How to Stop Smoking

Priyanga Jayakumar, MD[a]; Hema Madhuri Mekala, MD[a]; Rajashekar Reddy Yeruva, MD[a]; and Steven Lippmann, MD[a,*]

ABSTRACT

Despite the known dangers of cigarette smoking, many smokers do not use effective means for cessation. Smoking-cessation guidelines recommend a variety of psychological and medicinal options that include nicotine-replacement products, pharmaceuticals, and electronic cigarettes. This article describes these smoking-cessation options and provides guidance for physicians.

Prim Care Companion CNS Disord 2017;19(3):16br02077
https://doi.org/10.4088/PCC.16br02077

[a]University of Louisville School of Medicine, Louisville, Kentucky

**Corresponding author:* Steven Lippmann, MD, 401 East Chestnut St, Ste 610, University of Louisville Clinic, Louisville, KY 40202 (sblipp01@louisville.edu).

Smoking is the leading cause of preventable mortality.[1] Among 70% of smokers who report that they are willing to stop smoking, only 50% attempt to do so, and only one-third of those apply effective smoking-cessation techniques.[2] The US Public Health Service[3] and the US Preventive Services Task Force[4] guidelines for smoking cessation include several effective pharmaceutical options such as nicotine in transdermal patches, gum, lozenges, inhalers, and nasal sprays in addition to the medications varenicline and bupropion.[5]

NICOTINE REPLACEMENT

Nicotine replacement therapy (NRT) provides nicotine to suppress potential nicotine withdrawal. Patches, gum, and lozenges are NRT products available over-the-counter, while the inhaler and nasal spray versions require a prescription. NRT is most effective when utilized in a combination—simultaneous application of different NRT products with varying time-related bioavailability.[2] The patch offers long-term (approximately 24 hours), low levels of nicotine that do not suppress acute withdrawal but tend to somewhat mitigate the desire to smoke. Whereas, gum, lozenges, inhalers, and nasal sprays provide nicotine in an immediate-onset format that diminishes acute withdrawal and cravings on an as-needed basis but is not long-lasting.[6] The conjoint use of these 2 methods provides more consistent suppression of nicotine craving and withdrawal.

The patch may cause skin irritation, insomnia, and vivid dreams when left on overnight.[2] The short-acting NRT agents require repeated use throughout the day, yielding variable nicotine levels, and require more instruction for correct use. Longer, continued NRT durations of 2 to 3 months may improve cessation rates for those wanting to stop smoking.[7]

VARENICLINE

As a partial agonist of the $\alpha_4\beta_2$ nicotinic receptor, varenicline reduces symptoms of nicotine withdrawal and blocks nicotine from binding to receptors, thereby slightly reducing the rewarding aspects of nicotine exposure.[8] Varenicline is associated with neuropsychiatric and cardiovascular concerns.[9] In 2009, the US Food and Drug Administration (FDA) required varenicline packaging to include a "black box" warning about potential side effects. An advisory[10] was issued stating that varenicline may induce impairment of the ability to drive or operate heavy machinery; however, in observational research, varenicline was not associated with an increase in transportation accidents.[11] Cardiovascular risks include angina pectoris, myocardial infarction, and peripheral vascular disease. In late 2016, the black box warning about neuropsychiatric events was removed.[12]

There is a major clinical concern about varenicline inducing suicidal thoughts or behaviors. Case reports[13] from 1998 to 2010 identified 3,249 vignettes about suicidal or self-injurious activities and depression in patients prescribed varenicline treatment for smoking

Clinical Points

- Cigarette smoking induces significant health problems, thus doctors should encourage cessation and provide safe and effective guidance.
- Nicotine replacement products and the pharmaceuticals varenicline and bupropion are commonly recommended smoking-cessation methods.
- Electronic cigarettes offer a new form of nicotine replacement and are increasing popular; however, their aerosols contain potentially dangerous substances, and their long-term safety and efficacy for tobacco cessation are unknown.

cessation. Use of varenicline was associated with 90% of such outcomes, followed by bupropion at 7% and NRT at nearly 3%.[14] However, a 2015 assessment[15] of 39 randomized trials involving over 10,000 participants, including subjects with psychiatric illness, documented that compared with placebo those prescribed varenicline did not have an increased risk of suicide (attempts or ideation), depression, aggression, or death. Nevertheless, clinical concerns remain regarding varenicline-induced risks for suicidal issues.

BUPROPION

Bupropion acts by enhancing central nervous system noradrenergic and dopaminergic release. There are concerns about neuropsychiatric side effects; however, a randomized trial[16] comparing bupropion, varenicline, and the nicotine patch with placebo reported no difference in adverse events. Precipitating ictal events have been a concern for physicians when prescribing bupropion. Physicians should advise patients and their families to stop bupropion and contact them if patients experience seizures, anger, agitation, or depression and if suicidal ideas, planning, or behaviors occur.

ELECTRONIC CIGARETTES

Electronic cigarettes (e-cigarettes) originated in 2003 in China and entered the United States and European markets in 2006.[17] Over 13% of adults have vaped an e-cigarette, and the incidence has been dramatically rising, especially among adolescents. Between 2011 and 2014, e-cigarette consumption increased to over 13% of high-school students and to nearly 4% of middle schoolers.[18] The amount of nicotine delivered and the level of nicotine in the blood varies depending on the e-cigarette nicotine cartridge content and other component concentrations in the selected liquid, puffing intensity, device characteristics, and vaping or battery power technique.[19]

Some of the carcinogenic products used in e-cigarettes are formaldehyde, heavy metals, nitrosamines, propylene glycol, and phenolic, carbonyl, or volatile organic compounds.[20,21] E-cigarettes are not approved by the FDA for smoking cessation, and they have not been endorsed for safety or efficacy as a smoking-cessation technique. A survey[22] of over 45,000 students revealed that e-cigarette use was associated with respiratory symptoms regardless of smoking status. There is a link between cytotoxicity and certain flavorings in e-cigarette liquids such as diacetyl and benzaldehyde.[23,24] Both chemicals are associated with respiratory diseases and pulmonary irritation and are contained especially in the sweet and cherry-flavored e-cigarette liquids.[23,24] Since the e-cigarette nicotine delivery systems currently available are fairly new, there are no long-term follow-up research data on human health.

E-cigarette vapor contains the heavy metals lead, nickel, and cadmium, which may cause significant health issues with long-term exposure.[25] Lead is a neurologic and hematologic toxin, nickel leads to respiratory irritation, and cadmium negatively affects almost all organs including the heart, kidneys, brain, and reproductive systems. The safe levels of long-term exposure have not yet been established, and even low concentrations are not advised.[25]

PSYCHIATRIC COMORBIDITIES

Persons with mental illnesses who smoke are often approached with a variety of personally individualized smoking-cessation models including nicotine replacement, various medications, and psychotherapy. Commonly, cognitive-behavioral therapy is the psychotherapy selected, which aims to alter dysfunctional thinking, feelings, and behavior.

Clinical indications for treating smokers with depression would follow conventional guidelines. Obviously, bupropion would be highly considered in someone who became depressed during cigarette cessation or in a patient with depression who wants to stop utilizing tobacco products. Beyond nicotine and psychotherapy, medicinal choices, dosages, or even combining antidepressant agents, along with increased light exposure, would follow conventional practice and individual patient parameters. Varenicline is usually not advised in clinical circumstances that involve an elevated risk for suicide.

Antipsychotic drugs and mood-stabilizer pharmaceuticals might be prescribed if indicated by psychotic symptoms or cases of mood lability. People with schizophrenia evidence a widely accepted phenomenon of smoking more than the general population. There may be a biochemical predisposition in patients with schizophrenia, with isolation or inactivity reinforcing smoking behaviors. Interventions aimed at smoking cessation or reduction should be more intensive for patients with mental illness than for others. Such programs might help at improving coping skills that decrease stress and anxiety or facilitate greater socialization. Many physicians also encourage exercise, proper diet, weight control, and seeking appropriate medical care.

Smokers with depression may be at higher risk to experience depression during smoking cessation than nondepressed smokers, but the data remain unclear.[26] Cigarette abstinence is sometimes associated with a depressive illness relapse and may even induce a major depressive episode. Prescribing prophylactic antidepressant

pharmacotherapy is not a widely accepted preventative measure but can be appropriate on an individualized basis. Early mood symptoms may be a predictor of such occurrences. Abstinence following nicotine dependence itself may be a contributing factor for relapse. Fortunately, such individuals also respond well to bupropion and other conventional treatments for depression.[26]

DISCUSSION

A 2013 meta-analysis[27] of 9 randomized trials revealed that nicotine patches administered with short-acting NRT products (ie, gum, spray, or inhalers) were more effective than any single type of NRT alone. A study[28] of 1,086 smokers compared 12 weeks of utilizing varenicline, nicotine patches, and nicotine patches combined with nicotine lozenge therapy and revealed no differences in biochemically confirmed rates of smoking abstinence among the 3 groups.

This result was confirmed in controlled research[16] that compared varenicline with nicotine patches, bupropion, and placebo in over 8,000 smokers. At 3- to 6-month follow-up, varenicline produced a higher rate of continuous tobacco abstinence compared with the other 3 groups; however, the study did not compare varenicline with combination NRT therapies. A 2016 meta-analysis[29] of 8 trials comparing varenicline with nicotine patches documented more cigarette abstinence with varenicline treatment after 24 weeks.

In a study[30] of 657 e-cigarette smokers assigned to utilized nicotine liquid containing 16 mg, a nicotine-free liquid, or 21-mg nicotine patches, cigarette abstinence rates did not differ significantly between the groups at 6-month follow-up. E-cigarettes might have efficacy similar to the nicotine patch for smoking cessation, but a definitive conclusion remains unclear. The "quit" rates observed, however, were less than in other clinical research, suggesting a selection bias or other issues.[30]

A trial[31] in 300 smokers who did not wish to quit smoking compared 2 strengths of e-cigarettes with an e-cigarette placebo with no nicotine; this investigation revealed no abstinence differences. Some studies[31] document that e-cigarettes are not associated with higher rates of quitting or reducing smoking. In fact, research confirms that most people who claim to use e-cigarettes to stop smoking tobacco do not do so; often, this results in using both products, with exposure to their combined and independent risk factors. It also means that they remain nicotine addicted.[31] The risk for lung cancer and ischemic cardiac disease is increased 3-fold by smoking just 4 tobacco cigarettes a day.[32] Though people sustain dual use of both tobacco and electronic cigarettes, there are still chances of reducing the amount of future smoking. However, there are no studies that fully explain the relation between the number of conventional cigarettes smoked and disease risk factors or harm reduction. Even in small amounts, tobacco smoke is injurious to health; the same might be true for e-cigarette smoking.

CONCLUSION

Smokers should be encouraged to maintain their interest in smoking cessation and advised to utilize the most safe and effective treatments. These individuals should first utilize approved products as a means to stop tobacco use because of insufficient evidence endorsing the role of e-cigarettes in smoking cessation. Smokers who previously failed conventional treatments might be assessed for medicinal therapies or consider second-line options like e-cigarettes.

It is up to the physician to make the decision to recommend the use of e-cigarettes for harm reduction or as an aid to stop smoking. Everyone should be aware of the uncertainty about e-cigarette long-term safety and efficacy as a therapeutic device to stop smoking. Always provide warnings about the risk for dual use of tobacco and e-cigarettes.

Submitted/accepted: November 22, 2016; accepted April 7, 2017.

Published online: June 8, 2017.

Potential conflicts of interest: None.

Funding/support: None.

REFERENCES

1. Anthonisen NR, Skeans MA, Wise RA, et al; Lung Health Study Research Group. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med*. 2005;142(4):233–239.
2. Harrell PT, Simmons VN, Correa JB, et al. Electronic nicotine delivery systems ("e-cigarettes"): review of safety and smoking cessation efficacy. *Otolaryngol Head Neck Surg*. 2014;151(3):381–393.
3. US Department of Health and Human Services. Agency for Healthcare Research and Quality. Public Health Service. Treating Tobacco Use and Dependence: 2008 Update. https://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/index.html.
4. US Preventive Services Task Force. Tobacco Smoking Cessation in Adults, Including Pregnant Women: Behavioral and Pharmacotherapy Interventions. https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/tobacco-use-in-adults-and-pregnant-women-counseling-and-interventions1.
5. Haddad A, Davis AM. Tobacco smoking cessation in adults and pregnant women: behavioral and pharmacotherapy interventions. *JAMA*. 2016;315(18):2011–2012.
6. Hartmann-Boyce J, Aveyard P. Drugs for smoking cessation. *BMJ*. 2016;352:i571.
7. Schnoll RA, Goelz PM, Veluz-Wilkins A, et al. Long-term nicotine replacement therapy: a randomized clinical trial. *JAMA Intern Med*. 2015;175(4):504–511.
8. Hays JT, Ebbert JO. Varenicline for tobacco dependence. *N Engl J Med*. 2008;359(19):2018–2024.
9. Kotz D, Viechtbauer W, Simpson C, et al. Cardiovascular and neuropsychiatric risks of varenicline: a retrospective cohort study. *Lancet Respir Med*. 2015;3(10):761–768.
10. US Food and Drug Administration. Public Health Advisory: Important Information on Chantix (varenicline). FDA website. http://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm077547.htm. Accessed March 28, 2017.
11. Molero Y, Lichtenstein P, Zetterqvist J, et al. Varenicline and risk of psychiatric conditions, suicidal behaviour, criminal offending, and transport accidents and offences: population based cohort study. *BMJ*. 2015;350:h2388.
12. UpToDate. https://www.uptodate.com. Accessed May 10, 2017.
13. Moore TJ, Furberg CD, Glenmullen J, et al. Suicidal behavior and depression in smoking cessation treatments. *PLoS One*. 2011;6(11):e27016.
14. Moore TJ, Furberg CD, Glenmullen J, et al. Suicidal behavior and depression in smoking cessation treatments. *PLoS One*. 2011;6(11):e27016.
15. Thomas KH, Martin RM, Knipe DW, et al. Risk of neuropsychiatric adverse events associated with varenicline: systematic review and meta-

analysis. *BMJ*. 2015;350:h1109.
16. Anthenelli RM, Benowitz NL, West R, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet*. 2016;387(10037):2507–2520.
17. Hajek P, Etter JF, Benowitz N, et al. Electronic cigarettes: review of use, content, safety, effects on smokers and potential for harm and benefit. *Addiction*. 2014;109(11):1801–1810.
18. Arrazola RA, Singh T, Corey CG, et al; Centers for Disease Control and Prevention (CDC). Tobacco use among middle and high school students: United States, 20112014. *MMWR Morb Mortal Wkly Rep*. 2015;64(14):381–385.
19. Vansickel AR, Eissenberg T. Electronic cigarettes: effective nicotine delivery after acute administration. *Nicotine Tob Res*. 2013;15(1):267–270.
20. Laino T, Tuma C, Moor P, et al. Mechanisms of propylene glycol and triacetin pyrolysis. *J Phys Chem A*. 2012;116(18):4602–4609.
21. Pisinger C, Døssing M. A systematic review of health effects of electronic cigarettes. *Prev Med*. 2014;69:248–260.
22. Wang MP, Ho SY, Leung LT, et al. Electronic cigarette use and respiratory symptoms in chinese adolescents in Hong Kong. *JAMA Pediatr*. 2016;170(1):89–91.
23. Allen JG, Flanigan SS, LeBlanc M, et al. Flavoring chemicals in e-cigarettes: diacetyl, 2,3-pentanedione, and acetoin in a sample of 51 products, including fruit-, candy-, and cocktail-flavored e-cigarettes. *Environ Health Perspect*. 2016;124(6):733–739.
24. Kosmider L, Sobczak A, Prokopowicz A, et al. Cherry-flavoured electronic cigarettes expose users to the inhalation irritant, benzaldehyde. *Thorax*. 2016;71(4):376–377.
25. Smith L, Brar K, Srinivasan K, et al. E-cigarettes: how "safe" are they? *J Fam Pract*. 2016;65(6):380–385.
26. Lembke A, Johnson K, DeBattista C. Depression and smoking cessation: does the evidence support psychiatric practice? *Neuropsychiatr Dis Treat*. 2007;3(4):487–493.
27. Cahill K, Stevens S, Perera R, et al. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database Syst Rev*. 2013;(5):CD009329.
28. Baker TB, Piper ME, Stein JH, et al. Effects of nicotine patch vs varenicline vs combination nicotine replacement therapy on smoking cessation at 26 weeks: a randomized clinical trial. *JAMA*. 2016;315(4):371–379.
29. Cahill K, Lindson-Hawley N, Thomas KH, et al. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev*. 2016;(5):CD006103.
30. Bullen C, Howe C, Laugesen M, et al. Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet*. 2013;382(9905):1629–1637.
31. Caponnetto P, Campagna D, Cibella F, et al. EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. *PLoS One*. 2013;8(6):e66317.
32. Bjartveit K, Tverdal A. Health consequences of smoking 14 cigarettes per day. *Tob Control*. 2005;14(5):315–320.