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.

### Nicotine

**Evidence Summary**
Nicotine may have modest effects on cognition. Ongoing trials in AD patients may shed more light on efficacy. Nicotine can have negative effects on sleep and cause gastrointestinal complaints and chest pain.

**Neuroprotective Benefit:** May improve cognitive function, though larger studies are needed. There are brain health benefits for smokers if used as smoking cessation aid.

**Aging and related health concerns:** There is little data on the impact of nicotine on age-related diseases. Nicotine replacement therapy can significantly increase the chance of quitting smoking, which reduces incidence of various age-related diseases.

**Safety:** Nicotine treatment can cause gastrointestinal complaints, headache, sleep issues, and chest pain / heart palpitations, along with administration-specific side effects. There is little data on long-term safety.
**What is it?**

Nicotine is an alkaloid created by members of the nightshade plant family, particularly the tobacco subfamily (Sieg mund et al., 1999). Nicotine is most often associated with smoking tobacco, which is the single greatest cause of preventable death in the world (Stringhini et al., 2017). It is thought that nicotine drives much of the addictive potential of tobacco products. As nicotine itself is at minimum a far lower health risk than smoking tobacco, nicotine has been widely studied and used as an effective smoking cessation aid (Samet et al., 2013). However, some groups hypothesize that nicotine itself at certain doses may have beneficial effects.

Along with acetylcholine and other specific agonists, nicotine binds to and typically activates nicotinic acetylcholine receptors (nAChRs). Each nAChR is made up of 5 subunits out of a possible 17 subunits in vertebrates, and different subunit combinations lead to receptors with a variety of different physiological behaviors. These receptors are expressed throughout the human body, including on immune cells and certain cancer cells (Terry Jr. et al., 2023). Neuronal nAChRs modulate neurotransmission of various neurotransmitters and most research has focused on the neurological function and consequences of neuronal nAChRs. As the cholinergic system is highly implicated in cognition, nicotine has been under particular interest as a cognitive enhancer and/or a treatment for Alzheimer’s disease, though nAChRs may play a role in a number of other neurological and psychiatric disorders (Yu et al., 2014; Hoskin et al., 2019).
Neuroprotective Benefit: May improve cognitive function, though larger studies are needed. There are brain health benefits for smokers if used as smoking cessation aid.

Types of evidence:
- 1 Cochrane review
- 6 clinical trials
- 3 observational studies
- 6 reviews
- 1 laboratory studies

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.

Disease-modifying associations require longer studies to detect but so far 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 raises the risk of dementia (RR=1.79; 95% CI 1.43 to 2.23) (Anstey et al., 2007) although it does not accelerate the rate of decline in patients (Blom et al., 2013). 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) (Swan & Lessov-Schlaggar, 2007).

As smoking increases the risk of dementia, nicotine in the form of nicotine replacement therapy (NRT) as a smoking cessation aid would likely mitigate that risk. This neuroprotective section will focus on nicotine for non-smokers as cognitive enhancement therapy, not NRT as a risk mitigation tool.

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

There is some evidence that nicotine may enhance cognitive function in cognitively intact individuals. Min et al., 2001 tested the effects of 5 mg nicotine or placebo patches in 63 healthy non-smoking elderly subjects. The researchers administered cognitive testing at baseline and at 5.5 hours after application of
the patch. They found that nicotine administration was associated with improved short-term verbal memory, and that this effect was correlated with plasma levels of nicotine.

The cognitive enhancing activities of nicotine may depend on the age or genetics of the subject population. A study of 56 non-smokers aged 18 to 30 gave participants either placebo or 1 mg nicotine nasal spray, and then administered cognitive testing. The study found that nicotine enhanced the performance of the APOE4 carriers on measures of decision making, prospective memory, and verbal fluency, and did not affect performance of non-APOE4 carriers (Marchant et al., 2010). Another study of 40 adults aged 18 to 30 also tested 1 mg of nicotine nasal spray or placebo, but instead assessed cognition through tasks performed in an fMRI. This study also found that nicotine improved reaction time specifically in APOE4 carriers, and that nicotine administration changed brain activity as measured by fMRI in different ways in APOE4 carriers as compared to non-carriers (Evans et al., 2013).

A 2014 randomized, double-blinded crossover trial examined the effects of acute administration of placebo or nicotine in 16 young (aged 18 to 30) and 16 healthy older (aged 60 to 75) adults on cognitive function. They found that in young adults, there was no impact on the cognitive functions assessed by the trial, whereas nicotine decreases visual and working memory in older adults. However, they found that the effect was dependent on baseline cognitive function. Those with baseline performance that was below average had improved performance with nicotine, whereas those with above average performance had decreased performance (Niemegeers et al., 2014).

Acute nicotine administration was found to improve performance on certain auditory processing tasks. The 2021 randomized, single-blinded crossover study enrolled 10 young (19 to 23 year old) and 10 older (61 to 80 year old) adults. Participants received either placebo or nicotine and underwent auditory processing testing. They found that nicotine treatment improved discrimination of intensity, but not frequency modulation. The authors reported that there was more improvement for those with lower baseline performance (Sun et al., 2021).

Overall, these results imply that nicotine may improve certain aspects of cognitive function in some groups. However, the small size of the trials is a significant limitation. These trials also do not touch on chronic use of nicotine.
Human research to suggest benefits to patients with dementia:

For nicotine independent of smoking, multi-year evidence for cognitive function effects is not available. The longest human study on nicotine alone reported, in a double-blind RCT, 6 months of 15 mg/d nicotine patch mildly improved attention, memory, psychomotor speed in 67 non-smoking patients with mild cognitive impairment (Newhouse et al., 2012). The study has been criticized for failing to statistically control for false positives given the variety of cognitive outcomes tested. In one small trial, lower doses of nicotine patches (5-10 mg) improved some but not most aspects of cognitive function in patients with age-associated memory impairment (White & Levin, 2004). These effects might indicate neuroprotection but more likely indicate symptomatic improvements in cognition that are well-known for nicotine (Anstey et al., 2007).

Curiously, many studies have found that people who smoke tobacco have a lower rate of Parkinson’s disease (PD) than non-smokers. Former smokers are estimated to have a 20% lower risk of PD, and current smokers can have a 30% to 50% lower risk (Gallo et al., 2019; Mappin-Kasirer et al., 2020). The relationship appears to be dose-related, though it is uncertain whether duration of smoking or intensity of smoking is more related, and it does not appear to be a result of selective mortality (Piao et al., 2009; Gallo et al., 2019). While these results have been replicated in many observational studies, it is still difficult to separate association from causation. It is also difficult to say whether the protective effect is due to nicotine rather than other compounds in tobacco smoke, though one study did find that PD diagnosis was inversely associated with dietary consumption of vegetables in the nightshade family (Nielsen et al., 2016).

A blinded trial of 163 people with PD randomized participants to either transdermal nicotine patches or placebo for 1 year. The study found that nicotine treatment did not slow progression compared to placebo (Oertel et al., 2023). These results replicate other trials in PD (Villafane et al., 2018). More work is needed to identify whether nicotine itself can be preventative of PD or if the lower risk of PD in smokers stems from either a confounded association – for instance, that people who will develop PD are predisposed to start smoking – or to a different compound in tobacco smoking.

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

Nicotine modulates the cholinergic system through its binding to nAChRs; given the importance of the cholinergic system in cognition and AD, nicotine and other nAChRs agonists have been under
investigation for their symptom modulation and potentially neuroprotective roles. nAChRs are composed of 5 of a possible 17 subunits, resulting in a dizzying number of possible protein combinations, all that would have their own physiological functions. Two nAChR variants known as α4β2 and α7 nAChRs based on their subunit composition are the most widely expressed in the human brain, and therefore many of the neuroprotective roles theorized about nicotine are thought to be mediated through one of these two receptors (Terry Jr. et al., 2023; Wang et al., 2023).

Studies have found that expression of α4β2 nAChRs is reduced in patients with AD, and correlations have been observed between the loss of α4β2 and cognitive decline. The picture is more complex for α7 nAChRs, with different studies finding different trends of expression in AD. One hypothesis for this discrepancy in results is that the α7 nAChR expression patterns vary based on stage of the disease (Terry Jr. et al., 2023).

Rodent and cell culture studies report both protective and harmful effects of nicotine. Nicotine exacerbated tau aggregation and phosphorylation in two rodent models (Oddo et al., 2005; Deng et al., 2010) yet protected against beta-amyloid pathology or toxicity in a variety of models (Xue et al., 2014; Inestrosa et al., 2013; Brown et al., 2013; Guo et al., 2015; Xue et al., 2015), in part through the α7 nAChRs (Echeverria & Zeitlin, 2012). 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 (Moreno-Gonzalez et al., 2013).

The cholinergic system is involved in inflammatory processes, and nAChRs, particularly α7 nAChRs, are found on many immune cells such as microglia. Nicotine is thought to have a number of anti-inflammatory effects through its modulation of nAChRs, such as reducing expression of TNF-α and IL-1β and modulating levels of a variety of other cytokines. These anti-inflammatory actions have been shown to improve cognition in preclinical models of disease such as ischemic stroke (Han et al., 2020), and could be a mechanism of action in neuroprotection in other contexts as well. Nicotine can activate a variety of signaling pathways such as AMPK that may underlie other nicotine effects (Zhang et al., 2022; Wang et al., 2023).

nAChRs have been the target of many drug development programs for Alzheimer’s disease, though these trials have largely failed. Studies have found that α4β2 nAChR expression is decreased in brain tissue from AD patients and that levels of α7 nAChRs appear to vary, potentially based on disease stage (Terry Jr. et al., 2023). Chronic nicotine treatment increases the levels of α7 nAChRs and other nicotinic
receptors. However, increased expression of α7 nAChRs will not necessarily be protective as both
neuroprotective and neurodegenerative properties have been observed. Although nicotinic binding to
α7 nAChRs protects neurons in some assays, Aβ also activates the α7 nAChRs, possibly exacerbating
intracellular plaque accumulation and pathology at high Aβ levels. Some researchers speculate that the
ideal therapeutic strategy will block Aβ binding to the α7 nAChRs and/or desensitize the α7 nAChRs (Oz
et al., 2013) while other researchers have been developing ligands to activate or raise the activity of α7
nAChRs (Posadas et al., 2013).

There are other factors that may contribute to the general failures of nicotine or other nAChR agonist
trials. While there are mechanisms of action through both the α7 and α4β2 nAChRs, it is unclear
whether targeting just one or the other might be more useful. The exact dosage of nicotine is also
important, as there appears to be a U-shaped dose response curve to nicotine (Wang et al., 2023).
Genetic factors may also be involved. A 2020 paper suggested that response to nAChR agonists may
partly depend on whether an individual is a carrier of CHRFAM7A, a fusion gene found only in humans
that affects function of α7 nAChRs in a way that may decrease response to cholinergic modulators. The
authors estimated that approximately 75% of individuals are carriers of this gene, leaving 25% of the
population that might respond better to nAChR agonists. They hypothesize that this gene may
contribute to the response rate of acetylcholinesterase inhibitor drug trials (Szigeti et al., 2020).

APOE4 interactions:

It is not yet clear whether nicotine treatment interacts with APOE4 status in patients with dementia.
However, there is some preliminary evidence to suggest that nicotine treatment may be more effective
in APOE4 carriers. Newhouse et al., 2012 found that participants who had two APOE4 copies had greater
improvement from daily 15 mg nicotine patch treatment than individuals with either one or no copies of
APOE4. A randomized blinded study of 56 non-smokers aged 18 to 30 gave participants either placebo
or 1 mg nicotine nasal spray, and then administered cognitive testing to compare the performance of
individuals with two copies of APOE3 to individuals with at least one copy of APOE4. The study found
that nicotine enhanced the performance of the APOE4 carriers on measures of decision making,
prospective memory, and verbal fluency, and did not affect performance of non-APOE4 carriers
(Marchant et al., 2010). Another study of 40 adults aged 18 to 30 used the same study design, but
instead assessed cognition through tasks performed in an fMRI. This study also found that nicotine
improved reaction time specifically in APOE4 carriers, and that nicotine administration changed brain
activity as measured by fMRI in different ways in APOE4 carriers as compared to non-carriers (Evans et al., 2013).

One hypothetical mechanism of action suggested by both studies is that APOE4 carriers have altered cholinergic signaling compared to non-APOE4 carriers – for instance, older APOE4 carriers may have less of the precursors and machinery needed to produce acetylcholine – and may therefore be more responsive to nicotine treatment which can enhance cholinergic signaling.

**Aging and related health concerns:** There is little data on the impact of nicotine on age-related diseases. Nicotine replacement therapy can significantly increase the chance of quitting smoking, which reduces incidence of various age-related diseases.

**Types of evidence:**
- 1 meta-analysis
- 2 reviews

Nicotine has been studied for its effects on health conditions ranging from pain to cancer, though many of these studies are confounded as they study tobacco smokers rather than treatment with nicotine. Nicotine is a known analgesic, though long-term exposure can cause increased sensitization to pain (Iida et al., 2022). While it is unclear whether nicotine itself is a carcinogen, nicotine is thought to have several actions that can promote cancer, such as stimulating cell proliferation and angiogenesis (Wessler & Kirkpatrick, 2008; Bele et al., 2023). The clinical effect of nicotine in these contexts – particularly of long-term use – remains to be fully elucidated.

**Lifespan:** UNCLEAR EFFECT

Smoking accelerates aging and shortens expected lifespan; as of 2023, it is thought to be the greatest contributor to preventable deaths (Stringhini et al., 2017). In a fruit fly model of Parkinson’s disease, nicotine increased lifespan (Chambers 2013). However, the effects of nicotine independent of smoking cessation on aging and lifespan have not been significantly studied. A nicotine receptor locus has been associated with lifespan in men but the locus has been correlated with the probability of smoking, which probably explains that association (Pilling 2016).
Smoking Cessation: BENEFIT AS NICOTINE REPLACEMENT THERAPY

Smoking tobacco is the greatest preventable health threat to humans, harming nearly every organ in the body and raising risk of diseases such as cancer, cardiovascular disease, respiratory disease, and stroke (CDC). A 2018 Cochrane review and meta-analysis of more than 130 RCTs comprising 64,640 participants investigated the relative efficacy of NRT vs. placebo or no treatment for smoking cessation. The authors found high-quality evidence that all forms of nicotine replacement therapy (NRT) increases the rate of quitting smoking tobacco by 50% to 60% (Hartmann-Boyce et al., 2018).

Safety: Nicotine treatment can cause gastrointestinal complaints, headache, sleep issues, and chest pain / heart palpitations, along with administration-specific side effects. There is little data on long-term safety.

Types of evidence:
- 1 Cochrane meta-analysis
- 1 meta-analysis
- 1 observational study
- 1 laboratory study

As nicotine is a common first-line treatment for smoking cessation, the adverse events in populations trying to quit smoking are fairly well understood. A Cochrane review and meta-analysis of the efficacy of NRT in more than 130 studies including 64,640 subjects found that adverse events typically were related to the route of NRT administration. They were not able to analyze the incidence of most of the adverse events due to the variation of reporting of these adverse events. Common adverse events included headache, dizziness, gastrointestinal disturbances including nausea / vomiting, sleep disturbances such as insomnia or nightmares, skin reactions, oral reactions, hiccups, and chest palpitations. The most common adverse events by product type are included below:
<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Adverse Events Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gum</td>
<td>Hiccups, GI disturbances, jaw pain, orthodontal problems</td>
</tr>
<tr>
<td>Lozenge</td>
<td>Hiccups, burning / smarting sensation in mouth, sore throat, coughing, dry lips, mouth ulcers</td>
</tr>
<tr>
<td>Nasal Spray</td>
<td>Nasal irritation, runny nose</td>
</tr>
<tr>
<td>Oral Spray</td>
<td>Hiccups, throat irritation, coughing, oral burning</td>
</tr>
<tr>
<td>Transdermal Patch</td>
<td>Skin sensitivity and irritation</td>
</tr>
</tbody>
</table>

Prior meta-analyses had found statistically significant increases in rates of chest pain and heart palpitations in NRT users as compared to those in placebo group. The authors of the Cochrane review were able to analyze this specific adverse event. They too found a statistically significant increase in chest pain and heart palpitations (OR=1.88; 95% CI 1.37 to 2.57; 15 studies; 11,074 participants). However, these events are rare, occurring at a rate of 2.5% of individuals in the NRT group and 1.4% in the placebo group (Hartmann-Boyce et al., 2018).

Other meta-analyses have also found that NRT is significantly associated with cardiovascular events (RR=2.29; 95% CI 1.39 to 3.82), but sensitivity analyses indicated that this risk was driven by less serious events such as tachycardia and arrhythmia. NRT is not significantly associated with serious cardiovascular events such as myocardial infarction (RR=1.95; 95% CI 0.26 to 4.30) (Mills et al., 2014).

It should be noted that NRT doses are often higher than those used in cognitive enhancement studies. Additionally, NRT is used for individuals who smoke or smoked, a group with known increased rates of cardiovascular disease (Mills et al., 2014). The risks of these events at lower doses and in non-smoking populations remains to be determined.

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 (Newhouse et al., 2012). 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 (Jaehne et al., 2012; Jaehne et al., 2014). A short-term RCT reported several effects of 16 mg but not 8 mg patches (Jaehne et al., 2014). For cancer, nicotine is far safer than tobacco itself but some laboratory studies report that nicotine can promote tumor growth and metastasis (Davis et al., 2009).
and stabilize β-catenin, part of the canonical Wnt pathway (Inestrosa et al., 2013). The effects likely differ based on the type of cancer, similar to smoking.

Nicotine use may be habit-forming, though this has largely not yet been studied in humans who do not already have a dependence on nicotine. Addiction risk is lower with lower doses and with gum, lozenge, or patch route of delivery instead of inhaler or nasal spray.

**Drug interactions:**

According to drugs.com, nicotine has no severe interactions with other medications but does have 21 moderate and 10 minor drug interactions. There are also 8 disease interactions of nicotine, including cardiac and pulmonary vascular disease, diabetes, liver disease, and renal dysfunction. 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 by Sobieraj et al., 2013).

**Research underway:**

There are more than 300 trials that involve nicotine currently registered on clinicaltrials.gov. Many of these trials are evaluating smoking cessation programs in different populations or investigating the effects of nicotine products such as e-cigarettes or vaping in different groups. There are five ongoing trials that are evaluating the effects of nicotine on cognition.

NCT02720445, called the MIND Study (Memory Improvement through Nicotine Dosing) aims to assess whether nicotine patches can improve cognitive, clinical, and functional performance in early dementia. The randomized and blinded 2-year study will enroll 380 patients with MCI. Half of the participants will be given nicotine patches to wear during waking hours and change each day. They will titrate up from 3.5 mg patches to 21 mg patches over the course of the first 6 weeks. They will maintain that dose for 22.5 months, and then titrate down in the final month of treatment. The placebo group will receive placebo patches to wear during waking hours for the same amount of time. The outcome measures are
the change in performance on various measures of cognitive and functional abilities, including volumetric MRI. CSF will also be collected from a subset of patients for biomarker analysis. The study is currently enrolling and projects study completion in 2025.

Two trials are focusing on the effects of nicotine on age-related auditory impairment. NCT04971954 is a double-blinded cross-over study that plans to enroll 48 non-smoking participants in two groups: adults 18-28 years of age, and adults 60-85 years of age to assess whether nicotine can help counteract age-related hearing impairment. Each subject will be given either 6 mg nicotine or placebo gum and then receive assessments of auditory and cognitive function as well as physiological assessments like heart rate. They will then have another separate session of the same assessments, but this time with the other type of gum. Outcome measures include measures of auditory function, heart rate, and cognitive performance. NCT05018117 has the same study design but will assess fMRI responses in the auditory cortex.

NCT05746273 is a randomized, blinded study evaluating the impact of nicotine on mood and cognition in older adults with late-life depression. The study will enroll 60 to 80 adults with depression who are 60 years of age or older. Participants will be randomized 2:1 to either nicotine patches or placebo, which they will wear while awake and change daily. The nicotine patch dose will start at 3.5 mg and titrate up to 7 mg over 3 weeks; participants can titrate up to a maximum of 14 mg based over 12 weeks. There will be a taper-off period of 2-3 weeks at the end of the 12 week dosing. Subjects will receive fMRI scans as well as assessments of depression, cognition, anxiety, and executive function. There is also a 12-15 week open-label extension to this study, registered as NCT05746546.

NCT05301660 is a randomized blinded study in 80 non-smoking patients with schizophrenia. The study aims to assess whether nicotine can improve cognition in these patients through changes in glycolipid metabolism. The study will randomize participants to either a 14 mg nicotine patch or placebo patch daily and will run for 8 weeks. The outcome measures include cognitive function, brain MRI measurements, blood lipid profiles, measures of brain metabolites, and psychiatric symptoms.
Search terms:
Pubmed, Google: nicotine
  • Dementia, Alzheimer’s, Parkinson’s, cognition, inflammation, cancer

Websites visited for nicotine:
  • Clinicaltrials.gov
  • Examine.com
  • Drugs.com: Nicotine Gum & Lozenge; Nicotine Patch; Nicotine Inhaler; Nicotine Nasal Spray
  • WebMD.com: Nicotine Gum, Nicotine Lozenge, Nicotine Patch, Nicotine Inhaler, Nicotine Nasal Spray
  • PubChem
  • DrugBank.ca
  • Cafepharma

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