Chapter 6
Interventions for Smoking Cessation and Treatments for Nicotine Dependence

Introduction

There are now more former cigarette smokers than current smokers in the United States (U.S. Department of Health and Human Services [USDHHS] 2014). For more than a decade, national surveillance data on smoking cessation have revealed a similar pattern, with modest improvement—two-thirds of adult cigarette smokers indicate a desire to quit, and just over half try to quit each year; however, less than 10% of smokers who try to quit succeed in quitting for 6 months or longer (Babb et al. 2017). A large body of evidence highlights the efficacy of multiple treatments that can double or triple the rate of success in quitting smoking (Fiore et al. 2008; Prochaska and Benowitz 2016). This chapter reviews both evidence-based and emerging potential treatments for smoking cessation.

Current evidence-based treatment approaches to smoking cessation include several behavioral treatments—such as individual, group, and telephone counseling—and seven pharmacotherapies approved by the U.S. Food and Drug Administration (FDA). These treatments have been shown to be effective when delivered across a wide variety of settings, via several platforms, and to a diversity of populations—including groups that have been disproportionately impacted by tobacco use, such as low-income populations, and populations with other comorbid medical conditions, including behavioral health conditions (U.S. Preventive Services Task Force [USPSTF] 2015). Evidence indicates that the combined use of both behavioral interventions and pharmacotherapies produces the largest cessation effects (Fiore et al. 2008; Stead and Lancaster 2012a; Stead et al. 2015), but the evidence also indicates that several of these treatments are effective when used alone (Fiore et al. 2008; Cahill et al. 2013; USPSTF 2015; Lancaster and Stead 2017).

The cost-effectiveness of smoking cessation has been documented extensively (Jha et al. 2015) (see Chapter 5. The Benefits of Smoking Cessation on Overall Morbidity and Economic Costs). For example, Maciosek and colleagues (2017a,b) assessed the potential impact of 28 evidence-based clinical preventive services in terms of their cost-effectiveness and clinically preventable burden (measured by quality-adjusted life-years [QALYs] saved). The assessment, which included clinical preventive services for a variety of different risk factors, found that two of the three highest ranking preventive services were related to tobacco, including (a) tobacco use screening and a brief counseling intervention to encourage cessation among adults and (b) counseling to prevent initiation of tobacco use among youth.

Data indicate that despite the availability of evidence-based treatments to achieve smoking cessation, less than one-third of adult cigarette smokers who attempt to quit use any type of cessation counseling and/or FDA-approved cessation medication (Babb et al. 2017). Furthermore, undertreatment is common among smokers who use cessation treatments; rates of relapse are high (above 50%) (García-Rodríguez et al. 2013); and most smokers attempt to quit without using treatment (i.e., they try to quit unassisted or "cold turkey"), with success rates of approximately 7–8% (Fiore and Jaen 2008; Prochaska and Benowitz 2016; Babb et al. 2017; Caraballo et al. 2017). Unaided quitting likely remains common for a number of reasons, including the frequent lack of health insurance among tobacco users (nearly 30% of adult cigarette smokers are uninsured [Jamal et al. 2018]); inadequate public and private insurance coverage of cessation treatments (DiGiulio et al. 2018); inadequate and cumbersome reimbursement for cessation treatments offered by clinicians and hospitals (Fiore et al. 2008); inadequate promotion of cessation treatments to smokers and healthcare providers, which can contribute to low use of these treatments (Fiore et al. 2008); the widespread perception that quitting cold turkey is at least as effective as quitting with the help of counseling and/or medication (Fiore et al. 2008); underfunding of state tobacco quitlines and other cessation services (USDHHS 2014; Campaign for Tobacco-Free Kids 2018); and inadequate integration of tobacco use screening and cessation interventions into routine clinical care (Babb et al. 2017). In addition, because of a lack of specialized training about nicotine dependence and treatment, many clinicians report being hesitant to engage patients in conversations about cessation because they feel they lack the requisite knowledge to do so effectively (Zapka et al. 1999; Simoyan et al. 2002; Blumenthal 2007).

In the past, the tobacco industry has spread the misconceptions that smoking is a personal choice or simply a bad habit, that quitting is a matter of willpower, and that addiction to nicotine is akin to being addicted to caffeine (Henningfield et al. 2006). These messages have contributed to most smokers trying to quit through sheer determination instead of combining a strong motivation to quit with the use of evidence-based cessation treatments. The reality is that nicotine is addictive, and smoking is not merely a habit (USDHHS 1988). Although habitual components of smoking reinforce use, nicotine is a highly addictive drug, like heroin and cocaine (USDHHS 1988, 2014), and nicotine addiction is a chronic, relapsing

condition. Although a majority of smokers in the United States who quit successfully do so without assistance, smokers who use medication and/or behavioral support as part of a quit attempt substantially increase their chances of quitting (Fiore et al. 2008). The conceptualization of nicotine dependence as a chronic, relapsing condition is not new (Fiore et al. 2008), but it has led to reframing the delivery of smoking cessation treatment as "chronic disease management," which in turn has given rise to more systematic approaches to delivering nicotine dependence treatment in healthcare settings (Steinberg et al. 2008; Foulds et al. 2010).

Literature Review Methods

This chapter reviews the evidence base for current and potential emerging treatments for smoking cessation, adding to research from the U.S. Public Health Service's Clinical Practice Guideline on *Treating Tobacco Use and Dependence: 2008 Update* (hereafter referred to as the *Clinical Practice Guideline*) (Fiore et al. 2008). It also explores approaches to increase the impact of smoking cessation treatments through improved efficacy and increased reach. The impact of a smoking cessation intervention is a function of effectiveness (i.e., success as measured in sustained quit rates of, for example, greater than 6 months) multiplied by reach (i.e., the proportion of the population of smokers engaged in treatment). Importantly, interventions that increase reach (i.e., those that are more broadly available and accessible to people, have greater appeal, and are therefore more widely used) may sacrifice efficacy or intensity, while interventions that are more intensive and more effective may have limited reach (Glasgow et al. 2011; Zhu et al. 2012). Given the reality of funding constraints, most states, healthcare systems, and other stakeholders do not have the option of maximizing both the effectiveness and reach of cessation treatments; in practice, they have to balance these approaches.

For this chapter, 38 Cochrane reviews were examined in early 2017. Additional literature searches of English-language articles in PubMed were used to identify new literature published since the original Cochrane reviews. Searches were primarily restricted to randomized controlled trials (RCTs) of smoking cessation interventions using the terms *smoking cessation* and *randomized controlled trial*. In areas where RCTs were not available, the chapter discusses the available science and identifies areas that lacked depth of evidence from RCTs. Consistent with previous Surgeon General's reports on tobacco, the content in this report was revised throughout the review process to include studies and information not available at the time the chapters were initially drafted, most notably for topics in which the available science is rapidly emerging (e.g., electronic cigarettes [e-cigarettes]) (King et al. 2018a).

Data reviewed in this chapter are overwhelmingly drawn from studies of adult cigarette smoking cessation, as opposed to cessation of other forms of tobacco products (e.g., cigars, cigarillos, smokeless tobacco, hookah, and e-cigarettes). The paucity of research on cessation treatments for noncigarette tobacco products does not allow for a separate and comprehensive scientific evaluation of such treatments.

This chapter is divided into seven sections: behavioral and psychological treatments, pharmacologic treatments, teachable moments, considerations for subpopulations, emerging intervention approaches, summary of the evidence, and conclusions.

Behavioral and Psychological Treatments

Notable discoveries in the behavioral and social sciences have broadened and deepened understanding of psychosocial influences on the nature and treatment of nicotine dependence, which has given rise to new approaches to behavioral treatment. It has become clear that, as acute nicotine withdrawal dissipates as the length of the quit attempt increases, several factors—including intermittent negative emotional states, repeated urges to smoke, diminished motivation, and decreased self-efficacy about quitting—can persist throughout the cessation process and undermine quitting (Liu et al. 2013; Ussher et al. 2013). Furthermore, encountering environments and situations previously associated with smoking, such as going to establishments that serve alcohol or interacting with friends who smoke, has been shown to increase risk of relapse (Conklin et al. 2013). Intensive behavioral cessation treatment models for smokers with mental health conditions and substance use disorders that have been adapted to address these factors have been shown to improve quit rates (Das and Prochaska 2017).

Behavioral and psychological strategies that have been shown to be effective in treating tobacco use and nicotine dependence include behavioral therapy and cognitive behavioral therapy (CBT) (Sykes and Marks 2001; Fiore et al. 2008; Perkins et al. 2008), motivational interviewing (Lindson-Hawley et al. 2015), acceptance and commitment therapy (Bricker et al. 2013), and contingency management or incentive-based interventions (which have been found to be effective while incentives are in place) (Cahill et al. 2015). These strategies can be individual- or group-based and can vary in intensity (from brief to more intensive) and in the mode of delivery (e.g., delivery by a clinician, counselor, telephone, or computer). Most research on behavioral treatments has considered packages of multiple treatment elements instead of comparing one element with another (e.g., studies of treatment optimization), making a review of each treatment approach challenging (Piper et al. 2016). In general, the data show a robust dose-response curve, with more intensive behavioral and psychological treatments (e.g., higher amounts of contact time, more sessions) yielding greater odds of sustained cessation (Fiore et al. 2008; USPSTF 2015).

Treatment Strategies

Behavioral Therapy

A large body of scientific literature supports the use of behavioral therapy to help people quit smoking (Fiore et al. 2008; Stead et al. 2016; Lancaster and Stead 2017). Such approaches can be delivered by various types of healthcare providers or counselors to individual persons or groups. Behavioral therapy, which is commonly used with smokers who are contemplating quitting or preparing to quit, seeks to address the historical learning processes directly relevant to smoking and the current contextual factors that make it difficult to quit (e.g., social, behavioral, and environmental factors) (Webb et al. 2010b).

Available evidence supports the effectiveness of both brief cessation interventions and longer, more intensive interventions. USPSTF (2015) and the *Clinical Practice Guideline* (Fiore et al. 2008) each concluded that both minimal (<20 minutes in a single visit) and intensive (≥20 minutes plus one or more follow-up visits) interventions delivered by clinicians are effective in increasing the proportion of adults who successfully quit smoking and remain abstinent for at least 6 months, which is commonly referred to as recent successful cessation. USPSTF (2015) and the *Clinical Practice Guideline* (Fiore et al. 2008) each also concluded that there is a dose-response relationship between the intensity of counseling and quitting success—that is, the greater the intensity of counseling, the higher the likelihood an individual will quit. Accordingly, behavioral therapy approaches for smoking cessation are delivered over several weeks and focus on the physiological, psychological, social, and environmental aspects of smoking and nicotine dependence (Fiore et al. 2008; USDHHS 2010, 2014). Group treatment typically occurs weekly for several weeks in a series of 60- to 90-minute sessions (Foulds et al. 2006; Kotsen et al. 2017). For example, Public Health England (2017) recommended weekly visits for 6–12 weeks for individuals (30–45 minutes per visit) and groups (60 minutes per visit).

Behavioral treatment approaches equip smokers with practical strategies to avoid and/or cope with triggers, manage cravings, and reduce withdrawal symptoms (Center for Substance Abuse Treatment 2006). These interventions often cover a wide variety of topics—including advice on quitting smoking; assessment of prior quit attempts and lessons that can be drawn from them; assessment of current motivation to quit; identification of cues and triggers for smoking and ways to avoid or manage them; tips on ways to manage mood; and promotion of adherence to treatment engagement (such as using medications correctly) and continued treatment engagement. Adherence to treatment engagement and continued treatment engagement can be promoted by addressing skill building; self-managing withdrawal symptoms; accepting social support; and managing such associated health issues as stress, moodiness, and other substance use (Fiore et al. 2008).

Cognitive Therapy

Cognitive therapy, which includes CBT, is a psychotherapeutic approach rooted in the idea that behavioral problems can be maintained by cognitive factors, including beliefs that lead to automatic thoughts about particular situations. The model uses specific therapeutic strategies to target maladaptive cognitions and help change problematic behaviors (Ellis 1962; Beck 1970; Butler et al. 2006). Contemporary applications of CBT typically emphasize cognitive factors and emotional, physiological, and behavioral components that can reinforce behavior (Butler et al. 2006; Hofmann et al. 2013). CBT is among the most researched psychotherapeutic approaches (Hofmann et al. 2012), with studies addressing a wide variety of behavioral and cognitive disorders, including smoking cessation.

Treatments based on CBT techniques have been found to be highly effective in smoking cessation (Sykes and Marks 2001; Fiore et al. 2008; Perkins et al. 2008). In a systematic review of cognitive therapies from 21 RCTs

that were conducted with 4,946 participants since 2009, the Norwegian Institute of Public Health concluded that:

- Cognitive therapies have similar effects to usual care or minimal interventions in terms of rates of smoking abstinence (up to 6–12 months; n = 3 studies);
- Cognitive therapies combined with nicotine replacement therapy (NRT) result in higher abstinence rates (up to 12 months) compared with other interventions that are combined with NRT (n = 8 studies);
- Cognitive therapies result in a higher smoking abstinence rate (up to 12 months) compared with other interventions (e.g., advice to quit, exercise, health education) (n = 6 studies); and
- Cognitive therapies plus medications improve smoking abstinence rates (up to 12 months) compared with medication only (n = 5 studies) (Denison et al. 2017).

CBT has also been studied in relation to other cessation treatments and was found in a meta-analysis by Garcia-Vera and Sanz (2006) to be superior, both alone and in combination with NRT, compared with NRT alone.

Studies have also shown CBT to be effective for smoking cessation in specific populations. For example, in a sample of African Americans, Webb and colleagues (2010a) found that CBT at least doubled the likelihood of cessation through the 6-month follow-up compared with a control group that received only health education. In a separate study, Webb Hooper and colleagues (2017) found that culturally specific CBT resulted in double the 7-day point-prevalence cessation rate compared with nonculturally specific CBT and was significantly more effective at 3-month follow up. CBT has been shown to increase cessation when combined with NRT or other cessation medication in populations who use tobacco and have comorbid substance use or mental health conditions (Haas et al. 2004; Ziedonis et al. 2008; Magill and Ray 2009). However, studies assessing the use of CBT in smokers with schizophrenia, either with or without other intervention components, have yielded more mixed findings (Gelkopf et al. 2012; Tsoi et al. 2013; Rüther et al. 2014; Brody et al. 2017).

Recent research has focused on improving smoking cessation outcomes from previous CBT trials. For example, in a 2017 two-arm, parallel group RCT of a community-based adult sample (n = 219), extended CBT treatment of 48 weeks did not yield better cessation outcomes compared with 26 weeks of treatment (Laude et al. 2017). Research has also focused on adapting CBT interventions to mobile health (mHealth) and web-based platforms and adding technology-based components to further enhance CBT, including testing the effectiveness of CBT in an app-based format (vs. a non-CBT app) (Tudor-Sfetea et al. 2018) and adding virtual reality to CBT to create an immersive and interactive cue exposure paradigm (e.g., exposure to smoking cues without reinforcement, with the goal of dis-associating those cues) to standard treatment (Culbertson et al. 2012).

Motivational Interviewing

Both motivational interviewing and adaptations of this approach make use of a distinct style of counseling that is directive, patient-centered, nonconfrontational, nonjudgmental, and highly collaborative (Miller and Rollnick 2002). Motivational interviewing—which can be delivered by healthcare providers, counselors, or quitline coaches—aims to help people explore and resolve any ambivalence about making a behavior change, such as quitting smoking (Miller and Rollnick 2002; Lindson-Hawley et al. 2015). This technique is typically used with persons who are not yet ready to quit tobacco (Miller and Rollnick 2002; Fiore et al. 2008). Counseling techniques—such as expressing empathy, actively listening, reflecting back on what one heard, and building self-efficacy—are at the core of motivational interviewing (Miller and Rollnick 2002).

Motivational interviewing was initially developed to treat alcohol addiction (Miller 1983) and was subsequently adapted for use in tobacco cessation. Lindson-Hawley and colleagues (2015) reviewed 28 studies that compared motivational interviewing to brief advice or usual care for the treatment of tobacco use. Motivational interviewing was used in one to six sessions lasting from 10 to 60 minutes and was delivered by clinicians in primary care settings, emergency departments, or hospitals; in the community; via telephone quitlines; and in military settings. Motivational interviewing was found to significantly increase successful quitting compared to those not receiving the intervention (relative risk [RR] = 1.26; 95% confidence interval [CI], 1.16–1.36; 28 studies; N = 16,803). Short motivational interviewing interventions (<20 minutes per session) had an RR of 1.69 (95% CI, 1.34–2.12; 9 trials; N = 3,651). Both single-session (RR = 1.26; 95% CI, 1.15–1.40; 16 trials; N = 12,103) and multiple-session (RR = 1.20; 95% CI, 1.02–1.42; 11 trials; N = 3,928) treatments increased the likelihood of quitting compared with controls. In summary, motivational interviewing is an evidence-based approach that has been shown, when delivered by clinicians or trained counselors, to be more effective in increasing readiness to quit and in helping people quit smoking than brief advice or usual care (e.g., self-help materials) (Lindson-Hawley et al. 2015).

Acceptance and Commitment Therapy

Acceptance-based therapies (ACTs) draw on cognitive therapies but focus on changing psychological events directly. Specifically, ACTs seek to change the function of those events and the relationship an individual has to them (Hayes 2004; Hayes et al. 2006). ACTs focus on the context and functions of psychological phenomena, emphasizing contextual and experiential change strategies to help individuals become more willing to experience their physical sensations, emotions, and thoughts (Hayes et al. 1999; Hayes et al. 2006). In ACTs, "acceptance" is rooted in accepting intense physical sensations (e.g., nicotine withdrawal or urges to smoke) and the emotions and thoughts that accompany those sensations (e.g., anger or sadness, thoughts about wanting a cigarette, etc.). In contrast, "commitment" focuses on articulating what is particularly important to or valued by an individual and leveraging those values to motivate and guide specific actions, like quitting smoking (Hayes et al. 2001, 2006, 2013; Bricker et al. 2010). Clinical treatment research supports ACTs for general behavior change and condition management, including in populations diagnosed with such disorders as major depression, anxiety disorders, borderline personality disorder, chronic pain, and substance abuse (including tobacco use) (Khoury et al. 2013; Kelly et al. 2015; Linehan et al. 2015; Cristea et al. 2017; Meyers et al. 2017). With regard to smoking cessation, a quasi-experimental study (n = 81 adult smokers) by Hernández-López and colleagues (2009) compared ACT with CBT using seven weekly 90-minute sessions in a group format. The 30-day point-prevalence quit rate at 12-month follow-up was 30.2% in the ACT condition and 13.2% in the CBT condition (odds ratio [OR] = 5.13, p <.02). A randomized trial of 302 adult smokers compared individual and group ACT therapy with bupropion to bupropion only (Bricker et al. 2014a). In this study, intent-to-treat quit rates at 12-month follow-up were 32% in the ACT arm versus 18% in the bupropion-only arm (p <.05). ACT has also been studied as part of a telephone-based intervention. For example, in a pilot randomized trial on telephone-delivered ACT versus telephone-delivered CBT in 121 uninsured callers to the South Carolina state quitline, Bricker and colleagues (2014a) found no significant difference in 30-day point-prevalence quit rates at 6- month follow-up.

In recent years, ACT has also been adapted and pilot tested as (a) a smartphone application to reduce smoking (Singh et al. 2017) and to motivate smoking cessation (Bricker et al. 2014b; Bricker et al. 2017) and (b) a web-based intervention (Bricker et al. 2013; Bricker et al. 2018). For example, in a single-arm pilot trial of a smartphone application of ACT (SmartQuit® 2.0) among smokers, Bricker and colleagues (2017) found that at 2-month follow-up, quit rates were 21% for 7-day point prevalence (vs. 23% for SmartQuit®) and 11% for 30-day point prevalence (vs. 13% for SmartQuit®), and 75% of participants reduced their smoking frequency (vs. 57% for SmartQuit®). Among program completers (24% of the total sample), quit rates were 33% for 7-day point prevalence and 28% for 30-day point prevalence, and 88% of participants reduced their smoking frequency. ACT has also been explored in specific populations, including smokers with depressive symptoms (Jones et al. 2015), smokers with bipolar disorder (Heffner et al. 2015, 2018), veterans with posttraumatic stress disorder (Kelly et al. 2015), and female smokers with cessation-related weight concerns (Bloom et al. 2017). More research is needed to better understand populations and delivery modalities for which ACT is particularly promising as a smoking cessation approach compared with existing cognitive therapies.

Contingency Management and Monetary Incentives

A large body of evidence (Ainscough et al. 2017) supports contingency management, which involves the use of incentives (including money, gift cards, or other tangible goods) to motivate people to change health behaviors, including motivating them to maintain abstinence from substance use over an extended period of time (Lussier et al. 2006). Monetary incentives for quitting or not initiating smoking or tobacco use, such as paying persons for engaging in cessation services and for achieving cessation-related outcomes (e.g., abstinence or participation in treatment), have been tested alone and in combination with cessation medication or counseling as an approach to increase compliance with nicotine dependence treatment and sustained abstinence from tobacco use. In a meta-analysis of the use of incentives for smoking cessation, Cahill and colleagues (2015) analyzed 21 trials of incentive programs that were implemented in a variety of settings for mixed populations and special groups (e.g., pregnant women). The OR for quitting with incentives (compared with controls) at the longest period of follow-up (at least 6 months) was 1.42 (95% CI, 1.19–1.69). Additionally, incentive-based programs increased rates of smoking cessation among pregnant women at both end-of-pregnancy and postpartum assessments. In an analysis by Cahill and Perera (2011), the primary benefit of incentive-based interventions was often seen only while the incentive was still in place. Only one of the reviewed studies (Volpp et al. 2009) in the analysis showed a statistically significant effect of the incentive program after the active incentive phase ended.

A key factor in the success of incentives in motivating smokers to quit may be the behavior that is being incentivized (quitting vs. engaging in treatment) and how the incentive is framed (reward vs. punishment). For example, in the study by Cahill and Perera (2011),

the participating employer opted to charge employees who smoked more for their insurance, rather than paying them for quitting, because nonsmoking employees viewed the latter approach as unacceptable. However, charging employees who smoke higher insurance premiums could have potential unintended consequences, such as leading them to forgo health insurance because it is too expensive or to conceal their smoking status to avoid the surcharges, making it harder to provide these employees with quitting support (Friedman et al. 2016; also see Chapter 7). As this example shows, contingency management could have unintended effects if improperly designed.

In 2011, the Centers for Medicare & Medicaid Services (CMS) launched the Medicaid Incentives for Prevention of Chronic Disease program in 10 states to assess the effectiveness of incentives in increasing certain preventive health behaviors, such as weight management and smoking cessation, among Medicaid beneficiaries as a strategy to improve the management of noncommunicable disease (CMS 2011, 2018). The results described in the final report on the project generally support the incentive approach (Hoerger et al. 2017). Five states (California, Connecticut, New Hampshire, New York, and Wisconsin) implemented incentive programs for smoking cessation. In the three states that tested impacts on program utilization (Connecticut, New Hampshire, and Wisconsin), incentives significantly increased the use of program services. Four of the states (California, Connecticut, New Hampshire, and Wisconsin) assessed the impact of incentives on rates of smoking cessation (which were biochemically verified in Connecticut, New Hampshire, and Wisconsin and self-reported in California); in all four states, rates of smoking cessation increased among those in the incentive group relative to those in the control group (Witman et al. 2018).

In general, motivation to quit and rates of cessation may increase while monetary incentives are in place, but these outcomes are rarely sustained after such incentives are removed. It is unclear whether a monetary incentive-based strategy is practical outside a research setting, given the reluctance of employers and insurers to pay smokers to quit and the potential unintended consequences of charging smokers more for health insurance. More research is needed to (a) explore whether any approaches to incentivizing smoking cessation sustain their effects over time and do not lead to counterproductive outcomes and (b) identify what types of approaches meet these criteria.

Relapse Prevention and Recovery

Most smokers make multiple quit attempts before finally succeeding in quitting for good. Indeed, one study estimated that smokers may make an average of 30 or more quit attempts (i.e., serious attempts to quit smoking) before eventually succeeding (Chaiton et al. 2016). This means that most quit attempts end in relapse. Most relapses occur during the first few hours, days, or weeks of a quit attempt (Fiore et al. 2008). Although the risk of relapse declines over time, even former smokers who have quit for months or years can relapse (Hawkins et al. 2010).

Several treatment strategies include components designed to prevent relapse or to help smokers recover from relapses. Examples include relapse prevention therapy, which equips smokers with skills for avoiding or coping with high-risk environments and situations (Collins et al. 2010); acceptance and commitment therapy, which teaches smokers coping strategies to help them avoid lapsing into states of distress or giving in to strong urges to smoke (Bricker et al. 2014b); and motivation-enhancing interventions, which have been used to encourage smokers to make a quit attempt even if they are not ready to quit (Fiore et al. 2008; Lindson-Hawley et al. 2015). Each of these treatment models has demonstrated efficacy that is greater than brief advice (Lindson-Hawley et al. 2015) but not substantially greater than an equal-intensity intervention based on the *Clinical Practice Guideline* that addresses relevant risks of smoking, rewards of quitting, roadblocks to cessation, and repetition at each visit (Catley et al. 2016).

Despite the availability of relapse prevention and recovery interventions, scientific literature reviews on the topic highlight the difficulty of preventing and addressing relapse (Agboola et al. 2010; Hajek et al. 2013c). For example, in a Cochrane Review meta-analysis of relapse prevention interventions among smokers during the first 6 months of a quit attempt, Hajek and colleagues (2013c) found no evidence of benefit for additional post-cessation behavioral interventions or combined behavioral and pharmacologic interventions, either overall or for any subgroup. Many of the studies included in the Cochrane Review used small sample sizes and had limited statistical power to detect modest but potentially clinically significant effects, and the interventions may have been insufficient to achieve the desired effect. In addition, some studies focused on long-term abstinence. Therefore, these studies may have overlooked potentially beneficial recycling or recovery effects that result in increased frequency of secondary quit attempts. In a more recent review, Livingstone-Banks and colleagues (2019) found that the evidence does not support the use of behavioral treatments to help prevent relapse following smoking cessation among assisted abstainers. Instead, the most promising treatments involved extending treatment with certain pharmacotherapy, namely varenicline; extending treatment with bupropion was not shown to prevent relapse.

Furthermore, the review found insufficient evidence on extending treatment with NRT in preventing relapse in assisted abstainers. However, evidence for extending NRT in unassisted abstainers suggested a benefit. At present, more research is needed on specific behavioral interventions that can be delivered during the early stages of cessation to help smokers avoid short-term relapse.

Intervention Delivery Modalities

Research demonstrates that behavioral therapy approaches for smoking cessation can be delivered effectively through face-to-face counseling (individually or in groups) and brief clinical interventions (Fiore et al. 2008); and technology-mediated approaches, including telephone-based tobacco quitlines, mHealth, short message service (SMS) texts, web-based interventions, and smartphone applications; and, under certain circumstances, tailored self-help materials (The Community Guide 2011b, 2012b; Whittaker et al. 2012; Stead et al. 2013b, 2017; Lancaster and Stead 2017).

Self-Help Materials

In general, self-help materials for smoking cessation that are not tailored to a particular person or group have limited effectiveness when they are not coupled with in-person or technology-based interventions (Fiore et al. 2008). In a review of behavioral counseling interventions for tobacco cessation among adults, Patnode and colleagues (2015) did not find evidence of increased cessation in a comparison between nontailored self-help materials and no self-help materials. However, tailored self-help materials that are based on specific characteristics or concerns of smokers have been shown to be effective (Fiore et al. 2008; Patnode et al. 2013). Additionally, a Cochrane Review found some efficacy for tailored self-help materials in print, audio, and video forms compared with nontailored materials, but the absolute size of the effect was small (RR = 1.28; 95% CI, 1.18–1.37), and the review did not examine Internet-based materials (Hartmann-Boyce et al. 2014). Still, an effect size of 1.28 can be consequential given how inexpensive tailored self-help materials are relative to cessation medications or multisession counseling. The Cochrane Review also concluded that, although tailored self-help materials may offer some benefit, smokers trying to quit should also seek out more intensive cessation treatments.

Face-to-Face Counseling

Face-to-face counseling—whether delivered in traditional healthcare settings, behavioral healthcare settings, or community settings—has traditionally been the gold standard for behavioral treatment of nicotine dependence, and its effectiveness is well-established in the scientific literature (Fiore et al. 2008). Noting substantial variability in the specific content of counseling delivered and in the skills of those delivering the counseling, the *Clinical Practice Guideline* concluded that individual in-person counseling achieved an average abstinence rate for cigarette smoking of 16.8%, compared with 10.8% for the control conditions (OR = 1.7; 95% CI, 1.4–2.0) (Fiore et al. 2008). In contrast, in-person group counseling achieved a 13.9% abstinence rate (OR = 1.3; 95% CI, 1.1–1.6).

In a Cochrane Review, Lancaster and Stead (2017) assessed the effectiveness of intensive counseling delivered by a cessation counselor on a one-on-one basis. All 49 RCTs they reviewed, which included approximately 19,000 participants combined, contained a face-to-face intervention component; however, some trials also included the use of other behavioral intervention modalities. The review concluded that individual counseling was more effective than minimal contact (brief advice, usual care, or self-help materials) when pharmacotherapy was not systematically offered to any participants (RR = 1.57; 95% CI, 1.40–1.77). Additionally, there was moderate evidence of a benefit for (a) the addition of intensive counseling (vs. usual care) when cessation pharmacotherapy was offered to all participants (RR = 1.24; 95% CI, 1.01–1.51) and (b) more intensive counseling compared with brief counseling (with or without the addition of cessation pharmacotherapy) (RR = 1.29; 95% CI, 1.09–1.53).

Brief Clinician-Delivered Advice

Clinical and other healthcare settings are a natural channel for delivering brief cessation interventions because at least 70% of tobacco users visit a physician each year (Fiore et al. 2008), almost one-third visit a dentist (Fiore et al. 2008; Carson et al. 2012), and millions see a specialist or are hospitalized (National Center for Health Statistics 2018). Encounters with clinicians represent a key opportunity to engage smokers in cessation treatments because clinical visits can provide teachable moments for patients who are experiencing or at risk for tobacco-related diseases (Fiore et al. 2008). Clinicians can take advantage of this opportunity and enhance the impact of their advice to quit by delivering this advice in a personalized manner that places it in the context of the patient's specific diagnosis and health history (Fiore et al. 2008). Furthermore, smokers respect and trust physicians and expect them to address their tobacco use (Quinn et al. 2005) and are more satisfied with healthcare providers when the providers discuss cessation with them (Bernstein and Boudreaux 2010; Winpenny et al. 2017; Holla et al. 2018).

Evidence increasingly suggests that healthcare providers other than physicians can also be effective in advising smokers to quit. For example, in a Cochrane Review of 11 studies, Rice and colleagues (2017) found moderate evidence that behavioral support provided by nurses can motivate and sustain smoking cessation. In another Cochrane Review of 14 studies totaling more than 10,500 participants, Carr and Ebbert (2012) found evidence suggesting that behavioral interventions conducted by oral health professionals (e.g., dentists and dental hygienists) as part of an oral examination in a dental office or other community setting could increase cessation rates in cigarette smokers and users of smokeless tobacco (pooled OR = 1.71; 95% CI, 1.44–2.03). Research is also emerging about the role that pharmacists and community pharmacies can play in helping to promote tobacco cessation (Augustine et al. 2016; Greenhalgh et al. 2016).

Based on the strong evidence base for brief tobacco cessation interventions, USPSTF (2015) recommends, as a "Grade A" recommendation, that clinicians deliver such interventions to all adult smokers. Even brief (<3 minutes) advice from a physician improves cessation rates (OR = 1.66; 95% CI, 1.42–1.94) (Stead et al. 2013a) and is highly cost-effective (Maciosek et al. 2017a).

As a framework, the 5 A's method is considered the gold standard for delivering a brief tobacco cessation intervention. The 5 A's method consists of the following steps:

1. Ask all patients about tobacco use;

2. Advise tobacco users to quit (e.g., "quitting is the best thing you can do for your health");

3. Assess the patient's willingness to make a quit attempt (e.g., "have you thought about quitting or are you interested in trying?");

4. Assist in the quit attempt with medications, counseling, and referrals to behavioral treatment programs; and

5. Arrange follow-up (Table 6.1) (Fiore et al. 2008, p. 39).

Implementation of the 5 A's by physicians is effective in increasing tobacco cessation and quit attempts among patients and in increasing engagement among patients in other empirically validated cessation treatments (Quinn et al. 2009). Compared with patients who received only one or none of the 5 A's, delivering all of the 5 A's increased patients' receipt of counseling (OR = 11.2; 95% CI, 7.1–17.5), use of FDA-approved cessation medications (OR = 6.2; 95% CI, 4.3–9.0), and combined use of counseling and medication (OR = 14.6; 95% CI, 9.3–23.0) (Kruger et al. 2016).

In practice, however, despite the robust evidence for the effectiveness of brief tobacco interventions, many clinicians do not consistently address tobacco use and nicotine dependence. For example, in nationally representative data from 2000 to 2015, Babb and colleagues (2017) found that 57% of smokers who had seen a health professional in the past year reported receiving advice to quit. In an earlier study, King and colleagues (2013) found that patient reports of their physicians providing each of the 5 A's typically decreased as the steps progressed, with "Asking" about tobacco use (87.9%) being more prevalent than "Assisting" with a quit attempt (78.2% of those who wanted to quit) and the prevalence of "Assisting" being far more prevalent than "Arranging for follow-up" (17.5% overall). Thus, in practice, clinicians are rarely performing all five actions in the 5 A's approach. One way to address this problem is by delegating some of the steps of the 5 A's (e.g., Ask, Assist, Arrange) in whole or in part to other members of the healthcare team (e.g., nurses, physician assistants, roomers, etc.) (Fiore et al. 2008). This approach

Table 6.1 The 5 A's model for treating tobacco use and dependence

Ask about tobacco use	• Identify and document tobacco use status for every patient at every visit.
Advise to quit	• In a clear, strong, and personalized manner, urge every tobacco user to quit.
Assess readiness to make a quit attempt	• Is the tobacco user willing to make a quit attempt at this time?
Assist in quit attempts	• For the patient willing to make a quit attempt, offer medication and provide or refer for counseling or additional treatment to help the patient quit. • For patients unwilling to quit at the time, provide interventions designed to increase future quit attempts.
Arrange follow-up	• For the patient willing to make a quit attempt, arrange for follow-up contacts, beginning within the first week after the quit date. • For patients unwilling to make a quit attempt at the time, address tobacco dependence and willingness to quit at next clinic visit.

Source: Fiore and colleagues (2008, p. 39).

lessens the burden on physicians and emphasizes the importance of quitting to patients (Fiore et al. 2008).

A diagnosis of a tobacco-related disease has been associated with an increase in quit attempts, use of cessation resources (Patel et al. 2009; Schauer et al. 2014b; Gallaway et al. 2019), and cessation and can provide a teachable moment for patients, especially because quitting can often improve a patient's prognosis or symptoms. Studies indicate that healthcare providers may be leveraging this opportunity. For example, in a study of patient-reported receipt of the 5 A's in a nationally representative population of past-year cigarette smokers with and without chronic obstructive pulmonary disease (COPD), Schauer and colleagues (2016c) found that patients with COPD were more likely than those without COPD to receive each step in the 5 A's approach: Ask = 95.4% vs. 85.8%; Advise = 87.5% vs. 59.4%; Assess = 63.8% vs. 37.9%; Assist = 58.6% vs. 34.0%; and Arrange = 14.9% vs. 5.2%.

Barriers that can prevent clinicians from consistently conducting brief cessation interventions include time constraints; a lack of knowledge, training, and confidence; inadequate clinical and/or institutional support; a lack of adequate reimbursement for delivering tobacco treatment; and inadequate or confusing insurance cessation coverage (Fiore et al. 2008; Sheffer et al. 2012). Concerns about the lack of adequate training to effectively deliver cessation interventions are also reported by other healthcare providers, such as nurses, psychologists, and social workers (Steinberg et al. 2006a,b; Applegate et al. 2008; Sheffer et al. 2012).

Alternative Approaches to the 5 A's

Research supports the value of alternative treatment approaches that do not deliver all steps of the 5 A's approach in the clinical setting. One such alternative that is widely used is the Ask-Advise-Refer (AAR) approach, which involves a provider in a clinical setting Asking about tobacco use; Advising patients to quit; and Referring interested patients to another cessation resource, such as a quitline (see Chapter 7), to complete the remaining "Assess," "Assist," and "Arrange" steps (Schroeder 2005; Gordon et al. 2010). Gordon and colleagues (2010) compared the use of the 5 A's with the use of the AAR approach in 68 dental clinics. At 12 months, participants receiving either the 5 A's or the AAR were more likely to report tobacco cessation than those who received only usual care. Additionally, there was no significant difference (using a threshold of $p < 0.05$) in rates of 9-month prolonged cessation between participants receiving the 5 A's method and the AAR approach (3% vs. 2%, $p < .10$ for 9 months of prolonged abstinence) (Gordon et al. 2010).

Limited research supports a third approach, Ask-Advise-Connect (AAC). Compared with AAR, AAC provides a more active and direct connection to an outside cessation resource (Vidrine et al. 2013a,b). One example of providing such a direct connection is referring smokers to tobacco quitlines via an electronic referral or "eReferral" that securely transfers patient registration information from electronic health records to the quitlines (Boyle et al. 2011, 2014; Sheffer et al. 2012; Adsit et al. 2014; Tindle et al. 2016) (see Chapter 7 for more details on electronic health records and eReferrals). Some research suggests that AAC may be more effective than AAR in reaching smokers and engaging them in treatment. Specifically, in a pair-matched, two-treatment-arm, group-randomized study conducted in 10 family practice clinics in one metropolitan area, 7.8% of all identified smokers enrolled in treatment in the AAC arm compared with just 0.6% who enrolled in the AAR arm (OR = 11.6; 95% CI, 5.5–24.3) (Vidrine et al. 2013a).

Finally, because many smokers are ambivalent about quitting or have transient motivation to quit, a fourth hypothetical version of the 5 A's might build on such approaches as the 5 R's (Relevance, Risks, Rewards, Roadblocks, and Repetition) (Agency for Healthcare Research and Quality 2012), which is used for smokers who are not yet ready to quit and focuses on providing interventions and supports to all smokers, even those who are initially assessed as not ready to quit. This approach is appealing from a theoretical standpoint because of the lack of clear evidence demonstrating that a very brief assessment of readiness to quit is sufficient to withhold an offer of more robust cessation support to these individuals. One potential downside of this approach could be that providing support to smokers who are not ready to quit could turn out to be time-consuming and inefficient. To date, randomized trials have not assessed this approach.

As tobacco cessation interventions are increasingly integrated into inpatient care and into care in other settings, such as pharmacies and behavioral health treatment facilities, updates to the 5 A's model may emerge that more explicitly coordinate and distribute cessation interventions across an integrated care team and across different clinical environments.

Intensive Face-To-Face Counseling

Intensive in-person behavioral treatment, which is sometimes combined with pharmacologic interventions, typically consists of multiple face-to-face counseling sessions that last long periods of time (e.g., ≥10 minutes) by clinicians who have been trained in specialized smoking cessation interventions (Fiore et al. 2008). Although intensive interventions are intended primarily for moderately to heavily addicted smokers, the effectiveness and cost-effectiveness of such interventions are not limited to heavy or highly dependent smokers (Fiore et al. 2008; USPSTF 2015). A range of intensive treatment programs

are available at the individual and group levels in some communities, worksites, and healthcare systems (Institute of Medicine 2007). However, availability varies widely from community to community, and geographic location and temporal availability are major barriers to utilization. In practice, such intensive cessation approaches are generally the exception rather than the rule in the United States. Compared with the United States, some countries have invested more heavily to ensure that most smokers have access to intensive face-to-face counseling. For example, in addition to making brief cessation interventions delivered by primary care physicians and some pharmacists widely available, the United Kingdom has established Stop Smoking Services, which mainly target highly addicted smokers and are staffed by counselors who are trained in behavioral approaches to smoking cessation (Dobbie et al. 2015; Public Health England 2017). Both intensive individual and group cessation treatments have been shown to be effective when delivered outside of healthcare clinics, particularly in workplace settings. For example, Cahill and Lancaster (2014) reported on rates of tobacco cessation in eight trials in workplace settings that involved intensive group treatments (N = 1,309) and individual treatments (N = 3,516). Relative to controls, the OR for successful quitting among those in the intensive group treatments (OR = 1.71; 95% CI, 1.05–2.80) was generally comparable in magnitude to that for those receiving individual treatments (OR = 1.96; 95% CI, 1.51–2.54), suggesting that well-designed group counseling can be effective in workplace settings.

Although a strong evidence base exists for in-person behavioral approaches to treating tobacco use and nicotine dependence, few U.S. smokers use face-to-face individual and group counseling when trying to quit, possibly because of a lack of investment in these approaches and practical barriers to use (e.g., time, transportation, schedule, etc.) (Dobbie et al. 2015; Public Health England 2017). For example, in a U.S. study, Babb and colleagues (2017) found that in 2015 31.2% of U.S. adult cigarette smokers reported using cessation counseling and/or medication when trying to quit, 6.8% reported using counseling, 29.0% reported using medication, and 4.7% reported using both counseling and medication. In terms of specific types of counseling, 4.1% of smokers reported using a telephone quitline; 2.8% one-on-one counseling; and 2.4% a stop-smoking clinic, class, or support group (Babb et al. 2017).

Technology-Mediated Delivery Approaches

Evidence supports the effectiveness of certain non-face-to-face delivery approaches for tobacco cessation, including telephone-based quitlines (The Community Guide 2012a) and mHealth-based interventions (The Community Guide 2011b). These approaches have characteristics that can remove or reduce time, transportation, and child care issues that may hinder face-to-face service delivery, thereby potentially leading to more widespread use. The following section reviews technology-mediated tobacco cessation intervention delivery approaches, including quitlines, SMS texting, web-based interventions, and smartphone applications. Telehealth approaches, which are discussed later in the "Emerging Behavioral Treatments" section of this chapter, are another emerging technology that can be used to deliver tobacco cessation interventions.

Tobacco Quitlines

Staffed by trained counselors or coaches, tobacco quitlines typically deliver a variety of services, including individual counseling, practical information on how to quit, referrals to other cessation or health-related resources, mailed self-help materials, information on FDA-approved cessation medications, and, in some cases, provision of limited quantities of free or discounted cessation medications (Keller et al. 2010; Anderson 2016). Publicly funded quitlines are available at no cost to U.S. residents in every state, the District of Columbia, Guam, and Puerto Rico (North American Quitline Consortium n.d.b). However, specific services vary across states, largely as a result of funding constraints that vary across states and jurisdictions and over time (Centers for Disease Control and Prevention [CDC] 2014; Anderson 2016). In addition to publicly funded state quitlines, some public and private health insurance plans and employers also offer quitline services (CDC 2014).

Since the 1990s, a large body of clinical literature has consistently demonstrated the effectiveness of tobacco quitlines (Zhu et al. 1996; Fiore et al. 2008). Although research on single- and multi-call quitline protocols has demonstrated that both are effective, better outcomes have been reported for multi-call approaches. Better outcomes have also been documented for proactive quitline services, which make multiple outbound calls to engage the tobacco user in ongoing treatment, compared with reactive quitline services, which simply respond to incoming calls from tobacco users. For example, in a meta-analysis of 49 studies that compared proactive quitlines with reactive quitlines, The Community Guide (2012b) estimated that proactive quitlines yielded a median 3.1-percentage-point increase (0.5–3.3 percentage points, 12 studies) in quitting and a 4.2 percentage-point increase when promoted through mass-reach health communication interventions.

Similarly, in a Cochrane Review of 77 trials that assessed counseling provided through quitlines, Stead and colleagues (2013b) concluded that multiple sessions of proactive telephone counseling significantly boosted rates of smoking cessation (nine studies; >24,000 participants; RR for cessation at longest follow-up = 1.37; 95% CI, 1.26–1.50). There was some evidence of a dose-response

effect—that is, more completed quitline counseling calls yielded higher rates of cessation. Even reactive calls to quitlines were effective in increasing cessation (51 studies, >30,000 participants, RR for cessation = 1.27; 95% CI, 1.20–1.36).

A toll-free national portal (1-800-QUIT-NOW) operated by the National Cancer Institute (NCI) links callers to their state quitline based on their area code. An electronic telecommunications device for the deaf (TDD) is also available to serve persons who are deaf or hard of hearing. From 2010 to 2015, state quitlines received an estimated 1.1–1.3 million calls annually and provided cessation counseling and/or cessation medications to an estimated 342,000–475,000 tobacco users each year (CDC, National Quitline Warehouse Database, unpublished data).

NCI also operates 1-855-DÉJELO-YA (1-855-335-3569), a national portal that routes Spanish-speaking callers to Spanish-language services available through their state quitlines. From February 2013 (the portal's inception) through December 2018, 1-855-DÉJELO-YA received more than 40,000 calls (CDC, NCI, unpublished data).

In addition, the Moores Cancer Center at the University of California–San Diego operates a nationwide Asian Smokers' Quitline, which offers direct counseling services in Chinese, Korean, and Vietnamese (Asian Smokers' Quitline n.d.). Nearly 5,800 callers from 48 states enrolled in the Asian Quitline between 2012 and 2014; 31% spoke Chinese (Cantonese or Mandarin), 38% spoke Korean, and 31% spoke Vietnamese (Kuiper et al. 2015). Nearly all eligible callers to the Asian Quitline (99%) received nicotine patches. Approximately 85% of smokers who called the Asian Quitline enrolled in counseling, completing an average of four sessions (Kuiper et al. 2015).

Quitline counseling is readily accessible because it is free, convenient, and confidential, and it removes or reduces barriers related to time, transportation, child care, and other factors (World Health Organization [WHO] 2011). As a result, quitline counseling has the potential for broad reach. Quitline counseling has also been found to be effective with an array of subpopulations (Baezconde-Garbanati et al. 2011). Tobacco users can be connected with a quitline in several ways: by calling directly; by having a healthcare provider's office fax, send an online referral, or submit an eReferral through the patient's electronic health record; by sending an e-mail; or by enrolling online. Most state quitlines provide at least one counseling session to any adult tobacco user who calls, and many state quitlines provide a multi-call program that includes both reactive and proactive calls. Some state quitlines prioritize multi-call services for subpopulations with a higher prevalence of tobacco use and/or limited access to other tobacco cessation services (e.g., persons who lack health insurance or are unemployed) (Anderson 2016). A study of quitline eReferrals in Wisconsin randomized 23 primary care clinics from two healthcare systems to one of two methods for referring adult patients who smoked to the Wisconsin quitline: a paper-based, fax-to-quit referral process or an eReferral process (Fiore et al. 2019). The eReferral process involved sending referrals to the quitline from patients' electronic health records and receiving outcome reports from the quitline back into the electronic health records. The fax referral process transmitted the same information in both directions via fax. A total of 14,636 smokers were seen in the two systems. Compared with clinics that were randomized to the fax referral process, clinics that were randomized to the eReferral process generated quitline referral rates that were 3- to 4-times higher and also generated higher rates of connecting patients with quitlines (i.e., having patients accept a quitline call and at least begin the process of registering for quitline services). The eReferral method generated especially high rates of referrals among Medicaid recipients. The study, which was the first randomized study of this topic, concluded that eReferrals provide an effective means of referring patients who smoke to quitline services.

A major innovation in quitline services that occurred over the past decade was the integration of NRT and, in some cases, other FDA-approved cessation medications into state quitline services, along with counseling. A series of randomized and quasi-randomized trials (Cummings et al. 2006; Hollis et al. 2007; Tinkelman et al. 2007) demonstrated that quitlines can feasibly and safely provide NRT to callers, either directly via mail order or by pharmacy voucher. This involved having quitlines screen callers for the medical appropriateness of NRT use, educate callers on how to properly use the NRT, and continue to provide callers with behavioral counseling. Making cessation medication available to callers and promoting its availability results in more smokers calling quitlines and has the potential to increase quit rates among callers by providing them with the optimal combination of cessation counseling plus medications (An et al. 2006). Even 2-week NRT "starter kits" have demonstrable benefits, including increased call volume to quitlines, higher quit rates, and increased caller satisfaction with the quitline (Bush et al. 2008; Deprey et al. 2009; Kerr et al. 2018). Distributing NRT through quitlines can be cost-effective (Fellows et al. 2007; Cummings et al. 2011). For example, Fellows and colleagues (2007) estimated that the total cost per quit was $2,688 lower for callers who received free NRT ($1,050) compared with persons who called the Oregon quitline before it began offering the nicotine patch to callers ($3,738).

The reach of state quitlines varies across states, over time, and by demographic factors, such as race/ethnicity (North American Quitline Consortium n.d.a). Despite reaching thousands of smokers each year in most states,

state quitlines reach an average of 1% of smokers annually (CDC 2014). Data suggest that even among smokers who tried to quit in the previous year and were aware of quitlines, quitline reach was around 8% (Schauer et al. 2014a). This limited awareness and reach, along with the variation in quitline services and eligibility for these services across states and over time, are largely the result of limited state funding for operating and promoting quitlines (e.g., state quitline expenditures) (CDC 2004; Schauer et al. 2014a). States have developed the capacity to carefully titrate their activities to promote quitlines and the level of quitline services they provide to match available funding. Some states have been able to temporarily attain higher levels of reach, in some cases higher than 6%, during periods when they can fund quitlines at higher levels, often while also conducting specific policy and promotional efforts that drive increased calls to the quitline (Woods and Haskins 2007; Mann et al. 2018).

Call volume to quitlines is highly sensitive to promotional activities (Anderson 2016). For example, *Tips From Former Smokers* (*Tips*), a national tobacco education campaign conducted annually by CDC for varying periods of time from 2012 to 2019, includes a message on the majority of its television ads directing smokers to call 1-800-QUIT-NOW for free help quitting. From 2012 to 2018, this campaign generated more than 1.3 million additional calls to 1-800-QUIT-NOW (Nathan Mann, RTI International, personal communication, May 6, 2019). Call volume to 1-800-QUIT-NOW consistently increases when the campaign airs and decreases when it goes off the air (Zhang et al. 2016; McAfee et al. 2017; Murphy-Hoefer et al. 2018).

In part, to maintain or improve their reach, state quitlines increasingly offer ancillary cessation services, such as Internet interventions, e-mail, chat, texting, and the dispensing of NRT both alone and in combination with counseling (Anderson 2016; Keller et al. 2016). This shift in quitline practice stems in part from the recognition that many younger adults prefer to access cessation assistance through these alternative channels rather than over the telephone (Dreher et al. 2015). For example, to increase both reach and quitting behavior, Minnesota implemented a model for state quitline services in 2014 that expanded tobacco users' options for accessing cessation services, allowing tobacco users to enroll via telephone or online and to choose one or more cessation services from a menu of options that includes quitline counseling, a medication starter kit, text messaging, an e-mail program, and a quit guide (Keller et al. 2016). Between March 2014 and February 2015, 15,861 unique tobacco users registered for cessation services in the state—a 169% increase over calendar year 2013. More than four in five (83.7%) of the participants made a quit attempt, and the 30-day point-prevalence abstinence rate (among responders) was 26.1% for the overall program (regardless of services used); 29.6% for quitline services; and 25.5% for individual non-quitline services. Thus, the reach of quitlines can be expanded, and new populations can be engaged in cessation services when quitlines (a) broaden their cessation service offerings beyond traditional telephone-based quitline services and (b) allow tobacco users to choose the service that best meets their needs and suits their preferences (Keller et al. 2016).

Mobile Health Intervention Strategies

Desktop or laptop computer-based interactive program modalities for delivering smoking cessation support have been developed and tested (USPSTF 2015), first via programs operated from a CD-ROM or hard drive, later via Internet downloads, and more recently from "the cloud" (Strecher et al. 2005; Haskins et al. 2017). The current state of science and technology also allows the leveraging of mobile phone and tablet applications (e.g., mHealth interventions) to deliver treatment for nicotine dependence (Whittaker et al. 2016). mHealth strategies can be broadly defined as the use of technology to remotely monitor, track, respond to, and/or deliver an intervention for health-related events. mHealth treatment platforms have expanded greatly during the past 20 years and especially in the past decade, with the development of electronic and mHealth technologies. These platforms include applications offered by for-profit and not-for-profit organizations and academic institutions and by federal agencies involving standardized text messages that enhance motivation to quit smoking or inform persons about quitting strategies, some of which offer real-time, live peer or professional advising or counseling (Smokefree.gov n.d.). Preliminary evaluations suggest that these applications benefit users (Cole-Lewis et al. 2016; Squiers et al. 2016, 2017; Taber et al. 2016) and that the cost of delivery is low.

Uptake of mobile technologies has been seen across almost all segments of the U.S. population (Pew Research Center 2017b). In 2016, cell phone ownership and usage were widespread: 95% of American adults owned a cell phone; 77% had a smartphone; and ownership levels were generally similar across all categories of race/ethnicity, age, education level, income level, and rural versus urban status (Pew Research Center 2017b). Texting is common among cell phone users, and many smartphone users report using their phones for texting, accessing the Internet, watching videos, and using apps (applications). Importantly, despite the widespread adoption of mobile technology, some populations—including some low-income and rural individuals and veterans—do not have equal access to mobile technology (Koutroumpisa and Leiponenb 2016; Markham et al. 2016).

Despite some remaining gaps in the availability and coverage of mobile technology, these technologies offer considerable potential to serve as platforms for delivering smoking cessation interventions. In 2011, the Community Preventive Services Task Force recommended mobile phone-based interventions, specifically automated texting programs, for tobacco cessation on the basis of sufficient evidence of their effectiveness in increasing tobacco use cessation among persons interested in quitting (The Community Guide 2011b).

Potential advantages of mHealth interventions include greater reach to some disproportionately impacted populations (Markham et al. 2016; Anguiano et al. 2017) and reduced costs because mHealth interventions can be less costly to provide than other behavioral interventions. In terms of reach, the Smokefree.gov initiative—a large federal mHealth behavioral intervention program that focuses primarily on smokers—reaches 5–6.5 million persons each year, including more than 3.6 million visitors to the Smokefree.gov website in 2018 (Yvonne Prutzman, NCI, personal communication, January 23, 2019). In addition, mHealth interventions may improve engagement through increased access to intervention services, decreased barriers to participation (e.g., by removing barriers related to scheduling, transportation, or child care), seamless integration of users' interactions with treatment into their daily lives, and the ability to personalize treatment based on passively (e.g., GPS [global positioning system] location) or actively (e.g., self-report of craving) gathered information (Atienza and Patrick 2011; Nilsen et al. 2012; Free et al. 2013; Borrelli et al. 2015; Marzano et al. 2015).

The potential benefits from mHealth interventions are tempered by several challenges, including (1) inconsistent access to cell phones among low-income populations (despite the increasing adoption of cell phones, low-income populations may still struggle to maintain cell phone contracts, have regular access to minutes, and have data plans that allow for repeated use of interventions), (2) different types of devices (e.g., cell phone vs. smartphone), (3) possible sharing of devices among multiple users, (4) differences in fee structures and costs for using cell phones, (5) the challenges of delivering content to populations with low literacy, and (6) lack of broadband coverage (Atienza and Patrick 2011; Katz et al. 2012; Free et al. 2013; Marzano et al. 2015; McClure et al. 2016; Federal Communications Commission n.d.).

At this time, optimal methods are not in place to fully assess the expanding array of available mHealth cessation interventions. Future research should address the components of the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) impact model (addressed later in this chapter) to determine the effectiveness of mobile cessation interventions under ideal conditions and their impact when used in real-world settings (Stearns et al. 2014). Research should include both process measures, such as engagement and reengagement, and measures of the interventions' impact on quit attempts and successful quitting. In addition, assessing the comparative effectiveness and cost-effectiveness of mHealth cessation interventions relative to other modalities, such as in-person and quitline interventions, will be important. Because of the rapid cycle of technological development, the use of adaptive and iterative research methods in assessing development and performing evaluations may be necessary. Although opportunities are available for conducting large cohort studies at a relatively low cost, the potential for selection bias and other types of bias in such studies underscores a need for RCTs in clinical settings.

Short Message Service Texting Interventions. Interventions based on SMS texting—which involve sending automated, one-way messages—offer a low-cost, convenient method of delivering smoking cessation interventions. Text messaging is a basic feature of almost all cell phones, making the delivery of cessation interventions via SMS texts an accessible and promising mHealth platform. A series of three studies from New Zealand and the United Kingdom provided the initial evidence supporting the use of this platform for delivering smoking cessation interventions (Rodgers et al. 2005; Free et al. 2009, 2011). Notably, a large-scale RCT in the United Kingdom that compared smokers receiving a text-based intervention with controls who received SMS texts related to the importance of trial participation, found a significant difference in biochemically verified abstinence at 6-month follow-up: 9.2% of smokers in the texting intervention achieved abstinence versus 4.3% of smokers in the control group (RR = 2.14; 95% CI, 1.74–2.63) (Free et al. 2011). A subsequent meta-analysis of a limited number of text-based cessation interventions found that, compared with control conditions, such interventions improved the 7-day point-prevalence of abstinence (OR = 1.38; 95% CI, 1.22–1.55) and continuous abstinence (OR = 1.63; 95% CI, 1.19–2.24) (Scott-Sheldon et al. 2016).

Although the findings from studies of cessation texting interventions are generally encouraging, a review of these interventions found that, while smoking cessation outcomes measured at less than 6 months were better than those for controls, outcomes measured at 6 months or longer often failed to show differences between treatment and control groups (Scott-Sheldon et al. 2016). In addition, the review found that the studies' findings were mixed and the analyses were based on a small number of RCTs. One reason for these mixed findings may be the substantial variation in key features of the interventions, including frequency of messages per day and per week;

length of programs; use of unidirectional versus bidirectional messages; and, to a lesser extent, message content. Another reason may be variation in study design, such as the endpoint used for measuring abstinence (Free et al. 2013; Kong et al. 2014; Scott-Sheldon et al. 2016). This variability has presented a challenge when interpreting findings from specific studies. Nevertheless, the overall evidence supports the efficacy of text-based smoking cessation treatment programs. However, to inform the optimization of treatment, more research is needed to better understand the contributions of various treatment elements.

Web-Based Interventions. Web-based cessation interventions (i.e., cessation interventions delivered via the Internet) have the potential to achieve broad reach, as 88% of American adults report regularly accessing the Internet, including a majority of low-income Americans and members of various racial/ethnic groups (Pew Research Center 2017a). However, evidence on the effectiveness of web-based smoking cessation interventions is mixed. Such interventions date back to the early 2000s, with studies exploring several approaches for delivering treatment and examining user behavior (Etter 2005; Stoddard et al. 2005; Strecher et al. 2005; Cobb and Graham 2006). Initial research findings were inconsistent, and several reports found that websites frequently failed to deliver recommended elements of behavioral treatment for smoking cessation (Bock et al. 2004, 2008; Fiore et al. 2008).

In its 2011 review, the Community Preventive Services Task Force found insufficient evidence to determine the effectiveness of Internet-based interventions in increasing tobacco cessation (The Community Guide 2011a). Later, a study on web-based tobacco cessation interventions by Civljak and colleagues (2013) concluded that some Internet-based interventions, particularly interventions that are interactive and tailored to individuals, can assist in achieving longer term smoking cessation. However, trials that compared Internet interventions with usual care or self-help did not show consistent effects. As web-based interventions have grown more sophisticated, incorporating better website design and improved functionality, the efficacy of such interventions for smoking cessation has improved significantly (Graham et al. 2016). A meta-analysis of web-based cessation interventions found that, although sites with largely static content did not perform significantly better than printed materials in increasing abstinence (RR = 0.83; 95% CI, 0.63–1.10), sites that incorporated interactive elements significantly increased abstinence (RR = 2.10; 95% CI, 1.25–3.52) (Graham et al. 2016). Comparisons of web-based cessation interventions with face-to-face counseling and quitline counseling suggest that these different modalities have the potential to produce similar cessation outcomes (Graham et al. 2016; McCrabb et al. 2019).

In a meta-analysis, McCrabb and colleagues (2019) assessed the effectiveness of 45 RCTs of adult-focused Internet cessation programs, as well as the number and type of behavior change techniques employed in the intervention (Michie et al. 2013), to determine how behavior change techniques impact program effectiveness. The study found short-term effectiveness for all measured cessation outcomes (e.g., prolonged abstinence and 30-day point-prevalence abstinence) (OR = 1.29; 95% CI, 1.12–1.50) and for long-term outcomes (OR = 1.19; 95% CI, 1.06–1.35). Interventions used more behavior change techniques than comparison groups (6.6 vs. 3.1, $p < .0002$). Interventions that included goals and planning, social support, natural consequences, comparison of outcomes, reward and threat, or regulation were significantly associated with increased intervention effectiveness in the short and long terms, when compared with study arms that did not include the domain(s).

The fact that web technologies and web-based cessation interventions continue to evolve, along with the potential reach and customizability of web-based technologies, suggests that future interventions could further improve on current ones. For example, advances in web technologies could improve user experience, enhance content management, better incorporate interactive elements, and better integrate various types of media (e.g., videos and audio). The increasing penetration of smartphones and the broad availability of free Wi-Fi may also allow for access to the web in many nontraditional settings. In response to this changing landscape, many websites are using adaptive design (i.e., changing the format to match the type of device used) and are optimized for use on mobile devices (i.e., are designed to offer easy navigation and high-quality user experience when accessed via such devices). Such sites have the potential to achieve broad population-level reach and widespread engagement with target audiences. Taken as a whole, the available evidence suggests that web interventions with interactive components can increase abstinence to tobacco. As with text-based cessation programs, more research is needed to better understand the specific components that can further enhance the effectiveness of web-based interventions for smoking cessation.

Smartphone Applications. Although most mobile phone interventions have traditionally relied on text messaging platforms (Whittaker et al. 2016), the increasing use of smartphones offers a platform to combine elements of texting and the web to create more interactive and visual interventions (Abroms et al. 2011). In their 2013 review of smartphone apps for smoking cessation, Abroms and colleagues (2013) identified 252 such apps for Apple's iOS and 148 apps for Google's Android operating systems. The review then analyzed nearly 100 of the most popular

cessation apps and their adherence to an index criteria based on the *Clinical Practice Guideline* (Fiore et al. 2008). The average score suggested that overall levels of the apps' adherence to evidence-based cessation approaches were low (Abroms et al. 2011). However, smartphone apps for smoking cessation continue to evolve, both as standalone interventions and in combination with other approaches to cessation interventions. For example, in 2017 FDA granted marketing authorization for a carbon monoxide breath sensor system that can be paired with a smartphone via Bluetooth technology to measure carbon monoxide in exhaled breath and show smokers in real time how their cigarette smoking is impacting their levels of carbon monoxide (FDAnews 2017). The Smokefree.gov initiative now includes two free smoking cessation apps: QuitGuide, which helps smokers understand their smoking patterns and build skills to quit, and quitSTART, which gives smokers tailored tips and motivation to quit. These federally funded apps provide opportunities to learn more about the components that make a smoking cessation smartphone application effective. In particular, more research is needed to assess the efficacy of smartphone applications that combine texting and web-based features.

As reviewed, a variety of technology-mediated approaches exist to deliver behavioral interventions for smoking cessation, and these interventions stand to further increase the reach of cessation interventions. However, technologies are evolving, as are the ways in which people interact with and use technology. Therefore, ongoing research is warranted to ensure that technology-based approaches to cessation remain relevant and meet current user preferences. The elements that make a particular technology effective for cessation may shift as technologies evolve. For example, preferences for texting may shift as that technology becomes integrated into smartphone applications and user interfaces.

In summary, a variety of behavioral and counseling approaches are available through various delivery modalities to motivate and aid successful smoking cessation. However, most smokers still try to quit on their own without using behavioral or counseling interventions. Therefore, innovative, technology-based delivery modalities have the potential to help increase the reach and use of these interventions, but more research is needed to better understand the impact that different delivery modalities have on motivating and sustaining cessation in different subpopulations.

Pharmacologic Treatments

Nicotine is the drug in tobacco that leads to addiction (USDHHS 1988). Epidemiologic and laboratory evidence indicates that nicotine delivered in tobacco products is substantially more addictive than nicotine delivered through current medications (USDHHS 2010). In addition to behavioral and environmental components, constituents other than nicotine in tobacco products and product delivery methods play critical supporting roles in promoting nicotine addiction. A major conclusion from the 2010 Surgeon General's report is, "Sustained use and long-term exposures to tobacco smoke are due to the powerfully addicting effects of tobacco products, which are mediated by diverse actions of nicotine and perhaps other compounds, at multiple types of nicotinic receptors in the brain" (USDHHS 2010, p. 9). The general rationale for having smokers use smoking cessation medications as part of a quit attempt is to reduce physical symptoms resulting from nicotine withdrawal, thus allowing smokers to focus on the behavioral and psychological aspects of quitting smoking (Prochaska and Benowitz 2016). Cessation medications also have the additional benefit of eliminating or greatly reducing the immediate reinforcing effects of nicotine absorbed from tobacco smoke by desensitizing the nicotinic receptors (Prochaska and Benowitz 2016). Although not FDA-approved for smoking cessation, the prescription medications clonidine hydrochloride and nortriptyline hydrochloride are recommended as second-line agents in the U.S. Public Health Service's *Clinical Practice Guideline* (Fiore et al. 2008). Lack of an FDA-approved indication for smoking cessation, as well as some side effects, currently preclude these medications from being classified as first-line agents; therefore, they are not reviewed in this report.

To date, seven FDA-approved, first-line medications have been found to be safe and effective for treating nicotine dependence—although there are some contraindications for use (e.g., recent myocardial infarction for most NRT formulations, seizure disorder for bupropion), as well as insufficient evidence of effectiveness and, in some cases, safety in certain populations (e.g., pregnant women, light smokers, adolescents, and smokeless tobacco users) (Fiore et al. 2008). The seven medications include five nicotine-based medications (the nicotine patch, gum, lozenge, nasal spray, and oral inhaler) and two non-nicotine oral medications, bupropion and varenicline. Table 6.2 offers in-depth information on these seven medications. The nicotine patch, gum, and lozenges are available over the counter; however, a prescription may still be required for insurance coverage of over-the-counter products. The nicotine nasal spray and oral inhaler, bupropion, and varenicline

Table 6.2 Pharmacologic product guide: FDA-approved medications for smoking cessation

	NRT formulations						
	Gum	**Lozenge**	**Transdermal patch**	**Nasal spray**	**Oral inhaler**	**Bupropion SR**	**Varenicline**
Product	**Nicorette,[a] ZONNIC,[b] 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[c]** Rx Metered spray 10 mg/ml aqueous solution	**Nicotrol Inhaler[c]** Rx 10-mg cartridge delivers 4-mg inhaled vapor	**Zyban,[a] Generic** Rx 150-mg sustained-release tablet	**Chantix[c]** Rx 0.5-mg, 1-mg tablet
FDA approval	Nicorette: • 2 mg (Rx) 1984 • 4 mg (Rx) 1991 ZONNIC: • 2 mg (OTC) 1996 • 4 mg (OTC) 1996	Lozenge: • 2 mg (OTC) 2002 • 4 mg (OTC) 2002 Mini-lozenge: • 2 mg (OTC) 2009 • 4 mg (OTC) 2009	• Rx: 1991–1992 • OTC: 1996–2002	Rx: 1996	Rx: 1997	Rx: 1997	Rx: 2006

Table 6.2 Continued

	NRT formulations						
	Gum	**Lozenge**	**Transdermal patch**	**Nasal spray**	**Oral inhaler**	**Bupropion SR**	**Varenicline**
Precautions	• Recent (≤2 weeks) myocardial infarction • Serious underlying arrhythmias • Serious or worsening angina pectoris • Temporomandibular joint disease • Pregnancy[d] and breastfeeding • Adolescents (<18 years of age)	• Recent (≤2 weeks) myocardial infarction • Serious underlying arrhythmias • Serious or worsening angina pectoris • Pregnancy[d] and breastfeeding • Adolescents (<18 years of age)	• Recent (≤2 weeks) myocardial infarction • Serious underlying arrhythmias • Serious or worsening angina pectoris • Pregnancy[d] (Rx formulations, category D) and breastfeeding • Adolescents (<18 years of age)	• 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[d] (category D) and breastfeeding • Adolescents (<18 years of age)	• Recent (≤2 weeks) myocardial infarction • Serious underlying arrhythmias • Serious or worsening angina pectoris • Bronchospastic disease • Pregnancy[d] (category D) and breastfeeding • Adolescents (<18 years of age)	• Concomitant therapy with medications/conditions known to lower the seizure threshold • Hepatic impairment • Pregnancy[d] (category C) and breastfeeding • Adolescents (<18 years of age) • Treatment-emergent neuropsychiatric symptoms[e]: Boxed warning removed December 2016 **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 during preceding 14 days; concurrent use of reversible MAO inhibitors	• Severe renal impairment (dosage adjustment is necessary) • Pregnancy[d] (category C) and breastfeeding • Adolescents (<18 years of age) • Treatment-emergent neuropsychiatric symptoms[e]: Boxed warning removed December 2016

Table 6.2 Continued

	NRT formulations						
	Gum	**Lozenge**	**Transdermal patch**	**Nasal spray**	**Oral inhaler**	**Bupropion SR**	**Varenicline**
Dosing	• 1st cigarette ≤30 minutes after waking: 4 mg • 1st cigarette >30 minutes after waking: 2 mg • Weeks 1–6: 1 piece every 1–2 hours • Weeks 7–9: 1 piece every 2–4 hours • Weeks 10–12: 1 piece every 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 every 1–2 hours • Weeks 7–9: 1 lozenge every 2–4 hours • Weeks 10–12: 1 lozenge every 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 • No food or beverages 15 minutes before or during use • Duration: up to 12 weeks	• >10 cigarettes/day: – 21 mg/day for 4–6 weeks – 14 mg/day for 2 weeks – 7 mg/day for 2 weeks • ≤10 cigarettes/day: – 14 mg/day for 6 weeks – 7 mg/day for 2 weeks • Rotate patch application site daily; do not apply a new patch to the same skin site for at least 1 week • 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 (1 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 every 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 • No food or beverages 15 minutes before or during use • Duration: 3–6 months	• 150 mg po every morning for 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 every morning • 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 • May initiate up to 35 days before target quit date • May reduce smoking over a 12-week period of treatment prior to quitting and continue treatment for an additional 12 weeks

Table 6.2 Continued

	NRT formulations						
	Gum	**Lozenge**	**Transdermal patch**	**Nasal spray**	**Oral inhaler**	**Bupropion SR**	**Varenicline**
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 adherence 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 adherence 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 adherence problems • Offers a different mechanism of action for patients who have failed other agents

Table 6.2 Continued

	NRT formulations						
	Gum	**Lozenge**	**Transdermal patch**	**Nasal spray**	**Oral inhaler**	**Bupropion SR**	**Varenicline**
Disadvantages	• Need for frequent dosing can compromise adherence • Might be problematic for patients with significant dental work • Proper chewing technique is necessary for effectiveness and to minimize adverse effects • Gum chewing might not be acceptable or desirable for some patients	• Need for frequent dosing can compromise adherence • 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 adherence • 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 adherence • 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[e] (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[e] (see PRECAUTIONS)
Cost/day[f]	2 mg or 4 mg: $1.90–$3.70 (9 pieces)	2 mg or 4 mg: $3.36–$3.78 (9 pieces)	$1.52–$3.48 (1 patch)	$6.67 (8 doses)	$11.35 (6 cartridges)	$2.58–$7.87 (2 tablets)	$11.86 (2 tablets)

Source: Reproduced with permission from Rx for Change: Clinician-Assisted Tobacco Cessation program. The Regents of the University of California. Copyright © 1999–2017.

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

Drug Administration; **MAO =** monoamine oxidase; **mg =** milligram; **ml =** milliliter; **NRT =** nicotine replacement therapy; **Rx =** prescription product; **SR =** sustained release.

[a]Marketed by GlaxoSmithKline.

[b]Marketed by Niconovum USA (a subsidiary of Reynolds American, Inc.).

[c]Marketed by Pfizer.

[d]The *Clinical Practice Guideline* (Fiore et al. 2008) 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.

[e]In July 2009, 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, or 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. Based on results of a mandated clinical trial, FDA removed this boxed warning in December 2016.

[f]Wholesale acquisition cost from Red Book Online. Thomson Reuters, December 2016.

are available by prescription only (FDA 2017). The use of FDA-approved cessation medications generally doubles quit rates relative to placebo, but results vary somewhat across products (ORs range from 1.82 for bupropion and 1.84 for NRTs to 2.88 for varenicline) (Cahill et al. 2013). Certain combinations of NRTs have been shown to further increase quit rates, including using the transdermal patch with any of the other forms of NRT (nicotine gum, lozenges, nasal spray, or inhalers).

The seven cessation medications vary in their mechanisms of action and modes of delivery. Each of the seven FDA-approved, first-line cessation medications is described below. In addition to a review of these medications and combination pharmacotherapy, this section also reviews evidence around longer term and pre-quit use of NRT.

Nicotine Replacement Therapy

NRT delivers nicotine to address physical nicotine dependence without exposing the person who is trying to quit to the toxic constituents generated by combustion or other additives. NRT delivers plasma nicotine concentrations that are lower than those in conventional cigarettes and that rise more slowly, thereby reducing the behaviorally reinforcing effect of smoking. Five forms of NRT are available in the United States: the transdermal nicotine patch, nicotine gum, nicotine lozenge, nicotine nasal spray, and nicotine inhaler; the latter two products are available only by prescription (Table 6.2).

The five forms of NRT are similar in efficacy. Lindson and colleagues (2019) observed similar quit rates among persons who used a fast-acting form of NRT, such as gum or lozenge. Similarly, a meta-analysis of 117 clinical trials found that the RR for 6 or more months of abstinence for any form of NRT versus controls was 1.60 (95% CI, 1.53–1.68), with an RR of 1.49 (95% CI, 1.40–1.60) for nicotine gum, 1.64 (95% CI, 1.52–1.78) for the nicotine patch, 1.95 (95% CI, 1.61–2.36) for nicotine lozenges, 2.48 (95% CI, 1.24–4.94) for the nasal spray, and 1.90 (95% CI, 1.36–2.67) for the inhaler (Stead et al. 2012). An older randomized study found that medication adherence was lowest for the nasal spray and inhaler, moderate for the gum, and greatest for the patch; the study did not include the lozenge (Hajek et al. 1999).

NRT is sold in different dosages (Table 6.2). Some healthcare providers recommend higher dosages of NRT or combinations of two forms of NRT for more dependent smokers, with dependence being defined by the number of cigarettes smoked per day or the time to first cigarette after awakening (Shiffman et al. 2013). Lindson and colleagues (2019) found that, compared with a 2-milligram (mg) dose of nicotine gum, using a 4-mg dose increases smokers' chances of successfully stopping smoking. The review also found that higher dose nicotine patches appeared to be associated with higher rates of abstinence than lower dose patches, but this finding was less certain due to the quality of the evidence. Nicotine patches, which are applied in the morning, deliver nicotine slowly over 16–24 hours to achieve a continuous level of nicotine in the blood (Wadgave and Nagesh 2016). Several nicotine patches are marketed, some of which have tapering dosages (i.e., gradually lowering the dosage over time). The 24-hour patch can be removed at bedtime if it causes side effects, such as insomnia or bothersome dreams. Oral NRT formulations include the nicotine gum, lozenge, and inhaler (Table 6.2). The nicotine inhaler is a cigarette-like plastic device that delivers nicotine to the throat and upper airway. Nicotine in gum and lozenges is primarily absorbed in oral mucosa, with a rapid absorption of the nicotine when used properly (Wadgave and Nagesh 2016). However, these oral medications are "short acting" and result in relatively low levels of nicotine in the blood, initially requiring use every 1–2 hours to suppress withdrawal symptoms.

The nicotine nasal spray is administered with one spray per nostril; each spray contains 0.5 mg of nicotine (Wadgave and Nagesh 2016). The medication can be used every 20–60 minutes, with a maximum of 5 doses per hour or 40 doses per day. Dosage is based on the number of cigarettes smoked per day before starting the medication (Pfizer 2010). Of all NRT products, the nasal spray delivers nicotine most rapidly, but inhaling cigarette smoke still delivers nicotine faster (Wadgave and Nagesh 2016). During initial treatment, irritation of the nose commonly produces burning, sneezing, and watery eyes; users generally develop tolerance to these effects in 1–2 days (Pfizer 2010). Other side effects are minor and may include cough or headache (Table 6.2); however, NRT use, including long-term use, has been generally found to be safe for most adults (Fiore et al. 2008). Some users may opt to start the nasal spray a few days before their quit date to work through the initial nasal irritation (Wadgave and Nagesh 2016).

Persons with higher levels of nicotine dependence are at increased risk for difficulty quitting, abstinence distress, and relapse (Piper et al. 2008). NRT has been shown to be particularly effective in highly nicotine-dependent smokers (e.g., Stead et al. 2012) relative to smokers with lower levels of nicotine dependence and in trials of smoking cessation pharmacotherapy in which the majority of participants are at least moderately dependent on nicotine. The evidence regarding the efficacy and effectiveness of smoking cessation pharmacotherapies focuses mostly on highly dependent daily smokers (e.g., Stead et al. 2012). Lindson and colleagues (2019) note that there is little evidence on the role of NRT for persons smoking fewer than 15 cigarettes a day. Evidence supports the efficacy

of tailoring the dose of NRT to markers of dependence (e.g., time to first cigarette after waking) (e.g., Baker et al. 2007), given that more highly nicotine-dependent smokers benefit more from higher doses of NRT than less nicotine-dependent smokers (e.g., Stead et al. 2012).

Bupropion

Bupropion is a prescription medication that blocks reuptake of dopamine and, to a lesser extent, norepinephrine. It also has some nicotine receptor-blocking activity (Slemmer et al. 2000). Thus, bupropion increases levels of dopamine and norepinephrine in the brain, simulating nicotine's effects on these neurotransmitters. In studies with rats, bupropion in low doses was found to block nicotine's rewarding effects, as assessed by the intracranial self-stimulation threshold, and to reverse the negative affective actions of nicotine withdrawal (Cryan et al. 2003). For humans, bupropion's blocking of nicotine receptors could contribute to lessened reinforcement from cigarettes in the event of a lapse or relapse during a quit attempt (Prochaska and Benowitz 2016). Bupropion was originally marketed and is still widely used as an antidepressant. However, the sustained-release formulation of bupropion was found to help smokers quit independent of whether smokers had a history of depression (Hurt et al. 1997). Bupropion is initiated 1 week before the scheduled quit date to allow time for the smoker to reach steady state therapeutic levels (Corelli and Hudmon 2002). In the sustained release formulation, bupropion is started at 150 mg/day. If the initial dose is adequately tolerated, it is increased on day 4 to 300 mg/day (the recommended maximum daily dose), given as two 150-mg doses taken at least 8 hours apart. If the 300-mg dose is not well tolerated, the dose is reduced to 150 mg/day, which is still efficacious (Swan et al. 2003).

In a meta-analysis of 65 RCTs of bupropion for smoking cessation, Hughes and colleagues (2014) concluded that bupropion alone significantly increased long-term cessation of 6 months or greater (RR = 1.62; 95% CI, 1.49–1.76) relative to placebo; this level of efficacy was comparable to NRT (RR = 0.96; 95% CI, 0.85–1.09) and lower than varenicline (RR = 0.68; 95% CI, 0.56–0.83). In an RCT conducted in 2001, participants who had quit successfully by week 7 of the trial were randomized to receive bupropion or placebo for 1 year to prevent relapse (Hays et al. 2001). Bupropion was found to be safe and effective and significantly better than placebo at delaying relapse (median time to relapse 156 days vs. 65 days, p = 0.021). Bupropion also resulted in less weight gain among participants. However, 1 year after treatment, quit rates did not differ between the bupropion and placebo groups (41.6% vs. 40.0%) (Hays et al. 2001).

FDA continues to evaluate the safety and effectiveness of cessation medications after they enter the marketplace. Following the introduction of bupropion, the agency received and assessed case reports of serious changes in mood and behaviors in patients taking bupropion. As a result, in 2009 the agency required new boxed warnings for bupropion's product labeling (FDA 2018a). At the time, FDA also required the manufacturer to conduct a large clinical trial to evaluate the side effects. Based on FDA review of the findings from that clinical trial (Anthenelli et al. 2016), which is discussed further in the section on varenicline, the agency determined the risk of serious side effects on mood, behavior, or thinking was lower than previously suspected and determined the product labeling should be revised accordingly. FDA noted that while these mental health side effects were present, especially in those with current or mental illness, they were rare (Anthenelli et al. 2016). Additionally, side effects were rarely serious enough to result in hospitalization, and the occurrence of side effects was no greater for persons randomized to bupropion compared with those randomized to nicotine patch or placebo.

Varenicline

Varenicline is a prescription medicine marketed specifically for smoking cessation. The drug is a partial agonist of the α4β2 nicotinic acetylcholine receptor subtype, 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 about 50% that of nicotine, relieving the symptoms of nicotine withdrawal, including craving, and at the same time blocking the effects of nicotine on the receptor, thereby diminishing the rewarding effects of cigarettes (Aubin et al. 2014). Thus, the desire to smoke and, in the event of a lapse or relapse, the likelihood of continued smoking are reduced. As with bupropion, varenicline is initiated 1 week before the quit date (Pfizer 2018). The dose of varenicline starts at 0.5 mg/day and then increases on day 4 to 0.5 mg twice per day and on day 7 to 1 mg twice per day (the recommended maximum daily dose). This dosing regimen allows for gradual titration of the dose to minimize treatment-related nausea and insomnia (Pfizer 2018). The dosage can be lowered temporarily or permanently for patients experiencing intolerable, treatment-associated adverse effects (Pfizer 2018). Notably, smokers taking varenicline often reduce their smoking even before their target quit day (Ashare et al. 2012; Ebbert et al. 2015; Nakamura et al. 2017).

The largest clinical trial to date of approved tobacco cessation medications, the Evaluating Adverse Events

in a Global Smoking Cessation Study (EAGLES), which was primarily conducted to examine adverse effects, found that (a) varenicline was more effective for quitting smoking than placebo, the nicotine patch, or bupropion and (b) bupropion and the nicotine patch were more effective than placebo and were comparable to each other in efficacy (Anthenelli et al. 2016). This triple-blinded randomized trial enrolled 8,144 daily smokers, about half of whom had a stably treated but active psychotic disorder or a history of a psychiatric disorder. In the nonpsychiatric cohort, continuous abstinence rates (for weeks 9–24) at the 6-month follow-up were 25.5% for varenicline, 18.8% for bupropion, 18.5% for nicotine patch, and 10.5% for placebo. In the psychiatric cohort, continuous abstinence rates at the 6-month follow-up were 18.3% for varenicline, 13.7% for bupropion, 13.0% for nicotine patch, and 8.3% for placebo (Anthenelli et al. 2016).

Taking varenicline for 6 months has been shown to be effective in preventing relapse, including among smokers with schizophrenia (Evins et al. 2014). Varenicline is FDA-approved for extended (up to 6 months) treatment (Tonstad et al. 2006). Common side effects include nausea, vomiting, and insomnia (Cahill et al. 2013). Neuropsychiatric side effects—including depression, psychosis, aggression, and suicidality—have been reported to FDA, and the agency required that boxed warning labels for both varenicline and bupropion note those possible side effects (FDA 2018a). In the EAGLES trial, the primary endpoint was neuropsychiatric safety; the frequency of moderate to severe neuropsychiatric events was less than 3% in the nonpsychiatric cohort and less than 7% in the psychiatric cohort, with no significant difference by medication condition (Anthenelli et al. 2016). Notably, the findings in EAGLES were generally consistent with prior clinical trials and observational data. In previous clinical trials of varenicline conducted among smokers with depression and schizophrenia, neuropsychiatric side effects had not been observed at higher levels relative to those observed in control groups (Williams et al. 2012; Anthenelli et al. 2013; Cinciripini et al. 2013); this was also the case in large clinical cohort studies (Thomas et al. 2013; Kotz et al. 2015). Importantly, smoking itself has been found to be associated with mood disturbance, including suicidality (Oquendo et al. 2004; Li et al. 2012). Nicotine withdrawal experienced during quitting attempts is also characterized by disturbances in mood—including agitation, depressive symptoms, and anxiety—and can cause sleep disturbance with associated mood effects (Prochaska and Benowitz 2019).

With regard to the cardiovascular safety of varenicline, an initial meta-analysis raised concerns, showing a small but significant RR for serious adverse cardiovascular events compared with placebo (Singh et al. 2011). However, a second, larger meta-analysis found the absolute risk to be small and statistically nonsignificant (Prochaska and Hilton 2012). In addition, a 52-week RCT that examined cardiovascular safety in the EAGLES cohort found no significant difference relative to placebo for varenicline, bupropion, or nicotine patch on the time to occurrence of a major adverse cardiovascular event (Benowitz et al. 2018). The three time points of interest were during the medication treatment period, 30 days post-medication use, and at 52 weeks (which marked the end of the study). At all three time points, the hazard ratio for major cardiovascular events associated with varenicline was less than 0.50, which was statistically nonsignificant and suggests a reduced risk compared with placebo (Benowitz et al. 2018). A biological mechanism by which varenicline could produce cardiovascular toxicity has not been identified.

Additional Approaches to Medication Therapy

The seven FDA-approved cessation medications have been evaluated in multiple research protocols, with many of the study variations aimed at improving our understanding of the reach and short- and long-term efficacy of treatment under conditions other than the labeled FDA-approved use. These approaches have included combination pharmacotherapy (i.e., using more than one form of medication at a time), pre-loading (starting the medication before the quit date), gradual reduction (using medication as part of an attempt to gradually reduce consumption of tobacco products as a prelude to quitting, instead of quitting abruptly), extended treatment (longer use of the medication aimed at preventing relapse), and precision medicine (tailoring the medication to differences in drug metabolism). The following sections discuss each of these approaches in detail.

Combination Pharmacotherapy

Combination pharmacotherapy combines the use of cessation drugs that have different mechanisms and/or different pharmacokinetic profiles. Dual regimens of NRT have generally demonstrated superior efficacy compared with a single form of NRT (Ebbert et al. 2010; Tulloch et al. 2016; Windle et al. 2016). Dual NRT regimens combine the use of a transdermal patch, which acts slow and provides a base level of nicotine, with any of the other forms of NRT (nicotine gum, lozenges, nasal spray, or inhalers)—all of which act faster and can be used to offset acute episodes of craving or other relapse triggers. Based on evidence in their review of 11,356 participants across 14 studies, Lindson and colleagues (2019) concluded that combining fast-acting forms of NRT with the nicotine patch results in

long-term quit rates that are higher than those observed among persons who use a single form of NRT (RR = 1.25; 95% CI, 1.15–1.36,). Similarly, in a meta-analysis of nine trials, combining the nicotine patch with nicotine gum, lozenges, inhalers, or nasal spray was shown to be more effective than using individual NRT products (RR = 1.34; 95% CI, 1.18–1.51) (Stead et al. 2012). A different meta-analysis found that combination NRT had an effect comparable to that of varenicline (OR = 1.06; 95% CI, 0.75–1.48) (Cahill et al. 2013).

Emerging evidence also suggests that combining varenicline with bupropion or NRT may be more effective than taking varenicline alone, particularly among heavier smokers (Koegelenberg et al. 2014; Chang et al. 2015). Two trials examined the combined use of varenicline and the nicotine patch. One trial (N = 435) compared the nicotine patch with a placebo patch, both administered 2 weeks before the target quit date, followed by the addition of varenicline for 1 week before the target quit date; the nicotine patch and varenicline were continued for 12 additional weeks. Use of the nicotine patch plus varenicline resulted in significantly greater quit rates than use of the placebo patch plus varenicline at 12 weeks (55.4% vs. 40.9%, p = 0.007) and 24 weeks (49% vs. 36.2%, p = 0.004) (Koegelenberg et al. 2014). The other trial, which was smaller and likely underpowered (N = 117), tested varenicline alone 1 week before the target quit date and then with the nicotine patch added at the quit date. The trial found statistically nonsignificant differences at 12 weeks (38% vs. 29% quit, p = 0.14) (Hajek et al. 2013b). The mechanism of benefit from combining varenicline and NRT is unclear: varenicline may not fully block α4β2 receptors or, compared with varenicline alone, the nicotine from NRT may affect additional nicotinic receptors that contribute to the addictive effects of nicotine. The combination was well tolerated by users in both studies, with vivid dreams being the most common side effect (Hajek et al. 2013b; Koegelenberg et al. 2014).

In addition, combination therapy with bupropion and NRT has been shown to produce better outcomes than either medication used by itself (Ebbert et al. 2010). In a meta-analysis of eight trials, use of bupropion plus the nicotine patch was more effective than use of bupropion alone (RR = 1.24; 95% CI, 1.06–1.45) (Stead et al. 2012), but a different meta-analysis that reviewed 12 studies in which bupropion was added to NRT reported insufficient evidence of long-term benefit (at least 6 months) over NRT alone (RR = 1.19; 95% CI, 0.94–1.51) (Hughes et al. 2014). One randomized trial compared the use of bupropion plus varenicline versus the use of varenicline alone for 12 weeks (Ebbert et al. 2014); the combination significantly increased continuous abstinence through 12 weeks (53.0% vs. 43.2%) and through 26 weeks (36.6% vs. 27.6%) but not through 52 weeks (30.9% vs. 24.5%). In a different randomized trial, use of bupropion plus varenicline was associated with greater depressive symptoms over the first 2 weeks, but no differences in depressive symptoms were observed by week 4 (Hong et al. 2015).

Pre-Loading Medication

Pre-loading with NRT, or providing NRT in advance of a quit attempt, has been tested to see whether it increases abstinence rates. The underlying mechanism would be to saturate and/or desensitize nicotinic cholinergic receptors to decrease the reward from nicotine delivered by smoking. Lindson and colleagues (2019) found with a moderate level of certainty that using NRT before quitting, instead of using it from the quit date, may improve quit rates, but noted that more research is needed to confirm this finding. In a meta-analysis of four studies, pre-loading with the nicotine patch doubled the odds of quitting at 6 weeks (OR = 1.96; 95% CI, 1.31–2.93) and at 6 months (OR = 2.17; 95% CI, 1.46–3.22) (Shiffman and Ferguson 2008). In contrast, a large pragmatic randomized trial in New Zealand in which smokers called a quitline found no boost in abstinence rates when NRT was preloaded, but such pre-loading was determined to be safe, acceptable, and easy to implement (Bullen et al. 2010). A meta-analysis of eight trials by Stead and colleagues (2012) found a moderate but statistically nonsignificant effect of pre-loading NRT on abstinence, but effects were significant when restricted to the six trials that tested preloading with a nicotine patch. These findings suggest that pre-loading in advance of a quit attempt, especially with the nicotine patch, can increase abstinence rates.

Gradual Reduction

Gradually reducing the number of cigarettes smoked per day leading up to a quit attempt, rather than quitting all at once, may be preferred by smokers who are unwilling to quit abruptly (Prochaska and Benowitz 2016). Nationally representative data from the 2010–2011 Tobacco Use Supplement to the Current Population Survey suggest that more than 40% of adult smokers in the United States who had tried to quit smoking in the past year reported gradually cutting down on their cigarette use as a cessation strategy (Schauer et al. 2015b). A meta-analysis of 10 trials evaluating gradual smoking reduction relative to quitting abruptly found comparable efficacy, with no difference by treatment approach (e.g., self-help, behavioral, pharmacologic) (Lindson-Hawley et al. 2012).

In a different placebo-controlled randomized trial of varenicline, Ebbert and colleagues (2015) studied smokers who were unwilling to quit in the next month but who were willing to reduce smoking immediately and to make a quit

attempt within 3 months. Participants received medication or placebo for 12 weeks before the quit attempt and were advised to reduce the number of cigarettes they smoked daily by 50% at 4 weeks, by 75% or more at 8 weeks, and then to quit completely at 12 weeks. Varenicline or placebo was continued for an additional 12 weeks after the quit date. Quit rates increased approximately threefold in the varenicline versus placebo-treated group from week 21 to 24 (37.8% vs. 12.5%) and from week 21 to 52 (27.0% vs. 9.9%). Pretreatment with varenicline may reduce craving for cigarettes and extinguish the rewarding effects of cigarettes, thus making it easier to quit. Importantly, gradual reduction of cigarette consumption should be used only as an interim strategy on the path to completely quitting smoking, since in the absence of quitting, reduction of cigarette consumption alone does not substantially reduce health risks (Stead and Lancaster 2007; USDHHS 2014, 2016; Lindson-Hawley et al. 2016).

Extended Treatment

Currently, NRT package inserts indicate that these products should be used for up to 8–12 weeks, depending on the type of product. However, studies have explored using cessation medications for much longer periods (up to 1 year) in an attempt to prevent relapse (Prochaska and Benowitz 2016). Similar to chronic disease management approaches, this approach underscores the idea that smoking is a chronic, relapsing disease that warrants ongoing treatment.

The literature is insufficient, however, to determine whether extended NRT is more efficacious than standard-duration NRT (Carpenter et al. 2013). For example, an RCT with older smokers found that extended cessation treatment—consisting of NRT gum and bupropion for 12 weeks combined with counseling (group and then individual) extending to 1 year—resulted in abstinence rates exceeding 50% at the 2-year follow-up (Hall et al. 2009). Notably, the study showed that extending NRT to 52 weeks (with no bupropion) did not increase abstinence beyond what was achieved with 12 weeks of NRT gum combined with bupropion. A trial that assessed point-prevalence abstinence in smokers randomized to receive 12 weeks of behavioral counseling plus 8, 24, or 52 weeks of nicotine patches found that, after 24 weeks of treatment, 21.7% of participants in the 8-week arm were abstinent compared with 27.2% ($p = 0.17$) in the 24- and 52-week arms (Schnoll et al. 2015). Participants in the 52-week arm did not report greater abstinence rates than those in the 24-week arm (20.3% vs. 23.8%, $p = 0.57$), suggesting that using NRT beyond 24 weeks may not confer added benefit.

In contrast, varenicline dosed over 6 months has been shown to be effective in preventing relapse (Tonstad et al. 2006; Evins et al. 2014). Currently, FDA labeling recommends 12 weeks of therapy, but treatment can be extended another 12 weeks if needed. However, patients are encouraged to stop sooner if they feel ready. Livingstone-Banks and colleagues (2019) found that with a moderate level of certainty, because of unexplained statistical heterogeneity, extended treatment with varenicline helped to prevent relapse. In an RCT, Joseph and colleagues (2011) tested a chronic care model for smoking cessation. Participants in the extended care arm received counseling by telephone and NRT for 1 year, and participants in the usual care arm received counseling and NRT for 8 weeks. At 18 months, the proportion of subjects who were abstinent for 6 months or longer did not differ significantly by condition: 30% for extended treatment and 24% ($p = 0.13$) for usual care. Finally, in a meta-analysis of extended interventions for preventing relapse, Hajek and colleagues (2013c) reported insufficient evidence to support either extended cessation counseling or extended pharmacotherapies (NRT, varenicline, or bupropion). More research is warranted to continue to assess extended behavioral and/or pharmacological treatments for smoking cessation.

Precision Medicine

Precision medicine is an emerging approach to smoking cessation treatment (Prochaska and Benowitz 2016). The goal of precision medicine is to enable clinicians to quickly, efficiently, and accurately predict the most appropriate course of action for a patient based on genetic and lifestyle factors (Aronson and Rehm 2015). Cessation medications are effective in increasing abstinence, but with long-term quit rates rarely surpassing 30% (Perkins and Scott 2008), there is great interest in identifying differences in response to medications to inform personalized treatment, which could potentially increase quit rates. Smokers differ from each other in many ways. One is the rate at which they metabolize nicotine, which has been studied as a possible basis for selecting medications (Prochaska and Benowitz 2016). On average, a person who metabolizes nicotine rapidly smokes more heavily and appears to be more dependent on nicotine than a person who does not metabolize nicotine rapidly (Malaiyandi et al. 2005). CYP2A6, a liver enzyme, is the chief metabolizer of nicotine; CYP2A6 also metabolizes cotinine, the primary metabolite of nicotine, which is reduced to 3'-hydroxycotinine (USDHHS 2010).

The cotinine/3'-hydroxycotinine ratio, also termed the nicotine metabolite ratio, can be measured in urine, blood, or plasma as a biomarker for the rate at which a smoker metabolizes nicotine (USDHHS 2010). In retrospective studies, slow metabolizers received no incremental benefit from bupropion, but they responded well to the nicotine patch, while normal metabolizers responded better to bupropion than to the patch (Prochaska and

Benowitz 2016). In a clinical trial that stratified participants by slow or normal nicotine metabolite ratio and compared treatment with placebo, the nicotine patch, or varenicline (Lerman et al. 2015), slow metabolizers experienced more side effects from varenicline and evidenced no benefit in quitting when taking varenicline relative to using the nicotine patch (OR = 1.13, p = 0.56), but normal metabolizers had greater success with varenicline relative to the patch (OR = 2.17, p = 0.001). Thus, use of the nicotine metabolite ratio shows promise in aiding in treatment selection, given that the nicotine patch may be as effective as varenicline for slow metabolizers of nicotine, while costing less and exposing them to fewer side effects. However, use of the nicotine metabolite ratio in clinical practice is not yet possible because there is no widely available clinical test for this measure.

Other precision medicine approaches are under investigation, including pharmacogenomic variation and variance in both behavioral and pharmacologic responses between men and women and among persons with certain mental health conditions. For example, pharmacogenomic evidence suggests that variants in gene regions that impact dopaminergic neurotransmission, nicotine receptor expression, and nicotine and other drug metabolism may predict response to various cessation pharmacotherapies (Chenoweth and Tyndale 2017). Some evidence suggests that (a) the superior efficacy of varenicline relative to bupropion and NRT may be greater among women than among men and (b) certain mental health conditions may also alter responses to behavioral and pharmacological treatments (Luo et al. 2015; McKee et al. 2016; Piper et al. 2017; Smith et al. 2017).

Real-World Effectiveness of Cessation Medications

In RCTs, the provision of cessation medications has consistently increased successful quitting, particularly among heavy cigarette smokers. Several studies have reported similar findings in real-world settings (West and Zhou 2007; Kasza et al. 2013). For example, the International Tobacco Control Four Country Survey found increased 6-month continuous abstinence from smoking among smokers who reported using varenicline, bupropion, and the nicotine patch but not among those who reported using oral NRTs (Kasza et al. 2013). However, some population-based studies have found that smokers who used NRT (Pierce and Gilpin 2002), and in some cases bupropion and varenicline (Leas et al. 2018), reported similar or lower rates of quit success compared with those not using these medications. These studies have raised questions about the real-world effectiveness of these medications, and reviews have highlighted conflicting results in the scientific literature (Hughes et al. 2011; Pierce et al. 2012).

Leas and colleagues (2018), using nationally representative data from the 2002–2003 and 2010–2011 waves of the Tobacco Use Supplement to the Current Population Survey, assessed the effectiveness of cessation medications among adults who smoked at baseline and attempted to quit prior to 1 year of follow-up. The study's authors used propensity score matching to control for 12 potential confounders, including smoking intensity, nicotine dependence, previous quit history, and self-efficacy to quit. The study did not find evidence that the use of varenicline, bupropion, or NRT increases the likelihood of smokers being quit for 30 or more days at 1-year follow-up. Similarly, a study by Kotz and colleagues (2014) conducted in the United Kingdom using cross-sectional data from aggregated monthly waves of the Smoking Toolkit Study, a household survey, found that smokers who purchased NRT over the counter with no behavioral support had similar odds of quitting as smokers who tried to quit with no quitting aids.

Several other studies have also found no effects of NRT on cessation. For example, a randomized study conducted in New Zealand among 1,410 adult smokers who called the national quitline, found that subjects who were randomized to receive a free 1-week supply of their choice of NRT, followed by a voucher for a free 8-week supply of that product, did not have higher rates of abstinence at 7 days or 6 months compared with those receiving usual care from the quitline (Walker et al. 2011). Similarly, a prospective cohort study of a probability sample of 787 adult smokers from Massachusetts who had quit smoking found that those who quit using NRT were just as likely to relapse over the following year as were those who had quit without using medications (Alpert et al. 2013). Finally, in a parallel group, factorial design RCT of 2,591 smokers 16 years of age and older in England, Ferguson and colleagues (2012) found, contrary to findings from multiple U.S. randomized trials in quitline settings (An et al. 2006; Hollis et al. 2007; Smith et al. 2013), that adding NRT to proactive counseling offered through a quitline had no additional effect on abstinence.

Several possible explanations exist for these contradictory findings. Some of the studies that have found limited impact of the real-world effectiveness of cessation medications have specific limitations. For example, Alpert and colleagues (2013) measured whether prior use of NRT had a residual benefit of preventing relapse, which differs from assessing whether use of NRT increases cessation success. McAfee (2012) noted several potential issues that could have impacted the findings of Ferguson and colleagues (2012), including (a) many differences and limitations in how NRT was provided in the Ferguson

trial compared with U.S. trials that found a positive effect (e.g., medications were provided through a voucher that had to be redeemed by telephone, adding an extra step for participants) and (b) caveats for interpreting the results. For example, in a large randomized trial with methods similar to those used for the Ferguson trial, which involved more than 4,600 U.S. adults who called a quitline, overall receipt of study medications was low (43%) compared with the 90% rate at initial intake and the 80% rate of medication receipt at 5 weeks. The trial also included youth smokers (16–18 years of age), for whom NRT has not been found to be effective (Hollis et al. 2007).

More broadly, most real-world studies have been nonrandomized cohort studies that have examined the association between self-selected use of cessation medications and quitting success. Without randomization, the study design cannot exclude the potential for residual confounding, even with multivariable adjustment. Researchers have suggested that conclusions about the real-world effectiveness of cessation medications may be the result of systematic biases that affect the outcomes of cross-sectional surveys (Borland et al. 2012). For example, participants may be more likely to recall failed medication-assisted quit attempts than failed unassisted quit attempts. Furthermore, smokers who choose to use medications as part of a quit attempt may smoke more heavily and be more addicted, and therefore may be less likely to succeed, than smokers who try to quit without medications. Either of these factors could lead to an overrepresentation of failed quit attempts among smokers using medications, even if these medications actually conferred benefits (Borland et al. 2012). However, Leas and colleagues (2018) used propensity score matching on 12 potential confounders, including nicotine dependence and smoking intensity, and concluded that confounding cannot explain the lack of effectiveness of cessation medications in increasing long-term cessation in real-world settings.

Another potential factor that could contribute to the findings of studies suggesting a lack of real-world effectiveness for cessation medications is the important role that behavioral support can play in complementing medication use to maximize cessation, in part by ensuring that smokers use cessation medications appropriately and effectively (Fiore et al. 2008; USPSTF 2015). While cessation medication and counseling are each effective alone, they are more effective when combined (Fiore et al. 2008; USPSTF 2015). In particular, providing counseling or decision support to help ensure that consumers use the appropriate medication correctly at the correct dose and for a recommended duration, could increase the effectiveness of over-the-counter (nonprescription) cessation medications in the general population. This type of support is typically present in RCTs but is often absent in real-world settings, which could explain why many therapies, including cessation medications, might perform more poorly in the real world than in clinical trials. The study by Leas and colleagues (2018) supports this hypothesis. Using data from the Tobacco Use Supplement to the Current Population Survey, they found that only 32 of 186 adult smokers who used bupropion and only 9 of 118 smokers who used varenicline as part of a quit attempt, reported receiving any form of behavioral counseling. Similarly, Kotz and colleagues (2014) found that smokers who purchased NRT over the counter with no behavioral support had similar odds of quitting as smokers who tried to quit with no quitting aids—also highlighting the important role that behavioral support can play in enhancing the effectiveness of cessation medications. Further support for this explanation includes the markedly shorter duration of use of medications in real-world settings compared with study settings, averaging 1–2 weeks rather than the recommended 8–12 weeks (Pierce and Gilpin 2002; Zhang et al. 2015).

In the absence of behavioral support, tobacco users in the general population may not receive adequate information or education about how to use cessation medications and what to expect from them (as described previously), or they may face barriers to accessing information, including such financial barriers as lack of insurance, copays, and cost-prohibitive prices (Pacek et al. 2018). Smokers may also have misconceptions about the safety of using a medication that contains nicotine (Pierce and Gilpin 2002; Zhang et al. 2015). Furthermore, many tobacco users may not be aware of changes to the labeling of over-the-counter NRT products introduced in 2013, indicating that it is safe to use NRT (a) longer than the recommended period, in consultation with a physician if necessary to avoid relapsing, and (b) concurrently with smoking (e.g., following a lapse) or with another NRT product (*Federal Register* 2013; FDA 2013). These and other misconceptions about smoking cessation medications could lead people to use them ineffectively, for example, by stopping use prematurely or by not using enough of the medication.

Some researchers who have questioned the real-world effectiveness of cessation medications have suggested that an excessive emphasis on the role of medications in helping smokers quit may overmedicalize and mystify smoking cessation. They also suggest that such an approach may discourage smokers from quitting without help (i.e., quitting "cold turkey"), which remains the predominant way that smokers try to quit—and, as a result, the predominant way that smokers succeed in quitting—in the United States (Pierce et al. 2012). In addition, some evidence suggests that direct-to-consumer advertisements for smoking cessation medications may give smokers a false sense of security, suggesting that using these medications will make quitting easy (Frosch et al. 2007).

Combination Treatment—Behavioral Therapy and Pharmacotherapy

Although behavioral therapy and pharmacotherapy are each effective interventions for increasing quit rates when used alone, combining them is more effective (Fiore et al. 2008) and represents the "gold standard" in smoking cessation treatment. Use of cessation medications is more effective when accompanied by counseling, and use of cessation counseling is more effective when accompanied by medications (Fiore et al. 2008). USPSTF (2015) recommends combining medications with multisession, intensive group or individual counseling to achieve the highest quit rates; using medication to target physical addiction; and employing behavioral therapy and counseling to target psychological and behavioral addiction. A meta-analysis by Stead and colleagues (2016) found that behavioral therapy increased the efficacy of pharmacotherapy (RR = 1.27; 95% CI, 1.02–1.58), probably in part because it allows healthcare professionals who are delivering the behavioral therapy to instruct smokers on using cessation medications properly, managing side effects from the medications, understanding and managing cravings and withdrawal symptoms, and simultaneously addressing the behavioral aspects of tobacco dependence. Similarly, in the Smoking Toolkit study from the United Kingdom, Kotz and colleagues (2014) found that, compared with smokers who used neither cessation medications nor behavioral support, those who used prescription cessation medications combined with behavioral support from specialists had 3.25 times the adjusted odds (95% CI, 2.05–5.15) of remaining abstinent up to the time of the survey; those who used prescription cessation medications combined with brief advice to quit had 1.61 times the adjusted odds (95% CI, 1.33–1.94) of remaining abstinent; and those who used NRT purchased over the counter had 0.96 times the odds (95% CI, 0.81–1.13) of remaining abstinent. The authors concluded that smokers who use a combination of behavioral support and cessation medications in their quit attempts have almost three times the odds of successfully quitting than smokers who use neither.

Notably, evidence from 40 studies with more than 15,000 participants found a significant increase in smoking abstinence at 6 months or longer compared with controls when pharmacotherapy was added to behavioral treatment (RR = 1.82; 95% CI, 1.66–2.00) (Stead and Lancaster 2012b; Stead et al. 2016). Earlier, Mottillo and colleagues (2009) conducted a meta-analysis of individual, group, and telephone counseling in clinical settings from 50 RCTs (N = 26,927) and found that medications (the nicotine patch, bupropion, or nortriptyline) combined with counseling led to higher quit rates compared with controls. The ORs were similar for individual counseling (1.49; 95% CI, 1.08–2.07), group counseling (1.76; 95% CI, 1.11–2.93), and telephone counseling (1.58; 95% CI, 1.15–2.29). These results suggest that the highest quit rates are achieved through intensive individual or group counseling combined with pharmacotherapy.

Modified and Alternative Tobacco Products

Very-Low-Nicotine-Content Cigarettes

Experimental very-low-nicotine-content (VLNC) cigarettes (also see Chapter 7) are engineered to have reduced content of nicotine in the tobacco used in the cigarette compared with conventionally manufactured cigarettes. The smoke of VLNC cigarettes delivers lower levels of nicotine compared with cigarettes that were marketed by the tobacco industry in the past as "light" or "ultra-light," which did not have lower levels of nicotine in the tobacco itself (Benowitz and Henningfield 2013). Instead, light and ultra-light cigarettes relied on design features, such as ventilation holes in the filter, to allow these products to be rated as low nicotine (and low tar) when subjected to machine smoking employing a standardized method. However, through compensatory behaviors, such as blocking ventilation holes with lips and/or fingers, drawing larger puffs, and inhaling more deeply, smokers were able to obtain levels of nicotine (and tar) that were as high as those delivered by conventional (regular strength) cigarettes (Benowitz and Henningfield 1994). Scientists have suggested that reducing the nicotine content of cigarettes to approximately 0.5 mg per cigarette (compared with 10–15 mg per cigarette in most currently marketed cigarettes) would render cigarettes nonaddictive. This would potentially prevent adolescents from developing nicotine addiction and make it easier for adult smokers to quit, because cigarettes would be less reinforcing (Benowitz and Henningfield 1994).

Several clinical trials have compared the effects of experimental VLNC cigarettes and conventional cigarettes on smoking and cessation behaviors. These trials suggest that VLNC cigarettes may reduce smoking, reduce nicotine dependence, increase cessation rates, and reduce exposure to toxicants (Benowitz et al. 2007, 2012; Donny et al. 2007, 2014, 2015; Donny and Jones 2009; Hatsukami et al. 2010, 2013, 2018; Dermody et al. 2018). For example, Donny and colleagues (2015) and Fiore and Baker (2015) conducted a large, multisite clinical trial that randomized 840 daily smokers to their own cigarettes or to one of six variants of study-specific cigarettes with levels of nicotine ranging from 0.4 mg of nicotine per gram of tobacco to

15.8 mg of nicotine per gram of tobacco (levels typical of commercial brands). At 6 weeks, persons assigned to cigarettes with the lowest level of nicotine content smoked fewer cigarettes per day and reported less dependence and craving than those who smoked regular strength cigarettes (i.e., 15.8 mg of nicotine per gram of tobacco). In a randomized, parallel arm, semi-blind study in which 165 smokers were randomly assigned to either 0.3 mg nicotine yield cigarettes, 0.5 mg nicotine yield cigarettes, or 4 mg nicotine lozenges, Hatsukami and colleagues (2010) found that use of 0.5 mg nicotine yield cigarettes was associated with reduced carcinogen exposure and reduced nicotine dependence and product withdrawal scores, and led to a similar rate of cessation to the nicotine lozenge.

More recently, Hatsukami and colleagues (2018) published findings from another large, multisite clinical trial that assessed the effects of immediate versus gradual reductions in the levels of nicotine content in cigarettes. The authors randomized 1,250 smokers who were not interested in quitting into three groups: those who (a) continued to smoke conventional cigarettes containing 15.5 mg of nicotine per gram of tobacco; (b) smoked cigarettes in which the level of nicotine content was gradually reduced over 6 months from 15.5 mg to 0.4 mg of nicotine per gram of tobacco; or (c) switched immediately from conventional cigarettes to cigarettes with 0.4 mg of nicotine per gram of tobacco and continued to smoke those cigarettes for 6 months. The study found that smokers who switched immediately to cigarettes with low levels of nicotine tended to show greater benefits than smokers in the other two conditions. For instance, compared with gradual reduction of nicotine, immediate reduction yielded significantly lower levels of biomarkers of exposure to toxic smoke constituents, a greater reduction in the number of cigarettes smoked per day, a greater reduction in nicotine dependence, and more days entirely free of cigarettes. Those in the immediate reduction group had significantly lower levels of breath carbon monoxide compared with those in the gradual reduction group (difference = 4.1 parts per million; 95% CI, -4.89 to -3.23; P <.0055) and with those in the control group (difference = 3.4 parts per million; 95% CI, -4.40 to -2.36; P <.0055). Significantly lower levels in the immediate versus gradual and control groups were also observed for acrolein (difference = 17% and 19%, respectively) and phenanthrene tetraol (difference = 12% and 14%, respectively). However, for carbon monoxide, acrolein, and phenanthrene tetraol, there were no significant differences between the gradual reduction and control groups. Lower dependence scores (scale ranges from 0 to 10, with higher scores associated with greater dependence) were observed in (a) the immediate reduction group versus the gradual reduction group (mean = 4.27 [low dependence] vs. 5.13 [moderate dependence]; adjusted mean difference = -0.99 [95% CI, -1.27 to -0.71]; p <.00057) and (b) the immediate reduction group versus the control group (mean = 4.27 [low dependence] vs. 5.48 [moderate dependence]; adjusted mean difference = -1.44 [95% CI, -1.75 to -1.12]; p <.00057). No differences were found in the gradual reduction group versus the control group (mean = 5.13 [moderate dependence] vs. 5.48 [moderate dependence]; adjusted mean difference = -0.45 [95% CI, -0.76 to -0.13]; p = .006) (Hatsukami et al. 2018).

However, a study with longer term follow-up reported that reducing the nicotine content in cigarettes over 12 months did not result in sustained reductions in nicotine intake or increases in smoking cessation over the subsequent 12 months (Benowitz et al. 2015). Experimental cigarettes were likely less acceptable because conventional cigarettes were readily available to the participants in the study. The lack of effect of nicotine intake on smoking cessation may be the result of compensatory behaviors, including consumption of regular-nicotine-content cigarettes. Compensatory smoking (i.e., altering smoking behaviors to continue to obtain enough nicotine to satisfy addiction) has been posited as a possible countervailing effect of setting a nicotine product standard (Gottlieb and Zeller 2017). However, in its advisory report on a global nicotine reduction strategy, which summarized the literature available at that time, WHO (2015) concluded that the use of cigarettes with a nicotine content of 0.4 mg/g (or less) of cigarette tobacco filler does not significantly increase craving or withdrawal and does not result in compensatory smoking behaviors. Studies have found this to be consistent in populations highly vulnerable to nicotine addiction, including individuals with serious mental illness (Denlinger-Apte et al. 2018). However, among participants in clinical trials, levels of acceptability have been lower for experimental VLNC cigarettes than for commercially available cigarettes; and nonadherence has been prevalent, with one trial reporting greater than 70% of participants having substituted traditional cigarette brands for VLNC cigarettes (Nardone et al. 2016). Additionally, 25–45% of participants dropped out of these studies (Nardone et al. 2016; Mercincavage et al. 2017).

Combining VLNC cigarettes with nicotine patches was hypothesized to perhaps aid with the transition to VLNC cigarettes and increase compliance. However, Hatsukami and colleagues (2013) did not find that such a combination improved long-term quit rates of conventional cigarettes. Furthermore, in a two-by-two factorial RCT, Smith and colleagues (2019) found that assignment to the patch, along with VLNC cigarettes, did not significantly reduce cigarette smoking compared with assignment to VLNC cigarettes alone (Smith et al. 2019).

If, as outlined by Benowitz and Henningfield (1994, 2013) and summarized by USDHHS (2014), potential

"end-game" options to complement existing, proven tobacco control interventions include reducing the nicotine content of *all* cigarettes to make them less addictive, then problems with adherence and attrition would not be an issue, unless there was widespread contraband, and long-term cessation rates would likely be higher than observed in the trials. Because a product standard reducing the nicotine content of cigarettes has not yet been implemented, studies have not examined the impact of a product standard that would reduce the level of nicotine in all cigarettes or other tobacco products would have on cessation.

Importantly, the advisory report from WHO (2015) noted that the ultimate health benefits of a nicotine reduction strategy aimed at individual smokers would require that the standard include all combustible tobacco products. The WHO report also noted that such a strategy needs to be accompanied by the provision of cessation treatments to help people quit, including behavioral support and NRT or other medications. In a randomized trial comparing the use of experimental VLNC cigarettes with the use of cigarettes with conventional levels of nicotine over an 8-week period, Hatsukami and colleagues (2017) found that smokers in the VLNC cigarette arm (a) had consumed fewer combustible products at almost all visits compared with those in the conventional nicotine arm ($p < .02$); (b) had higher rates of abstinence (VLNC cigarette arm vs. conventional nicotine arm: RR = 9.96; 95% CI, 5.01–19.81); and (c) used significantly more alternative tobacco products, including nonstudy cigarettes, noncigarette combustible products, and noncombustible products (RR = 2.18; 95% CI, 1.94–2.46 for the VLNC cigarette arm vs. RR = 1.64; 95% CI, 1.46–1.85 for the conventional nicotine arm). As outlined by WHO (2015), for persons who switched from cigarettes to noncombustible forms of tobacco to sustain their nicotine intake, the health benefits of not smoking conventional cigarettes depended on the level of tobacco-related toxicants delivered by the noncombustible products and the patterns and duration of use of such products.

Although evidence to date is suggestive but not sufficient to infer that VLNC cigarettes could reduce smoking and nicotine dependence and increase smoking cessation, further research could help better understand the impact that a nicotine product standard could have on increasing cessation from conventional cigarettes. Several issues warrant continued consideration regarding the impacts of a nicotine product standard on cigarette cessation, including whether compensatory behaviors would occur in the given policy framework (Gottlieb and Zeller 2017), whether there would be illicit trade for products with higher nicotine yield and how to minimize such effects (Ribisl et al. 2019), and how populations that are more vulnerable to nicotine may be impacted, including those with mental illness and substance use disorders (USDHHS 2016).

Product standards to decrease nicotine in all cigarettes will likely have a greater impact on smoking cessation if they are accompanied by a comprehensive cessation strategy that promotes available cessation treatments, including FDA-approved medications and behavioral support.

E-Cigarettes

E-cigarettes (also called electronic nicotine delivery systems [ENDS], vapes, vape pens, tanks, mods, and pod-mods) are battery-powered devices designed to convert a liquid (often called e-liquid) into an aerosol for inhalation by the user (Figure 6.1). E-liquid contains solvents (propylene glycol and vegetable glycerin) to produce the aerosol and typically contains nicotine, flavorings, and other compounds. E-cigarettes, which have been available in the United States since at least 2007 (USDHHS 2016), have been discussed as a potential harm-reduction tool for current smokers (Fagerstrom et al. 2015). For this reason, smokers, scientists, clinicians, and policymakers have an interest in understanding how e-cigarettes will impact the smoking cessation landscape.

As e-cigarettes are products designed to deliver nicotine to the body through the pulmonary route, which results in more rapid absorption and delivery of nicotine to the brain than through other modes of administration (i.e., mouth, transdermal), it is useful to consider their ability to deliver nicotine in the context of a smoker attempting to use e-cigarettes to quit cigarette smoking. The design and components of many e-cigarettes are intended to generate aerosols that can rapidly deliver boluses of nicotine to the brain, similar to nicotine delivery by conventional cigarettes (Farsalinos et al. 2016). E-cigarettes vary in their ability to deliver nicotine to the body (Vansickel and Eissenberg 2013). However, the pharmacokinetics of nicotine delivery of certain e-cigarette products, such as more recent generation e-cigarettes, resemble those of conventional cigarettes, and thus have the potential to mirror the pharmacologic effects of conventional cigarettes (National Academies of Sciences, Engineering, and Medicine 2018). Therefore, for smokers of conventional cigarettes who seek a product with a rapid onset of the dose of nicotine similar to cigarettes, e-cigarettes that deliver nicotine in a similar way to conventional cigarettes could have greater appeal than current FDA-approved NRTs. However, although rapid boluses of nicotine could increase the appeal of these products relative to NRTs, whether this pharmacokinetic profile supports an effective method of cessation has not been extensively studied (Shihadeh and Eissenberg 2015). However, when considering e-cigarettes as a potential cessation aid

Figure 6.1 The evolution of e-cigarettes, by product generation and characteristics

Source: Photos by James Gathany and Lauren Bishop, CDC.

for adult smokers, it is also important to take into account factors related to both safety and efficacy. NRT has been proven safe and effective, whereas the same has not been proven for any e-cigarette. There is no safe tobacco product. Although e-cigarette aerosol generally contains fewer toxic chemicals than conventional cigarette smoke, all tobacco products, including e-cigarettes, carry risks.

Other features of e-cigarettes that may enhance their appeal to conventional cigarette smokers are the ways in which e-cigarettes mirror some of the sensorimotor features of conventional cigarette smoking, including stimulation of the airways, the sensation and taste of e-cigarette aerosol in the mouth and lungs, the hand-to-mouth movements and puffing in which e-cigarette users engage, and the exhalation of aerosol that may visually resemble cigarette smoking. Given the potentially important role of such sensorimotor factors in the reinforcing and addictive qualities of conventional cigarettes (Chaudhri et al. 2006), these attributes could make e-cigarettes more appealing to smokers than FDA-approved NRTs. However, the sensiromotor aspects of e-cigarettes could (a) facilitate uptake for use as a cessation aid, with the goal of attaining complete nicotine abstinence, similar to how NRTs are intended to be used or (b) facilitate the use of e-cigarettes as a long-term substitute for conventional cigarettes to sustain nicotine use. The potential abuse liability of e-cigarettes that deliver nicotine in a manner comparable, or higher than, conventional cigarettes should also be considered, including long-term dual use and decreased likelihood of cessation through maintenance of addiction. When considering the potential role of e-cigarettes used in smoking cessation, it is important to consider the intent of therapeutic FDA-approved NRT (i.e., that they are intended to act as a support for attaining complete abstinence from smoking).

Two previous Surgeon General's reports have addressed e-cigarettes. However, to date, no Surgeon General's report has reviewed the available science related to e-cigarettes and cessation. E-cigarettes were first discussed in the 2014 Surgeon General's report (USDHHS 2014), which noted that the use of e-cigarettes could have positive and negative public health impacts at the individual and population levels. Additionally, the 2016 Surgeon General's report (USDHHS 2016), *E-Cigarette Use Among Youth and Young Adults,* examined many topics related to e-cigarettes, including patterns of use and health risks of e-cigarettes among young people, as well as the importance of population-based strategies to prevent and reduce the use of e-cigarettes among this population. USDHHS (2016) underscored the need to understand any effects of e-cigarettes on adult smoking cessation, as well as the risks that the products pose to youth and young adults. This is especially important in light of alarming increases in e-cigarette use among adolescents, which threaten decades of progress in tobacco control

(USDHHS 2016; Miech et al. 2018; Gentzke et al. 2019). Additionally, e-cigarette, or vaping, product use may be associated with other health risks beyond youth initiation and use. For example, CDC, FDA, state and local health departments, and public health and clinical partners have been investigating a multistate outbreak of e-cigarette, or vaping, product use associated lung injury (EVALI) (Siegel et al. 2019). The latest national and state findings show e-cigarette, or vaping, products containing THC—particularly those from informal sources, such as friends, family, or in-person or online dealers—are linked to most of the cases of lung injury and play a major role in the outbreak (Moritz et al. 2019; Navon et al. 2019). In particular, vitamin E acetate is closely associated with EVALI (Blount et al. 2019). Vitamin E acetate has been identified in several tested products used by EVALI patients, and has been identified in bronchoalveolar lavage (BAL) fluid samples from 48 of 51 assessed EVALI patients, but not in the BAL fluid from a control group. However, as of January 2020, evidence is not yet sufficient to rule out the contribution of other chemicals of concern among some EVALI patients.

Current use of e-cigarettes among adults rose through 2014 (Adkison et al. 2013; Dockrell et al. 2013; Goniewicz et al. 2013; Agaku et al. 2014; Kasza et al. 2017), but has since declined gradually through 2017 (Wang et al. 2018). In 2017, 2.8% of adults were current users of e-cigarettes (Wang et al. 2018). More than half of current adult e-cigarette users also currently smoke cigarettes, which is commonly known as "dual use" (CDC 2016; Mirbolouk et al. 2018). Among current e-cigarette users in 2016, 15.0% were never cigarette smokers, 30.4% were former smokers, and 54.6% were current smokers (Mirbolouk et al. 2018). Data from the National Youth Tobacco Survey showed that among high school students, current (past 30-day) e-cigarette use rose from 1.5% in 2011 to 20.8% in 2018 (Cullen et al. 2018), including a 78% increase from 2017 to 2018 (USDHHS 2018a). E-cigarette use among middle school students has also risen dramatically in the same time period, with a 49% increase from 2017 to 2018 (3.3% to 4.9%) (USDHHS 2018a). Dual use is also common among youth. In 2018, approximately half of youth who used tobacco products reported using two or more products; among high school students who reported currently using two or more tobacco products, the most common combinations reported were e-cigarettes and cigarettes (14.8%) (Gentzke et al. 2019).

Since its introduction into the U.S. marketplace in 2015, the JUUL brand e-cigarette has been increasingly popular among U.S. youth (USDHHS 2018a), and increases in sales in recent years have corresponded with the previously described increases in current e-cigarette use among U.S. youth in recent years. For example, sales of JUUL increased 600% during 2016–2017, largely driven by uptake among youth and young adults, giving it the greatest market share of any e-cigarette in the United States by the end of 2017 (King et al. 2018b). Sales have continued to increase since that time; in the assessed channels by the end of 2018, JUUL held approximately 75% of the market share of total U.S. e-cigarette sales (Truth Initiative 2018). JUUL's popularity with youth appears to stem from several factors:

- Appearance of a flash drive,
- Ease of concealment (small and does not emit as much aerosol or odor as some other types of e-cigarettes),
- Availability in a variety of flavors,
- Widespread promotion through a variety of media, including social media, and
- High nicotine content delivered in a form (e.g., nicotine salt) that may facilitate easier initiation (Cullen et al. 2018; Goniewicz et al. 2018a; Spindle and Eissenberg 2018).

E-cigarettes may appeal to adult smokers of conventional cigarettes because they mimic cigarettes in several ways: size, appearance (at least in the case of first-generation e-cigarettes), method of inhalation, production of a smoke-like aerosol, and the taste and ritual behaviors associated with smoking (Prochaska and Benowitz 2016). In terms of exposure risks, as part of a comprehensive review on the public health consequences of e-cigarette use, the National Academies of Sciences, Engineering, and Medicine (2018) concluded that for current cigarette smokers, completely substituting e-cigarettes for combustible tobacco products would reduce exposure to several toxicants and carcinogens present in tobacco cigarettes. For example, an analysis of 12 first-generation brands of e-cigarettes found that toxicants (including carcinogenic compounds) were present in the e-cigarettes' aerosol across brands at varying levels, ranging from about 9- to 450-times lower than cigarette smoke to levels in some brands that were comparable to levels in the NRT inhaler (Goniewicz et al. 2014). In a separate analysis of urine samples from 5,105 adult participants in the 2013–2014 wave of the Population Assessment of Tobacco and Health (PATH) Study, Goniewicz and colleagues (2018b) concluded that the exclusive use of e-cigarettes was associated with exposure to known tobacco-related toxicants (e.g., tobacco-specific nitrosamines, such metals as cadmium and lead, and some volatile organic compounds), but that this exposure was markedly lower than that associated with both cigarette smoking and dual use of

cigarettes and e-cigarettes. However, depending on the toxicant analyzed, dual users (n = 792) had similar or higher exposures to toxicants compared with users of only conventional cigarettes (n = 2,411). Among dual users, the frequency of cigarette use was positively correlated with exposure to both nicotine and toxicants. These findings suggest that exclusive use of e-cigarettes can result in markedly lower exposure to tobacco-related toxicants compared with exclusive use of conventional cigarettes, but that using e-cigarettes concurrently with conventional cigarettes does not meaningfully reduce exposure to potentially harmful toxicants. Of note, ingredients unique to e-cigarettes (i.e., not found in conventional cigarettes) pose potential harms (Erythropel et al. 2019). It is important to note that the findings from the PATH Study analysis pertain to e-cigarette products used in 2013–2014, and because the landscape of e-cigarette products continues to diversify and evolve rapidly, the findings may or may not be generalizable to behaviors surrounding the use of these products years later (e.g., in 2019). Moreover, the National Academies of Science Engineering and Medicine (2018) concluded that exposure to nicotine and exposure to potentially toxic substances in aerosol from e-cigarettes are highly variable and depend on product characteristics (e.g., e-liquid constituents and device characteristics and settings), how the device is operated, and user behavior.

Although the available scientific evidence indicates that e-cigarettes generally have a markedly lower number and level of harmful toxicants than conventional cigarettes, use of the products is not without potential health risks; the long-term health effects of using these products remain unknown, and short-term risks are only slowly coming into focus (National Academies of Sciences, Engineering, and Medicine 2018). However, the National Academies of Sciences, Engineering, and Medicine (2018) concluded that there is substantial evidence that e-cigarette use is associated with several adverse health outcomes that are precursors to disease, including acute endothelial cell dysfunction, formation of reactive oxygen species/oxidative stress, and increased heart rate (National Academies of Sciences, Engineering, and Medicine 2018). The report also concluded that there is substantial evidence that some chemicals present in e-cigarette aerosols are capable of causing DNA damage and mutagenesis, which supports the biologic plausibility that long-term exposure to e-cigarette aerosols could increase risk of cancer and adverse reproductive outcomes; however, whether the levels of exposure are high enough to contribute to human carcinogenesis remains uncertain. The report further noted that there is no available evidence whether e-cigarette use is associated with certain longer term health outcomes, including clinical cardiovascular outcomes and subclinical atherosclerosis, intermediate cancer endpoints in humans, respiratory diseases, and pregnancy outcomes (National Academies of Sciences, Engineering, and Medicine 2018). Additionally, Gotts and colleagues (2019) reviewed the available science to date on risks to the respiratory system from using e-cigarettes or being exposed to aerosol from e-cigarettes. The study found negative impacts on cellular and organ physiology and immune function (Gotts et al. 2019). Accordingly, more research is warranted to assess the extent to which e-cigarette use may impact the likelihood of these and other health outcomes. Of note, some studies have found that after accounting for conventional cigarette smoking, e-cigarette use is associated with increased risk of having had a myocardial infarction (Alzahrani et al. 2018; Alzahrani and Glantz 2019; Osei et al. 2019). However, the cross-sectional nature of these studies limits the ability to ascertain causality (Farsalinos and Niaura 2019a). A longitudinal study using data from the PATH Study found that having had a myocardial infarction at Wave 1 of the study did not predict e-cigarette use at Wave 2 (Bhatta and Glantz 2019). This finding, according to the study's authors, suggests that reverse causality cannot explain the cross-sectional association between e-cigarette use and myocardial infarction observed at Wave 1. However, further longitudinal research is warranted to fully account for the time period when myocardial infarction has occurred relative to e-cigarette use.

Research on the impact of e-cigarettes on smoking cessation is limited but growing. In addition to the review of this topic by the National Academies of Sciences, Engineering, and Medicine (2018), multiple systematic reviews have assessed the literature on e-cigarette use and smoking cessation, some of which conducted meta-analyses of RCT data and observational studies (Franck et al. 2014; Grana et al. 2014; Harrell et al. 2014; McRobbie et al. 2014; Lam and West 2015; Rahman et al. 2015; Hartmann-Boyce et al. 2016; Kalkhoran and Glantz 2016; Khoudigian et al. 2016; Malas et al. 2016; El Dib et al. 2017).

Few RCTs have been conducted that directly investigate the utility of e-cigarettes for smoking cessation, and no RCTs on this topic have been conducted in the United States. Only four RCTs—a clinical trial of smokers in Italy who were not motivated to quit (Caponnetto et al. 2013), a clinical trial of smokers in New Zealand who were motivated to quit (Bullen et al. 2013), another clinical trial of smokers in New Zealand who were motivated to quit (Walker et al. 2019), and an RCT of adults using the stop-smoking service of the UK National Health Service (Hajek et al. 2019)—have directly tested the efficacy of using e-cigarettes for smoking cessation with a follow-up timepoint of at least 6 months; none were funded by the tobacco or e-cigarette industries. In a randomized clinical trial of smokers who were not motivated to quit, Caponnetto and colleagues (2013) found that the use of

first-generation e-cigarettes resulted in a nonsignificant (p = 0.24) increase in the likelihood of smoking abstinence at 52-weeks follow-up compared with those who used first-generation e-cigarettes that did not contain nicotine (placebo e-cigarette). Abstinence rates were 13% in Group A (12-weeks supply of 7.2 mg nicotine cartridges), 9% in Group B (one 6-week supply of 7.2-mg nicotine cartridges and one 6-week supply of 5.4-mg nicotine cartridges), and 4% in Group C (cartridges without nicotine). However, in an intention-to-treat analysis, a statistically significant increase in the abstinence rate was observed at 52-weeks follow-up: 11.0% when Groups A and B were combined compared with 4.0% in Group C (p = 0.04). The RCT by Bullen and colleagues (2013) also showed (a) a nonsignificant elevated RR of 6-month continuous abstinence rates for smokers who were assigned to use first generation e-cigarettes that contained nicotine compared with those who were assigned to use first generation e-cigarettes that did not contain nicotine (7.3% vs 4.1%, RR 1.77, p = 0.44) and (b) a nonsignificantly elevated RR for 6-month continuous abstinence (RR = 1.26; p = 0.46) between smokers who were assigned to use e-cigarettes that contained nicotine (7.3%) and those who were assigned to use nicotine patches (5.8%). As reviewed in National Academies of Sciences, Engineering, and Medicine (2018), the results of these two RCTs were pooled in two different, rigorous meta-analyses. A 2016 Cochrane review that pooled data from these two RCTs showed (a) no significant statistical heterogeneity between the two studies and (b) that use of nicotine-containing e-cigarettes was associated with statistically significant higher abstinence rates than use of placebo e-cigarettes (RR = 2.29; 95% CI, 1.05–4.96; 9% for nicotine e-cigarette group vs. 4% in placebo e-cigarette group, among 662 participants) (Hartmann-Boyce et al. 2016). El Dib and colleagues (2017) pooled the same two RCTs into a meta-analysis and found a nonsignificant increase in smoking cessation for nicotine e-cigarettes compared with placebo e-cigarettes (RR = 2.03; 95% CI, 0.94–4.38; p = 0.07). A notable difference in the methodology between these two reviews was that Hartmann-Boyce and colleagues (2016) considered participants with missing data as smokers and retained them in the analysis, increasing their sample size to 662 compared with the 481 cases analyzed by El Dib and colleagues (2017) (National Academies of Sciences, Engineering, and Medicine 2018).

A few notable limitations to two RCTs (Bullen et al. 2013; Caponnetto et al. 2013) should be noted: They both produced fairly low quit rates in all conditions (range: 4–13%) and used first generation e-cigarettes that do not have comparable nicotine pharmacokinetics as cigarettes. Furthermore, Bullen and colleagues (2013) found that rates of compliance were substantially lower among smokers in the nicotine patch condition than among those in either of the e-cigarette conditions, suggesting that the similar efficacy among users of e-cigarettes with nicotine and of the nicotine patches might be mediated by different mechanisms of action. The greater adherence to e-cigarettes could be driven, in part, by past experience of failed quit attempts with patches and/or greater appeal of e-cigarettes.

The third RCT (Hajek et al. 2019) randomly assigned 886 adults attending stop-smoking services from the UK National Health Service. Participants received either an NRT medication of their choice or an e-cigarette starter pack, which included a newer generation refillable e-cigarette with one bottle of nicotine e-liquid (18 mg per milliliter [ml]). Both conditions received face-to-face smoking cessation counseling from a trained counselor for at least 4 weeks. At 1 year, the biochemically verified cigarette smoking abstinence rate was 18.0% in the e-cigarette group compared with 9.9% in the NRT group. Of note, participants in both the e-cigarette and NRT groups rated their assigned products as less satisfying than cigarettes. However, participants who were assigned to use e-cigarettes reported that e-cigarettes provided them with greater satisfaction and rated e-cigarettes as more helpful to refrain from smoking than participants in the NRT group rated NRT medications (Hajek et al. 2019). The study concluded that use of e-cigarettes was more effective than use of NRT for smoking cessation in the trial when both were accompanied by behavioral support. Of note, among participants with 1-year abstinence, 80% of participants in the e-cigarette group were using e-cigarettes at 52 weeks follow-up and 9% of participants in the NRT group were using NRT, suggesting greater likelihood of complete abstinence from all products in the long term from NRT use compared with e-cigarette use. This also suggests that, among those who use e-cigarettes for smoking cessation, cigarette abstinence may be predicated on long-term use of e-cigarettes, which may pose unknown long-term health risks, in addition to short-term risks that are only slowly coming into focus. Limitations of the study should also be considered. First, participants were enrolled through the UK National Health Service's stop-smoking service, so they were motivated to quit. Participants also received evidence-based cessation counseling in addition to e-cigarettes or NRT. Furthermore, the policy and regulatory environment regarding both e-cigarettes and tobacco products in the United Kingdom differs greatly from that of the United States. For example, compared with the United States, the United Kingdom limits the amount of nicotine permitted in e-cigarettes (maximum concentration 20 mg/ml) and has more restrictions on the advertising and marketing of e-cigarettes, which aligns with its advertising restrictions on tobacco products more generally. Further

well-designed RCTs will ultimately be important before any substantive conclusions can be made about the comparative efficacy of e-cigarettes relative to NRT, other cessation pharmacotherapies, or not using a cessation aid.

A fourth RCT conducted in 2016–2017 in New Zealand explored e-cigarettes, with and without nicotine, as an adjunct to the nicotine patch (Walker et al. 2019). The study randomized smokers motivated to quit (n = 1,124) to receive either nicotine patch, nicotine patch plus nicotine-containing e-cigarettes, or nicotine patch plus nicotine-free e-cigarettes. Participants randomized to the e-cigarette conditions received a tank-style device and tobacco-flavored e-liquid in either 0 mg/ml or 18 mg/ml concentration, depending on assigned group; and all participants received 21 mg nicotine patches. Smokers using nicotine-containing e-cigarettes were more likely to have biochemically verified, continuous cigarette abstinence at 6-month follow-up than those randomized to patch plus nicotine-free e-cigarettes or to nicotine patch alone (7%, 4%, and 2%, respectively). However, the study had higher than expected rates of attrition: 50% in the patch-only group, 32% in the patch plus nicotine-containing e-cigarettes group, and 33% in the patch plus nicotine-free e-cigarettes group. Moreover, quit rates were much lower than expected among all three randomized groups.

In addition to the aforementioned RCTs, an additional RCT assigned smokers employed by 54 companies to one of four workplace smoking-cessation interventions or to usual care (Halpern et al. 2018). Usual care consisted of access to information about the benefits of smoking cessation and to a motivational text-messaging service. The four interventions consisted of usual care and one of the following interventions: free access to cessation aids (NRT or pharmacotherapy, with e-cigarettes if standard therapies failed); free access to e-cigarettes, without a requirement that standard therapies had been tried; free access to cessation aids and $600 in rewards for sustained abstinence; or free access to cessation aids plus $600 in redeemable funds, with money removed from the account if cessation milestones were not met. The study found that rates of sustained abstinence through 6 months were 0.1% in the usual care group, 0.5% in the free cessation aids group, 1.0% in the free e-cigarettes group, 2.0% in the rewards group, and 2.9% in the redeemable funds group. Of note, the free e-cigarettes intervention was not superior to usual care (p = 0.20) or to the free cessation aids intervention (p = 0.43), and among smokers who received usual care, the addition of free cessation aids or e-cigarettes did not significantly enhance cessation efficacy. However, the study did not assess actual use of e-cigarettes, only access to the products, nor did it compare free access to e-cigarettes with free access to conventional cessation aids without any option for e-cigarettes (Halpern et al. 2018).

In addition to the data from the previously summarized RCTs, multiple observational studies have explored the effectiveness of using e-cigarettes for smoking cessation. Several systematic reviews have synthesized the observational literature on the impact of e-cigarette use on smoking cessation (Franck et al. 2014; Grana et al. 2014; Harrell et al. 2014; McRobbie et al. 2014; Lam and West 2015; Rahman et al. 2015; Hartmann-Boyce et al. 2016; Kalkhoran and Glantz 2016; Khoudigian et al. 2016; Malas et al. 2016; El Dib et al. 2017). The review by El Dib and colleagues (2017), which used a methodology known as GRADE (Grading of Recommendations Assessment, Development, and Evaluation) to formally assess the certainty of evidence by outcome, concluded that the findings on this topic from two RCTs (Bullen et al. 2013; Caponnetto et al. 2013) and eight observational studies (Vickerman et al. 2013; Borderud et al. 2014; Prochaska and Grana 2014; Al-Delaimy et al. 2015; Biener and Hargraves 2015; Brose et al. 2015; Harrington et al. 2015; Manzoli et al. 2015) were of very low quality. Several of the reviews noted that findings from the observational studies varied, and differences in study design and the selection of participants made it difficult to make conclusive comparisons. Similarly, a review conducted by USPSTF (2015), which also considered the existing RCTs, concluded that the current evidence was insufficient to recommend e-cigarettes for tobacco cessation in adults, including pregnant women.

In one of the prospective observational studies, Manzoli and colleagues (2015) reported that the rate of quitting smoking did not differ between smokers who had used e-cigarettes weekly for at least 6 months and smokers who did not use e-cigarettes. However, in a longitudinal study of a nationally representative population of adults surveyed in 2012 and 2014, Zhuang and colleagues (2016) found that long-term e-cigarette users appeared to have (a) higher rates of quit attempts than short-term e-cigarette users or nonusers of e-cigarettes (72.6% vs. 53.8% and 45.5%, respectively) and (b) higher rates of cigarette cessation (42.4% vs. 14.2% and 15.6%, respectively). Adjusting for smoking characteristics and demographics, long-term e-cigarette users were significantly more likely than nonusers of e-cigarettes to try to quit smoking (OR = 2.94; 95% CI, 1.34–6.44) and to do so successfully (OR = 4.14; 95% CI, 1.50–11.42); cessation outcomes for short-term e-cigarette users were similar to those for nonusers. The study also found that 43.7% of adults who were dual users of cigarettes and e-cigarettes at baseline were still using e-cigarettes at follow-up. In a study of multiple years of nationally representative data from the U.S. Current Population Survey Tobacco Use Supplement, Zhu and colleagues (2017) found that the smoking cessation rate for the overall population increased from 4.5% in 2010–2011 to 5.6% in 2014–2015,

and in 2014–2015, e-cigarette users were more likely than nonusers to attempt to quit smoking (65.1% vs. 40.1%; percentage point change = 25%; 95% CI, 23.2–26.9%) and to succeed in quitting (8.2% vs. 4.8%, p <0.001). The study also examined the potential impact on cessation of other tobacco control efforts that were underway during the study period (e.g., mass media campaigns and increased taxation of cigarettes) and concluded that their effects could not fully account for the observed increase in the quit rate, leaving the use of e-cigarettes as a potential explanation. Finally, in a cross-sectional household survey of smokers 16 years of age and older in England, Beard and colleagues (2016) found that the success rate of attempts to quit cigarettes increased by 0.098% (p <.001) for every 1% increase in the prevalence of e-cigarette use among smokers, and by 0.058% for every 1% increase in the prevalence of e-cigarette use during a recent quit attempt. The study concluded that increases in e-cigarette use in England have been associated with increased success in quitting cigarette smoking.

As noted previously, some of the literature suggests potential utility of e-cigarettes for smoking cessation. However, the current literature is limited by small numbers of trials, low event rates, and wide confidence intervals. Moreover, interpretation of results is further complicated by the wide variation in e-cigarette products (i.e., types of devices and components and levels of nicotine content in e-liquids) and the contexts in which they are used, including the motivation of smokers to quit and whether the products are used with behavioral support. Accordingly, more well-designed RCTs and prospective observational studies are needed to determine whether and how e-cigarettes influence smoking cessation, including whether the type of e-cigarette and the setting in which it is used impacts the potential for e-cigarette use to help smokers quit.

Existing research suggests that the frequency of e-cigarette use and the type of product are important factors that influence the extent to which the products increase the likelihood of smoking cessation. As part of a comprehensive report on the public health consequences of e-cigarettes, the National Academies of Sciences, Engineering, and Medicine (2018) reviewed three RCTs (Bullen et al. 2013; Caponnetto et al. 2013; Adriaens et al. 2014)—one of which assessed smoking reduction and not actual cessation (Adriaens et al. 2014)—and results from several prospective cohort studies or repeated cross-sectional design studies (Biener and Hargraves 2015; Brose et al. 2015; Hitchman et al. 2015; Delnevo et al. 2016; Malas et al. 2016; Zhuang et al. 2016; Levy et al. 2018) on the effectiveness of e-cigarettes for smoking cessation. The review concluded that while the overall evidence from observational trials is mixed, there is moderate evidence from observational studies that more frequent use of e-cigarettes is associated with an increased likelihood of cessation. For example, in a cross-sectional study using data from the 2016 and 2017 National Health Interview Survey, Farsalinos and Niaura (2019b) found that daily e-cigarette use was not associated with being a former smoker when quit duration was ignored, but was positively associated with being a former smoker of less than 1 year (adjusted prevalence ratio [aPR] = 3.44; 95% CI, 2.63–4.49), 1–3 years (aPR = 2.51; 95% CI, 2.13–2.95), and 4–6 years (aPR = 1.84; 95% CI, 1.49–2.26). Moreover, using data from waves 1 (2013–2014) and 2 (2014–2015) of the Population Assessment of Tobacco and Health Study, Berry and colleagues (2019) found that after adjusting for covariates, (a) cigarette smokers who initiated e-cigarette use between waves and reported that they used e-cigarettes daily at wave 2, had 7.88 (95% CI, 4.45–13.95) times the odds of 30-day cigarette cessation compared with nonusers of e-cigarettes at wave 2, and (b) nondaily e-cigarette users had significantly lower odds of cessation compared with nonusers. Similarly, in a longitudinal sample from two U.S. municipalities, Biener and Hargraves (2015) found that after accounting for demographic characteristics and tobacco dependence, intensive users of e-cigarettes (used e-cigarettes daily for at least 1 month) were six times more likely than nonusers to quit smoking (OR = 6.07; 95% CI, 1.11–33.2); a comparable relationship was not observed between intermittent users (used e-cigarettes regularly but not daily for more than 1 month) and nonusers/triers (used e-cigarettes only once or twice). Furthermore, among a longitudinal sample of smokers in Great Britain, Hitchman and colleagues (2015) found that compared with smokers who did not report using e-cigarettes at follow-up, nondaily users of disposable e-cigarettes were less likely to have quit smoking since baseline (p = 0.0002); daily users of disposable e-cigarettes and nondaily users of tank-style e-cigarettes were no more or less likely to have quit (p = 0.36 and p = 0.42, respectively); and daily users of tank-style e-cigarettes were more likely to have quit (p ≤0.01). These findings are consistent with findings from the RCT by Hajek and colleagues (2019), which found greater efficacy for cessation from the use of more recent generations of e-cigarettes with higher nicotine yield, and from studies showing that open tank e-cigarettes, which allow the user to refill the nicotine liquid and to titrate the dose of nicotine, result in greater nicotine absorption (Farsalinos et al. 2013a,b; 2015). Most recently, Gomajee and colleagues (2019) assessed longitudinal data from the CONSTANCES (Consultants des Centres d'Examens de Santé) cohort and found that among the 5,400 daily smokers, daily e-cigarette use was associated with a significantly higher decrease in the number of cigarettes smoked per day compared with daily smokers who did

not use e-cigarettes (-4.4 [95% CI, -4.8 to -3.9] vs. -2.7 [95% CI, -3.1 to -2.4]), as well as a higher adjusted RR of smoking cessation (1.67; 95% CI, 1.51–1.84]). However, among 2,025 former smokers, e-cigarette use was associated with an increase in the rate of smoking relapse (adjusted hazard ratio = 1.70; 95% CI, 1.25–2.30) compared with former smokers who did not use e-cigarettes. In addition to frequency of use and product type, some data suggest that the reason for using e-cigarettes (e.g., to quit or reduce smoking vs. all other reasons) may be an important factor that influences the effectiveness of e-cigarettes for smoking cessation (Vickerman et al. 2017). Taken together, these findings suggest that the type and design of e-cigarettes (e.g., open tank systems vs. closed systems vs. disposable) and the way in which they are used (e.g., more frequent use vs. less frequent use) may affect their utility for cessation (Hitchman et al. 2015).

The landscape of e-cigarettes continues to evolve, with the arrival of a new generation of devices and e-liquids that can more efficiently deliver nicotine (Farsalinos et al. 2014; USDHHS 2018b). For example, some e-cigarettes contain nicotine salt e-liquids (also called nic salts); nicotine salts are created by adding an acid to the nicotine to lower the overall pH (Goniewicz et al. 2018a; Spindle and Eissenberg 2018). Nicotine salt-based liquids allow users to inhale aerosols with high levels of nicotine more easily and with less irritation than the freebase nicotine e-liquids that have been used in e-cigarettes since they were first introduced into the marketplace (USDHHS 2018b; O'Connell et al. 2019). Nicotine salt e-liquids may also help deliver nicotine to the brain faster and in a way that is more comparable to the nicotine delivery achieved via conventional cigarettes (Goniewicz et al. 2018a). Although justifiable concerns exist that nicotine salts could promote initiation of e-cigarette use among youth, this new product formulation also has the potential to enhance the dose and efficiency with which nicotine is delivered to adult smokers who may be attempting to quit smoking, thus potentially increasing the likelihood that they are able to transition completely to e-cigarettes. However, this formulation could also make it more difficult for those who fully transition to e-cigarettes to eventually quit using these products completely.

The 2014 Surgeon General's report noted that "the promotion of noncombustible products is much more likely to provide public health benefits only in an environment where the appeal, accessibility, promotion, and use of cigarettes and other combusted tobacco products are being rapidly reduced" (USDHHS 2014, p. 874). Therefore, it is particularly important to consider both the potential benefits of e-cigarettes for smoking cessation and the high level of e-cigarette use among youth, which increased to unprecedented levels between 2017 and 2018 primarily because of the introduction of JUUL and other e-cigarettes shaped like USB flash drives (Cullen et al. 2018). As noted by the National Academies of Sciences, Engineering, and Medicine (2018), the specific time frame and magnitude of population health effects of e-cigarettes will depend on their impact on the rates of initiation and net cessation of combustible tobacco cigarettes and their intrinsic harm, and the risks of the high level of e-cigarette use among youth. To date, a variety of modeling projections have estimated the potential magnitude of these effects, but it is important to note that results can vary greatly depending on parameter inputs, underlying assumptions, and other factors. Using a Mendez-Warner modeling approach, the National Academies of Sciences, Engineering, and Medicine (2018) found that the use of e-cigarettes will generate a net public health benefit, at least in the short term. The model found that the harms from increased initiation by youth will take time to manifest, occurring decades after the benefits of increased cessation are observed. However, for long-term projections, the net public health benefit was projected to be substantially less and was negative under some scenarios in the model. Importantly, irrespective of the range of assumptions used, the model projected a net public health harm in the short and long terms if the products do not increase net combustible tobacco cessation in adults. Warner and Mendez (2019) used a similar approach, concluding that potential life-years gained as a result of e-cigarette-induced smoking cessation are projected to exceed potential life-years lost due to e-cigarette-induced smoking initiation, and that these results held over a wide range of assessed parameters. In contrast, Soneji and colleagues (2018), using a Monte Carlo stochastic simulation model, found that 2,070 additional current cigarette smoking adults (25–69 years of age) (95% CI, -42,900–46,200) would, because of e-cigarette use in 2014, quit smoking in 2015 and remain continually abstinent from smoking for 7 or more years. The model also estimated 168,000 additional never-cigarette smoking adolescents (12–17 years of age) and young adults (18–29 years of age) (95% CI, 114,000–229,000) would, because of e-cigarette use in 2014, initiate cigarette smoking in 2015 and become daily cigarette smokers at 35–39 years of age. Based on the existing scientific evidence related to e-cigarettes and optimistic assumptions about the relative harm of e-cigarette use compared with cigarette smoking, the authors concluded that e-cigarette use currently represents more population-level harm than benefit.

In summary, the evidence is inadequate to infer that e-cigarettes, in general, increase smoking cessation; factors contributing to the uncertainty include the changing characteristics of e-cigarettes, the many different contexts in which they are used, and the limited number of studies conducted to date. However, the evidence is suggestive

but not sufficient to infer that the use of e-cigarettes containing nicotine is associated with increased smoking cessation compared with the use of e-cigarettes not containing nicotine; of important note, the evidence to support this conclusion lacks comparison to standard evidence-based therapy, and more research on this topic is warranted. The evidence is also suggestive but not sufficient to infer that more frequent use of e-cigarettes is associated with increased smoking cessation compared with less frequent use of e-cigarettes; however, future research on this topic is also warranted because existing evidence is primarily from observational studies that did not control for confounding based on motivation to quit smoking or assess potential characteristics of e-cigarette use that may be correlated with frequency of use, such as duration of use and product nicotine levels. The effects of e-cigarette use on smoking cessation will likely be determined by a combination of the physical characteristics of these products; how they are used; and how society, policymakers, manufacturers, smokers, and clinicians approach such products. Well-controlled clinical trials and rigorous, large-scale observational studies with long-term follow-up will be critical to better understand the impact of various e-cigarettes under various conditions. E-cigarettes could help adult smokers, by reducing the risk of smoking-attributable disease, if they completely switch from conventional cigarettes to e-cigarettes and do not partake in an extended period of dual use that delays quitting. It is also important to consider the extent of health risks posed by ingredients that are unique to e-cigarettes but not present in conventional cigarettes (Clapp and Jaspers 2017; Gotts et al. 2019; Madison et al. 2019). Among those who have transitioned completely, the ultimate goal should be to also quit the use of e-cigarettes completely in order to achieve the maximum individual and public health benefit. However, at the population level, any potential benefits these products confer in terms of increasing cessation among adult smokers would need to outweigh potential risks related to use among youth (USDHHS 2014), including the already unprecedented increase in the use of e-cigarettes among youth that has occurred in recent years (Cullen et al. 2018; Miech et al. 2019). It is particularly important to emphasize the current diversity of e-cigarette products: they do not comprise a homogenous product category, and they have changed rapidly in design and characteristics since first entering the U.S. marketplace in 2007. Consequently, much of the existing scientific literature on cessation relates to past generations of e-cigarette products. Therefore, further research is needed on the effects that e-cigarettes have on smoking cessation, including research on:

- Differential effects based on the type of e-cigarette product (e.g., newer vs. older devices),
- Comparison groups (e.g., e-cigarettes that do not contain nicotine, NRT, no cessation aid),
- Components in e-cigarette devices and the settings at which they are used (e.g., temperature of the heating coils),
- Frequency of use (e.g., daily vs. less frequent use),
- Informational context (e.g., forms of marketing and promotion, communication about risk and harm, behavioral support for use as a cessation aid),
- Potential variations in effects across geographies, and
- Real-world use of e-cigarettes in different regulatory contexts.

Such research will shed light on whether and how it may be possible to leverage e-cigarettes (or certain types of e-cigarette products) to maximize positive smoking cessation outcomes while minimizing adverse consequences related to youth initiation and use.

Teachable Moments

Teachable moments—including life changes, disease diagnoses, medical procedures, and screening results—can motivate patients to make and sustain a quit attempt. Smokers often come into contact with healthcare professionals—including physicians, nurses, medical staff, dentists, and pharmacists—during such moments. In addition to the specific situations described below, several other situations can also serve as teachable moments (e.g., when a pharmacist is dispensing a drug that interacts with cigarette smoking or when a dentist, periodontist, or dental hygienist is treating a smoker).

Hospitalization

Hospitalization can present an opportunity to change behavior, especially if the patient has been hospitalized for a condition caused or exacerbated by tobacco

use. In most cases, hospitalization involves a temporary stay in a smokefree (and sometimes tobacco-free) clinical environment, with ready access to smoking cessation counseling and pharmacotherapy, at a time when health concerns are acutely relevant. Patients who use cessation medications for relief of withdrawal symptoms while hospitalized also have the opportunity to familiarize themselves with these medications and their benefits while in a clinical setting, potentially leading to a greater likelihood that they will subsequently use them to quit smoking (Fiore et al. 2012). Research indicates that tobacco cessation interventions delivered in the hospital can reduce tobacco use, improve postsurgical outcomes, reduce readmissions, and improve overall patient survival (Cummings et al. 1989; Mullen et al. 2015; Mullen et al. 2017; Nolan and Warner 2017; Cartmell et al. 2018b).

Research also indicates that post-hospital follow-up is key to achieving and sustaining smoking abstinence, as reported in a 2012 Cochrane meta-analysis of 50 randomized or quasi-RCTs evaluating smoking cessation interventions initiated in hospital settings (Rigotti et al. 2012). The meta-analysis found that intensive counseling interventions that were initiated in an acute care hospital and included at least 1 month of supportive care after discharge from the hospital were effective in increasing smoking cessation rates postdischarge (RR = 1.37; 95% CI, 1.27–1.48); adding NRT further increased the treatment effect (RR = 1.54; 95% CI, 1.34–1.79). No benefit was found for less intensive programs, or for adding bupropion. However, a multicenter, double-blind, randomized, placebo-controlled trial in which smokers with acute coronary syndrome were randomized to receive varenicline initiated in hospital or placebo for 12 weeks, found that patients randomized to varenicline had significantly higher rates of smoking abstinence and reduction than patients randomized to placebo (47.3% 6-month point-prevalence abstinence vs. 32.5% in the placebo group, $p < .05$) (Eisenberg et al. 2016). All patients in this trial also received low-intensity counseling.

Rigotti and colleagues (2012) found a comparable effect for intensive counseling in rehabilitation hospitals after acute care for stroke, coronary heart disease, or cancer or chronic disorders, such as diabetes or asthma (RR = 1.71; 95% CI, 1.37–2.14). Although not included in Rigotti and colleagues (2012), other research has found that treatment of tobacco use during a visit to a smokefree psychiatric emergency room or during psychiatric hospitalization was associated with reductions in agitation, greater abstinence from smoking, and lower readmission rates (Allen et al. 2011; Prochaska et al. 2014). For example, Allen and colleagues (2011) found that at baseline, participants were at least moderately agitated, and 28% reported aggressive behavior during the previous week. The mean Agitated Behavior Scale scores for the nicotine replacement group were 33% lower at 4 hours and 23% lower at 24 hours than the respective scores for the placebo group.

Trials designed to link hospitalized smokers with quitline services have shown mixed results relative to standard, brief stop-smoking interventions (Rigotti et al. 2014, 2016; Cummins et al. 2016; Warner et al. 2016). For example, in a 2014 RCT of 397 smokers who received a cessation intervention during hospitalization at Massachusetts General Hospital, those assigned to the treatment condition that included postdischarge follow-up care were significantly more likely to achieve biochemically validated abstinence 6 months after discharge than those assigned to usual care (a referral to the state tobacco quitline) (27% vs. 16%; RR = 1.70; 95% CI, 1.15–2.51; $p = 0.007$) (Rigotti et al. 2014). However, in a 2016 RCT, patients were randomized to receive brief, in-hospital cessation advice or a brief, 5-minute quitline facilitation intervention that consisted of either a fax referral or a "warm handoff" (direct phone call to enroll the patient and arrange for an initial counseling call) to a tobacco quitline. Compared to those who received the brief, 5-minute cessation advice, less than 50% of the intervention group completed the first quitline intervention call, and results suggested no difference in rates of abstinence 6 months after discharge (Warner et al. 2016).

Overall, studies suggest that hospital-based cessation programs can lower readmission rates and are cost-effective for hospitals. For example, the Ottawa Model for Smoking Cessation—which identifies hospitalized smokers and provides in-hospital cessation counseling and medications and post-hospitalization follow-up—demonstrated increased smoking abstinence; lower rates of all-cause readmissions, smoking-related readmissions, and all-cause emergency department visits; and reduced healthcare costs (Mullen et al. 2017). The continuous 6-month abstinence rate was 29.4% for the intervention group versus 18.3% for controls (Reid et al. 2010). The largest absolute risk reductions (ARRs) were for all-cause readmissions at 30 days (13% vs. 7%; ARR = 6% [3–9%]; $p < 0.001$); 1 year (38% vs. 27%; ARR = 12% [7–17%]; $p < 0.001$); and 2 years (45% vs. 34%; ARR = 12% [7–17%]; $p < 0.001$) (Mullen et al. 2017). The greatest reduction in risk for all-cause visits to the emergency department was at 30 days (21% vs. 16%; ARR = 5% [0.4–9%]; $p = 0.03$). Reduction in mortality was significant by year 1 (11% vs. 5%; ARR = 6% [3% to 9%]; $p < 0.001$) and continued to be significant at year 2 (15% vs. 8%; ARR = 7% [4–11%]; $p < 0.001$). From the hospital payer's perspective, delivery of in-hospital cessation services was cost-effective, with 1-year cost per QALY gained of $C1,386 (Canadian dollars), and lifetime cost per QALY gained of $C68 (Mullen et al. 2015).

In a study of acute care patients who were current smokers and were admitted to and discharged from the Medical University of South Carolina between November 2014 and June 2015, researchers compared unplanned readmissions at 30, 90, and 180 days postdischarge between (a) current smokers who were exposed to a nicotine dependence treatment service while hospitalized with unplanned readmissions and (b) smokers who did not receive the service (Nahhas et al. 2017; Cartmell et al. 2018b). The treatment service consisted of at least a bedside consult and/or one interactive voice response (IVR) follow-up call. At 30 days postdischarge, smokers exposed to the nicotine dependence treatment service were about half as likely to be smoking as those who did not receive the service (51% abstinence vs. 27%) and had significantly lower odds of readmission (OR = 0.77, $p < .05$) than those who did not receive the service (Nahhas et al. 2017). Odds of readmission remained lower among smokers exposed to the intervention at both 90 and 180 days postdischarge but were no longer statistically significant (Cartmell et al. 2018b). In a separate follow-up study, Cartmell and colleagues (2018a) assessed cost savings to the hospital at 12 months postdischarge, finding that overall adjusted mean healthcare charges for smokers exposed to the intervention were about $7,300 lower than charges for those who did not receive the intervention.

Based on evidence of the effectiveness and benefits of interventions to help hospitalized smokers quit, The Joint Commission released an updated set of performance measures on tobacco cessation for hospitals (Fiore et al. 2012) (also see Chapter 7), but the final measures no longer contain the postdischarge follow-up component. Despite the growing body of evidence that hospital-initiated tobacco cessation interventions, especially programs that continue postdischarge, can increase abstinence, reduce readmission rates, and lead to cost savings, only about 5% of accredited acute care hospitals in the United States have selected and are reporting on the tobacco cessation measures from The Joint Commission, even without the follow-up component, and the number of hospitals reporting on these measures has decreased in recent years (The Joint Commission, personal communication, March 18, 2019). This is likely due to the voluntary nature of the measures (they are not currently tied to payment)—coupled with the fact that certain other measure sets from The Joint Commission are required or tied to payment, with the fact that performance measures are increasingly being reported electronically and the Joint Commission cessation measures have still not been fully converted electronically, and with the perception that other measure sets may be easier to implement and report on (Freund et al. 2008, 2009). If the cessation measures from The Joint Commission are not included in a CMS rule or otherwise tied to payment or required, then the number of acute care hospitals reporting on these measures is likely to continue to decline. In contrast, two of these measures (offering cessation counseling and medication during hospitalization and again at discharge) are embedded in the Inpatient Psychiatric Facility Quality Reporting Program, and inpatient psychiatric facilities are accordingly required to report on these measures.

Surgery

Like being hospitalized, undergoing surgery can be a source of motivation to quit smoking, especially if the surgery is related to a health condition caused by smoking and presents an opportunity for patients to quit and stay quit. Smoking is a risk factor for perioperative and postoperative complications (e.g., wound infection, respiratory failure, lengthy hospital stays, admission to intensive care unit, in-hospital mortality, and readmission) (Lavernia et al. 1999; Delgado-Rodriguez et al. 2003; Barrera et al. 2005; Warner 2006) across a variety of surgical specialties (Brooks-Brunn 1997; Glassman et al. 2000; Møller et al. 2002; Thomsen et al. 2010). Quitting smoking before surgery can improve outcomes and reduce healthcare costs (American College of Surgeons 2014). Surgery also presents an opportunity for patients to quit and stay quit. For example, a large cross-sectional study found that having a major surgery doubled the likelihood of quitting smoking—particularly for surgery related to conditions caused or exacerbated by smoking, such as cancer and heart disease (Shi and Warner 2010). Even having minor surgery increased quit rates by 28%—a finding that, because of the high occurrence of such surgeries, could have a substantial impact on population-level tobacco abstinence (Keenan 2009). Requiring tobacco cessation and offering cessation treatments before elective surgery could further increase this effect. In one study, perioperative patients who were given a brief consultation by a nurse, smoking cessation brochures, and access to 6 weeks of NRT and were referred to a quitline were 2.7 times more likely to achieve long-term cessation than patients who received usual treatment, which did not include such components (Lee et al. 2015). Although little research has focused on surgeons as providers of tobacco treatment, even brief counseling on smoking cessation by a vascular surgeon was found to increase patients' interest in cessation and awareness of the harms of smoking, and this effect was maintained 3 months after the intervention (Newhall et al. 2017).

The evidence suggests that cessation interventions delivered before and in connection with surgery can increase smoking cessation among patients and improve surgical outcomes. Based on data from observational

studies and systematic reviews of RCTs by Nolan and Warner (2017), offering evidence-based tobacco treatments before and/or immediately around the time of surgery improves surgical, cardiovascular, pulmonary, and wound-healing outcomes in the short and long terms. Across more than 400 studies, effect sizes for improvement of outcomes ranged from 1.56 to 2.73 in the treatment group compared with placebo, usual care, or brief advice. Thomsen and colleagues (2014) suggested that while the optimal intensity and timing of preoperative intervention remain unclear, based on indirect comparisons and evidence from two small trials, cessation interventions that begin 4–8 weeks before surgery, include weekly counseling, and use NRT are beneficial to reduce postoperative surgical complications and increase long-term smoking cessation.

Lung Cancer Screening

Lung cancer screening with low-dose computed tomography (LDCT) is associated with an estimated 20% lower mortality rate from lung cancer relative to chest x-ray because of earlier detection of the cancer (Aberle et al. 2011; Bach et al. 2012). Based on findings from large, well-controlled clinical trials, USPSTF (2015) recommends that LDCT screening be offered to patients at high risk for lung cancer, defined as adults 55–80 years of age with a 30-pack-year smoking history who currently smoke or have quit smoking within the past 15 years. USPSTF recommends that screening continue annually until the patient has remained abstinent from smoking for 15 years or reaches 80 years of age (Moyer 2014). In February 2015, CMS issued a national coverage determination requiring Medicare to cover LDCT screening for lung cancer if certain eligibility requirements are met, including being aged 55–77 years of age, having no signs or symptoms of lung cancer, having a tobacco smoking history of at least 30 pack-years, being a current smoker or one who has quit smoking within the past 15 years, and receiving a written order for LDCT that meets several criteria (CMS 2015). In 2015, an estimated 6.8 million current and former U.S. smokers met the criteria for LDCT lung cancer screening (Jemal and Fedewa 2017). Medicare reimbursement of lung cancer screening requires that smoking cessation be addressed (CMS 2015). The shared decision-making visit must include counseling on the importance of maintaining cigarette smoking abstinence (if the patient is a former smoker) or counseling on the importance of smoking cessation (if the patient is a current smoker), and providers must offer information about tobacco cessation interventions. In addition, eligibility criteria for radiology imaging facilities must include making smoking cessation interventions available for current smokers.

Because of the criteria for lung cancer screening, the population receiving screening by definition includes a large number of current longtime smokers. Given the heightened awareness of smoking-related cancers among patients presenting for LDCT screening, these men and women could be especially receptive to smoking cessation advice and interventions delivered throughout the screening process (including before, during, and after the screening). Research on the perceptions and beliefs about smoking and negative health outcomes among high-risk older smokers found high levels of awareness of the dangers of continued smoking and strong interest in quitting, even if the screening results showed no signs of lung cancer (Cataldo 2016).

Several studies of smokers undergoing a lung cancer screening trial found that (a) motivation to quit and quit rates were higher among study participants than among those in the general population and (b) persons with abnormal LDCT scans were significantly more likely to quit smoking than those without abnormal results (Taylor et al. 2007; Styn et al. 2009; Slatore et al. 2014; Tammemägi et al. 2014). For example, in the National Lung Screening Trial (a study of 53,454 current or former heavy smokers, 55–75 years of age, with 30 or more pack-years of smoking), participants with suspicious results (a nodule ≥4 mm on the computed tomography scan) reported approximately 6% lower rates of smoking compared with those with normal results from the scan (Slatore et al. 2014; Tammemägi et al. 2014).

Despite these findings, some researchers have posited that, in the absence of a comprehensive cessation component, lung cancer screening could potentially have a negative impact on smoking cessation, with smokers believing that they have already taken sufficient action to protect their health simply by undergoing screening (Harris 2015; Zeliadt et al. 2015). Such an impact could be especially pronounced among smokers who receive negative screening results (i.e., no sign of cancer), since they might interpret the results to mean that they have a clean bill of health and a green light to continue smoking (Harris 2015; Zeliadt et al. 2015). In the clinical guideline on *Pairing Smoking-Cessation Services with Lung Cancer Screening* issued by the Association for the Treatment of Tobacco Use and Dependence and the Society for Research on Nicotine and Tobacco, Fucito and colleagues (2016) reported that a limited amount of data are available on the topic. The small number of studies conducted to date have yielded mixed findings.

Several studies seeking to add cessation interventions to LDCT scans have not observed improved cessation outcomes (e.g., Clark et al. 2004; van der Aalst et al. 2012; Marshall et al. 2016). Most of these trials used minimally intensive cessation interventions (e.g., self-help

materials, lists of resources, tailored computer information), which may have contributed to the lack of significant findings. Some evidence suggests that more intensive cessation interventions delivered in this setting might be more effective, and that the timing of such interventions may matter. For example, in a pilot study in which 18 patients were offered one face-to-face counseling session and follow-up telephone counseling with medications, Ferketich and colleagues (2012) found biochemically confirmed quit rates of 33.3% when the cessation intervention was delivered before the lung cancer screening (vs. 22.2% when it was delivered later). In addition, Park and colleagues (2015) reported increased quit rates when patients undergoing lung cancer screening received multisession, more intensive visits that included providing assistance (e.g., providing cessation counseling and/or prescription medication) and arranging follow-up.

In summary, although studies of LDCT scans have had positive effects on cessation behaviors, the optimal smoking cessation strategy for smokers who undergo LDCT screening remains unclear (Marshall et al. 2016), and research on the effectiveness of cessation interventions among persons receiving LDCT is still limited (Piñeiro et al. 2016). More research is needed to identify the most effective types of messaging and other types of cessation interventions to increase motivation to quit, quit attempts, and successful cessation among smokers who undergo lung cancer screening. Eight large RCTs of smoking cessation interventions for patients undergoing lung cancer screening are underway (Joseph et al. 2018; Taylor et al. 2019). These studies, along with future surveillance of populations undergoing lung cancer screening, will be critical to better understanding the impact of lung cancer screening on smoking and smoking cessation behaviors. In the interim, it is important for clinicians and lung cancer screening sites to deliver cessation interventions to this high-risk population and to evaluate and report the results to inform best practices in this area.

Readiness to Quit and Approaches for Quitting Ambivalence

The *Clinical Practice Guideline* recommends providing brief motivational counseling to smokers who are ambivalent about quitting (Fiore et al. 2008). Although nearly 7 out of 10 adult cigarette smokers reported that they want to stop smoking completely (Babb et al. 2017), just over 5 out of 10 reported trying to quit in the past year (Babb et al. 2017), suggesting that a substantial number of smokers are not yet ready to quit or are ambivalent about quitting. The Stages of Change Model provides a framework for assessing readiness to quit and for tailoring interventions accordingly. Cessation strategies tailored to a smoker's readiness to quit are less likely to be perceived as overwhelming because the smoker is less likely to feel that these strategies are rushing them into action (Hall et al. 2006; Fiore et al. 2008; Prochaska et al. 2014). Readiness to quit can be conceptualized as a continuum of stages proceeding from precontemplation (no immediate intention to stop smoking) to contemplation (intending to quit in the next 6 months) to preparation (considering quitting in the next month, with at least one quit attempt in the past year) to action (has quit smoking for less than 6 months) and finally to maintenance (has quit smoking for at least 6 months) (Prochaska and DiClemente 1983). It should be noted, however, that smokers' progression through the stages of change is not necessarily sequential or orderly. Rather, smokers' motivations and readiness to quit are transient and fluctuate over time, and smokers may make spontaneous, unplanned quit attempts without first passing through all the stages of change (West 2005).

Unlike clinically based models, tailoring treatments to a smoker's stage of readiness to change recognizes that individual smokers may not always be receptive to certain types of cessation interventions. Part of the utility of this model is that it identifies a patient's stage of readiness and suggests interventions that can help move the patient to a point where he or she is ready to take advantage of standard treatment models. Motivational interviewing and adaptations of this approach (reviewed previously in this chapter) follow an intervention framework that is distinct from, but generally consistent with, stage-based approaches.

Stage-based, computer-delivered interventions have demonstrated efficacy for supporting smokers through the process of quitting, including smokers with depression or serious mental illness (Prochaska et al. 1993, 2001a,b, 2014; Velicer et al. 1999; Hall et al. 2006). In their review of 22 stage-based cessation interventions, Riemsma and colleagues (2003) found stronger effects in higher quality studies and with interventions tailored to all constructs of the Transtheoretical Model (Prochaska and DiClemente 1983), not just to the stage of change (Spencer et al. 2002). The review noted generally positive outcomes of the interventions and indicated a clear relationship between study quality and statistical significance: only 1 of 5 (20%) low-quality studies, 8 of 14 (57%) moderate-quality studies, and 3 of 4 (75%) of the highest quality studies yielded a significant finding. However, 1 of the 4 studies in the highest quality group had a small sample and a short follow-up, and was group-matched on only one stage of the Transtheoretical Model.

Some have argued that applying the Transtheoretical Model and Stages of Change Model to smoking cessation assigns smokers to stages based on arbitrary time periods that are not rooted in the science of smoking cessation

(e.g., a smoker ready to quit in 30 days is considered to be in the preparation stage, but one ready to quit in 31 days is in the contemplation stage [West 2005]). Another potential limitation of a stage-based approach is that it assumes that smokers make coherent and stable plans about quitting, but other research suggests that intentions to quit may be unstable (Hughes et al. 2005) and that smokers may make spontaneous quit attempts with no planning or preparation (Larabie 2005; Cooper et al. 2010). Finally, because the Stages of Change Model prioritizes intervening with smokers who are preparing to quit or actively engaged in quitting, some have argued that this approach may fail to offer effective interventions to smokers who might have been receptive to them (e.g., smokers who are contemplating a quit attempt or who may be ambivalent [West 2005]). Indeed, some evidence suggests that cessation assistance should be offered to as broad a spectrum of smokers as possible, because current motivation to quit does not necessarily predict future abstinence (Pisinger et al. 2005).

Although the Transtheoretical Model and the Stages of Change Model have been widely applied to the field of smoking cessation and can be used to assess interest in and ambivalence about quitting and to tailor cessation interventions accordingly, clinicians should also be advised that the manner in which smokers approach quitting at a population level may not map onto these models. Offering support to as wide a range of smokers as possible is likely the best approach to increase quit attempts and successful quitting. However, more research is needed on such an approach, including unintended consequences. For example, offering widespread support could reduce cost-effectiveness, as interventions could be given to more numbers of smokers who are not ready and, as a result, would not quit.

Considerations for Subpopulations

As the prevalence of cigarette smoking in the general U.S. population has declined over time, increased attention has been devoted to tobacco cessation interventions focused on certain subgroups that may be more likely to smoke, be heavier smokers, bear a disproportionate burden of smoking-related morbidity and mortality, and face special challenges in quitting. In some cases, certain populations or conditions may warrant specific cessation interventions and/or lack an indication for or have certain considerations or contraindications related to cessation medication. This section outlines the evidence and considerations for cessation interventions across specific populations and/or conditions for which existing interventions are not indicated and/or are less effective.

Pregnant Women

Pregnant women are a priority population for tobacco cessation because of the health risks that tobacco use during pregnancy poses to the mother and the fetus (USDHHS 2001, 2004, 2014). Furthermore, pregnancy can offer an opportunity to quit smoking because pregnant women are highly motivated to take actions to protect the health of their babies (DiClemente et al. 2000). The literature indicates that, among American women who smoked during the 3 months before they became pregnant, about 50% quit during pregnancy (Tong et al. 2013; Curtin and Mathews 2016). However, rates of postpartum relapse among women who quit smoking during pregnancy may be as high as 50% (Tong et al. 2013). Large variations in rates of smoking during pregnancy are seen across subpopulations and states (Curtin and Mathews 2016; Drake et al. 2018). Rates of smoking during pregnancy are higher among younger women, women with lower levels of education, economically disadvantaged women, and women who have not planned their pregnancy (Mosher et al. 2012; Curtin and Mathews 2016; Drake et al. 2018). Pregnant women and women of reproductive age who smoke are also more likely to live in low-resource environments that potentially subject them to high levels of stress (Coleman-Cowger et al. 2016; Mazurek and England 2016), and being pregnant may represent an additional stressor for these women. This context provides important insights into the potential challenges of providing smoking cessation treatment during pregnancy.

The *Clinical Practice Guideline* concluded that there was insufficient evidence for the effectiveness of smoking cessation medications in pregnant women (Fiore et al. 2008). Similarly, USPSTF (2015) concluded that evidence is not sufficient to assess the balance of benefits and harms of pharmacotherapy interventions for tobacco cessation in pregnant women. More research is needed before definitive guidance can be provided on this topic (Fiore et al. 2008; Coleman et al. 2012a, 2015; Myung et al. 2012). Results have been mixed in reviews of the use of cessation pharmacotherapies (with most of the studies focusing on NRT) in women who smoke during pregnancy. These findings suggest that adding NRT to behavioral interventions may not increase quitting in this population (Coleman et al. 2012a, 2015; Myung et al. 2012). This may be due in part to a low medication adherence rate in trials to

date (Wisborg et al. 2000; Pollak et al. 2007; Coleman et al. 2012b).

Pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before using pharmacologic approaches. In individual cases, however, women and their physicians may opt to use cessation medications, including such alternatives to NRT as bupropion or varenicline. However, these decisions should be made in consultation with a physician after carefully considering the specific circumstances and weighing the risks of using medication against the risks of continued smoking (Fiore et al. 2008).

With regard to behavioral cessation interventions for pregnant women, USPSTF (2015) recommends that, as a Grade A intervention, clinicians ask all pregnant women about tobacco use, advise pregnant women who use tobacco to stop, and provide behavioral cessation interventions to pregnant women who use tobacco. Recent studies have suggested that social support is highly predictive of successful smoking cessation during pregnancy (Smedberg et al. 2014; Boucher and Konkle 2016). In addition, intervention approaches that address the health of the mother and the health of the fetus may increase long-term abstinence (Flemming et al. 2015; Bauld et al. 2017). Cessation interventions that are more intensive, are tailored, and go beyond advice to quit are more effective in this population (Fiore et al. 2008; Lumley et al. 2009). WHO (2013) recommends behavioral cessation interventions—such as health education, counseling, social support, and incentives for abstinence—as effective approaches to increasing cessation during pregnancy and to improving health outcomes for both the baby and the mother. Quitline counseling may be a useful cessation intervention for pregnant smokers, but more research is needed on the specific features that make this intervention optimally effective (e.g., the timing and frequency of calls during pregnancy and/or postpartum for relapse prevention and tailoring approaches) (Bombard et al. 2013; Cummins et al. 2016).

A growing body of evidence suggests that incentives and contingency management techniques (reviewed in detail elsewhere in this chapter) are effective cessation interventions for pregnant women (Higgins et al. 2004, 2010b, 2014; Heil et al. 2008; Cahill et al. 2015). For example, Cahill and colleagues (2015) found that incentive-based smoking cessation programs produced better outcomes for pregnant women than among controls (OR = 3.6; 95% CI, 2.39–5.43), with assessments out to 3 months postpartum. The same review concluded that such programs improve abstinence while the incentives remain in place. Despite these promising results, more evidence is needed to fully understand the effectiveness of incentive interventions in producing sustained cessation outcomes in pregnant women who smoke. Although it may be challenging to convince payers to implement incentive interventions on a population scale, they may be more willing to consider doing so in this case, given the high costs of smoking-related adverse birth outcomes and the short-term cost savings associated with preventing these outcomes.

Lesbian, Gay, Bisexual, and Transgender Populations

In part because the tobacco industry has directly targeted the lesbian, gay, bisexual, and transgender (LGBT) population with marketing and outreach (Washington 2002; Stevens et al. 2004; Dilley et al. 2008), the prevalence of cigarette smoking and other tobacco use is substantially higher in these groups than in non-LGBT populations (Hu et al. 2016). For example, in a large national health survey (Jamal et al. 2016), the prevalence of smoking was higher among adults who were lesbian, gay, or bisexual (20.6%) than among heterosexual adults (14.9%). In 2015, gay, lesbian, and bisexual adult smokers, as a group, reported a lower prevalence of cessation counseling and/or medication use (14.5%) when trying to quit than did straight smokers (31.7%) (Babb et al. 2017). In addition, transgender adults report higher use of cigarettes and other tobacco products than cisgender persons (people whose gender identity matches the sex they were assigned at birth). Data from a 2013 nationally representative survey found that 35.5% of transgender adults reported past-month cigarette use compared with 20.7% of cisgender adults (Buchting et al. 2017). Although data are not available on the use of tobacco cessation treatments by transgender adults, as a group they are more likely to postpone general medical care and to report barriers in accessing care, primarily because they encounter discrimination when seeking care and cannot afford care (Grant et al. 2010).

Reviews of cessation treatments in LGBT populations have found that such treatments can be effective, but data are limited (Lee et al. 2014; Berger and Mooney-Somers 2016). In addition to the inclusion of elements of standard behavioral cessation treatment, most studies of this topic have investigated the effect of cessation interventions that have been modified to address LGBT-specific issues, including providing information about the tobacco industry's targeting of LGBT communities, the role of tobacco use in LGBT social activities, LGBT-specific smoking triggers, and social justice considerations (Berger and Mooney-Somers 2016). Notably, a systematic review of 19 LGBT-focused cessation interventions reported cessation rates of 30–40% out to 3–6 months (Berger and Mooney-Somers 2016). Although these results appear promising, none of the studies used adequate control groups, so a rigorous evaluation of efficacy was not possible.

To more actively engage LGBT communities in smoking prevention and cessation, some national smoking cessation campaigns (e.g., *Tips From Former Smokers* [CDC]) have included multimedia promotional materials designed specifically for LGBT populations. In May 2016, FDA launched *This Free Life,* a tobacco public education campaign that aims to prevent the escalation to daily tobacco use among lesbian, gay, bisexual, and transgender (LGBT) young adults, 18- to 24 years of age, who are nondaily or occasional smokers (FDA 2019b). *This Free Life* uses a range of primarily digital marketing tactics, including social media and online advertisements, to deliver messages to diverse subpopulations of the LGBT community. Evaluations of the effect of these large-scale promotions are ongoing, but the data are not yet available.

Populations with Mental Health Conditions and Co-Occurring Substance Use Disorders

Mental health conditions and substance use disorders commonly co-occur with smoking. Adults with mental health or substance use disorders account for 40% of all cigarettes smoked (Substance Abuse and Mental Health Services Administration 2013). In 2012–2014, the prevalence of cigarette smoking was higher among adults with any mental illness than among adults with no mental illness (33.3% vs. 20.7%, respectively, $p < .05$) (Lipari and Van Horn 2017). Nationally representative data from 2017 suggest that tobacco is used by 40.8% of individuals with serious psychological distress and 18.5 % of those without serious psychological distress (Wang et al. 2018). In 2013, 65.2% of adult cigarette smokers also reported using alcohol (vs. 48.7% of nonsmoking adults), and 18.9% reported past-month use of other drugs (vs. 4.2% of nonsmoking adults) (Substance Abuse and Mental Health Services Administration n.d.). Behavioral health conditions also affect smoking patterns in ways that can make quitting more difficult. For example, the average number of cigarettes smoked in the past month was higher among adult smokers with any mental illness (326) than among adult smokers with no mental illness (284) (Lipari and Van Horn 2017).

The high prevalence of smoking among persons with mental illness is due in part to their lower rates of quitting smoking over time (Prochaska et al. 2017). In addition, mental illness is associated with heavier smoking, greater nicotine dependence, more pronounced withdrawal symptoms when quitting, and lower quit rates (Hall and Prochaska 2009). Although research on smoking and mental illness has increased markedly in recent years, cessation intervention studies on this population are still limited. A statistical analysis of the literature on tobacco and mental illness documented a steady increase in research publications in this area for three 2-year periods: 1993–1995 (n = 65), 2003–2005 (n = 153), and 2013–2015 (n = 329) (Metse et al. 2017). However, the study designs remained predominantly descriptive in form (>80%), and few experimental studies tested cessation interventions (<13%).

A meta-analysis of 26 tobacco intervention studies found that smoking cessation was significantly associated with decreases in anxiety, depression, and stress and with improvements in overall mood and quality of life (Taylor et al. 2014). Notably, the strength of these relationships did not vary based on the presence or absence of a psychiatric diagnosis. In trials of tobacco cessation interventions conducted among smokers with psychiatric disorders, quitting smoking was associated with reductions in depression, anxiety, and symptoms of posttraumatic stress disorder and psychosis and with rapid changes in mood (Potkin et al. 2003; McFall et al. 2010; Kahler et al. 2011; Krebs et al. 2016). A meta-analysis that focused on smokers in treatment for substance use disorders found that tobacco cessation interventions were associated with a 25% increased likelihood of abstinence from alcohol and other drugs relative to usual care (Prochaska et al. 2004). A randomized trial of smokers recruited from inpatient psychiatric facilities found that a tobacco cessation intervention was associated with a significantly lower likelihood of readmission (Prochaska et al. 2004). In the past, many behavioral health clinicians believed that treating nicotine dependence and tobacco cessation jeopardize sobriety or mental health recovery (Baca and Yahne 2009), a misconception that has been actively fostered by the tobacco industry (Prochaska et al. 2008; Hall and Prochaska 2009). However, smoking cessation and the delivery of tobacco cessation treatments are associated with enhanced clinical outcomes, including improved sobriety, fewer symptoms of posttraumatic stress disorder, and lower rates of hospitalization.

Another RCT was conducted in 10 community mental health centers to determine whether smokers with schizophrenia or bipolar disease have higher rates of tobacco abstinence with pharmocotherapy than with standard treatment (Evins et al. 2014). There were 87 smokers with schizophrenia or bipolar disease who received 12 weeks of varenicline and achieved 2 weeks or more of continuous abstinence by week 12 who were randomly assigned to receive cognitive behavioral therapy and varenicline or placebo. At week 52, biochemically verified 7-day point-prevalence abstinence rates were 60% in the varenicline group (24 of 40) versus 19% (9 of 47) in the placebo group (OR = 6.2; 95% CI, 2.2–19.2; $P < .001$). The authors concluded that among smokers with serious mental illness who attained initial abstinence with standard treatment,

maintenance pharmacotherapy with varenicline and cognitive behavioral therapy improved prolonged tobacco abstinence rates compared with cognitive behavioral therapy alone after 1 year of treatment and at 6 months after treatment discontinuation (Evins et al. 2014).

Approaches to smoking cessation with demonstrated efficacy among smokers with mental illness or addictive disorders include motivational and stage-based treatments and behavioral therapy that is offered outside of or integrated within mental health or addictions treatment, delivered in person or via a quitline, and combined with cessation pharmacotherapy (Hall and Prochaska 2009). The California Smokers' Helpline reported that nearly 1 in 4 of 844 smokers who called the helpline in 2007 and were screened for depression, met criteria for a current major depressive disorder and that quit rates at the 2-month follow-up were lower in this group (19%) than among callers without depression (28%) (Hebert et al. 2011). More generally, the convenience and accessibility of quitlines make them an important option for clinician referrals among this population. Supplementary cessation services and treatments that can complement clinician and quitline interventions, such as in-person counseling and cessation medication, may further increase quit rates. A randomized trial of 577 mental health patients in the Veterans Health Administration found that a specialized quitline for smokers referred by a mental health provider outperformed standard state quitlines, with significantly greater 30-day abstinence at 6 months (26% vs. 18%) and greater patient satisfaction (Rogers et al. 2016).

A Cochrane Review of trials testing smoking cessation interventions that included specific mood management components for depression versus a standard intervention showed a significant positive effect for smokers with current depression (11 trials; N = 1,844; RR = 1.47; 95% CI, 1.13–1.92) or past depression (13 trials; N = 1,496; RR = 1.41; 95% CI, 1.13–1.77) (van der Meer et al. 2013). The interventions largely followed a behavioral therapy approach, offering group or individual counseling sessions. For example, the treatments encouraged participants to monitor their mood with a daily rating scale and to learn and apply skills to decrease negative moods and increase pleasant ones—such as by recognizing maladaptive thoughts, disputing negative thinking, engaging in pleasant activities, increasing positive social contacts, and setting realistic goals (Hall et al. 1994, 1996).

Researchers have also tested the use of medications for mood management when quitting smoking. In one systematic review, use of bupropion and nortriptyline, which are both antidepressants, resulted in a statistically significant increase in tobacco abstinence, irrespective of depression history, but selective serotonin reuptake inhibitors (e.g., fluoxetine, sertraline) and monoamine oxidase inhibitors (MAOIs) were not found to increase smoking cessation (Hughes et al. 2014).

Postmarketing reports, which are mandated by FDA, have raised concerns that persons taking varenicline may experience increased intoxicating effects when consuming alcoholic beverages. However, these effects have not been observed in clinical trials. Instead, evidence suggests that varenicline may aid in quitting smoking while also reducing drinking in men who drink excessively. A double-blind RCT of 131 smokers (30% women) with alcohol use disorders found that varenicline with medical management resulted in an increased rate of smoking abstinence overall and in decreased heavy drinking among men (O'Malley et al. 2018). These findings are important in light of the high rate of comorbid smoking and heavy drinking, but more research is needed.

In conclusion, individuals with behavioral health conditions smoke at a significantly higher rate than the general population and generally have a more difficult time quitting, despite being equally interested in quitting. However, evidence increasingly suggests that quitting smoking does not jeopardize the success of treatment for mental health conditions or substance abuse and may actually enhance recovery outcomes (McKelvey et al. 2017). Additional research is needed on which tailored tobacco cessation interventions are most effective in helping persons with behavioral health conditions quit smoking.

Adolescents

Nearly 9 out of 10 smokers first try smoking by 18 years of age, with 99% of smokers doing so by age 26 (USDHHS 2012, 2014). Accordingly, tobacco use can be considered a pediatric disorder (USDHHS 2012). Other data suggest that initiating tobacco use at 13 years of age or younger is associated with continuous daily and nondaily use during adolescence and with the development of nicotine dependence, compared with initiating tobacco use at 14 years of age and older (Sharapova et al. 2018). Once adolescents progress to established smoking, few of them attempt to quit, few quit successfully when trying on their own (7%), very few seek help quitting, and success rates are low—even among those who obtain help (12%) (Sussman et al. 1999; USPSTF 2016). Estimates suggest that quitting smoking before 35 years of age prevents much of the harm from smoking (Doll et al. 2004; Jha et al. 2013; Pirie et al. 2013). However, the average age of quitting in the United States is approximately 40 years of age, and this age did not change significantly between 1997–98 and 2011–12 (Schauer et al. 2015a). Because most smokers start young and because quitting is difficult once smoking becomes established, efforts to prevent adolescents from

ever starting to smoke and to help adolescents who start smoking to quit as soon as possible are critical.

The evidence for the effectiveness of cessation interventions targeting youth is mixed. A 2013 systematic review by USPSTF found stronger evidence for interventions by primary care providers to prevent youth smoking initiation than for provider actions to help youth who already smoke quit. The review concluded that, while primary care-based behavioral interventions may prevent smoking initiation among youth, these interventions, alone or in combination with cessation medications (bupropion or bupropion plus NRT), have not been shown to increase rates of smoking cessation among youth (Patnode et al. 2013). The review included studies of smokeless tobacco cessation interventions and very brief advice, as well as limited print-based interventions. In a Cochrane Review of primary care- and school-based tobacco cessation interventions for young people, which had broader criteria for including trials, included smokers younger than 20 years of age, and pooled data from 28 controlled trials, Stanton and Grimshaw (2013) identified as "promising" those approaches that were based on the Stages of Change Model (pooled RR = 1.56 at 1 year; 95% CI, 1.21–2.01) or included motivational enhancement therapy (RR = 1.60; 95% CI, 1.28–2.01). Only 3 of the 28 trials tested pharmacologic approaches, and those trials reported limited efficacy.

Cessation medications are not approved by FDA for use with children or adolescents, and NRT cannot be purchased over-the-counter by persons younger than 18 years of age (Johnson et al. 2004; Karpinski et al. 2010). However, cessation medications can be prescribed for and used by youth under the supervision of a physician. The *Clinical Practice Guideline* found insufficient evidence for the effectiveness of cessation medications in adolescents (Fiore et al. 2008). A study of 120 smokers 13–17 years of age found that the nicotine patch, but not nicotine gum, had a statistically significant effect on prolonging abstinence relative to placebo (Moolchan et al. 2005). More explicit evidence-based recommendations are needed to guide clinicians and parents in weighing the potential benefits and risks of specific smoking cessation medications in adolescent patients (*Federal Register* 2018).

With regard to behavioral smoking cessation interventions for children and adolescents, a 2016 meta-analysis of such interventions in primary care settings found a 34% increase in quit rates relative to control conditions (RR = 1.34; 95% CI, 1.05–1.69), with an absolute effect of 7.98% for cessation and a number needed to treat of 13 (95% CI, 6–77) (Peirson et al. 2016). The review excluded studies of smokeless tobacco, brief counseling, print materials, and NRT. Of the four studies reviewed, the intervention with the strongest effect (a 24% reduction in smoking) was based on the Stages of Change Model and was personalized, computer assisted, and motivationally tailored (Hollis et al. 2005). Adolescents were recruited in a clinic setting, and the intervention lasted 12 months. The intervention focused solely on tobacco use (rather than addressing tobacco use in conjunction with additional risk behaviors) and included educational components (Hollis et al. 2005). Further research is needed to identify and replicate best practices for tobacco cessation interventions with adolescent smokers. However, recruitment is a major challenge to research on cessation among youth, in part because of parental consent and youth emancipation laws that are in place in most states. At this juncture, focusing on prevention efforts in youth (USDHHS 2012) is likely to yield the greatest impact in terms of reducing the prevalence of tobacco use in future generations. However, continued efforts are warranted to develop effective cessation treatments and interventions for young people who are already established cigarette smokers or established users of e-cigarettes or other tobacco products and who may already be addicted to nicotine.

Dual Tobacco Product Users

Dual tobacco use, which is commonly defined as the use of cigarettes concurrently with other tobacco products (including e-cigarettes), has become increasingly common. Among current adult e-cigarette users in the 2017 National Health Interview (NHIS) Survey, 49.6% were current smokers of conventional cigarettes (NHIS public use data 2017). Per data from NHIS, nearly 60% of adult e-cigarette users in 2015 were also current cigarette smokers, suggesting that dual use of e-cigarettes and cigarettes is a common pattern (CDC 2016). In fact, this was the most common product combination among adults who reported using two or more tobacco products. A study using data from the PATH Study found that more than one-third (37.8%) of adult tobacco users in 2013–2014 were multiple-product (or polytobacco) users, with the most common combination being cigarettes plus e-cigarettes (Kasza et al. 2017). Among the sample of youth (12–17 years of age) in the PATH Study, 43% of those using tobacco in the previous 30 days were multiple-product users; again, cigarettes plus e-cigarettes was the most common combination, followed by cigarettes plus cigarillos. In the 2018 National Youth Tobacco Survey, the prevalence of multiple product use among current tobacco users of high school age was 37% for girls and 45% for boys (Gentzke et al. 2019). A probability-based survey of 1,836 cigarette smokers found that concurrent use of cigarettes and alternative tobacco products (loose leaf chewing tobacco, moist snuff, snus, dissolvable tobacco, or e-cigarettes) was positively associated

with making cessation attempts and having intentions to quit but was not associated with quit success (Popova and Ling 2013). A larger study of quit attempts and interest in quitting among 26,000 smokers found no clear differences between cigarette-only use versus dual use of cigarettes and cigars or smokeless tobacco (Schauer et al. 2016b).

A few studies have compared quitting behaviors between adult cigarette-only users and dual users. In the 2010–2011 Tobacco Use Supplement to the Current Population Survey, cigarette-only and dual users (defined as users of cigarettes plus cigars or smokeless tobacco) reported a comparable prevalence of attempts to quit cigarettes, with both groups making suboptimal use of evidence-based cessation treatments (Schauer et al. 2016b). Other studies have suggested that many cigarette smokers who are trying to quit are using e-cigarettes as one method of quitting, as discussed previously in this chapter (Caraballo et al. 2017; Zhu et al. 2017). An online survey of 1,324 adults found that dual use of cigarettes with smokeless tobacco was associated with past attempts to quit smoking by switching to smokeless products, while dual use of cigarettes with e-cigarettes was associated with prior use of cessation medications and strong sentiment against the tobacco industry (Kalkhoran et al. 2015).

Although at least one-third of tobacco users are dual users, most trials of tobacco treatments focus exclusively on cigarette smoking cessation and do not address cessation interventions for other types of tobacco products. While noting that all tobacco products deliver toxicants and pose health risks, the 2014 Surgeon General's report concluded that the overwhelming burden of death and disease from tobacco use in the United States is caused by cigarettes and other combustible tobacco products (USDHHS 2014). The report also acknowledged that the recent shift in patterns of tobacco use could have several potential impacts, ranging from the positive effect of accelerating the rate at which smokers completely quit smoking cigarettes to the negative effect of delaying complete cessation of all tobacco products, especially cigarettes. Despite the general acceptance of a continuum of risk across tobacco products (USDHHS 2014), the specific risk posed by each class of tobacco products has not been established and is difficult to estimate with precision because of the wide spectrum of products within each product class and the differences in how they are used.

Although the use of noncombustible tobacco products does not expose users to the same mix of toxicants via the same mode of administration as cigarette smoking, all tobacco products carry inherent risks. Risks for dual users may be particularly harmful if they delay cessation from combustible tobacco (USDHHS 2014, 2016). For example, smokeless tobacco has been shown to cause cancers of the mouth, esophagus, and pancreas; diseases of the mouth; and adverse reproductive outcomes (WHO and International Agency for Research on Cancer 2007; USDHHS 2014; NCI and CDC 2014). E-cigarettes emit fewer and lower levels of certain harmful substances than conventional cigarettes, but the long-term health risks of using these products remain unknown, and short-term risks are only slowly coming into focus. Several studies demonstrate e-cigarette aerosol contains fine and ultrafine particles, such that use of the products could potentially increase cardiovascular and respiratory risks (USDHHS 2016; Alzahrani et al. 2018; Nabavizadeh et al. 2018; National Academies of Sciences, Engineering, and Medicine 2018; Gotts et al. 2019). Therefore, only complete cessation of all tobacco products fully eliminates all tobacco-related health risks. Nevertheless, based on currently available evidence, nonpregnant adults would be expected to reduce their risk of smoking-attributable disease and death if they completely substituted all combustible tobacco products with noncombustible tobacco products. Whether these products will realize the potential of harm reduction depends in part on how their use affects smokers' attempts to quit cigarettes—either by switching completely to a noncombustible tobacco product or by discontinuing all tobacco use—combined with their impact on youth uptake of e-cigarettes and other tobacco products.

The *Clinical Practice Guideline* called for more research on effective cessation medications and counseling interventions for persons who are dual users of cigarettes and smokeless tobacco (Fiore et al. 2008), but research in this area remains sparse more than 10 years after the *Guideline* was released. In one study, an interactive, tailored, web-based intervention for smokeless tobacco use was found to significantly increase (nearly double) the likelihood of participants abstaining from all tobacco products (Severson et al. 2008). Another study examined the impact of a 40-minute, single contact, tobacco cessation intervention among 1,055 airmen enrolled in technical training in the U.S. Air Force (USAF) (Little et al. 2016). The USAF intervention addressed cigarettes, smokeless tobacco, snus, cigars, cigarillos, pipes, e-cigarettes, "roll your own" cigarettes, and hookah. From before the training to immediately after the training, perceptions of harm increased for all nine tobacco products among both tobacco users and nonusers, but intention to consume tobacco products was reduced mainly among existing tobacco users. Behavioral outcomes were not assessed, given the short assessment window (Little et al. 2016).

Much remains to be learned about best practices for achieving and sustaining abstinence from all tobacco products among dual users. Although few interventions have been studied for cessation from all tobacco products, some cessation medications (bupropion, varenicline, NRT) have been found to be effective for cessation

from cigarettes and smokeless products (independently) (Ebbert et al. 2007; Fagerström et al. 2010; Cahill et al. 2016; Schwartz et al. 2016; Hartmann-Boyce et al. 2018). Such medications could be candidates for tobacco cessation efforts among dual users of those two products. More also needs to be learned about (a) the degree to which e-cigarettes may promote or impede efforts to quit smoking and (b) the relative health benefits or harms from cessation of one tobacco product, but not all tobacco products, among dual or multiple tobacco product users.

Light and Nondaily Tobacco Users

The prevalence of daily smoking has decreased over the past two decades, but the proportion of light cigarette smoking (usually defined as 10 or fewer cigarettes smoked per day) has generally increased (Pierce et al. 2009; Jamal et al. 2018) and the prevalence of nondaily smoking has been generally stable (Schauer et al. 2016a). For example, among current U.S. smokers, the proportion of daily smokers was 76.1% in 2016, which declined from 80.8% in 2005 (p trend <0.05) (Jamal et al. 2018). During 2005–2016, increases occurred in the proportion of daily smokers who smoked 1–9 cigarettes per day (16.4% to 25.0%) or 10–19 (36.0% to 39.0%) cigarettes per day, and decreases occurred in the proportion of daily smokers who smoked 20–29 (34.9% to 28.4%) or ≥30 (12.7% to 7.5%) cigarettes per day (p trend <0.05) (Jamal et al. 2018). Nationally representative data from 2015 indicate that 24.3% of all smokers were nondaily smokers, and 25.1% of current daily smokers were light smokers (defined in this study as smoking 1–9 cigarettes per day) (Jamal et al. 2016). Nondaily smokers often do not consider themselves to be smokers; up to 42% classify themselves as nonsmokers when asked (Fergusson and Horwood 1995). Consequently, nondaily smoking is under-recognized by clinicians (Schane et al. 2009), which might result in their being less likely to deliver cessation interventions to this group of smokers. Studies have also pointed to potential challenges in motivating light and nondaily smokers to quit, given they are more likely to concurrently use other tobacco products than are heavier smokers (Reyes-Guzman et al. 2016). On the other hand, some studies have found that nondaily smokers report greater intention to quit and are more likely to succeed in quitting than daily smokers (Hennrikus et al. 1996; Sargent et al. 1998). Whereas daily smokers' intentions to quit may be driven in part by their level of nicotine dependence, nondaily smokers' intentions to quit may be more related to situational cues and sociodemographic characteristics (Fagan et al. 2007; Shiffman et al. 2014).

Most tobacco cessation interventions target daily heavy smokers (Fiore et al. 2008). However, cessation interventions are also critically important for nondaily and light smokers, but cessation approaches for these populations may require a new treatment paradigm (Hassmiller et al. 2003; Wortley et al. 2003). The *Clinical Practice Guideline* concluded that there was insufficient evidence for the effectiveness of using cessation medications in persons who smoke fewer than 5–10 cigarettes per day (Fiore et al. 2008). A review by Lindson and colleagues (2019) identified few studies on the role of NRT for persons smoking fewer than 15 cigarettes per day.

Furthermore, preliminary data suggest that standard cessation counseling that focuses on calling attention to personal health risks may not motivate nondaily or light smokers to quit, in part because they may believe that they have already minimized their health risks by using tobacco less intensively (Hyland et al. 2005; Tong et al. 2006). Despite these beliefs, studies indicate that light and nondaily smoking significantly increases risk for tobacco-related disease, especially cardiovascular and respiratory harms (Luoto et al. 2000; Hackshaw et al. 2018; Kameyama et al. 2018) and all-cause mortality (Inoue-Choi et al. 2017; Løchen et al. 2017). Moreover, the dose-response relationship between cigarette consumption and cardiovascular risk is not linear (USDHHS 2010).

Studies testing the impact of messages about the health harms associated with cigarette smoking generally have not focused on specific tobacco-related harms that are relevant to light and nondaily smoking. Messages about these effects could be more impactful for these groups of smokers, both clinically and at a population level, and should continue to be studied.

Data from observational and pilot studies of treatments suggest that counseling nondaily smokers on the dangers that their secondhand smoke poses to others could also be an effective approach for motivating them to quit (Tong et al. 2006; Schane and Glantz 2008; Schane et al. 2013). In the 1970s, research conducted by the tobacco industry concluded that social, infrequent, or nondaily smokers felt immune to the personal health effects of tobacco use but were concerned about the effects that their secondhand smoke might have on others (Schane et al. 2009).

Although further research on cessation interventions for nondaily smokers is needed, emerging evidence suggests that educating nondaily smokers about the dangers that secondhand smoke poses to nonsmokers is a powerful cessation message and may be more effective than traditional smoking cessation counseling that emphasizes the health consequences for the smoker (Schane et al. 2013). In addition, improved clinical identification of light and nondaily smokers is needed to help clinicians target these groups with strong messages emphasizing that no level of smoking is safe.

Emerging Intervention Approaches

Emerging Behavioral Treatments

In considering potential future directions for behavioral smoking cessation treatments, a wide variety of possible strategies exist to increase their reach while maintaining or improving their efficacy, thus increasing their impact. Two innovative approaches are (1) the expansion of treatment targets and (2) the use of emerging technologies to better time and personalize the delivery of behavioral cessation interventions.

Expanding Behavioral Treatment Targets

Although behavioral therapy is well established as the mainstay of most empirically based behavioral cessation interventions, applying constructs from other psychological theories could potentially enhance the efficacy of these interventions. Two examples are (1) treatments drawn from self-determination theory (SDT) (Ryan and Deci 2000; Ng et al. 2012) and (2) comprehensive, intensive group treatment for nicotine dependence (Hajek et al. 1999; Foulds et al. 2006; Hall and Prochaska 2009; Hall et al. 2011; Kotsen et al. 2017).

SDT postulates that a necessary condition for sustained change in health behavior is satisfaction of the basic psychological needs that a person has for autonomy, competence, and relatedness (Williams et al. 2016). Persons will be more motivated to change their behaviors and perceive themselves as more capable of successfully changing their behaviors in social contexts that support these needs (Ng et al. 2012). SDT-based interventions target adaptive and maladaptive behaviors and motivations for behavioral change. SDT-based treatments focus on shifting a patient's motivation for behavior change from the external (e.g., because others want the patient to change) to the internal (e.g., the patient wants to change because it is consistent with his or her personal values). SDT involves working with clients to better align their motivations and behaviors to enhance motivation that supports sustained behavioral change (Ryan et al. 2008). SDT-based interventions have demonstrated efficacy in a variety of contexts and populations, including among persons attempting to achieve long-term changes in health behavior, such as quitting smoking, losing weight, and engaging in physical activity (Williams et al. 2002, 2006a,b, 2009, 2011, 2016; Pesis-Katz et al. 2011; Teixeira et al. 2015).

Although not a new concept, intensive comprehensive tobacco use treatment at the group level likely brings to bear unique cessation mechanisms that have consistently led to high quit rates. Such treatment is professionally led and addresses key mechanisms of behavior change, such as group interactions, intergroup discussions between smokers, development of cohesion among group members, and support for interventions that are unique to this cessation format (Hajek et al. 1985, 1989; Yalom and Leszcz 2005; Kotsen et al. 2017). Professionally led, group-based treatment has been a standard of care in all programs designed to treat other types of addictions, and has been shown to yield high rates of satisfaction and positive experiences for smokers (Dobbie et al. 2015). For more than two decades, these group smoking cessation interventions have shown robust feasibility, acceptability, and efficacy in a range of research and practice settings (Connett et al. 1993; Foulds et al. 2006; Hall et al. 2009; Dobbie et al. 2015; Kotsen et al. 2017; Public Health England September 2017), to the point that they can be applied in all healthcare settings (including primary and specialty care) and behavioral healthcare settings. However, group interventions have traditionally been limited by their reach, because having to travel to an in-person meeting at a set meeting time can be a barrier for many smokers, particularly those with lower incomes. Future research could explore whether combining medication with intensive group smoking cessation treatment led by a tobacco treatment specialist is feasible in a virtual telemedicine, telehealth, or other technology-based format, which could broaden the reach and availability of this approach.

Use of Emerging Technology

Given the dynamic, quickly evolving nature of the personal technology modalities used in mHealth, it is challenging to predict future developments in this area. More sophisticated applications are being developed that involve context-dependent, adaptive interventions and that are tailored to the needs of each individual. For example, just-in-time interventions are designed to prevent relapse when a smoker is at greatest risk, including using sensors (e.g., through GPS monitoring) that track a person's location and trigger support when the person enters a high-risk environment (e.g., when the person approaches a tobacco retailer) (Naughton 2016). Such innovations may lead to interventions that improve cessation outcomes in ways that could not have been achieved without such technology. Furthermore, the commercialization of smoking cessation interventions delivered by a variety of mobile applications may lead to some promising approaches. However, the proliferation of these applications has far surpassed the capacity for the scientific evaluation of their content and effectiveness—thus, raising

concerns about their effectiveness and about how these interventions adhere to evidence-based recommendations for cessation (Abroms et al. 2013).

Ongoing smoking cessation research is exploring the utility of two specific approaches that do not rely on a particular technology platform. The first approach involves improving both the personalization of mHealth platforms and engagement with these platforms via the *use of human-technology interactions* that mimic human–human interactions. Basic versions, which are already widely used in commercial settings for other purposes, include voice phone trees and web pop-ups that are designed to help triage the caller or website user to the appropriate customer service representative or salesperson. More complex versions help consumers make decisions about which product to buy in a manner that structures the interaction as a conversation (commonly called "chatbots"). Future mHealth cessation interventions may leverage these structured human-technology interactions to deliver highly personalized, real-time cessation support.

A second strategy involves *integrating treatment data* from multiple sources so that the person delivering the cessation intervention and the smoker have access to a broader array of information and treatment options across multiple contexts. One example is integrating data from a quitline's database with a cessation application on a caller's smartphone. Although many cessation treatment approaches, such as quitlines, employ mHealth resources, integration across multiple platforms is rare. As with integration across treatment resources, the wide availability of electronic health records has created the possibility for increased connectivity between healthcare providers engaged in cessation treatment (see Chapter 7).

A large number (>500) of smartphone apps for quitting smoking have been developed, and these apps have generated great interest (>20 million downloads globally) (Bricker et al. 2014b). These apps include interactive features, present content in various formats, and collect information that the smartphone then exchanges with external databases. Apps have many characteristics that can be leveraged to deliver behavioral treatment and to improve adherence to medication. Although reviews have identified some high-quality cessation apps, many cessation apps lack appropriate, empirically based clinical approaches that are consistent with cessation guidelines (Abroms et al. 2011, 2013; Choi et al. 2014; Hoeppner et al. 2016; Ubhi et al. 2016). As with SMS text programs, there is wide variability in content, functionality, and user experience across even those apps that use empirically based cessation treatment approaches, which makes evaluating their utility difficult.

Social media sites are visited by 80% of U.S. adults who have access to the Internet, and most of these adults visit such sites daily (Greenwood et al. 2016). Research into the potential utility of social media platforms for delivering and supporting cessation treatment is in its early stages. One logical and promising strategy is to leverage social media's potential for facilitating self-help groups. This potential has not been fully realized to date because, as with such previous technologies as online bulletin boards and listservs, prolonged engagement is often poor, with initially high levels of interest often waning over time (Danaher et al. 2006; An et al. 2008; Stoddard et al. 2008; Prochaska et al. 2012). In one example of an emerging cessation intervention, Twitter is being used to create small, private groups of 20 smokers who interact for 100 days, with twice-daily automessages sent to encourage group engagement among members (Lakon et al. 2016). The intervention builds on successful past work with "buddy interventions" in which smokers were assigned physically proximal "buddies" who were also trying to quit (West et al. 1998; May and West 2000; May et al. 2006). Preliminary results for the Twitter intervention indicate that participants in quit-smoking groups often form mutually reciprocated, strong, and enduring social bonds that support smoking cessation (Lakon et al. 2016).

In another intervention, which was assessed in an RCT pilot, all 160 participants were linked to Smokefree.gov and provided with nicotine patches. A subgroup of these participants was randomized to participate in a quit-smoking group on Twitter; the study found that they were twice as likely to report sustained abstinence as those who used the website and patch alone (40% vs. 20%, OR = 2.67; 95% CI, 1.19–5.99) (Pechmann et al. 2017). Similar efforts are underway to leverage Facebook and WhatsApp to engage young adults in cessation treatment. Cessation interventions leveraging these social media platforms have shown encouraging short-term effects (Cobb et al. 2014; Cheung et al. 2015; Haines-Saah et al. 2015; Ramo et al. 2015; Baskerville et al. 2016).

Emerging Pharmacologic Approaches

Cytisine, which is not currently approved for use in the United States, was first used for quitting smoking more than 50 years ago in Eastern and Central Europe, well before the approval of any smoking cessation aids in the United States. 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 hours (maximum of six tablets total per day) for days 1–3, with a scheduled quit date at day 5, tapered to one or two tablets daily by days 21–25 (Jeong et al. 2015). In meta-analyses, the

treatment effect of cytisine was comparable to published effects for NRT, bupropion, nortriptyline, and clonidine (Hajek et al. 2013a). Two randomized placebo-controlled trials also found that cytisine was effective for smoking cessation (pooled effect: RR = 3.98; 95% CI, 2.01–7.87) (Vinnikov et al. 2008; West et al. 2011), as reviewed by Cahill and colleagues (2016), but the quality of evidence from the reviewed trials was low, in part because of small sample sizes and loss to follow-up. Furthermore, the absolute sustained long-term quit rates were modest (8.5% for cytisine vs. 2.1% for placebo at 1 year), which is generally consistent with cessation rates in the United States (Babb et al. 2017; Wang et al. 2019). The modest sustained quit rates were attributed to the minimal behavioral support provided and to the study locations, which included countries with more limited tobacco control policies than the United States. In an open-label, randomized comparative effectiveness trial conducted in New Zealand, Walker and colleagues (2014) reported 22% sustained abstinence for cytisine at the 6-month follow-up compared with 15% for the nicotine patch (RR = 1.4; 95% CI, 1.1–1.8).

The reported side effects of cytisine are primarily gastrointestinal, including abdominal discomfort, dry mouth, dyspepsia, and nausea. Notably, the cost of cytisine in places where it is available has increased, but it is still one-half to one-twentieth the cost of other cessation medications.

In February 2019, the FDA Center for Drug Evaluation and Research (2019) issued a draft version of guidance intended to assist sponsors in the clinical development of NRT drug products, including but not limited to products intended to help cigarette smokers stop smoking. This guidance incorporates feedback received from an FDA public hearing in January 2018 and from a notice in the *Federal Register* in November 2017 requesting comments on the FDA's approach to evaluating the safety and effectiveness of NRT products, including how these products should be used and labeled (*Federal Register* 2017; FDA 2019a).

Summary of the Evidence

The prevalence of cigarette smoking in the general U.S. population has declined steadily since the 1960s (USDHHS 2014), due in part to the development and concerted implementation of evidence-based tobacco control interventions, including cessation interventions. Since 2002 the number of former smokers has been greater than the number of current smokers (CDC 2005). However, as of 2017, there were still 34 million adult current cigarette smokers in the United States (Wang et al. 2018). This chapter highlighted key topics and developments associated with the content and delivery of smoking cessation interventions, with a focus on emerging evidence that can inform future smoking cessation efforts.

The evidence indicates that nicotine addiction is a chronic, relapsing disorder and that the chances of successfully sustaining a quit attempt and avoiding relapse increase with the use of evidence-based cessation treatments, with those chances generally increasing with higher dose, duration, and intensity of treatment. A large number of high-quality studies continues to support the use of behavioral counseling, pharmacologic interventions, and combined counseling and pharmacologic interventions for smoking cessation, with the latter combination being the most effective approach. Effective counseling interventions include diverse behavioral treatments that can be delivered effectively in a variety of formats, including individual, group, and telephone counseling. There are currently seven FDA-approved medications for use as first-line tobacco cessation treatments. Although the products are not approved for combination use, there is clear scientific evidence that combinations of short- and long-acting forms of NRT are more effective in promoting cessation than individual forms of NRT (Lindson et al. 2019). Both behavioral and pharmacologic tobacco cessation treatments have been shown to be highly cost-effective (see Chapter 5).

Nationally representative data indicate that about three in five U.S. adults who ever smoked have quit successfully and that just over half of current smokers try to quit each year, but the success of any given quit attempt remains low (Babb et al. 2017). Despite progress over the past 30 years, the reach and use of smoking cessation interventions remain low, with less than one-third of smokers using any proven cessation treatments (counseling and/or medication) from 2000 to 2015 (Babb et al. 2017). Regardless of the generally wide availability of proven cessation treatments, about two-thirds of smokers still attempt to quit without using these treatments, contributing to low rates of success (Hughes et al. 2004; Fiore et al. 2008).

Increasing smoking cessation will require several strategies, including (1) increasing the appeal, reach, and use of existing evidence-based cessation interventions; (2) further increasing the effectiveness of those interventions; and (3) developing additional cessation interventions that have greater reach and/or effectiveness than existing interventions or that appeal to and are used by different populations of smokers. Increasing cessation at the population level will also require increasing quit

attempts (including the number of smokers making quit attempts and the number of quit attempts that individual smokers make) and quit success, with quit attempts being driven primarily by the reach of cessation interventions and quit success being driven primarily by the intensity of these interventions (Zhu et al. 2012).

Additional research is needed to better understand (a) how e-cigarette use impacts smoking cessation, including determining which types of e-cigarettes and which patterns and contexts of e-cigarette use may facilitate or hinder smoking cessation among adults, and (b) the negative impacts of e-cigarette use (e.g., increases in youth initiation of e-cigarettes, conventional cigarettes, and other tobacco products; dual use of e-cigarettes and other combusted tobacco products; decreased use of evidence-based cessation treatments; and decreased or delayed complete cessation of conventional cigarettes and other combustible tobacco products). The research will need to track the changes in products over time.

Promising directions include leveraging emerging technologies to enhance the sustained engagement of smokers in cessation treatment, accelerating the integration of cessation services across multiple platforms and within healthcare systems, and developing new tobacco cessation medications and new indications for existing cessation medications. Although this chapter focuses on cessation interventions at the individual level, several population- and policy-based approaches (discussed in Chapter 7) have also been found to be effective in increasing tobacco cessation. Many of these broader approaches can be leveraged to complement and further increase the use of the cessation treatments described in this chapter.

Conclusions

1. The evidence is sufficient to infer that behavioral counseling and cessation medication interventions increase smoking cessation compared with self-help materials or no treatment.

2. The evidence is sufficient to infer that behavioral counseling and cessation medications are independently effective in increasing smoking cessation, and even more effective when used in combination.

3. The evidence is sufficient to infer that proactive quitline counseling, when provided alone or in combination with cessation medications, increases smoking cessation.

4. The evidence is sufficient to infer that short text message services about cessation are independently effective in increasing smoking cessation, particularly if they are interactive or tailored to individual text responses.

5. The evidence is sufficient to infer that web or Internet-based interventions increase smoking cessation and can be more effective when they contain behavior change techniques and interactive components.

6. The evidence is inadequate to infer that smartphone apps for smoking cessation are independently effective in increasing smoking cessation.

7. The evidence is sufficient to infer that combining short- and long-acting forms of nicotine replacement therapy increases smoking cessation compared with using single forms of nicotine replacement therapy.

8. The evidence is suggestive but not sufficient to infer that pre-loading (e.g., initiating cessation medication in advance of a quit attempt), especially with the nicotine patch, can increase smoking cessation.

9. The evidence is suggestive but not sufficient to infer that very-low-nicotine-content cigarettes can reduce smoking and nicotine dependence and increase smoking cessation when full-nicotine cigarettes are readily available; the effects on cessation may be further strengthened in an environment in which conventional cigarettes and other combustible tobacco products are not readily available.

10. The evidence is inadequate to infer that e-cigarettes, in general, increase smoking cessation. However, the evidence is suggestive but not sufficient to infer that the use of e-cigarettes containing nicotine is associated with increased smoking cessation compared with the use of e-cigarettes not containing nicotine, and the evidence is suggestive but not sufficient to infer that more frequent use of e-cigarettes is associated with increased smoking cessation compared with less frequent use of e-cigarettes.

11. The evidence is sufficient to infer that certain life events—including hospitalization, surgery, and lung cancer screening—can trigger attempts to quit

smoking, uptake of smoking cessation treatment, and smoking cessation.

12. The evidence is suggestive but not sufficient to infer that fully and consistently integrating standardized, evidence-based smoking cessation interventions into lung cancer screening increases smoking cessation while avoiding potential adverse effects of this screening on cessation outcomes.

13. The evidence is suggestive but not sufficient to infer that cytisine increases smoking cessation.

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