AV. Rasagiline: A second-generation monoamine oxidase type-B inhibitor for the treatment of Parkinson's disease. *Am J Health Syst Pharm.* May 15 2006;63(10):915-928.
26. Parkinson Study Group. Tyramine challenge to assess the safety of rasagiline monotherapy in placebo-controlled multi-center trial for early Parkinson's disease (TEMPO Study). Paper presented at: 53rd Annual Meeting of the American Academy of Neurology; May 5-11, 2001; Philadelphia, PA.
27. Suchowersky O, Reich S, Perlmutter J, Zesiewicz T, Gronseth G, Weiner WJ. Practice Parameter: diagnosis and prognosis of new onset Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* Apr 11 2006;66(7):968-975.