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The Past, Present, and Future of Nicotine Addiction Therapy

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Abstract

The tobacco addiction treatment field is progressing through innovations in medication development, a focus on precision medicine, and application of new technologies for delivering support in real time and over time. This article reviews the evidence for combined and extended cessation pharmacotherapy and behavioral strategies including provider advice, individual counseling, group programs, the national quitline, websites and social media, and incentives. Healthcare policies are changing to offer cessation treatment to the broad population of smokers. With knowledge of the past and present, this review anticipates what is likely on the horizon in the clinical and public health effort to address tobacco addiction.

Keywords

smoking; tobacco; cessation; cigarette; vape; quitline

INTRODUCTION

Tobacco use remains the leading preventable cause of disease, disability, and mortality in the United States, where it causes an estimated 480,000 deaths annually and accounts for approximately 90% of deaths from lung cancer, 60% from pulmonary disease, and 30% from heart disease (1). Globally, more than six million deaths each year are attributed to tobacco use, with the accumulated loss of life expected to reach one billion by the end of the 21st century (2).

Cigarettes are the most commonly used form of tobacco in the United States, although cigars, smokeless tobacco, and dual use of tobacco products are increasingly common and are also of clinical and public health concern. In 1964, when the first Surgeon General's report on the negative consequences of smoking was published, half of US men and a third

DISCLOSURE STATEMENT

Dr. Prochaska and Dr. Benowitz have served as expert witnesses against the tobacco companies in lawsuits and have received fees for that work. They have provided consultation to Pfizer, which makes medications for quitting smoking. Additionally, Dr. Benowitz has served as a consultant to GlaxoSmithKline with respect to smoking cessation medications.

of women smoked cigarettes. Today, in the United States, 20.5% of men and 15.3% of women smoke (3). Although this is a commendable reduction, the declines in use since the year 2000 have been modest at ~1% per year. More than 42 million Americans currently smoke; every day another 3,000 adolescents smoke their first cigarette and >2,000 youth and young adults progress from being occasional to daily cigarette smokers (4). Most smokers (>70%) want to quit, and 40% attempt to do so each year; yet, only about 5% are successful (2). Further, declines in smoking have not been achieved equally. Disparities in the prevalence of tobacco use and tobacco-related diseases exist across groups defined by race and ethnicity, educational level, socioeconomic status, mental health status, and US region (1).

Nicotine Addiction

Nicotine addiction is a chronic brain disorder. Prolonged tobacco use results in physiologic dependence and a behavioral compulsion to use tobacco. Nicotine establishes and maintains tobacco addiction by complex actions that affect the neurochemistry of the brain (5). Nicotine from cigarette smoke is rapidly absorbed in the lungs and then quickly passes into the brain. The rapidity of absorption is an important determinant of the addictiveness of a drug, and cigarette smoking is the most rapid method of nicotine delivery. Nicotine diffuses readily into brain tissue, where it binds to nicotinic acetylcholine receptors (nAChRs), which are ligand-gated ion channels. The nAChR complex is composed of five subunits. In the mammalian brain, there are as many as nine alpha subunits (α2–10) and 3 beta subunits (β2–4); α4β2, α3β4, and α7 (homomeric) are the most abundant receptor subtypes in the brains of humans, and the α4β2 receptor subtypes predominate, believed to be the main receptor mediating nicotine dependence. Stimulation of central nAChRs by nicotine results in the release of a variety of neurotransmitters in the brain, most importantly dopamine, critical in signaling pleasure. Nicotine results in positive, though transient, psychological effects of pleasure, arousal, and mood modulation.

With chronic nicotine exposure, as is experienced by addicted smokers, neuroadaptation occurs, such that more nicotine is required to deliver the same neurochemical effect. As the brain becomes tolerant, nicotine is needed to maintain normal brain functioning. In this context, stopping smoking is associated with altered neurotransmitter release and withdrawal symptoms of irritability, anxiety, problems getting along with others, difficulty concentrating, hunger, and weight gain. Thus, nicotine addiction is sustained both by positive effects of pleasure and arousal and by avoidance of the unpleasant effects of nicotine withdrawal.

In addition to the pharmacologic aspects of nicotine addiction, conditioning plays an important role in sustaining tobacco use. Smoking becomes associated with specific behaviors such as drinking coffee or alcohol, talking on the phone, driving a car, and/or completing a meal. Through conditioning, these behaviors become cues for smoking and contribute to maintained use. Smoking also facilitates nicotine addiction through sensorimotor factors associated with the act of smoking, e.g., the smell, taste, and feel of the cigarette smoke.

Our review is a 20-year update covering many notable advances in the field. When Dr. Jed Rose wrote his 1996 review for the *Annual Review of Medicine*, nicotine replacement therapy (NRT) in the form of gum and patch was the only smoking cessation medication approved by the US Food and Drug Administration (FDA), and bupropion's effects for promoting cessation were just being recognized; behavioral treatments were largely limited to in-person delivery, with quitlines available in only three states (California, Massachusetts, and Arizona). Twenty years later, the number of FDA-approved medications for quitting smoking has tripled; support for combination NRT has grown; a quitline consortium makes free cessation counseling available nationwide (1-800-QUIT-NOW); and technological innovations, including the internet, texting, and social media, have increased the access and convenience of cessation support. Our review also builds upon prior reviews focused on the pharmacology of nicotine and smokers with mental illness (6, 7).

The tobacco use control field is progressing through innovations in medication development, a focus on precision medicine, and application of new technologies for delivering support in real time and over time. In addition, healthcare policies are changing to offer preventive care, including tobacco addiction treatment, to the broad population of smokers. With knowledge of the past and present, we anticipate what is likely on the horizon.

The Scope of Our Review

Consistent with US Clinical Practice Guidelines, our review covers cessation medications and counseling and support for addressing the physiologic and behavioral patterns of tobacco addiction (8). We briefly review mechanisms of action and use of the FDA-approved first-line cessation medications in single and combination form; second-line pharmacologic treatments with evidence, but not FDA approval; and emerging pharmacologic strategies, including prequit medication use and reduce-to-quit approaches. The second half of our review covers counseling and psychosocial treatments, including interpersonal, telephonic, internet-based, and social media–based modalities. Use of incentives and health policy approaches also are highlighted. Although the medication and counseling approaches for treating nicotine addiction are relatively straightforward, most quit attempts today are still unassisted (with a success rate of only 2–5%), undertreatment is common, and relapse is the norm. Unaided attempts remain common due to beliefs among smokers that quitting is an act of willpower and free choice, combined with the healthcare system's general failure to acknowledge tobacco use as an addiction warranting medical attention and intervention. We close with discussion of recent changes brought about by the Affordable Care Act that increase coverage of, and ostensibly access to, cessation treatments.

CESSATION PHARMACOTHERAPY

US Public Health Service guidelines recommend all smokers trying to quit be offered pharmacotherapy, unless contraindicated (8). Table 1 summarizes precautions, dosing guidelines, adverse effects, advantages, and disadvantages of the seven FDA-approved first-line smoking cessation medications: NRT (in the form of patch, gum, lozenge, spray, and inhaler), bupropion, and varenicline. Generally, all approved cessation medications, if used

properly, double quit rates compared with placebo treatments (9, 10), and the costs per patient are lower than that of a pack of cigarettes per day in the United States.

Although they have various mechanisms of action, the general rationale of cessation medications is to reduce physical withdrawal from nicotine; to eliminate, through desensitization of nicotinic receptors, the immediate, reinforcing effects of nicotine that is absorbed via tobacco smoke; and to allow patients to focus on behavioral and psychological aspects of tobacco cessation. Although cessation medications are recommended by the manufacturers for relatively short-term use (generally 8–12 weeks), the use of these medications for six months or longer is safe and may be helpful for those who fear relapse without medications (11). Traditional medication guidance is for use in smokers ready to quit, but evidence also has shown benefit of NRT and varenicline in reducing cigarette consumption to facilitate abstinence.

Nicotine Replacement Therapy

Nicotine replacement therapy (NRT) provides nicotine to address physical dependence without exposure to toxic combustion products. In general, NRT provides lower and slower-rising plasma nicotine concentrations than do cigarettes, reducing the behaviorally reinforcing effect of smoking. All forms of NRT appear to have comparable efficacy, though in a randomized study, compliance was greatest for the patch, lower for gum, and very low for the spray and inhaler (12). Meta-analysis of 117 clinical trials found the risk ratio (RR) for any form of NRT versus control was 1.60 [95% confidence interval (CI) 1.53–1.68], and specifically RR = 1.49 (1.40–1.60) for nicotine gum, 1.64 (1.52–1.78) for the patch, 1.95 (1.61–2.36) for nicotine lozenges, 1.90 (1.36–2.67) for the inhaler, and 2.48 (1.24–4.94) for the nasal spray (13).

The different forms of NRT are sold in different strengths (Table 1); higher dosages or combinations of NRT (discussed below) should be used with more dependent smokers, defined by number of cigarettes per day or time to first cigarette (i.e., smoking within 30 min of waking indicates greater dependence). Nicotine patches, applied in the morning, deliver nicotine slowly over many hours. Several different nicotine patches are marketed, some with tapering dosages, although clinical trials have not found that tapering improves cessation rates, and tapering is considered optional. If the patient is experiencing insomnia or disturbing dreams from wearing the 24-h patch at night, it can be removed at bedtime. The oral NRT formulations, including gum and the inhaler (a cigarette-like plastic device, which actually delivers nicotine to the throat and upper airway), result in relatively low levels of nicotine in the blood; thus, they require many pieces or cartridges per day (initially every 1–2 h) to suppress withdrawal symptoms. Nicotine nasal spray, one spray per nostril, delivers 0.5 mg nicotine systemically and can be used every 30–60 min. Local irritation of the nose commonly produces burning, sneezing, and watery eyes during initial treatment, but tolerance to these effects develops in 1–2 days.

Bupropion

Bupropion is a blocker of dopamine and, to a lesser extent, norepinephrine reuptake and has some nicotine receptor–blocking activity (14). Thus, bupropion increases brain levels of

dopamine and norepinephrine, simulating the effects of nicotine on these neurotransmitters. In rats, bupropion in low doses blocks the rewarding effects of nicotine as assessed by intracranial self-stimulation threshold and reverses the negative affective actions of nicotine in withdrawal (15). The blockade of nicotine receptors could contribute to reduced reinforcement from a cigarette in the case of a lapse. Bupropion was originally marketed and is still widely used as an antidepressant. Sustained-release bupropion (Zyban®) was found to aid smoking cessation independent of whether a smoker is depressed or not (16). Bupropion used for one year for relapse prevention was demonstrated to be safe and effective and significantly better at promoting cessation (55%) than placebo (42%, point prevalence of smoking abstinence) (17).

Varenicline

Varenicline is a partial agonist of the α4β2 receptor, which mediates dopamine release and is thought to be the major receptor involved in nicotine addiction. Varenicline activates the α4β2 nicotinic cholinergic receptor with a maximal effect ~50% that of nicotine. This action relieves nicotine withdrawal symptoms, including craving, and at the same time blocks effects of nicotine from tobacco use on the receptor, thereby diminishing the rewarding effects of cigarettes that are smoked. Hence, both the desire to smoke and, in the case of a lapse, the likelihood of continued smoking are reduced. Smokers taking varenicline often reduce the number of cigarettes smoked per day even before their target quit day.

In clinical trials, varenicline treatment for 12 weeks was more effective than 300 mg sustained-release bupropion and placebo (18). Continuous abstinence rates from 9 to 52 weeks were 23% for varenicline, 15% for bupropion, and 10% for placebo. Varenicline for six months has been shown effective in preventing relapse, including among smokers with schizophrenia (19), and is approved by the FDA for extended treatment (20). Meta-analysis suggests that varenicline is also more effective than a single form of NRT and comparable to combination NRT (10). Major side effects of varenicline are nausea, vomiting, and insomnia (10). Neuropsychiatric side effects, including depression, psychosis, and suicide, have been reported anecdotally, but these have not been observed in clinical trials, including among smokers with depression and schizophrenia (21–23), nor in large clinical cohort studies (24, 25). The causal relationship between varenicline and these neuropsychiatric events has not been established, and smoking itself is associated with mood disturbances, including suicidality (26). Cardiovascular safety concerns about varenicline were raised by a meta-analysis showing a significant but small relative risk; a second, larger meta-analysis showed the absolute risk to be small and nonsignificant (27, 28). We are not aware of a biological mechanism by which varenicline should produce cardiovascular toxicity.

Combination Pharmacotherapy

Combination NRT—combining the nicotine patch (slow release) with nicotine gum, lozenge, inhaler, or nasal spray (rapid release)—has been shown to be more effective than individual NRT products in a meta-analysis of nine trials (RR = 1.34; 1.18–1.51 CI) (13) and is recommended as initial therapy in some smoking cessation guidelines (29). Combination NRT and varenicline are equally effective [odds ratio (OR) = 1.06; 0.75–1.48 CI] (10). Recent trials have examined use of varenicline and NRT patch together, with conflicting

results. One trial (N = 435) compared nicotine with placebo patch administered two weeks prior to target quit date, followed by varenicline for one week prior to target quit date, and then 12 additional weeks of both. Combination treatment resulted in significantly greater quit rates at 12 (55.4% versus 40.9%, p = 0.007) and 24 weeks (49% versus 36.2%, p = 0.004) (30). A smaller, and likely underpowered, clinical trial (N = 117) initiated varenicline one week prior to quit date and then the NRT patch at the target quit date and found small and nonsignificant differences at 12 weeks (38% versus 29% quit, p = 0.14) (31). The mechanism of benefit of combined varenicline and NRT is unclear, since varenicline is an α4β2 partial agonist expected to block the full agonist effects of nicotine from the patch. Possibly varenicline does not fully occupy α4β2 receptors, allowing nicotine from NRT to work to some degree, or nicotine from NRT affects different nicotinic receptors that are contributing to the addictive effects of nicotine (e.g., α7 or α3β4). In both studies, the combination was well tolerated, with the most common side effect being vivid dreams.

Bupropion has been examined in combination with NRT and varenicline. Bupropion with nicotine patch was more effective than bupropion alone (RR = 1.24; 1.06–1.45 CI) (13). Adding bupropion to combination NRT appeared to improve efficacy over combination NRT alone (32). One clinical trial examined adding bupropion to varenicline compared to varenicline alone for 12 weeks (33). The combination resulted in significantly greater prolonged abstinence (from week 2) at 12 (53.0% versus 43.2%) and 26 weeks (36.6% versus 27.6%), but not at 52 weeks (30.9% versus 24.5%). Subjects receiving combination therapy reported greater anxiety and depressive symptoms over the first two weeks, with no difference in depressive symptoms by week 4 (34).

Preloading Nicotine Replacement Therapy

Preloading NRT before the quit date has been tested as a strategy to boost efficacy via saturation and/or desensitization of nicotinic cholinergic receptors, resulting in less reward from nicotine delivered by cigarette smoking. Meta-analysis of four studies using precessation patch treatment found nicotine patches doubled the odds of quitting both at six weeks (OR = 1.96; 1.31–2.93 CI) and six months (OR = 2.17; 1.46–3.22 CI) (35). Yet, a more recent large pragmatic randomized trial conducted in New Zealand with smokers calling a quitline found that although precessation NRT was safe, acceptable, and easy to implement, the effects were no different than those of a standard course of NRT (36). A narrative review of nine trials of precessation NRT concluded that, with the exception of two studies showing large effects, most evidence indicates modest effects on long-term abstinence (37). Another meta-analysis of eight trials found a weak nonsignificant effect of NRT preloading on abstinence and weak support for the investigators' mediational hypotheses, with the exception that efficacy was enhanced by the patch over acute NRT. Overall, the findings for prequit NRT are mixed and differ by NRT type.

Gradual Reduction

Gradual reduction may be preferred by some smokers unable or unwilling to quit abruptly. A meta-analysis of 10 trials comparing smoking reduction to quitting abruptly found the strategies comparable in efficacy and invariant by treatment approach (i.e., self-help, behavioral, or pharmacologic) (38). A recent trial studied smokers who were unwilling or

unable to quit in the next month, but willing to reduce smoking and make an attempt to quit within three months (39). Subjects received varenicline or placebo for 12 weeks prior to a quit attempt, with a recommendation to reduce cigarettes per day by 50% at four weeks, 75% or more at eight weeks, and then quit completely at 12 weeks. Subjects continued to use varenicline or placebo for an additional 12 weeks after the quit date. Quit rates were substantially higher in the varenicline versus placebo-treated group from week 21 to 24 (37.8% versus 12.5%) and week 21 to 52 (27.0% versus 9.9%). The mechanism of the beneficial effect of varenicline pretreatment may be reduced cigarette craving and extinguished reward effects of cigarettes.

Precision Medicine

Precision medicine is an emerging approach to treatment. Although cessation pharmacotherapy works, long-term quit rates rarely exceed 30%, and there is interest in understanding individual differences in medication response and ways to personalize treatment. An individual's rate of nicotine metabolism has been proposed as a basis for medication selection. Rapid nicotine metabolizers on average smoke more cigarettes per day and appear more dependent. Nicotine is metabolized primarily by the liver enzyme CYP2A6. Cotinine is the primary metabolite, further metabolized to 3′-hydroxycotinine by the same enzyme. The cotinine/3′-hydroxycotinine ratio, termed the nicotine metabolite ratio (NMR), can be measured in smokers' blood, plasma, or urine, as a biomarker of the rate of nicotine metabolism. In retrospective studies, slow metabolizers respond well to the nicotine patch and gain no incremental benefit from bupropion. Normal metabolizers respond better to bupropion than the patch. A recent clinical trial stratified subjects by slow or normal NMR and compared treatment with nicotine patch, varenicline, or placebo (40). Varenicline was more effective than the patch in normal (OR = 2.17, $p = 0.001$) but not slow (OR = 1.13, $p = 0.56$) metabolizers. Side effects from varenicline were more common in slow metabolizers. Thus, use of NMR appears to inform differential response such that slow metabolizers are predicted to do well on patch, with lower cost and potentially fewer side effects. Whether this approach is cost effective remains to be determined, and at present there is no widely available clinical test for the NMR.

Second-Line Generic Cessation Treatments

Second-line generic cessation treatments are nortriptyline and clonidine, shown in clinical trials to promote smoking cessation but unapproved by regulatory authorities for this purpose (10). Nortriptyline is a norepinephrine reuptake blocker and as such simulates some actions of nicotine in the brain. Clonidine is an α2 adrenergic receptor agonist that acts primarily on the brain to reduce sympathetic neural outflow. The results are sedation and anxiolysis, as well as potential hypotension, bradycardia, and dry mouth. Clonidine's benefit in smoking cessation is thought related to its calming and anxiolytic effects, and this drug appears to be most useful to smokers who experience a high degree of anxiety when trying to quit smoking (41).

Cytisine

Cytisine was first used for quitting smoking >50 years ago in Eastern and Central Europe, before the approval of any smoking cessation aids in the western world. A plant alkaloid

with high affinity for the α4β2 nicotinic acetylcholine receptor subtype, cytisine is derived from the plant *Cytisus laburnum*. The course of treatment starts at one tablet every 2 h (six total) on days 1–3, with a scheduled quit date at day 5, tapered to 1–2 tablets daily by days 21–25. In meta-analyses, cytisine's treatment effect was comparable to published effects for NRT, bupropion, nortriptyline, and clonidine (42) and was even stronger when restricted to the two most recent and higher-quality randomized placebo-controlled trials (RR = 3.98; 2.01–7.87 CI) (43). The absolute sustained long-term quit rates, however, were modest (8.5% for cytisine versus 2.1% for placebo at one year), attributed to the minimal behavioral support provided and the study locales: Poland and Kyrgyzstan, nations still fairly permissive with public tobacco use, where 37% to 45% of men smoke (44). Most recently, an open-label randomized comparative effectiveness trial in New Zealand reported 22% sustained abstinence for cytisine at six months follow-up compared to 15% for NRT patch (RR = 1.4; 1.1–1.8 CI) (45). Reported side effects are primarily gastrointestinal, including abdominal discomfort, dry mouth, dyspepsia, and nausea. Naturally grown and inexpensively produced, cytisine is one-half to one-twentieth the cost of other cessation medications and, based on existing efficacy data, should be considered as a cessation aid globally, especially where other treatments are unavailable or unaffordable.

It has been nearly a decade since the FDA last approved a cessation medication, and there are no new candidate medications likely to be approved in the near future, although several drugs are in development. Table 2 presents cessation medications in the pipeline for development and testing and those that have been tried and failed.

COUNSELING AND PSYCHOSOCIAL TREATMENTS

Pharmacotherapy is much more effective when combined with counseling and behavioral treatments. Clinical Practice Guidelines delineate the "five A's" framework for tobacco cessation counseling: *Ask* all patients about tobacco use; *Advise* tobacco users to quit; *Assess* readiness to make a quit attempt; *Assist* with the quit attempt; and *Arrange* follow-up care.

Provider Cessation Advice

The value of a medical provider's brief advice to quit smoking is supported by decades of research. A meta-analysis of 29 studies determined that relative to no treatment, brief provider advice doubled the likelihood of a patient abstaining from smoking out to five months follow-up (8). In a separate meta-analysis, more intensive provider cessation advice achieved a higher likelihood of quitting when compared to minimal advice (OR = 1.37; 1.20–1.56 CI), and direct comparison suggested a benefit of follow-up visits (46). A number of tobacco-treatment curricula have been developed to enhance providers' knowledge, skills, and behaviors, with demonstrated increases in provision of cessation treatment (47–49).

Individual and Group Counseling

Individual and group counseling, provided by a trained therapist, typically teaches behavioral techniques with support to address the ingrained habit of smoking. Group therapy offers the added value of fostering peer support and is likely to be more cost effective than

individual counseling, though few head-to-head comparisons have been conducted. Meta-analyses of group (RR = 1.98; 1.60–2.46 CI) and individual (RR = 1.39; 1.24–1.57 CI) cessation counseling have demonstrated their effectiveness relative to self-help treatments (50, 51). Further, meta-analyses indicate counseling increases the efficacy of pharmacotherapy (RR = 1.27; 1.02–1.59 CI), and there is now evidence from 40 studies with >15,000 participants supporting the use of combination pharmacotherapy and behavioral treatment (RR = 1.82; 1.66–2.00 CI) (52).

Extended Treatment

Extended-treatment approaches have been tried as a relapse-prevention strategy. A randomized controlled trial with older smokers found extended cessation treatment—NRT gum and bupropion for 12 weeks with counseling (group and then individual) extending to 1 year—resulted in abstinence rates exceeding 50% out to two years follow-up (53). Notably, 52 weeks of NRT did not increase abstinence. In the literature, there is weak evidence that extended NRT is more efficacious than standard-duration NRT (37). A recent randomized trial showed no benefit in efficacy and poorer adherence when NRT patch treatment was provided for 52 weeks compared to 24 or eight weeks (54). In contrast, as mentioned above, varenicline dosed over six months has been shown to be effective in preventing relapse (19, 20), and varnicline is FDA approved for extended treatment.

Tobacco Quitlines

Tobacco quitlines providing cessation counseling by telephone have proliferated over the past decade with demonstrated efficacy, including for smokeless tobacco, and with stronger effects when multiple counseling sessions are provided (RR = 1.37; 1.26–1.50 CI) (8, 55, 56). The national toll-free quitline number was created in 2004 (1-800-QUIT-NOW), and at no cost all Americans can receive cessation counseling; yet, only 8% of smokers who are trying to quit and who are aware of quitlines actually use them (57). Clinicians serve an important role by referring smokers to the quitline.

EMERGING TECHNOLOGIES FOR CESSATION

Web-Based Cessation Programs

Web-based cessation programs are being disseminated widely, and a meta-analysis demonstrated their efficacy, particularly for programs that are interactive and tailored to the individual (RR = 1.48; 1.11–2.78 CI) (58). A model example is http://www.smokefree.gov from the National Cancer Institute, which combines evidence-based guidelines for quitting smoking, tailored to readiness to quit, with availability of professional assistance via instant messaging and a telephone quitline (1-877-44U-QUIT). The site gets approximately 1.5 million visitors a year. A randomized trial recommended Smokefree.gov as a population-based intervention for smoking cessation with a quit rate of 34.2% at seven months follow-up (59).

Texting Interventions

Texting interventions sending automated one-way messages offer low-cost, convenient delivery of cessation treatment. In a series of three trials in New Zealand and the United

Kingdom, daily messages were sent up to the quit day, followed by an intensive month of 5–6 messages per day and then a maintenance phase of one message every two weeks. Messages included quitting advice, general information, motivational messages, and distraction strategies. In the randomized controlled trial evaluation, sustained biochemically confirmed abstinence at six months was 9.2% in the texting intervention versus 4.3% in the control (RR = 2.14; 1.74–2.63 CI) (60). A recent review, however, found that of 15 randomized trials of texting interventions, only three interventions significantly improved abstinence relative to controls, suggesting the need for further refinement and discovery of active components and ways to boost the absolute quit rates (61).

Social Media Sites

Social media sites, such as Twitter and Facebook, are being explored for cessation treatment. In the United States, 73% of online adults report using social media, with 42% using multiple sites and often daily (62). Social media's potential for facilitating self-help groups, however, has not yet been realized, because (as with predecessor technologies such as bulletin boards and listservs) prolonged engagement is often poor; that is, initial interest may be high but then wanes (63–66).

Novel and still being proven, Twitter is being leveraged to create small, private groups of 20 smokers who interact for 100 days, with twice-daily automessages sent to encourage frequent and concurrent check-in. The intervention builds on successful past work in buddy interventions, in which smokers are assigned physically proximal buddies who try to quit with them (67–69). In the Twitter groups, smokers virtually meet 19 potential buddies, and preliminary research shows that they often form mutually reciprocated, strong and enduring social bonds that support smoking cessation (70). In a randomized controlled pilot trial (N = 160), Twitter group membership added to Smokefree.gov and NRT patch fostered peer-to-peer support for quitting and doubled the likelihood of reported sustained abstinence relative to the website and patch alone (40% versus 20%; OR = 2.67; 1.19–5.99 CI). Similar efforts are being developed on Facebook, with a focus on engaging young adults in cessation treatment (71–73).

Electronic Nicotine Delivery Systems

Electronic nicotine delivery systems (ENDS; e-cigarettes, e-hookah, vape pens) are battery-powered devices that generate an aerosol, typically containing nicotine, for inhalation. Vigorous debate in the public sphere and scientific literature concerns the potential for ENDS as a "safer" alternative to tobacco cigarettes for smokers unable or unwilling to quit or for use as a cessation aid (74, 75). Use has been rising rapidly (76–81). Proponents argue ENDS are appealing to smokers because they mimic cigarettes in appearance, method of inhalation, production of smoke-like aerosol, and taste. Analysis of 12 first-generation (cigarette-like) brand ENDS found varying levels of toxic and carcinogenic compounds in the aerosol across brands, about 9 to 450 times lower than in cigarette smoke, and toxicants in some brands, on some measures, were comparable to the NRT inhaler (82).

Research on ENDS is limited but growing; most studies to date have been descriptive. Only two randomized controlled trials have tested the efficacy of ENDS for smoking cessation

and both found no significant difference for nicotine-containing versus placebo devices. In a trial with 300 smokers not intending to quit in the next month, 12-month quit rates were 4% for non-nicotine ENDS, 9% for nicotine ENDS tapered 7.2 to 5.4 mg, and 13% for 7.2-mg nicotine ENDS, not significantly different by condition (83). In a trial with 657 smokers interested in quitting, verified six-month prolonged abstinence was 7% for 16-mg nicotine ENDS, 6% for 21-mg NRT patch, and 4% for placebo ENDS, not significantly different by condition (84). Adherence was greater for ENDS than for patches (78% versus 46% at one month), though confounded by differences in distribution (i.e., ENDS were mailed directly to participants, whereas NRT vouchers were provided for redeeming at local pharmacies). Large observational studies indicate e-cigarette users are more motivated to quit smoking and hence may be seeking e-cigarettes as a cessation tool. Some have argued that daily e-cigarette use is needed to support cessation, but a recent large web-based epidemiologic study found no overall benefit for quitting smoking among daily e-cigarette users relative to nondaily e-cigarette users and nonusers (85). However, quitting was substantially higher among daily tank-style ENDS users compared to nonusers (OR = 2.63). The tank-style devices deliver higher levels of nicotine than the cigarette-like devices, supporting the idea that nicotine is a critical aspect of promoting cessation (86).

ENDS are believed to be a form of harm reduction relative to conventional cigarettes. Of concern is the increase in use observed among youth. ENDS are sold in child-friendly flavorings (e.g., cotton candy, gummy bear, Froot Loops®, Oreo, Skittles) and in low-cost single units with broad marketing on social media and even television and radio, which have successfully banned tobacco advertising since the 1970s. The most recent data from the United States indicate a one-year tripling in use among high school students, 13.4% in 2014, surpassing past-month use of combustible cigarettes (80). With only a few years of surveillance data, it is uncertain whether ENDS use in adolescence could be a gateway to nicotine addiction, later conventional tobacco use, and other drugs of abuse (i.e., vaping cannabis).

INCENTIVES AND POLICY APPROACHES

Monetary Incentives

Monetary incentives for cessation have been tested. In a meta-analysis of nine trials, competitions or incentives increased abstinence while the events and payment schedules were ongoing, but effects were lost once the rewards ended; variable versus fixed payment made little difference, as did paying for outcome (quitting) versus participation (program attendance) (87). Competitions spurred engagement but cessation rates ultimately were similar to those of noncontestants. One trial, which provided a substantial cash reward of $750, reported a threefold increase in quitting from 5% to 14.7% after 9–12 months (88). In real-world implementation, the participating company opted for insurance premium penalties for smokers rather than payment incentives for quitting because payment was viewed as unacceptable among the nonsmoking employees (89). The research evidence for charging greater insurance premiums to incentivize behavior change is weak (87). Notably, the claims made in the highly publicized Safeway case study that led to the Safeway

Amendment in the Affordable Care Act were later found to be too late to deserve credit for the flattening in costs observed (90).

Policy-Based Approaches

Policy-based approaches relevant for informing a comprehensive population-level tobacco control strategy include laws that restrict smoking, excise taxation on tobacco products, regulation of advertising and promotion, graphic warning labels, plain packaging, and media campaigns (91). For patients, home smoking bans reduce harmful secondhand smoke exposure, increase quit attempts and abstinence, and decrease cigarette consumption in adult smokers (92).

CONCLUSIONS

Evidence-based nicotine addiction treatments include 10 cessation medications and many behavioral options, including provider advice, individual counseling, formal group programs, websites (e.g., Smokefree.gov), and the national quitline (1-800-QUIT-NOW). A combination of pharmacologic and behavioral treatment is recommended.

Despite innovations and progress in nicotine addiction therapies, it is notable that the oldest method of quitting smoking remains the most frequently used, despite being the least effective. That is, most smokers attempt to quit “cold turkey” without medication or support, with a failure rate of 95–98%. Cost and access are barriers to care.

The Affordable Care Act

The ACA makes major changes to the US health insurance market and places a greater emphasis on prevention, including coverage of tobacco cessation treatment. The ACA recommends coverage of at least two cessation attempts per year, to include four counseling sessions, each lasting at least 10 min, and any FDA-approved tobacco cessation medications (prescribed or over-the-counter) for a 90-day treatment regime when prescribed by a healthcare provider. The ACA could dramatically improve access to clinical treatment of tobacco addiction, although in practice, not all insurers are advertising or implementing this benefit (93). It is concerning that the ACA allows employers to charge smokers up to 50% more in premiums. Given the higher prevalence of smoking among the less educated, lower income, unemployed, and mentally ill, premium surcharges for risk behaviors such as smoking could dramatically raise the cost for those least able to afford it.

More than 30 healthcare organizations, including the American Academy of Family Physicians, have called for efforts to ensure that all tobacco users in the United States are aware of and have barrier-free access to all evidence-based FDA-approved therapies and counseling as recommended by Clinical Practice Guidelines. Tobacco cessation treatments are cost effective. Massachusetts saved more than $3 for every $1 spent on cessation services for state Medicaid program beneficiaries (94). Investment in comprehensive tobacco cessation programs at the state and federal levels is warranted, as is continued research on novel medication development and delivery, diagnostics for precision medicine, and technological innovations in counseling engagement and reach.

Recommendations

This review summarizes the evidence for combined pharmacologic and counseling approaches to treat nicotine addiction. Nicotine addiction is a chronic, relapsing disorder for many smokers, necessitating ongoing care. Increasing quit rates will likely require a combination of counseling and personalized medications, with a chronic disease management approach, supported by healthcare policies that make tobacco use costly and inconvenient and nonsmoking the norm. It is recommended that clinicians, at a minimum, incorporate brief tobacco interventions as part of their routine care with all patients and provide referrals. As community members and leaders, healthcare providers are further encouraged to become advocates for smoke-free clinics and hospitals, agencies, workplaces, and public places. With continued concerted effort and clinical involvement, the 2020 Healthy People goal to reduce tobacco use to 12% for adults nationally will become a reality (95).

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Table 1

Pharmacologic product guide: FDA-approved medications for smoking cessation

	Nicotine Replacement Therapy (NRT) Formulations					Bupropion SR	Varenicline
	Gum	**Lozenge**	**Transdermal Patch**	**Nasal Spray**	**Oral Inhaler**		
Product	**Nicorette**,[a] **Generic** OTC 2 mg, 4 mg original, cinnamon, fruit, mint	**Nicorette Lozenge**,[a] **Nicorette Mini Lozenge**,[a] **Generic** OTC 2 mg, 4 mg; cherry, mint	**NicoDerm CQ**,[a] **Generic** OTC (NicoDerm CQ, generic) Rx (generic) 7 mg, 14 mg, 21 mg (24-hour release)	**Nicotrol NS**[b] Rx Metered spray 10 mg/mL aqueous nicotine solution	**Nicotrol Inhaler**[b] Rx 10 mg cartridge delivers 4 mg inhaled nicotine vapor	**Zyban**,[a] **Generic** Rx 150 mg sustained-release tablet	**Chantix**[b] Rx 0.5 mg, 1 mg tablet
Precautions	• Recent (≤2 weeks) myocardial infarction • Serious underlying arrhythmias • Serious or worsening angina pectoris • Temporomandibular joint disease • Pregnancy,[c] and breastfeeding • Age <18 years	• Recent (≤2 weeks) myocardial infarction • Serious underlying arrhythmias • Serious or worsening angina pectoris • Pregnancy[c] and breastfeeding • Age <18 years	• Recent (≤2 weeks) myocardial infarction • Serious underlying arrhythmias • Serious or worsening angina pectoris • Pregnancy[c] (Rx formulations, category D) and breastfeeding • Age <18 years	• Recent (≤2 weeks) myocardial infarction • Serious underlying arrhythmias • Serious or worsening angina pectoris • Underlying chronic nasal disorders (rhinitis, nasal polyps, sinusitis) • Severe reactive airway disease • Pregnancy[c] (category D) and breastfeeding • Age <18 years	• Recent (≤2 weeks) myocardial infarction • Serious underlying arrhythmias • Serious or worsening angina pectoris • Bronchospastic disease • Pregnancy[c] (category D) and breastfeeding • Age < 18 years	• Concomitant therapy with medications/ conditions known to lower the seizure threshold • Hepatic impairment • Pregnancy[c] (category C) and breastfeeding • Age <18 years **Warning:** • Black-boxed warning for neuropsychiatric symptoms[d] **Contraindications:** • Seizure disorder • Concomitant bupropion (e.g., Wellbutrin) therapy • Current or prior diagnosis of bulimia or anorexia nervosa • Simultaneous abrupt discontinuation of alcohol or sedatives/ benzodiazepines • MAO inhibitors in preceding 14 days; concurrent use of reversible MAO inhibitors (e.g., linezolid, methylene blue)	• Severe renal impairment (dosage adjustment is necessary) • Pregnancy[c] (category C) and breastfeeding • Age <18 years **Warning:** • Black-boxed warning for neuropsychiatric symptoms[d]
Dosing	*1st cigarette ≤30 minutes after waking*: 4 mg *1st cigarette >30 minutes after waking*: 2 mg Weeks 1–6: 1 piece q 1–2 hours Weeks 7–9: 1 piece q 2–4 hours Weeks 10–12: 1 piece q 4–8 hours • Maximum, 24 pieces/ day • Chew each piece slowly • Park between cheek and gum when peppery or tingling sensation appears (~15–30 chews) • Resume chewing when tingle fades • Repeat chew/park steps until most of the nicotine is gone (tingle does not return; generally 30 min) • Park in different areas of mouth • No food or beverages 15 minutes before or during use • Duration: up to 12 weeks	*1st cigarette ≤30 minutes after waking*: 4 mg *1st cigarette >30 minutes after waking*: 2 mg Weeks 1–6: 1 lozenge q 1–2 hours Weeks 7–9: 1 lozenge q 2–4 hours Weeks 10–12: 1 lozenge q 4–8 hours • Maximum, 20 lozenges/day • Allow to dissolve slowly (20–30 minutes for standard; 10 minutes for mini) • Nicotine release may cause a warm, tingling sensation • Do not chew or swallow • Occasionally rotate to different areas of the mouth	*≥10 cigarettes/day:* 21 mg/day × 4–6 weeks 14 mg/day × 2 weeks 7 mg/day × 2 weeks *≤10 cigarettes/day:* 14 mg/day × 6 weeks 7 mg/day × 2 weeks • May wear patch for 16 hours if patient experiences sleep disturbances (remove at bedtime) • Duration: 8–10 weeks	1–2 doses/hour (8–40 doses/day) One dose ≤ 2 sprays (one in **each** nostril); each spray delivers 0.5 mg of nicotine to the nasal mucosa • Maximum – 5 doses/ hour or – 40 doses/ day • For best results, initially use at least 8 doses/day • Do not sniff, swallow, or inhale through the nose as the spray is being administered • Duration: 3–6 months	6–16 cartridges/day Individualize dosing; initially use 1 cartridge q 1–2 hours • Best effects with continuous puffing for 20 minutes • Initially use at least 6 cartridges/day • Nicotine in cartridge is depleted after 20 minutes of active puffing • Inhale into back of throat or puff in short breaths • Do NOT inhale into the lungs (like a cigarette) but "puff " as if lighting a pipe • Open cartridge retains potency for 24 hours	150 mg po q AM × 3 days, then 150 mg po bid • Do not exceed 300 mg/day • Begin therapy 1–2 weeks **prior** to quit date • Allow at least 8 hours between doses Avoid bedtime dosing to minimize insomnia • Dose tapering is not necessary • Duration: 7–12 weeks, with maintenance up to 6 months in selected patients	Days 1–3: 0.5 mg po q AM Days 4–7: 0.5 mg po bid Weeks 2–12: 1 mg po bid • Begin therapy 1 week **prior** to quit date • Take dose after eating and with a full glass of water • Dose tapering is not necessary • Dosing adjustment is necessary for patients with severe renal impairment • Duration: 12 weeks; an additional 12-week course may be used in selected patients

	Nicotine Replacement Therapy (NRT) Formulations					Bupropion SR	Varenicline
	Gum	Lozenge	Transdermal Patch	Nasal Spray	Oral Inhaler		
		• No food or beverages 15 minutes before or during use • Duration: up to 12 weeks			• No food or beverages 15 minutes before or during use • Duration: 3–6 months		
Adverse Effects	• Mouth/jaw soreness • Hiccups • Dyspepsia • Hypersalivation • Effects associated with incorrect chewing technique: – Lightheadedness – Nausea/vomiting – Throat and mouth irritation	• Nausea • Hiccups • Cough • Heartburn • Headache • Flatulence • Insomnia	• Local skin reactions (erythema, pruritus, burning) • Headache • Sleep disturbances (insomnia, abnormal/vivid dreams); associated with nocturnal nicotine absorption	• Nasal and/or throat irritation (hot, peppery, or burning sensation) • Rhinitis • Tearing • Sneezing • Cough • Headache	• Mouth and/or throat irritation • Cough • Headache • Rhinitis • Dyspepsia • Hiccups	• Insomnia • Dry mouth • Nervousness/difficulty concentrating • Nausea • Dizziness • Constipation • Rash • Seizures (risk is 0.1%) • Neuropsychiatric symptoms (rare; see Precautions)	• Nausea • Sleep disturbances (insomnia, abnormal/vivid dreams) • Constipation • Flatulence • Vomiting • Neuropsychiatric symptoms (rare; see Precautions)
Advantages	• Might serve as an oral substitute for tobacco • Might delay weight gain • Can be titrated to manage withdrawal symptoms • Can be used in combination with other agents to manage situational urges	• Might serve as an oral substitute for tobacco • Might delay weight gain • Can be titrated to manage withdrawal symptoms • Can be used in combination with other agents to manage situational urges	• Once daily dosing associated with fewer compliance problems • Of all NRT products, its use is least obvious to others • Can be used in combination with other agents; delivers consistent nicotine levels over 24 hours	• Can be titrated to rapidly manage withdrawal symptoms • Can be used in combination with other agents to manage situational urges	• Might serve as an oral substitute for tobacco • Can be titrated to manage withdrawal symptoms • Mimics hand-to-mouth ritual of smoking • Can be used in combination with other agents to manage situational urges	• Twice daily oral dosing is simple and associated with fewer compliance problems • Might delay weight gain • Might be beneficial in patients with depression • Can be used in combination with NRT agents	• Twice daily oral dosing is simple and associated with fewer compliance problems • Offers a different mechanism of action for patients who have failed other agents
Disadvantages	• Need for frequent dosing can compromise compliance • Might be problematic for patients with significant dental work • Proper chewing technique is necessary for effectiveness and to minimize adverse effects • Gum chewing may not be acceptable or desirable for some patients	• Need for frequent dosing can compromise compliance • Gastrointestinal side effects (nausea, hiccups, heartburn) might be bothersome	• When used as monotherapy, cannot be titrated to acutely manage withdrawal symptoms • Not recommended for use by patients with dermatologic conditions (e.g., psoriasis, eczema, atopic dermatitis)	• Need for frequent dosing can compromise compliance • Nasal administration might not be acceptable or desirable for some patients; nasal irritation often problematic • Not recommended for use by patients with chronic nasal disorders or severe reactive airway disease	• Need for frequent dosing can compromise compliance • Cartridges might be less effective in cold environments (≤60°F)	• Seizure risk is increased • Several contraindications and precautions preclude use in some patients (see Precautions) • Patients should be monitored for potential neuropsychiatric symptoms[d] (see Precautions)	• Should be taken with food or a full glass of water to reduce the incidence of nausea • Patients should be monitored for potential neuropsychiatric symptoms[d] (see Precautions)

[a] Marketed by GlaxoSmithKline.

[b] Marketed by Pfizer.

[c] The US Clinical Practice Guideline states that pregnant smokers should be encouraged to quit without medication based on insufficient evidence of effectiveness and theoretical concerns with safety. Pregnant smokers should be offered behavioral counseling interventions that exceed minimal advice to quit.

[d] In July 2009, the FDA mandated that the prescribing information for all bupropion- and varenicline-containing products include a black-boxed warning highlighting the risk of serious neuropsychiatric symptoms, including changes in behavior, hostility, agitation, depressed mood, suicidal thoughts and behavior, and attempted suicide. Clinicians should advise patients to stop taking varenicline or bupropion SR and contact a healthcare provider immediately if they experience agitation, depressed mood, and any changes in behavior that are not typical of nicotine withdrawal, or if they experience suicidal thoughts or behavior. If treatment is stopped due to neuropsychiatric symptoms, patients should be monitored until the symptoms resolve.

Abbreviations: MAO, monoamine oxidase; NRT, nicotine replacement therapy; OTC, over-the-counter (non-prescription product); Rx, prescription product.

For complete prescribing information and a comprehensive listing of warnings and precautions, please refer to the manufacturers' package inserts.

Table 2

Tobacco addiction medication pipeline

In drug development	In Phase II trials	Tried and failed
atomoxetine, N-acetylcysteine, tiagabine, vigabatrin	baclofen, carvedilol, d-cycloserine, labetalol, lorcanserin, topiramate	buspirone, EVT 302, GSK598809, lobeline, mecamylamine, menthyl valerate/eucalyptus oil/camphor/quinine (nicobrevin), naltrexone, reboxetine, rimonabant, selegiline silver acetate, surinabant, vaccines