Smoking cessation for the neurologic patient

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Summary

Given the vast health and socioeconomic effects of tobacco use, smoking cessation is no longer a topic reserved for the primary care physician. As a modifiable risk factor that can lead to stroke, dementia, multiple sclerosis, and other neurologic diseases, cigarette smoking should be addressed by all health care providers, including neurologists. Counseling, nicotine replacement therapies, and other medications are the mainstays of treatment. However, even brief advice from a health care professional at the end of a routine office visit can increase a patient's chances of quitting. Armed with a better understanding of smoking's effect on neurologic disease and available resources, such as toll-free quit lines and Web-based interventions, neurologists can help their patients who smoke take the first step to successful cessation.

Tobacco use is the leading preventable cause of morbidity and mortality in the United States, which accounts for almost 20% of all deaths.¹ Of the nearly half a million Americans who die each year due to smoking-related diseases, 10% (49,400) will be due to secondhand smoke exposure.² The economic effect of smoking is also striking. With over 45 million current smokers in the United States, the total cost of health care expenses and loss of productivity is estimated at nearly \$200 billion annually.² Fortunately, smoking cessation at any age can improve overall health. In fact, quitting before the age of 35 may reduce mortality rates to those of nonsmokers.³ In recent years, efforts by the government, mass media campaigns, and most importantly health care professionals have helped to increase the number of smokers who wish to quit.

The neurobiology of smoking

Within 10 seconds of inhaling a cigarette, nicotine is carried by smoke particles into the lung and then the brain, where it binds to cholinergic receptors triggering the release of dopamine and other neurotransmitters.⁴ Dopamine, in particular, is responsible for the sensation of pleasure and heightened reward-based behavior associated with smoking and other forms of substance abuse. Almost immediately after exposure to nicotine, the smoker experiences mood enhancement, improved concentration, reduced feelings of stress and anxiety, and relief of withdrawal symptoms.⁵ Over time, the smoker's anticipation of these effects leads to condi-

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Passive smoke exposure in the workplace and home where individuals live with a smoking spouse has been found to increase the risk of ischemic stroke and transient ischemic attack even in nonsmokers.

tioned behavior. In combination with other features of smoking, such as the habit of physically manipulating cigarettes or social cues as when smoking is done with friends or following meals, the conditioned behavior can result in craving, addiction, and long-term use.⁵ Another potential contributor to nicotine addiction is the acetaldehyde contained in cigarette smoke, which inhibits monoamine oxidase type B enzymes resulting in reduced dopamine metabolism.⁶ The subsequent increase in dopamine levels may further promote the positive reinforcement and compulsive behavior associated with smoking.

Genetics and smoking

Recent gene association studies have demonstrated how genetic risk factors may play a role in smoking habits and nicotine dependence. Variants in nicotinic cholinergic receptor genes on chromosome 15 have been associated with an increased tendency toward tobacco dependence, increased number of cigarettes smoked per day, higher urine levels of tobacco-related carcinogens, and increased rates of cancer and other smoking-related diseases.^{5,7,8} Smoking behaviors and tobacco addiction may also be determined by the rates of nicotine metabolism. Individuals with a faster metabolism of nicotine via the CYP2A6 pathway in the liver may be at higher risk for addiction and find it more difficult to quit than those with a slower metabolism, as can be seen with women compared to men.^{5,9}

Neurologic complications of smoking

Along with nicotine, cigarette smoke contains hundreds of toxic compounds known to cause cancer and cardiovascular and pulmonary diseases. Repeated exposure to these toxins can also lead to multiple neurologic complications that range from cognitive decline to a catastrophic stroke. Recent epidemiologic studies have implicated tobacco use as a potential risk factor for several neurodegenerative diseases, although some associations remain controversial due to conflicting data and small sample sizes. A literature search of clinical trials and reviews was conducted using the search terms of smoking and neurologic disease via Medline.

Cerebrovascular disease

Tobacco use is widely accepted as a major dose-related risk factor for all types of stroke.^{10–13} Proposed mechanisms of ischemic disease are similar to those seen with cardiovascular complications and are thought to be primarily due to endothelial cell dysfunction, inflammation, platelet aggregation, vasoconstriction, and accelerated atherosclerosis.^{10,11} The increased risk of subarachnoid hemorrhage may be related to the higher incidence of aneurysms in smokers, while primary cerebral hemorrhage has been associated with tobacco's disruptive effects on small vessel walls within the brain.^{12,13}

The effect of secondhand smoke on cerebrovascular disease in both smokers and nonsmokers is also gaining attention. Passive smoke exposure in the workplace and home where indi-

The association between smoking and cognitive decline has been attributed to smoking's role in producing oxidative damage and increasing inflammation, which may accelerate neurodegeneration in AD and other dementias.

viduals live with a smoking spouse has been found to increase the risk of ischemic stroke and TIA even in nonsmokers. In an Australian case-control study involving 452 consecutive patients admitted with first-time ischemic stroke, nonsmoking subjects with a smoking spouse were associated with a higher risk of stroke compared to those married to nonsmokers (OR 2.7; 95% CI 0.98–2.92).¹⁴ The increased risk was also seen in a cohort study that included over 27,000 lifelong nonsmokers; those with passive tobacco exposure of ≥ 20 hours per week at home were associated with a 1.50-fold (95% CI 1.07–2.09) increased risk of ischemic stroke.¹⁵ Other authors have suggested a potential “threshold effect” of passive exposure on stroke risk rather than a linear dose-related effect as seen with active smoking.^{16,17} Patients who are able to quit smoking significantly reduce their stroke risk, which improves not only their health, but also that of their families and coworkers.

Multiple sclerosis

Numerous observational studies have shown that cigarette smoking adversely affects several aspects of multiple sclerosis (MS). Not only has smoking been linked to a higher risk of developing MS (RR 1.9; 95% CI 1.4–2.6),¹⁸ but it may also cause acute exacerbations,¹⁹ accelerate progression of disease,²⁰ interfere with treatment by increasing interferon antibody levels,²¹ and lead to faster conversion from clinically isolated syndrome to clinically definite MS.²² Smoking may also increase the risk of progression from a relapsing-remitting course to secondary progressive disease. In a cohort study of 179 subjects, the risk of secondary progression was 3 times more likely in smokers than nonsmokers over a mean of 5 years (hazard ratio [HR] 3.6; 95% CI 1.3–9.9).²³ The underlying pathophysiology of how smoking directly affects MS is still unclear, but inflammation, endothelial cell dysfunction, and free radical production are thought to play a primary role. Animal studies have demonstrated how nicotine increases cerebral blood flow and causes leakage across the blood–brain barrier,²⁴ while human studies have found increased gadolinium-enhancing lesions in smokers with MS compared to nonsmokers ($p < 0.001$).²⁵ A link between secondhand smoke and MS has not yet been established.

Amyotrophic lateral sclerosis

Although a pooled meta-analysis of earlier case control and cohort studies showed only a marginal association between smoking and amyotrophic lateral sclerosis (ALS) risk that was strongest in women (RR 1.66; 95% CI 1.31–2.10),²⁶ a more recent analysis consisting of 5 ongoing longitudinal studies showed that cigarette smoking was significantly associated with a higher risk of ALS (RR 1.42; 95% CI 1.07–1.88).²⁷ The prospective study, which included nearly 1.2 million participants of which 832 had ALS, also found that the risk of ALS increased with younger ages at smoking onset ($p = 0.03$).²⁷ A dose-response relationship is not well established, although some studies have found an increased risk with duration, number of cigarettes smoked per day, and pack-year history.^{27,28} Neurotoxic effects have been attributed to the particulates in cigarette smoke or their byproducts, which include nitric oxide, lead, formaldehyde, and other chemicals that can lead to oxidative damage.^{27,29,30}

Seizures

Very few studies have evaluated the effects of smoking and epilepsy. Most early reports were focused on maternal smoking, which in one study was associated with an increased risk of febrile seizures.³¹ However, a large prospective cohort study of 116,363 women followed over a 16-year period found a 2-fold increased risk of seizures in current smokers compared to never-smokers independent of stroke, hypertension, and other confounding factors (RR 2.60; 95% CI 1.53–4.42).³² One potential explanation is related to nicotine's role in enhancing glutamate release, leading to excitatory stimulation of neurons.³³

Parkinson disease

In contrast to its adverse effects on other diseases, cigarette smoking is associated with a reduced risk of Parkinson disease (PD) as reported by multiple epidemiologic studies.^{34–37} In the large NIH-AARP cohort study that included 305,468 participants, of whom 1,662 had a diagnosis of PD, the OR was 0.78 (95% CI 0.70–0.86) for past smokers and 0.56 (95% CI 0.45–0.70) for current smokers as compared to never-smokers.³⁶ Fifty years after the first study reporting this inverse association was published, it is still unknown if the reduced risk is a result of a biological or possibly even a neuroprotective effect. Alternatively, it may be due to reverse causation, in which environmental factors, genetics, or personality traits (e.g., decreased reward mechanisms due to loss of dopamine producing cells) lead to a reduced incidence of smoking in patients with PD.³⁷ Supporting a direct causal effect are studies showing an inverse dose-response relationship where increased duration of smoking in pack-years, higher number of cigarettes smoked per day, and more recent smoking (quitting less than 25 years prior) were associated with a nearly 60% reduced risk of PD.^{38,39} While mouse models suggest a neuroprotective effect of nicotine,^{38,39} this is not supported by longitudinal human studies, which have shown no significant differences in mortality, disease progression, or cognitive impairment between smokers and nonsmokers with PD.^{40,41}

Essential tremor

Similarly, the risk of essential tremor (ET) has also been found to be significantly reduced in smokers compared to nonsmokers independent of alcohol use, age, and dementia.^{42,43} The association appears to be dose-responsive as suggested by a case-control study of 884 patients (221 subjects with ET compared to 663 controls), which found that heavy smokers were one-third less likely to have essential tremor compared to nonsmokers (OR 0.39; 95% CI 0.22–0.69).^{40,41} The mechanism is unclear, but the authors cite the potential neuroprotective effects of nicotine as seen in animal studies.^{38,39,43}

Multisystem atrophy and progressive supranuclear palsy

Unlike the consistent findings seen with PD and ET, the risk of multisystem atrophy (MSA) in smokers varies among different study populations, which is likely due in part to small sample sizes. In a case-control study of 100 Korean patients, the prevalence of MSA was found to be higher in heavy smokers (>40 pack-years) compared to controls (OR = 3.44; 95% CI 1.05–11.23).⁴⁴ Conversely, a multicenter European study of 76 patients with MSA demonstrated an inverse association as seen with PD that was characterized by reduced smoking habits among patients with MSA.⁴⁵ The study, which also included patients with progressive supranuclear palsy, found no association between that disease and tobacco use; this was further supported by similar results in a French case-control study of 79 patients.^{45,46}

Dementia

As the aging population continues to expand, studies on dementia and its potential risk factors have increased exponentially in the last several years. At the forefront is smoking, which in older individuals has been associated with an increased risk of impaired global cognition, adversely affecting memory, reasoning skills, verbal fluency, and other executive functions.^{47–49} In a meta-analysis of longitudinal studies involving over 26,000 patients with up to a 30-year follow-up, current smokers were associated with a nearly 80% increased risk of

Alzheimer disease (AD) and vascular dementia (independent of multiple factors including stroke history) as compared to never smokers.⁴⁷ Tobacco's effect on dementia and AD is thought to be dose-related, which is supported by longitudinal studies centered on midlife smoking. In 1 multiethnic study spanning over 20 years that included over 21,000 participants, of whom 5,367 were diagnosed with dementia, heavy midlife smokers (>2 packs per day) were found to have a greater than 100% increase in the risk of AD (HR 2.57; 95% CI 1.63–4.03), dementia (HR 2.14; 95% CI 1.65–2.78), and vascular dementia (HR 2.72; 95% CI 1.20–6.18) even when adjusted for stroke, heart disease, and alcohol use.⁵⁰ Secondhand smoke exposure may also lead to an increased risk of dementia. In a large Chinese cross-sectional study, never-smokers over the age of 60 who had been regularly exposed to smoking at home, work, or other places were twice as likely to develop AD (RR 2.28; 95% CI 1.82–2.84).⁵¹

The association between smoking and cognitive decline has been attributed to smoking's role in producing oxidative damage and increasing inflammation, which may accelerate neurodegeneration in AD and other dementias.⁵² While some studies were able to establish smoking as a risk factor independent of alcohol use, nutritional status, and amount of exercise, it is likely that unhealthy lifestyle factors that often accompany tobacco use may also play a role in its association with dementia.

On a more promising note, the risk of AD among former smokers was significantly reduced compared to current smokers, and was not statistically different from never-smokers.^{47,48} Although further studies are required for more definitive analyses, these findings are suggestive that smoking cessation (if done early enough) can potentially help reduce the risk of AD to that of nonsmokers.

Smoking cessation: Helping your patients quit

Despite the well-known dangers of smoking, it is estimated that only 20% of smokers are interested in quitting at any one time.⁵³ Furthermore, 95% of attempts at smoking cessation without the help of counseling, pharmacotherapy, or other medically based interventions end in failure.⁵⁴ However, when a health care professional provides advice on quitting, the rate of successful smoking cessation nearly triples.⁵⁵ With physician intervention, abstinence rates are significantly increased even when the duration of discussion is 3 minutes or less.⁵⁶ Thus, it is imperative that neurologists join all health care providers in regularly identifying smokers in their practice and discussing tobacco cessation. As recommended by the US Agency for Health Care Policy and Research, one protocol for treating smokers is known as the 5 A's^{54,56}:

1. **Ask**—screen for smokers, which may be done as part of the vital signs.
2. **Advise** patient to quit.
3. **Assess** willingness to quit—if the patient agrees, then proceed with the next step. If not, then provide brief motivational counseling.
4. **Assist** in quitting—establish a target quit date, offer counseling, and discuss pharmacologic therapies, such as nicotine replacement treatment.
5. **Arrange** for follow-up.

Counseling To increase the rate of successful cessation, patients may be referred for individual and group counseling, online resources (www.smokefree.gov or www.women.smokefree.gov), and a toll-free telephone quit line at 1-800-QUIT-NOW (1-800-784-8669), which connects them to counseling and further information. For smokers who are unwilling to quit, providers may encourage them to consider reducing the amount of their daily smoking or revisit the topic at follow-up visits. If time permits, providers may also engage in motivational interviewing, a nonconfrontational counseling technique that involves discussions on how tobacco may affect an individual's long-term health goals, supporting the patient's autonomy, and asking empathetic questions pertaining to why patients may be hesitant about quitting.⁵⁵

Medications While counseling may increase the 1-year success rate of smoking cessation to 16% compared to an unaided attempt, counseling combined with pharmacologic therapy

Table Pharmacologic therapy of smoking cessation

	Dose	Duration	Side effects
Nicotine-based			
Nicotine patch	If >10 cig/d, 21 mg/d for 6 wk, then 14 mg/d for 2 wk, then 7 mg/d for 2 wk; if <10 cig/d, 14 mg/d for 6 wk, then 7 mg for 2 wk	8–10 wk	Skin irritation, palpitation, vivid dreams, insomnia, dizziness, headaches
Nicotine lozenge	1 lozenge (2 or 4 mg each) every 1–2 h for 6 wk, then taper; do not eat or drink 15 min prior; no more than 20 lozenges/d; 2 mg if first cig after 30 minutes on waking, 4 mg if first cig within 30 minutes on waking	Up to 3 mo	Mouth or stomach irritation, hiccups
Nicotine nasal spray	1 spray each nostril every 1–2 h while awake; use 8–40 times/day	Up to 6 mo	Nasal irritation, palpitations, diarrhea
Nicotine gum	1 piece (2 or 4 mg each) chewed slowly every 1–2 h for 30 min total up to 24 pieces/d; 2 mg if smokes 1 ppd, 4 mg if smokes >1 ppd	Up to 3 mo	Hiccups, mouth or stomach irritation, soreness of jaw
Nicotine inhalers	Inhale from cartridge; no more than 16 cartridges/d	Up to 3 mo	Mouth and throat irritation, cough
Non-nicotine-based			
Bupropion SR (Wellbutryn SR, Zyban)	150 mg daily for 3 d, then twice daily	Up to 6 mo	Dry mouth, dizziness, seizures, depression, anxiety, suicidal ideations
Varenicline (Chantix)	Day 1–3, 0.5 mg each AM; day 4–7, 0.5 mg twice daily; weeks 2–12, 1 mg twice daily	Up to 3 mo	Nausea, vomiting, headaches, insomnia, vivid dreams, depression, anxiety, suicidal ideations, chest pain
Abbreviations: cig = cigarettes; ppd = packs per day; SR = sustained release.			

may further increase this to 24% to 30%.⁵⁷ Currently, there are 7 FDA-approved medications for smoking cessation, which have all been shown to help with smoking abstinence compared to placebo (table). Five are nicotine replacement therapies (NRT) in the form of gum, inhalers, lozenges, nasal sprays, and patches. Side effects are mild and typically limited to local irritation, although nicotine toxicity can occur with increased doses or concomitant heavy smoking. One successful dosing strategy is to initiate the nicotine patch 2 weeks prior to the set quit date although effects are variable.⁵⁵ Another option that may provide additional benefit would be to combine 2 or more forms of NRT, although evidence supporting increased efficacy is modest.^{57–59}

The 2 non-nicotine medications, bupropion SR and varenicline, have each been shown to be more effective than placebo, especially when combined with counseling. Unfortunately, both carry a black box warning from the FDA due to potentially severe neuropsychiatric side effects, which include psychosis and suicidal ideation.⁵⁵ In addition, both have been reported to cause seizures, with a risk of 1 in 1,000 estimated for bupropion; reports are anecdotal for varenicline.^{57,60,61} Although not a contraindication, varenicline may increase the risk of cardiovascular events, while bupropion is contraindicated in patients with eating disorders.⁵⁷

The risks and benefits of pharmacologic therapy must be considered for each individual patient, followed by careful monitoring upon initiation of the selected medication. With the appearance of any serious side effects, the medication should be stopped immediately.

As there is no standard recommendation as to which medication should be started first or which one the patient will respond to best, patient preference and contraindications can help guide the clinician, although referral to counseling should be considered for all patients given the favorable risk-benefit ratio. For patients who fail monotherapy, are highly tobacco dependent, or have multiple fail attempts, combination therapy with one of the NRT and either bupropion SR or varenicline may be indicated.⁵⁷

Nonpharmacologic therapies, such as exercise (running, cycling, walking), can help with nicotine withdrawal symptoms, weight gain, and feelings of stress and anxiety associated with quitting.⁶² Meditation, yoga, and other mind-body therapies may also reduce stress and can help promote adherence to a smoking cessation program.

Smoking cessation treatments are more cost-effective than many other preventive services, including hypertension and mammography. A 2004 financial analysis of tobacco cessation coverage by managed care organizations found that the increase in net cost per member per month over the first 5 years was only \$0.61, while the total cost per life-year saved could potentially reach as high as \$4,730.⁶³ Although patients often relapse during their attempts to quit, follow-up discussions on their progress and ongoing encouragement from health care professionals can help with subsequent attempts and ultimately cessation.

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