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.

Zileuton

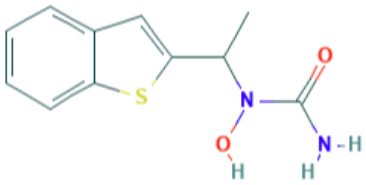
Evidence Summary

Zileuton is beneficial in Alzheimer's animal models, but no human studies have been conducted.

Neuroprotective Benefit: Multiple preclinical studies suggest a benefit in animal models.

Aging and related health concerns: Little evidence exists that zileuton is beneficial in age-related diseases.

Safety: Other than a rare increase in liver enzymes, zileuton is associated with few side effects.

Availability: Rx; in tablet form	**Dose**: 600mg 4 times per day for asthma; Alzheimer's animal studies estimated at 0.6-0.8mg/day	**Chemical formula**: $C_{11}H_{12}N_2O_2S$ **Molecular Weight:** 236.29 g/mol  **Source:** Pubchem
Half life: 2.5 hours	**BBB**: Unknown in humans. Possibly penetrant in animals	
Clinical trials: largest trial included 2,947 asthma patients	**Observational studies**: None	

What is it?

Zileuton is an asthma drug and an inhibitor of 5-lipoxygenase (5-LO). 5-LO inserts oxygen into free or esterified fatty acids, such as arachidonic acid which leads to the downstream production of various leukotrienes such as leukotriene B4 (LTB4). LTB4 mediates inflammatory processes and protects against infection. 5-LO is reported to be increased in the brains of Alzheimer's patients. In addition to its effect on 5-LO, zileuton is also reported to modulate gamma secretase, leading to the production of non-amyloidogenic products, and is reported to prevent the phosphorylation of tau (Chu and Pratico, 2016).

Neuroprotective Benefit: Multiple preclinical studies suggest a benefit in animal models.

Types of evidence:

- 13 preclinical studies in different Alzheimer's animal models
- 2 post-mortem studies in dementia patients

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

Post-mortem studies suggest ~40% increase in 5-LO in patients with progressive supranuclear palsy (PSP), a tau-degenerative disease (Giannopoulos et al, 2015). Additionally, 5-LO is increased in Alzheimer's patients and is found in glia, neurons, plaques, and tau tangles (Ikonomovic et al, 2008). A

pilot study suggested a mutation in 5-LO was increased in Alzheimer's patients (Qu et al, 2001), but a larger study did not confirm these results (Alvarez et al, 2008).

Human research to suggest benefits to patients with dementia:
None

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
In an Alzheimer's animal mode, 10-month treatment with zileuton in a prevention paradigm or genetic knockout of 5-LO improved cognition, decreased soluble and insoluble Aβ40 and 42, decreased amyloid plaques, decreased gamma secretase (which cleaves amyloid precursor protein – APP), decreased ptau, and decreased neuroinflammation (Chu et al, 2013). In a treatment paradigm, zileuton, an unspecified 5-LO inhibitor, and inhibition of 5-LO activating protein improved cognition, increased LTP, decreased soluble Aβ42 (but not Aβ40), decreased amyloid plaques, decreased gamma secretase, and decreased ptau. However, zileuton did not change neuroinflammation or synaptic markers (Di Meco et al, 2014; Giannopoulos et al, 2014; Chu and Pratico, 2013; Joshi et al, 2013; Giannopoulos et al, 2013). Likewise, genetic overexpression of 5-LO or overexpression with an adeno-virus in an Alzheimer's animal model decreased cognition, increased soluble and insoluble Aβ40 and 42, increased plaques, increased ptau, and increased gamma secretase (Chu et al, 2012a; Chu et al, 2012b).

In a tau Alzheimer's animal model, zileuton in treatment and prevention paradigms and genetic deletion of 5-LO improved cognition, reduced ptau, increased synaptic markers, and reduced neuroinflammation (Giannopoulos et al, 2018a; Giannopoulos et al, 2018b; Giannopoulos et al, 2015; Chu and Pratico, 2013; Vagnozzi et al, 2017). The reduction in amyloid pathology with zileuton treatment is reported to be independent of the reduction in tau pathology (Giannopoulous et al, 2015). *In vivo* studies suggest that zileuton downregulates downstream products of 5-LO suggesting that it crosses the blood brain barrier. *In vitro* studies suggest that downregulation of 5-LO decreases tau phosphorylation (Vagnozzi et al, 2017).

APOE4 interactions:
None

Aging and related health concerns: Little evidence exists that zileuton is beneficial in age-related diseases.

Types of evidence:

- 6 preclinical studies in various animal models

In vitro studies suggest that zileuton prevented H2O2-induced cell death of cardiac myogenic cells (Kwak et al, 2010). In a rat model of myocardial infarction, zileuton was associated with a trend toward decreased tissue injury (not significant), a decrease in apoptotic cells, a decrease in NF-kB staining, but no decrease in serum TNFα (Abueid et al, 2017). However, leukotriene production may be important for the production of pro-resolving mediators and tissue healing (Hoxha et al, 2017), and, in fact, zileuton increased mortality in a mouse model of myocardial infarction (Blomer et al, 2013).

Another 5-LO inhibitor, CJ-13610, reduced pain in a rat model of osteoarthritis-like pain (Cortes-Burgos et a, 2009). Preclinical studies also suggest that zileuton may attenuate brain damage after ischemia (Tu et al, 2016).

Safety: Other than a rare increase in liver enzymes, zileuton is associated with few side effects.

Types of evidence:

- One large clinical study
- One review

In a 12-month clinical trial of 2,947 asthma patients, zileuton increased liver enzymes in 4% of patients. It also may cause indigestion and nausea (Dube et al, 1999; Lazarus et al, 1998). Rare reported side effects include flu-like symptoms, itching, stomach pain, and tiredness (drugs.com).

Drug interactions:
Reported major drug interactions include leflunomide, lomitapide, mipomersen, pimozide, pseudoephedrine, terfenadine, teriflunomide, and tizanide (drugs.com). There are many moderate drug interactions as well (drugs.com). Alcohol should be avoided with zileuton due to the risk of liver injury.

Sources and dosing:
600mg 4 times per day for asthma; Alzheimer's animal studies estimated at 0.6-0.8mg/day (zileuton was given in drinking water).

Research underway:
There are no clinical trials underway.

Search terms:
Pubmed: **zileuton + alzheimer, aging, cardiovascular, osteoarthritis, longevity, atherosclerosis, hypotension, neuropathy, infarction**