Review Article

The Importance of Smoking Cessation to Reducing Cardiovascular Disease Risk

by Allison Gorrilla, MPH

Abstract

Tobacco dependence treatment is an important cornerstone in the primary and secondary prevention of cardiovascular disease. Though safe and effective tobacco dependence treatments exist, clinicians and health systems fail to consistently or effectively treat their patient's tobacco use. In addition to systematically screening patients for their tobacco use and offering evidence-based treatments, tobacco use ought to be viewed as a chronic disease. Similar to the treatment of other modifiable cardiovascular disease risk factors like hypertension and diabetes, tobacco treatment requires multiple interventions over time.

This article reviews the literature on how smoking contributes to cardiovascular disease (CVD), the benefits of cessation to reducing CVD risk, and provides an overview of treatments for tobacco dependence. Additionally, updates in the treatment of tobacco use for patients with CVD will be provided, including the safety of pharmacotherapy for patients with CVD, and how to address electronic nicotine delivery systems (ENDS) in treatment.

Over the past half-century, there has been a remarkable decline in the death rate from cardiovascular disease (CVD). Several analyses have concluded that over half of the decline in CVD mortality was attributed to reductions in major CVD risk factors, including smoking.[1] Despite this progress, the decline in smoking has slowed in the past decade, and as the United States population ages, the prevalence of persons living with CVD has increased.[2] In 2008, the National Heart, Lung, and Blood Institute estimated numbers of people in the US with CVD related to smoking were: history of myocardial infarction, 7.9 million; angina pectoris, 9 million; stroke, 7 million; heart failure, 5.7 million, atrial fibrillation, 2.2 million; and peripheral arterial disease (PAD), 8.3 million. Today, CVD is the leading cause of death for both men and women, causing 610,000 deaths annually.[3]

We have long known cigarette smoking to be a major risk factor for CVD. Since the 1964 Surgeon General's report on smoking was released, our understanding of the mechanisms by which smoking leads to CVD has advanced considerably. Nicotine, many harmful chemicals, and carbon monoxide in combustible tobacco trigger acute cardiovascular events through the promotion of atherosclerosis.[4] The mechanisms by which these three elements contribute to atherosclerosis are: endothelial damage, promotion of blood clots, inducing inflammation, and altered lipid metabolism.[4]

Nicotine contributes to endothelial damage by acting as a sympathomimetic agent that increases heart rate and cardiac contractility, increasing the demand for myocardial oxygen and blood.[5] At the same time, nicotine induces vasoconstriction, decreasing the supply of myocardial blood and oxygen, thereby forcing the heart to work harder and putting stress on blood vessels.[5] While the nicotine in cigarettes plays a role in contributing to atherosclerosis, data from clinical trials of nicotine patches suggests that chemical components in cigarette smoke, particularly oxidant gases, free radicals, metals, and polycyclic aromatic hydrocarbons, are more prominent contributors to vascular endothelial damage and inflammation.[6,7]

Carbon monoxide, produced by combustion, contributes to oxygen depletion by binding with more affinity to hemoglobin thereby replacing some of the oxygen circulating throughout the body.[5] The combination of restricted blood flow and decreased availability of oxygen may precipitate myocardial and cerebral ischemic events. Lastly, cigarette smoking increases risk of CVD by influencing other cardiovascular risk factors, such as an increase in low-density lipoprotein cholesterol and triglyceride, a decrease in high-density lipoprotein cholesterol, and an increased risk of type 2 diabetes.[8,9]

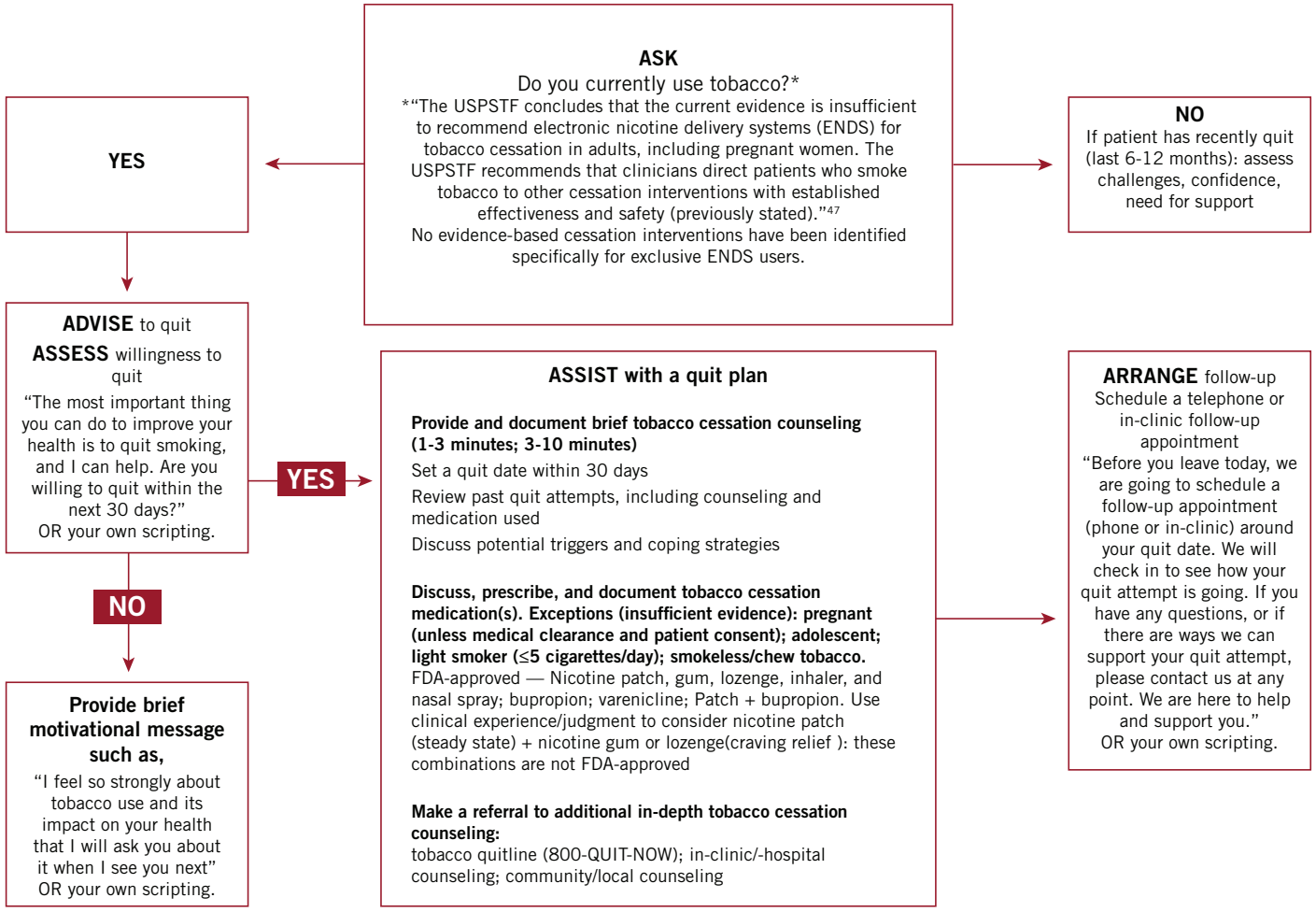
The Benefits of Smoking Cessation to Reducing CVD Risk

Quitting tobacco early in life gives smokers the greatest reduction in risk of CVD morbidity and mortality.[10,11] The 2004 Surgeon General's report detailed how the benefits of smoking cessation occur almost immediately and continue with years of abstinence.[4]

- Within 20 minutes of quitting, blood pressure and heart rate drops
- After 12 hours of quitting, carbon monoxide levels in the blood return to normal
- 2 weeks to three months after quitting, heart attack risk begins to drop
- 1 year after quitting, risk of coronary heart disease is cut in half
- 5-15 years after quitting, stroke and coronary heart disease risk is reduced to that of a non-smoker[4]

Rapid improvements in endothelial function and reduced risk of blood clots

FIGURE 1. Tobacco Cessation Brief Clinical Intervention Protocol[16]



contribute to the immediate and long-term reversal of damage to the cardiovascular system from smoking.[12] For this reason, quitting smoking even after an acute cardiovascular event, such as myocardial infarction or stroke, is one of the most effective actions for secondary prevention of CVD.

Helping Your Patients to Quit: Putting the Guidelines into Practice

There is a desire to quit among the US population who smoke, with surveys consistently reporting that 70% of adult smokers want to quit and more than half tried to do so in the past year.[13] However, the success rate of those who try is only around 6%.[13] Reasons for the low success rate are the limited utilization of evidence-based treatments that can enhance success in quitting and the dual challenge smokers face when they try to quit. These challenges include nicotine withdrawal symptoms and exposure to smoking cues or stimuli that can trigger cravings.[14,15] To counter these barriers, the 2008 United States Public Health Service (USPHS) Clinical Practice Guideline *Treating Tobacco Use and Dependence* recommends health professionals provide brief counseling and pharmacotherapy (unless contraindicated) for smoking-cessation treatment.[16] Counseling enhances the motivation to quit and builds coping skills, while pharmacotherapy relieves nicotine withdrawal. The combination of these treatments yield higher quit rates than using either alone.[17] The Clinical Practice Guideline recommends these treatments be provided to all smokers using the 5As protocol. (See Table 1: Tobacco Cessation Brief Clinical Intervention Protocol)

The 5As protocol ensures every patient who presents to a health care facility is asked about tobacco (Ask), advised to quit (Advise), has willingness to quit assessed (Assess), and if patient is willing, is provided assistance to quit with brief counseling advice and medication (Assist).[16] Lastly, because relapse is common, a follow up contact should be arranged soon after quitting, preferably during the first week (Arrange). Smokers who receive all of the 5As during a medical encounter are more likely to use counseling and medication to quit, compared to smokers who receive one or none of the 5As.[18]

A Chronic Disease Approach to Tobacco Treatment

Beyond providing evidence-based counseling and pharmacotherapy to your patients who smoke, the Clinical Practice Guideline emphasizes the importance of viewing smoking as a chronic disease.[16] Since the majority of tobacco users persist in tobacco use for many years,

TABLE 1. Enhancing Motivation to Quit Tobacco - The "5Rs"[16]

Relevance	Encourage the patient to indicate why quitting is personally relevant, being as specific as possible. Motivational information has the greatest impact if it is relevant to a patient's disease status or risk, family or social situation (e.g., having children in the home), health concerns, age, gender, and other important patient characteristics (e.g., prior quitting experience, personal barriers to cessation).
Risks	The clinician should ask the patient to identify potential negative consequences of tobacco use. The clinician may suggest and highlight those that seem most relevant to the patient. The clinician should emphasize that smoking low-tar/low-nicotine cigarettes or use of other forms of tobacco (e.g., smokeless tobacco, cigars, and pipes) will not eliminate these risks. Examples of risks are: • Acute risks: Shortness of breath, exacerbation of asthma, increased risk of respiratory infections, harm to pregnancy, impotence, infertility. • Long-term risks: Heart attacks and strokes, lung and other cancers (e.g., larynx, oral cavity, pharynx, esophagus, pancreas, stomach, kidney, bladder, cervix, and acute myelocytic leukemia), chronic obstructive pulmonary diseases (chronic bronchitis and emphysema), osteoporosis, long-term disability, and need for extended care. • Environmental risks: Increased risk of lung cancer and heart disease in spouses; increased risk for low birth-weight, sudden infant death syndrome (SIDS), asthma, middle ear disease, and respiratory infections in children of smokers.
Rewards	The clinician should ask the patient to identify potential benefits of stopping tobacco use. The clinician may suggest and highlight those that seem most relevant to the patient. Examples of rewards follow: • Improved health • Food will taste better • Improved sense of smell • Saving money • Feeling better about oneself • Home, car, clothing, breath will smell better • Setting a good example for children and decreasing the likelihood that they will smoke • Having healthier babies and children • Feeling better physically • Performing better in physical activities • Improved appearance, including reduced wrinkling/aging of skin and whiter teeth
Roadblocks	The clinician should ask the patient to identify barriers or impediments to quitting and provide treatment (problemsolving counseling, medication) that could address barriers. Typical barriers might include: • Withdrawal symptoms • Fear of failure • Weight gain • Lack of support • Depression • Enjoyment of tobacco • Being around other tobacco users • Limited knowledge of effective treatment options
Repetition	The motivational intervention should be repeated every time an unmotivated patient visits the clinic setting. Tobacco users who have failed in previous quit attempts should be told that most people make repeated quit attempts before they are successful.

cycling through periods of remission and relapse, a successful treatment approach recognizes the chronic and relapsing nature of tobacco dependence and provides ongoing education, counseling, and advice.[16] Targeting the goal of quitting but incorporating failures, setting interim goals, and continuing care until the desired outcome is achieved are tenets of a chronic disease management approach.[19] This approach has also been demonstrated to be more effective at accomplishing long-term abstinence than delivery of discrete, episodic care.[19]

Addressing Ambivalent Smokers

As mentioned previously, the majority of smokers would like to quit smoking and have tried to do so with little success. Repeated quit attempts with no success can leave smokers feeling demoralized and even ambivalent about making another quit attempt. Understanding the reasons for ambivalence is key to maintaining patients' motivation to keep trying to quit. Motivational interviewing techniques can help clinicians explore a patient's ambivalence.[20] One strategy used to understand patient's feelings, beliefs, and values regarding tobacco use is the 5Rs.[21] (see Table 2: Enhancing motivation to quit tobacco-the "5Rs") The open-ended questions of the 5Rs can give clinicians an opportunity to listen and respond to the real (or perceived) barriers affecting a patient's motivation to quit.

Smoking Cessation Counseling

Individual, group, and telephone counseling are effective, and their effectiveness increases with treatment intensity.[16] Brief counseling advice should be clear, strong, and personally relevant to the patient. Counseling to smokers who are willing to quit should focus on developing problem-solving skills and identifying social support.[16]

State tobacco-cessation quitlines have broad reach, are effective, and can connect smokers to a more intensive counseling experience than what can typically be delivered in the health-care setting due to time constraints and lack of training.[16] In a meta-analysis conducted for the 2008 USPHS Clinical Practice Guideline, quitlines, compared to minimal or no counseling, increased smoking cessation by an odds ratio of 1.6 (95%CI: 1.4-1.8). Furthermore, when quitline counseling is added to smoking cessation medication, cessation is significantly increased by an odds ratio of 1.3 (95%CI: 1.1-1.6), compared to medication alone.[16,22] Tobacco users in Wisconsin can access the free services of the Wisconsin Tobacco Quit Line 24 hours a day/7 days a week

via 1-800-QUIT-NOW, or can be fax-referred by a health-care provider to be proactively contacted by a quitline coach. When added as an extension to a clinical tobacco intervention, the Wisconsin Tobacco Quit Line provides clinicians an easy, convenient, evidence-based referral resource, and increases the number of patients making quit attempts using counseling and medication.[16]

Pharmacotherapy

There are seven first-line pharmacotherapy treatments (five nicotine and two non-nicotine) that have a substantial body of evidence supporting their efficacy and safety to help smokers quit. Dosing instructions can be referenced in Table 2: Tobacco Dependence Treatment Medications. An electronic tobacco-cessation medication chart is available on the University of Wisconsin Center for Tobacco Research and Intervention Website.[16,23,24]

Tobacco Cessation Medication Chart - University of Wisocnsin Center for Tobaccco Research and Intervention: https://www.ctri.wisc.edu.

Nicotine Replacement Therapy

The five forms of nicotine replacement therapy (NRT) are patch, gum, lozenge, inhaler, and nasal spray. They promote abstinence by reducing craving and nicotine withdrawal symptoms and, according to a meta-analysis conducted by Stead et al, can double a smoker's likelihood of achieving long-term abstinence from smoking compared to placebo RR 1.60 (95%CI: 1.53-1.68).[17] NRT has two distinct patterns of nicotine delivery. The patch delivers a steady state of nicotine for 24 hours with a single application and a slow onset of action (2-3 hours). In contrast, the nicotine gum, lozenge, inhaler, and nasal spray have a more rapid onset (5-30 min) and are designed to be used as needed multiple times over the course of the day.[25] The NRT forms were originally developed to be used as monotherapies; however, Stead's meta-analysis concluded the most effective way to use NRT is to combine the nicotine patch with a short-acting product (RR 1.34 of combo therapy compared to monotherapy over 9 trials; 95%CI: 1.18-1.51).[17] This combination is particularly effective in helping smokers resist cue-induced cravings that can lead to relapse.[26]

A growing body of research supports the safety and efficacy of other ways of using NRT to promote abstinence. Researchers have found the use of the NRT patch prior to the quit date or for smoking reduction as part of a quit attempt is safe and may increase smoking abstinence.[27] Additionally, about 6% of smokers will use over-the-counter NRT for 6 months or more.[28] A meta-analysis by Fucito et al concluded that, while uncommon, long-term nicotine patch and gum use is safe and may be more effective for heavier, more nicotine dependent smokers who do not feel confident in their ability to maintain abstinence as they near the end of the standard three-month NRT duration.[29]

Varenicline and Sustained-Release Bupropion

Varenicline is a partial agonist of the $\alpha_4\beta_2$ nicotinic receptor. It relieves nicotine withdrawal symptoms by stimulating nicotinic receptors and blocks the reinforcing properties of smoking by preventing nicotine from binding to receptors. A Cochrane meta-analysis showed varenicline was superior to both single forms of NRT or bupropion monotherapy in increasing the odds of quitting by 1.57 (95%CI: 1.29-1.91) and 1.59 (95%CI: 1.29-1.96) respectively.[30]

Bupropion SR is thought to be an effective smoking-cessation medication by blocking the neuronal reuptake of norepinephrine and dopamine and acting as nicotine receptor antagonist.[31] Bupropion's mechanism of action is unclear but it may attenuate symptoms of withdrawal by mimicking the nicotinic effects of norepinephrine and dopamine,

TABLE 2. Tobacco Dependence Treatment Medications[16,23,24]

Medication	*Cautions/Warnings*	*Side Effects*	*Dosage*	*Use*	*Availability*
Combination Nicotine Replacement Therapy (NRT) 1. Patch + lozenge 2. Patch + gum	Follow instructions for individual medications	See individual medications below	See below	See below	See below
Varenicline	Use with caution in patients: • With siginificant renal impairment • With serious psychiatric illness • Undergoing dialysis	• Nausea • Insomnia • Abnormal, strange dreams	• Days 1-3: 0.5 mg every morning • Days 4-7: 0.5 mg twice daily • Days 8-end: 1 mg twice daily	• Start 1 week before quit date & use for 3-6 months • Typically quit on day 8 • Optional: quit between days 8-35	Prescription only: • Chantix
Nicotine Patch (7 mg, 14 mg or 21 mg)	Do not use if you have severe eczema or psoriasis	• Local skin reaction • Insomnia	• One patch per day • If ≥ 10 cigs/day: 21 mg 4 wks, 12 mg 2-4 wks, 7 mg 2-4 wks • if < 10 cigs/day: 14 mg 8 wks	• Post-quit: 12 weeks • OPTIONAL pre-quit: Up to 6 months prior to quit date with smoking reduction	OTC or prescription: • Generic • Nicoderm CQ • Nicotrol
Nicotine Lozenge (2 mg or 4 mg)	• Do not eat or drink 15 minutes before or during use • One lozenge at a time • Limit 20 in 24 hours	• Hiccups • Cough • Heartburn	• If smoke > 30 mins after waking: 2 mg • if smoke ≤ 30 mins after waking: 4 mg • Wks 1-6: 1 every 1-2 hrs • Wks 7-9: 1 every 2-4 hrs • Wks 10-12: 1 every 4-8 hrs	3-6 months • OPTIONAL Pre-quit: Up to 6 months prior quit date with smoking reduction • Recommended mini-lozenge due to more rapid nicotine blood level and ease of use	OTC Only: • Generic • Commit
Nicotine Gum (2 mg or 4 mg)	• Caution with dentures • Do not eat or drink 15 minutes before or during use	• Mouth soreness • Stomachache	• 1 piece every 1-2 hrs • 6-15 pieces per day • if smoke > 30 mins after waking: 2 mg • If smoke ≤ 30 mins after waking: 4 mg	• Post quit: Up to 12 weeks • OPTIONAL Pre-quit: Up to 6 months prior quit date with smoking reduction	OTC Only: • Generic • Nicorette
Nicotine Inhaler	May irritate mouth/throat at first (improves with use)	Local irritation of mouth & throat	• 6-16 cartridges/day • Inhale 80 times/cartridge • May save partially-used cartridge for next day	• Post-quit: Up to 6 months; taper at end • OPTIONAL Pre-quit: Up to 6 months prior quit date with smoking reduction	Prescription Only • Nicotrol inhaler
Nicotine Nasal Spray	• Not for patients with asthma • May irritate nose (improves over time) • May cause depression	Nasal irritation	• 1 "dose" = 1 squirt per nostril • 1 to 2 doses/hr; 8 to 40 doses/day • Do NOT inhale	3-6 months; taper at end	Prescription Only • Nicotrol NS
Bupropion SR 150	• Not for use if you: • Use monoamine oxidase (MAO) inhibitor • Use bupropion in any other form • Have a history of seizures • Have a history of eating disorders	• Insomnia • Dry mouth	• Days 1-3: SR 150 mg each morning • Days 4-end: SR 150 mg twice daily	Start 1-2 weeks before quit date; use 2 to 6 months	Prescription Only • Generic • Zyban • Wellbutrin SR

and by acting as an antagonist, bupropion may prevent relapse by attenuating the reinforcing effects of nicotine.[31] Evidence from several randomized controlled trials show that bupropion doubled smoking-cessation rates compared with placebo (OR 2.0 (95%CI: 1.8-2.2)).[16] When paired with the nicotine patch, bupropion was more effective (OR 2.5 (95%CI: 1.9-3.4)) in achieving abstinence at one year than placebo, patch alone, or bupropion alone.[32]

In December of 2016, the Food and Drug Administration (FDA) removed the black box warnings on varenicline and bupropion for serious neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, suicidal thoughts or behavior.[33] A review of a large clinical trial showed there was not a significant increase in rates of moderate-to-severe neuropsychiatric adverse events attributable to use of varenicline or bupropion in those with or without psychiatric disorders. The severity and frequency with which the side effects occurred in the clinical trial demonstrated the benefits of stopping smoking outweighed the risks of using varenicline and bupropion.[33,34]

Safety of Pharmacotherapy for Patients with CVD

There has been concern about the safety profile of cessation therapies with regard to cardiovascular events, particularly among users who continued to smoke. When NRT first came on the market, there were concerns about nicotine's stimulating effects increasing myocardial workload and adversely affecting patients with CVD. Clinical trials and research with CVD populations indicated that NRT was safe even with a high-dose patch, combination NRT, and concurrent smoking.[35,36] The current guidelines endorse the use of NRT for patients with stable CVD, but recommend caution in using NRT in smokers with unstable angina, MI in the past two weeks, or serious arrhythmia.[16] While much of the concern over varenicline's safety came from mixed results of meta-analyses on the drug's safety, the most recent FDA safety communication related to a 2012 meta-analysis looking at major adverse cardiovascular events (MACEs) and found that an increased risk of CVD events was not statistically significant.[37] Studies of bupropion in patients with CVD have not shown an increase in CVD-specific events compared with placebo.[38]

Addressing Electronic Nicotine Delivery Systems (ENDS)

Electronic nicotine delivery systems (ENDS), of which electronic cigarettes are the most common product, are designed to look like conventional tobacco counterparts (cigarettes, cigars, cigarillos, pipes, or hookahs). They do not burn or use tobacco leaves; rather, they vaporize a solution the user inhales. The constituents of the solution in electronic cigarettes, or e-cigarettes, are nicotine, propylene glycol, and flavorants.[39] The vapor usually contains some carcinogenic compounds and other toxicants found in tobacco smoke but at much lower levels. Since the products are relatively new and have not been well researched, there are no long-term safety data on the use of e-cigarettes or risk of prolonged exposure by non-users or bystanders to "secondhand vapor". Though it is very likely ENDS products produce lower exposure to nicotine and toxicants than combustible tobacco, there is sufficient evidence to caution children and adolescents, pregnant women, and women of reproductive age about ENDS use because of the potential for fetal and adolescent nicotine exposure to have long-term consequences for brain development.[40]

Despite the fact that the FDA prohibits e-cigarette marketers from making claims that the devices are smoking cessation aids, many individuals who use e-cigarettes believe that these products will help them quit smoking conventional cigarettes.[41] A meta-analysis of clinical trials examining the efficacy of e-cigarettes for smoking cessation yield a pooled odds ratio of 0.61 (95%CI: 0.50-0.75), indicating that e-cigarettes use in the real world is associated with significantly lower odds of quitting smoking cigarettes.[39] Among adults, reductions in cigarettes per day were observed in several studies.[42,43] While reduction in cigarettes could have benefit if it leads to subsequent cessation, this has not yet been seen with e-cigarettes. This is particularly concerning given that all population-based studies of adult use show the highest rate of e-cigarette use among current smokers, followed by former smokers, with little use among non-smokers, and smoking, even at reduced rates, is associated with markedly elevated risk of cardiovascular disease.[44-46]

The 2015 United States Preventive Services Task Force provided recommendations to clinicians on how to address e-cigarettes, and concluded that the evidence was lacking and insufficient to recommend ENDS for cessation. Given the established safety and effectiveness of behavioral and pharmacotherapy interventions, clinicians should direct patients who smoke to these other interventions.[47] If a patient insists on trying to quit using e-cigarettes, the patients should be advised to set a quit date for their e-cigarette use and not plan to use indefinitely, given the lack of long-term safety data. It should be stressed that dual-use of e-cigarettes and conventional cigarettes is not a good long term goal; patients should quit smoking cigarettes entirely.

Conclusion

Clinicians have an important role to play in educating their patients who smoke about the primary and secondary prevention benefits of quitting to cardiovascular health. By systematically integrating tobacco dependence treatment and taking a chronic care approach, clinicians can listen to and address the concerns of their patients, sustain motivation to quit and, most importantly, offer the treatments that can enhance their patients' success.

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