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## Nicotine

### Evidence Summary

Nicotine can improve cognitive function, particularly attention, but there is no clear evidence for neuroprotection. Evidence from non-smokers is weak and it may have a negative impact on sleep quality.

**Neuroprotective Benefit:** Can improve attention. Low dose patches have been reported to improve cognition in the elderly, but the evidence is weak.

**Aging and related health concerns:** No compelling data on the effects of nicotine on aging outside the context of tobacco use, which is associated with shorter lifespan.

**Safety:** Low dose nicotine patches (5-15 mg) are generally well-tolerated, but high doses are associated with reduced sleep quality, headaches, and gastrointestinal side effects. It also has addictive potential.

**What is it?** Nicotine is an alkaloid created by the nightshade family of plants that can act as both a stimulant and a relaxant by activating the nicotinic acetylcholine receptors (nAChRs) of the parasympathetic nervous system. A variety of nicotinic receptors exist. Each receptor is made up of 5 subunits out of a possible 17 subunits in vertebrates. Neuroprotection most likely occurs through the  $\alpha 4\beta 2$  and  $\alpha 7$  nAChRs, since they are the most widely expressed in the human brain.

**Neuroprotective Benefit:** Can improve attention. Low dose patches have been reported to improve cognition in the elderly, but the evidence is weak.

*Human evidence:* Nicotine treatment, as opposed to smoking or tobacco use, may protect against age-related neurodegeneration but the evidence is mixed. It is also complicated by acute cognitive effects and by inadequate long-term data on nicotine independent of smoking and tobacco. For nicotine independent of smoking, multi-year evidence for cognitive function effects is not available. The longest human study on nicotine alone was a 6 month double-blind RCT, testing a 15 mg/day nicotine patch; the treatment mildly improved attention, memory, psychomotor speed in 67 non-smoking patients with mild cognitive impairment [1]. However, this study has been criticized for failing to statistically control for false positives given the variety of cognitive outcomes tested. In two small trials, lower doses of nicotine patches (5-10 mg) led to significant improvements in only a few of the various cognitive function measures tested in patients with age-associated memory impairment [2] or healthy elderly patients [3]. It is unclear whether these effects are due to neuroprotective activity, since nicotine is well-known to provide also produce symptomatic improvements in cognition [4].

Long-term epidemiological studies have focused on the most common form of nicotine delivery – tobacco smoke – which contains 4700 compounds, many of which are highly toxic. Smoking likely raises the risk of dementia (Risk ratio (RR): 1.79, 95% CI 1.43-2.23) [5] although it does not accelerate the rate of decline in patients [6]. The association is primarily restricted to current rather than former smokers, which is surprising if smoking accelerates underlying pathology. Some earlier studies reported a protective association with smoking but this was likely due to healthy survivor bias (smokers who would have gotten Alzheimer's left the study early due to other comorbidities) [7].

*Mechanistic rationale:* Rodent and cell culture studies report both protective and harmful effects of nicotine. Nicotine exacerbated tau aggregation and phosphorylation in two rodent models [8, 9] yet protected against beta-amyloid pathology or toxicity in a variety of models ([10-14]), in part through the  $\alpha 7$  nAChRs [15]. In transgenic mice, high-dose but not low-dose cigarette smoke worsened amyloid beta load, plaque density, microglial activation, reactive astrogliosis, and tau hyperphosphorylation but not neuronal death [16].

The  $\alpha 7$  nAChRs are the target of many drug development programs for Alzheimer's disease. However, these programs have so far been unsuccessful, and the effective treatment strategy is not clear, whether for novel drugs or nicotine treatment. Chronic nicotine treatment increases the levels of  $\alpha 7$  nAChRs and other nicotinic receptors. In contrast, these receptors are typically reduced in Alzheimer's disease patients. However, since both neuroprotective and neurodegenerative properties have been observed with  $\alpha 7$  nAChR activation, it is not clear whether increased expression of  $\alpha 7$  nAChRs would be protective in patients. Although nicotinic binding to  $\alpha 7$  nAChRs protects neurons in some assays, A $\beta$  also activates the  $\alpha 7$  nAChRs, possibly exacerbating intracellular plaque accumulation and pathology. Some researchers speculate that the ideal therapeutic strategy would be to block A $\beta$  binding to the  $\alpha 7$  nAChRs and/or desensitize the  $\alpha 7$  nAChRs [17] while other researchers have been developing ligands to activate or raise the activity of  $\alpha 7$  nAChRs [18].

**Aging and related health concerns:** No compelling data on the effects of nicotine on aging outside the context of tobacco use, which is associated with shorter lifespan.

**Lifespan:** Smoking accelerates aging and shortens expected lifespan but the effects of nicotine independent of smoking cessation on aging and lifespan have not been significantly studied. In a fruit fly model of Parkinson's disease, nicotine increased lifespan ([Chambers 2013](#)). A nicotine receptor locus has been associated with lifespan in men but the locus has been correlated with the probability of smoking, which likely explains that association ([Pilling 2016](#)).

**Safety:** Low dose nicotine patches (5-15 mg) are generally well-tolerated, but high doses are associated with reduced sleep quality, headaches, and gastrointestinal side effects. It also has addictive potential.

**Safety (for nicotine rather than tobacco):** Nicotine therapy is well-tolerated but there are a few safety concerns. In a 6-month clinical trial in elderly with mild cognitive impairment, a nicotine patch at 15 mg/day caused more adverse events than placebo (82 vs 52) although most of these events were mild and related to *gastrointestinal and neurologic symptoms* [1]. Nicotine can impair *sleep quality*, based on both short-term clinical trials of nicotine treatment in non-smokers and epidemiological comparisons of smokers and nonsmokers, but these effects may be dose-dependent [19, 20]. A short-term RCT reported several effects of 16 mg but not 8 mg patches [20]. For *cancer*, nicotine is far safer than tobacco itself but some laboratory studies report that nicotine can promote tumor growth and metastasis [21] by stabilizing  $\beta$ -catenin, part of the canonical Wnt pathway [11]. The effects likely differ based on the type of cancer, similar to smoking. *Addiction:* Nicotine is probably slightly addictive although this is controversial. The surgeon general and others argue that nicotine is extremely addictive [22] but other scientists have argued that their reports are biased and fail to cite evidence such as de-nicotinized tobacco cigarettes resolving cravings and the lack of evidence for positive

reinforcing effects for nicotine per se [23]. On the other hand, nicotine replacement therapy does mitigate symptoms of nicotine withdrawal syndrome, suggesting that nicotine has at least some addictive properties. Nicotine may act on the  $\alpha 4 \beta 2$  receptor in the ventral tegmental area of the brain to influence the dopaminergic reward pathway.

**Drug Interactions:** Nicotine is reported to have no severe interactions with other medications but has 12 moderate and 41 minor drug interactions according to [drugs.com](https://www.drugs.com). **Cardiovascular indications** are unlikely a serious concern for low-dose nicotine therapy. Although smoking raises the risk of cerebrovascular events, in part because nicotine raises heart rate, blood pressure, and myocardial contractility, nicotine replacement therapy has not consistently reported these effects on heart rate/blood pressure. A meta-analysis of 34 RCTs reported no increased risk of stroke, myocardial infarction, palpitations, angina, arrhythmia, or hypertension with nicotine treatment (reviewed in [24]).

**Dosing and Sources:** A variety of nicotine-replacement therapies are available that lack most of the harmful effects of tobacco. Patches containing 5-15 mg of nicotine improved some cognitive outcomes in small trials [1-3]. Doses at the lower end of that range may have reduced detrimental effects on sleep [20].

**Drugs in development:** Pharmaceutical companies and other groups have been working to develop selective nAChR agonists for Alzheimer's, Parkinson's disease, and other CNS indications, many of which target the  $\alpha 7$  nAChRs. Several programs are reviewed in [18]. Most of these programs have failed due to poor oral bioavailability, side effects, or a lack of efficacy. Additionally, it is still unclear whether the correct therapeutic strategy will be increased or decreased activity of the  $\alpha 7$  nAChRs [17]. Another molecule – anatabine – is a tobacco alkaloid similar in structure to nicotine that is also suggested to protect against Alzheimer's disease based on three preclinical studies from one lab (e.g. [25]), but there is no data yet to support a role for aging biology or longevity.

**Cotinine** is a major natural metabolite of nicotine that accumulates in the body after tobacco exposure but is reported to be 100 times less toxic than nicotine, non-addictive, safe for the cardiovascular system, and bioavailable for a much longer period than nicotine. Cotinine had behavioral and memory-improving effects in several studies in either large mammals or transgenic rodents. The mechanism of action is unclear but possibly involves positive allosteric modulation of the  $\alpha 7$  nAChRs [15].

At this point, pharma development of  $\alpha 7$  nicotinic receptor agonists has been largely halted.

Search terms

- nicotine + lifespan, aging, dementia, Alzheimer's, cognitive

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If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact [INFO@alzdiscovery.org](mailto:INFO@alzdiscovery.org). To view our official ratings, visit [Cognitive Vitality's Rating page](#).