NCI Monograph 23
Treating Smoking in Cancer Patients:
An Essential Component of Cancer Care

Chapter 3
Treating Tobacco Use and Dependence in Cancer Populations

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Introduction

Smoking by patients with cancer is causally associated with all-cause and cancer-specific mortality.[1] Although some patients with cancer who smoke at the time of their diagnosis may quit after learning of their illness,[2,3] a substantial proportion of patients will continue to smoke after receiving a cancer diagnosis or relapse back to smoking shortly thereafter.[4] For these patients, access to evidence-based behavioral and pharmacological treatments to quit smoking is a critical priority.

Effective smoking cessation treatments exist but are too rarely implemented in oncologic care,[4–9] and tobacco use has not been consistently addressed by cancer centers.[13,14] However, the National Cancer Institute (NCI) Cancer Moonshot[SM] Cancer Center Cessation Initiative (C3I)[10] has propelled more cancer centers to address this treatment gap (see chapter 4), emphasizing the need to evaluate the effectiveness of smoking cessation treatments in cancer populations.

This chapter discusses current treatments to quit smoking and considerations that may affect successful smoking cessation. The discussion of smoking cessation treatments primarily focuses on cigarette smoking because it is the type of tobacco use that is most prevalent among adults,[15] and is the most frequent target of cessation research. First, the chapter addresses motivation to quit smoking, a key construct that determines a person's willingness to enter treatment for smoking. Second, the chapter reviews the current scientific evidence regarding the elements of effective smoking cessation treatment approaches. The relevant scientific literature reviewed includes studies of patients with cancer as well as those of the general population in order to broaden the evidence base for this evaluation. However, it is noted that smoking cessation research on people without cancer diagnoses may not generalize fully to patients with cancer. The smoking cessation treatment approaches evaluated include medications and behavioral interventions, with the latter including discussions of delivery via quitlines and internet/mobile devices. Third, the chapter discusses unique issues and challenges concerning the treatment of cigarette smoking among patients with cancer, including patient- (e.g., psychiatric comorbidity, treatment engagement); clinician- (e.g., training in and beliefs about treating tobacco use); and systems- (e.g., infrastructure, policy) level factors that can critically affect the success of smoking cessation treatments (systems-level factors are covered more extensively in chapter 4). Fourth, this chapter addresses special topics related to effective treatments for smoking including personalized treatment and chronic care models and the need to consider gender, race and ethnicity, and socioeconomic status in the provision of smoking cessation treatment (which is addressed more fully in chapter 5). Fifth, electronic nicotine delivery systems (ENDS) are discussed with regard to their prevalence, short- and long-term health effects, and potential relevance to smoking cessation treatment approaches, with an emphasis on patients with cancer.

This chapter, along with the rest of this monograph, evaluates and characterizes the current research literature on its targeted topics. It is not intended to provide specific treatment recommendations as would be contained in a clinical practice guideline, nor is it intended to provide fine-grained or "how to" information on intervention methods, which are available elsewhere.[16,17]

Motivation to Quit

Quitting motivation, measured using self-report questionnaires like readiness rulers or ladders[18] or by recorded quit attempts, is an important marker of eventual tobacco cessation. In the general population, engaging in steps toward smoking cessation by making a quit attempt and expressing motivation to quit increases the probability of smoking cessation.[19–22]

Data from the general population show that the great majority of individuals who smoke exhibit meaningful levels of quitting motivation and such motivation often predicts making quit attempts,[23,24] although success in those quit attempts appears to be more highly determined by factors such as nicotine dependence.[20,25,26] With regard to quitting motivation, national surveys[27,28] consistently show that more than two-thirds of individuals who smoke in the general population report interest in quitting smoking. Although quit rates can vary by socioeconomic status, a readiness or interest in quitting cuts across socioeconomic strata with one study showing past-year quit attempts of 66%, 68%, and 72% for those with no insurance, private insurance, or Medicaid, respectively.[29] Data from the 2017 Behavioral Risk Factor Surveillance System show a past-year quit attempt rate with a median of 65.4%.[30] Further, analyses of nationally representative data suggest that the prevalence of quit attempts has increased over the past 25 years among individuals who smoke in the general population.[31]

In the context of cancer care, patients may exhibit higher levels of readiness to quit smoking and attempts to quit than those in the general population as suggested by cancer patients' high quit rates.[2] Indeed, the cancer diagnosis itself is thought of as a teachable moment, meaning that motivation to quit and receptivity to smoking cessation treatment is unusually strong at this time.[32] Studies of patients with cancer who smoke indicate high levels of readiness to quit and quit attempts.[33] One study found that more than two-thirds of patients with smoking-related cancers report that they were ready to quit smoking in the next 30 days and a quarter of patients reported that they have made a quit attempt in the past year.[34] A study of patients with head and neck cancer reported that, among those who continued using tobacco after surgery, 92% were considering quitting and 84% made at least 1 quit attempt following surgery.[35] Gritz and colleagues found that almost 90% of a sample of patients with head and neck cancer enrolled in a smoking cessation trial (N = 186) had tried to quit smoking at least once since their diagnosis.[36] In a sample of 74 patients with head and neck or lung cancer participating in an observational study, 38% of those who were currently smoking reported having made a quit attempt in the previous 6 months.[37] Cooley and colleagues reported that more than 40% of a sample of 37 patients with lung cancer who smoked expressed an interest in smoking cessation intervention.[38] Little and colleagues examined quitting motivation in a retrospective cross-sectional survey.[39] Results showed that one-third of a sample of 110 cancer survivors reported being ready to quit in the next 30 days and another third reported being ready to quit in the next 6 months; 46% of the overall sample reported trying to quit when they were diagnosed. In a national study with more than 2,500 cancer survivors identified in the 2015 National Health Interview Survey (NHIS),

57% of individuals currently smoking reported wanting to quit smoking and 49% reported making a quit attempt in the past year.[8] Likewise, in a sample of close to 1,700 patients with cancer who reported smoking, more than 90% reported that they were ready to quit.[40] Finally, using 2017 NHIS data, Gritz and colleagues found that among the 681 cancer survivors who were smoking at the time of cancer diagnosis, 309 (43.96%) reported having successfully quit smoking and 372 (56%) reported continuing smoking.[41] Among continuing smokers, more than half (*N* = 176, 57%) reported an unsuccessful quit attempt in the last 12 months.

Elements of Effective Smoking Cessation Treatments

Cigarette smoking can produce nicotine dependence, a chronic, relapsing condition.[1] Dependence arises, in part, because cigarette companies intentionally designed cigarettes to maximally exploit the addictive properties of nicotine.[1,42] Despite the intransigence of nicotine dependence, multiple types of treatments can increase an individual's chances of quitting smoking successfully two- to threefold.[17] Dependence is a condition in which heavy or regular use of a drug or agent is associated with compulsive use, tolerance, and withdrawal symptoms when drug use is discontinued. Dependence is often associated with addiction, which occurs when heavy or compulsive drug use exacts significant costs in important life spheres such as health, social and vocational status, and functioning.[17] This section reviews evidence on the nature of nicotine dependence and reviews evidence on the effectiveness of treatments for smoking generally (i.e., within the general population of people who smoke cigarettes).

The prevailing therapeutic approach to treating cigarette smoking involves the use of medication to reduce the withdrawal associated with nicotine abstinence, along with psychosocial interventions to address the behavioral aspects of nicotine dependence and cessation.[17,31,43–46] The U.S. Food and Drug Administration (FDA) has approved seven medications for treating nicotine dependence, which include nicotine replacement therapies (NRTs), bupropion, and varenicline.[31] These were developed to alleviate the symptoms of nicotine withdrawal and craving, which peak soon after smoking has ceased and may persist or recur long after that time.[47,48] Withdrawal and associated craving are major causes of smoking relapse.[49,50] The psychological influences of nicotine dependence are addressed through counseling that teaches strategies that foster quitting and reduce the risk of relapse. This treatment model is rooted in scientists' understanding of the neurobiological, behavioral, and motivational processes associated with nicotine use. This chapter will focus on approaches to smoking cessation treatment that are supported by the research literature (e.g., Table 3.1)[17,46,51] and will also discuss the use of ENDS, with a focus on cancer patients and survivors.

Table 3.1 Findings Regarding Interventions for Smoking Cessation and Treatments for Nicotine Dependence From the 2020 Surgeon General's Report on Smoking Cessation

The evidence is sufficient to infer that:	• Behavioral counseling and cessation medication interventions increase smoking cessation compared with self-help materials or no treatment. • Behavioral counseling and cessation medications are independently effective in increasing smoking cessation, and even more effective when used in combination. • Proactive quitline counseling, when provided alone or in combination with cessation medications, increases smoking cessation. • Short text message services about cessation are independently effective in increasing smoking cessation, particularly if they are interactive or tailored to individual text responses. • Web- or internet-based interventions increase smoking cessation and can be more effective when they contain behavior-change techniques and interactive components.
The evidence is inadequate to infer that:	• Smartphone apps for smoking cessation are independently effective in increasing smoking cessation. • Electronic nicotine delivery systems (ENDS), in general, increase smoking cessation.
The evidence is suggestive but not sufficient to infer that:	• The use of ENDS containing nicotine is associated with increased smoking cessation compared with the use of ENDS not containing nicotine. • More frequent use of ENDS is associated with increased smoking cessation compared with less frequent use of ENDS.

Note: The Surgeon General's report refers to e-cigarettes, which are also known as ENDS.
Source: U.S. Department of Health and Human Services 2020.[31]

Neurobiological and Behavioral-Motivational Dimensions of Cigarette Smoking: Relevance to Treatment

Neurobiological Dimensions of Cigarette Smoking

Nicotine induces increased dopamine activity in the ventral striatum (e.g., the shell of the nucleus accumbens)[52] and the prefrontal cortex.[53] Such increased dopaminergic activity is experienced as rewarding and pleasurable, which is thought to be a critical mechanism in nicotine dependence development.[54,55] Dopamine can also inflate the incentive value of nicotine cues, leading to a heightened positive anticipation or wanting to use an addictive agent such as nicotine.[56,57] Both nicotine reward and its incentive effects build with repeated use, greatly increasing the appeal of nicotine use in the chronic user. Numerous animal studies[58,59] and neuroimaging studies[60,61] have documented the important role of dopamine as a key mechanism of nicotine dependence. Within this conceptualization, nicotine's addictive properties are rooted in the positive-reinforcing and incentive effects that arise from chronic use and the consequent enhancement of dopamine levels. In turn, FDA-approved medications for nicotine dependence affect key nicotine receptors and augment endogenous levels of dopamine, as well as other neurotransmitters.[54] Thus, use of such medications with dopaminergic effects may allow individuals to experience positive anticipation of and reward from non-drug stimuli or events without the use of nicotine.

Chronic use of nicotine (from cigarettes or other tobacco products) produces physical dependence in addition to sensitization to its rewarding and incentive effects.[54,62] Physical dependence manifests as a characteristic withdrawal syndrome when nicotine levels in the body decrease after chronic exposure, a syndrome that is associated with activation of the

extrahypothalamic corticotrophin-releasing factor system.[54] Withdrawal symptoms include hunger, anxiety, and irritability,[50,63] and people report strong cravings to resume nicotine use during withdrawal.[64–66] Anhedonia, an inability to experience pleasure from normally rewarding stimuli, also occurs following decreased nicotine use after chronic exposure.[67,68] This inability may arise from the loss of anticipatory excitement in response to incentive stimuli[56] or from actual decrements in reward processing that occur with disuse of nicotine.[59,68] Anhedonia, along with other withdrawal symptoms, is alleviated by agents that increase dopaminergic activity, including FDA-approved smoking cessation medications.[67,69–71.]

Behavioral-Motivational Dimensions of Cigarette Smoking

In parallel with research on the neurobiological effects of nicotine, behavioral research shows that nicotine reward, incentive effects, and negative reinforcement play crucial roles in sustaining nicotine use. For instance, neuropharmacologic and neuroimaging studies of brain regions and neurocircuitry involved in nicotine use have documented that nicotine can enhance fine motor functions, attention, concentration, and working and episodic memory in the short term.[73,74] Such effects may account, in part, for the rewarding effects of nicotine, along with the direct experience of rush, enjoyment, or pleasure and the speed and consistency of nicotine's effects. Research also suggests that withdrawal from nicotine can decrease function in some cognitive domains.[74,75] Smoking is reinforced by the reversal of multiple types of withdrawal symptoms associated with stopping tobacco use, including concentration difficulties, negative affect, craving, anhedonia, and hunger.[67,76,77]

Behavioral research, including both human and animal studies, suggests that negative affective states or distress may increase the motivation to smoke and motivate relapse or a resumption in nicotine self-administration.[77–81] Indeed, there is evidence that just the expectation of smoking reduces anxiety.[82] Perceptions among those dependent on nicotine may account for the strong relationship between stressor exposure and smoking urges and self-administration.[81,83] As of this writing, whether nicotine reduces affective distress arising from external stressors is unresolved.[84,85] If nicotine produces any stress relief, it is short lived; evidence suggests that former smokers experience less stress, anxiety, and depression after quitting smoking than they did before quitting.[86,87]

Behavioral research also shows that exposure to smoking-related cues significantly heightens the motivation to smoke.[88–90] In fact, research indicates that point-of-sale tobacco displays, tobacco industry advertising, and promotions heighten urges to smoke and increase tobacco use.[91–95] Thus, cues such as seeing others smoking, consuming alcohol, or the perceived opportunity to smoke, can elicit powerful urges to smoke and lead to a resumption of nicotine use in rats[96,97] and people previously dependent on nicotine.[80,98] In addition, over time, the ritual of smoking or any nicotine administration ritual can become automatic and reflexively elicited by smoking-related cues.[99–101]

Summary: Neurobiological and Behavioral-Motivational Dimensions of Cigarette Smoking

Regular cigarette smoking can produce dependence, which is accompanied by changes in affect, cognition, and physiology. As a result, smoking is repeatedly reinforced, becoming automatic and refractory, especially in contexts in which it has frequently occurred. Additionally,

discontinuing smoking acutely results in negative moods, craving for nicotine, a loss of pleasure, and adverse cognitive effects that may impede decision-making. These symptoms decline over time with long-term quitters reporting improved mood and reduced stress. Moreover, FDA-approved medications and behavioral interventions are effective at reducing the physical and psychological symptoms of nicotine withdrawal even early in the quitting period when symptoms would otherwise be at their highest.

Smoking Cessation Treatments in the General Population

Approach

This section reviews the state of the science with regard to pharmacological, counseling, and digital/internet treatments for cigarette smoking within the general population. This section relies heavily upon prior systematic reviews[17,31,102–109] and several highly relevant and informative individual studies. The intent here is to extrapolate from the existing literature to identify approaches that might be most effective with cancer patient populations. An intervention approach is deemed effective if supported by meta-analyses or consistent findings from randomized controlled trials (RCTs), and preferably both, in synthesizing the evidence. Information on sample size, significance levels, certainty of evidence, and magnitude of effects is strategically presented for key studies where it is especially important to assess the generalizability of findings, their magnitude, their statistical significance, and whether an effect was tested with sufficient statistical power. Certain interventions are also deemed promising if supported by a consistent body of nonexperimental evidence, such as observational studies. Observational studies have value because they yield evidence, though not definitive, on smoking cessation treatments in real-world conditions, including treatment delivery by clinical staff to a broad representative range of patients. Clear instructions for the use and dosing of pharmacotherapies are available in the Public Health Service (PHS) Clinical Practice Guideline, *Treating Tobacco Use and Dependence: 2008 Update,*[17] and the American College of Cardiology Expert Consensus Decision Pathway on Tobacco Cessation Treatment.[110]

Finally, it is important to note that the majority of RCTs that evaluated medications for smoking also provided counseling or behavioral support in the active-treatment and placebo or control arms. Medications for smoking cessation are typically less effective when used without any behavioral support.[111]

Medications for Smoking Cessation

The 2020 Surgeon General's report concluded that behavioral counseling and cessation medications are independently effective in increasing smoking cessation.[31] The PHS Clinical Practice Guideline, *Treating Tobacco Use and Dependence: 2008 Update,* recommends the use of FDA-approved smoking cessation medications, which include nicotine gums, nicotine inhalers, nicotine lozenges, nicotine nasal sprays, nicotine patches, bupropion, and varenicline.[17] Medication adherence (using the medication for the prescribed or indicated amounts and duration) is positively associated with smoking cessation.[112]

This section will discuss the effectiveness of medications as they are used for smoking cessation in the general population (see Table 3.2). In addition, several specialized pharmacotherapy strategies will also be discussed. Two such strategies are designed to extend smoking

abstinence.[105,113] These will be discussed because the majority of individuals who smoke, including patients with cancer,[114] will relapse back to smoking after making an aided or unaided quit attempt. One of these pharmacologic approaches is the extended use of medication (beyond the standard 8–12 weeks) among all who start it. The second pharmacologic approach is relapse prevention (i.e., providing a longer course of medication to those who have already become abstinent). Other strategies include providing medication to those who are not yet motivated to quit smoking and providing medication for an extended period prior to a person's target quit date (i.e., preloading).

Table 3.2 Effectiveness and Abstinence Rates for Various Medications and Medication Combinations Compared to Placebo at 6-Months Post-quit

Medication	Number of arms	Estimated odds ratio (95% CI)	Estimated abstinence rate (95% CI)
Placebo	80	1.0	13.8
Monotherapies			
Varenicline	5	3.1 (2.5–3.8)	33.2 (28.9–37.8)
Nicotine nasal spray	4	2.3 (1.7–3.0)	26.7 (21.5–32.7)
High-dose nicotine patch (> 25 mg) (these included both standard or long-term duration)	4	2.3 (1.7–3.0)	26.5 (21.3–32.5)
Long-term nicotine gum (>14 weeks)	6	2.2 (1.5–3.2)	26.1 (19.7–33.6)
Varenicline (1 mg/day)	3	2.1 (1.5–3.0)	25.4 (19.6–32.2)
Nicotine inhaler	6	2.1 (1.5–2.9)	24.8 (19.1–31.6)
Clonidine	3	2.1 (1.2–3.7)	25.0 (15.7–37.3)
Bupropion SR	26	2.0 (1.8–2.2)	24.2 (22.2–26.4)
Nicotine patch (6–14 weeks)	32	1.9 (1.7–2.2)	23.4 (21.3–25.8)
Long-term nicotine patch (> 14 weeks)	10	1.9 (1.7–2.3)	23.7 (21.0–26.6)
Nortriptyline	5	1.8 (1.3–2.6)	22.5 (16.8–29.4)
Nicotine gum (6–14 weeks)	15	1.5 (1.2–1.7)	19.0 (16.5–21.9)

Table 3.2 (continued)

Medication	Number of arms	Estimated odds ratio (95% CI)	Estimated abstinence rate (95% CI)
Combination Therapies			
Patch (long-term; >14 weeks) + ad lib NRT (gum or spray)	3	3.6 (2.5–5.2)	36.5 (28.6–45.3)
Patch + bupropion SR	3	2.5 (1.9–3.4)	28.9 (23.5–35.1)
Patch + nortriptyline	2	2.3 (1.3–4.2)	27.3 (17.2–40.4)
Patch + inhaler	2	2.2 (1.3– 3.6)	25.8 (17.4–36.5)
Patch + second generation antidepressants (paroxetine, venlafaxine)	3	2.0 (1.2–3.4)	24.3 (16.1–35.0)
Medications not shown to be effective			
Selective serotonin re-uptake inhibitors	3	1.0 (0.7–1.4)	13.7 (10.2–18.0)
Naltrexone	2	0.5 (0.2–1.2)	7.3 (3.1–16.2)

Note: *N* = 86 studies. Visit https://www.ahrq.gov/prevention/guidelines/tobacco/clinicians/references/meta/meta03.html#t626 for the studies used in this meta-analysis. NRT = nicotine replacement therapy.
Source: Adapted from Fiore et al. 2008: Table 6.26.[17]

Nicotine Replacement Therapies (NRTs). NRT agents occupy nicotine receptors, as does nicotine contained in cigarette smoke, but their pharmacodynamics cause them to reduce withdrawal symptoms and craving (e.g., hunger, negative affect) without the highly rewarding effects that would sustain dependence or relapse. The FDA has approved five forms of NRT for smoking cessation: patch, gum, lozenge (and mini lozenge), nasal spray, and inhaler; the first three are available over the counter or by prescription, while the last two are available only by prescription. The safety of NRTs has been well-established in numerous studies consisting of people who smoke differing in age, gender, race and ethnicity, psychiatric status, and other important factors.[17] Moreover, there are few contraindications for the use of NRTs, with some of the more common ones being an allergy to the nicotine patch adhesive, temporomandibular joint disease for the nicotine gum, and gastric or duodenal ulcer for the nicotine nasal spray.[115] Other contraindications can be found in the package inserts for each product. Systematic reviews show that NRTs can increase quit rates compared with placebo,[17] yielding long-term (i.e., 6–12 months) quit rates of about 20%-25% (Table 3.2). Further, systematic reviews have shown that individual types of NRTs are similarly effective to one another but that combination NRT (e.g., combining a long-acting NRT like the nicotine patch with a short-acting NRT like nicotine gum) yields significantly higher rates of long-term abstinence than does a single type of NRT (i.e., NRT monotherapy)[17,116] (Table 3.2). Because research shows that the different NRT medications produce very similar effects of smoking abstinence, this chapter rarely distinguishes among the different NRT types in evaluating the evidence.

Evidence also suggests that NRT effectiveness can be increased by specialized use strategies.[31] These include adjusting the NRT dose based on the individual's level of nicotine dependence (e.g., time to first cigarette of the day) and initiating NRT prior to a designated quit attempt (i.e., preloading),[116–118] an effect that may be greatest with the nicotine patch.[31,116]

NRT can increase smoking cessation rates even among those not motivated to make quit attempts (see section "Patient-Level Barriers to Treating Tobacco Use in Cancer Care Settings"). A systematic review and meta-analysis indicate that long-term use of NRT (6–18 months) and behavioral support can double the likelihood of smoking cessation compared with placebo even in individuals who initially report no intention to quit smoking.[119,120] In addition, there is evidence that medication sampling with NRT products, or the provision of 2–4 weeks of NRT with minimal accompanying instructions, prior to the quit attempt, can increase the likelihood of long-term abstinence; this finding applies to people who smoke and who are willing or unwilling to make a quit attempt.[121]

Extended Use. The evidence regarding the effects of extending NRT beyond its standard period of use (typically 8–12 weeks) is mixed.[31] Thus, no firm conclusions regarding the efficacy of extended medication use can be drawn as of this writing.

Relapse Prevention. A Cochrane Review meta-analysis showed that providing nicotine gum significantly reduced relapse likelihood in individuals who were abstinent at study start and who had previously quit smoking without using formal smoking cessation treatment (2 studies, N = 2,261, risk ratio [RR] = 1.24, 95% confidence interval [CI] = 1.04–1.47). However, additional NRT did not significantly increase long-term abstinence among those who initially became abstinent in response to formal smoking cessation treatment (2 studies, N = 553, RR = 1.04, 95% CI = 0.77–1.40, low certainty evidence).[105] Thus, it is difficult to draw conclusions about the ability of NRT to prevent relapse given the small number of relevant studies and the modest effect sizes obtained.[105]

Bupropion. Bupropion was originally introduced as an antidepressant and was later found to increase the likelihood of smoking cessation. Bupropion increases dopamine and norepinephrine activity in the brain; the former is likely responsible, in part, for its ability to reduce nicotine withdrawal. Bupropion is also a nicotinic receptor antagonist, which may reduce smoking reward.[54] Meta-analyses of clinical trials of bupropion show that its impact on long-term abstinence is similar to NRTs (e.g., yielding abstinence in about 25% of users, an increase in abstinence of about 50% to nearly 80% relative to placebo)[17,104,122,123] (Table 3.2).

Preloading. Only a single small study (N = 95) has been done to determine whether extended preloading with bupropion prior to the targeted quit date (4 weeks of prequit use) increases abstinence rates when compared with a normal course of bupropion treatment (1 week of prequit use).[124] Further study is needed regarding the effectiveness of extended preloading with bupropion.

Extended Use. The limited available data indicate that extending the duration of use of bupropion does not reliably increase its efficacy.[125]

Relapse Prevention. A Cochrane Review meta-analysis of six studies evaluating relapse prevention with bupropion showed no significant effect. Livingstone-Banks and colleagues noted that there was considerable variation in key study characteristics (e.g., the nature of the smoking cessation treatment, the length of the extended bupropion treatment), which may have increased error in effect estimates.[105]

Safety. Due to early reports of serious changes in mood and behavior related to bupropion use, the FDA required a boxed warning for bupropion and required a large clinical trial to be conducted to address bupropion safety. The double-blinded, triple-dummy, randomized trial involving 8,144 people who smoked found no significant increase in neuropsychiatric adverse events attributable to bupropion relative to nicotine patch or placebo. Therefore, the evidence suggested that bupropion was safe and effective and the product labeling was revised accordingly.[31,126]

Varenicline. The FDA approved varenicline for treating smoking cessation in 2006, and it is now approved for up to 6 months of treatment.[31,127] Varenicline, a nicotine acetylcholine $\alpha 4\beta 2$ receptor partial agonist, is one of the most efficacious medications for nicotine dependence, with most evidence suggesting that it yields long-term quit rates of about 19%–30%.[17,128,129] The drug's presumed mechanisms of action involve preventing nicotine from binding with nicotinic acetylcholine receptors and stimulating dopamine release. These actions reduce smoking reward and abstinence-induced withdrawal symptoms.[130] There may also be a secondary agonist effect on $\alpha 7$ nicotinic receptors, which alter the reinforcing capacity of salient stimuli.[131] Varenicline also mitigates adverse psychological effects, including depressive symptoms and the temporary cognitive impairment associated with quitting smoking.[130,132–135]

Several systematic reviews and meta-analyses indicate that varenicline can more than double the likelihood of smoking cessation compared with placebo and is more effective than single NRT or bupropion[17,128] (Table 3.3). Evidence of the relatively greater effectiveness of varenicline led the American Thoracic Society to recommend varenicline over nicotine patch and bupropion monotherapy as a first-line smoking cessation treatment in their clinical practice guideline.[136] Two factors that moderate varenicline's effectiveness are an individual's rate of nicotine metabolism and whether an individual is adherent to the medication. Individuals who metabolize nicotine relatively rapidly tend to achieve higher smoking abstinence rates than those who metabolize nicotine more slowly, a relation that has led to a medication treatment algorithm.[137] As has been found with other smoking cessation medications, individuals who are adherent to varenicline tend to achieve significantly higher long-term abstinence rates than are those who are only partially adherent or nonadherent.[138]

Preloading. One small study ($N = 60$) suggests that preloading with varenicline, extending its pre-cessation use for 4 weeks before the quit date,[139] may increase its effectiveness. Similarly, a study with a large sample ($N = 1{,}510$) showed that prolonged varenicline use prior to the quit date (i.e., 12 weeks) increases abstinence rates among people who smoke and who are not willing to make an immediate quit attempt.[140]

Extended Use. There are limited data about whether extended treatment with varenicline after the quit day enhances outcomes. The normal course of varenicline treatment is 12 weeks (1 week

pre-quit and 11-weeks post-quit). One study with a large sample (N = 1,251) showed no benefit of 24 weeks of varenicline versus the standard 12-week duration.[141]

Relapse Prevention. A meta-analysis suggests that varenicline is an effective relapse prevention intervention for individuals who have recently become abstinent in response to a prior smoking cessation treatment. This meta-analysis included 2 studies (N = 1,297) and yielded a small but significant effect of varenicline on abstinence at 12-month follow-up (RR = 1.23, 95% CI = 1.08–1.41).[105]

Safety. Substantial evidence supports the safety of varenicline. At one time, the FDA required boxed warning labels for varenicline due to concern over neuropsychiatric side effects. However, considerable evidence shows that varenicline produces no greater rates of such side effects than does placebo.[31,126] Concerns were also raised that varenicline might increase the occurrence of major cardiovascular events.[142] However, multiple studies subsequently have shown no meaningful increase in such events related to varenicline use.[31,110]

In June 2021, Pfizer Pharmaceuticals voluntarily recalled varenicline tablets because some batches were found to contain a nitrosamine impurity (N-nitroso-varenicline) at levels above FDA's acceptable intake limit. N-nitroso-varenicline may increase cancer risk if exposure exceeds the acceptable limit (37 ng/day) over a long period of time.[143] However, as of September 2021, varenicline that met FDA criteria for safety became available from other manufacturers.

Medication Combination. Given the efficacy of individual FDA-approved medications for smoking cessation, researchers have examined the potential for increased efficacy by combining these medications. A review of four studies reported that the combination of bupropion and varenicline yields significant benefits compared with varenicline alone,[144] although this has not been a consistent finding.[145] Studies have also examined the combination of NRT (nicotine patch) and varenicline versus varenicline alone. Although two small studies reported no significant benefit from combination therapy,[146,147] one study reported that adding NRT to varenicline significantly increased long-term abstinence rates versus varenicline alone.[148] A 2020 meta-analysis by a committee of the American Thoracic Society conditionally recommended the use of varenicline and nicotine patch over varenicline alone based on the available data.[136] However, a subsequent large sample study (N = 1,251) showed that there was no difference in long-term abstinence rates produced by the combination of varenicline and the nicotine patch versus varenicline alone.[141] Therefore, it is unclear that the combination of varenicline and the nicotine patch enhances long-term smoking abstinence in comparison with varenicline only.

Meta-analytic evidence shows that adding NRT to bupropion does not significantly improve long-term abstinence rates relative to either medication alone.[104] Several studies have shown that combination NRT is more effective than a single form of NRT or bupropion alone and is similar to varenicline monotherapy.[17,104,149,150]

Summary: Medications for Smoking Cessation. All seven FDA-approved medications improve long-term smoking abstinence rates relative to placebo. Moreover, varenicline and combination NRT are the two most effective pharmacotherapies available. Either therapy is more effective than placebo and NRT monotherapy. Varenicline and combination NRT are similarly considered first-line treatments in cancer populations.

Table 3.3 Odds of Smoking Cessation Using Medications

Comparison	Odds ratio (95% credible interval)	Number of studies with a direct comparison[a]
Treatments vs. placebo		
Patch vs. placebo	1.91 (1.71–2.14)	43
Gum vs. placebo	1.68 (1.51–1.88)	56
Other NRT vs. placebo	2.04 (1.75–2.38)	16
Combination NRT vs. placebo	2.73 (2.07–3.65)	2
Bupropion vs. placebo	1.85 (1.63–2.10)	36
Varenicline vs. placebo	2.89 (2.40–3.48)	15
Treatments vs. patch		
Gum vs. patch	0.88 (0.75–1.03)	0
Other NRT vs. patch	1.07 (0.91–1.26)	6
Combination NRT vs. patch	1.43 (1.08–1.91)	3
Bupropion vs. patch	0.97 (0.83–1.13)	6
Varenicline vs. patch	1.51 (1.22–1.87)	0
Treatments vs. gum		
Other NRT vs. gum	1.21 (1.01–1.46)	0
Combination NRT vs. gum	1.63 (1.21–2.20)	1
Bupropion vs. gum	1.10 (0.93–1.30)	0
Varenicline vs. gum	1.72 (1.38–2.13)	0
Other inter-treatment comparisons		
Combination NRT vs. other NRT	1.34 (1.00–1.80)	1
Bupropion vs. other NRT	0.91 (0.75–1.09)	2
Varenicline vs. other NRT	1.42 (1.12–1.79)	0
Varenicline vs. bupropion	1.56 (1.26–1.93)	3

Note: Smoking cessation duration varied by study. NRT = nicotine replacement therapy.
[a]When direct comparisons were not available for two medications, effect sizes were estimated based on their effects relative to comparison medications they had in common. Medications were typically tested with the same level and type of behavioral intervention in all treatment arms that were compared.
Source: Adapted from Cahill et al. 2013.[104]

Behavioral Interventions for Smoking Cessation

In addition to medications, which address the physiological components of nicotine dependence, behavioral interventions provide people who smoke with strategies to overcome the effects of nicotine withdrawal and other threats to their smoking abstinence (e.g., smoking cues). Counseling is the predominant behavioral or psychosocial intervention, and different types of counseling and their effectiveness are reviewed in this section. In addition, telephone and video-based interventions receive additional, focused review because the mode or conduit of behavioral

intervention delivery could influence its effectiveness. These intervention delivery routes may hold advantages over in-person delivery modes in terms of efficiency, cost, and patient burden (e.g., travel); therefore, data on their effectiveness may be of great interest to health care systems. Additionally, contingency management (CM) and digital approaches are reviewed. Table 3.4 provides information derived from systematic reviews on the effectiveness of different types of behavioral interventions. The discussion of treatment approaches provided below briefly describes therapy types and their research support based upon smoking cessation studies among the general population (i.e., not restricted to individuals with cancer).

Table 3.4 Odds of Smoking Cessation Using Behavioral Interventions

Comparison	Odds ratio, risk ratio, or *g* (95% CI)	Number of studies included in the respective review
Counseling treatments		
Cognitive behavioral therapy vs. control (Fiore et al. 2008)[17]	1.5 (1.3–1.8)[a]	64
Mindfulness vs. control (Maglione et al. 2017)[165]	2.52 (0.76–8.29)	6
Acceptance and commitment therapy vs. control (Lee et al. 2015)[171]	0.42 (0.19–0.64)[b]	5
Behavioral activation	N/A	N/A
Motivational interviewing vs. control (Lindson et al. 2019)[189]	0.84 (0.63–1.12)	4
Contingency management vs. control (Notley et al. 2019)[200]	1.49 (1.28–1.73)[a]	30
Digital treatments		
Website interventions vs. control (McCrabb et al. 2019)[249]	1.19 (1.06–1.35)[a,c]	31
Text message intervention vs. control (Whittaker et al. 2019)[107]	1.54 (1.19–2.0)[a]	13

Note: N/A = not applicable. Smoking cessation measure varied by study.
[a]Indicates benefit for active treatment vs. control. [b]*g* statistic indicating benefit of acceptance and commitment therapy vs. control. [c]*N* and effect estimate for the study by McCrabb and colleagues are for all long-term (6-month) outcomes (prolonged abstinence, 7-day point-prevalence abstinence, and 30-day point-prevalence abstinence). Variation was found by outcome measure, with significant effects for prolonged abstinence, but no significant effects for 7- and 30-day point-prevalence abstinence determined at 6-month follow-up.
Source: Adapted from systematic reviews and meta-analyses from Fiore et al. 2008,[17] Maglione et al. 2017,[165] Lee et al. 2015,[171] Lindson et al. 2019,[189] Notley et al. 2019,[200] McCrabb et al. 2019,[249] and Whittaker et al. 2019.[107]

Cognitive Behavioral Therapy (CBT). CBT is the most thoroughly researched and commonly used behavioral approach to treating nicotine dependence. CBT is sometimes referred to as problem solving, skills training, or behavior therapy,[17] and because of their overlap,[113] this chapter includes all of these interventions as CBT. Such therapies focus on clinician–patient collaboration to improve coping skills; boost self-efficacy; modify cognitions that serve as barriers to smoking cessation; provide support; and develop, modify, and improve cognitive and behavioral skills (i.e., learning how to avoid smoking triggers, contexts, and reframing thoughts about smoking).[151] Key elements include establishing a quit date, identifying potential risks for

relapse, developing skills to manage smoking urges, and learning how to elicit and rely on social support during the quit attempt. In addition, CBT is often delivered with other counseling components such as intra-treatment social support and suggestions on the use of smoking cessation medications.[17] These adjuvant counseling elements would typically be added to any of the other counseling approaches reviewed below (see Table 3.5 for examples of representative content delivered in a CBT counseling intervention).[17] There is little evidence regarding which of these elements are especially determinant of cessation success,[109,113,152] and it may be that a good portion of their effectiveness is due to general features of therapy (e.g., support). However, CBT treatments have produced meaningful and reliable benefits across many different populations of people who smoke.[17] CBT can be delivered effectively by telephone (e.g., via a quitline) and in-person, via video or telehealth,[153] and individually or in a group.[17]

Table 3.5 Elements of Brief Tobacco-Cessation Counseling Based on the PHS Clinical Practice Guideline, *Treating Tobacco Use and Dependence: 2008 Update*

Action	Strategies for implementation
Help the patient with a quit plan.	*A patient's preparations for quitting*: • ***S****et* a quit date. Ideally, the quit date should be within 2 weeks. • ***T****ell* family, friends, and co-workers about quitting, and request understanding and support. • ***A****nticipate* challenges to the upcoming quit attempt, particularly during the critical first few weeks. These include nicotine withdrawal symptoms. • ***R****emove* tobacco products from your environment. Prior to quitting, avoid smoking in places where you spend a lot of time (e.g., work, home, car). Make your home smokefree.
Recommend the use of approved medication, except when contraindicated or with specific populations for which there is insufficient evidence of effectiveness.	Recommend the use of medications found to be effective. Explain how these medications increase quitting success and reduce withdrawal symptoms. The first-line medications include: bupropion sustained release (SR), nicotine gum, nicotine inhaler, nicotine lozenge, nicotine nasal spray, nicotine patch, and varenicline.
Provide practical counseling (problem-solving/skills training).	Abstinence. Emphasize that the ultimate goal is abstinence. Past-quit experience. Identify what helped and what hurt in previous quit attempts. Build on past success. Anticipate triggers or challenges in the upcoming attempt. Discuss challenges/triggers and how the patient will successfully overcome them (e.g., avoid triggers, alter routines). Alcohol. Because alcohol is associated with relapse, the patient should consider limiting/abstaining from alcohol while quitting. Other people who smoke in the household. Quitting is more difficult when there is another person who smokes in the household. Patients should encourage housemates to quit with them or not to smoke in their presence.

Table 3.5 (continued)

Action	Strategies for implementation
Provide intra-treatment social support.	Provide a supportive clinical environment while encouraging the patient in his or her quit attempt. "My office staff and I are available to assist you." "I'm recommending treatment that can provide ongoing support."
Provide supplementary materials, including information on quitlines.	*Sources*. Federal agencies, nonprofit agencies, national quitline network (1-800-QUIT-NOW, Text QUITNOW to 333888, or local/state/tribal health departments/quitlines).

Source: Adapted from Fiore et al. 2008.[17]

Meta-analytic studies of CBT skills-based behavioral smoking cessation treatments indicate that this counseling model can increase smoking cessation rates by about 50% compared with no-intervention controls.[17] RCTs have demonstrated the efficacy of CBT-based smoking cessation treatments in hospitalized patients who smoke[154] and African-American people who smoke.[155] There is evidence that even relatively brief exposures to CBT can significantly increase long-term abstinence rates. The PHS Clinical Practice Guideline, *Treating Tobacco Use and Dependence: 2008 Update*, presented meta-analyses that related counseling intensity to its effectiveness. These meta-analyses suggest that CBT counseling lasting between 4–30 minutes of total contact time may increase long-term abstinence rates from about 11% to almost 19% in the general population.[17] It is unclear if increasing total contact time of cessation counseling beyond 30–90 minutes increases long-term abstinence.[17,45] However, there is evidence that more contacts or sessions are associated with increased long-term abstinence with the greatest increase in abstinence observed with up to four contacts or more.[17] Some evidence suggests that neither extending CBT beyond the amounts noted above nor use of CBT for relapse prevention significantly boosts long-term abstinence[31,45,105,108]; although a very small number of studies have reported a benefit of highly intense, extended CBT.[156]

Mindfulness-Based Therapy. In the 1990s, mindfulness-based stress reduction (MBSR)[157] gained prominence as a treatment for a range of conditions, including stress. Rooted in a Buddhist tradition, MBSR is a structured, multisession counseling model that is intended to train individuals to learn to focus on the present and assume an open acceptance of thoughts and emotions. Mindfulness-based counseling (mindfulness meditation) for nicotine dependence focuses on increasing self-awareness, decreasing smoking urges, and reducing the risk of relapse.[158,159] To date, four RCTs have evaluated mindfulness-based counseling for smoking cessation, using appropriate control arms, long-term follow-up of smoking, and biochemical verification of abstinence. A meta-analysis of 4 RCTs[160–163] indicated significant benefits on long-term abstinence, with a near doubling of the quit rates (i.e., 25.2% vs. 13.6%).[164] A second meta-analysis (N = 10) concluded that mindfulness-based smoking cessation treatments were not more effective than comparator treatments or no treatment.[165] As of this writing, the efficacy of mindfulness-based smoking cessation treatment, particularly relative to CBT, remains uncertain. Further, the level of counselor training required for this approach and its lack of appeal to some individuals who smoke may limit its translation potential.

Acceptance and Commitment Therapy (ACT). Another novel counseling smoking cessation treatment developed and tested over the past decade is ACT, an approach with established efficacy for treating depression and substance use.[166,167] The central focus of ACT is to help the

individual manage "experiential avoidance," which underlies ineffective attempts to exert control over unwanted behaviors like smoking and to help them commit to basing their behaviors upon intrinsically valued goals. ACT focuses on identifying and accepting aversive thoughts and feelings, such as cravings or withdrawal during a quit attempt, to mitigate the threat and negative affective and cognitive reactions to such symptoms.[168] In an early clinical trial that compared ACT to CBT in 7 weekly small group (N = 81) sessions, ACT yielded more than a twofold greater quit rate than CBT.[169] Other small sample studies and a 2015 meta-analysis provide some evidence that ACT may be effective as a tobacco use intervention.[170,171] However, most relevant studies are limited by small sample sizes and self-reported cessation without biochemical confirmation. A large RCT found nonsignificantly lower long-term abstinence rates in an ACT condition than in a CBT condition when both were delivered via group counseling.[172] In sum, the available evidence is consistent with the 2020 Surgeon General's report, which notes that ACT may be promising but that more research is needed to determine the effectiveness for this counseling approach.[31]

Behavioral Activation Therapy (BA). Negative affect, including depressed mood and anhedonia, and a lack of positive affect are widely recognized, critical barriers to the successful treatment of nicotine dependence.[173–176] Developed as a treatment for depression,[177–179] BA focuses on increasing engagement in rewarding activities by reducing patterns of avoidance, withdrawal, and inactivity.[178,180] BA is effective in treating depression[181,182] and may be well-suited for those who smoke as a primary means of reducing or avoiding negative affect.[183] However, studies of this approach have tended to have relatively small sample sizes, have lacked biochemical confirmation of follow-up self-report, and have yielded mixed findings.[184–186] Thus, the supportive evidence for CBT is much stronger than it is for BA. More research is needed to determine the effectiveness of BA as a treatment for smoking.

Motivational Interviewing (MI). MI is a client-centered, directive counseling technique that aims to encourage readiness for behavior change by helping clients explore and resolve ambivalence about such change.[187,188] Its core techniques include expressing empathy, active listening, reflecting on the patient's thoughts and emotions, and supporting self-efficacy. A Cochrane Review meta-analysis of 4 studies using the longest follow-up outcome provided by the studies showed no benefit of MI versus no treatment (RR = 0.84, 95% CI = 0.63–1.12, adjusted N = 684, 4 studies).[189] There was also no evidence that MI added significantly to the effectiveness of other forms of behavioral intervention for tobacco use (RR = 1.07, 95% CI = 0.85–1.36, adjusted N = 4,167, 12 studies) or that it was relatively more effective than other behavioral interventions (RR = 1.24, 95% CI = 0.91–1.69, N = 5,192, 19 studies). The studies involved a wide range of populations, clinicians (including counselors), and settings. Thus, there is little evidence that MI significantly increases the likelihood of long-term smoking abstinence relative to no treatment, brief treatment, or self-help material. It is also unclear that MI reliably increases motivation to quit.[190]

Contingency Management (CM). The effectiveness of financial rewards for smoking cessation (cash payments or vouchers) has been demonstrated among adolescents,[191] pregnant women,[192–194] hospitalized patients,[195] Medicaid recipients,[196] employees,[197,198] and in the general population.[199] In a 2019 meta-analysis that included 33 studies (of which 2 involved patients with cancers of the head and neck), CM smoking interventions yielded a 40%–50% increase in the likelihood of smoking cessation versus control conditions, a difference that was maintained at

follow-up once the incentives were discontinued[200]; however, some studies used multiple additional treatment components (e.g., brief advice, MI, and/or self-help material) which may have added to the CM effects.

In addition, multiple studies have explored the use of financial incentives to increase engagement with smoking cessation treatment rather than smoking abstinence itself.[31] These trials demonstrated that financial incentives for engagement in smoking cessation treatment by low-income populations not only increase treatment engagement but also increase smoking cessation success.[201–205] As such, the evolving literature on CM-based interventions shows their effectiveness, although rigorous comparisons with other behavioral approaches are lacking.

The 2020 Surgeon General's report noted that the effects of CM interventions may largely dissipate once the contingency is no longer in force.[31] However, a meta-analytic review of behavioral approaches to treating tobacco use found that the use of financial incentives increased long-term abstinence rates with a high degree of certainty.[109] Also, the effects of CM may be sustained by incentivizing treatment engagement as opposed to smoking cessation, and the former has increased long-term abstinence.[202,203] Digital or technologic strategies may enhance the feasibility or reach of CM approaches by monitoring smoking and providing incentives as individuals go about their daily lives.[206,207]

The 2020 Surgeon General's report acknowledges that it may be difficult to institute financial incentives outside the research setting and notes the need for more research on the long-term effects of CM interventions and how they might be best implemented in real-world settings.[31] However, the report also notes that the use of financial incentives to promote quitting during pregnancy may be appealing to insurers and policymakers, given the high costs of adverse birth outcomes and the short-term cost savings of providing pregnant women with help to quit. The use of financial incentives to assist patients with cancer to quit may also appeal to insurers and policymakers, given the likely financial benefits to doing so.

Relapse Prevention and Chronic Care. Although smoking cessation counseling is clearly effective in increasing initial success, the majority of individuals who make a quit attempt ultimately relapse.[208] In fact, about two-thirds or more of individuals who try to quit smoking with and without counseling relapse in the first month after their quit attempt.[209–211] For this reason, many smoking cessation treatment programs arrange for counseling sessions to start early in the quit attempt. The high rate of relapse has led to the development and evaluation of relapse-prevention treatments (i.e., treatments added to smoking cessation treatments intended to reduce the likelihood of future relapse). Such treatments typically teach people to recognize situations that confer a high risk for relapse and train them on strategies to cope with such challenges.[105] The weight of evidence from RCTs suggests that counseling interventions, either in the form of extended treatment or relapse-prevention interventions, do not consistently and meaningfully increase long-term abstinence rates among those already abstinent. For instance, a Cochrane Review meta-analysis addressed the effectiveness of behavioral relapse prevention interventions, focusing on studies that had randomized relapse prevention interventions among individuals who had previously established abstinence.[105] The authors conducted several meta-analyses that focused on different populations, such as pregnant women, hospital inpatients, and the general population. The number of studies reviewed ranged from 4 to 15 depending on the population involved. None of the meta-analyses found significant relapse prevention effects of

behavioral interventions. The types of interventions used in these studies included support groups, group skill-training sessions, tailored counseling calls, and social media interventions, as well as low-intensity interventions, such as booklets. Although the authors note that different formats of relapse prevention were used in the studies analyzed, the major therapy content in most of the studies involved CBT emphasizing training skills for coping with relapse precipitants (e.g., smoking cues, stressors).[105] Therefore, most available evidence as of this writing does not support the effectiveness of psychosocial interventions for relapse prevention across different populations of people who smoke.[109]

Because smoking is a chronically relapsing condition,[31] chronic care approaches, such as those commonly used to treat asthma, high blood pressure, high cholesterol, and diabetes, have been used to address smoking relapse. Chronic care strategies involve periodically reaching out to people who smoke (via calls, letters, or electronic health record [EHR] messages sent out approximately every 6 months) to offer them re-treatment if they have relapsed. This strategy has been shown to increase both treatment re-entry and smoking cessation rates, albeit to a modest extent.[212–219]

Combinations of Medications With Behavioral Interventions for Smoking Cessation. Combining medication and counseling is more effective than the use of either alone.[17,31,149] A 2019 meta-analysis of 83 studies found that adding counseling to the provision of medication increased the likelihood of smoking cessation by about 10%–20% versus medication alone and that this effect was consistent across the FDA-approved medications.[220] This increased effect was present when counseling was conducted either in-person or via telephone, and the incremental effect increased modestly as a function of counseling intensity. A meta-analysis of 49 trials compared the provision of individual counseling alone with the combination of individual counseling and an FDA-approved medication; the combination treatment produced significantly higher long-term abstinence rates, typically 6 months or longer.[108] The combination of counseling with an FDA-approved medication has also been shown to be more effective than usual care and brief smoking cessation advice.[45,149] Lastly, some evidence suggests that the combination of varenicline with counseling is more effective than are other medications when used with counseling,[221] although not all reviews have reported this.[220]

Summary: Behavioral Interventions for Smoking Cessation. Counseling interventions play a key role in promoting smoking cessation. Of the counseling approaches examined, CBT has the most robust support as its effectiveness has been demonstrated in numerous, different populations of people who smoke. Evidence also shows that abstinence rates increase up to a point, as the dose of CBT counseling (e.g., number or duration of sessions) increases; intensities of at least 30 minutes of total contact time for a quit attempt and multiple treatment contacts are needed to optimize benefit. Counseling approaches such as ACT and BA require more experimental evaluation before their effectiveness can be adequately gauged, especially their effects relative to comparably intensive CBT. Similarly, further evaluation is needed to understand whether engagement approaches such as MI will be effective to include in smoking cessation interventions. Substantial evidence indicates that combining counseling with pharmacotherapy produces higher long-term abstinence rates than is produced by either type of intervention when used by itself. CM or incentive treatments appear to be effective in producing high initial smoking cessation rates; one promising use of this approach is to incentivize

engagement in smoking cessation treatment. In sum, data from the general population suggest that among the various types of counseling approaches, CBT, especially when paired with smoking cessation medication, produces the most reliable and robust benefits and can be effective when delivered via a variety of routes, including in-person, via videoconferencing, or by phone.

Beyond In-Person Counseling: Telephone, Telehealth, and Digital Approaches for Smoking Cessation

Telephone Counseling. In 2002, a subcommittee of the U.S. Department of Health and Human Services Interagency Committee on Smoking and Health recommended the establishment of a national network of tobacco cessation quitlines—a single nationwide 1-800 portal providing uniform access to state quitlines.[222] The National Network of Tobacco Cessation Quitlines launched in 2004, with funding from the Centers for Disease Control and Prevention and the National Institutes of Health via NCI, to provide telephone-based cessation services to individuals in all states, Washington DC, and U.S. Territories. Quitlines are a commonly used resource; the National Network of Tobacco Cessation Quitlines (1-800-QUIT-NOW) received its 10 millionth call in 2019.[222,223]

Quitline services can include telephone-based coaching and counseling, referrals, mailed materials, training for clinicians, mobile phone–based and web-based services, and free smoking cessation medications.[224] The level and types of services vary across states. For instance, some quitlines offer text message services while others do not; also, the individual state quitlines offer different amounts and types of medication.[225,226] In general, state quitlines provide counseling comprising CBT and adjuvant intra-treatment social support and motivational content, and most provide some amount of smoking cessation medication.[113,227] Access to other adjuvants such as web resources may be offered in addition to this base treatment. Users can receive support by proactively calling the quitline or by registering online (not universally available) or through health care program or clinician referral via fax or EHR-mediated referral.[9,228] Referred patients are called by the quitline and the patient must answer the call to register for service. Quitlines strive to match a client with services that reflect their preferences and needs, but clients are generally offered both counseling and a range of other resources.[225,229] Quitlines often have intervention protocols designed for special populations such as youth and pregnant women.

Quitlines receive approximately half a million direct calls annually,[226,230] reflecting the advantages to their use: they require no travel or health insurance and are free to the user. These features also make them especially appropriate for populations that have a dearth of other treatment options. Almost half of quitline users had a GED degree or less than a high school education.[226] One limitation of referring patients to quitlines is that only half or fewer of referred patients ultimately accept a quitline call and receive treatment.[9,228] In addition, the intensity of the smoking cessation treatment offered by many state quitlines is modest, in some cases consisting of only 1 counseling call and a 2–4 week starter supply of medication (although individuals can recontact the quitline).[226,231]

A 2019 Cochrane Review evaluated the effects of multisession counseling in 14 trials among individuals from the general population who called a quitline.[232] This analysis compared experimental conditions that differed in counseling intensity but not in other treatment factors

such as medication. The results indicated that multisession counseling increased long-term abstinence relative to control conditions that provided self-help or briefer counseling contact (RR = 1.38, 95% CI = 1.19–1.61, *N* = 32,484). Thus, smoking cessation counseling appears similarly effective when delivered via phone as it is in face-to-face contexts. Other analyses in this report found mixed evidence regarding the relative effectiveness of more versus less intense counseling on long-term abstinence. In sum, studies showed that individuals from the general population who called a quitline and received multisession quitline counseling had modestly higher long-term abstinence rates than did individuals who received only self-help or a single quitline call. The magnitude of this effect was to increase the chances of long-term abstinence on average from about 7% to 10% relative to the control conditions.

The 2019 Cochrane Review cited above also indicated that proactive phone counseling (where treatment personnel call individuals to deliver treatment) is effective among the general population.[232] Proactive telephone counseling was evaluated in 35 trials in which it was compared with minimal intervention (e.g., self-help). The resulting meta-analysis yielded a significant effect (RR = 1.35, 95% CI = 1.16–1.57, *N* = 22,917). Importantly, a 2018 RCT with patients with cancer compared intense (4 weekly sessions plus 4 biweekly and monthly sessions and FDA-approved smoking cessation medication for 12 weeks) versus less intense (4 weekly sessions and medication advice) smoking counseling delivered by phone to patients with cancer.[233] This study showed significant benefit of telephone counseling (see "Behavioral Interventions for Smoking Cessation Among Patients With Cancer" for an extended discussion of this study).

Video-Based Counseling. Audiovisual (video) counseling (or telehealth) can be delivered to patients through a smartphone, tablet, or computer. In such treatment, the health care program typically contacts a patient in response to clinician referral or because a patient responded to health system outreach. The treatment is largely determined by each health care system; however, if it follows clinical practice recommendations,[17] it should include CBT, motivational intervention, intra-treatment support, and medication recommendation and provision.

Video counseling can expand access to evidence-based smoking cessation treatment and improve treatment adherence. Video delivery allows clinicians to respond to nonverbal cues that may improve the communication and the therapeutic alliance achieved during counseling sessions, allowing patients to feel better supported by their clinician.[234] However, there are also challenges with video counseling. Some patients may not have access to necessary resources, such as reliable, high-speed internet, or they may lack the knowledge to use needed resources effectively. For these patients, phone counseling may be more appropriate. Video counseling also requires that a health system or program provide the technologic and personnel support to make routine intervention feasible.

Video counseling for smoking cessation treatment has not been evaluated extensively in either the general population or in patients with cancer. A Cochrane Review identified two studies that compared real-time video counseling for smoking cessation with telephone counseling in individuals from the general population.[235] The meta-analysis revealed no significant difference between the 2 counseling types (RR = 2.15, 95% CI = 0.38–12.04, *N* = 608). However, the authors of the meta-analysis rated the certainty of this finding as very low due to methodologic limitations and imprecision in the effect estimate. Another systematic review also found mixed

evidence regarding the effectiveness of video counseling for smoking cessation treatment versus telephone counseling or face-to-face counseling.[236] Carlson and colleagues compared group video counseling treatment delivery to rural residents with in-person group tobacco cessation treatment to urban residents in a nonrandomized study.[237] The two approaches yielded similar long-term abstinence rates.

Evidence suggests that video counseling is acceptable, feasible, and yields encouraging engagement rates in cancer patient populations.[238] LeLaurin and colleagues used a pragmatic design, giving patients with cancer who smoke (median age 58; one-third rural residents) a choice of traditional quitline (N = 39), in-person group counseling (N = 14), or individual video counseling via smartphone (N = 37).[239] The video counseling patients gave especially favorable ratings to their intervention, mainly due to the treatment's convenience. In another study, patients with cancer undergoing radiation treatment completed surveys appraising their smoking cessation treatment delivered during office (N = 726) or video (N = 351) visits. Patients gave similarly high satisfaction ratings to the two types of interventions.[240]

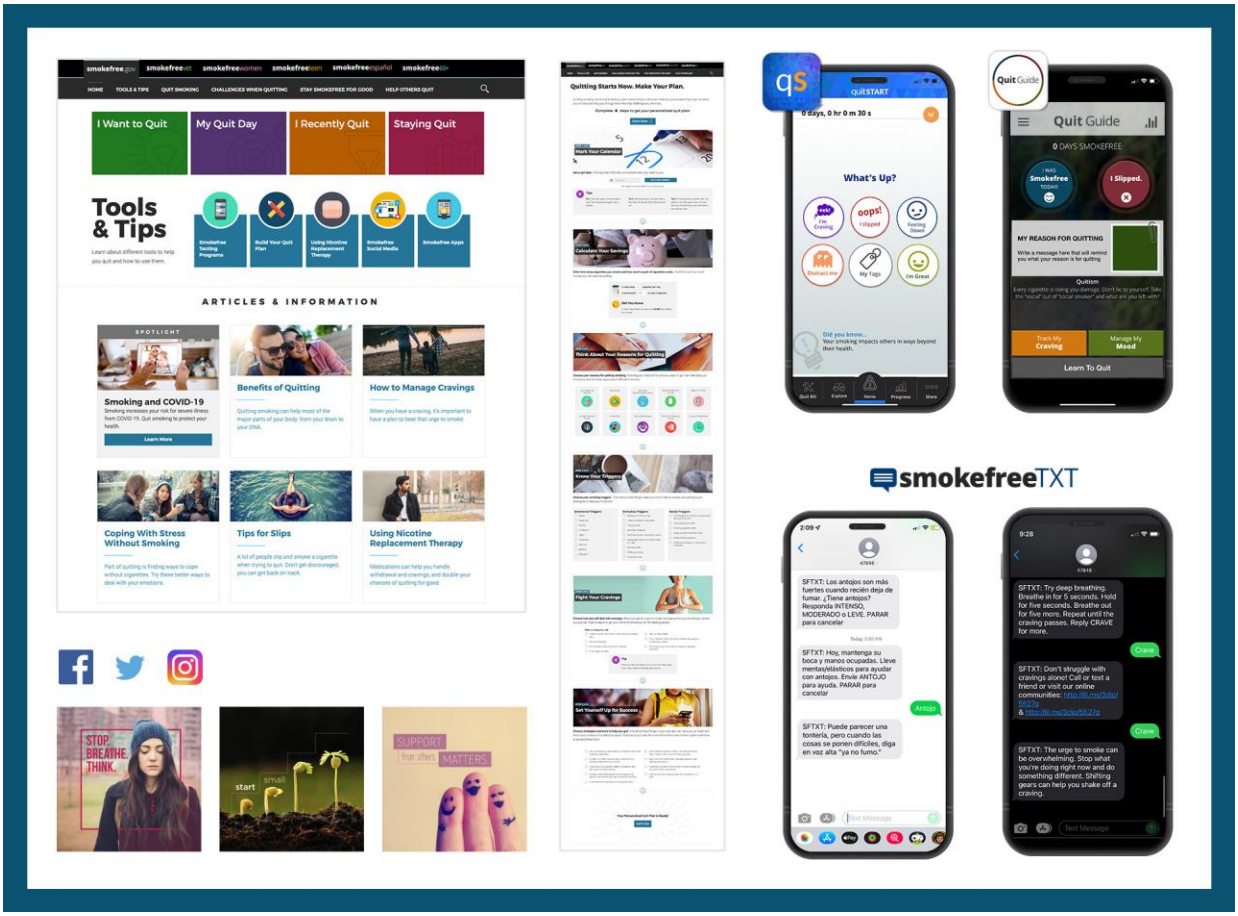
In sum, limited evidence suggests that video counseling may be similar in effectiveness to phone counseling when used with the general population. Further research is needed to establish its effectiveness relative to phone counseling as well as to other behavioral treatment approaches. Similar comparative effectiveness research is clearly needed to establish its effectiveness in cancer patient populations.

Digital Interventions. Digital interventions include web-based and mobile phone delivery of smoking cessation treatment. These web- and mobile-based interventions have tremendous promise because of their potential population reach given that cell and/or smartphones are widely available.[241] In addition, they can often be delivered at relatively low cost once the needed infrastructure is implemented, permit easy tailoring, allow for good quality control of content, are continuously available to the user, and permit easy collection of data on use.[31,242] They may be especially beneficial for groups that have limited access to other forms of treatment (e.g., in-person counseling), health care, or transportation resources.[243] Additionally, digital interventions may align with recent trends in telehealth and help reach rural smokers,[244] although internet access remains lower among rural residents than among suburban and urban residents. [245,246]

Evaluating digital interventions for smoking cessation treatment is difficult because of their diversity, rapid development, and continuous evolution.[31] For example, websites vary with regard to interactivity, personalization, recruitment route (search engines, advertising, health care referral), whether their content is evidence based, and their goals (i.e., an intervention vs. a referral resource). What follows is a summary of the current literature on three types of digital channels for delivering smoking cessation interventions: website, short message service (SMS), and smartphone app. The present review of these intervention strategies is brief, relies on prior authoritative reviews, and is focused on the potential for these interventions to benefit patients with cancer who smoke. In addition, this review tries to address whether such interventions are effective relative to no treatment or minimal treatment controls and how they compare with other forms of treatment such as person-to-person counseling and pharmacotherapy. These comparisons are relevant to decisions about whether to use such interventions and whether to use them in lieu of other types of interventions. Again, these data arise from research on the general population but may be relevant to patients with cancer as well.

The National Cancer Institute's Smokefree.gov Initiative (SFGI) provides free, evidence-based cessation support to the public through a multimodal suite of digital interventions (Figure 3.1), including six mobile-optimized websites, seven text messaging programs (in English and Spanish), and two mobile applications. In addition to digital resources directed at the general population, the SFGI includes population-targeted resources for adolescents, women, military veterans, Spanish speakers, and older adults. All SFGI resources are free for use or download; data fees may apply for some text message subscribers. Additional details about SFGI interventions are provided in the subsections below as examples of resources available to clinicians and public health professionals.

Figure 3.1 Smokefree.gov Initiative Digital Interventions



Website/Web-Based Interventions. A website or web-based intervention can present either (or both) static content that is the same for every user or interactive content so that user performance influences the nature of the material that is presented or available. Early evidence on the effectiveness of web-based interventions shows a mixed picture,[31] in part because of the range of web-based interventions and combinations that have been evaluated in studies,[247,248] which makes it difficult to isolate the effects of any individual component (e.g., a website). Taylor and colleagues conducted a meta-analysis comprising 8 studies (N = 6,786) that showed a modest but significant benefit of web-based interventions on long-term abstinence, compared with no treatment (6–12 months) (RR = 1.15, 95% CI = 1.01–1.30).[248] On the other hand, one meta-

analysis of 5 trials that compared web-based interventions with active comparison conditions (such as face-to-face or telephone counseling) found that the pooled effect estimate was not significant (RR = 0.92, 95% CI = 0.78–1.09, N = 3,806, I^2 = 0%).[248] Another meta-analysis compared web-based interventions (with interactivity and tailoring) with more basic or comparison conditions (no intervention, usual care, more basic web-based interventions, or non-web interventions).[249] About half of the active or web-based intervention conditions included other types of interventions so data on effectiveness might not reflect the effects of web-based interventions alone. The evidence showed a significant effect of web-based intervention on long-term (6-months or more) abstinence when assessed with pooled outcome measures (e.g., measures of prolonged and point-prevalence abstinence [PPA]: odds ratio [OR] = 1.19, 95% CI = 1.06–1.35, p = .004, 34 trials). However, significant effects were not found for standard outcomes such as 30-day PPA (OR = 0.87, 95% CI = 0.76–1.00, p = .054, 8 studies), or 7-day PPA (OR = 1.20, 95% CI = 0.93–1.55, p = .155, 17 studies).[249] Thus, like the Taylor meta-analysis, the McCrabb and colleagues' meta-analyses suggest that web-based interventions can significantly increase long-term smoking abstinence, but the effect may not be wholly attributable to the web-based intervention and is not robust across different sets of studies or outcomes. Also, many digital interventions (including web-based) experience retention problems or high dropout rates, which might reduce the effectiveness of the intervention or challenge outcome ascertainment.

Smokefree.gov Websites

Smokefree.gov (https://smokefree.gov) is the National Cancer Institute's (NCI's) public-facing smoking cessation website. The website provides information, support, motivational enhancement, and interactive tools to assist people who smoke in quitting. The website serves as an entry point for all Smokefree.gov Initiative (SFGI) digital resources and tools, as well as the NCI's telephone and online smoking cessation counseling services (https://smokefree.gov/tools-tips/speak-expert). A quit plan–builder tool guides users through the steps to prepare for making a quit attempt. Quizzes allow users to assess factors such as their level of nicotine dependence and perceived stress level to inform their quit experience. SFGI social media platforms offer inspiration and encouragement to support people during their quit attempts and beyond.

Other meta-analyses have found that more active and complex web-based interventions can yield significantly higher long-term abstinence rates than do various control conditions. Graham and colleagues found that interactive interventions were more effective than no-treatment controls and assessment controls or print-based smoking cessation materials.[247] McCrabb and colleagues performed meta-analyses on many of the same web-based internet interventions analyzed by Graham and colleagues and found that the effectiveness of the web-based interventions was positively related to certain content that addressed active treatment elements such as making goals and planning and obtaining social support.[249]

In sum, there is meaningful evidence that web-based interventions, such as interactive websites, can be more effective than no intervention. However, the benefits of web-based interventions tend to be modest in size compared with the effects of medication and person-to-person

counseling,[103,109,248,250] and static or simple website interventions composed of few components may impart little benefit.[31,247–249] Thus, some care must be taken in assessing the nature and quality of such interventions. This task is challenging because many of the web-based interventions that were evaluated and reported in the literature no longer exist.[249] However, it is important to note that even small benefits from web-based interventions may be important because they are highly accessible, can be provided at low cost, and require no clinical personnel.

SMS Interventions. In SMS text messaging interventions, individuals are sent automated smoking intervention text messages for an extended time period (typically starting prior to the target quit date and extending for multiple weeks thereafter). Text message–based interventions may also have bidirectional functionality, which enables individuals to send or respond to messages (i.e., request on-demand help or provide information about withdrawal symptoms, smoking status, and desire for additional or tailored interventions). The potential reach of texting interventions is considerable given that 85% of Americans owned a smartphone as of 2021 and 97% of Americans owned a cell phone of some kind.[241] Further, texting is common among smartphone users in the United States.[251]

Meta-analyses suggest that SMS interventions significantly enhance long-term smoking cessation rates.[107,252] A Cochrane Review meta-analysis of 13 studies showed that the effects of the SMS interventions were significant when using both point prevalence and continuous measures of abstinence and when abstinence reports were biochemically confirmed.[107] In these meta-analyses, the SMS interventions were compared with control conditions that typically involved no or minimal intervention (reduced-intensity texts); only one study compared the SMS intervention to counseling and pharmacotherapy.

Smokefree.gov Initiative's Text Messaging Programs

SmokefreeTXT is Smokefree.gov Initiative's (SFGI) text messaging−based cessation program. The fully automated service provides people who smoke with up to 8 weeks of encouragement, advice, and quitting tips. SmokefreeTXT users are asked to set a quit date within the next 2 weeks. Subscribers who are ready to quit right away can begin receiving cessation support immediately; those not yet ready can receive up to 2 weeks of preparation messages. Text messages are delivered daily (approximately 3−5 messages per day) and are timed around the quit date selected by the user. In addition to the main SmokefreeTXT program, SFGI offers text messaging-based cessation programs for pregnant women, adolescents, Spanish speakers, military veterans, and other populations.

The 2020 Surgeon General's report concluded that SMS interventions are effective at increasing smoking cessation, particularly if the text messages are interactive or tailored to the user's responses.[31] The Community Preventive Services Task Force similarly noted that mobile phone text messaging interventions are effective when implemented alone or with other interventions, especially when an intervention delivers tailored content, interactive features, or both.[102] However, the 2020 Surgeon General's report[31] noted that although the effects of SMS

interventions are often significant in the short term (less than 6 months), their long-term effects tend to be highly variable across studies[253] and recommended additional research to increase understanding of the effect of various treatment aspects of these interventions. In sum, SMS interventions can be effective relative to no treatment, but the effectiveness of SMS interventions can vary meaningfully across different versions of the interventions (e.g., content, tailored vs. untailored, nature of the comparison condition) or populations studied (e.g., age, race and ethnicity), suggesting a need for research on factors that influence their effectiveness.[31]

Smartphone Applications (Apps). Apps are integrated software units designed to run on mobile devices such as smartphones or tablets. They are typically highly interactive and can present information in multiple different formats, monitor data, and provide feedback to users in the service of some goal. There are hundreds of apps for smoking cessation,[254] and these vary greatly in their content and the approaches they take to promote smoking cessation.[254,255] A 2019 Cochrane Review meta-analysis of five studies compared smoking cessation smartphone apps with either a less intense app or minimal support. The evidence was deemed of very low certainty and yielded no evidence that smartphone apps improved the likelihood of smoking cessation (RR = 1.00, 95% CI = 0.66–1.52, I^2 = 59%, *N* = 3,079).[107] The uncertainty of the evidence may arise from the great variability among apps. A 2020 study shows evidence of such variability in app effectiveness. Bricker and colleagues completed a large randomized clinical trial (*N* = 2,415) that compared an ACT-based smoking cessation smartphone app with NCI's smoking cessation smartphone app (i.e., QuitGuide).[256] The latter was designed based on the treatment recommendations in the PHS Clinical Practice Guideline, *Treating Tobacco Use and Dependence: 2008 Update*.[17] The primary smoking cessation outcomes were based on unconfirmed self-report; the 30-day PPA rates at 12-month follow-up were significantly greater for the ACT app than for the NCI QuitGuide app (28.2% vs. 21.1%, OR = 1.49, 95% CI = 1.22–1.83).[256]

Smartphone Apps

The Smokefree.gov Initiative supports two smartphone-based mobile apps (https://smokefree.gov/tools-tips/apps), accessible on both iPhone and Android platforms, designed to guide people who smoke through quitting and to help them build skills to maintain cessation. QuitGuide was developed for a general adult audience; quitSTART was developed for adolescents and young adults who smoke. These mobile apps provide real-time monitoring of cessation progress, including tracking of cigarettes, cravings, mood, triggers, and lapses.

Apps can be provided to patients at relatively low cost, and they create little burden for clinical staff. However, the selection of a smartphone app is critical because they can differ meaningfully in guiding theoretical model and change strategies[257,258]; such differences could substantially affect their effectiveness. This variability also makes it difficult to make general statements about their effectiveness.[31] Also, as with websites and SMS interventions, it is unclear that they have the same level of effectiveness as relatively intense interventions including person-to-person counseling and pharmacotherapy.

Summary: Digital Interventions for Smoking Cessation. There is strong evidence that phone counseling delivered by quitlines or delivered proactively by smoking cessation treatment programs increases long-term abstinence rates in individuals in the general population. In addition, an RCT conducted with patients with cancer who smoke showed that more intense telephone-based smoking cessation treatment counseling is more effective than less intense telephone-based smoking cessation treatment counseling. Two drawbacks of quitline treatment are that patients often do not take quitline calls even when they previously accepted a referral to it, and patients with cancer may need more intense treatment than is typically provided by quitlines.

There is little research evidence on the effectiveness of video-based smoking cessation counseling. Telehealth (i.e., video counseling) remains an understudied model of delivering smoking cessation treatment; however, limited evidence from the general population suggests that it is similar in effectiveness to phone counseling for smoking cessation. Video counseling for smoking cessation appears to be quite acceptable to patients and feasible for use in health care settings, including in cancer treatment programs. These features increase the importance of establishing its effectiveness in cancer patient populations.

Digital interventions for smoking cessation hold considerable promise given their potential reach and there is evidence that they can be effective (Table 3.3), which has led the U.S. Preventive Services Task Force (USPSTF) to recommend them for the treatment of nicotine dependence.[46] The evidence of their effectiveness is greatest and most robust when they are being compared with control conditions involving little or no treatment. Most data suggest that they are less effective than the combination of moderately intense person-to-person counseling and pharmacotherapy. Furthermore, there is evidence of substantial variability within the different types of digital interventions (i.e., among web-based, SMS interventions, and smartphone apps). Thus, such interventions must be selected with care. Moreover, more data are needed to guide decisions about whether such interventions are best used as adjuvants to, or substitutes for, other types of evidence-based smoking cessation treatments. Finally, health care systems using such resources must consider how to encourage patients to use digital interventions (e.g., after referral), a topic addressed in chapter 4. In sum, there is some evidence of effectiveness for both web-based and SMS interventions, which, given their great potential reach, encourages their consideration for use as smoking cessation strategies.

Smoking Cessation Treatments Among Patients With Cancer

Many patients with cancer are motivated to quit smoking and are receptive to smoking cessation treatment. This section reviews pharmacological, behavioral, and program-level treatments for smoking among patients with cancer. This section includes results from individual RCTs and some nonexperimental studies (e.g., single-arm trials) with the former permitting stronger inference regarding causality.

Patients with cancer who smoke differ from the general population of people who smoke in several ways: They are often more nicotine dependent and face challenges related to their cancer diagnosis, including anxiety, stress, pain, and the demanding nature of cancer treatment.[7,259] Many also feel ashamed that they smoke, and experience stigma related to their smoking.[260] These and other factors could complicate cessation treatment in this population.

Medications for Smoking Cessation Among Patients With Cancer

Table 3.6 describes the smoking cessation studies conducted with patients with cancer. Many of the trials included small sample sizes and relied on the self-report of smoking abstinence, rather than on biochemically confirmed abstinence. Several reviews summarize smoking cessation studies among patients with cancer.[261–264] Trials that have experimentally evaluated FDA-approved smoking cessation medications in patients with cancer are rare and only one such trial has used a placebo-controlled clinical trial design.[265] Further, most trials involving smoking cessation medication also involve adjuvant counseling so the effects of medication and counseling cannot be accurately distinguished.

Cancer patient populations often have high levels of nicotine dependence,[7,33,266] so there is a strong rationale for using smoking cessation medications with this population. No study has tested the use of NRTs, or combination NRT, with patients with cancer using a placebo-controlled design. Two RCTs compared a usual-care treatment arm (i.e., smoking cessation advice and referral) with a treatment arm that included NRT and counseling,[267,268] and neither trial found a significant difference in biochemically confirmed quit rates at 6–12 months. A pilot study by Pollak and colleagues compared an active condition involving NRT (type unspecified) and four 60-minute sessions of counseling with a waiting-list control condition.[269] This study reported somewhat higher short-term (2-month) abstinence rates in the active treatment condition than in the control condition (14% vs. 6%). However, the sample size was quite small ($N = 30$) and no long-term (≥6 month) follow-up outcomes were reported. Also, waiting-list control conditions may encourage individuals to wait to make a quit attempt until treatment is available. A 2020 single-cohort observational study provided patients with cancer who smoke with brief counseling and a free 4-week supply of nicotine patches. Among patients with complete follow-up data, 35% reported smoking cessation, although self-reported quit rates were not biochemically confirmed.[270]

A placebo-controlled RCT of bupropion found no overall smoking cessation effect for the medication, but bupropion increased abstinence rates more for patients with depressive symptoms versus those without depressive symptoms.[265]

Four studies have evaluated the use of varenicline for treating tobacco use among patients with cancer. One nonrandomized cohort-type study compared patients with cancer who received counseling and varenicline with those who previously received usual care (historical controls; no smoking cessation treatment). The quit rate for the counseling and varenicline arm was higher than for usual care (34% vs. 14%), but this difference was not significant likely due in part to the small sample size ($N = 49$).[271] An open-label study in which all patients were given varenicline ($N = 132$) found a quit rate of 40% after 12 weeks of treatment.[12] The placebo-controlled randomized phase of one study examined the effects of extended varenicline (24 weeks) versus standard duration varenicline therapy (12 weeks of varenicline plus 12 weeks of placebo). The 2 varenicline treatments did not differ significantly in abstinence rates at 24-week follow-up (30% in both groups).[272] The last study was a very small study that randomized patients with cancer ($N = 29$) to either: (1) a control arm that received a single counseling session, educational material, and a referral to a smoking cessation program; or (2) an intervention arm that received 8 weekly MI sessions; CM ($5 per report of biochemically verified abstinence); and the choice of combined NRT, varenicline, or bupropion. At week 8, a significantly greater proportion of

intervention-arm patients had quit smoking (biochemically confirmed) than was found in the control arm (74% vs. 30%).[273]

One study with patients with cancer as participants evaluated the effect of access to multiple FDA-approved smoking cessation medications. Duffy and colleagues compared a usual-care intervention with an intervention comprising counseling and access to either NRT or bupropion (*N* = 184) and reported significantly increased quit rates for the active-treatment arm.[274] This effect is difficult to interpret because a portion of the participants who were treated in this study were not currently smoking at the beginning of their participation in the study. A second study also involved use of multiple FDA medications[233] but differences in the medication condition were confounded with different counseling intensities. This study is discussed in the section, "Behavioral Interventions for Smoking Cessation Among Patients With Cancer."

Table 3.6 reveals that only 3 RCTs have a sample size >100 and had measures of biochemically confirmed abstinence at long-term follow-up (>6 months).[265,268,272] None of these three studies showed a significant benefit of medication in whole sample analyses.

It is important to note that smoking cessation medications have been judged to be quite safe when used by patients with cancer, consistent with their being recommended for the treatment of smoking in patients with cancer by the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology.[16] However, clinicians should ensure that smoking cessation pharmacotherapies are appropriate given the patient's cancer, their existing pharmacologic regimens, and the effects of their cancer treatment. For example, use of oral NRT may be contraindicated for patients with cancers of the oral cavity.[275]

Table 3.6 Studies of Smoking Cessation Interventions Among Patients With Cancer

Study	Sample size	Intervention arm	Control arm	Timing of quit rate assessment[a]	Quit rate[b] intervention arm	Quit rate control arm	Methodological comments
Studies of smoking cessation medications (with or without counseling)							
Randomized studies							
Rettig et al. 2018[273]	29	Combined NRT, bupropion, or varenicline; counseling	Counseling, referral	8 weeks from baseline	74%	30%	Randomized, biochemical confirmation
Schnoll et al. 2019[272]	207	24 weeks varenicline, counseling	12 weeks varenicline, counseling	24 weeks from baseline	61% (adherent patients), 10% (nonadherent)	45% (adherent patients), 13% (nonadherent)	Randomized, biochemical confirmation
Duffy et al. 2006[274]	184	NRT or bupropion, counseling	Counseling, referral	6 months from baseline	31%	15%	Randomized, self-reported cessation
Schnoll et al. 2010[265]	246	Bupropion, patch, counseling	Placebo, patch, counseling	12 and 27 weeks from baseline	27% (12wk), 18% (27wk)	24% (12wk), 17% (27wk)	Randomized, biochemical confirmation
Pollak et al. 2018[269]	30	NRT, counseling	Waitlist control (received NRT and counseling 2 months after randomization)	2 months after randomization	14%	6%	Randomized, biochemical confirmation
Thomsen et al. 2010[267]	130	NRT, counseling	Advice, referral	12 months postoperative	13%	9%	Randomized, self-reported cessation
Wakefield et al. 2004[268]	137	NRT, counseling	Advice, referral	6 months from baseline	5%	6%	Randomized, biochemical confirmation
Nonrandomized studies							
Park et al. 2011[271]	49	Varenicline, counseling	Varenicline	12 weeks from baseline	34%	14%	Quasi-experimental, biochemical confirmation

Table 3.6 (continued)

Study	Sample size	Intervention arm	Control arm	Timing of quit rate assessment[a]	Quit rate[b] intervention arm	Quit rate control arm	Methodological comments
Arifin et al. 2020[270]	117	NRT, counseling	None	Median 9 months from baseline (interquartile range, 5.7—11.6 months)	35%	N/A	Single-cohort observational, self-reported cessation
Studies of behavioral smoking interventions (with or without medications)[d]							
Randomized studies							
Stanislaw and Wewers 1994[278]	26	Counseling	Advice	5 weeks after hospital discharge	75%	43%	Randomized, biochemical confirmation
Gritz et al. 1993[36]	186	Counseling	Advice	1, 6, and 12 months from baseline	69% (1m), 71% (6m), 69% (12m)	76% (1m), 74% (6m), 79% (12m)	Randomized, biochemical confirmation
Schnoll et al. 2005[280]	109	Tailored counseling (cognitive behavioral therapy, including 3 phone sessions and 1 in-person session), NRT	Standard counseling (general health education), NRT	1 and 3 months after intervention completion	45% (1m), 43% (3m)	47% (1m), 39% (3m)	Randomized, self-reported cessation
Park et al. 2020[233]	303	Extended counseling 11 counseling sessions over about 24 weeks) and NRT, bupropion, or varenicline	Counseling (4 counseling sessions over 4 weeks) and medication advice	6 months from baseline	35%	22%	Randomized, biochemical confirmation
Wewers et al. 1994[279]	80	Counseling	Advice	5 to 6 weeks after hospital discharge	38%	26%	Randomized, self-reported cessation
Ostroff et al. 2014[290]	185	Counseling, NRT, scheduled smoking reduction	Counseling, NRT	6 months after hospitalization	32%	32%	Randomized, biochemical confirmation

Table 3.6 (continued)

Study	Sample size	Intervention arm	Control arm	Timing of quit rate assessment[a]	Quit rate[b] intervention arm	Quit rate control arm	Methodological comments
Ghosh et al. 2016[289]	14	CM	Advice, smoking cessation classes	6 months from baseline	33%	0%	Randomized, biochemical confirmation
Griebel et al. 1998[277]	28	Counseling	Advice	6 weeks after intervention completion	21%	14%	Randomized, self-reported cessation
Bricker et al. 2020[291]	59	Quit2Heal (smartphone app)	NCI QuitGuide	2 months from baseline	20%	7%	Randomized, self-reported cessation
Schnoll et al. 2003[281]	432	Counseling	Advice, referral	6 and 12 month from baseline	14% (6m), 13% (12m)	12% (6m), 14% (12m)	Randomized, self-reported cessation
Nonrandomized studies							
Browning et al. 2000[276]	25	Counseling	Advice	6 months from baseline	71%	55%	Quasi-experimental, biochemical confirmation
Charlot et al. 2019[288]	18	Mindfulness-based group visits	None	3 months from baseline	0%	N/A	No control arm, self-reported cessation
Cinciripini et al. 2019[334]	3,245	CBT/MI counseling 8 visits	N/A	6 months	46%	N/A	Prospective cohort with no control arm, self-reported cessation

Note: NRT = nicotine replacement therapy. NCI = National Cancer Institute. CBT = cognitive behavioral therapy. CM = contingency management. MI = motivational interviewing. N/A = not applicable. [a]"Baseline" refers to study enrollment or start of cessation treatment. Some studies have deceased patients removed from the sample (e.g., Arifin et al. 2020) in determining abstinence percentage. [b]Quit rates are rounded to nearest integer. [C]Studies of smoking cessation medications are those in which medication varied across trial arms. [d]Studies of behavioral smoking interventions are those in which the counseling intervention varied across trial arms.

Summary: Medications for Smoking Cessation Among Patients With Cancer. At present, strong conclusions about the level of effectiveness and optimal regimen of cessation medications in patients with cancer are difficult to draw because of a paucity of adequately powered, well-controlled clinical trials in this population. Patients with cancer who smoke may differ in multiple and important ways from the general population. Patients with cancer, for instance, may achieve higher quit rates in the absence of smoking cessation treatment due to their greater motivation to quit, they may experience greater affective distress, and the burden of imminent and taxing medical treatment may increase their level of stress. This suggests that it is possible that FDA-approved medication treatments for tobacco use may differ in effectiveness for patients with cancer compared with the general population. Demonstrating a benefit for cessation medications among patients with cancer can also be challenging because many patients quit without assistance after being diagnosed with cancer; patients who either do not attempt to quit or do not succeed in quitting are likely to have the most difficulty doing so, even when receiving smoking cessation treatment.

Some evidence indicates that smoking cessation medications may be effective for patients with cancer. Specifically, one study showed significant benefit in a subset of participants.[272] Further, some of the studies presented in Table 3.6 show modestly better abstinence rates in the active-medication arms than in the control arms. However, as noted, most of these studies had small samples and, thus, were under-powered, of questionable generalizability, and may not be reproducible.

The PHS Clinical Practice Guideline, *Treating Tobacco Use and Dependence: 2008 Update*,[17] concluded that counseling and medication treatments found effective for patients in general are likely to be effective when used in a variety of subpopulations who smoke. This underlies guideline recommendations that all patients with cancer be encouraged to use evidence-based smoking cessation counseling and medication.[16] More evidence on the effectiveness of smoking cessation treatment in cancer patient populations is needed to identify the optimal cessation medication regimens for patients with cancer, including the optimal combination of medication with different levels of counseling (e.g., brief vs. intense).

Behavioral Interventions for Smoking Cessation Among Patients With Cancer

This section addresses two key questions: (1) is behavioral intervention, or counseling, for smoking cessation effective in increasing abstinence rates among patients with cancer, and (2) is there evidence that adapting behavioral intervention for patients with cancer makes it more effective?

To address these questions, studies should ideally permit causal inferences about counseling intensity; for example, RCTs where participants are randomized to intense counseling versus no or minimal counseling. In such studies, smoking cessation medication should either not be used or should be the same across the treatment arms. Counseling interventions for smoking in patients with cancer have been researched more extensively than have medication treatments, although many of the counseling studies are small, underpowered, and lack methodological rigor.[263]

Counseling studies have typically used standard cognitive behavioral frameworks and psychoeducational approaches to guide counseling. Very early studies compared usual care to nurse-led, multiweek counseling treatments.[276–279] These were very small studies (<50 participants each) that used self-reported smoking cessation outcomes without biochemical confirmation. Although quit rates were often higher among patients in the intervention arm, the effects in these studies were not significant (Table 3.6), likely due in part to small sample sizes that reduced power.

However, studies with larger sample sizes have also not found significant effects. For example, a study with 96 patients randomized to usual care or a multiweek counseling intervention found no significant effect for the counseling intervention after 12 months.[36] Although this study was larger, it was still underpowered given the likely effect sizes expected from counseling. Later studies used counseling models that were more tailored to address specific barriers to smoking cessation among patients with cancer, such as emphasizing the benefits of smoking cessation for reducing recurrence, managing psychological distress, and/or reducing fatalism. A study using a randomized trial design to compare CBT-based smoking cessation counseling tailored to the needs of patients with cancer who smoke (e.g., addressing fatalistic beliefs) to a general health education intervention found no significant differences between the two groups; both intervention arms produced quit rates close to 40%.[280] One of the largest studies (N = 432) compared a physician-based counseling intervention with usual care and found low overall quit rates for both arms at the 12-month follow-up assessment (< 15%) and no difference between treatment arms in self-reported cessation.[281]

More recently, Park and colleagues used a randomized clinical trial design to compare standard smoking cessation treatment (four weekly counseling phone calls and medication advice) with a more intensive treatment that included seven additional counseling calls over 3 months and the choice of an FDA-approved smoking cessation medication provided at no charge. Thus, conditions differed in both counseling intensity and medication. However, this study is best conceptualized as one comparing 2 levels of counseling because participants in both arms used medication (77.0% in the intensive arm and 59.1% in the standard arm). Smoking cessation counseling was delivered by certified tobacco treatment counselors. Participants had recently been diagnosed with cancer (breast, gastrointestinal, genitourinary, gynecological, head and neck, lung, lymphoma, or melanoma cancers). At a 6-month follow-up, there was a significant increase in the biochemically confirmed PPA rate for the intensive treatment versus standard care (34.5% vs. 21.5%)[233] (Table 3.6). In all, this study is important because of its sample size (N=303) and long-term biochemically confirmed follow-up. Therefore, it provides important evidence on the effectiveness of intense versus less intense smoking cessation counseling on long-term smoking abstinence in patients with cancer where many patients in both conditions use medication.

Two meta-analyses included studies using combinations of counseling and pharmacotherapy treatments delivered to patients with cancer.[282,283] Klemp and colleagues conducted a systematic review and meta-analysis of smoking cessation treatment studies with patients with head and neck cancer.[282] They found that counseling can help such patients quit smoking, compared with various control conditions (i.e., brief advice, general health education, or no cessation treatment). However, this meta-analysis may not provide a sensitive test of counseling effects because only three of the eight studies analyzed were RCTs and counseling differed among the eight studies;

only one of the RCTs found a significant effect. Furthermore, participants in the cohort and case series studies received pharmacotherapy in addition to counseling. Thus, the effects of these different types of interventions cannot be disentangled.

Sheeran and colleagues analyzed 21 RCTs that were intended to evaluate smoking cessation treatments in cancer populations.[283] The trials analyzed comprised a mixture of pharmacologic and/or behavioral smoking cessation treatments. Also, the trials involved diverse samples; some included recently diagnosed patients and others included long-term survivors of childhood and adolescent/young adult (AYA) cancer (additional discussion on childhood and AYA cancer survivors is below). This meta-analysis did not find evidence of a significant benefit of smoking cessation treatment, compared with the control condition, in terms of increased smoking cessation at follow-up. This negative outcome may largely reflect limitations of the analyzed studies. One paper evaluated in the meta-analysis by Sheeran and colleagues was not evaluated in this chapter because it was reported only as an abstract and provided insufficient information on the treatments and outcomes.[284] Additionally, two of the papers in the meta-analysis were not evaluated in this chapter because only a very small proportion (12% or fewer) of the sample smoked[285,286]; results for only the subsample that smoked were broken out by Sheeran and colleagues. In one of the studies,[287] only a portion of the sample had cancer diagnoses (i.e., 29%) and the authors reported that no smoking cessation treatment was provided in the study (the study tested the effects of providing genetic cancer susceptibility information on smoking cessation). Finally, this meta-analysis did not include the RCT by Park and colleagues[233] previously discussed (Table 3.6), which suggested that large, well-designed RCTs, with guideline-recommended smoking cessation treatment delivered with high treatment fidelity can support the effectiveness of smoking cessation treatment in cancer populations.

Smoking Cessation Intervention Effectiveness Among Childhood, Adolescent, and Young Adult Cancer Survivors

In the U.S., an estimated 10,470 children (age 0–14) will be diagnosed with cancer and 1,050 will die from their disease in 2022.[483] Additionally, in 2020, an estimated 89,500 U.S. adolescents and young adults (AYA: age 15–39 years) were diagnosed with cancer and an estimated 9,270 died from their disease.[483] The population of childhood and AYA cancer survivors varies widely with regard to cancer site, age at diagnosis, type and intensity of treatment, and survival. Due to advances in diagnosis, treatment, and supportive care, most childhood and AYA cancer survivors are expected to be cured.[484–486] Yet, childhood and AYA cancer survivors often experience acute, chronic, and late adverse effects from their cancer and its treatment,[486] including "cardiovascular disease, renal dysfunction, severe musculoskeletal problems, and endocrinopathies."[487,p.1580] Additionally, both childhood and AYA cancer survivors are at risk for developing second primary malignancies due to their cancer history.[488] Smoking increases the risk of long-term negative health outcomes among survivors of childhood cancer[489] and among survivors of AYA cancer.[490]

Two studies provide nationally representative estimates of the prevalence of tobacco use among survivors of AYA cancers, relative to their same-age peers who have not had cancer. Kaul and colleagues analyzed data from the 2012–2014 NHIS to determine the prevalence of cigarette smoking among adults (18 and older) who had been diagnosed with cancer between the ages of 15 and 39, and who were at least 5 years post-diagnosis, compared with an age-matched

comparison group of adults who had not been diagnosed with cancer.[491] This analysis found that 32.9% of cancer survivors currently smoked compared with 22.1% in the comparison group (p < .001). Current smoking among survivors was associated with a higher number of comorbid health conditions (e.g., heart disease) and with a greater likelihood of reporting only fair or poor health. Similarly, a study using data from the 2015–2018 National Survey of Drug Use and Health (NSDUH), found that past-year tobacco use was higher among AYA cancer survivors age 12–34, compared with their non-cancer age-matched peers (38.4% vs. 32.9%, p = .02).[492] The Childhood Cancer Survivors Study (CCSS) is a large cohort study of survivors who were diagnosed with cancer before the age of 21.[493] A CCSS follow-up study compared the smoking rates of adult (18 years and older) CCSS participants to siblings without cancer and with the general population, matched for age, sex, and race, using 2007 NHIS data.[494] At an average of 12.5 years after enrollment in the CCSS, survivor participants had a smoking prevalence of 14%, compared with 16% among siblings without cancer, and 20% in the U.S. general population. Differences in smoking prevalence between the CCSS participants compared with the other cancer survivor populations may be related to younger age at diagnosis, cognitive impairment, or other sample differences.

As described above, despite the serious health risks, smoking is not uncommon among survivors of childhood and AYA cancer and warrants focused attention from oncologists and other clinicians. The effectiveness of smoking cessation treatments may differ in survivors of childhood and AYA cancer in comparison with patients who develop cancer later in life. These groups may differ in important ways, including emotional reaction to their health status, engagement in active cancer treatment, stress of making multiple life changes in response to their illness, and perception of an imminent threat of smoking. For this reason, research on smoking cessation treatment with other populations with cancer might not generalize to the child and AYA survivor population and vice-versa.

The Partnership for Health (PFH) study is one of the few large-scale studies focused on addressing smoking cessation among childhood and AYA cancer survivors. The PFH-1 randomized 796 currently smoking CCSS participants to either a self-help condition, involving receipt of a cessation brochure (N = 398) or to telephone counseling provided by counselors who were themselves childhood cancer survivors (N = 386).[495] Participants in the peer-delivered telephone counseling group received a written report that provided feedback tailored to their smoking status, cancer type, treatment regimen, and other survivorship topics; peer-counselors worked with participants over the course of the intervention, providing up to six calls over a 7-month intervention period. Telephone counseling group participants were able to receive free NRT for themselves and spouses/partners; the self-help group was advised of the utility of NRT but were required to purchase it themselves. At both 8- and 12-month follow-up, the peer-delivered telephone counseling condition had significantly higher quit rates than the self-help group (16.8% vs. 8.5% at 8 months and 15% vs. 9% at 12 months, respectively; at 12 months, OR = 1.99, 95% CI = 1.27–3.14). In a subsequent long-term assessment of the PFH study (2–6 years post baseline), cessation rates continued to be significantly higher among the peer-delivered telephone counseling group than in the self-help control group (20.6% vs. 17.6%; p < .0003).[496] The authors attribute the higher quit rates seen at the later follow-up time point to both sustained cessation among participants who had quit previously and additional quitting efforts made by participants in the study. Especially high long-term abstinence rates were associated with high levels of self-efficacy for smoking cessation at baseline and by NRT use during treatment.

A follow-up study, PFH-2, designed to enhance scalability of the intervention, tested a web-based version (*N* = 230) and a print version (*N* = 144) of the original PFH intervention among childhood or AYA cancer survivors who were currently smoking.[497] Participants were recruited from 5 cancer centers in the U.S. and Canada, as well as from survivorship websites; all had been diagnosed with cancer before age 35 and had completed their cancer treatment at least 2 years before the study. Both study arms received a letter from an oncologist encouraging smoking cessation, pharmacotherapy for themselves and their spouse/partner, and tailored and targeted content based on PFH-1 delivered either in print (organized into a series of manuals) or via the web (in discrete sessions). A procedure intended to lead participants to believe that smoking status was being biochemically verified (bogus pipeline) was used to encourage accurate self-report. At the final assessment at 15-months post-randomization, 16.5% of web participants (22/132) and 15.5% of print participants (20/127) reported being abstinent from smoking for the previous 30 days. No differences in smoking cessation (OR = 1.07, 95% CI = 0.50–2.26) and intervention satisfaction were found between conditions suggesting that the more scalable web-based version was similar in effectiveness to the print version.

However, another study raises questions about the effectiveness of evidence based treatments to significantly increase long-term cessation among survivors of childhood and AYA cancer. A study of adult survivors of childhood cancer (n=519) who were enrolled in either the CCCS or the St. Jude Lifetime Cohort study and reported they were "regular smokers" were randomized to receive either a proactive quitline intervention or a reactive quitline intervention.[498] In the proactive condition the quitline called the participant and offered 6 sessions of counseling and 4 weeks of NRT with additional NRT if the participant became abstinent. In the reactive quitline condition, participants who called the quitline were offered the same 6-session counseling intervention as well as 2 weeks of NRT and were encouraged to seek more NRT. These conditions were chosen to mirror "real life" quitline services. The counseling intervention provided to both groups discussed preparing to quit, the quitting process, and short- and long-term relapse prevention strategies tailored to survivors of childhood cancer. Proactive calls were much more effective at increasing counseling treatment engagement than were the invitations to call that occurred in the reactive condition. Of those in the reactive condition, 84% attended ≤1 session while about 75% of participants in the proactive condition attended 2 or more sessions. At 12-month follow-up, the study found only very low and nonsignificant differences in biochemically verified smoking cessation (<2%) in the two study arms. Thus, although the proactive group received more NRT and had a much greater exposure to counseling, the two conditions did not differ in terms of long-term abstinence. Although not all participants were able to be tested for cotinine, the study also documented extremely high rates of inaccurate disclosure of smoking status (80%) among those who were tested.

To better understand inaccurate disclosure of smoking status in this population, a study was conducted among adult survivors of childhood cancer (n=287) enrolled in the St. Jude Lifetime Cohort Study.[499] In addition to assessing tobacco use (both self-reported and cotinine verified) the study also asked participants about marijuana use. The authors found that a substantial portion of both self-reported never and past smokers had biochemical evidence of active smoking (2.5%–6.7% and 19.7%–36.9%, respectively). Inaccurate disclosure was more common among younger survivors, men, and those who were either past or current marijuana users.

In summary, there is evidence from one RCT with long-term follow-up that a peer counseling intervention is more effective than self-help in treating smoking among childhood and AYA cancer

survivors. A second study suggests that this intervention may also be effective when implemented using either a print or web-based format. Confidence in the effectiveness of this peer counseling treatment would be bolstered by replication. However, another RCT found little evidence of long-term (12-month) benefit of providing adult survivors of childhood cancer more intensive counseling and longer NRT versus less counseling and a shorter duration of NRT. Studies also indicate that self-reported smoking status among childhood cancer survivors is often inaccurate and that co-occurring substance use (e.g., marijuana) should also be assessed. More research is needed to determine the effectiveness of widely available evidence-based treatments in this population, such as those recommended in the PHS Clinical Practice Guideline, *Treating Tobacco Use and Dependence: 2008 Update*,[17] the Community Preventive Service Task Force reports,[102,103] and the NCCN Guideline.[16] Research questions that should be addressed with this population include how to increase engagement and adherence to smoking cessation treatments and whether particularly effective pharmacotherapies such as varenicline and combination NRT increase long-term abstinence rates. All such research should include biochemical assessment of smoking status, given the unreliability of self-report in this population.

In the past several years, researchers have focused on evaluating behavioral smoking interventions targeted specifically to patients with cancer. Charlot and colleagues conducted a single-arm study with 18 patients with cancer to obtain pilot data on a mindfulness-based smoking intervention.[288] Smoking intensity (cigarettes per day) declined significantly over time among participants in the study, but there was no apparent effect on smoking cessation. Likewise, a small study of CM with 14 patients with cancer yielded long-term cessation among just 2 participants.[289] A relatively large RCT randomized 185 presurgical patients with cancer to either a handheld computer intervention or to NRT plus standard CBT-based counseling.[290] The handheld computer intervention was intended to guide the patient in a scheduled, progressive smoking reduction program to support eventual smoking cessation. Both groups received phone counseling, plus one hospital bedside visit delivered by nurse practitioners over 5 weeks; the majority of participants used smoking cessation medications. At 6 months, the biochemically confirmed quit rate for both groups was 32%. A small pilot study evaluated a smartphone app-based behavioral intervention in 59 patients with cancer.[291] Patients were randomized to the NCI QuitGuide app or to Quit2Heal, an app adapted for patients with cancer, which provided behavioral support for smoking cessation treatment by addressing internalized shame, cancer stigma, depression, and anxiety. At a 2-month follow-up, self-reported cessation was 7% for the QuitGuide app and 20% for the Quit2Heal app. No study has directly evaluated the effects of ACT on smoking abstinence among patients with cancer. However, several small studies have found that ACT significantly improves their emotional well-being and quality of life.[292]

Summary: Behavioral Interventions for Smoking Cessation Among Patients With Cancer. As with studies of smoking cessation pharmacotherapy for patients with cancer, there is a dearth of high-quality research evidence about the effectiveness of smoking cessation counseling or other types of behavioral interventions on long-term smoking abstinence among patients with cancer (follow-up ≥6 months). That is, few large studies used experimental designs that randomized the presence, type, or intensity of counseling so that causal inferences could be made. In addition, there is little evidence that identifies the features or dimensions of counseling

that might be especially effective in this population (e.g., targeted to cancer patient's concerns, duration, content, timing). These study characteristics lead to an inability to determine how effective behavioral or counseling interventions are when delivered to patients with cancer and how to deliver them optimally.

In sum, RCTs evaluating counseling in cancer populations have not yielded clear and consistent evidence of counseling effectiveness. However, the consistent effectiveness of smoking cessation counseling with many other populations supports providing patients with cancer with smoking cessation treatments found to be beneficial in the general population.

Relapse Prevention and Chronic Care for Cancer Populations

Little evidence exists regarding relapse prevention interventions in cancer populations. Simmons and colleagues have evaluated the potential use of the Forever Free© relapse prevention self-help guides for use with cancer patients and survivors.[293] Initial work used qualitative methods to inform the development of relapse prevention interventions in the cancer context and to provide specific feedback on the redesign of the guide.[294] A subsequent prospective study with 154 patients with cancer identified predictors of relapse including psychiatric comorbidity, low self-efficacy, fears of cancer recurrence, and low risk perceptions associated with continued smoking.[114] This work led to the development of the Surviving Smokefree® DVD relapse prevention intervention.[295] The DVD was developed with patient and clinician input, embedding patient and clinician testimonials into the program. Initial usability assessments ensured that the program was appealing, promoted comprehension, and was relatable and acceptable to patients.[295] However, an RCT of the Surviving Smokefree relapse prevention program (N = 412) did not show benefit of this self-help treatment versus usual care.[296]

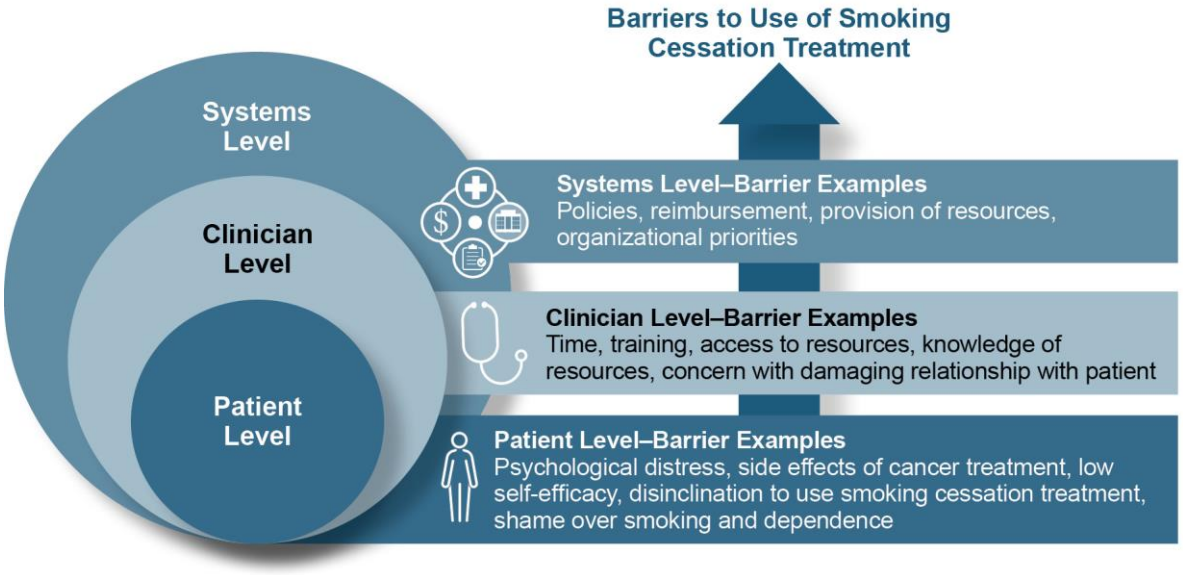
Another approach to the problem of smoking relapse after treatment is the use of chronic care interventions. These interventions are designed to offer treatment opportunities repeatedly over time to those who continue to smoke or who have relapsed after prior quit attempts. Although there have been no studies of chronic care interventions for cancer populations, data from studies of the general population suggest that this approach has promise. A chronic care approach might be feasible in cancer care because cancer treatment often involves extended contact over time, during which renewed offers of smoking cessation treatment and treatment delivery could be provided. In addition, because research in the general population shows that certain pharmacotherapies, such as varenicline, can sustain abstinence in those who have quit successfully,[105] this approach should be evaluated in patients with cancer who have recently succeeded in quitting. Finally, the development of effective relapse prevention or chronic care treatments might be informed by research that reveals factors that predict a decreased likelihood of patients with cancer quitting successfully or staying quit.[297]

Summary: Relapse Prevention and Chronic Care for Cancer Populations. Little is known about how to sustain smoking cessation among patients with cancer or how to increase renewed quitting efforts among those who have relapsed. Strategies that have shown promise in the general population include provision of varenicline to those who have recently quit successfully and chronic care approaches that periodically offer smoking cessation treatment over time to individuals who have not attained stable abstinence.

Special Considerations and Barriers Concerning Smoking Cessation Treatment in Cancer Care Settings

It has long been clear that effective smoking cessation treatments exist but that these are too rarely implemented in the cancer care setting.[10,11] NCI has made substantial investments in implementation science efforts to increase the use of evidence-based treatments in general and for risk behaviors such as tobacco use across the cancer care continuum.[298] Such efforts are guided by established conceptual models and utilize implementation strategies[299,300] that prioritize the identification of patient-, clinician-, and systems-level determinants of implementation success[301] (Figure 3.2). The discussion that follows addresses the first two of these influences on implementation success in order to inform future efforts to develop effective methods for treating tobacco use in the cancer care context. Systems-level barriers are discussed briefly in this chapter but are discussed at length in chapter 4.

Figure 3.2 Examples of Patient-, Clinician-, and Systems-Level Barriers to the Use of Smoking Cessation Treatment in Cancer Care Settings



Patient-Level Barriers to Treating Tobacco Use in Cancer Care Settings

When considering the design of studies of smoking interventions for patients with cancer or when considering the implementation of a smoking cessation treatment program within the context of cancer care, it is vital to consider patient characteristics that might influence treatment effectiveness. Patient factors such as psychiatric comorbidity, oncology treatment–related challenges, and willingness to engage in and adhere to smoking cessation treatment, can be key determinants of treatment effectiveness.

Psychiatric Comorbidity

A cancer diagnosis and its medical treatment can lead to clinically significant psychological distress[302] that typically involves symptoms of depression and/or anxiety[303,304] as well as anhedonia.[305] For example, a study of the tobacco cessation treatment program at the University

of Texas MD Anderson Cancer Center found that more than 40% of patients with cancer enrolled in tobacco use treatment had a current psychiatric disorder, including depression and anxiety.[306] Such symptoms have been extensively examined as important correlates of smoking behavior.

With regard to research on individuals in the general population, a systematic review and meta-analysis of smoking cessation treatment outcomes among people who smoke with and without past major depressive disorder (MDD) examined 42 RCTs published between 2000 and 2008. This review found that people who smoke with past MDD had 17% lower odds of short-term abstinence and 19% lower odds of long-term abstinence than people who smoke without past MDD.[307] Research has also explored the relationship between anxiety and smoking cessation. Systematic reviews have demonstrated that anxiety disorders are associated with an increased risk of both initiating tobacco use[308] and developing nicotine dependence.[309] Studies indicate that individuals with anxiety disorders tend to have less smoking cessation success than other people who smoke[310] and relapse at higher rates even when provided evidence-based smoking cessation treatment.[311,312] In sum, and as also discussed in chapter 5, psychiatric comorbidities, particularly depressive symptoms and active substance use disorders, are associated with a lower likelihood of quitting after a cancer diagnosis and with an increased risk of relapse.[313–317]

The reasons for the reduced quitting success of people with anxiety and depression diagnoses are unclear. Some evidence suggests that individuals with anxiety and depressive disorders have stronger withdrawal symptoms than individuals without these disorders[318] but other evidence counters this explanation.[319]

Few studies have evaluated the relationship between depression and anxiety symptoms and smoking cessation outcomes in patients with cancer. However, the available literature shows that greater symptoms of depression and anxiety are associated with continued smoking following a cancer diagnosis.[114,313,320,321] In a prospective study with 175 patients with cancer, higher levels of baseline depressive symptoms predicted a greater likelihood of smoking relapse at follow-up.[322] In an analysis of more than 2,000 patients with cancer who received smoking cessation counseling and medication, patients with a history of panic attacks were significantly less likely to quit smoking than those without a history of panic attacks.[323] Research is needed to develop additional treatment strategies that mitigate some of the risk posed by the psychiatric comorbidities that are common among patients with cancer. Conceptual frameworks that focus on the link between affect and smoking are leading to new treatment approaches that may mitigate the effects of psychiatric disorders and symptoms on smoking cessation success.[324,325] Chapter 5 reviews evidence regarding the relationship between severe mental illness and smoking and smoking cessation success.

Oncology Treatment–Related Challenges

A cancer diagnosis is often also accompanied by stress due to physical and other challenges related to debilitating surgeries and prolonged adjuvant chemotherapeutic and radiation therapies. The stress related to cancer and its treatment can make quitting smoking more difficult.[326] For clinicians, these challenges can make it difficult to prioritize and deliver smoking cessation treatment; they also make it difficult for patients to engage in smoking cessation treatment themselves. More significantly, these challenges can undermine the patient's hope for

recovery and promote fatalism, casting doubt on the benefits of smoking cessation or the effort needed to attain it.[32,37] These challenges need to be considered when developing models of smoking cessation treatment in cancer care settings.

Physical Concerns

Several practical, physical challenges facing patients with cancer should also be considered. Patients with head and neck cancer, in particular, may experience impaired swallowing, which could make it difficult to take oral medications like varenicline and certain NRTs. Similarly, some phases of cancer treatment may also make it difficult to take oral medications for tobacco cessation (i.e., chemotherapy and radiation often cause xerostomia [dry mouth]).[327] Chemotherapy often causes nausea and vomiting, which are also common side effects of varenicline and bupropion,[328,329] so their use may exacerbate such symptoms and reduce use. Indeed, nausea reactions from varenicline are associated with discontinuation of its use.[330] Pain is also a very common complication of both cancer and cancer treatment; pain has been associated with a higher rate of smoking among patients with cancer[331] and in the general population.[332] Further, although patients may make frequent visits to the clinical setting for medical care, cancer treatment–related complications may impair the patient's ability to attend in-person counseling visits for smoking cessation treatment. Phone and video counseling may be used to address this barrier.

Psychological Aspects

There are also broader psychological aspects of cancer treatments and their associated complications, symptoms, and side effects that create challenges for smoking cessation treatment. Lack of sleep and feelings of hopelessness may contribute to stress, which can interfere with participation in treatment programs.[34,333] Further, for patients with advanced disease and limited life expectancy, the effects of smoking cessation treatment on the patient's quality of life, either negatively or positively, should be considered when exploring patients' goals regarding quitting smoking. Cancer and its treatment entail considerable stress; striving to quit smoking and engage in smoking cessation treatment may add to this stress in the short-term.

Therefore, addressing the physical and psychological factors associated with the treatment of cancer should be part of planning for smoking cessation treatment in cancer care settings. Patients with cancer often report thinking that smoking will help them manage their stress, so clinicians need to consider how best to help patients find healthy methods to cope with stress. In addition, the clinician needs to help the patient focus on the long-term benefits of quitting smoking and to counter any sense of guilt or self-blame the patient may have regarding their smoking.[259] The provision of support and treatments that address cancer-related stress during the patient's smoking cessation and cancer treatment may be needed to optimize patient outcomes.[233, 290,334]

Treatment Engagement and Adherence

A wealth of evidence derived from the general population shows that using FDA-approved smoking cessation medications increases the likelihood of smoking cessation success during aided quit attempts.[17,21,149,335] Unfortunately, the vast majority of those who smoke and who try to quit do not use FDA-approved medications in their attempts. Data from Medicaid,[336]

Medicare,[337] and outpatient health care settings[338] show that fewer than 30% of patients interested in quitting use medication in their quit attempt.[27] Likewise, although research suggests that patients with cancer are very receptive to treatment referral,[339] only about one-third to one-half of patients with cancer report using FDA-approved medication in previous quit attempts.[340,341] Indeed, an analysis using data from the Population Assessment of Tobacco and Health (PATH) study showed that, among 331 participants with a cancer history, one-half attempted smoking cessation without any form of treatment, only 36.5% used medication and/or counseling, and 13.2% used e-cigarettes in lieu of treatment (see "ENDS Use and Cessation From Cigarettes in Cancer Populations").[342] Importantly, medication use was associated with a greater likelihood of tobacco cessation in this study. Another study suggested that providing cessation treatment by tobacco treatment specialists to patients with cancer via smartphone video may be preferred by patients and may increase overall treatment engagement.[239]

This avoidance of treatment can also occur in tobacco users in the general population.[27] This preference for unassisted smoking cessation attempts may reflect patient guilt about their smoking, depression, poor self-efficacy, or a lack of appreciation that evidence-based smoking cessation treatments can mitigate withdrawal symptomatology and enhance quitting success.[341,343] Lung cancer, in particular, is associated with stigma emanating from the perception that the patient's cancer is a self-induced disease[344]; this frequently leads to guilt, negative judgment, isolation, and defensiveness,[345] which may impede patients from seeking appropriate intervention.[346,347]

In addition to low levels of use of evidence-based treatments for smoking, low rates of treatment adherence are also a concern. There is a growing literature from studies conducted in the general population that shows that adherence to smoking cessation medication is a critical determinant of treatment efficacy.[348–350] Reviews show that rates of nonadherence to varenicline (i.e., taking <80% of medication) and the nicotine patch (i.e., using the patch <5/6 days per week) are very high (~40% or higher in many studies), and nonadherence significantly diminishes the likelihood that people who smoke will successfully quit.[348,351] For example, in the general population, 55% of patients receiving varenicline in a primary care setting were adherent and quit rates were nearly doubled for these patients versus those who were nonadherent or partially adherent.[138] Additionally, evidence using electronic monitoring of smoking cessation medication supports a causal model in which decreases in medication use precede the occurrence of lapses in smoking cessation.[352] Such findings appear to be highly relevant to patients with cancer.

Additional studies have shown that adherence to varenicline among patients with cancer is about 43%–55% and greater adherence is associated with improved quit rates.[12,272,353] Thus, strategies that enhance adherence to smoking cessation medication have the potential to increase smoking cessation rates both among the general population and among patients with cancer. Several studies point to the rate and intensity of side effects as important factors associated with nonadherence, which argues for efforts to monitor side effects in patients with cancer and adjust medication accordingly.[330,349,354,355] The above evidence suggests that medication adherence be monitored and encouraged when medication is used in smoking cessation treatment with cancer patients. This is consistent with the NCCN clinical practice guidelines in oncology.[16] Kotsen and colleagues discuss the need for tailoring medication usage, medication effectiveness and side effects, and behavioral interventions in the context of multisession counseling treatment.[356]

Clinician-Level Barriers to Treating Tobacco Use in Cancer Care Settings

Leveraging the Opportunity for Intervention

Oncology clinicians are well positioned to refer or to initiate the treatment for nicotine dependence for their patients with cancer who continue to smoke, given the frequency with which they typically interact with patients and patients' willingness to follow their treatment advice. Indeed, ample evidence from the general population suggests that clinicians can boost smoking cessation rates if they deliver smoking cessation treatment.[17,106] As such, several professional organizations such as the American Association for Cancer Research,[6] the NCCN,[16] the American Society of Clinical Oncology,[357] and the International Association for the Study of Lung Cancer[358] have developed and disseminated tobacco use treatment guidelines to help clinicians incorporate cessation intervention into their oncology workflow. Unfortunately, consistently addressing tobacco use among patients with cancer is a clinical practice gap at the clinician and systems levels.[10,11,13,14,281,359,360] Although more than 80% of patients are routinely screened for tobacco use during oncology visits, fewer than half of oncology clinicians provide formal assistance with smoking cessation, including referral, medications, or counseling.[361,362] This is consistent with observations in other practice settings such as in primary care, where identification of smoking status often exceeds 95% and recommendations to quit exceed 65%, but performance of the more complex, second-order components of delivering smoking cessation treatments and providing follow-up remain suboptimal.[17,31,363,364]

Barriers to Intervention and Strategies to Overcome Them

Oncology clinicians generally understand that continued tobacco use during cancer care significantly affects treatment outcomes and recognize their potential role in promoting abstinence.[361] Close to 90% of oncologists agree that tobacco cessation treatment should be a standard part of cancer care. However, several practical factors impede the integration of tobacco cessation treatment into practice workflows. For example, almost half of oncology clinicians report limited available time during the visit for counseling or for arranging referrals.[361,362,365] Oncologists must balance competing priorities in cancer care, including cancer therapy decisions, cancer therapy side effects, treating and managing medical comorbidities, infection control, psychological distress, and sometimes acute life-threatening issues that demand immediate attention. Further, many clinicians report having too little time to intervene with smoking, having too few tobacco cessation treatment resources for their patients or being unaware of those that exist, and having too little training to deliver nicotine dependence treatment effectively.[361,362,365,366] All of these factors or beliefs likely discourage oncology clinicians from delivering smoking cessation treatment with their patients who smoke. Finally, a perceived lack of reimbursement for tobacco intervention or billing difficulties are also cited as obstacles to care by oncology clinicians.[361,362,365]

Importantly, advances have been made over the past 2 decades that can help clinicians overcome the barriers noted above. These include mechanisms for direct reimbursement for both the evaluation and management of tobacco dependence[136] and a national quitline portal (see "Telephone Counseling"). Chapter 4 contains additional information on strategies that clinicians can use to provide their patients with smoking cessation resources.

Despite advances, more progress is needed. For example, despite the availability of computerized reminders, comparative feedback, and even direct payments for meeting

performance metrics, referral to smoking quitlines remains low.[9,113,367] The NCI C3I (see chapter 4) has provided funding to develop programs designed to increase the availability of onsite tobacco cessation treatment resources in 52 NCI-Designated Cancer Centers. Though screening rates for tobacco use are fairly high at many cancer centers,[368] one center reported that, despite implementation of an opt-out referral process designed specifically to minimize oncology workflow interruption (i.e., a standard default order in the EHR to a tobacco cessation treatment program for all patients who smoke), up to 60% of automated orders for referral were canceled by the treatment team.[369] These orders were cancelled due to factors such as clinician concerns about low patient interest, the appropriateness of addressing tobacco use at a given point in time, a perceived lack of smoking cessation treatment efficacy, caseload, and patient characteristics (e.g., treatment stage, cancer type). Such findings suggest that clinician education should be a part of any smoking cessation treatment program implementation. This accords with other evidence that identifies clinician factors that impede tobacco use intervention in cancer care.

Common myths among oncology clinicians that may reduce the likelihood that they would provide smoking cessation treatment to patients include: (1) it is too late to quit once a person has cancer, (2) the time of diagnosis is not suited to addressing tobacco use, (3) patients with cancer lack interest in quitting, (4) quitting smoking among patients with advanced disease is unimportant, and (5) it is not the oncologist's job to address tobacco use.[370,371] In addition, clinician surveys have found that at least 58% of oncologists queried felt they would be unable to get patients to quit using tobacco, and more than two-thirds believed their patients would be resistant to cessation treatment.[361,362,365] This therapeutic nihilism appears to stem from the influence of several key cognitive biases, one of which is a focus solely on immediate medical needs rather than on the long-term benefits of quitting smoking.[372] In addition, culpability bias (i.e., the illness is implicitly interpreted as the result of a controllable decision) may negatively influence the willingness of some clinicians to offer help to patients (with cancer or other diseases) and has been identified among general practice clinicians caring for people who smoke.[373] This bias may, in part, be responsible for the differences in patterns of referral to and use of tobacco cessation treatment observed in patients with advanced lung cancer compared to patients with advanced breast cancer.[374]

Changing Clinician Approaches to Smoking Cessation Treatment

A patient's diagnosis and treatment of cancer are teachable moments when the patient and the patient's family members may be receptive to information about the heightened risks of smoking and the benefits of quitting.[375] There are approaches that clinicians can take to better leverage such opportunities for intervention. The literature supports adoption of several simple practice changes in the oncologic approach to smoking cessation. First, clinicians can help patients feel less defensive by reframing smoking cessation treatment as treating an underlying illness (dependence) rather than focusing on smoking as a personal behavior.[376] This approach gives clinicians the opportunity to focus their discussion on the nature of dependence and on anticipated pharmacotherapeutic effects to achieve their goal.[377] Second, adopting an empathic communication strategy wherein the clinician actively seeks to understand the patient's experience and point of view is associated with higher rates of patient satisfaction with treatment and lower levels of psychological distress.[378,379] Lastly, clinicians' model of care should incorporate treating tobacco use as a means of improving the effectiveness of their medical

approach to cancer treatment, which is relevant to all patients with cancer regardless of whether their tumor is tobacco-related (see chapter 4).

Care teams can facilitate smoking cessation by adopting a proactive outreach approach.[380] Developing an approach that automates or routinely identifies tobacco use status as an important topic of discussion before the clinical care visit can increase the patient's comfort with the tobacco discussion. Such a proactive approach has the additional advantage of being independent of the clinician's estimation of the patient's ability to quit. Chapter 4 provides more information on strategies to incorporate smoking cessation treatment into oncology workflows and contexts.

Systems-Level Barriers to Treating Tobacco Use in Cancer Care Settings

Ensuring the consistent and comprehensive delivery of evidence-based treatments for tobacco use requires consideration of the broader systems or organizations within which cancer care is delivered[381] (see also chapter 4). Leadership, policies and protocols, and infrastructure can play critical roles in influencing the delivery and uptake of evidence-based smoking cessation treatments for patients with cancer (see chapter 4). In particular, institutional commitment, organization-wide policies, and the availability of critical resources to support smoking cessation treatment in cancer care can influence patient engagement in such services.[369,382]

Systems-wide changes can have a significant impact on the provision of smoking cessation treatment in the clinic. Leadership teams can explicitly support smoking cessation treatment; direct financial support of personnel, medications, and equipment can meaningfully increase smoking cessation treatment in a cost-effective way[383] and may enhance patient satisfaction.[384] Evidence from primary care contexts suggests that EHR enhancements that promote smoking cessation treatment engagement can also lead to a greater likelihood of smoking intervention with medically underserved and vulnerable populations.[9,228] Integrating smoking cessation treatment into existing service-line quality metrics creates new norms and can have a powerful influence on organizational change.[31,385] Finally, the language used in promotional materials and patient communications should impart a supportive, destigmatizing message and normalize conversations around tobacco use.[376]

Chapter 4 further discusses systems-level challenges, opportunities to deliver smoking cessation treatment, and provides information on the costs of smoking and the cost-effectiveness of smoking cessation treatment in cancer populations.

Summary: Special Considerations and Barriers Concerning Smoking Cessation Treatment in Cancer Care Settings

The success of coordinated efforts to address smoking by patients with cancer largely depends on the ability to overcome a range of patient-, clinician-, and systems-level barriers. Patient-level barriers include competing demands related to their cancer treatment, pain, psychological distress, and guilt regarding their tobacco use. Clinician-level barriers include limited time per encounter, clinicians' beliefs that FDA-approved cessation medications are ineffective, an actual or perceived lack of training in providing smoking cessation treatment, and beliefs that the patient will be uninterested or unable to quit smoking successfully. Systems-level barriers include a lack of clear and consistent emphasis on tobacco intervention by organizational leadership and a lack of policies, protocols, and infrastructure that support smoking cessation

treatment. Remaining mindful of these issues as cancer care programs adopt new policies and actions to address patient tobacco use will help increase the ultimate impact of these efforts.

Special Topics in the Treatment of Smoking in Patients With Cancer

This section discusses two special topics relevant to the treatment of smoking in the cancer care setting. First, it is important to identify and address patient motivation to quit smoking and engage in evidence-based smoking cessation treatment. Second, a discussion about whether smoking cessation treatments require targeting or adaptation with regard to biological factors and sociodemographic variables (including race and ethnicity and gender) is included. Research on the general population is reviewed in these sections and the potential relevance to cancer populations is considered.

Addressing Motivation to Quit

As discussed at the beginning of this chapter, data indicate that many patients with cancer are motivated to quit smoking and are receptive to offers of smoking cessation treatment. However, some patients will not express interest in quitting, and these patients should be offered specific motivational interventions. Some interventions have shown promising effects in increasing smoking cessation motivation in the general population literature and may be useful in promoting quitting motivation in patients with cancer. These include NRT sampling[386,387] and the use of varenicline or NRT in the context of a smoking reduction effort.[119,140] These approaches have not been tested with patients with cancer, but other approaches such as opt-out referral strategies[388,389] have been used successfully to increase patient engagement (see chapter 4).

Relevance of Pharmacogenetic Intervention: Steps Toward Personalized Medicine

Multiple factors influence the likelihood of smoking cessation (e.g., exposure to others smoking),[390] and it is now widely acknowledged that genetic factors do so as well.[391,392] Twin studies have concluded that as much as two-thirds of the variability in the ability to quit smoking may be attributable to genetic factors,[393–395] including the results of smoking cessation attempts,[395] the duration of smoking cessation,[396] and the self-reported level of withdrawal symptoms.[395] The heritable dimensions of smoking cessation have also been suggested by adoption studies, which have shown that a person's ability to quit smoking is strongly associated with their adopted-away, biological sibling's ability to quit smoking.[397] A greater understanding of the neurobiology of nicotine dependence, and a growing recognition of the genetic influences on both dependence and the ability to quit smoking, have prompted researchers to explore specific genetic polymorphisms, or groups of genetic polymorphisms, linked with smoking-related phenotypes, such as the ability to quit smoking and the response to specific treatments. For instance, one polygenic model applied to longitudinal, developmental smoking data predicted the escalation of smoking, the development of dependence, and the likelihood of smoking cessation.[398]

Genetic markers, such as variants in nicotinic acetylcholine receptors and variants in the dopaminergic, serotonergic, or opioid pathways, have been examined as potential moderators of response to treatments for nicotine dependence.[399,400] Candidate gene studies, genome-wide association studies, and linkage analysis studies have evaluated variability in nicotinic receptors (e.g., *ChAT* or the *CHRNA5* gene) and nicotine metabolizing genes (*CYP2A6*),[401] variability in

dopaminergic genes (e.g., *ANKK1*, *DRD2*), variability in serotonergic genes (e.g., *5-HTTLPR*), variability in the opioid pathway (e.g., *OPRM1* gene), and variability in markers of bupropion metabolism (*CYP2B6*) as potential moderators of response to NRT, bupropion, and varenicline; however, results have been mixed thus far.[399,400,402]

In contrast, studies of the nicotine metabolite ratio (NMR), a biomarker of individual differences in nicotine metabolism, affected by both genetic variation from *CYP2A6* variants and other factors that influence nicotine metabolism (e.g., race, sex), have yielded more consistent effects and suggest a method for personalized treatment for nicotine dependence.[137] More specifically, four studies have shown that individuals who smoke and have slower nicotine metabolism report higher quit rates with NRT compared to individuals who smoke and have faster (i.e., normal) nicotine metabolism.[403–406] A secondary analysis of a placebo-controlled bupropion study showed that bupropion significantly enhanced quit rates for fast metabolizers of nicotine, but not for slow metabolizers,[407] and a prospective study showed that varenicline was more effective at treating nicotine dependence for faster nicotine metabolizers than was NRT.[408]

The studies cited above using retrospective analysis linking NMR to treatment response led to the first prospective NMR-stratified pharmacogenetic trial of treatments for nicotine dependence, in which 1,246 individuals who smoked were characterized as slow or fast (i.e., normal) metabolizers of nicotine. These individuals were randomized to placebo patch and placebo pill, nicotine patch and placebo pill, or varenicline and placebo patch.[409] The results showed that, at both end-of-treatment and 6 months after the target quit date, faster metabolizers had significantly higher quit rates if treated with varenicline versus the nicotine patch and that slow metabolizers exhibited similar quit rates across the two treatments but reported more severe side effects if treated with varenicline. In a number-needed-to-treat (NNT) analysis, there was little difference in the NNT to yield 1 successful quitter (10.3 for patch vs. 8.1 for varenicline) among slow metabolizers. However, among fast metabolizers, the NNT to yield 1 successful quitter was 26 for the patch versus 4.9 for varenicline. Thus, treating slow nicotine metabolizers with the patch and fast nicotine metabolizers with varenicline may maximize effectiveness, minimize side effects, and reduce costs (e.g., versus treating all individuals with varenicline). Future studies might examine the possibility that translating this NMR-based treatment algorithm into clinical practice improves quit rates.[137] This approach may have heightened relevance for patients with cancer because some evidence suggests that faster nicotine metabolism is associated with a greater cancer risk, presumably because faster metabolism leads to higher levels of nicotine intake and consequently greater carcinogen exposure.[399,410–412] Studies are needed to examine the potential use of the NMR to personalize treatment for tobacco use in the cancer context as a way to improve treatment effectiveness. In addition, a quick and inexpensive assay of NMR might increase research use and clinical application of this approach to smoking cessation treatment personalization.[31]

Future research may also reveal the potential for genetic data to enhance patient activation or readiness to quit. Information on the relationship between nicotine metabolism and cancer risk might be used to motivate quitting by patients with cancer, cancer survivors, and any individual who smokes. Similarly, education about the high-risk variants in *CHRNA5* on chromosome 15q25 may be used to enhance quitting motivation. Status of the *CHRNA5* variant rs16969968 has been shown to predict delayed smoking cessation among the general population; smokers with the high-risk genotype quit at mean age 56 versus age 52, the mean age at which individuals

with the low-risk genotype variant quit.[413] Similarly, those with the high-risk genotype had a 4-year earlier age of lung cancer diagnosis (61 years) compared to those with the low-risk genotypes (65 years).[413,414] The use of genetic risk feedback for people with cancer who smoke remains an understudied but potentially useful intervention tool.

Treatment Effectiveness and Access Across Different Populations

Although smoking prevalence has declined significantly in the general population over the past half-century, it is disproportionally higher among some populations.[93,415,416] In addition, differences exist in the likelihood of successful smoking cessation across sexes,[417] racial and ethnic groups,[418,419] and by socioeconomic status.[93,420–423] Some racial and ethnic minority groups and people of lower socioeconomic status may be less likely to receive advice to quit smoking, use evidence-based smoking cessation treatments, and be successful in their quit attempts.[27,418,424,425]

Differences in smoking patterns, smoking effects, and cessation success among different populations may raise the question as to whether evidence-based smoking cessation treatments are effective in these populations. For example, sex differences in the effects of nicotine, reactivity to smoking cues, abstinence-induced withdrawal, and response to smoking cessation intervention have been documented.[426–430] A 2017 meta-analysis examined the efficacy of pharmacotherapy in women compared with men. Compared with placebo, medications improved quit rates for both sexes. There was a statistically significant difference in 6-month abstinence among women treated with varenicline compared with women treated with transdermal nicotine or sustained-release bupropion, suggesting that clinicians may wish to prescribe varenicline as a first treatment option for female patients.[431] There are also smoking cessation treatments that have been adapted for certain populations. For instance, a group-based culturally specific CBT for smoking cessation among low-income African Americans has been shown to be effective.[432] However, there is substantial evidence that smoking cessation treatments for the general population are effective in women, different racial and ethnic minority groups, and groups with lower incomes.[17,433–435] Such interventions are widely available and therefore can achieve high reach in different populations of persons who smoke. Considerations for delivering smoking cessation treatment to vulnerable and medically underserved populations are further discussed in chapter 5.

The Use of Electronic Nicotine Delivery Systems (ENDS) in Patients With Cancer

ENDS comprise a rapidly changing class of tobacco products (e.g., e-cigarettes, vapes, mods, tank systems). Despite their heterogeneity, all ENDS deliver an aerosol to the user that typically contains a mixture of nicotine, propylene glycol, vegetable glycerin, and flavoring chemicals. Over the past decade, the prevalence of ENDS use has dramatically increased, particularly among youth and young adults.[436] ENDS use has increased both in the general population and in cancer patients and survivors.[437,438] In the United States, ENDS are classified as tobacco products and no ENDS product has been approved by the FDA for use as a smoking cessation aid. However, patients often ask oncologists and other clinicians about ENDS as an alternative to cigarette smoking and whether they can be used as a smoking cessation aid.[439,440] This section provides a brief overview of the current literature on the prevalence of use, the health effects, and the effects of ENDS on smoking cessation, with specific attention to patients with cancer.

The literature on ENDS is complicated by several factors. For example, many of the studies discussed below were conducted before 2018 and involved early-generation ENDS products (e.g., cig-a-likes). Compared to ENDS devices available as of 2022, these earlier products, particularly the cig-a-likes, tended to have lower nicotine yield profiles than that of cigarettes.[441] Newer ENDS products contain nicotine salt formulation and/or have customizable design features that can facilitate increased nicotine delivery that more closely mimics cigarette smoking.[441,442] Therefore, many of the studies discussed below do not reflect the design features and nicotine delivery efficiencies of newer ENDS products. Also, many studies are heterogeneous regarding the type of ENDS devices used and their characteristics (e.g., settings, nicotine content, and formulation), or do not measure these factors. The literature also includes both RCTs as well as observational studies; as discussed below, both study types have strengths and limitations.

Prevalence of ENDS Use

As of 2019, 4.5% of U.S. adults reported current (every day or some days) ENDS use. Among adult current ENDS users, 36.9% were also current cigarette smokers, 39.5% were former cigarette smokers, and 23.6% were never cigarette smokers. Young adults (ages 18–24 years) had the highest prevalence of ENDS use of all age groups (9.3%); more than half of young adult ENDS users (56%) reported they had never smoked cigarettes.[443] The primary reasons that adult dual users (i.e., individuals who report current use of both cigarettes and ENDS) offer for using ENDS are to mitigate withdrawal symptoms during times when smoking is not permitted, to reduce the number of cigarettes smoked and exposure to the harmful constituents in cigarettes, and as a way to quit smoking.[31,444–446] Indeed, more than one-half of dual users report using ENDS as a way to quit smoking[444,446,447] and about 80% indicate that they perceive ENDS to be less harmful than cigarettes.[446,448]

Several studies have reported the prevalence of ENDS use among patients with cancer and/or among those with a history of cancer; across these studies, the overall prevalence of current ENDS use ranged from 1.6% to 4.1%.[449–454] Across samples of patients with cancer or those with a history of cancer who report current use of cigarettes, the prevalence of current ENDS use ranged from 11.6% to 23.1%.[452–458] Similar to ENDS users without a cancer diagnosis, the majority of cancer patients and cancer survivors who use ENDS report doing so to help them quit smoking and because they perceive them to be less harmful than cigarettes.[454,457–459] Additionally, Correa and colleagues found that patients with cancer believed that ENDS were less addictive, less expensive, less stigmatizing, and less likely to affect cancer treatment than cigarettes.[459]

Health Effects of ENDS

Research has demonstrated that the exposure to toxicants in ENDS aerosols varies by device type, e-liquid composition, user behavior, and other factors.[445] In general, ENDS expose users to fewer toxicants and lower levels of toxicants than cigarettes. For example, a report of the National Academies of Sciences, Engineering, and Medicine concluded that, “taken together, the evidence in support of these conclusions suggests that e-cigarette aerosol contains fewer numbers and lower levels of toxicants than smoke from combustible tobacco cigarettes”.[445,p.6] However, while noting the relatively lower toxicant exposure from ENDS, this report also noted that ENDS

emit numerous harmful and potentially harmful substances, including carcinogens and metals, and that the amounts vary greatly across different types of ENDS products. Preclinical and clinical, as well as epidemiological, studies published after the National Academies of Sciences, Engineering, and Medicine report demonstrate that ENDS products can have adverse respiratory, cardiovascular, and immunological effects.[460] Moreover, as noted above, some ENDS users also smoke cigarettes (i.e., engage in dual use), often employing ENDS as a mechanism to cope with settings in which cigarette smoking is not allowed. Some studies indicate that dual use of cigarettes and ENDS may lead to greater toxicant exposure and risks of health harms than use of cigarettes alone[461–463]; however, other studies do not find such effects.[464,465]

A recent nationally representative longitudinal study analyzed the association of ENDS use with any self-reported cardiovascular disease, using data collected in five waves of the PATH study from 2013 to 2019.[466] Participants (N = 24,027) were categorized as nonusers (no current use of ENDS or cigarettes), exclusive cigarette smokers, exclusive ENDS users, or dual users of ENDS and cigarettes. In this study, the risk of cardiovascular disease was similar among dual users (of ENDS and cigarettes) and exclusive cigarette smokers; exclusive ENDS use was associated with a small, nonsignificant increase in risk of any cardiovascular disease, relative to individuals who used neither ENDS nor cigarettes. These authors' findings accord with the uncertainty regarding the harms of exclusive ENDS use but clear and significant risk of dual use of ENDS and cigarettes.

An appraisal of the net health effects of ENDS is currently limited by the fact that many studies are preclinical in nature, assess only short-term or acute ENDS use, or are nonrandomized, cross-sectional studies that do not permit strong inference. Rigorous assessment of the health effects of long-term ENDS use remains a critical priority; assessment of existing and novel biomarkers of cardiovascular harm and cancer-related progression and outcomes can increase researchers' understanding of long-term health risks.[460] Finally, it is also important to note that ENDS use will serve to increase harm if it delays complete cessation from cigarette products.[31]

ENDS Use and Cessation From Cigarettes in the General Population

Most of the research on the relationship between ENDS use and smoking cessation comes from cross-sectional and prospective cohort studies conducted in the general population. This research provides mixed evidence that the use of ENDS may help or hinder adult smoking cessation.[467–471] Some studies and meta-analyses found no statistically significant association between ENDS use and quitting smoking.[31,470,472] The 2020 Surgeon General's report concluded that "the evidence is inadequate to infer that e-cigarettes, in general, increase smoking cessation".[31,p.11] In addition, the report found suggestive but not sufficient evidence that "more frequent use of e-cigarettes is associated with increased smoking cessation compared with less frequent use of e-cigarettes".[31,p.11] Consistent with this, a meta-analysis published after the 2020 Surgeon General's report found evidence that daily use of ENDS was positively associated with increased smoking cessation in observational or population studies; less than daily use was associated with reduced smoking cessation.[473] Finally, some cohort studies show that former smokers may relapse back to smoking if they use ENDS following cigarette cessation.[474–476] A 2017–2019 analysis of data from the nationally representative PATH Study found that among individuals attempting to quit smoking cigarettes, those who used ENDS in their quit attempt were less likely to be successful.[471]

Inferences from nonrandomized cross-sectional and prospective cohort studies about the effects on ENDS on smoking cessation can be limited by: (1) potential selection biases in sampling; (2) intrinsic differences in those who choose to use ENDS and those who do not, differences that can be difficult to control for statistically; (3) imprecise measurement of ENDS product characteristics and use behavior, which may affect the observed relation between ENDS use and smoking cessation[31]; and (4) heterogeneity in ENDS use (type, intensity) over time and across individuals. Therefore, observational studies do not afford as strong a level of inference about the effects of ENDS on cessation as do RCTs designed to test the efficacy of ENDS as cessation aids.[31] However, an important potential limitation of RCTs is that their results reflect the ENDS product used in the study, with the chosen device characteristics, and not the effects of ENDS products in general. Also, volunteers for such studies might not reflect the effects of ENDS in nonvolunteers. For instance, volunteers may be much more motivated to stop smoking and therefore achieve higher cessation rates when provided ENDS devices. Therefore, generalizability of RCT findings may not translate to the plethora of ENDS products on the market, nor the context of real-world use.

Randomized Controlled Trials

A 2021 Cochrane Review evaluated RCTs that compared interventions using nicotine-containing ENDS against several different comparison conditions.[477] The authors identified 34 RCTs with follow-up data for at least a 6-month period. A meta-analysis of 4 RCTs (N = 1,924) found that individuals who were randomized to nicotine-containing ENDS achieved higher long-term smoking abstinence rates than did those assigned to use NRT (RR = 1.53, 95% CI = 1.21–1.93). The estimate is that this effect would yield three more cigarette abstainers per 100 (95% CI = 1–6) than would occur with NRT use. This finding was rated with a moderate level of certainty of the evidence, limited by imprecision. In addition, 5 studies randomized people to nicotine-containing ENDS or placebo (non-nicotine) ENDS (N = 1,447). A meta-analysis of these studies yielded moderate-certainty evidence, limited by imprecision, that long-term cigarette abstinence rates were higher in individuals randomized to nicotine-containing ENDS than placebo ENDS (RR = 1.94, 95% CI = 1.21–3.13). In absolute terms, this might lead to an additional 7 more abstainers per 100 (95% CI = 2–16) than would occur with placebo ENDS. Finally, the authors conducted a meta-analysis of 6 studies (N = 2,886) in which individuals assigned to ENDS use were compared with individuals who received only behavioral support or no behavioral support (with no pharmacologic or ENDS provision). Compared to the group receiving behavioral support or no behavioral support, the long-term abstinence rates were statistically significantly higher for participants who were randomized to nicotine-containing ENDS (RR = 2.61, 95% CI = 1.44–4.74). It was estimated that 6 more cigarette abstainers per 100 (95% CI = 2–15) would be found if ENDS were used in the quit attempt as opposed to behavioral support only or no support. However, this finding was of very low certainty due to imprecision and risk of bias. The authors of this Cochrane Review concluded that, under the conditions of an experimental trial, nicotine-containing ENDS versus non-nicotine-containing ENDS or NRT helps more people attain long-term abstinence from cigarette smoking.

The authors found little evidence of harm from ENDS use but noted that the longest follow-up period used in the studies they analyzed was 2 years.[477] The authors also acknowledged several limitations including: (1) the small number of studies for some analyses; (2) that the type of ENDS used varied across time and study; and (3) that the trials primarily include data from

disposable and refillable ENDS tank devices rather than from pod devices, which may deliver nicotine more efficiently due to their frequent inclusion of high nicotine content in the nicotine salt formulation, which facilitates inhalation. In addition, the proportion of participants who become dual users or who become long-term exclusive ENDS users should also be considered in weighing the overall benefits and harms of this approach.

An additional meta-analysis of ENDS effects on smoking cessation involved nine RCTs in which individuals were randomized to either ENDS use to aid smoking cessation or to a control condition that did not include ENDS use.[473] In seven of the nine studies, the control condition received some form of smoking intervention, typically NRT or a means to access it easily. Like the 2021 Cochrane Review,[477] this meta-analysis also found that the provision of ENDS significantly increased the likelihood of long-term smoking abstinence (RR = 1.555, 95% CI = 1.173–2.061, p = .002).[473] The proportions of participants who became dual users were not reported in this meta-analysis.

Eisenberg and colleagues conducted a study in which individuals motivated to quit smoking (N = 376) were randomized to 1 of 3 conditions: nicotine-containing ENDS (N = 128), non-nicotine ENDS (N = 127), and no ENDS (N = 121).[478] Participants in all study arms also received counseling; outcomes included biochemically confirmed PPA from smoking at 12 and 24 weeks after the target quit day. The authors stated that the study had to be terminated early due to ENDS product manufacturing delays and is only adequately powered for the 12-week PPA analyses rather than the planned 52-week PPA analyses. Participants assigned to nicotine-containing ENDS had significantly higher abstinence rates than did those in the counseling-only condition at 12-weeks follow-up (21.9% vs. 9.1%, risk difference [RD] = 12.8, 95% CI = 4.0–21.6), but not at 24-weeks follow-up (17.2% vs. 9.9%, RD = 7.3, 95% CI = –1.2–15.7). Participants assigned to the non-nicotine ENDS condition did not have higher abstinence rates than did those in the counseling-only condition at 12-weeks follow-up (17.3% vs. 9.1%, RD = 8.2, 95% CI = –0.1–16.6), but did have significantly higher abstinence rates at 24-weeks follow-up (20.5% vs. 9.9%, RD = 10.6, 95% CI = 1.8–19.4). This study suggests that nicotine-containing ENDS plus counseling can produce higher short-term abstinence rates than counseling only, but that the effect diminishes with time. It also suggests that some of the benefit of ENDS use regarding smoking cessation may be due to the self-administration ritual rather than to nicotine delivery alone. Finally, Eisenberg and colleagues reported that there was significant e-cigarette use in the post-intervention follow-up period (by 24 weeks) among all 3 study groups, with 37% of the nicotine-containing ENDS plus counseling group, 23% of the non-nicotine ENDS plus counseling group, and 17% of the counseling-only group reporting non-study ENDS use.

The 2020 Surgeon General's report noted that the evidence from RCTs suggests that the use of nicotine-containing ENDS increases the likelihood of smoking cessation relative to comparison conditions.[31] Research published since that Surgeon General's report is consistent with this statement.[477,478] However, the 2020 Surgeon General's report noted that more studies are needed to increase confidence in conclusions drawn on this issue and that findings from RCTs might not generalize to real world ENDS use.[31] Also, any potential benefit of ENDS for smoking cessation must consider the potential for ENDS use to become long term, which may have negative health effects and/or lead to relapse back to smoking. For example, Hajek and colleagues found that of those assigned ENDS use as a cessation strategy and who had become abstinent from cigarettes,

80% were still using ENDS 1 year later.[479] In addition, the evaluation of ENDS effects on cessation should consider the potential for prolonged dual use of cigarettes and ENDS. As described above, dual use may do little to reduce the harms of cigarette smoking if it does not lead to smoking cessation and may confer additional risk above that of exclusive smoking.[31,461–463]

ENDS Use and Cessation From Cigarettes in Cancer Populations

Several studies have examined the use of ENDS for smoking cessation in cancer populations. Borderud and colleagues examined the use of ENDS among patients with cancer referred to the tobacco cessation program (*N* = 1,074) at an NCI-Designated Cancer Center from January 2012 to December 2013.[480] At enrollment in cessation treatment, approximately one-fourth (26.5%) of patients reported they had used ENDS in the past 30 days; most ENDS users (92%) were dual users of ENDS and cigarettes. ENDS use increased substantially over time from 10.6% in early 2012 to 38.5% in 2013. ENDS users smoked more cigarettes per day, had higher cigarette dependence scores, and were more likely to be highly nicotine dependent compared with nonusers. The authors reported that the relationship between ENDS use at baseline and smoking status at 6-month follow-up differed by type of analysis. Using a complete case analysis, ENDS users and nonusers were equally likely to be abstinent from smoking at 6-month follow-up (44.4% vs. 43.1%, self-reported 7-day point prevalence). However, using an intent-to-treat model, patients who did not use ENDS had twice the rate of smoking abstinence as ENDS users (30% vs. 14.5%, self-reported 7-day point prevalence). The study authors note several limitations: the findings represent a clinical cohort at a single comprehensive cancer center, abstinence data were self-reported, the two use populations were not randomly assigned, and a substantially higher percentage of ENDS users were lost to follow-up compared with nonusers.

Akinboro and colleagues analyzed 2014–2017 data from the NHIS, a nationally representative survey of the U.S. civilian noninstitutionalized adult population.[455] The study sample consisted of NHIS participants who reported having ever received a diagnosis of a smoking-related cancer (*N* = 3,162) (68% of whom were long-term survivors, defined as 5 or more years since initial cancer diagnosis). In addition to sociodemographic variables, participants were asked about their use of cigarettes and quit attempts in the past year, their ENDS use (current and ever), and their alcohol use. The weighted prevalence of ENDS use in the overall study sample was 3.2%. The use of ENDS was higher among current smokers (11.6%), compared with former smokers (2.2%) and never-smokers (0.2%). Current ENDS use did not differ between smokers who had made a quit attempt in the past year (11.6%) and those who had not (11.3%). The authors concluded that "e-cigarette use among patients and survivors of smoking-related cancers was not associated with increased quit attempts in the prior year."[455,p.2093]

Finally, Salloum and colleagues analyzed data from the 2013-2014 (Wave 1) PATH Study, which asked participants about their smoking status, quit attempts, and cancer diagnosis.[342] Among the 565 adult smokers who reported they had received a cancer diagnosis, more than half (57.1%) had tried to quit smoking in the past year. Reported quitting methods included medication only (22.7%); e-cigarettes only (13.2%); medication and e-cigarettes (6.7%); medication, e-cigarettes, and counseling (2.6%); e-cigarettes and counseling (0.2%); as well as attempting to quit without assistance (49.5%). The authors conducted logistic regression analyses to examine the association between smoking cessation methods and quitting success with

statistical adjustment for potential confounders. They found that participants who used FDA-approved smoking cessation medications had higher odds of success, compared with all other cessation methods (adjusted odds ratio [aOR] = 3.77, 95% CI = 1.04–13.68).

Published Guidelines on ENDS Use Among Patients With Cancer

Several organizations have published position statements and guidelines for clinicians regarding the use of ENDS in the oncology context, including the American Society of Clinical Oncology, the American Association for Cancer Research,[481] the NCCN,[16] and the International Association for the Study of Lung Cancer.[482] As of this writing, no professional organization recommends the use of ENDS as a smoking cessation strategy for patients with cancer. USPSTF commissioned a review, published in 2021, to evaluate the benefits and harms of primary care–based smoking cessation interventions.[46] Although aimed at clinicians caring for the general population, USPSTF guidelines represent up-to-date clinical guidance regarding ENDS use and smoking cessation. Similar to the current guidance provided by oncology professional associations, the USPSTF review concluded that "the current evidence is insufficient to assess the balance of benefits and harms of electronic cigarettes (e-cigarettes) for tobacco cessation in adults, including pregnant persons. The USPSTF recommends that clinicians direct patients who use tobacco to other tobacco cessation interventions with proven effectiveness and established safety."[46,p.266]

Summary: The Use of ENDS in Patients With Cancer

Evidence from RCTs conducted among the general population suggests that ENDS use may increase the likelihood of smoking cessation among adults who smoke and who are sufficiently motivated to make a quit attempt and participate in a cessation study. However, this might not reflect the effects of ENDS use outside of the clinical trial setting. In addition, the potential harms of ENDS use as a smoking cessation aid are not well understood but may include persistent ENDS use (both alone and in combination with cigarettes) and short-term and long-term negative health effects including an increased risk of relapse back to smoking. Moreover, the available observational studies do not present a clear or consistent picture of the relationship of ENDS use with smoking cessation. Finally, the specific health effects of ENDS use for patients with cancer are unknown; however, available data on the respiratory, cardiovascular, and immunological effects raises concerns that warrant additional study in the context of cancer and its treatment. Cessation from ENDS use is also an important topic for study in the context of cancer patients and survivors.

A small number of observational studies have been conducted among patients with cancer; these found no association between ENDS use and increased smoking cessation in cancer populations. Additional high-quality, longitudinal, observational studies and RCTs are needed to understand the short- and long-term health effects of ENDS use and to better understand their effects on smoking cessation in the general population and in patients with cancer. Further studies of ENDS use among patients with cancer are important because studies have reported moderate to high levels of ENDS use among patients with cancer who smoke. It is important to determine whether ENDS use undermines the motivation of patients with cancer to use FDA-approved smoking cessation medications and/or cessation counseling, which are safe and effective evidence-based smoking cessation treatments.

Patients who have been diagnosed with cancer and who continue to use tobacco products—especially cigarettes—are at high risk for disease caused by tobacco use, as well as from risks related to their cancer and its treatment. For this reason, assisting patients with cancer to quit smoking should be a very high priority for all cancer care programs and clinicians. The potential utility of ENDS to improve tobacco cessation in this medically vulnerable population must be weighed against the limited data regarding both short- and long-term adverse health effects of these products, as well as the potential for other effects including prolonged exclusive ENDS use or dual use of ENDS and cigarettes and a heightened vulnerability to smoking relapse. Fortunately, as described in this monograph, many effective treatments for tobacco cessation are currently available, and have a strong safety profile, including for use in the oncology setting.

Summary

Regular cigarette smoking can produce dependence, which is accompanied by changes in affect, cognition, and physiology. All seven FDA-approved smoking cessation medications improve long-term smoking abstinence rates relative to placebo as shown in research using multiple, diverse populations. Varenicline and combination NRT are the two most effective pharmacotherapies available. Data from the general population suggest that smoking cessation counseling produces reliable and robust increases in long-term abstinence from cigarette smoking, and that it adds significantly to the benefits of FDA-approved smoking cessation medications. CBT or skills training counseling has received the greatest level of experimental support. Smoking cessation counseling can be effective when delivered via a variety of routes, including in-person, via videoconferencing, or by phone. Digital interventions such as websites and texting interventions have also been shown to significantly increase long-term abstinence rates in the general population of individuals who smoke. Patients diagnosed with cancer differ from other individuals in ways that may affect their likelihood of quitting smoking. Although patients diagnosed with cancer who smoke may have especially great motivation to quit smoking, they may experience greater affective distress, and the burden of imminent and taxing medical treatment may constitute competing demands for their time and attention. Such differences suggest that the effectiveness of smoking cessation treatments may differ when used by patients with cancer in comparison with other patients who smoke. RCTs evaluating smoking cessation medications and counseling in cancer populations have not yielded clear and consistent evidence of effectiveness. However, research with the general population of individuals who smoke strongly suggests that smoking cessation counseling and medication can be effective with patients with cancer. Little is known about how to sustain smoking cessation among patients with cancer or how to increase renewed quitting efforts among those who have relapsed. However, research from the general population suggests that chronic care approaches that periodically re-offer smoking cessation treatment over time can increase smoking quit attempts and abstinence. When considering the effectiveness of smoking cessation treatment, it is important to acknowledge and address challenges and opportunities that can occur at the patient-, clinician-, and health systems-levels. Finally, ENDS use is becoming increasingly common among patients with cancer. ENDS use appears to increase smoking cessation rates in RCTs conducted among the general population, but this may not reflect real-world use patterns. Additionally, no research demonstrates that ENDS help patients with cancer quit smoking. Moreover, ENDS use may entail risk, as these products can deliver potentially harmful chemicals to the user, may sustain nicotine dependence resulting in prolonged ENDS use or dual use of cigarettes and ENDS, and may increase the likelihood that individuals will relapse back to

cigarette smoking after a quit smoking attempt. More research is needed before the harms and benefits of this diverse category of products can be accurately assessed.

Conclusions

1. Despite the heightened risks for adverse cancer-related outcomes due to continued smoking after a cancer diagnosis, too few patients with cancer who smoke are offered evidence-based smoking cessation treatment and too few engage in such treatment.
2. Patients with cancer who smoke generally have strong motivation to quit, and a high percentage make one or more quit attempts during their cancer treatment.
3. Research with the general population of individuals who smoke has identified effective smoking cessation intervention strategies, including counseling, medications, and web-based and short message service (SMS) (text) digital interventions.
4. Although more research on the effectiveness of smoking cessation treatments in cancer populations is needed, the consistent effects of these treatments across diverse populations who smoke suggests that they are likely effective in cancer populations as well. Smoking cessation treatments may benefit from adaptation (e.g., addressing fatalism and depression) to best meet the needs of cancer populations and provide optimal benefit.
5. The combination of cognitive behavioral therapy (CBT) counseling with either nicotine replacement therapy (NRT) or varenicline is an especially effective smoking cessation treatment among the general population of people who smoke. CBT counseling has been shown to be effective in the general population when delivered via several different routes, such as in-person, in groups, and by phone. These treatments are recommended for use with patients who smoke in the Public Health Service (PHS) Clinical Practice Guideline, *Treating Tobacco Use and Dependence: 2008 Update*, and for patients with cancer who smoke in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology.
6. Patients who have been diagnosed with cancer face significant patient-level barriers to smoking cessation that include competing demands due to their cancer treatment, complications and side effects of cancer treatment, pain, psychological distress, and guilt regarding tobacco use. These barriers should be assessed and addressed in strategies used to offer and deliver smoking cessation treatment to patients with cancer.
7. Clinician-level barriers to providing smoking cessation treatment to patients with cancer include limited time per encounter, clinicians' beliefs that FDA-approved cessation medications are ineffective, and lack of confidence or training in providing smoking cessation treatment.
8. The efficacy of electronic nicotine delivery systems (ENDS) as an aid for smoking cessation for patients with cancer is not established. Additionally, the short- and long-term health effects of ENDS use (alone or in combination with cigarettes) by patients with cancer, remain to be determined.
9. Many patients with cancer who try to quit smoking will relapse. Data from the general population suggest that periodic, repeated offers of additional smoking cessation treatment to patients with cancer diagnoses who have relapsed will lead to increased quit attempts and quitting success.

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