



Nicotine

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Nicotine is an addictive alkaloid created by the nightshade family of plants, which is commonly found in tobacco products. Nicotine can act as both a stimulant and a relaxant by activating the nicotinic acetylcholine receptors (nAChRs) of the parasympathetic and sympathetic nervous systems.

Tobacco products are unquestionably dangerous. The [World Health Organization](#) estimates that tobacco kills up to half of its users, resulting in nearly 6 million deaths per year. Moreover, tobacco smoke is estimated to contain over 4,700 compounds, many of which are highly toxic [1]. Smoking tobacco will likely raise the risk of dementia. Nicotine, when taken independently from tobacco, may protect against cognitive decline or dementia, though the evidence is mixed.

EVIDENCE AND POTENTIAL BENEFIT FOR BRAIN HEALTH

Rated 3/4 based on 2/4 evidence

The quality of the available research is limited, in part, because information on long-term nicotine use in humans comes entirely from the use of tobacco, a practice that likely raises the risk of dementia and delivers thousands of compounds other than nicotine, many of which are highly toxic.

Randomized controlled trials: There is some evidence for nicotine treatment independent of tobacco from short clinical trials. In a meta-analysis of 41 randomized controlled trials, nicotine improved aspects of fine motor skills, attention, and memory in healthy adult non-smokers or smokers who are not tobacco-deprived [2]. These enhancements may be seen even in elderly people but may have little to do with the long-term risk of dementia or cognitive aging.

In two small trials, lower doses of nicotine patches (5–10 mg) improved some but not most aspects of cognitive function in patients with age-associated memory impairment [3] or healthy elderly patients [4]. These effects could suggest neuroprotection but more likely indicate symptomatic improvements in cognition that are well-known for nicotine [2].

For patients with mild cognitive impairment, the longest and largest known trial treated 74 non-smokers for 6 months with a starting dose of 5 mg/day of nicotine that increased to 15 mg/day by day 21. The double-blind randomized trial reported improved attention, memory, and psychomotor speed, but no global improvement as rated by clinicians [5]. It was high quality for an initial exploratory trial, but it needs to be replicated and was not intended to conclusively determine effects on cognition [6; 7]. In an even smaller trial in elderly patients



with memory problems, a lower dose of nicotine patches (5–10 mg for 16 hours/day for 4 weeks) did improve scores on attention and the [clinician rating of global improvement](#) but had no effect on memory [3]. A new trial is underway with support from the National Institute of Aging and the [Alzheimer's Drug Discovery Foundation](#) (enter “Newhouse” under “Search Grants”) to more conclusively test the effects of transdermal nicotine in patients with mild cognitive impairment [8].

Biology: Many variations of nicotinic receptors exist, with each receptor made up of 5 subunits. The nicotinic receptors most highly expressed in the brain are the $\alpha_4\beta_2$ and α_7 nicotinic acetylcholine receptors (nAChRs) [9]. Acetylcholine is a very important neurotransmitter in the body and brain that aids memory and attention. In Alzheimer's disease patients, acetylcholine in the brain is dramatically reduced because neurons releasing it are damaged or dead.

Animal and cell culture studies report both harmful and protective effects of nicotine. Tau protein aggregation and beta-amyloid plaque buildup are both components of Alzheimer's disease. Nicotine exacerbated the tau features of Alzheimer's disease pathology in two animal models [10; 11], yet protected against the beta-amyloid features in other models [12; 13; 14], in part through activating the α_7 nAChRs [15]. Nicotine can also impair sleep [16], which could theoretically increase the risk of dementia because some studies suggest that proper sleep is important for the clearance of toxic proteins from the brain [17].

The α_7 nAChRs are the target of many drug development programs for Alzheimer's disease. These programs have so far been unsuccessful and the treatment strategy is unclear. Chronic nicotine treatment increases the levels of α_7 nAChRs and other nicotinic receptors [18]. In contrast, these receptors are typically reduced in Alzheimer's disease [19]. However, increased expression of α_7 nAChRs will not necessarily be effective as both neuroprotective [12; 13; 14] and neurodegenerative [10; 11] properties have been observed. Although nicotine binding to α_7 nAChRs protects neurons in some assays, A β also activates the α_7 nAChRs, possibly exacerbating intracellular plaque accumulation and pathology. Some researchers speculate that the ideal therapeutic strategy will block A β binding to the α_7 nAChRs and/or desensitize the α_7 nAChRs [20] while other researchers have been developing ligands to activate or raise the activity of α_7 nAChRs [9]. The pharmaceutical industry has looked carefully at whether selective drugs for the α_7 receptor for nicotine could treat Alzheimer's disease but nicotine itself is unlikely to be a successful drug against this receptor, in part because it causes a rapid desensitization [21].

APOE4 carriers: There is no substantive evidence that nicotine will be more or less protective in APOE4 carriers versus non-carriers. Nicotine may have stronger cognitive enhancing effects in APOE4 carriers, based on a handful of experiments from one laboratory on young or middle-aged healthy adults [22; 23; 24], but older smokers with



APOE4 were the most likely group to have impaired cognition and low brain metabolism [25]. However, in studies of Alzheimer's disease patients, APOE4 status did not alter the association of smoking history on disease progression or the pathological signs of Alzheimer's disease in the brain [26]. For more information on what the APOE4 gene allele means for your health, read our [APOE4 information page](#).

For Dementia Patients

Alzheimer's patients are not likely to benefit much from nicotine treatment, although the evidence is based on a handful of small clinical trials that were judged to be of poor quality in a 2001 meta-analysis by the Cochrane Collaboration [27].

SAFETY

Rated 2/4

Nicotine therapy not provided through tobacco is well-tolerated but there are some safety concerns including impaired sleep, addiction, interactions with other medications, gastrointestinal symptoms, and possibly cardiovascular effects. Some individuals may have health conditions that substantially raise safety risks of nicotine. If you are considering nicotine use, discuss the safety with your health care provider.

Most experts agree that nicotine is highly addictive [28], although some scientists disagree and argue that tobacco use is addictive for reasons other than nicotine [29]. Nicotine interacts with many drugs so the use of other medications can impact the safety of nicotine treatment.

Nicotine can impair sleep quality, as shown in short clinical trials in nonsmokers and in observational studies that compare smokers and nonsmokers [30]. Sleep impairment is likely worse with higher doses. A short randomized controlled trial reported that nicotine patches of 16 mg but not 8 mg impaired sleep in young healthy adults [31]. Longer studies in older patients would be helpful to understand the potential risks of nicotine on sleep in older patients susceptible to sleeping problems.

Tobacco dependence seriously raises risks for cardiovascular diseases, but it is unclear whether nicotine replacement therapy carries similar risks, particularly with the low doses (5–15 mg/ day) used in trials for cognition. Nicotine activates the sympathetic nervous system and encourages blood clotting [32], suggesting that nicotine treatment does have the same risks. High doses of nicotine can have major effects on blood pressure and heart rate (e.g., 21–63 mg/day) but lower doses might also have negative effects in non-smokers who are unaccustomed to regular tobacco use. Most evidence has been gathered from the use of nicotine replacement therapy in smokers trying to quit. In that situation, many clinical trials report that nicotine replacement therapy does not increase the risk of stroke, heart attacks, palpitations, angina, arrhythmia, or hypertension [32; 33].



If nicotine treatment does prove helpful to elderly people with mild cognitive impairment, more research would be needed to ensure the safety of low-dose nicotine patches in elderly non-smokers. In a six-month clinical trial in elderly patients with mild cognitive impairment, a nicotine patch at 15 mg/day caused some adverse effects [5]. However, most of these effects were mild and related to gastrointestinal and neurological symptoms.

Some experts have cautioned that the flavorings used in e-cigarettes might pose a risk, particularly for lung toxicity. The most commonly cited flavoring is diacetyl, which provides a buttery or creamy flavor and previously caused severe and acute-onset lung disease in people who worked in a microwave popcorn production plant. Many other flavorings are used in these products, most of which have little to no evidence for safety when inhaled rather than eaten [34].

HOW TO USE

Tobacco use will likely raise the risk of dementia and undoubtedly cause many severe illnesses. Nicotine that is not delivered through tobacco is typically sold as nicotine replacement therapy, marketed to help people stop using tobacco. Therapies include patches, gum, nasal sprays, inhalers and e-cigarettes, and lozenges. Patches, gum, and lozenges can typically be purchased over-the-counter while inhalers and nasal sprays require a doctor's prescription. These products usually contain no tobacco but rather synthetic nicotine and other compounds. More information about nicotine replacement therapy, including the side effects of different doses, can be found from the [American Cancer Society Guide to Quitting Smoking](#).

The most common nicotine replacement therapy used in studies of cognition is patches, probably because the dose is more reliable. The dose of nicotine that improved some aspects of cognition in small trials ranged from 5–15 mg/day [3; 4; 5]. Higher doses likely have greater risk of sleep side effects [19].

Discuss the pros and cons of nicotine use with your healthcare providers, including a review of all your medications and supplements since nicotine can interact with some drugs. Nicotine has some safety risks as described above and is an addictive substance that may cause withdrawal symptoms when stopped.

WHAT'S THE FUTURE?

More clinical research is underway on the effects of nicotine independent of tobacco, particularly in elderly people and in people with neurodegenerative diseases including Alzheimer's. A phase 2 clinical trial will be testing the effects of transdermal nicotine in 300 patients with mild cognitive impairment, supported in part by the [Alzheimer's Drug Discovery Foundation](#) (enter "Newhouse" under "Search Grants"). Another trial is currently underway to test whether nicotine can slow cognitive decline in adults with Down's



syndrome. Two clinical trials examining the effects of nicotine on cognitive performance and neural networks (the default network of resting brain function) in healthy nonsmokers have been completed but their results have not been published yet. More information about these and other clinical trials can be found at clinicaltrials.gov.

Pharmaceutical companies and other groups have been working to develop selective nAChR agonists for Alzheimer's, Parkinson's disease, and other CNS indications, often though not always to target the $\alpha 7$ nAChRs [9]. Most of these programs have failed due to poor oral bioavailability, side effects, or a lack of efficacy. As described above, it is still unclear whether the correct therapeutic strategy will be increased or decreased activity of the $\alpha 7$ nAChRs [20].

Cotinine is being evaluated as a possible replacement for nicotine. It is a natural metabolite of nicotine that accumulates in the body after tobacco exposure, but is reported as less toxic, 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 large mammals or transgenic rodents [15]. However, we are aware of no clinical research underway to test whether these cognitive effects occur in humans.

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