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Smoking Addiction and Strategies for Cessation

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Cigarette smoking is the leading cause of chronic obstructive pulmonary disease (COPD) worldwide. Smoking cessation is thus integral to the treatment of COPD. Nicotine addiction is a disease dependent on the complex interactions of neurotransmitter pathways, conditioned behaviors, environmental cues, genetic predisposition, and personal life circumstances, which render some more susceptible to tobacco abuse than others. The most successful smoking cessation programs are individualized, comprehensive, and utilize combinations of clinician counseling, behavioral reinforcement, community resources, advanced technology support (eg, smartphone apps, and Internet Web sites), and pharmacotherapy (both nicotine-based and nonnicotine medications). E-cigarettes were introduced to the US market in 2006 and touted as a safer alternative to tobacco cigarette smoking. Unfortunately, over the last 5 to 10 years, recreational e-cigarette use, or "vaping," has increased in popularity, especially among adolescents. This has introduced nicotine addiction to an entire generation of nonsmokers and resulted in numerous cases of acute lung disease, now known as e-cigarette or vape product use-associated lung injury (EVALI). In light of these adverse events, e-cigarettes and vape products are not currently recommended as a smoking cessation aid. **Key words:** *nicotine addiction*, *nicotine replacement therapy*, *smoking cessation*, *stages of change*, *vaping*

TOBACCO use is the leading cause of preventable disease, disability, and death in the United States.[1] In 2018, the Centers for Disease Control and Prevention (CDC) estimated that 13.7% of US adults 18 years and older currently smoked cigarettes. This number has decreased compared with 2005 when 20.9% of US adults smoked cigarettes.[2] Although this downtrend in tobacco use is encouraging, greater than 34 million adults are still actively smoking, with roughly 480 000 deaths every year attributed to cigarette use.[2,3] More than 16 million Americans suffer from a smoking-related disease, predominantly chronic obstructive pulmonary disease (COPD).[3] Despite the detrimental health effects, 38% of patients with COPD still smoke cigarettes.[4] Smoking cessation slows the progression of lung disease, reduces mortality, and is an essential component of COPD treatment.[5-7] In this article, we discuss the pathophysiology of nicotine addiction, the clinician approach to addressing tobacco dependence, pharmacologic treatment to aid cessation, and behavioral therapy interventions. Lastly, we examine the role of e-cigarettes in smoking cessation and their contribution to the alarming rise of recreational vaping and emergence of vaping-related lung injury.

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NICOTINE ADDICTION

Approximately 70% of smokers desire to quit; however, less than 10% are able to do

so successfully each year.[8,9] It is the effects of nicotine that drive addiction to tobacco products and make sustained smoking cessation a challenge. Tobacco addiction is complex and is dependent on the interplay of pharmacology, learned and conditioned behaviors, social and environmental cues, and genetic makeup.[10]

Pharmacology of addiction and tolerance

Inhalation of smoke particles from a cigarette results in transmission of nicotine directly to the lung alveoli. Once in the lungs, nicotine can be rapidly absorbed into the pulmonary venous circulation. Nicotine subsequently enters the arterial circulation and is quickly transported to the brain where it binds to nicotinic cholinergic receptors.[10,11] Activation of these receptors triggers the release of a variety of neurotransmitters in the brain, among which is dopamine. Dopamine plays a critical role in reward-motivated behavior and the sensation of pleasure.[10,12] In addition to nicotine, inhaled cigarette smoke contains substances that block the enzymatic breakdown of dopamine in the body. The inhibition of the enzymes, monoamine oxidase type A and type B, thus increases dopamine levels in the brain, further adding to the addictiveness of smoking.[13,14]

With repeated cigarette smoke exposure, tolerance (also known as neuroadaptation) develops to some of the effects of nicotine.[10,15] Desensitization occurs when nicotine receptors close and become unresponsive to prolonged nicotine stimulation.[15] Consequently there is a reduction in the primary rewarding and reinforcing effects of nicotine, which leads individuals to smoke more to achieve the same pleasurable effect as before.[16] Desensitization is followed by upregulation of nicotinic cholinergic receptors in the brain.[17] The symptoms of craving and withdrawal occur when desensitized receptors become responsive during periods of smoking abstinence, such as nighttime sleep or attempts to quit. Smoking alleviates craving and withdrawal by providing the nicotine needed to activate nicotinic cholinergic receptors in the brain, propagating a viscous cycle of physical dependence.[18]

Conditioned behavior

Nicotine reduces stress levels and anxiety in smokers. Daily smokers become dependent on cigarettes to enhance their mood, improve concentration, optimize performance of various tasks, and decrease appetite.[10,19] Cessation of smoking has the opposite effect, causing irritability, depression, anger, restlessness, anxiety, and weight gain.[20] Even when the physical symptoms of withdrawal have diminished, the urge to resume smoking frequently persists, at this point having more to do with conditioned behaviors and smoking-related environmental cues. Smokers often associate cigarette use with breaks from work, alcoholic beverages with friends, coffee consumption, driving in the car, and relief from stressful states.[21,22] The anticipated soothing and pleasurable effects of nicotine in such situations are powerful cues that sustain smoking in active users, and trigger relapse in those who have recently quit.

Risk factors for smoking dependence

Tobacco use typically begins during adolescence. Routine exposure to nicotine at a young age increases the risk of smoking dependence and addiction.[3,23] The CDC reports that 90% of adult tobacco users began smoking by the age of 18 years.[3] Risk factors for smoking in childhood or adolescence include exposure from parents, peer pressure, poor academic performance, behavioral issues (impulsivity, defiance), mood disorders (anxiety, depression), low self-esteem, and genetic influences (Table 1).[24-26] Animal studies support the vulnerability of our youth to addiction by demonstrating that nicotine exposure in developing rat brains can lead to permanent changes. Adolescent rats exposed to nicotine have higher rates of nicotine self-administration as adults, findings that are consistent with trends seen in human populations.[10,27,28]

Table 1. Risk Factors for Smoking Addiction

Onset of tobacco smoking during childhood or adolescence (<18 y)
Parental exposure
Peer pressure
Poor academic performance
Behavioral issues (ie, impulsivity, defiance)
Mood disorders (ie, anxiety, depression)
Low self-esteem
Mental illness
Substance abuse
Lower socioeconomic status
Genetic predisposition

Additional risk factors for smoking addiction include mental illness, substance abuse, and lower socioeconomic status. In a 2016 national survey, 32% of adults with mental illness reported current use of tobacco compared with 23% of adults without mental illness. In that same survey, 64% of adult cigarette smokers reported co-use of alcohol compared with 53% of adult nonsmokers. Twenty-five percent of cigarette smokers reported co-use of illicit drugs (marijuana, cocaine, heroin, inhalants, and hallucinogens) compared with 7% of nonsmokers.[29] Smoking is also more prevalent among adults with a GED certificate only compared with adults with graduate degrees (36% vs 3.7%), and among adults with an annual household income less than $35 000 compared with those with an annual household income more than $100 000 (31% vs. 7.3%).[2]

Genetic influences

There is increasing evidence that genetics play a role in susceptibility to nicotine addiction. Numerous studies exploring smoking patterns and related behaviors among family members, adopted relatives, and twins have found consistent heritability suggesting a substantial genetic contribution. As one such example, nicotine is metabolized primarily by the liver enzyme CYP2A6. Individuals with a genetic variant of CYP2A6 have reduced enzyme activity and metabolize cigarettes slower. Slow metabolizers smoke fewer cigarettes daily and are more likely to successfully quit compared with rapid metabolizers who experience more severe withdrawal symptoms.[30]

CLINICIAN APPROACH TO SMOKING CESSATION

Health care providers play a pivotal role in identifying patients with cigarette addiction and providing them with the support and tools needed to effectively quit smoking. Guidelines from the United States Preventive Services Task Force (USPSTF) recommend clinicians use a 5-step guide, known as the "5 As" approach, when counseling on smoking cessation.[31]

Ask

First step is to *ask* about tobacco use and smoking habits, past and present. This allows clinicians to identify at-risk persons, including both active smokers and those who have recently quit but may be vulnerable to relapse.[31] It is crucial to inquire about all forms of tobacco and nicotine use such as cigars, pipes, chewing tobacco, hookahs, and e-cigarettes/vape devices. Nineteen percent of tobacco users cite use of 2 or more tobacco products.[32] Additional questions should pertain to frequency of tobacco use, number of cigarettes (eg, cigars and vapes) smoked daily, history of quit attempts, withdraw symptoms, and willingness to cease tobacco use at this time.[33]

Advise

Second step is to *advise* your patient to quit smoking in a clear, strong, and personalized manner.[34,35] Several studies have shown that any face-to-face counseling, even when brief (<10 minutes), can effectively help patients quit tobacco smoking and remain abstinent for 1 year.[31,36] There does, however, appear to be a dose-response relationship between intensity/duration of counseling and quit rates.[34] Administering advice that encourages smoking cessation should not be restricted to physicians and can be provided

by nurses, social workers, case managers, and psychologists.[37]

Assess

Third step is to *assess* readiness to quit smoking.[34] This can be challenging as many tobacco users are simply not interested in smoking cessation. Clinicians may fear isolating patients by repeatedly inquiring about their willingness to stop tobacco use. Fundamental to the third step is understanding that a smoker's inclination toward cessation is dynamic and their decision to quit usually a gradual one.[35] Providers may find patients in any 1 of the following 5 "stages of change": precontemplation (not interested in quitting), contemplation (self-reflection on tobacco use, weighing pros/cons of quitting), preparation (commitment made to quit, has begun developing a plan), action (actively engaging in cessation plan), and maintenance (abstinence from smoking at least 6 months) (Table 2).[38,39]

For those contemplating quitting, assistance should be provided (see the "*Assist*" subsection). For those in the precontemplative stage, motivational interviewing techniques may be useful and can help clinicians more effectively explore the smoker's own perception of their addiction. Examples of such techniques include using empathic and reflective listening with regard to the patient's reasons for not quitting, acknowledging personal barriers to cessation, highlighting patient values and goals that conflict with smoking, discussing risks associated with ongoing tobacco use, building on past cessation success, providing patients with choices and control over how to proceed, and leaving the door open to future conversations.[34,35]

Assist

Fourth step is to *assist* smokers who are ready to quit.[34] Clinicians should support quit attempts via a combination of cessation counseling, pharmacotherapy, and community resources (see the "Pharmacologic Treatments" and "Behavioral Interventions and Resources" sections). Past quit attempts should be reviewed to identify methods that were successful and the factors that contributed to relapse. A quit date should be set within 2 weeks and tobacco products should be removed from all environments (home, work, car, etc). It is beneficial for family, friends, and coworkers to be informed of the quit attempt, as their encouragement can promote success. Anticipating temptations, triggers, cravings, and withdrawal symptoms allows patients to formulate a plan to overcome the urge to return to smoking.[34,35]

Arrange

Fifth step is to *arrange* follow-up. This can be done in person or via phone call. Follow-up should occur within 1 to 2 weeks with the intention of providing ongoing

Table 2. Five Stages of Behavior Change

Stage	Description
Precontemplation	Not interested in quitting; may be unaware of need to change; overestimates cost of change; underestimates benefit
Contemplation	Self-reflection on tobacco use; weighing pros/cons of quitting; may consider change within the next 6 mo
Preparation	Commitment made to quit; has begun developing a plan; will take action in the next month
Action	Actively engaging in cessation plan; has quit within the last 6 mo; needs encouragement to remain tobacco-free; at high risk of relapse
Maintenance	Abstinence from smoking at least 6 mo; living a smoke-free lifestyle; may benefit from reminders about high-risk situations

support, to monitor impact of both pharmacologic and behavioral treatments, to address adverse side effects and to discuss barriers to success the patient may be experiencing.[34,35] While total abstinence from smoking is the ultimate goal, it is realistic to recognize that many smokers will experience a relapse during their quit attempt. Up to 50% of smokers relapse in the first year.[40,41] On average, smokers make between 8 and 11 quit attempts before successfully quitting.[42] Patients who have failed a quit attempt should be encouraged to try again, and to smoke as little as possible during periods of relapse. Reduced smoking has been associated with subsequent cessation.[35]

PHARMACOLOGIC TREATMENTS

Food and Drug Administration (FDA)-approved pharmacotherapy for smoking cessation consists of short-acting nicotine replacement products (gum, lozenge, nasal spray, and inhaler), long-acting nicotine replacement therapy (transdermal patch), and the nonnicotine medications, varenicline, and sustained-release bupropion (Table 3). Nortriptyline is an alternative non-FDA-approved medication for smoking cessation.[7]

Nicotine gum

Nicotine gum is one of the more commonly used nicotine replacement therapies (NRTs) for smoking cessation. It has been shown to have higher smoking success rates at 1 year compared with placebo gum (23% vs 13%).[63] To achieve optimal effect, a special technique is required, which consists of slow chewing alternating with parking the gum between the cheek and the gums of the mouth. Recommended duration of nicotine gum use is up to 3 months.[43]

Advantages to nicotine gum include over-the-counter (OTC) availability, flexible dosing, and fast delivery of nicotine for quick relief of cravings. Furthermore, the habit of gum chewing can be likened to the habit of smoking, but with far less toxic effects.[50] Disadvantages include the inability to eat or drink 15 to 30 minutes prior to use, frequent dosing, jaw fatigue and soreness, gastric distention, hiccups, and nausea.[50,51] An additional drawback is that some smokers have reported becoming addicted to nicotine gum.[59] Nicotine gum is contraindicated in patients with dental problems (ie, loose teeth, dentures), temporomandibular joint syndrome, and in the 2 to 4 weeks following myocardial infarction, uncontrolled arrhythmias, and unstable angina. It should be noted that these cardiovascular precautions apply to all nicotine products.[39,51] Nicotine gum is a US FDA pregnancy category C drug.[39]

Nicotine lozenges

Nicotine lozenges are administered orally and contain 25% more nicotine than gum.[61] They have a 6-month success rate of 24% compared with 14% for placebo.[52] Lozenges should be sucked slowly until the taste becomes strong and occasionally moved from one side of the mouth to the other. It is normal for a warm or tingling sensation to be felt in the mouth. Lozenges should not be chewed or swallowed.[44] Recommended duration of lozenge use is 3 to 6 months.[35,44]

Advantages to lozenges include OTC availability, flexible dosing, ability to be used by denture wearers, and fast onset of effect to produce prompt relief of cravings.[51,52] Studies have shown delayed weight gain with lozenge use compared with unassisted smoking cessation.[52] Lozenges possess many of the same disadvantages as nicotine gum: inability to eat or drink 15 to 30 minutes prior to use, hiccups, mouth and throat irritation, belching, nausea, and vomiting.[35,39,51] Other side effects include headache, dizziness, diarrhea, anorexia, and sweating.[60] Because of the potency of nicotine lozenges, there is a risk of overdose, especially if taken with some other form of nicotine.[61,60] As with all nicotine replacement products, lozenges are contraindications in acute cardiovascular disease. It is a US FDA pregnancy category D drug.[51]

Table 3. FDA-Approved Pharmacotherapy for Smoking Cessation

Medications	Dose/Instructions	Advantages	Disadvantages
Nicotine gum	Use 4-mg gum if first cigarette <30 min after waking; use 2 mg if first cigarette >30 min after waking. Chew 1 piece every 1-2 h, then taper; chew up to 24 pieces a day; use gum for up to 3 mo[43]	OTC availability, flexible dosing, fast delivery of nicotine for quick relief of cravings; habit of gum chewing can be likened to the habit of smoking[50]	Cannot eat or drink 15-30 min prior to use, frequent dosing,; may cause jaw fatigue/soreness, gastric distention, hiccups, and nausea[50,51]; potential for addiction[59]; c/i if dental problems, TMJ syndrome; CV precautions[39,51]
Nicotine lozenges	Use 4-mg lozenge if first cigarette <30 min after waking; use 2 mg if first cigarette >30 min after waking. Start with 1 lozenge every 1-2 h, then taper. Do not use >20 lozenges in a day[44]; use for 3-6 mo[35]	OTC availability, flexible dosing, can be used by denture wearers, fast onset of effect[51,52]; delayed weight gain with lozenge use compared with unassisted smoking cessation[52]	Cannot eat or drink 15-30 min prior to use; may cause hiccups, mouth and throat irritation, belching, nausea, vomiting, headache, dizziness, diarrhea, anorexia, sweating[35,39,51,60]; overdose concern because of high potency[61,60]; CV precautions[39]
Nicotine nasal spray	1 dose is equal to 1 spray in each nostril; use 1-2 doses every hour, up to 40 doses per day; use spray for up to 3 mo[45]	Control over dosing; fast delivery of nicotine provides immediate rewarding effects[35]	Requires a prescription due to highly addictive potential[51]; frequently causes nasal irritation (which lasts several weeks into treatment), runny nose, sneezing, throat irritation, coughing, and watery eyes[45,53]; CV precautions[39]
Nicotine inhaler	Use 6-16 cartridges per day; each cartridge delivers 80 inhalations. Use inhaler for an initial 12-wk period, followed by a gradual taper over 12 wk[46]	Control over dosing; mimics the hand-to-mouth motion of smoking a cigarette[53]	Visible use of device; may cause mouth and throat irritation, coughing, rhinitis[46]; requires a prescription; CV precautions[39]

(*continues*)

Table 3. FDA-Approved Pharmacotherapy for Smoking Cessation (*Continued*)

Medications	Dose/Instructions	Advantages	Disadvantages
Nicotine patch	If >10 cigarettes per day, use 21-mg patch daily for 6 wk, then 14-mg patch daily for 2 wk, then 7-mg patch daily for 2 wk. If <10 cigarettes per day, use 14-mg patch daily for 6 wk, then 7-mg patch daily for 2 wk[47]	OTC availability, once daily application, discreteness, reliable nicotine levels, low risk of habituation[50,51]	Less flexible dosing schedule; may cause skin irritation, insomnia if worn at night, tachycardia, nausea, vomiting, dizziness[35,62]; slow release of nicotine does not suppress acute cravings; CV precautions[39]
Sustained-release bupropion	Take 150-mg by mouth in the morning for 3 d, then increase to 150 mg twice a day; consider dose reduction in renal and hepatic impairment. Begin therapy 1-2 wk before the quit date, and continue for 3-6 mo[48]	Low potential for abuse; decreases cessation-related weight gain compared with placebo and NRT; safer than NRT among pregnant/lactating women and patients with CV disease[54,55]; bupropion can be combined with nicotine patch to increase efficacy[36]	May cause insomnia, vivid dreams, dry mouth, rhinitis, headaches, nausea, and anxiety; lowers seizure threshold; may cause serious neuropsychiatric symptoms including depression, psychosis, suicidal thoughts/attempts[48]; c/i in those with eating disorders, recent head trauma, and those taking MAOIs[35,39]
Varenicline	0.5 mg by mouth once daily for 3 d, then 0.5 mg twice a day for 4 d, then 1 mg twice a day; reduce dose in patients with renal impairment and on dialysis. Begin therapy 1 wk before quit date and continue for 3-6 mo[49]	Very effective monotherapy for smoking cessation (increases quit rates by 2-3 times compared with placebo)[56,57]; varenicline can be combined with nicotine patch to further increase efficacy[58]	May cause headache, nausea, insomnia, abnormal/vivid dreams, flatulence, new or worsening seizures, increased rates of accidental injury; neuropsychiatric symptoms have been reported; there may be an increased risk of CV events in patients with underlying CV disease[49]

Abbreviations: c/i, contraindicated; CV, cardiovascular; MAOI, monoamine oxidase inhibitor; NRT, nicotine replacement therapy; OTC, over-the-counter; TMJ, temporomandibular joint.

Nicotine nasal spray

Of all the nicotine replacement products, nasal sprays provide the fastest delivery and highest levels of nicotine.[64] Despite this, they do not provide nearly the amount of nicotine that cigarettes do.[65] Nicotine nasal

spray has a 6-month success rate of 31% compared with 14% for placebo.[66] Recommended treatment duration is 3 months.[45]

Advantages of nicotine nasal spray include control over dosing and fast delivery of nicotine, which provides immediate rewarding effects similar to that of smoking.[35] Disadvantages include its highly addictive potential and thus a prescription requirement for purchase.[51] Additional side effects include nasal irritation, runny nose, sneezing, throat irritation, coughing, and watery eyes.[45,53] While the severity of nasal irritation declines with continued use of nicotine nasal spray, the majority of patients (81%) still report mild to moderate symptoms after several weeks of treatment.[45] Nicotine nasal spray is a US FDA pregnancy category D drug.[39]

Nicotine inhaler

Nicotine inhalers consist of a nicotine-filled cartridge attached to a plastic mouthpiece.[51] The majority of nicotine (>95%) is absorbed in the mouth rather than in the airways of the lungs[46] Nicotine inhaler use has been shown to double cessation rates at 6 months when compared with placebo (23% vs 11%).[66] Use is recommended for an initial 12 weeks' period, followed by a gradual taper over 12 weeks.[46]

The advantage of the nicotine inhaler is that it mimics the hand-to-mouth motion of smoking a cigarette, which may attenuate some of the behavioral challenges associated with cessation.[53] Disadvantages include conspicuous use, mouth and throat irritation, coughing, rhinitis, and prescription requirement.[46] Nicotine inhalers differ from vape devices and e-cigarettes in that they are FDA approved, available via prescription only, have an exact and stated amount of nicotine, and do not involve a heating element. Additionally, nicotine inhalers deposit most of the nicotine in the mouth as opposed to transporting it to the lungs as occurs in vaping.[67] Vaping has been discussed in more detail in an upcoming section. Nicotine inhaler is a US FDA pregnancy category D medication.[39]

Nicotine transdermal patch

When applied to a dry and hairless area daily, nicotine transdermal patches release nicotine in a steady fashion over several hours.[47] Patches have been shown to increase cessation rates by 1.5 to 2 times when compared with placebo.[68-70] Nicotine patches are available in 3 strengths: 7, 14, and 21 mg per 24 hours.[47] Selection of patch strength and treatment duration depend on how many cigarettes are smoked daily (refer to Table 1). The nicotine patch should not be placed on the same area again for at least 1 week.

Advantages to nicotine patch use include OTC availability, once daily application, discreteness, reliable nicotine levels, and low risk of habituation.[50,51] Disadvantages include less flexible dosing schedule, skin irritation, insomnia if worn at night, tachycardia, nausea, vomiting, and dizziness.[35,62] Unfortunately, the slow release of nicotine does not suppress acute nicotine cravings. It is a US FDA pregnancy category D drug.[51]

Sustained-release bupropion

Bupropion is an atypical antidepressant that inhibits the reuptake of dopamine and noradrenaline in the central nervous system and is a noncompetitive nicotine receptor antagonist. The antismoking effect of bupropion is likely secondary to attenuation of nicotine withdrawal symptoms after cessation.[71] In several studies, sustained-release bupropion demonstrated 6-month success rates ranging from 21% to 30% compared with 10% to 19% for placebo.[72-75] A Cochrane database review of 44 trials revealed that when bupropion was used as sole pharmacotherapy, it increased long-term cessation rates by 1.6 times.[76] Bupropion therapy should be started 1 to 2 weeks before the quit date, and continued for 3 to 6 months after cessation.[48]

Bupropion has low potential for abuse, and is observed to have decreased cessation-related weight gain compared with placebo and NRT. It is also felt to be safer than nicotine among pregnant/lactating women

and patients with cardiovascular disease.[54,55] Commonly experienced adverse effects are insomnia, vivid dreams, dry mouth, rhinitis, headaches, nausea, and anxiety. Serious neuropsychiatric symptoms have been reported and include depression, mania, psychosis, hostility, agitation, paranoia, homicidal ideation, suicidal thoughts and behavior, and attempted suicide. There is a boxed warning for increased suicidal thoughts and behaviors in children, adolescents, and young adults aged 18 to 24 years.[48] Bupropion is contraindicated in patients with eating disorders, recent head trauma, and those already taking monoamine oxidase inhibitors.[35,39] The medication should also be avoided in smokers with a seizure history, and in combination with drugs that lower the seizure threshold. Extreme caution should be taken in those who concomitantly use alcohol, benzodiazepines, barbiturates, and antiepileptics, as abrupt discontinuation of these substances can precipitate seizures.[48] Bupropion is a US FDA pregnancy category C drug.[39]

Varenicline

Varenicline is a selective nicotine receptor partial agonist. It reduces cravings and withdrawal symptoms through partial activation of the receptor, while limiting nicotine's ability activate the mesolimbic dopamine system. This attenuates the reinforcing and rewarding effects that lead to dependence.[77] Several studies demonstrate that varenicline increases the chance of a successful quit attempt two- to threefold compared with no pharmacologic assistance.[56,57] In one randomized controlled trial (RCT), using varenicline 1.0-mg dose increased abstinence rates at 52 weeks by 5 times when compared with placebo (22.4% vs 3.9%).[78] Pooled results from 4 trials comparing bupropion with varenicline show a 32% higher quit rate when varenicline is used.[76] The medication should be started 1 week before quit date and continued for 3 to 6 months.[49]

Disadvantages to varenicline use include headache, nausea, insomnia, abnormal/vivid dreams, flatulence, the development of new or worsening seizures, and increased rates of accidental injury. Like bupropion, postmarketing neuropsychiatric symptoms have been reported and include behavioral change, hostility, agitation, depressed mood, suicidal thoughts, and attempted suicide. Surprisingly however, the boxed warning for neuropsychiatric symptoms was removed from varenicline in 2016 by the FDA after a study indicated these events occurred only rarely in those with preexisting psychiatric disease.[49]

In the past there have been conflicting data regarding varenicline's association with adverse cardiovascular events.[79] More recently, a 2016 meta-analysis of 38 RCTs with over 12 000 patients showed no evidence that varenicline increases the rate of serious cardiovascular events, including myocardial infarction, unstable angina, coronary artery disease, arrhythmias, congestive heart failure, transient ischemic attack, stroke, sudden death, and/or cardiovascular-related death.[80] The FDA is somewhat ambiguous in their position on this stating that patients with underlying cardiovascular disease may be at increased risk for cardiovascular events but these concerns need to be balanced with health benefits of smoking cessation. Varenicline is a US FDA pregnancy category C medication.[49]

Nortriptyline

Nortriptyline is a non-FDA-approved medication for smoking cessation. It is primarily prescribed as an antidepressant.[34] The mechanism through which it aids smoking cessation is unclear but may relate to dopaminergic and adrenergic activity.[81] Research has demonstrated that, when compared with placebo, nortriptyline can double abstinence rates.[76] It is available by prescription in oral form. Recommended dosing is 25 mg once daily begun 10 to 28 days prior to quit date. Dose can be titrated to 75 to 100 mg/day as needed. Therapy should be continued for 12 to 24 weeks after quit day.[34] Nortriptyline use is limited by an extensive side effect profile, which includes anticholinergic properties (dry mouth,

blurred vision, and urinary retention), psychiatric manifestations (hallucination, disorientation, delusions, and insomnia), neurologic symptoms (paresthesia, ataxia, tremors, and seizures), cardiovascular disease (myocardial infarction, stroke, and arrhythmias), hematologic dyscrasias (bone marrow suppression), endocrine abnormalities (gynecomastia, hyperglycemia, and impotence), and gastrointestinal disturbance (nausea, vomiting, abdominal pain, and diarrhea).[82] It is a US FDA pregnancy category C medication.[83]

Combination pharmacotherapy

Combining the nicotine patch with a more rapidly absorbed form of NRT (gum, lozenge, inhaler, and nasal spray) is more effective than using a single nicotine product alone for smoking cessation.[34,84-86] As such, combination therapy should be offered as initial treatment over monotherapy when NRT is chosen.[87] This combined regimen is considered safe because patients are still exposed to less nicotine overall than smoking cigarettes.[34]

Multiple studies have demonstrated that combination NRT has similar abstinence rates compared with use of varenicline alone, making either of these 2 approaches a first-line recommendation for smoking cessation.[88,89] For those using varenicline monotherapy who have cut back on smoking but are unable to quit completely, adding a nicotine patch increases the likelihood of cessation.[58]

Bupropion appears to be less effective than combination NRT or varenicline and as such should be considered second-line or alternative therapy.[87] In patients prescribed bupropion who fail to achieve complete tobacco abstinence, adding a nicotine patch increases efficacy over bupropion monotherapy.[36] The combination of bupropion and NRT does not appear to be more effective for smoking cessation than NRT alone.[76]

BEHAVIORAL INTERVENTIONS AND RESOURCES

Nonpharmacologic treatment of tobacco dependence is integral to successfully achieving smoking cessation. Personalized counseling, behavioral skills training, and motivational interviewing occur at various points throughout a patient's journey to smoking abstinence.[36] Some of these interventions occur during the initial stages of assessing one's readiness to quit tobacco and were discussed previously in the section "Clinician Approach to Smoking Cessation."

In-person counseling

There are several behavioral therapy modalities and counseling formats that can be employed when assisting a patient in their attempt to quit smoking. Strategies should be tailored to patient interest and availability.[87] Brief counseling sessions as part of routine office visits are what commonly occur for busy clinicians and patients with limited time. Counseling lasting less than 10 minutes can still increase the proportion of patients that quit and remain smoke free at 1 year.[34] More formal individual counseling consists of multiple one-on-one clinician visits dedicated to patient motivation and reinforcement of behavior change that begin even prior to the patient's quit date.[87] Patients should receive at least 4 in-person counseling sessions.[34] Group counseling involves participants meeting regularly with a facilitator who is trained in smoking cessation counseling. The strength of this approach is that patients can increase their supportive social network, model behavior discussed by other group members, get peer feedback and encouragement on their personal experiences, and reduce the cost as associated with treatment.[90]

Telephone counseling and text message/app support

Not all therapy and support must be provided in person. Telephone counseling interventions have been proven effective if patients are provided with at least 3 telephone calls by professionals trained to offer cessation advice and guidance over the phone.[36] Proactive, prearranged calling by a counselor is likely more efficacious than reactive patient-initiated calling.[91] In the Unites States,

patients have additional access to free telephone coaching by calling 1-800-QUIT-NOW. Patients can also register through the CDC to have free quit help and encouragement texted to their phone.[92] Individuals interested in more interactive technology can download free smartphone apps (ie, quitStart) that monitor smoking behavior, provide reminders for taking medication, and offer tailored tips and inspiration.[87,92]

Web site resources

Several Internet Web sites are available to aid smoking cessation efforts. These Web sites provide information on smoking addiction and its harms, tools on how to quit, and links to other treatment resources. Examples include www.smokefree.gov, www.quit.com, and www.lung.org/stop-smoking.[93-95] These sites should be used as an adjunct to other treatment approaches, as there is limited evidence that online resources as a stand-alone intervention are effective in increasing cessation rates.[87] The most successful Internet-based interventions involve Web sites that are interactive and specifically tailored to individuals.[96]

Unproven therapies

Exercise, acupuncture, and hypnotherapy have all been explored as alternative therapies to aid smoking cessation. Systematic reviews have demonstrated a lack of evidence that these treatment modalities are beneficial to improving quit rates.[97-99]

E-CIGARETTES AND VAPING

Electronic nicotine delivery systems (ENDS) are non-FDA-approved devices that include e-cigarettes and other vape products. While variations of the e-cigarette can be traced back to the 1960s, the modern e-cigarette was developed in 2003 by a Chinese pharmacist, Hon Lik. In 2006, e-cigarettes were first introduced in the United States for commercial sale and were marketed as a safer alternative to smoking cigarettes.[100] The emergence of e-cigarette or vaping product use-associated lung injury (EVALI) has certainly challenged that claim.

Composition of e-cigarettes/vape products

ENDS vary in size, shape, and composition but in general have 4 main components: a reservoir that holds the liquid to be aerosolized or "vaped" (also known as e-liquid), an atomizer, which is a heating element, a battery to power the atomizer, and a mouthpiece for inhalation.[100,101] The primary components of e-liquid consist of nicotine, synthetic flavoring, tetrahydrocannabinol, cannabidiol, and/or butane hash oils (dabs). A combination of these substances in varying ratios can be present in any one given vape product.[102] What is more alarming are the additional chemical constituents present in ENDS that are unbeknownst to the consumer. Propylene glycol, glycerin, polycyclic aromatic hydrocarbons, formaldehyde, nitrosamines, volatile organic chemicals, and inorganic toxic metals have all been detected in vape products.[103,104] Compounding matters further, substances in e-liquid undergo thermal decomposition by the metallic heating coils to produce novel toxic compounds.[102] Intense heat releases heavy metals such as iron, aluminum, zinc, nickel, tin, and lead into the aerosol. E-cigarette and vape users are thus potentially exposed to infinite combinations and permutations of inhalants with unknown adverse effects.[100]

Targeting youth

While flavoring of traditional tobacco cigarettes is prohibited, the e-liquids in vape products come in more than 7000 unique flavors, making them particularly appealing to the nation's youth. Since 2014, ENDS have been the most commonly used nicotine product among adolescents.[100] From 2017 to 2018, the prevalence of e-cigarette and vape device use increased from 11.7% to 20.8% among US high school students.[105] By 2019, 27.5% of high school students and 10.5% of middle school students endorsed vaping.[106] This amounts to over 5 million

middle and high school students engaged in current use of e-cigarette/vape products. In contrast, only 3.2% of US adults reported current e-cigarette/vape device use in 2018.[107] Of substantial concern is that use of ENDS has introduced nicotine addiction to an entire generation of nonsmokers and may become a bridge to future tobacco use.[100]

E-cigarette or vaping product use-associated lung injury

Since 2019, the CDC has linked vaping to the development of a severe form of acute lung disease, which they named EVALI (e-cigarette or vaping product use-associated lung injury).[108] EVALI is diverse in presentation with the following lung injury patterns reported: diffuse alveolar hemorrhage, exogenous lipoid pneumonia, acute eosinophilic pneumonia, hypersensitivity pneumonitis, respiratory bronchiolitis-interstitial lung disease, and organizing pneumonia.[102,109] Diagnosis consists of use of an ENDS within 90 days of symptom onset, pulmonary infiltrates on computed tomography of the chest or chest roentgenogram, absence of pulmonary infection on initial workup, and no alternative plausible diagnosis.[102] As of February 2020, there have been a total of 2807 hospitalized EVALI cases with 68 deaths.[108]

The role of e-cigarettes in smoking cessation

E-cigarettes and vape products are not currently approved by the FDA as smoking cessation aids.[107] Results from available studies regarding efficacy in smoking cessation are mixed. Evidence from a 2016 systematic review of 2 RCTs involving 662 participants found that e-cigarettes with nicotine increased long-term quit rates by twofold compared with nonnicotine e-cigarettes.[110] A 2019 RCT of 889 participants determined that e-cigarettes were more effective to achieve smoking abstinence at 1 year than NRT, when both products were accompanied by behavioral support (18% vs 9.9%).[111] In contrast, a CDC online survey of 15 000 smokers found that most adult e-cigarette users attempting to quit tobacco actually do not stop smoking traditional cigarettes, and instead become dual users of both products.[112] Despite the potential efficacy of e-cigarettes and vape devices as quit aids, safety concerns outlined previously in this article appear to outweigh the benefits of their use.

The USPSTF has formally concluded that there is insufficient evidence to recommend e-cigarettes for smoking cessation in adults. The CDC and the FDA recommend that adults currently using nicotine-containing e-cigarettes or vaping products as alternatives to cigarettes should not return to smoking. Instead, they should consider using FDA-approved smoking cessation medications. If patients choose to use e-cigarettes, they should completely stop use of traditional cigarettes and not partake in dual use of both products. ENDS should never be used by youths, adolescents, young adults, or women who are pregnant. Adults who do not currently use tobacco products should not start using e-cigarettes or vaping products.[108]

CONCLUSIONS

Despite its decline in recent years, tobacco smoking still continues to be a major threat to the health of millions of individuals in this country and even more worldwide. Nicotine addiction is complex and an understanding of the pharmacology, conditioned behaviors, risk factors for abuse, and genetic contribution is crucial for successful treatment. Smoking cessation programs are most effective when they implore a multimodal approach including clinician counseling, behavioral reinforcement, pharmacotherapy, and even interactive technology. Cessation strategies should be tailored to individual interests. Triumph over smoking is highly dependent upon maintenance of patient autonomy and input to this process. While there is some evidence that e-cigarettes and vape products may assist the effort to quit, overwhelming safety concerns render them an unadvised option at this point.

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