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PHARMACOTHERAPY OF SMOKING CESSATION: FOCUS ON VARENICLINE

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Smoking remains the leading cause of preventable death in the United States. Yet, an estimated 20.9 percent of all adults (44.5 million people) smoke cigarettes in the US.[1] The deleterious effects of tobacco use incur a great cost to society. Men and women smokers accrue $15,800 and $17,500, respectively, more in lifetime medical expenses and are absent from work more often than non-smokers.[2]

Smoking's harmful effects are not limited to the individual smoker. Second-hand smoke has detrimental effects to the body. According to the 2006 Surgeon General's Report, second-hand smoke contains toxic chemicals and carcinogens that cause disease and premature death in children and adults who do not smoke.[3] Specifically, children are at an increased risk for sudden infant death syndrome, acute respiratory infections, ear problems, and more severe asthma.[3] Second-hand smoke exposure to adults has immediate adverse effects on the cardiovascular system (CVS) and causes coronary heart disease (CHD) and lung cancer.[3]

Nicotine plays a complex role in mediating physical dependence and addiction that is not fully understood. Nicotine activates nicotinic acetylcholine receptors (nAChRs) on dopamine (DA) neurons in the ventral tegmental area (VTA), which projects to the nucleus accumbens (NAc), or the brain's "reward center."[4] The $\alpha_4\beta_2$ subtype plays a pivotal role in reinforcement, tolerance and sensitization.[5] Additionally, chronic smokers accumulate concentrations of nicotine in the brain which lead to prolonged desensitization of the nAChRs; thus DA overflow in the NAc no longer occurs over time.[6] Habitual use may be associated with the need to maintain nicotine concentrations at a certain level to avoid the aversive abstinence syndrome.[6]

There are six medications approved as first-line therapy for the treatment of nicotine dependence and addiction, including several dosage forms of nicotine replacement therapy (NRT) and the dopamine (DA) and norepinephrine (NE) reuptake inhibitor, bupropion SR (Zyban®).[7] On May 10, 2006 the FDA approved a new class of medication, varenicline (Chantix™ [chăn' tĭks]), for smoking cessation, a nicotine acetylcholine receptor (nAChR) agonist.[8] This article will review the current first-line pharmacotherapeutic agents and evaluate varenicline (vâr ĕ nĭk' lēn) for smoking cessation.

NRT Options Available

NRTs work by providing a source of nicotine

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to the brain to prevent withdrawal symptoms as well as aid the patient in weaning off nicotine dependence. NRTs come in a variety of dosage forms, some of which are available over-the-counter (OTC) (Table 1). Side effects (SEs) of NRTs include nausea, vomiting, headache, hypertension, irritability, insomnia and others typical of tobacco use.[8]

Nicotine gum and patches increased quit rates compared to placebo; however quit rates with NRTs are slightly lower without adjunct behavioral support.[9] A recent meta-analysis of eight studies concluded that OTC NRT produces similar quit rates compared with NRT obtained by prescription.[10] However, quit rates even among those who use NRT and behavioral therapy are less than desirable.

Cost is a barrier to using NRT. An 8-12 week course of NRT can cost $200-$350.[10] Several studies have shown that when cost barriers are reduced, NRT use increases.[11-13]

Other Available Pharmacotherapeutic Options

Bupropion SR (Zyban®)

Bupropion SR was approved for smoking cessation in 1997. Combination therapy with the nicotine patch was approved in 1999. It is unknown exactly how bupropion enhances the patient's ability to abstain from smoking; however it is likely related to its inhibition of dopaminergic and/or noradrenergic neuronal uptake. Cravings may be reduced by increased levels of DA, and increased norepinephrine (NE) may alleviate nicotine withdrawal symptoms.[8] The onset of activity for bupropion SR is approximately a week. Patients should set a target quit date at one to two weeks after initiating therapy (usually the eighth day of treatment).[8]

Doses of 150 to 300 mg per day are effective. In Hurt et al.[14] smoking cessation rates at one year were significant for 150mg (22.9%; P=0.02) and 300mg (23.1%; P=.01) versus placebo (12.4%). Doses as low as 100mg were not found to be statistically significant (P=0.09).

Jorenby et al.[15] compared bupropion SR, a downward titration of the nicotine patch, bupropion plus the patch and placebo in a double-blind, placebo-controlled study enrolling 893 participants. Treatment lasted 9 weeks, and abstinence rates were assessed for a 12 month period. At one year, abstinence rates were 15.6% for placebo, 16.4% for the patch only group, 30.3% for bupropion SR only (P<0.001), and 35.5% for the bupropion SR and nicotine patch group(P<0.001). The authors concluded that bupropion SR alone or in combination with the patch resulted in significantly higher long-term quit rates than either the patch alone or placebo.

Side effects statistically significant compared with placebo included insomnia (p<0.05) and dry mouth (p<0.05). Other reported SEs included headache, nausea, dizziness and dream abnormalities. Bupropion SR has been implicated in causing seizures and thus should not be used in patients with seizure disorder. Other contraindications include anorexia nervosa, concomitant MAO-I use, bulimia nervosa, and breast-feeding.

Varenicline (Chantix™)

Varenicline's activity is due to its selective, partial agonist activity at the $\alpha_4\beta_2$ neuronal nAChRs, eliciting a moderate and sustained increase in mesolimbic DA levels which counteracts low DA levels associated with the absence of smoking.[16] By competitively binding to this receptor, varenicline prevents nicotine-induced dopaminergic activation in

Table 1. FDA-approved nicotine replacement therapies (NRT)[10]

Nicotine Medication	Strength(s) available	Available OTC?	Advantages	Disadvantages
Gum	2 or 4 mg	Yes	Oral administration (PO); flavor options	Low compliance; under dosing is common
Patch	16-h patch: 15, 10, 5 mg; 24-h patch: 21, 14, 7 mg	Yes	Once a day administration	Fixed dose; slow delivery does not satisfy cravings
Nasal Spray	10 mg/ml, 0.5 ml per spray	No	Fast delivery	Unpleasant side effects
Inhaler	10 mg per cartridge	No	Simulates smoking habit; menthol flavor	Low compliance; under dosing is common
Lozenge	1, 2, or 4 mg	Yes	PO; faster delivery than gum	Low compliance; under dosing is common

the event that the patient smokes.[16] The smoker will not go into withdrawal, but also will not get the same 'high' or reward from smoking tobacco. Varenicline also binds to the 5-HT3 receptor with moderate affinity.[8]

Pharmacokinetics

Varenicline is almost entirely absorbed after oral administration and systemic availability is high.[8] Absorption is unaffected by food or time of dosing. The majority of varenicline is excreted unchanged in the urine.[17] It is a substrate for the organic cation transporter 2.[17] Varenicline should be used with caution in renal impairment and is removed by hemodialysis.[8] There is no significant hepatic metabolism. No significant drug-drug interactions have been elucidated.[8]

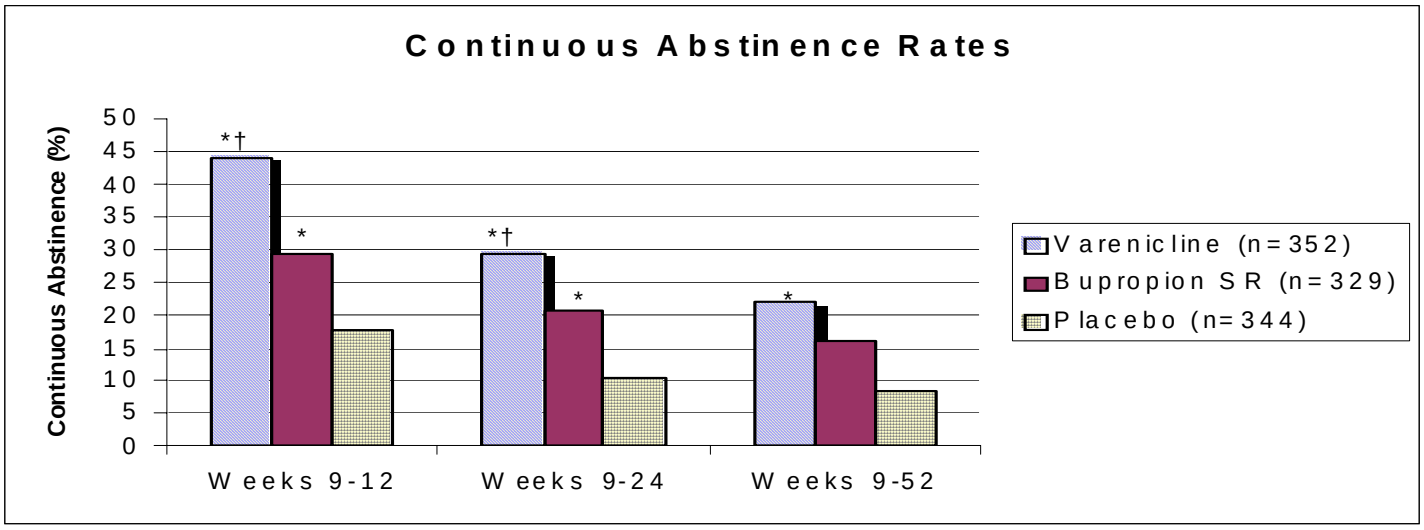
Clinical Trials

Two identical, randomized, double-blind, placebo- and active-treatment-controlled trials were conducted comparing varenicline with bupropion SR and placebo.[18,19] In each study, subjects were assigned varenicline titrated to 1 mg twice per day, bupropion SR titrated to 150 mg twice per day, or placebo for 12 weeks. All patients received counseling and were followed for 40 weeks. The primary end point for both studies was continuous abstinence from smoking during the last 4 weeks of treatment (weeks 9-12), as measured by exhaled carbon monoxide (CO). Continuous abstinence rates for weeks 9-24 and weeks 9-52 were secondary outcomes.

In Gonzales et al.,[18] 1025 participants were included in the analysis with completion rates of 60.5% for varenicline, 56% for bupropion SR, and 54% for placebo. Discontinuations were mostly due to loss of follow-up during the drug treatment phase (weeks 1-12). Continuous absence rates for weeks 9-12 were superior for varenicline (44%) versus placebo (17.7%) (OR, 3.85; 95% CI, 2.70-5.50; P<.001) and versus bupropion SR (29.5%) (OR, 1.93; 95% CI, 1.40-2.68; P<.001) (Figure 1). In addition, bupropion SR was superior to placebo (OR, 2.00; 95% CI, 1.38-2.89; P<.001). Continuous absence rates for varenicline were 2.5 times placebo and maintained statistical significance through weeks 9-24 and weeks 9-52 vs placebo. Varenicline preserved statistical significance compared with bupropion SR at weeks 9-24, but not through weeks 9-52.

Jorenby et al.[19] demonstrated similar results with higher completion rates in each group, at 70% in the varenicline group, 65% in the bupopion SR group, and 60% in the placebo group. Continuous abstinence rates for the varenicline group (43.9%) were significantly higher versus placebo (17.6%) (OR, 3.85; 95% CI, 2.69-5.50; P<.001) and versus bupropion SR (29.8%) (OR, 1.90; 95% CI, 1.38-2.62; P<.001) for the last four weeks of the treatment period (weeks 9-12) (Figure 2). For weeks 9-24, 29.7% of subjects in the varenicline group were continuously abstinent versus 13.2% in the placebo group (OR, 2.83; 95% CI, 1.91-4.19; P<.001) and 20.2% in the bupropion SR group (OR, 1.69; 95% CI, 1.19-2.42; P=.003). Varenicline maintained significance through weeks 9-52, with a continuous abstinent rate of 23% versus 10.3% in the placebo

Figure 1. Continuous abstinence rates for varenicline versus placebo[18]



*Value statistically significant vs placebo
†Value statistically significant vs bupropion SR

group (OR, 2.66; 95% CI, 1.72-4.11; P<.001) and 14.6% in the bupropion SR group (OR, 1.77; 95% CI, 1.19-2.63; P=.004). Bupropion SR did not maintain significance compared with placebo at the end of the study.

A major limitation of Gonzalez and Jorenby is their external validity. The exclusion criteria in both studies encapsulated a large percentage of the population that would benefit from smoking cessation, including those with serious medical illnesses (uncontrolled hypertension, history of cancer, diabetes requiring treatment, severe chronic obstructive pulmonary disease etc.) or current/recent depression.[19] While stringent requirements are necessary safety parameters for research in early stages, efficacy data of varenicline in at risk populations is needed.[20]

In a randomized, double-blinded, controlled study, Tonstad et al.[21] determined whether smokers who were abstinent at 12 weeks of treatment would maintain greater continuous abstinence rates with varenicline compared with placebo during an additional 12 weeks of treatment up until the 52nd week. After successfully completing the initial 12 weeks of treatment, a total of 1210 subjects received either 1 mg varenicline twice daily or placebo for an additional 12 weeks. The primary end point was CO-confirmed continuous abstinence rate for weeks 13-24. Continuous abstinence rates for weeks 13-52 were also assessed as a secondary end point. Participants randomized to varenicline had significantly higher continuous abstinence rates for weeks 13-24 as well as for weeks 13-52 (Table 2).

Adverse Effects

In all studies, nausea was the most commonly reported side effect for varenicline, occurring in as many as 33% of subjects.[18,19,21]. Nausea was dose-dependent, mostly mild to moderate in severity and rarely resulted in discontinuation[19,22]. Abnormal dreams and insomnia were also commonly reported.

Administration

The patient should set a quit date and initiate treatment 1 week prior to aforementioned date. To reduce the incidence of nausea, varenicline should be taken after eating and with a full glass of water. For days 1-3, 0.5 mg daily is recommended. The dose is increased to 0.5 mg twice daily for days 4-7. From day 8, the maintenance dose of 1 mg BID is recommended.[22]

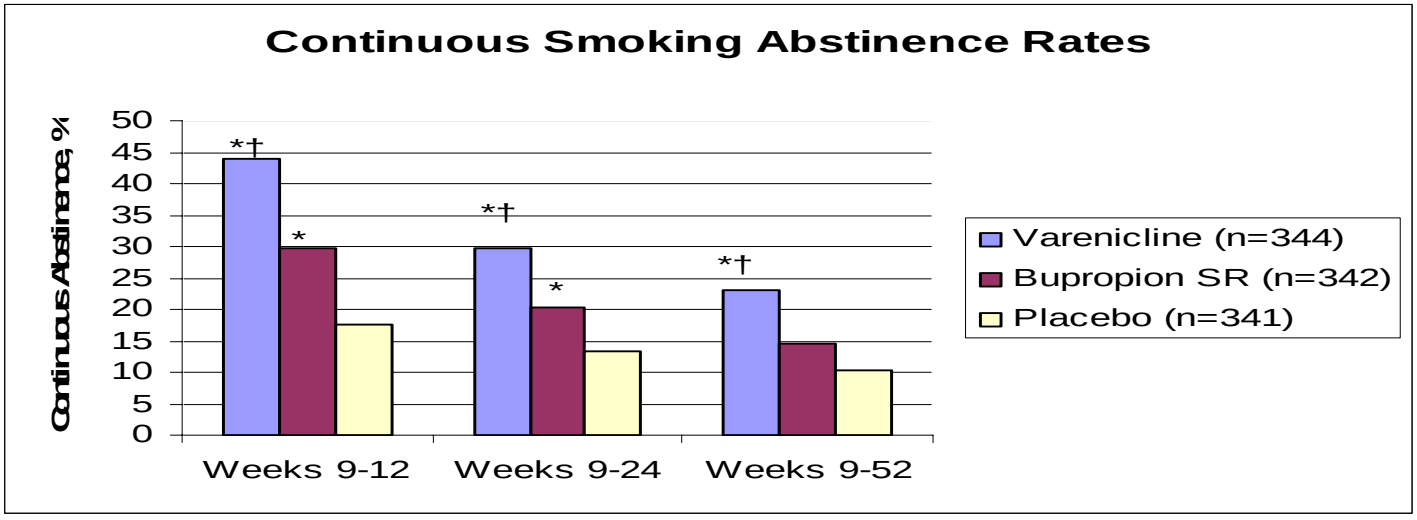
Cost

The average retail price from 3 different pharmacies for a 30 day supply of varenicline is $117 (range $113-$124). A starter pack is available containing both 0.5 mg and 1 mg strengths to titrate the dose to 1 mg twice daily. A one month supply (56 pills) is available for both the 0.5 mg and 1 mg dose.

Summary

Varenicline represents a new class of drug to treat smoking cessation. Currently there are six FDA-approved drugs for smoking cessation, includ-

Figure 2. Continuous abstinence rates for varenicline versus placebo[19]



*Value statistically significant vs placebo
†Value statistically significant vs bupropion SR

Table 2. Carbon monoxide-confirmed continuous abstinence rate at clinic visits[21]

Week	No. (%) abstinent	
Treatment phase*	**Varenicline**, n=603	**Placebo**, n=607
13	576 (95.5)	537 (88.5)
14	551 (91.4)	476 (78.4)
16	509 (84.4)	413 (68.0)
20	454 (75.3)	331 (54.5)
24	425 (70.5)	301 (49.6)
Non-treatment follow-up phase†		
25	408 (67.7)	293 (48.3)
28	361 (59.9)	282 (46.5)
36	306 (50.7)	257 (42.3)
44	280 (46.4)	239 (39.4)
52	263 (43.6)	224 (36.9)

*Weeks 13-24: OR, 2.48; 95% CI, 1.95-3.16; P<.001
†Weeks 13-52: OR, 1.34; 95% CI, 1.06-1.69; P=.02

ing various dosage forms of NRT and bupropion SR. Although all are significantly more effective than placebo, one-year continuous abstinence rates are still less than 50%. Varenicline may aid patients in successfully quitting and remaining smoke-free up to 52 weeks..

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RASAGILINE (AZILECT®): A NEW MONOAMINE OXIDASE B (MAO-B) INHIBITOR FOR THE TREATMENT OF PARKINSON'S DISEASE.

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Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder, after Alzheimer's disease, and affects one in 100 among the elderly population (>65 years of age).[1,2] PD is characterized by rigidity, bradykinesia, resting tremor and postural instability.[3,4] Other non-motor traits associated with Parkinson's disease include autonomic dysfunction (urinary dysfunction, erectile dysfunction, orthostatic dizziness), anxiety, depression, sleep disturbance and cognitive dysfunction.[4] Over 60,000 Americans are diagnosed each year with this chronic degenerative disease with no known regenerative treatment.[3] Options are aimed mostly at symptom improvement, enhancing patients' quality of life, and slowing disease progression.

Parkinsonian syndrome is characterized by degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) along with intracytoplasmic proteinaceous inclusions or Lewy bodies.[5] These dopaminergic neurons modulate the thalamus and its connections with the motor cortex. Degeneration of these neurons results in reduced striatal dopamine content and reduced thalamic excitation of the motor cortex which lead to the aforementioned cardinal symptoms of PD.[2] Oxidative stress, mitochondrial dysfunction, inflammation, excitotoxicity, and protein aggregation have all been implicated in the pathogenesis of neuronal death in PD.[5] Therapy is focused on enhancement of dopaminergic activity by replacing deficient dopamine, increasing dopamine storage, decreasing dopamine metabolism, and stimulating dopamine receptors.[2] Current pharmacologic treatments for motor symptoms of PD include: drugs that increase dopamine (levodopa) and a decarboxylase inhibitor (carbidopa); drugs that stimulate dopamine receptors, such as dopamine agonists (pramipexole, ropinirole, pergolide, and bromocriptine); and drugs that inhibit dopamine metabolism, such as catechol O-methyltransferase (COMT) inhibitors (tolcapone and entacapone) and monoamine oxidase type B (MAO-B) inhibitor (selegiline). Other pharmacologic approaches believed to improve parkinsonian symptoms and have antiparkinsonian activity include anticholinergics (trihexiphenidyl, benztropine, biperiden, orphenadrine, and procyclidine) and amantadine.

Selegiline (Eldepryl®) is a propargylamine MAO-B inhibitor that has traditionally been used in the treatment of PD. However, selegiline undergoes extensive first-pass metabolism to l-methamphetamine and l-amphetamine. Long-term exposure to these metabolites have been associated with oxygen-glucose deprivation-induced cell death and reduced neuroprotective effect of the parent drug.[6-8]

Rasagiline (Azilect®[ăz' ĭl ĕkt]) is a new selective and irreversible monoamine oxidase type B inhibitor approved by the FDA in May 2006. It is manufactured by Teva Pharmaceutical and is approved for use as initial drug therapy in early stages of Parkinson's disease and as an addition to levodopa in more advanced cases. In contrast to selegiline, rasagiline (ră săj' ă lēn) and its aminoindan metabolite have nonamphetamine features.[6-9] This article will examine the efficacy, safety, and tolerability of rasagiline.

Pharmacology and Pharmacokinetics

Dopamine is oxidized by monoamine oxidase (MAO) to generate hydrogen peroxide (H2O2). H2O2 is normally detoxified by glutathione but has the potential to react with ferrous iron to produce a highly cytotoxic hydroxyl radical. This cytotoxic free radical has been implicated in the pathogenesis of PD.[3] The MAO enzyme consists of two forms, type A and B. MAO-A is mainly found in the gastrointestinal tract and deactivates circulating catecholamines and dietary vasopressors. MAO-B is more abundant in the glial cells within the brain and is responsible for the metabolism of dopamine as well as endogenous amine that stimulates the release and inhibits neuronal reuptake of dopamine.[7,8] MAO-B converts 1-methyl,-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to MPP+, a neurotoxin, which selectively destroys the dopaminergic nigrostriatal neurons.[2] Selective inhibition of MAO-B results in elevations of synaptosomal dopamine concentrations. Propargylamine MAO inhibitors (selegiline and rasagiline) are neuroprotective by inhibiting apoptosis (programmed cell death) through inhibition of

GAPDH translocation (an enzyme involved in apoptosis).[5] Rasagiline increases superoxide dismutase (SOD) and catalase. SOD and catalase are antioxidative enzymes that reduce oxidative stress, which is associated with neuronal death thought to be implicated in neurodegenerative diseases such as PD.[10] Rasagiline inhibits MAO-B 93 times more potently than it inhibits MAO-A. Youdim et al.[11] showed that rasagiline was three to 15 times more potent than selegiline for inhibition of MAO-B in rat brain and liver in vivo.[7-8,11]

Rasagiline is rapidly absorbed by the gastrointestinal tract and readily crosses the blood brain barrier. The absolute bioavailability of a single 1 mg dose is approximately 36%. Rasagiline can be administered without regard to food since food does not significantly affect rasagiline's AUC. Rasagiline is primarily metabolized by hepatic CYP1A2-mediated N-dealkylation to form its main metabolite, 1-R-aminoindan, which has shown neuroprotective actions in vitro. Following oral administration of radiolabeled drug, 62% and 7% of the total dose was excreted in the urine and feces, respectively, over seven days. AUC and Cmax are increased by 80% and 38%, respectively, in patients with mild hepatic impairment, and by 586% and 83%, respectively, in patients with moderate hepatic impairment. Less than 1% of rasagiline is excreted unchanged in the urine, hence there is no need for dosage adjustment in patients with renal impairment. The pharmacokinetic profile of rasagiline does not differ between men and women.[7-8,12] Pharmacokinetic values of rasagiline in patients with PD are listed in Table 1.

Clinical Trials

Three main studies have investigated the safety, tolerability, and efficacy of rasagiline as monotherapy and as an adjunct to levodopa. These include: a multicenter, double-blind, placebo-controlled trial of rasagiline as monotherapy in early PD (TEMPO), and two studies that evaluated the efficacy of rasagiline as adjunctive therapy in more advanced PD (PRESTO and LARGO).

Efficacy of rasagiline as monotherapy

The TEMPO trial (Rasagiline Mesylate (TVP-1012) as Early Monotherapy in PD Outpatient), evaluated the safety and efficacy of rasagiline at doses of 1 mg and 2 mg per day in untreated patients with early PD who had not developed sufficient disability to require dopaminergic therapy. Four hundred and four eligible patients were randomly assigned to one of three groups: rasagiline mesylate, 1 mg/d; rasagiline mesylate, 2 mg/d; or matching placebo. Treatment began with a 1-week titration period during which all subjects on active treatment received 1 mg/d of rasagiline. After one week, subjects assigned to 2 mg/d of rasagiline took the maintenance dosage for the remaining 25-week period. No changes in anticholinergic therapy were allowed during the study. The primary efficacy measure in the trial was the change in total Unified Parkinson's Disease Rating Scale (UPDRS) score between baseline and the week 26 visit. Secondary endpoints included changes in mental, ADL and motor subscales of the UPDRS, symptom-based subscores, changes in the Hoehn and Yarh stage, the Schwab-England ADL scale, Beck Depression Inventory score, timed motor tests, and the Parkinson's Disease Quality of Life (PDQUALIF) scale. Safety, tolerability, frequency and severity of adverse effects were also assessed. Rasagiline at dosages of 1 mg and 2 mg per

Table 1. Pharmacokinetics of rasagiline in healthy volunteers and patients with PD [7,8]

Dose (mg)	**Cmax** (mg/mL)	**AUC_{0-24h}** (ng/h/mL)	**Tmax** (h)	**t½** (h)	**Vd** (L)	**Cl** (L/h)
			Healthy Volunteers[a]			
2	17.55 (3.51)	20.02 (4.81)	0.4 (0.2)	2.06 (1.14)	NR	0.56 (0.13)[b]
5	45.78 (19.26)	55.25 (12.23)	0.49 (0.15)	3.04 (0.94)	NR	0.15 (0.07)[b]
10	86.54 (27.47)	116.27 (19.83)	0.51 (0.29)	3.5 (1.5)	NR	0.32 (0.28)[b]
			PD patients[c]			
0.5	4.2 (2.6)	6.4 (3.1)	0.5-0.7	NR	NR	NR
1	8.5 (2.2)	12.4 (3.5)	0.5-0.7	NR	NR	NR
2	14.9 (10.5)	23.5 (10.5)	0.5-0.7	NR	NR	NR
4[d]	NR	NR	0.5[e]	1.34	182	94.3[f]

NR= not reported; [a]age range, 18 to 40 years. Values obtained after daily dosing for 10 days; [b]renal clearance; [c]age range, 40 to 70 years. Values obtained after daily dosing for 12 weeks; [d]values obtained between 1and 13 weeks of daily dosing; [e]median value; [f]hepatic clearance.

day resulted in better overall UPDRS performance compared with placebo. Total UPDRS score was improved by 4.2 points (P<.001; 95% CI -5.66 to -2.73) for the 1 mg group and by 3.56 points (P<.001; 95% CI -5.04 to -2.08) for the 2 mg group compared to placebo. There were no advantages in efficacy for 2 mg/d of rasagiline compared with the 1 mg/d dosage. Both active treatment groups showed significant improvements in PDQUALIF scores, motor and ADL subscales of the UPDRS compared with the placebo group. Mean changes in primary and secondary endpoints from baseline between placebo and treatment groups are summarized in Table 2. Adverse events were no more frequent in the active treatment groups than in the placebo group. The most commonly observed adverse events were infection (16%) and headache (12%). [13-15]

The TEMPO trial was extended for one year to evaluate the long-term effects of rasagiline on PD. Patients were randomized into: an immediate-treatment group where patients received 1 mg/day or 2 mg/day of rasagiline for the entire trial period, and a delayed-start group where patients received placebo for the first 6 months then 2 mg/day for the last half of the trial. Assessment of changes in total UPDRS score from baseline indicated that the patients who took 1mg/day and 2 mg/day of rasagiline throughout the trial had less functional decline than that of the placebo group.[16]

Efficacy of rasagiline as adjunctive therapy to levodopa

The PRESTO study (Parkinson's Rasagiline: Efficacy and Safety in the Treatment of Off), a multicenter, randomized, double-blind, placebo-controlled trial, and the LARGO study (Lasting effect in Adjunct therapy with RasaGiline), a randomized, placebo-controlled, double-blind, double-dummy, parallel-group trial, both evaluated the efficacy of rasagiline as adjunctive therapy to levodopa in patients with more advanced PD and motor fluctuations. Primary outcome measure of efficacy for both studies was the change from baseline in mean total daily off time, as measured by 24 hour diaries. In these diaries, patients recorded their status: on-time with troublesome dyskinesia, on-time without dyskinesia or with non-troublesome dyskinesia, off-time, or sleep. Off-time was defined as a period of poor overall function with worsening tremor, rigidity, balance, or bradykinesia. Secondary measures of efficacy include clinical global impression of patient improvement during the study by examiners from baseline, UPDRS activities of daily living subscale during off periods and motor examination scores during the on period. [15-18]

Patients in the PRESTO study were randomized to 0.5 mg/day rasagiline, 1.0 mg/day rasagiline, or matching placebo. Results of this 26-week trial showed that patients treated with 1.0 mg/day of rasagiline had 0.94 hour (95% CI, 0.51-1.36 hours; P<0.001) less off time per day compared with placebo. Patients in the 0.5 mg/day treatment had 0.49 hour (95% CI, 0.08-0.91 hour; P=0.02) less off time compared with placebo. Patients treated with 1.0 mg/day of rasagiline showed greater benefits compared with 0.5 mg/day of rasagiline, but differences between the two doses were not significant for most end points. PRESTO's efficacy end points are summarized in Table 3. Adverse events that were significantly more common in both doses of rasagiline

Table 2. TEMPO trial: primary analysis of changes between baseline and 26 weeks[14]

	Effect Size (95% Confidence Interval)	
	Rasagiline 1 mg/d vs Placebo	**Rasagiline 2 mg/d vs Placebo**
Total UPDRS score	-4.20 (-5.66 to -2.73) *	-3.56 (-5.04 to -2.08) *
UPDRS motor subscale	-2.71 (-3.86 to -1.55) *	-1.68 (-2.84 to -0.51) *
ADL subscale	-1.04 (-1.60 to -0.48) *	-1.22 (-1.78 to -0.65) *
Mental subscale	-0.14 (-0.44 to 0.15)	-0.26 (-0.56 to 0.04)
PIGD subscale	-0.15 (-0.41 to 0.11)	-0.20 (-0.46 to 0.06)
Rigidity	-0.38 (-0.80 to 0.03)	-0.39 (-0.81 to 0.03)
Tremor	-0.63 (-1.03 to -0.23) *	-0.38 (-0.78 to 0.02)
Bradykinesia	-1.51 (-2.19 to -0.82) *	-0.77 (-1.47 to -0.08) *
Schwab & England ADL scale	0.77 (-0.42 to 1.96)	0.39 (-0.81 to 1.58)
Hoehn & Yahr stage	-0.04 (-0.13 to 0.04)	-0.04 (-0.13 to 0.04)
PDQUALIF scale*	-2.91 (-5.19 to -0.64)*	-2.74 (-5.02 to -0.45) *
Beck Depression Inventory	-0.35 (-0.86 to 0.16)	-0.21 (-0.72 to 0.30)
Timed motor score	-0.55 (-1.19 to 0.08)	-0.36 (-1.00 to 0.28)

UPDRS indicates Unified Parkinson;s Disease Rating Scale; ADL, activities of daily living; PIGD, postural instability/gait disorder; PDQUALIF, Parkinson's Disease Quality of Life. * Statistically significant.

Table 3. PRESTO trial: efficacy end points[17]

	Mean (95% CI)	
Changes From Baseline	**Rasagiline, 0.5 mg/d vs Placebo**	**Rasagiline, 1.0 mg/d vs Placebo**
Primary end point of off time	-0.49 (-0.91 to -0.08) *	-0.94 (-1.36 to -0.51) *
Clinical global impression	-0.39 (-0.64 to -0.13) *	-0.68 (-0.94 to -0.42) *
ADL during off time	-1.20 (-2.08 to -0.32) *	-1.34 (-2.24 to -0.43) *
Motor performance during on time	-2.91 (-4.59 to -1.23) *	-2.87 (-4.58 to -1.16) *
PDQUALIF summary score	-2.18 (-4.49 to 0.14)	-1.48 (-3.86 to 0.90)
Daily on time w/o dyskinesias	0.51 (0.00 to 1.03)	0.78 (0.26 to 1.31) *
Daily on time with dyskinesias[a]	-0.05 (-0.41 to 0.31)	0.37 (0.00 to 0.74)

ADL, activities of daily living; PDQUALIF, Parkinson's Disease Quality of Life
[a]Analysis includes the treatment center interaction. [b]Potential ranges are 0 to 12 for dyskinesia, 0 to 20 for postural instability and gait, 0 to 20 for rigidity, 0 to 36 for bradykinesia, and 0 to 32 for tremor. * Statistically significant

mostly involved the gastrointestinal system and appeared to be dose related. The most common serious adverse events were related to accidental injury, arthritis, worsening PD, melanoma, stroke and urinary tract infection and were not significantly different between treatment groups and placebo.[15-17]

In LARGO, patients were randomized to, as adjunct treatment, 1 mg/day rasagiline, 200 mg entacapone with every levodopa/carbidopa dose, or placebo. The results of this 18-week trial showed that both rasagiline and entacapone reduced the mean total daily off-time from baseline to treatment by more than 1 hour, about three times more than the reduction with placebo ($p=0.0001$ and $p<0.0001$, respectively). Results suggest the addition of rasagiline to levodopa therapy significantly reduces off time with comparable efficacy to that of entacapone and levodopa. The mean change from baseline to treatment for all endpoints are summarized in Table 4. The frequency of adverse events, laboratory test values, physical examinations, electrocardiography, and vital signs (heart rate and blood pressure) were similar between treatment groups and placebo.[7,18]

Dosing and Administration

Rasagiline is available as 0.5 mg and 1.0 mg tablets to be taken orally, once daily without regard to food. The recommended rasagiline dose for the treatment of early PD as monotherapy is 1 mg administered once daily. Adjunctive therapy in patients with moderate to advanced disease should be initiated at a dose of 0.5 mg once daily and titrated upwards to 1 mg/day if the desired clinical response is not achieved.[12] Rasagiline can be administered at the recommended doses in the elderly since age has little effect on rasagiline's pharmacokinetics.[18,20] Rasagiline should be used with caution in patients with hepatic impairment due to decreased metabolism.[8]

Toxicity and Safety

Rasagiline's selectivity for MAO-B in humans has not yielded sufficient data to omit diet restrictions of amine containing drugs or tyramine containing foods (aged cheeses, meats, and fish). Selectivity for inhibiting MAO-B is usually diminished as the dose is increased. Ingestion of rasagiline and tyramine or amine-rich foods or medications can result in hypertensive crisis, otherwise known as the "cheese effect". Signs and symptoms of elevated blood pressure (BP) include blurred vision, headache, nausea/vomiting, or chest pains. Therefore, tyramine and amine containing products should be avoided in patients receiving rasagiline.[12] Clinical studies show that rates of adverse events such as confusion, hallucinations, postural hypotension and som-

Table 4. LARGO trial: primary and associated efficacy assessments[18]

	Adjusted mean change from baseline				
	Rasagiline	**Entacapone**	**Placebo**	**Rasagiline vs placebo (95% CI)**	**Entacapone vs placebo (95% CI)**
Daily off-time (h)	-1.18 (0.15)	-1.20 (0.15)	-0.40 (0.15)	-0.78 (-1.18 to -0.39) *	-0.80 (-1.20 to -0.41) *
Daily on-time w/o dyskinesia (h)	0.85 (0.17)	0.85 (0.17)	0.03 (0.17)	0.82 (0.36 to 1.27)	0.82 (0.36 to 1.27)
Daily on-time with dyskinesia (h)	0.23 (0.13)	0.18 (0.13)	0.14 (0.13)	0.09 (-0.28 to 0.46)	0.04 (-0.32 to 0.41)
Responder rate (number [%])[a]	113 (51%)	99 (45%)	70 (32%)	2.5[b] (1.62 to 3.85)*	2.0[b](1.29 to 3.06)*

Assessments measured in 24-h diaries. Off-time= period of poor overall function (increasing signs of PD). On-time= period of good overall function and mobility.
[a]Responders were defined as patients showing an improvement of 1h or more in the change from baseline in mean total daily off-time. [b]Odds ratio.
* Statistically significant

Table 5. Adverse events in monotherapy and adjunctive therapy studies in patients with PD[7]

	Percentage of patients		
Monotherapy		**Rasagiline 1 mg**	**Placebo**
Infection		14.9	15.9
Headache		10.1	14.2
Accidental injury		10.1	7.5
Dizziness		10.9	6.7
Asthenia		10.9	4.5
Nausea		7.2	5.2
Arthralgia		4.3	3.7
Back pain		5.1	5.2
Pain		5.8	6.0
Combination therapy	**Rasagiline 0.5 mg**	**Rasagiline 1 mg**	**Placebo**
Dyskinesia	18	10	
Weight Loss	2.4	9.4*	2.5
Vomitting	3.7	6.7**	1.3
Anorexia	1.8	5.4***	0.6
Balance difficulty	5.5**	3.4	0.6
Nausea	NR	3	4
Sleep disorder	NR	3	2
Dizziness	NR	3	2
Hallucinations	NR	2	1
Peripheral edema	NR	2	1
Postural hypotension	NR	2	0
Somnolence	NR	1	1

NR = not reported. Between-group differences were not statistically significant, unless otherwise noted.
* P= .02 (compared to placebo); ** P= .03 (compared to placebo); *** P= .04 (compared to placebo)

nolence related to rasagiline were not different from placebo.[18] In PRESTO, malignant melanoma was discovered through dermatologic examinations in three patients treated with rasagiline, one in the 0.5 mg/day group and two in the 1 mg/day group. One patient had already been diagnosed with melanoma before the study.[15,18] Adverse events associated with rasagiline compared with placebo are summarized in Table 5.

Drug Interactions

Treatment-emergent dyskinesias were seen with concomitant treatment of rasagiline and levodopa in the PRESTO study by potentiation of levodopa-induced motor activity. A reduction in levodopa can decrease such symptoms. Selegiline, the original MAO-B inhibitor, has been reported to interact with meperidine to produce serotonin-like syndrome, concurrent use of rasagiline with meperidine should be avoided. Selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and other MAOIs should also be avoided in patients taking rasagiline due to increased risk of developing serotonin-like syndrome.

Dextromethorphan should be avoided in patients taking rasagiline since psychosis has been associated with concurrent administration.

CYP1A2 inhibitors should be used with caution since ciprofloxacin, a CYP1A2 inhibitor, increases the AUC of rasagiline by 83%.[7-8,12]

Cost

The average retail price from 3 different pharmacies for a 30 day supply of rasagiline is $272 (range $242-$315). Cost is the same for 0.5 and 1 mg strengths.

Summary

Rasagiline is a novel agent that irreversibly and selectively inhibits MAO type B. It is indicated for the treatment of PD as monotherapy in the early stages of the disease and as adjunct therapy to levodopa in the late stages of the disease. Clinical trials demonstrate its efficacy and safety in patients varying in ages and comorbidities. Rasagiline has an advantage over selegiline in that it does not have methamphetamine metabolites that have been associated with neurotoxicity and decreased effect of the parent drug. Rasagiline's once daily dosing may improve compliance. Long-term trials are needed, however, to examine the longitudinal effects of rasagiline on PD.

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