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.

Selegiline (L-deprenyl)

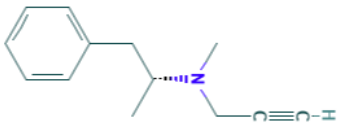
Evidence Summary

Selegiline may provide a small, though possibly not clinically meaningful, benefit for Alzheimer's disease; the longevity research is mixed.

Neuroprotective Benefit: There may be a small benefit to Alzheimer's patients who take selegiline, though it may not be clinically meaningful. However, the potential for prevention is not clear.

Aging and related health concerns: Selegiline has been reported to increase, decrease, or have no change in lifespan in animal models. The mechanism for an increase in lifespan is unclear.

Safety: Despite the potential for some side-effects, these are generally not serious. However, there are many potential drug interactions.

Availability: Available as a generic in a capsule or table	**Dose:** 10mg/day capsule	**Chemical formula:** $C_{13}H_{17}N$ **Molecular Weight:** 187.281 g/mol  **Source:** Pubchem
Half life: 10 hours (oral); 18-25 hours (transdermal)	**BBB:** Yes	
Clinical trials: 1 ongoing; 28 completed (the largest having 341 participants)	**Observational studies:** 2 for mortality risk in 999 and 941 patients	

What is it?

Selegiline is a monoamine oxidase B (MAO-B) inhibitor at lower doses (e.g. 10mg/day) but can inhibit MAO-A at higher doses (e.g. 40mg/day) (Birks and Flicker, 2010). Monoamine oxidases are enzymes located on the outer mitochondrial membrane and are important for breaking down monoaminergic neurotransmitters. Both MAO-A and MAO-B break down dopamine. MAO-B also breaks down phenethylamine and benzylamine while MAO-A primarily breaks down serotonin, melatonin, norepinephrine, tyramine, and epinephrine. Inhibiting the ability of MAO-A to break down tyramine causes the "cheese effect", which can lead to a hypertensive crisis.

Some concerns with selegiline were initially raised for the potential of abuse since two of selegiline's metabolites are methamphetamine and amphetamine, but the evidence to date suggest the concentration of metabolites is too small to be of concern (Fabbrini et al, 2012).

Neuroprotective Benefit: There may be a small benefit to Alzheimer's patients who take selegiline, though it may not be clinically meaningful. However, the potential for prevention is not clear.

Types of evidence:

- 1 meta-analysis for Alzheimer's disease
- 1 review for Parkinson's disease
- 2 studies in preclinical animals

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?
None.

Human research to suggest benefits to patients with dementia:
In a meta-analysis of 17 trials, Birks and Flicker (2003) suggested that there is no evidence that selegiline (10mg/day) would show clinically meaningful benefits to patients with Alzheimer's disease. They report that there were small benefits favoring selegiline in cognition at 4-6 weeks and 8-17 weeks and in activities of daily living at 4-6 weeks. They report that this may be explained by large benefits in two studies that were not replicated in others. In most studies there tends to be a very small benefit favoring selegiline on cognition. They reported no effect on global rating scales or emotional state. However, selegiline appeared to be safe, with side effects occurring similarly in placebo and drug groups.

Human research to suggest benefits to patients with Parkinson's disease:
In untreated patients diagnosed with Parkinson's disease, compared to placebo, selegiline (10mg/d) provided symptomatic benefit, reduced disability, and delayed the need for the introduction of levodopa therapy (by 9 months; levodopa is needed in more severe cases) (Fabbrini et al, 2012).

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
In an open-label study in dogs with cognitive dysfunction, selegiline was given at doses of 0.5mg/kg/day. There were benefits in multiple measures of cognition, but few details of the study were reported (Ruehl et al, 1998). The monoamine system plays an important role in cognitive processes, and MAO-B activity was reported to be elevated in Alzheimer's disease. Thus, selegiline treatment may normalize monoamine activity (Birks and Flicker, 2003). Selegiline was also reported to increase brain levels of anti-oxidants SOD and catalase in the brains of mice, rats, and dog – but it is dose-dependent, in an inverted U-shaped curve (i.e. doses too high may be detrimental) (Kitani et al, 1998)

APOE4 interactions:
One paper reported no influence on ApoE4 genotype on response to selegiline treatment (Kalman et al, 2003).

Aging and related health concerns: Selegiline has been reported to increase, decrease, or have no change in lifespan in animal model. The mechanism for an increase in lifespan is unclear.

Types of evidence:

- A meta-analysis of Parkinson's disease clinical trials
- 2 observational studies in Parkinson's patients
- Many preclinical studies in animal models suggesting increased and decreased lifespan

Lifespan

In a retrospective analysis of Parkinson's patients taking madopar (a drug that helps l-dopa get into the brain) + l-dopa compared to patients taking madopar, l-dopa, and selegiline (5-10mg), the later group of patients lived an average of 15.3 months longer. (Birkmayer et al, 1985). Another retrospective 7-year observational study reported that patients with Parkinson's disease taking levadopa were at a 2.45-fold increased risk for mortality compared to people without Parkinson's (avg age 72), but this risk was no longer significant when considering patients taking selegiline + levodopa (RR 0.92; 95%CI 0.37-2.31) (Doonan et al, 2000). In response to an open-label study from The Parkinson's Disease Research Group of the United Kingdom suggesting that selegiline increased the risk of mortality in Parkinson's patients, Olanow et a (1998) conducted a meta-analysis in four clinical trials comparing selegiline to non-selegiline treatments in Parkinson's patients and found no change in risk for mortality.

Joseph Knoll found a 35% increase in lifespan in rats in 1988. He and another group have conducted many studies since then. Life extension in rodent studies ranged from no change (4 studies), to slight single-digit increases (2 studies), to increases between 13%-24% (2 studies), to increases in lifespan above 30% (2 studies). Most of these studies come from Knoll and another Japanese group. The greatest increases in lifespan were seen in doses of 0.25mg/kg, 3 times per week (Mitteldorf blog).

Rodents with low sexual activity live shorter lifespans than those with high sexual activity. Selegiline increase the sexual activity in the rodents with low sexual activity and correspondingly increased lifespan. Lifespan was also increased when rodents with high sexual activity were given selegiline (Knoll et al, 1994). Very low doses of selegiline (0.1-0.001 mg/kg) did not increase lifespan in rats (Knoll and Miklya, 2016) while higher doses (1mg/kg 3 times per week) decreased lifespan (Kitani et al, 2006). In fact, Kitani et al (2006) reported that increasing doses of selegiline had an inverted U-shape effect on the expression of SOD1 and catalase in the striatum of rats.

Orthostatic hypotension
One potential side effect of selegiline is orthostatic hypotension, possibly by an increase in vasodilation mediated by increased dopamine levels, displacement of norepinephrine from nerve terminals, and decreased renin and aldosterone secretion (Bhattacharya et al, 2003). One study in 95 patients reported no difference in orthostatic hypotension measures comparing selegiline treatment (10mg/day) with levodopa (Bhattacharya et al, 2003). However, orthostatic hypotension is a potential side effect of levodopa, but most cases appear to involve selegiline + levodopa (Chrisp et al, 1991). This is an on-target side effect and can be managed with appropriate dosing.

Safety: Despite the potential for some side-effects, these are generally not serious. However, there are many potential drug interactions.

Types of evidence:

- 1 selegiline review

Selegiline has been in use since the 1960s. The most common side effects associated with selegiline use include headache (up to 26%), insomnia (11%), nausea (6%), fatigue (2%), dry mouth (2%), and anxiety (0.5%). Case reports of orthostatic hypotension have also been reported which may be associated with nonselective MAO inhibition. At higher doses selegiline becomes a non-selective MAO inhibitor (rather than a selective MAO-B inhibitor). Some cases of elevated liver enzymes have also been reported as well (Fabbrini et al, 2012). Orthostatic hypotension and increase in liver enzymes are rare though.

Drug interactions:
Selegiline should not be taken by individuals with liver or kidney disease, high blood pressure, or phenylketonuria. Additionally, you should not take it if you have taken fluoxetine within the past five weeks. It should also not be taken with cough medicines that contain dextromethorphan, cyclobenzaprine (Flexeril), meperidine or any other opioid pain medicine, methadone, St. John's wort, tramadol (Ultram), any antidepressants or MAO inhibitors (drugs.com). Many other potential drug interactions can be found here.

Sources and dosing:
Most Parkinson's studies used a 10mg tablet. A transdermal patch is also available for depression.

Research underway:
One clinical trial is underway testing a combination of selegiline and tadalafil in Parkinson's patients with erectile dysfunction.

ADDF is currently funding a clinical trial of rasagiline, a more specific MAO-B inhibitor, in patients with Alzheimer's disease.

Search terms:
Selegiline/selegiline + longevity, lifespan, alzheimer, cardiovascular, orthostatic hypotension