JAMA | Review

Treatment of Tobacco Smoking
A Review

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IMPORTANCE More deaths in the US are attributed to cigarette smoking each year than to any other preventable cause. Approximately 34 million people and an estimated 14% of adults in the US smoke cigarettes. If they stopped smoking, they could reduce their risk of tobacco-related morbidity and mortality and potentially gain up to 10 years of life.

OBSERVATIONS Tobacco smoking is a chronic disorder maintained by physical nicotine dependence and learned behaviors. Approximately 70% of people who smoke cigarettes want to quit smoking. However, individuals who attempt to quit smoking make an average of approximately 6 quit attempts before achieving long-term abstinence. Both behavioral counseling and pharmacotherapy while using nicotine replacement therapy (NRT) products, varenicline, or bupropion are effective treatments when used individually, but they are most effective when combined. In a meta-analysis including 19 488 people who smoked cigarettes, the combination of medication and behavioral counseling was associated with a quit rate of 15.2% over 6 months compared with a quit rate of 8.6% with brief advice or usual care. The EAGLES trial, a randomized double-blind clinical trial of 8144 people who smoked, directly compared the efficacy and safety of varenicline, bupropion, nicotine patch, and placebo and found a significantly higher 6-month quit rate for varenicline (21.8%) than for bupropion (16.2%) and the nicotine patch (15.7%). Each therapy was more effective than placebo (9.4%). Combining a nicotine patch with other NRT products is more effective than use of a single NRT product. Combining drugs with different mechanisms of action, such as varenicline and NRT, has increased quit rates in some studies compared with use of a single product. Brief or intensive behavioral support can be delivered effectively in person or by telephone, text messages, or the internet. The combination of a clinician's brief advice to quit and assistance to obtain tobacco cessation treatment is effective when routinely administered to tobacco users in virtually all health care settings.

CONCLUSIONS AND RELEVANCE Approximately 34 million people in the US smoke cigarettes and could potentially gain up to a decade of life expectancy by stopping smoking. First-line therapy should include both pharmacotherapy and behavioral support, with varenicline or combination NRT as preferred initial interventions.

JAMA. 2022;327(6):566-577. doi:10.1001/jama.2022.0395

Multimedia

Supplemental content

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Section Editor: Mary McGrae McDermott, MD, Deputy Editor.

More than an estimated 8 million smoking-attributed deaths occur globally each year, and approximately 34 million people in the US (14% of adults) currently smoke cigarettes.[1,2] One-third to one-half of people who regularly smoke cigarettes die of a tobacco-related disease, typically approximately 10 years earlier than people who do not smoke cigarettes.[3]

Most smoking-attributed deaths are due to cancer (34%), cardiovascular diseases (32%), or respiratory disease (21%).[3] Smoking is associated with cancers of the lung, oropharynx, larynx, esophagus, stomach, liver, pancreas, kidney, bladder, uterine cervix, and colon or rectum, as well as acute myeloid leukemia.[3] Nearly 90% of lung cancers are attributed to cigarette smoking.[3] Smoking is responsible for approximately 80% of chronic obstructive pulmonary disease deaths.[3]

The health risk from cigarette smoking is primarily due to chemicals produced by the burning of tobacco and not to nicotine.[3] More than 80% of tobacco users in the US use combustible products, primarily cigarettes but also cigars, pipes, and waterpipes (hookah).[2] In 2019, 19% of US tobacco users reported using multiple tobacco products.[2]

Disproportionately high rates of smoking occur among adults with lower education, lower incomes, nontobacco substance use disorders, psychiatric conditions, people living with HIV, American Indian or Alaska Native individuals, and members of the lesbian, gay, bisexual, transgender (LGBT+) community.[2,4] Black individuals experience higher rates of tobacco-related disease and death than any other race. Black men have the highest lung cancer death rate of any racial or ethnic group at 60.4 per 100 000, despite having similar smoking rates as White individuals.[2,5]

Worldwide, an estimated 1.3 billion individuals use tobacco products, and more than 80% of them live in low- and middle-income countries.[1] In the US, nearly 90% of adult daily smokers started

smoking by age 18 years,[3] and each day an estimated 2000 youths smoke their first cigarette.[6]

Quitting smoking is associated with a reduced risk of tobacco-related disease and premature death and improved quality of life.[7] Individuals who smoke and quit have been projected to gain up to a decade of life expectancy.[8] This review summarizes current evidence regarding management of tobacco smoking in clinical practice.

Methods

We searched the Cochrane Database of Systematic Reviews databases from inception (1996) through October 21, 2021, for all up-to-date Cochrane reviews of smoking cessation interventions that can be delivered by health care professionals. We defined up-to-date as having a search date of 2018 or later, or a search date before 2018 with results deemed to be stable over time (high certainty using Grading of Recommendations Assessment, Development and Evaluation [GRADE]). We searched for reviews with the words *smoking* or *tobacco* in the title, abstract, or key words. We also searched MEDLINE from database inception (1946) through October 21, 2021, for systematic reviews on smoking cessation and 5 topics: electronic health records (EHRs), internet-based interventions, mobile phone interventions, nicotine receptor partial agonists, and system change interventions. Of 444 reviews identified from these searches, 30 were included (eTable in the Supplement). In addition, 12 randomized clinical trials cited in national guidelines and 7 recent guidelines and evidence reviews were included. MEDLINE search strategies are in listed in the eAppendix in the Supplement.

Discussion

Pathophysiology

Cigarette smoking is a chronic relapsing disorder that generally begins in adolescence.[3] It is associated with both a physical dependence on nicotine and a learned behavior.[3,9] Nicotine binds to α4β2 nicotinic acetylcholine receptors in the brain, releasing neurotransmitters such as dopamine whose rewarding effects become associated with specific circumstances or behaviors or the relief of stress or negative emotions.[9] These behaviors, emotions, and situations become triggers to smoke. Repeated nicotine intake generates tolerance and physical dependence, which produce nicotine withdrawal symptoms when nicotine blood levels fall.[10] Withdrawal symptoms include cigarette craving and nonspecific symptoms such as irritability, restlessness, difficulty concentrating, anxiety, and anhedonia.[10] Individuals who attempt to quit smoking and experience these symptoms often do not recognize that they represent withdrawal. A tobacco product's addictive potential depends on the speed of nicotine delivery to the brain (most rapid with inhalation) and on nicotine dose.

Smoking cessation is a challenge because it requires individuals to overcome both physical nicotine dependence and a long-standing rewarding behavior. Individuals who smoke make an average of 6 attempts to quit before achieving long-term tobacco abstinence.[11,12] Among individuals attempting to quit smoking, abstinence for a few days or weeks is common, but most individuals relapse within 3 months after quitting smoking. However, many smokers who continue to attempt to quit can succeed. More than 60% of US adults who ever smoked are now former smokers.[13]

Clinical Presentation

More than two-thirds of current individuals who smoke are interested in quitting,[14] although only 20% report interest in quitting in the next 30 days.[7] In 2018, approximately 55% of smokers reported having attempted to quit smoking in the past year. But of these, only 7.5% remained abstinent for 1 year.[13] One reason for this low success rate is that only 31% of smokers trying to quit use any evidence-based treatment.[14] Clinicians have an important opportunity to close this treatment gap by helping smokers access cessation therapies and resources.

Clinicians often encounter smokers at "teachable moments" such as when a tobacco-related illness, hospitalization, or medical procedure occurs. These events can facilitate attempts to quit smoking and provide important opportunities for patients to initiate tobacco cessation treatment.[7] Clinicians can contribute to increasing population-level cessation rates by routinely delivering even modestly effective interventions to every smoker encountered in clinical practice.

Assessment and Diagnosis

Because any level of tobacco use is associated with increased health risks, any tobacco use, even intermittent cigarette smoking, warrants treatment.[3] Inquiring about past attempts to quit smoking and cessation treatments and assessing factors associated with greater difficulty quitting allows a clinician to tailor the treatment intensity and methods recommended for smoking cessation. An individual's level of nicotine dependence, which is associated with the individual's degree of difficulty quitting, can be assessed with 2 questions: how many cigarettes are smoked daily (a larger number indicates more dependence) and whether the day's first cigarette is smoked within 30 minutes of waking.[15] Other indicators of difficulty quitting include an earlier age of smoking initiation, a comorbid psychiatric or other substance use disorder, another smoker in the household, little social support for quitting, and an individual's low level of confidence in their ability to quit.[7]

Treatment

Two recent US government-sponsored evidence reviews, the 2020 Surgeon General's report[7] on smoking cessation and the 2021 US Preventive Services Task Force (USPSTF) recommendation statement[16] for smoking cessation interventions in adults, independently concluded that behavioral treatment and pharmacotherapy are safe and effective treatments for smoking cessation. The USPSTF assigned the evidence for behavioral treatment and pharmacotherapy an A grade, indicating a high level of certainty that these treatments had a significant net benefit. Professional societies concur with the USPSTF's overall recommendations.[17,18]

Pharmacotherapy and behavioral support are each effective when used alone, but combining them is more effective than using either individually because their actions are complementary.[16,19,20] Pharmacotherapy helps reduce nicotine withdrawal symptoms (ie, nicotine replacement therapy [NRT]) and/or minimizes the

favorable effects experienced while smoking (ie, varenicline), while behavioral interventions seek to change learned behaviors associated with smoking. Combined pharmacotherapy and behavioral interventions increased quit rates from a mean of 8.6% with brief advice or usual care to 15.2% in a pooled analysis (risk ratio [RR], 1.83; 95% CI, 1.68-1.98).[16,20] **Table 1** summarizes the evidence supporting specific treatments.

Pharmacotherapy

The US Food and Drug Administration (FDA) has approved 3 types of medication as safe and effective to assist with smoking cessation: bupropion, varenicline, and 5 nicotine replacement products (patch, gum, lozenge, oral inhaler, and nasal spray). All are considered first-line treatments and produce significantly higher quit rates for 6 months or more than does placebo.[16,39] A nicotine mouth spray is approved for use in countries such as England and Australia but not in the US. Table 1 and **Table 2** summarize each drug's effectiveness, dosing, administration, and common adverse effects. The initial treatment duration is typically 12 weeks but can be extended to 6 months. Many cessation experts will treat people who smoke for longer periods, even indefinitely, while continuing to monitor for possible adverse effects, until an individual is confident that they will not resume smoking. Most of the clinical trials demonstrating the effectiveness of these medications also provided behavioral support, and a meta-analysis of 65 randomized trials of 23 331 people reported that adding behavioral support to medication was associated with higher cessation rates at 6 months (20% vs 17%, RR, 1.15; 95% CI, 1.08-1.22).[19]

Nicotine Replacement Therapy

NRT promotes cessation by reducing symptoms of nicotine withdrawal. All forms of NRT are comparable in effectiveness as individual products. A meta-analysis reported that NRT was associated with higher increased quit rates than placebo or no support (17% vs 10%; RR, 1.55; 95% CI, 1.49-1.61; Table 1).[16,21]

The bioavailability of nicotine in NRT products differs, however. Patches have a slow-onset, long-acting pattern of nicotine delivery, providing withdrawal relief for 24 hours but requiring more than 1 hour to reach peak plasma nicotine concentration. In contrast, other NRT products deliver nicotine in a rapid-onset, short-acting pattern. Nicotine nasal spray reaches its peak plasma nicotine concentration in approximately 10 minutes, while orally absorbed NRT products (gum, lozenge, and mouth inhaler) reach peak levels in 20 to 30 minutes. Plasma nicotine levels from short-acting products decline toward baseline within 2 hours. The complementary bioavailability of these products allows them to be combined to generate higher smoking cessation efficacy than is achieved with a single product. A meta-analysis of 63 trials and 41 509 participants reported that supplementing the patch with as-needed use of a rapid-acting NRT product when nicotine cravings emerge during patch use was associated with improved cessation rates, from 13% to 16%, compared with a single NRT product (RR, 1.25; 95% CI, 1.15-1.36; Table 1).[7,24]

Varenicline

Varenicline acts as a selective partial agonist at the α4β2 nicotinic acetylcholine receptor. This receptor mediates nicotine dependence and releases dopamine. When bound to the receptor as a partial agonist, varenicline both reduces nicotine withdrawal symptoms and blocks nicotine inhaled in cigarette smoke from binding to the receptor, thereby reducing the rewarding effects of cigarettes smoked. Varenicline's effectiveness for smoking cessation is well established, with a meta-analysis of 12 625 patients in 27 randomized trials showing that varenicline was associated with a higher chance of quitting at the 6-month follow-up than placebo or no treatment (11% to 26%; RR, 2.24; 95% CI, 2.06-2.43; Table 1).[16,22]

Concern about possible neuropsychiatric effects such as depressed mood, suicidality, aggression and cardiovascular adverse effects such nonfatal myocardial infarction led the FDA to add a warning to the product label for varenicline in 2009. The warning was removed in 2016 after the Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES) trial found no evidence to support the concerns.[40,43] The EAGLES study was a double-blind randomized trial that compared the safety and efficacy of 12 weeks of varenicline, bupropion, nicotine patch, and placebo for smoking cessation among 8144 people who smoked, 4116 of whom had a mild to moderate psychiatric diagnoses at baseline and 4028 did not. The primary safety end point, a composite of moderate to severe neuropsychiatric adverse events including severe anxiety, depression, hostility, or suicidality occurred in 5.8% and 2.1% of participants with and without psychiatric comorbidities, respectively. Among participants with psychiatric diagnoses (such as anxiety or depression), the proportion who experienced a neuropsychiatric end point (an anxiety or depression event) was 6.5% with varenicline, 6.7% with bupropion, 5.2% with NRT, and 4.9% with placebo. The corresponding proportions among participants without a psychiatric diagnosis were 1.3% with varenicline, 2.2% with bupropion, 2.5% with NRT, and 2.4% with placebo. Serious neuropsychiatric events did not occur at a statistically significantly higher rate in the varenicline group than in the other groups, supporting the conclusion of no excess risk.

Bupropion

Bupropion sustained-release formulation is FDA-approved as both an antidepressant and a smoking cessation aid. It blocks reuptake of dopamine released by neurons stimulated when nicotine binds to nicotinic receptors, and thereby reduces nicotine withdrawal symptoms. A meta-analysis of 45 trials of 17 866 participants reported that at 6 months bupropion was associated with a higher rate of smoking cessation among individuals with and without depressive symptoms than control conditions (19% vs 11%; RR, 1.64; 95% CI, 1.52-1.77; Table 1).[16,23]

Comparative Effectiveness of Medications

In addition to generating data about medication safety, the EAGLES clinical trial provided direct comparisons of the efficacy of 12 weeks of treatment with the nicotine patch, varenicline, and bupropion. Biochemically verified continuous abstinence rates for weeks 9 through 24 were 21.8% (varenicline), 16.2% (bupropion), 15.7% (nicotine patch), and 9.4% (placebo).[40] The efficacy of each drug was statistically significant compared with placebo, and the efficacy of varenicline was statistically superior to bupropion and to the nicotine patch,[40] findings that were consistent with results of meta-analyses (Table 1). The EAGLES trial did not compare varenicline with combination NRT, and data about the relative effectiveness of these 2 treatments are limited. Varenicline and combination

Table 1. Evidence-Based Treatments for Cigarette Smoking Cessation

Source	Treatment	No. Trials[b]	No. Participants	No. quit/study population total (%)[a] Intervention	Control	RR (95% CI) for ≥6-mo cessation	Certainty of the estimate of benefit
Pharmacotherapy							
Hartmann-Boyce et al,[21] 2018	Any NRT product	133	64 640	5574/32 918 (17)	3315/31 722 (10)	1.55 (1.49-1.61)	High
	Nicotine						
	Patch	51	22 581			1.64 (1.53-1.75)	
	Lozenge	8	4439			1.52 (1.32-1.74)	
	Gum	56	25 754			1.49 (1.40-1.60)	
	Inhaler	4	976			1.90 (1.36-2.67)	
	Nasal spray	4	887			2.02 (1.49-2.73)	
	Mouth spray[c]	1	479			2.48 (1.24-4.94)	
Cahill et al,[22] 2016	Varenicline	27	12 625	1695/6632 (26)	668/5993 (11)	2.24 (2.06-2.43)	High
Cahill et al,[22] 2016	Cytisine[c]	2	937	40/470 (8)	10/467 (2)	3.98 (2.01-7.87)	Low
Howes et al,[23] 2020	Bupropion SR	45	17 866	1846/9714 (19)	900/8152 (11)	1.64 (1.52-1.77)	High
Lindson et al,[24] 2019	Short- + long-acting NRT	14	11 356	881/5218 (16)	852/6138 (13)	1.25 (1.15-1.36) vs single form	High
Howes et al,[23] 2020	Bupropion + NRT	12	3487	360/1648 (21)	342/1839 (18), NRT only	1.19 (0.94-1.51) vs NRT only	Low
Chang et al,[25] 2015	Varenicline + NRT[d]	2	787	NA	NA	OR, 1.62 (1.18-2.23) vs varenicline only; OR, 2.05 (0.82- 5.17) vs varenicline from network meta-analysis	Low
Howes et al,[23] 2020	Varenicline + bupropion	3	1057	136/525 (26)	114/532 (21), Varenicline alone	1.21 (0.95-1.55) vs varenicline	Moderate
Electronic nicotine delivery systems							
Hartmann-Boyce et al,[26] 2021	e-Cigarettes with nicotine	4 vs NRT	1924	183/1032 (18)	92/892 (10) NRT	1.53 (1.21-1.93) vs NRT	Moderate (vs NRT)
		5 vs nonnicotine	1447	75/947 (8)	22/500 (4) Nonnicotine	1.94 (1.21-3.13) vs nonnicotine e-cigarettes	Moderate (vs nonnicotine)
		6 vs no support	2886	38/1649 (2)	13/1237 (1) No support	2.61 (1.44-4.74) vs no support	Very low (vs non support)
Behavioral therapies							
Stead et al,[27] 2013	Physician brief advice	17	13 724	455/7913 (6)	216/5811 (4)	1.66 (1.42-1.94) vs minimal intervention	Moderate
Stead et al,[27] 2013	Physician brief counseling	11	8515	553/4670 (11)	246/3845 (6)	1.86 (1.60-2.15) vs no intervention	Moderate
Rice et al,[28] 2017	Nurse-delivered counseling	44	20 881	1607/11 319 (14)	1165/9562 (12)	1.29 (1.21-1.38)	Moderate
Hartmann-Boyce et al,[29] 2021; Livingstone-Banks et al,[30] 2019	Printed self-help materials						
	Nontailored	11	13 241	416/6723 (6)	331/6518 (5)	1.19 (1.03-1.37)	Moderate
	Tailored	10	14 359	501/6786 (7)	455/7573 (6)	1.34 (1.19-1.51)	
Hartmann-Boyce et al,[29] 2021; Matkin et al,[31] 2019	Telephone counseling						
	Quit line	14	32 484	2123/19 600 (11)	1004/12884 (8)	1.38 (1.19-1.61)	Moderate
	Nonquit line	65	41 233	2924/21 001 (14)	2229/20 232 (11)	1.25 (1.15-1.35)	
Tzelepis et al,[32] 2019	Real-time video counseling	2	608	30/301 (10)	22/307 (7)	2.15 (0.38-12.04) vs telephone counseling	Very low

(continued)

Table 1. Evidence-Based Treatments for Cigarette Smoking Cessation (continued)

Source	Treatment	No. Trials[b]	No. Participants	No. quit/study population total (%)[a] Intervention	Control	RR (95% CI) for ≥6-mo cessation	Certainty of the estimate of benefit
Hartmann-Boyce et al,[29] 2021; Stead et al,[33] 2017	Group counseling (in person)	13					
			4395	239/2388 (10)	116/2007 (6)	1.88 (1.52-2.33) vs self-help	Moderate
			7601	547/4815 (11)	196/2471 (8)	1.22 (1.03-1.43) vs brief advice	
			1098	119/623 (19)	32/475 (7)	2.60 (1.80-3.76) vs no intervention	
Hartmann-Boyce et al,[29] 2021; Lancaster and Stead,[34] 2017	Individual counseling (in-person +/− telephone follow-up)	27	11 100	604/5519 (11)	392/5581 (7)	1.57 (1.40-1.77)	High
Lindson et al,[35] 2019	Motivational interviewing	4	684	73/367 (20)	71/317 (22)	0.84 (0.63-1.12)	Low
Hartmann-Boyce et al,[29] 2021; Whittaker et al,[36] 2019	Text messaging	13	14 133	694/7324 (9)	382/6809 (6)	1.54 (1.19-2.00)	Moderate
Hartmann-Boyce et al,[29] 2021; Whittaker et al,[36] 2019	Mobile phone apps	5	3079	111/1535 (7)	119/1544 (8)	1.00 (0.66-1.52)	Very low
Hartmann-Boyce et al,[29] 2021; Taylor et al,[37] 2017	Internet-based interventions						
	Adjunct to behavioral therapy	5	2334	164/1368 (12)	75/966 (8)	1.69 (1.30-2.18)	Moderate
	Without additional support	8	6786	516/4020 (13)	356/2766 (13)	1.15 (1.01-1.30)	
Notley et al,[38] 2019	Financial incentives[e]	30	20 097	1336/12 800 (10)	516/7260 (7)	1.49 (1.28-1.73)	High
Behavioral therapy plus pharmacotherapy							
Hartmann-Boyce et al,[19] 2019	Behavioral therapy as an adjunct to pharmacotherapy	65	23 331	2291/11 630 (20)	2006/11 701 (17)	1.15 (1.08-1.22) vs pharmacotherapy alone	High
Stead et al,[20] 2016	Combined behavioral + pharmacotherapy	52	19 488	1529/10 070 (15)	808/9418 (9)	1.83 (1.68-1.98) vs brief advice or usual care	High

Abbreviations: NA, not available; NRT, nicotine replacement therapy; OR, odds ratio; RR, risk ratio; SR, slow release.

[a] As calculated from Cochrane meta-analyses.

[b] Number of trials represents those included in relevant evidence synthesis and comparison is to placebo or minimal control unless stated otherwise.

[c] Not approved by the US Food and Drug Administration as smoking cessation medication.

[d] No published reviews include RR calculation for this combination.

[e] Cash payments, vouchers, or return of money deposited by participants.

NRT had comparable effectiveness in a 2013 network meta-analysis and in a subsequent open-label randomized clinical trial. Based on expert opinion in clinical practice guidelines, the 2 therapies are considered approximately similar in efficacy and are considered the 2 most effective smoking cessation aids currently available.[17,18] In clinical practice, the choice of medication should consider patients' preference, cost, and medication adverse effect profiles (Table 2). The **Figure** illustrates an evidence-based strategy for selecting medications.

Combining Cessation Medications

Combining medications, such as varenicline with NRT or bupropion, might improve the success rates achieved by single agents. The greater effectiveness of combination NRT compared with single NRT products has been established.[24] The efficacy and tolerability of combining drugs with different mechanisms of action is less well studied, although some evidence suggests that combining pharmacotherapies increases quit rates more than single agents.[23] A recent network meta-analysis suggested that varenicline plus any NRT product may be associated with the greatest benefits.[44] However, although adding NRT to varenicline was well tolerated in 4 randomized trials,[42,45-47] only 1 trial[46] of 446 participants found significantly higher 6-month cessation rates from combined therapy than from varenicline alone (65.1% vs 46.7%; odds ratio [OR], 2.13; 95% CI, 1.32-3.43). In another trial,[48] adding bupropion to varenicline increased smoking cessation rates at 26 weeks

Table 2. US Food and Drug Administration–Approved Pharmacotherapies for Smoking Cessation in Adults

Drug	Nicotine replacement therapy						Varenicline	Bupropion
	Patch	Lozenge	Gum	Inhaler	Nasal spray	Combination nicotine therapy (short- + long-acting)		
Mechanism of action	Nicotine receptor full agonist Reduces nicotine withdrawal symptoms that occur when an individual with nicotine dependence stops smoking Bioavailability of nicotine varies by product, allowing for combination of slow-onset and long-acting patch with rapid onset and short-acting products (lozenge, gum, inhaler, nasal spray) to increase effectiveness of this category						α4β2 nicotinic receptor partial agonist Reduces withdrawal symptoms and blocks rewarding effects of smoking	Reduces nicotine withdrawal by inhibiting reuptake of dopamine and norepinephrine stimulated by nicotine binding to midbrain neurons
How sold	Rx or OTC	Rx or OTC	Rx or OTC	Rx only	Rx only	Rx or OTC	Rx only	Rx only
Doses available	21 mg 14 mg 7 mg	4 mg 2 mg	4 mg 2 mg	10 mg cartridge	10 mL bottle (10 mg nicotine/mL)	Varies depending on combination	0.5 mg tablet 1.0 mg tablet	150 mg tablet, sustained release
Dosing	21 mg for ≥10 cigarettes/d 14 mg for <10 cigarettes/d	4 mg if 1st cigarette is ≤30 min after waking 2 mg if 1st cigarette is >30 min after waking	4 mg if 1st cigarette is ≤30 min after waking 2 mg if 1st cigarette is >30 min after waking	1 Cartridge has 80 puffs	0.5 mg/spray 1 bottle has ≈ 200 sprays	Nicotine patch dose same as used for single NRT Dose short-acting form as directed but reduce maximum dose by half	Dose up-titration over 1 wk: Days 1-3, 0.5 mg/d Days 4-7, 0.5 mg 2/d Days ≥8, 1 mg 2/d	Days 1-3, 150 mg/d Days ≥4, 150 mg 2/d
Administration	Apply a new patch each morning to dry skin Rotate application site to avoid skin irritation Start patch on quit day or before quit date Keep using even if a slip occurs	1 Piece every 1-2 h as needed (20/d maximum) Place between gum and cheek, let it melt slowly. No food or drink 15 min before or during use	1 Piece/h as needed (24/d maximum) Chew briefly until mouth tingles, then park gum inside cheek until tingle fades; repeat chew-and-park each time tingle fades; discard gum after 30 min No food or drink 15 min before or during use	1 Cartridge every 1-2 h as needed. (16/d maximum) Puff into mouth and throat until cravings subside. Do not inhale into lungs Change cartridge when nicotine taste disappears	1 Spray to each nostril every 1-2 h as needed. (80 sprays/d maximum) Do not sniff, swallow, or inhale while spraying After use, wait 2-3 min before blowing the nose	Apply patch daily Use short-acting form as needed for cravings	Start 1-4 wk before quit date Alternative to abrupt quitting is gradual smoking reduction (start medication and reduce smoking to 50% by wk 4, 25% by wk 8, quit by wk 12)	Start 1-2 wk before quit date
Duration	Use ≥3 mo After 6 wk, continue original dose or taper to lower doses (either option acceptable)	Use ≥3 mo	Use ≥3 mo	Use ≥3 mo	Use ≥3 mo	Use ≥3 mo	Use 3-6 mo Longer use has demonstrated safety	Use 3-6 mo
Common adverse effects[a]	Skin irritation (5%-20%) Sleep problems (10%-11%)[b] Vivid dreams (12%)[b]	Mouth irritation (5%-24%) Hiccups (3%-24%) Heartburn (4%-11%) Nausea (9%-10%)	Mouth irritation (5%-24%) Jaw soreness (rate not available) Hiccups (3%-24%) Heartburn (4%-11%) Nausea (9%-10%)	Mouth and throat irritation (≤66%) Cough (32%), especially if inhaled too deeply	Nasal discomfort (94%) Throat irritation (≤66%) Rhinitis (23%) Sneezing (rate not available) Cough (32%)	Local irritation (itching/hives 18%; mouth problems 8%) Hiccups (6%) Insomnia (11%)[b] Vivid dreams (13%)[b] Nausea (15%) Indigestion (10%)	Nausea (16%-40%)[c] Insomnia (9%-19%)[d] Vivid dreams (8%-13%)[d] Headache (12%-19%)	Insomnia (11%-40%)[e] Agitation (3%-32%)[e] Dry mouth (7%-28%) Headache (9%-34%)

(continued)

Table 2. US Food and Drug Administration–Approved Pharmacotherapies for Smoking Cessation in Adults (continued)

	Nicotine replacement therapy							
Drug	Patch	Lozenge	Gum	Inhaler	Nasal spray	Combination nicotine therapy (short- + long-acting)	Varenicline	Bupropion
Advantages	Easiest nicotine product to use Provides a steady nicotine level	User controls nicotine dose Oral substitute for cigarettes Can be used by smokers with poor dentition or dentures	User controls nicotine dose Oral substitute for cigarettes	User controls nicotine dose Oral substitute for cigarettes Mimics hand-to-mouth ritual of cigarette smoking	User controls nicotine dose Most rapid nicotine delivery of all NRT products	Better than single agent at controlling cravings: patch provides steady nicotine level while short-acting product treats break through craving.	Oral agent (pill) Quit date can be flexible (1 wk to 3 mo after starting drug) Dual mechanism of action (relieves nicotine withdrawal and blocks reward of smoking)	Oral agent (pill) May lessen postcessation weight gain while drug is used
Disadvantages	User cannot alter dose if cravings occur during the day	Not used in the same way as other lozenges (should not be chewed, sucked, or swallowed)	Requires careful instruction for proper use Not chewed in same way as regular gum Can damage dental work and use is difficult for denture wearers	Frequent puffing required to achieve adequate nicotine delivery Use with caution in reactive airway disease	NRT product with most adverse effects Some users cannot tolerate local irritation to throat or nasal mucosa	Concurrent use of 2 forms adds complexity to the regimen	Some patients are reluctant to take due to prior FDA concerns of behavioral changes that are now refuted Reduce dose if moderate-severe kidney disease	Increases seizure risk (0.1% risk) Contraindicated in patients with seizure disorder or with predisposition to seizures

Abbreviations: OTC, over the counter (no prescription required); FDA, US Food and Drug Administration; NRT, nicotine replacement therapy; Rx, prescription required.

[a] Adverse event frequencies obtained from UpToDate, the EAGLES trial,[40] a meta-analysis of NRT adverse events based on trials and observational studies,[41] and one trial with one study arm (n = 421) randomized to nicotine patch and lozenge.[42]

[b] Remove patch at bedtime to manage insomnia or vivid dreams.

[c] Take varenicline with food and a full glass of water to minimize nausea.

[d] Skip nighttime dose of varenicline or take it earlier to manage vivid dreams or insomnia.

[e] Lower bupropion dose to 150 mg in the morning for insomnia or agitation.

(36.6% vs 27.6%) but not at 52 weeks (30.9% vs 24.5%). Several guideline panels recommend using combinations in selected situations such as when one medication is well tolerated but only partially helpful.[17,18] Given limited evidence of efficacy, increased cost, and the potential for more adverse reactions, a reasonable approach is to add a second medication class only when an initial drug does not produce complete abstinence rather than starting with 2 medication classes.

Starting Medication Prior to a Quit Attempt

Pharmacotherapy is typically prescribed for people who smoke when they are ready to attempt to quit, but medication can also be effective when used by people who smoke and plan to reduce their cigarette intake to prepare for a quit attempt. In a randomized, double-blind, placebo-controlled trial of 1510 individuals who reported that they were not ready to quit smoking in the next month but were willing to quit in 3 months, starting varenicline immediately produced a higher cessation rate than starting the drug on the planned quit date 3 months later (32.1% vs 6.9%; RR, 4.6; 95% CI, 3.5-6.1).[7,49] Some evidence also supports the effectiveness of NRT in people who smoke and do not plan to quit immediately.[50,51] Additionally, starting NRT 2 to 4 weeks before a planned quit date rather than on the quit date, may enhance NRT effectiveness. In a meta-analysis of 9 studies, nicotine therapy preloading was associated with a higher cessation rate (17% vs 14%) than starting NRT on the planned quit date (RR, 1.25; 95% CI, 1.08-1.44).[24]

Other Smoking Cessation Medications

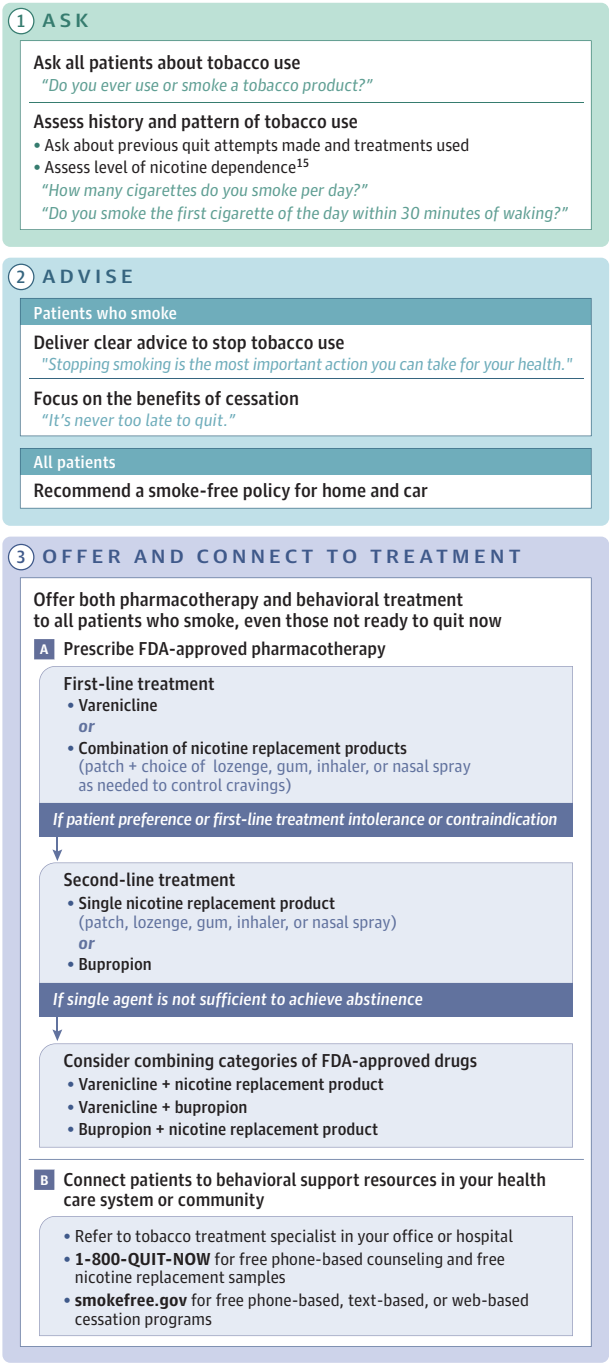
Nortriptyline and clonidine lack FDA approval as smoking cessation aids and are rarely used to assist with smoking cessation. Cytisine is a plant-based alkaloid with a similar mechanism of efficacy to varenicline that acts as a selective partial agonist at the α4β2 nicotinic acetylcholine receptor. Cytisine has been used for decades as a smoking cessation aid in Central and Eastern Europe but is not FDA-approved. Two large randomized trials in Poland and New Zealand demonstrated cytisine's effectiveness for smoking cessation compared with placebo and to NRT (Table 1).[52,53] Cytisine's effectiveness was roughly comparable with varenicline in 2 recent randomized trials.[54,55] In the US, a randomized trial to inform a possible future application of cytisine for FDA approval began in 2020 (NCT04576949).

e-Cigarettes

e-Cigarettes are battery-powered devices that generate an inhaled aerosol that usually contains nicotine. Because they do not burn tobacco to generate smoke, e-cigarettes expose users to lower amounts of toxins and are likely to be less harmful than cigarettes.[56] Nicotine e-cigarettes could be effective smoking cessation aids if people who smoked replaced combustible tobacco products with e-cigarettes and quit smoking cigarettes entirely.[57] However, e-cigarettes are controversial as cigarette smoking aids, due to a small number of high-quality randomized trials, limited evidence on current devices, and uncertainty about possible health risks of long-term use.[53,54] The severe lung injury associated with vaping in 2019 was related to tetrahydrocannabinol (THC)–containing e-cigarettes that contained vitamin E acetate and not to commercial nicotine e-cigarettes. The FDA regulates e-cigarettes as tobacco products, not as medical products and has not evaluated any e-cigarette for medical use as a cessation aid.

A 2021 Cochrane systematic review of 16 759 participants concluded with moderate certainty that e-cigarettes were associated with being more effective than NRT or nonnicotine e-cigarettes for smoking cessation.[26] This review found no evidence of serious harms for up to 2 years, but no studies provided data after a 2-year follow-up. The USPSTF review concluded that evidence was insufficient to evaluate the balance of benefits

Figure. Brief Tobacco Cessation Intervention Model for Clinical Practice



FDA indicates US Food and Drug Administration.

and risks of e-cigarettes for smoking cessation, primarily due to the paucity of randomized trials. It recommended that clinicians direct smokers to FDA-approved smoking cessation medications rather than to e-cigarettes. This is consistent with recommendations from other US professional organizations and the 2020 Surgeon General's report.[7,17,18] In contrast, in the UK nicotine e-cigarettes are encouraged as a cessation aid.[58,59] People who smoke and already use e-cigarettes to reduce health risks should be advised to switch completely from cigarettes and, given the uncertainty about the safety of long-term use, consider a longer-term goal of stopping e-cigarette use when the risk of relapse to smoking is judged to be low.

Behavioral Support

Behavioral interventions are diverse and vary in content, intensity, and delivery mode.[7,16,29,60] Some interventions are designed to help people who smoke decide to quit smoking (eg, by discussing the benefits of quitting). Other interventions use cognitive-behavioral techniques to increase the success rate of a quit attempt. These teach skills to reduce or manage the desire to smoke and to handle the negative emotions associated with nicotine craving, as well as encouraging environmental changes to reduce stimuli that promote smoking, provide social support, and improve self-confidence to quit. Individual strategies are often combined in multicomponent behavioral programs. Counselors who provide behavioral treatment can also direct a person to other interventions to help with smoking cessation, encourage pharmacotherapy use, promote medication adherence, and manage adverse effects. In a large network meta-analysis of 250 563 participants, counseling was associated with a higher odds of smoking cessation than was no intervention, regardless of provision of pharmacotherapy (6.0% vs 8.5%, OR, 1.44; 95% credibility interval, 1.22-1.70).[29]

Substantial evidence supports the effectiveness of advice and brief counseling vs no advice by physicians (8.0% vs 4.8%; RR, 1.76; 95% CI, 1.58-1.96)[27] and counseling vs brief advice or usual care by nurses (14.2% vs 12.2%; RR, 1.29; 95% CI, 1.21-1.38)[28] and counseling by nonphysician clinicians, who are generally bachelor's degree–educated individuals trained and certified as tobacco cessation specialists, vs control (11.4% vs 7.7%; RR, 1.48; 95% CI, 1.34-1.64).[34,61] Effective behavioral modalities include counselor-initiated telephone calls, mobile telephone text messaging, and internet-based support.[7,16] However, evidence for mobile telephone apps remains limited.[26] Counseling can be delivered effectively in health care settings and by referral to community resources such as state-based telephone quit lines. Delivering counseling using video call–based visits is a relatively newer method that expanded amid broader health system changes in response to the COVID-19 pandemic.[62,63] The effectiveness of video virtual visits compared with in-person counseling is not known, but limited evidence based on preliminary randomized trials suggests that video visits are no less effective than telephone counselling.[32,64,65]

Motivational interviewing is a patient-centered counseling technique that aims to help individuals resolve ambivalence about changing behaviors such as quitting smoking.[7] Evidence of its effectiveness for cessation is mixed. The USPSTF recommendation statement,[16] citing a 2019 Cochrane systematic review, determined the evidence insufficient to recommend motivational interviewing. However, the Surgeon General's report[7] endorsed it and it is commonly used with people who smoke cigarettes and are not ready to quit.[35] There is compelling evidence from randomized trials that guaranteed financial incentives such as payments or gift vouchers help people to quit.[7,38] There is no moderate or high-certainty evidence to support hypnosis or acupuncture as cessation aids.[16,66,67]

Cessation Therapies in Specific Groups of Smokers

The quit rates attained by cessation treatment are generally lower in population subgroups with higher prevalence of tobacco use, such as individuals with lower education or mental health conditions, than in the general population of people who smoke. However, the 2021 USPSTF recommendation on tobacco cessation interventions found no evidence that behavioral or pharmacological interventions differed in effectiveness in subgroups such as individuals with psychiatric comorbidity or in groups comprising people who represent ethnic minority groups.[16]

In addition to reviewing the safety and efficacy of smoking cessation interventions in all adults, the 2021 USPSTF recommendation statement also specifically considered the efficacy of these interventions for pregnant women who smoke.[16,68] The USPSTF reported that behavioral counseling increased smoking cessation rates from a mean of 10.8% to 14.5% (RR, 1.31; 95% CI, 1.16-1.47) and improved some perinatal outcomes. Behavioral counseling for pregnant women who smoke received an A grade, indicating strong evidence for a substantial net benefit.[16,68] In contrast, evidence about pharmacological treatment in pregnant women was judged to be insufficient to warrant a recommendation and received an I statement.[68]

Implementation

There is strong evidence and a broad consensus that all clinicians should ask all patients about tobacco use, advise all tobacco users to stop, and offer a brief office intervention.[7,16] However, integrating these practices into routine clinical care and infrastructures is challenging.[69] Ideally, tobacco treatment should be delivered in both primary and specialty care in all outpatient and inpatient settings.

An evidence-based 5-step framework proposed by the US Public Health Service[39] in 2008 guides clinicians' delivery of brief treatment for individuals who smoke. It directs clinicians to (1) ask about tobacco use at every visit; (2) advise people who use tobacco to quit; (3) assess readiness to quit; (4) assist people who smoke in making quit attempts by offering medication and providing behavioral support; and (5) arrange follow-up. Several abbreviated 3-step models adapted this framework to reflect changing practice patterns and newer approaches.[70-72] Newer models distribute the tasks across members of the health care team to minimize the work required of an individual clinician. They also encourage clinicians to routinely offer pharmacological and behavioral treatment to all individuals who smoke, rather than first asking if the individual is interested in quitting smoking.

The components of 3-step models are (1) Ask, (2) Advise, and (3) Assist or Refer or Connect (Figure). In the *Ask* step, a member of the care team assesses tobacco use at each visit and

documents it in the EHR. Tobacco use is best assessed with a general question such as "Do you ever use or smoke a tobacco product?" because not all tobacco users smoke cigarettes. Furthermore, 25% of US adults who smoke[13] do not smoke every day, and some people who do not smoke daily do not identify themselves as people who smoke.

The *Advise* step consists of delivering clear advice to stop tobacco use as soon as possible. Advice should focus on the benefits of cessation, highlighting that it is not too late to benefit, and be accompanied by the offer to help the smoker create a treatment plan. All patients should be advised to make their home and car smoke-free.

The third step, variously titled *Assist or Connect*, provides specific direction for the offer of assistance. It aims to actively connect, rather than passively refer, people who use tobacco to treatment.[72] This entails both prescribing pharmacotherapy and linking the patient to specific resources for behavioral support and explaining to the patient the additional value of behavioral support when added to pharmacotherapy.[70,72] Behavioral support can be provided by a tobacco treatment specialist who is located in the office, the health system, or the community (Figure). State-based telephone quit lines, available free nationwide, are a community-based resource that provide a series of counselor-initiated telephone calls and often offers free mailed NRT samples. Engaging patients with quit line services can be enhanced when EHRs send electronic referrals directly to quit lines, which then call the patient to offer services.[73] For people who are not ready to accept treatment for smoking, clinicians can explore the individual's perceived barriers and benefits to taking action.[74]

At a population level, the success of all of these evidence-based treatments is contingent on patient access. People from disadvantaged groups are more likely to smoke but are less likely to have access to stop-smoking interventions, many of which require either self-funding or insurance coverage.[7]

Tobacco control public policies that promote smoking cessation at the population level can also support the efforts made by clinicians and health care systems. For example, in January 2023, the FDA will require all cigarette packs to carry a large multicolor graphic and text warning label that illustrate the health consequences of smoking.[75] It has also announced the intention to ban menthol flavoring in cigarettes because menthol smokers, who are disproportionately Black persons or youths, have greater nicotine dependence and more difficulty quitting smoking.[76]

Prognosis

The 2020 Surgeon General's report[7] concluded that smoking cessation benefits all smokers, by reducing the risk of premature death and improving quality of life. People who smoke cigarettes and stop smoking by age 40 years gain the most—projected at up to a decade of life expectancy—but mortality benefits persist even for individuals who stop smoking after age 70 years or after developing tobacco-related diseases.[8,77,78] For people who smoke cigarettes, it is never too early or too late to attain benefits from smoking cessation.[79]

Limitations

This review has limitations. First, this review did not include a formal assessment of quality of included studies. Second, some relevant studies may have been missed. Third, pharmacotherapy not licensed in the US (eg, cytisine) was not a focus of this review and novel treatments for which there is little trial evidence (eg, novel behavioral approaches) were not covered. Fourth, tobacco control policies that promote smoking cessation at the population level were not covered in detail.

Conclusions

Approximately 34 million people in the US smoke cigarettes and could gain up to a decade of life expectancy by stopping smoking. First-line therapy should include both pharmacotherapy and behavioral support, with varenicline or combination NRT as preferred initial interventions.

ARTICLE INFORMATION

Accepted for Publication: January 12, 2021.

Conflict of Interest Disclosures: Dr Rigotti reported receiving grants from National Heart, Lung, and Blood Institute and Achieve Life Sciences and personal fees from UpToDate and Achieve Life Sciences. Dr Kruse reported having a family financial interest in Dimagi, Inc. Dr Hartmann-Boyce reported being the principal investigator on grants relevant to this work, for which funds were paid to the University of Oxford, from Cancer Research UK and the National Institute for Health Research (NIHR). No other disclosures were reported.

Funding/Support: Dr Livingstone-Banks is funded by the NIHR, via Cochrane Infrastructure funding to the Cochrane Tobacco Addiction Group.

Role of the Funder/Sponsor: The NIHR had no role in preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the NIHR, National Health Service, or the Department of Health and Social Care.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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