Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Rasagiline

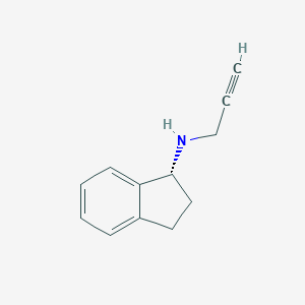
Evidence Summary

Rasagiline has potential neuroprotective actions beyond MAOB inhibition, including increasing Bcl2 and inhibiting the opening of the mPTP. Rasagiline does interact with many drugs and tyramine from food.

Neuroprotective Benefit: Rasagiline improved a few cognitive functions in PD patients but results were mixed and depended on several factors. In preclinical models, rasagiline has antioxidant actions, activates the anti-apoptotic protein Bcl2, and inhibits opening of the mitochondrial permeability transition pore.

Aging and related health concerns: Very few preclinical studies (and no human studies) have evaluated the potential for rasagiline in age-related health conditions; rasagiline decreased disease severity and increased survival in models of ALS and stroke.

Safety: Common adverse events include orthostatic hypotension, dyskinesia, and headache, but incidences are not higher than placebo. Rasagiline interacts dangerously with many drugs (other MAO inhibitors, anti-depressants, opioids) and tyramine-rich food.

Availability: Rx, used as adjunctive therapy with levodopa-carbidopa in Parkinson's disease.	**Dose:** Initial dose in Parkinson's patients on concomitant levodopa is 0.5 mg orally once a day; maintenance dose is 0.5-1.0 mg orally once a day.	**Chemical formula:** $C_{12}H_{13}N$ **MW:** 171.23  Source: PubChem
Half life: 3 hours	**BBB:** penetrant	
Clinical trials: Largest trial in Parkinson's disease patients included 1,176 patients.	**Observational studies:** none	

What is it? Rasagiline is a selective and irreversible inhibitor of the monoamine oxidase B (MAOB), an enzyme that regulates the degradation of dopamine and phenylethylamine. It is used as a monotherapy in early Parkinson's disease or as an adjunct therapy (in combination with levodopa and carbidopa) in more advanced disease (PubChem).

Neuroprotective Benefit: Rasagiline improved a few cognitive functions in PD patients but results were mixed and depended on several factors. In preclinical models, rasagiline has antioxidant actions, activates the anti-apoptotic protein Bcl2, and inhibits opening of the mitochondrial permeability transition pore.

Types of evidence:

- 4 meta-analyses or systematic reviews in Parkinson's patients (3 evaluated numerous drugs including rasagiline)
- 4 double-blind randomized controlled trials in Parkinson's patients
- 1 double-blind randomized controlled trial in progressive supranuclear palsy
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

No studies have evaluated whether rasagiline is neuroprotective in healthy adults. Several studies have evaluated whether rasagiline affects cognitive functions in Parkinson's patients without dementia.

In a meta-analysis of 10 randomized controlled trials including a total of 2,709 patients, rasagiline treatment at 1 mg/day showed small improvements in Part I (Mentation) of the Unified Parkinson's Disease Rating Scale (UPDRS) compared to placebo, but treatment at 2 mg/day did not improve this score (Chang et al., 2017). For UPDRS Part I, the difference in means for 1 mg/day rasagiline treatment group compared to placebo was 0.237 (95% CI=0.105 to 0.369, p<0.001), while no significant improvement was found for 2 mg/day rasagiline dose (difference in means=0.118, 95% CI=-0.060 to 0.295, p=0.194). The UPDRS Part I score ranges from 0 (normal) to 16.

In a large follow-up study of the ADAGIO trial, 683 Parkinson's patients were followed for 3 years to determine if early-starters of rasagiline treatment (72 weeks of rasagiline, 1 or 2 mg/day) fared better than delayed-starters (placebo for 36 weeks followed by rasagiline for 36 weeks, 1 or 2 mg/day)(Rascol et al., 2016). This study failed to demonstrate long-term benefits of early-start rasagiline treatment compared to the delayed-start rasagiline treatment. Based on the Kaplan-Meier analyses of time to milestones, early starters (longer rasagiline treatment) was associated with greater probability for cognitive function *decline*, though this comparison was not statistically significant. The absence of group differences may be due to the mere 9-month difference between groups in the duration of rasagiline treatment. In addition, most patients reported that they continued with rasagiline treatment during the gap between the original ADAGIO study and this follow-up study.

In a double-blind placebo-controlled trial of 50 patients with mild-to-moderate Parkinson's without dementia, rasagiline treatment for 6 months was not associated with significant changes in performance on neuropsychological measures of cognition compared to placebo (Frakey and Friedman, 2017). No significant treatment effects were observed in tests of attention, executive functioning, verbal fluency, language, visuospatial perception, or memory.

In a double-blind randomized controlled trial that enrolled 151 patients with mild cognitive impairment and Parkinson's disease, adjunct rasagiline treatment (1 mg/day) for 24 weeks did not significantly improve cognitive scores compared to placebo (Weintraub et al., 2016). No significant treatment effects were seen for Scales for Outcomes of Parkinson's Disease-Cognition scores (p=0.22), Montreal Cognitive Assessment test (p=0.84), Penn Daily Activities Questionnaire (p=0.48) scores, or in the distribution of Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADAS-Cog) modified for mild cognitive impairment (p=0.1).

In contrast to the negative findings from the studies described above, one double-blind randomized controlled trial reported that in Parkinson's patients who already had cognitive deficits, rasagiline treatment (1 mg/day) for 3 months improved a few cognitive functions (Hanagasi et al., 2011). Forty-eight patients with impairment in 2 of 4 cognitive domains (attention, executive function, memory, and visuospatial function) were enrolled. The rasagiline group showed significant improvement in attention (measured by digit span-backward; p=0.04), verbal fluency total score (p=0.038), and the composite attention domain Z score (P <0.005) compared with the placebo group. Trends favoring rasagiline were also seen in semantic fluency test (p=0.06) and Stroop spontaneous corrections (p=0.056). It is worth noting that because t-tests were used to examine group differences without corrections for multiple comparisons, some of the positive findings could have been due to chance. Also, there were no significant differences between rasagiline and placebo groups in the other cognitive tests assessing language, visuospatial function, and memory, as well as in the other cognitive domain Z scores.

Human research to suggest benefits to patients with dementia:

Alzheimer's disease: AWAITING RESULTS. A phase 2 double-blind randomized placebo-controlled clinical trial evaluated whether 24 weeks of rasagiline treatment (0.5 mg/day for weeks 1-4, 1 mg/day for weeks 5-28) affects regional brain metabolism as measured by FDG-PET in patients with mild-to-moderate Alzheimer's disease (NCT02359552). This trial was led by Jeffrey Cummings, MD, ScD, at the Cleveland Clinic, and recruitment was completed as of May 8, 2019. Results have not been posted, as of 6/20/2019.

Progressive supranuclear palsy: LACK OF BENEFIT. In a double-blind randomized controlled trial in 44 patients with progressive supranuclear palsy (of whom 26 completed the trial), rasagiline treatment (1 mg/day) for 1 year did not improve cognitive function, frontal executive function, depression, or posturographic measurements (Nuebling et al., 2016). Concerning cognitive function, a slow decline was seen in Mini-Mental State Examination (MMSE) scores (rasagiline, -0.5; placebo, -0.4), yielding a significantly *higher rate of decline with rasagiline treatment* in the intention-to-treat analyses (p=0.042), though per-protocol analysis did not show statistically significant differences (p=0.164).

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

There are several potential mechanisms of action of rasagiline that may result in neuroprotection. Rasagiline has a propargylamine moiety that activates the anti-apoptotic protein Bcl-2 and down-regulates the Bax proteins that regulate apoptosis (Hughes et al., 2016). Rasagiline also has antioxidant

actions as well as the ability to inhibit mitochondrial permeability transition pore-mediated calcium efflux, which may underlie its anti-apoptotic function in preclinical models (Wu et al., 2015).

Aged mice: In aged mice, rasagiline treatment (0.2 mg/kg) significantly improved cognitive scores (to those comparable to young mice), while increasing striatal dopamine and serotonin levels and decreasing their metabolism (Weinreb et al., 2015). In addition, rasagiline treatment elevated striatal mRNA expression levels of dopamine receptors D1 and D2. Furthermore, rasagiline increased levels of the synaptic plasticity markers BDNF, tyrosine kinase-B receptor, and synapsin-1, increased the Bcl-2 to Bax anti-apoptotic ratio, and the activity of the antioxidant enzyme, catalase, in the brains of aged mice. The mRNA levels of BDNF, Trk-B, synapsin-1, and GAP-43 in aged mice treated with rasagiline were restored to levels comparable to young mice treated with vehicle. Given that products of MAO-catalyzed reactions such as H_2O_2 and toxic aldehydes induce lipid peroxidation, inhibition of MAO-B by rasagiline may reduce oxidation and free radical formation.

Young rats: In young healthy rats, rasagiline treatment enhanced object recognition memory (Wong et al., 2010). A small effect was observed with 0.3 mg/kg rasagiline; at 1 mg/kg, rasagiline-treated animals spent twice as much time exploring the novel object. However, a significant reduction in locomotor activity was observed in animals treated with rasagiline at doses of 3 and 10 mg/kg.

Ischemia: In a rat model of brain ischemia (middle cerebral artery occlusion), a bolus (3 mg/kg) of rasagiline followed by a 3-hour infusion (3 mg/kg/h) initiated immediately after ischemia reduced infarct size by 48.6% and neurological severity score by 32.7% relative to saline treatment (Speiser et al., 2007). Cognitive function (measured by water maze test) 2-3 weeks after occlusion was also significantly improved with rasagiline treatment compared with saline-treated controls. Necrotic brain area was 35-50% smaller with rasagiline than with saline following a single bolus dose. The neuroprotective effect of rasagiline was present when administered within 2 hours following occlusion but not after 4 hours.

Mitochondria: In cell culture models, rasagiline suppresses neurotoxin- and oxidative stress-induced membrane permeabilization in isolated mitochondria (Wu et al., 2015). In SH-SY5Y cells, apoptosis was induced by PK11195, a ligand of the outer membrane translocator protein 18 kDa (TSPO). Rasagiline inhibited mitochondrial calcium efflux through the mitochondrial permeability transition pore (mPTP) in a dose-dependent manner. mPTP is thought to control the initiation step of apoptosis. The opening of mPTP was prevented by rasagiline (Maruyama et al., 2001). The activation of the apoptotic cascade by caspase 3 and DNA fragmentation was also inhibited by pretreatment with rasagiline.

APOE4 interactions: Unknown.

Aging and related health concerns: Very few preclinical studies (and no human studies) have evaluated the potential for rasagiline in age-related health conditions; rasagiline decreased disease severity and increased survival in models of ALS and stroke.

Types of evidence:

- Several laboratory studies

Stroke: POTENTIAL BENEFIT IN A RAT MODEL. In stroke-prone spontaneously hypertensive rats, cumulative survival was significantly increased from 56.09 ± 1.77 days in the untreated to 73.6 ± 2.22 days with rasagiline treatment (3-6 mg/kg/day)(Eliash et al., 2001). In these rats, stroke was delayed, its incidence was decreased, and its outcome was less severe than in the control group. Histological examination of the brains and kidneys showed that the effects on stroke and survival were associated with decreased infarcts and hemorrhages in the brains and decreased tubular nephropathy and glomerulopathy. The rise in systolic blood pressure in the untreated rats was significantly attenuated in the rasagiline group at 3 mg/kg/day. There were no significant effects on heart rate. Authors speculated that these potential benefits with rasagiline in a stroke model may be due to the central role renal dopamine plays in the regulation of salt balance.

ALS: POTENTIAL BENEFIT IN A MOUSE MODEL. In a mouse model of amyotrophic lateral sclerosis (ALS; G93A mice), rasagiline treatment alone (0.5 or 2.0 mg/kg/day in drinking water) or in combination with riluzole (ALS drug; 30 mg/kg/day) started at 60 days of age significantly improved motor function and survival (by ~20%) (Waibel et al., 2004). Controls had an average life expectancy of 210.9 days, whereas riluzole-treated animals died after 233.6 days. Animals treated with the low dose of rasagiline (0.5 mg/kg/day) alone survived 223.9 days; this extension of survival was not statistically significant. The higher dose of rasagiline (2.0 mg/kg/day) increased life span by 29 days (to 239.9 days), which was statisticaly significant ($p<0.001$). The largest extension of life span was observed with the combination of riluzole and rasagiline. The mean life expectancy was 247.9 days with the combination of 0.5 mg/kg/day rasagiline with riluzole; and 252.0 days with the combination of 2.0 mg/kg/day rasagiline with riluzole (statistically significant compared to controls as well as compared to treatment with riluzole alone).

Safety: Common adverse events include orthostatic hypotension, dyskinesia, and headache, but incidences are not higher than placebo. Rasagiline interacts dangerously with many drugs (other MAO inhibitors, anti-depressants, opioids) and tyramine-rich food.

Types of evidence:

- 3 meta-analyses
- 2 randomized controlled clinical trials that are not in the meta-analyses/syst rev

Numerous clinical trials have shown that rasagiline is generally well-tolerated. Common adverse reactions include orthostatic hypotension (incidence depends on dose and mono- vs adjunctive therapy), dyskinesia (e.g., involuntary muscle movements; 18% in adjunctive therapy), headache (14%), nausea, (6-12% in adjunctive therapy), dizziness (7%), peripheral edema (7%), joint pain (7%), and others (Drugs.com). Rasagiline may also cause exacerbation of hypertension.

Meta-analyses data: Of the three meta-analyses reporting on adverse events for Parkinson's medications, one from 2013 focused specifically on rasagiline (monotherapy and combination therapy) and evaluated 26 clinical trials including a total of over 1,000 patients (Solis-Garcia del Pozo et al., 2013). Although many adverse events with rasagiline have been reported, there is no significant difference in the occurrence of these effects when compared to placebo. The most frequently reported adverse effects for rasagiline as monotherapy were headache, dizziness, and insomnia. Depression, dizziness, somnolence, and other sleep disorders were reported when used in combination therapy. For example, with rasagiline monotherapy, headache appeared in 8.0% (81 out of a total of 1,013 patients) with rasagiline versus 7.4% with placebo. Dizziness was the second most frequently reported neuropsychological adverse effect with an occurrence of 7.9%. Insomnia affected 5.4% of patients. Although somnolence and hallucinations have been reported in almost all trials, occurrence rates were very low.

Nausea and vomiting were reported in 4.5% of patients (46/1,013) who participated in rasagiline monotherapy trials. Orthostatic hypotension and peripheral edema were the most frequent cardiovascular adverse effects. In rasagiline monotherapy studies, joint pain occurred in 7.1% of patients, back pain occurred in 5.2%, peripheral edema occurred in 2.2%, and orthostatic hypotension appeared in 0.6%. In the case of back pain, the relative risk was 0.97 and no significant differences were observed between rasagiline and placebo groups.

Other meta-analyses that evaluated numerous Parkinson's medications also reported that rasagiline did not significantly increase the risk for adverse effects compared to placebo (Elbers et al., 2015) or comparator treatment groups (Binde et al., 2018).

MCI in PD: MOSTLY MILD ADVERSE EVENTS. In a double-blind randomized controlled trial of 151 patients with mild cognitive impairment and Parkinson's disease, adjunct rasagiline treatment (1 mg/day) for 24 weeks was well-tolerated (Weintraub et al., 2016). The most common adverse events in both rasagiline and placebo groups were falls and dizziness. Treatment-emergent adverse events were reported in 62% (n=53) of rasagiline and 52% (n=44) of placebo patients. Adverse events that occurred in greater than 5% of patients and were at least twice as common in rasagiline-treated patients included: headache, arthralgia (joint pain), and orthostatic hypotension. Among rasagiline-treated patients reporting treatment-emergent adverse events, nearly all (96.2%) endorsed them as being mild or moderate in intensity. Two patients in the rasagiline group (and none in the placebo group) experienced adverse events categorized as severe (blurred vision and headache; pathological gambling), which were assessed by the site investigator as unrelated to the rasagiline treatment. Two patients experienced three serious adverse events: transient ischemic attack in a rasagiline-treated patient, and angina pectoris and atrial fibrillation in a placebo-treated patient.

Progressive supranuclear palsy: INCREASE IN VERTIGO, HALLUCINATIONS, ECG CHANGES. In a double-blind randomized controlled trial of 44 patients with progressive supranuclear palsy (of whom 26 completed the trial), rasagiline treatment (1 mg/day) for 1 year was well-tolerated with a slight increase of known side effects (hallucinations, ventricular extrasystoles)(Nuebling et al., 2016). Of the 18 participants not completing the trial, six (4 in rasagiline; 2 in placebo) were due to possible side effects (vertigo, hallucinations, ECG changes). A potential increase in adverse events in the rasagiline treatment group was seen concerning hallucinations (7 in rasagiline; 1 in placebo) and ventricular extrasystole (3/0 rasagiline/ placebo). However, there was a lower number of severe falls (3 in rasagiline, 9 in placebo) and back pain (0 in rasagiline, 4 in placebo) in the rasagiline group compared to placebo. None of the recorded severe adverse events (17 in rasagiline, 16 in placebo) were assumed to be possibly or probably related to rasagiline treatment. No alterations were detected in blood levels of creatinine, liver enzymes, blood count, and vitamin B12.

Drug interactions: Rasagiline has major interactions with 81 drugs and moderate interactions with 386 drugs (Drugs.com). Rasagiline should not be taken if you have used any other MAO inhibitor (isocarboxazid, linezoid, methylene blue, phenelzine, selegiline, tranylcypromine, etc.) in the past 14 days (Drugs.com). Other common drugs that can cause unwanted or dangerous effects when used with

rasagiline include cyclobenzaprine (muscle relaxer), dextromethorphan (active ingredient in some cough medicines), meperidine, methadone, St. John's wort, or tramadol. Stimulants, opioid medications, anti-depressants, migraine medications, and anti-nausea/vomiting medications may also interact with rasagiline and cause a serious condition called the serotonin syndrome.

Food/drink interactions: You can get a condition called "hypertensive crisis" if you take rasagiline with tyramine-rich foods/drinks such as aged cheese, fermented meats, tofu, soy sauce, red wine, and unpasteurized beers (Drugs.com). Consumption of very high levels (greater than 150 mg) of tyramine while on rasagiline treatment can lead to dangerous increases in your blood pressure. However, several clinical trials have concluded that rasagiline did not induce postprandial hypertension with an unrestricted diet and is not associated with tyramine-induced hypertensive reactions (deMarcaida et al., 2006; White et al., 2008; Solis-Garcia del Pozo et al., 2013).

Also, caffeine may increase the blood levels of rasagiline in some patients and may increase side effects of rasagiline such as drowsiness and dizziness.

Sources and dosing: Rasagiline is a prescription drug in tablet form used as a monotherapy in early Parkinson's disease or as an adjunct therapy (in combination with levodopa and carbidopa) in more advanced disease (PubChem). It is marketed as Azilect® by Teva Pharmaceutical. The initial dose in Parkinson's patients on concomitant levodopa is 0.5 mg orally once a day; the maintenance dose is 0.5-1.0 mg orally once a day (Drugs.com). The initial and maximal dose in Parkinson's patients not on levodopa is 1 mg orally once a day. Dose adjustments are recommended with mild liver dysfunction (to 0.5 mg/day) and with concomitant CYP450 1A2 inhibitors (e.g., ciprofloxacin; to a maximum dose of 0.5 mg/day). Rasagiline use is not recommended in people with moderate to severe liver dysfunction.

Research underway: There are 4 ongoing clinical trials based on ClinicalTrials.gov and all are testing rasagiline in Parkinson's disease patients. One is testing the long-term safety of rasagiline (NCT03727139) and the 3 others are testing other anti-Parkinson's drugs and using rasagiline as the comparator.

Several new drugs designed based on properties of rasagiline have been shown to produce neuroprotective activity *in vitro*. For example, M30, a brain-permeable iron chelator and brain selective MAO inhibitor, was designed on the rationale that MAO and iron are elevated in the brains of Alzheimer's patients, and this leads to oxidative stress and neurodegeneration (Youdim, 2006). M30 irreversibly inhibits both MAOA and MAOB and also regulates APP via its iron chelating ability, having

an effect on Aβ levels. A second-generation prodrug, M30D has also been designed from tacrine, rivastigmine, and rasagiline, having MAOA-, MAOB-, and acetylcholine esterase-inhibiting properties (Zheng et al., 2010). However, challenges of chelating therapy for Alzheimer's include the ability to cross the blood-brain-barrier and its ability to specifically sequester only harmful metals in the brain, without disrupting the essential metal stores in the body (Zheng et al., 2012).

Search terms:

Pubmed, Google: rasagiline

- + meta-analysis, + cognitive, + Alzheimer, + APOE, + cardiovascular, + diabetes, + mortality, + lifespan

Websites visited for Rasagiline:

- Clinicaltrials.gov
- DrugAge (o)
- Geroprotectors (o)
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- Cafepharma (o)
- Pharmapro.com (o)