Smoking Cessation, Version 3.2022

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ABSTRACT

Although the harmful effects of smoking after a cancer diagnosis have been clearly demonstrated, many patients continue to smoke cigarettes during treatment and beyond. The NCCN Guidelines for Smoking Cessation emphasize the importance of smoking cessation in all patients with cancer and seek to establish evidence-based recommendations tailored to the unique needs and concerns of patients with cancer. The recommendations contained herein describe interventions for cessation of all combustible tobacco products (e.g., cigarettes, cigars, hookah), including smokeless tobacco products. However, recommendations are based on studies of smoking cessation. The NCCN Smoking Cessation Panel recommends that treatment plans for all patients with cancer who smoke include the following 3 tenets that should be done concurrently: (1) evidence-based motivational strategies and behavior therapy (counseling), which can be brief; (2) evidence-based pharmacotherapy; and (3) close follow-up with retreatment as needed.

J Natl Compr Canc Netw 2023;21(3):297–322

NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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The complete NCCN Guidelines for Smoking Cessation are not printed in this issue of JNCCN but can be accessed online at NCCN.org.

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Disclosures for the NCCN Smoking Cessation Panel

At the beginning of each NCCN Guidelines Panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Smoking Cessation Panel members can be found on page 322. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.

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Overview
Tobacco smoking has been implicated in causing cancers of the lungs, mouth, lips, nose, sinuses, larynx, pharynx, esophagus, stomach, pancreas, kidney, bladder, uterus, cervix, colon/rectum, and ovary, and myeloid leukemia.\textsuperscript{1} Cancers linked to tobacco use comprise 40% of all cancer diagnoses, and cigarette smoking is linked to 30% of all cancer-related deaths nationwide.\textsuperscript{2} State-level data suggest that cigarette smoking is responsible for as high as 40% of cancer-related deaths in some geographic regions.\textsuperscript{3} Lung cancer is the leading cause of cancer-related death in both males and females.\textsuperscript{4}

Smoking tobacco after a cancer diagnosis decreases the efficacy of cancer treatments, increases the side effects of cancer treatment, increases the risk of death from all causes, and adds to treatment complexities and the cost of cancer care, as well as the probability of new or worsening comorbidities.\textsuperscript{5-8} Smoking cessation at any time after a cancer diagnosis is associated with improved cancer outcomes, enhanced quality of life, and reduced disease among cancer survivors.\textsuperscript{9-14} Yet, 29.2% of cancer survivors aged 18–44 years smoke cigarettes, which is double the national prevalence of smoking in the United States.\textsuperscript{9}

A life-threatening cancer diagnosis should be a strong incentive to quit smoking; however, cancer survivors face unique challenges. Nonetheless, the benefits of cessation are exceptionally compelling for cancer survivors. For these reasons, NCCN has developed these guidelines to emphasize the importance of smoking cessation in all patients with cancer and seek to establish evidence-based recommendations tailored to the unique needs and concerns of patients with cancer. The recommendations contained herein describe interventions for cessation of all combustible tobacco products (eg, cigarettes, cigars, hookah), including smokeless tobacco products. However, recommendations are based on studies of cigarette smoking.

General Principles of the Smoking Cessation Guidelines
The recommendations in these guidelines apply to cessation of cigarette smoking, which poses the greatest risk to patients with cancer. All patients, regardless of stage or treatment modalities, should be encouraged to achieve and maintain abstinence from all combustible tobacco products (eg, cigarettes, cigars, hookah) and smokeless tobacco products. Smoking cessation has health benefits even after a cancer diagnosis, regardless of site, stage, or prognosis—namely improvement in cancer treatment outcomes, primary cancer recurrence, and secondary cancers. Importantly, a diagnosis of cancer may present a
teachable moment and valuable opportunity for providers to encourage smoking cessation.15–18 It is the view of the NCCN Smoking Cessation Panel that it is never too late for patients with cancer at any stage to stop smoking cigarettes and experience health benefits. The panel recommends a multimodal approach to cessation therapy. The panel recommends that treatment plans for all patients with cancer who smoke include the following 3 concurrent methods: (1) evidence-based motivational strategies and behavior therapy (counseling), which can be brief; (2) evidence-based pharmacotherapy; and (3) close follow-up with retreatment as needed.

The panel asserts that a smoking cessation approach combining pharmacologic therapy and behavior therapy is the most effective and leads to the best results for achieving and maintaining abstinence from smoking, or smoking reduction for those not ready to quit. The 2 most effective pharmacotherapies are combination nicotine replacement therapy (NRT) (combined long- and short-acting NRT) and varenicline. There is a dose-response relationship for the success of counseling; high-intensity behavior therapy with multiple counseling sessions is most effective, but at least a minimum of brief counseling is needed and effective.19–22 Quitlines may be used as an adjunct, especially in lower-resource settings.23,24

The panel also emphasizes the importance of documenting smoking status and treatment plans in the patient health record. Patient health records should be updated at regular intervals to indicate changes in smoking status, quit attempts made, and interventions used.

The panel emphasizes that smoking relapse and brief slips are common and can be managed. Providers, the health care team, and tobacco treatment specialists should discuss this with patients and provide guidance and support to encourage continued abstinence from smoking. Additionally, providers should be aware that smoking slips do not necessarily indicate a need for an alternative intervention. More than one quit attempt with the same therapy may be necessary to achieve long-term cessation.

Treatment of smoking should be offered as an integral part of oncology treatment and continued throughout the oncology care continuum, including surgery, radiation therapy, systemic therapy, and end-of-life care. Emphasis on patient preferences and values is important when considering the best approach to smoking treatment in that setting. Cultural context is also important. For example, American Indians and Alaska Natives may use traditional tobacco for ceremonial or medicinal purposes.25 Smoking cessation efforts in this population should target reduction of commercial tobacco use, not use of sacred tobacco.
Electronic cigarettes (e-cigarettes) are not FDA-approved for the treatment of smoking. Patients should be counseled toward the use of evidence-based smoking treatment approaches. For patients who choose to use e-cigarettes exclusively for smoking cessation, despite recommendations to use evidence-based pharmacotherapies, encourage behavioral counseling and abstinence from smoking, working with the patient as they continue to use e-cigarettes. As the patient becomes more confident about quitting smoking, encourage cessation of e-cigarettes, but not at the risk of relapse to smoking combustible products. For a full discussion, see the section on “E-Cigarettes/Vaping” (page 315). For the full list of general principles of the NCCN Smoking Cessation Guidelines, see “INTRO” page in the algorithm (page 298).

**Evaluation and Assessment of Patient Smoking**

These NCCN Guidelines highlight the importance of evaluating and assessing smoking status and history in patients with cancer. The American Associate for Cancer Research (AACR) emphasized in a policy statement the need for universal assessment and documentation of tobacco use by patients with cancer both in the standard clinical setting and in oncology clinical trials. The NCI-AACR Cancer Patient Tobacco Use Assessment Task Force published proposed core and extension items to be used for the assessment of tobacco use in patients with cancer enrolled in research trials. Current practice is suboptimal, as inadequate or inconsistent assessment and documentation of smoking status has been reported both in the care setting and in the context of cancer registries and clinical trials.

Despite the demonstrated adverse effects of smoking during cancer treatment, a large proportion of cancer clinical trials do not collect adequate, up-to-date information regarding patient smoking status and history, particularly for malignancies other than well-known tobacco-related cancers (eg, lung, head and neck cancers). Such assessments are needed to make evidence-based determinations of the impact of smoking on patients, treatment efficacy, and side effects.

In a large study conducted at an NCCN member institution, a smoking assessment questionnaire was integrated into the electronic health records to automatically identify and refer appropriate candidates for onsite cessation services. The smoking assessment items incorporated into the electronic health record were refined based on analysis of responses from an initial patient screen containing 23 items. Response analysis revealed that the most effective questions for generating referrals included whether (1) patients smoked cigarettes every day, some days, or not at all; and (2) if or what other types of...
tobacco products were used. For patients who formerly smoked, it was important to assess the last time a patient smoked a cigarette, “even a puff,” and for established enrollees to the cessation program, what type(s) of cessation aids were being used. The study revealed that just 3 assessment questions made it possible to efficiently and accurately identify the vast majority (>98%) of patients who currently smoke or those at risk for smoking relapse. These questions are (1) have you smoked at least 100 cigarettes in your entire life (yes, no); (2) do you now smoke cigarettes every day, some days, or not at all; and (3) do you currently use any other tobacco products, such as cigars, pipes, chewing tobacco, snuff, dip, snus, clove cigarettes, kretekts, or bidis (every day/some days/not at all).

Determining Smoking Status
The NCCN Guidelines for Smoking Cessation advocate for smoking status to be updated in the patient’s health record at regular intervals to indicate any status changes or quit attempts (see SC-1, page 299). To do so, the panel recommends the providers initially ascertain: (1) whether the patient has ever smoked, and if so, then regularly assess; (2) whether the patient currently smokes; and (3) whether the patient has smoked within the past 30 days (as an arbitrary number to identify patients at very high risk of relapse). All information regarding smoking status of all tobacco products (including e-cigarettes) should be recorded in the medical record. As a follow-up to the initial evaluation, these guidelines direct providers to a tailored patient assessment based on smoking status and history. Specific algorithms for patients who currently smoke (patient smoked within the last 30 days) and formerly smoked who recently quit (more than 30 days to 1 year prior) are included. For patients who never smoked or those who quit more than 1 year prior, providers should urge patients to remain abstinent from smoking, explaining the benefits of remaining abstinent. For recommendations regarding lung cancer screening for current/former smoking, see the NCCN Guidelines for Lung Cancer Screening (available at NCCN.org).

Assessment of Current Smoking
In patients who currently smoke (or those who have smoked in the past 30 days), providers should assess nicotine dependence to understand the chances for success and risk of relapse, and document the findings in the patient’s health record (see SC-2, page 300). To assess nicotine dependency, providers should query patients regarding the amount currently smoked per day (including cigarettes, pipes, cigars, and e-cigarettes), the typical...
amount smoked, and how soon the patient smokes after waking up in the morning (ie, within 30 minutes). Though smoking within 5 minutes of waking is indicative of greater dependence,33 smoking within 30 minutes of waking is helpful to determine if higher levels of short-acting NRT dosing is needed. The Fagerstrom Test for Nicotine Dependence is an alternative standardized tool for assessing nicotine dependence.34 However, the panel has opted to recommend a more streamlined assessment for use in the oncology setting.

To best tailor treatment, providers should also gather information regarding the patient’s history of quit attempts and why they were or were not successful. Specifically, providers should ascertain the longest period of abstinence experienced, the date of the most recent quit attempt, what cessation aids were used, and why these failed. It is important to document the patient’s previous experience with smoking cessation aids, including any medications, behavior therapy, e-cigarettes, quitlines, websites, smart phone apps, or other media aids. The patient’s reasons for why these aids were unsuccessful are important pieces of information. For example, the patient may have experienced side effects and/or continued cravings with medication, and this may indicate a need for alternative or complementary treatment. If the medication seemed to be ineffective, then duration of use should be noted, as it is possible that it was discontinued too soon. In this discussion, the provider should avoid discouragement by normalizing previous failed attempts and counseling the patient that undergoing multiple attempts before quitting permanently is normal and that, with each try, something new is learned.

Providers are encouraged to engage patients in a personalized motivational dialogue about smoking and to ensure that patients are aware of the disease-specific risks of smoking and benefits of quitting, and to do so in a manner that does not blame the patient.35 Educational resources should be provided. The panel recommends that clinicians provide patients with reasons and ideas for smoking cessation, emphasizing the importance of both encouragement and directness with patients who smoke. When incorporating motivational interviewing (MI) to promote willingness to quit, the panel emphasized the importance of the following general principles: (1) express empathy, (2) develop discrepancy (ie, ask patients to identify conflicts between their values/priorities and current tobacco use), (3) roll with resistance, and (4) support self-efficacy.36,37 For a summary of the methods and data on MI for smoking cessation, see “Principles of Behavior Treatment of Smoking” (page 313).

Patient readiness to quit should be assessed jointly with the patient and provider (see SC-3, page 301). If
patients are not ready to quit, providers should assess and address patient-reported barriers and concerns regarding cessation. When possible, providers should work with patients to set a near future quit date (ie, 1–3 months, or longer for patients who may take longer to move from precontemplation to contemplating quitting) and/or consider smoking reduction with pharmacotherapy and counseling with the goal of achieving and maintaining abstinence from smoking in the future. Starting pharmacotherapy before having a quit date is also appropriate for these patients. A meta-analysis of 10 randomized trials in 3,760 patients with cancer found quit rates to be comparable when comparing abrupt cessation to gradual smoking reduction. Therefore, both options can be used after discussions with the patient. Trial data since then have continued to mirror this trend of comparable success rates with abrupt cessation and gradual reduction. At each visit, providers should reassess readiness to quit and engage in motivational dialogue as indicated.

**Assessment of Former Smoking**

Providers should evaluate and document the risk of relapse for patients with more than 30 days' abstinence (see SC-4, page 302). The panel suggests the following characteristics to identify patients at high risk for relapse: frequent/intense cravings; elevated anxiety, stress, or depression; current or prior history of psychiatric disorders; cohabitating or working with someone who uses tobacco; quitting within the past year; recently initiated smoking cessation pharmacotherapy or other nicotine delivery mechanisms; drug/alcohol use or misuse; recent history of a high level of tobacco dependence; and/or low self-confidence in ability to quit/maintain abstinence. Patients with poor pain control may also be at increased risk for smoking relapse. There is also an increased risk of relapse among patients living with HIV. The panel considers patients demonstrating at least one of these characteristics to be at higher risk for relapse and recommends a management plan tailored to prevent relapse. Providers should discuss risk of relapse with patients and provide guidance and support to promote continued smoking cessation attempts. As indicated, providers may refer patients with psychiatric and substance use disorders to a specialist (see the NCCN Guidelines for Distress Management, available at NCCN.org).

**Treatment of patients who show an elevated risk of relapse** includes behavior therapy with counseling on relapse risk factors (eg, identification of triggers for smoking urges or living with someone who smokes) and relapse prevention. Pharmacotherapy can be considered to promote maintenance of abstinence. Although NRT may be

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1. Four or more sessions of individual/group therapy is recommended, with additional sustained counseling as needed. Brief advice by physicians and other health care providers is associated with a small but important increase in smoking abstinence rates. Longer, more frequent sessions with trained counselors are associated with higher abstinence rates. Principles of Behavioral Treatment for Smoking (SC-E).
5. The use of marijuana, or other substances associated with smoking relapse, is discouraged for those attempting to quit smoking.
6. Combination NRT or varenicline are the preferred pharmacotherapy options. However, bupropion + NRT may be appropriate for select patients (eg, for those with depression or fatigue), SC-F.
7. Patient assistance programs may be available.
used long-term to help maintain abstinence, methods other than NRT may be considered to avoid reintroducing nicotine to patients who have been nicotine-free for an extended period of time (ie, $\geq 30$ days). Providers should review smoking-associated risks for patients with cancer, and the health benefits of abstinence. All management plans and counseling should be documented in the patient health record. For patients deemed to be at low risk for relapse, providers should reinforce success and highlight the importance of continued abstinence.

Regularly reevaluating patients’ smoking status and risk of relapse is important. If relapse occurs, patients should be evaluated per the recommendations for current smoking. Additionally, providers should remain aware that patient self-report of smoking status might underestimate the rate of current smoking among patients with cancer, as is evidenced by research comparing self-reported and objective measures.\textsuperscript{48-50} Patients who remain abstinent should regularly undergo reevaluation with documentation of any risk factor changes.

**Devising a Treatment Plan**

Following assessments, providers should establish a personalized quit plan for each patient which considers the patient’s nicotine dependency, prior quit attempts and any cessation aids used, and smoking treatment options. Providers should work with patients to set a quit date as soon as possible. Risks of relapse and slips should be discussed with the patient along with guidance and support for continued abstinence from smoking.

**Primary Treatment**

Based on clinical trial data of smoking cessation in patients with cancer, the panel recommends a combination frontline approach including pharmacotherapy and behavior therapy for smoking cessation for patients with cancer. Population studies and meta-analyses of randomized or quasi-randomized trial data support the addition of behavior therapy to pharmacotherapy to enhance the rate of success.\textsuperscript{51-53}

Preferred primary therapy options in these Guidelines include combination NRT (category 1) that uses long-acting NRT (nicotine patch) plus a short-acting NRT, such as nicotine gum, lozenge, inhaler, or nasal spray. An alternate option is oral varenicline (category 1). Patients commonly underdose when using combination NRT.\textsuperscript{54-56} Patients should be advised that, as with any medication,
adverse events may occur with nicotine replacement pharmacotherapy, but these are typically mild and short-lived and can be managed by their provider by changing the dose or product. For discussion of the evidence for and safety of individual pharmacotherapeutic regimens, see “Principles of Pharmacotherapy” (page 307).

Follow-up
Assessment of effectiveness of counseling and pharmacotherapy, smoking status, and adverse effects of pharmacotherapy should be performed in person or by phone/telehealth at a minimum of within 3 weeks of starting treatment (within 1 week preferred, if possible), and at 12 weeks. Assessment should continue on a periodic basis moving forward, including within about 12 weeks after completion of pharmacotherapy. Nicotine withdrawal symptoms typically peak 48 to 72 hours after quitting and last about 2 to 3 weeks before subsiding. Slips also commonly happen in the first week of abstinence. Patients who do not quit immediately may quit at a later point. Therefore, providers should encourage continued treatment adherence through and beyond brief slips, with adjustments to dose or behavior therapy frequency as indicated. Adverse effects may also warrant dose adjustments.

When possible, in-person follow-up during planned clinical visits or individual/group therapy sessions is preferred. To minimize the burden on patients in active cancer therapy, behavior therapy can be provided by a trained member of the healthcare team during oncology visits. Alternatives include phone or telehealth. During follow-up, providers should assess risk of relapse and, as indicated, consider adjusting the dose and or type of pharmacotherapy. Patients may slip or relapse, which is expected and can be managed. Maintain close follow-up through the duration of therapy. At 12 weeks, assessment of smoking status should be made in person or by phone/telehealth. For pharmacotherapy courses exceeding 12 weeks duration, assessment should be repeated at the end of the course of therapy. Longer duration therapy is encouraged for cancer patients undergoing therapy, including for the duration of the therapy (see additional discussion on duration of therapy in “Principles of Pharmacotherapy,” page 307).

For patients who remain abstinent, additional follow-up should take place at 6 and 12 months, either in person or by phone/telehealth. Motivational strategies should be used to promote continued abstinence. Duration of pharmacotherapy can be extended beyond 6 months if clinically indicated to maintain abstinence. For patients who experience smoking relapse, treatment...
with either combination NRT or varenicline should be reinitiated.

**Treatment of Relapse or Sustained Smoking**

For patients who continue to smoke or experience relapse, assess effectiveness or prior pharmacotherapies and medical adherence (ie, frequency and proper usage; see SC-6, page 304). The panel recommends 1 of 2 options in this setting. The first option is to continue or resume primary therapy, reinforce proper use of medication, and provide additional behavior therapy. The second option is switching to the alternate preferred option (combination NRT or varenicline). The panel recommends that these regimens be paired with additional behavior therapy. In most circumstances, both preferred primary therapy approaches (combination NRT and varenicline) should be tried before proceeding to any other pharmacotherapy options. However, bupropion with or without NRT may be appropriate in earlier treatment settings for select patients (eg, those with symptoms of depression or fatigue). For those being treated with varenicline, the addition of NRT or bupropion can be considered as clinically indicated to maintain abstinence despite continued urges to smoke. The decision to continue or switch therapy should be based on prior cessation success, patient preference, toxicity, cost and/or coverage, and/or a change in clinical status (eg, upcoming surgery).

After switching therapy or adjusting the dose of an existing regimen, follow-up should occur within 3 weeks and again after 12 weeks of therapy. Smoking status should be re-evaluated. For patients who remain abstinent, the course of pharmacotherapy can be extended as clinically indicated (see additional discussion on duration of therapy in “Principles of Pharmacotherapy,” page 307). Additional follow-up at 6 and 12 months after successful quitting is recommended. For further relapse or sustained smoking, extended duration of pharmacotherapy or switching to an alternate regimen can be considered. Additional or more intensive behavior therapy is also an option.

**Principles of Pharmacotherapy**

**General**

A minimum of 12 weeks of pharmacotherapy, but typically longer, is recommended for the initial quit attempt. Duration of therapy can be substantially extended to promote continued abstinence, for example a year or more.38 Research suggests that longer courses of certain cessation regimens may be associated with higher rates of abstinence.39

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Follow-up is recommended within 2 weeks of starting pharmacotherapy but can be extended to 3 weeks to coordinate with scheduled oncology appointments. For relapse or sustained smoking, options include continuation of the initial agent or a switch to the alternative preferred agent. Dose adjustments should be considered as clinically indicated. Attempts at smoking reduction should be tracked. If reduction efforts stall or if complete abstinence seems unlikely, providers should consider an alternative pharmacotherapy regimen.

In most circumstances, the side effects related to primary smoking treatment medications, which often peak in the first 1 to 2 weeks of administration, are minimal and are considered an acceptable risk compared with smoking. A review of postmarketing case reports on adverse neuropsychiatric effects from smoking treatment medications has generated some safety concerns in the past, but large-scale analyses of the data support the safety of these regimens. Although serious side effects of primary treatment approaches are extremely rare, providers should refer to manufacturer inserts for exhaustive lists of potential side effects and warnings.

Adherence to pharmacotherapy is important to promote optimal outcomes and success, and numerous studies have tested interventions designed to promote adherence and improve medication adherence. Nonadherence is associated with perceiving that cessation aids are not needed, adverse effects, forgetfulness, and limited finances. Data from various clinical trials are discussed in subsequent sections. Included in this discussion are findings from a Cochrane network meta-analysis that included data on pharmacologic interventions across 267 individual studies in 101,804 participants. The authors characterized positive treatment outcome as continuous or prolonged abstinence at least 6 months from the start of smoking treatment. Harm outcomes were measured by the incidence of serious adverse events associated with treatment.

Pharmacotherapy Options

For patients with cancer, the NCCN Guidelines recommend primary therapy with either combination NRT (long-acting patch plus a short-acting formulation) or varenicline, paired with behavior therapy. If smoking is sustained or relapse occurs while a patient is on an initial primary therapy regimen, providers should continue therapy with that initial regimen or switch to the alternate primary therapy option. Both
preferred primary therapy options (combination NRT or varenicline) should be used before trying other pharmacotherapy options. Bupropion with or without NRT may be appropriate for select patients (eg, those with symptoms of depression or fatigue). For those being treated with varenicline, the addition of NRT or bupropion can be considered as clinically indicated to maintain abstinence despite continued urges to smoke. Data supporting the recommended pharmacotherapy options are described in subsequent sections and algorithm pages (see SC-F 1, SC-F 2, and SC-F 3, above and pages 309 and 310).

**Varenicline**

**Efficacy**

Varenicline is a nonnicotinic partial agonist of the α4β2 subtype of the nicotinic acetylcholine receptor. Varenicline partially mimics the effects of nicotine in the brain’s reward center and competitively inhibits the binding of nicotine from cigarettes.67

Systematic reviews/meta-analyses have identified varenicline as the most effective single pharmacotherapy option for smoking cessation.66,68,69 However, medication adherence is an important factor in cessation success.57 Cochrane network meta-analysis data report that varenicline increases the odds of smoking cessation by almost 3-fold compared with placebo (odds ratio [OR], 2.88; 95% CI, 2.40–3.47).66 Direct comparison of the cumulative data suggest that varenicline was more efficacious than bupropion (OR, 1.59; 95% CI, 1.29–1.96) and single forms of NRT such as nicotine patch, nicotine gum, and other formulations (OR, 1.57; 95% CI, 1.29–1.91).66 Varenicline appeared to be equally as likely to promote smoking cessation as combined treatment with more than one form of NRT (OR, 1.06; 95% CI, 0.75–1.48), so that both may be offered depending on patient circumstances.66 An analysis from a Cochrane review including 11 studies showed that varenicline prevents relapse in those who abstain from smoking, based on moderate-certainty evidence (risk ratio [RR], 1.23; 95% CI, 1.08–1.41).70

Results published from the double-blind EAGLES randomized controlled trial (RCT) (n=8,144) revealed that patients treated with varenicline achieved higher abstinence than patients receiving placebo (OR, 3.61; 95% CI, 3.07–4.24), nicotine patch (OR, 1.68; 95% CI, 1.46–1.93), or bupropion (OR, 1.75; 95% CI, 1.52–2.01).71 A study that investigated the efficacy of varenicline specifically for patients with cancer revealed 84% retention and 40% abstinence at 12 weeks. Side effect profiles mimicked those observed in the general population, and...
abstinence improved cognitive function and reduced negative effect over time. Varenicline may also be efficacious for smoking reduction in those not ready to quit. A clinical trial enrolling 1,510 individuals revealed that a 24-week course of varenicline effectively promoted smoking cessation in patients who were unwilling to quit but willing to gradually reduce cigarette consumption. Therefore, this agent provides an alternative for patients who cannot or will not attempt abrupt cessation. A clinical trial in 1,236 individuals who smoke showed that an additional 12 weeks of varenicline maintenance therapy helped to sustain continued abstinence in those who successfully quit during initial treatment. A 2021 clinical trial among 1,251 treatment-seeking individuals found that extended therapy of varenicline for 24 (vs 12) weeks did not produce higher abstinence rates. Taken together, results of these trials suggest that tailoring extended varenicline therapy to individuals at high risk of relapse may be the most appropriate approach. Additionally, another RCT showed that varenicline was effective and well tolerated for treating patients who had previously received this agent (n=498).

Several studies have also suggested that varenicline dose increases beyond the standard 2 mg/day may boost treatment efficacy in patients who had a low or no response to standard dosing. A double-blind RCT of 503 patients who smoke found no evidence to suggest that gradual dose titration beyond the standard 2-mg dose (up to a maximum 5 mg/day) lessened frequency of urges and nicotine withdrawal symptoms, or increased cessation rates. However, dose increases did exacerbate adverse effects such as nausea and vomiting for some individuals. A propensity score-matched analysis including 214 patients who reduced smoking by 50% but were unable to quit showed that patients who received an increased dosage of varenicline (3 mg/day; n=72) reported greater 7-day abstinence, compared with patients who maintained the standard dose (2 mg/day; n=142) at 3- (RR, 2.9; 95% CI, 1.1–4.7), 6- (RR, 2.5; 95% CI, 1.1–5.2; P=.02), and 9-month follow-up (RR, 2.7; 95% CI, 1.2–5.2; P=.008), based on models adjusted for imputation and propensity score matching. In patients who have reduced smoking but not yet quit, a dosage increase to 3 mg/day may be considered, if tolerated.

Safety
Varenicline safety has been extensively examined to determine the risk of adverse effects, particularly serious cardiovascular events and neuropsychiatric changes. Initial phase III studies found varenicline to be safe and generally well tolerated compared with bupropion or placebo; common side effects included nausea, insomnia, and...
abnormal dreams with rates of approximately 28%–29%, 14%, and 10%–13%, respectively.80,81

Concerns regarding neuropsychiatric adverse effects of varenicline have been extensively investigated in patients who smoke and have comorbid psychiatric disorders.66 Despite reviews of case reports that raised concern,60 a 2015 systematic review and meta-analysis of 39 randomized controlled smoking cessation trials identified no evidence to suggest that varenicline increases risk of suicide or suicide attempts, suicidal ideation, depression, or death.82 Another trial showed that varenicline increased smoking cessation rates without exacerbating anxiety and depression symptoms in adults with stably treated current or past depression.82 Results were published from a large double-blind RCT (EAGLES trial) that enrolled 2 cohorts: individuals with psychiatric disorders (n=4,116) and those without psychiatric disorders (n=4,028). No significant increase in neuropsychiatric events was observed for varenicline relative to nicotine patch or placebo. Varenicline was associated with significantly higher abstinence than bupropion plus nicotine patch, or placebo.71

Cardiovascular risks have also been examined. Importantly, systematic reviews and meta-analyses of RCT data have not identified a significant link between varenicline and increased risk of serious cardiovascular adverse events.85-87 However, the cardiovascular safety of varenicline has remained a topic of interest and concern,86-88 although the cardiovascular risks of continued smoking have been extensively documented.89

In a 2015 retrospective review of 164,766 individuals who received pharmacotherapy for smoking cessation (varenicline, n=51,450; NRT, n=106,759; bupropion, n=6,557), neither varenicline nor bupropion posed an elevated risk of cardiovascular or neuropsychiatric (ie, depression, self-harm) events compared with NRT.90 Based on the current evidence base for safety risks, the panel considers varenicline to be safe and to have a favorable risk/benefit ratio for use in patients with cancer who smoke.

Although rare, elevated seizure risk can be a concern in certain individuals receiving varenicline therapy.91 In patients with brain metastases who have a history or elevated risk of seizure, varenicline should be used with caution. Dose reduction is indicated if there is renal impairment.

In September 2021, one brand of varenicline was voluntarily recalled by the manufacturer due to nitrosamine levels. Generic varenicline is now the only form of varenicline currently available and may be substituted.
Combination NRT (Long-Acting Patch Plus a Short-Acting Formulation)

Efficacy
NRT offers an alternative nicotine delivery method and can be used to ameliorate nicotine withdrawal symptoms during cessation attempts. Combination NRT incorporating long-term and short-acting NRT offers the greatest potential benefits for those who smoke.66,70,92–94 Multiple Cochrane reviews show that, compared with single forms of NRT, combination NRT using a patch plus short-acting NRT improved the odds of quitting.52–66,70,95 Data show that all forms of NRT are superior to placebo, but people who smoke using combination NRT were almost 3 times as likely to succeed (OR, 2.73; 95% CI, 2.07–3.65).66 Regarding duration of use, a 2015 study of 525 individuals seeking treatment for smoking found that NRT duration of 24 weeks was more efficacious than 8 weeks; however, NRT use beyond 24 weeks was safe but did not result in greater efficacy.58 This study focused on NRT monotherapy and did not vary duration of dual-use preparations.

The success of NRT is bolstered by concurrent behavior therapy to support cessation. In a large population study, over-the-counter NRT resulted in similar rates of cessation to those who used no aid.51 The addition of behavior therapy to NRT increased the odds of success nearly 3-fold.

Safety
The safety of combination NRT for use in humans, including long-term use, has been demonstrated, and benefits are considered to outweigh potential risks.67 Importantly, providers should be aware that blood nicotine levels from NRT, including combination NRT, are significantly less than that from smoking cigarettes.98–100 In fact, patients commonly underdose when using combination NRT,54–56 and although nicotine overdose is possible, it is rare and usually short-lived. Therefore, providers and patients who smoke should not be dissuaded from using NRT to foster quitting and long-term abstinence. Reviews of the data suggest that NRT is not linked to increased serious cardiovascular adverse events when used for smoking cessation.85,101 Although myocardial infarction has rarely been reported in NRT users, there is insufficient evidence that NRT increases the risk of myocardial infarction or cardiovascular disease.95,96,101,102 Data from large case series have not shown elevated risk with the use of NRT in patients with acute coronary syndromes.103,104

In the past, the safety of NRT has been evaluated in light of the bioactivity of nicotine and evidence that this drug can promote cell growth in certain types of cancer cells.105 Some in vitro data suggested that nicotine increased the malignant potential of small cell lung cancer cells106; induced chemoresistance in models using lung cancer cells107–109 and nasal epithelial cells110, and promoted chemo resistance and metastasis in pancreatic cancer cell and mouse models.111 However, other studies suggested no effects of physiologic levels of nicotine exposure on tumorigenesis in mouse lung cancer models.112,113 Moreover, there is no evidence from human studies that NRT causes cancer in humans.112–116 Evaluation of data from 3,320 participants in the Lung Health Study, which recorded in-study NRT use and smoking exposure, found that NRT was not a significant predictor of lung cancer, while smoking was.115

Varenicline + NRT
A study in 435 individuals who smoke found that the addition of nicotine patch to varenicline therapy significantly increased the cessation rates at the end of treatment (12 weeks), at 24 weeks, and at 6-month follow-up.117 No significant differences were noted for side effect incidence between varenicline/NRT and varenicline/placebo with the exception of skin reactions, which were increased with combination therapy (14.4% vs 7.8%; P=.03). However, one RCT of 341 individuals who smoke did not find enhanced cessation rates at 12- and 24-week follow-up among individuals receiving a combination of varenicline and nicotine patch, versus varenicline alone.118 The addition of nicotine patch to varenicline did not cause significant changes in side effect profiles. Similarly, a trial in 117 participants did not find evidence that the addition of nicotine patch to varenicline increased abstinence at 1, 4, or 12 weeks after the targeted quit date, and no between-group differences in adverse effects were found.119 Based on the evidence, varenicline combined with NRT may be considered as a pharmacotherapy option. Though the studies described previously specifically examined the nicotine patch,117,118 any form of NRT or combination NRT (ie, nicotine patch and short-acting NRT) may be used.

Bupropion + NRT
A large trial in the United Kingdom (n=1,071) examined the efficacy of NRT alone, bupropion alone, and NRT + bupropion.120 All participants received 7 weeks of behavior therapy support in addition to the pharmacologic interventions. Abstinence at 6-month follow-up ranged from 24.2% to 27.9% and did not differ significantly between cohorts. Several unwanted side effects were more common with bupropion than NRT (eg, disturbed sleep, dry mouth, headaches, nausea), and side effects of combination therapy were not significantly different versus bupropion alone. Five serious adverse events occurred in the bupropion group, including allergic reaction (n=3), neuropsychiatric symptoms (n=1), and chest pain (n=1). A trend toward improved efficacy of bupropion in patients with a history of depression was noted (chi-square = 2.86, P=.091).

A double-blind RCT compared bupropion + NRT, bupropion alone, nicotine patch alone, and placebo in 893
individuals who smoked at least 15 cigarettes per day. At 12 months, the highest abstinence rates were observed for the bupropion + NRT group (35.5%) and bupropion only group (30.3%), although these groups did not differ significantly. A smaller RCT studying the addition of bupropion to combination NRT and behavior therapy in patients with schizophrenia suggested that combination pharmacotherapy promoted smoking reduction and cessation, but also demonstrated a high relapse rate after discontinuation of treatment. A 2014 meta-analysis of 12 trials examining this combination revealed a nonsignificant trend in improved cessation with the addition of NRT to bupropion.

Bupropion

Bupropion was first approved to treat depression but its efficacy as a cessation aid also became apparent. In addition to its effects on the dopaminergic and adrenergic systems, this agent also acts as an inhibitor of nicotinic acetylcholine receptors. A 2014 Cochrane review of 44 trials examined bupropion efficacy, revealing an RR of 1.62 (95% CI, 1.49–1.76). Results from the EAGLES trial (n=8,144) revealed that patients receiving bupropion achieved superior abstinence compared with placebo (OR, 2.07; 95% CI, 1.75–2.45). Efficacy was similar to that for nicotine patch but less than that for varenicline. Some evidence suggests that bupropion may be particularly beneficial as a smoking cessation agent for persons with depression. Additionally, longer duration of bupropion treatment may help to prevent relapse in those who have successfully quit.

Bupropion is a CYP2B6 inhibitor and may increase the concentration of drugs that metabolize or that also inhibit CYP2B6 (ie, certain antidepressants, antipsychotics, beta-blockers, and Type 1C antiarrhythmics). Dose reduction of these agents may be considered when used concurrently with bupropion. The selective estrogen receptor modulator tamoxifen requires metabolic activation by CYP2D6 and may be less effective when used concurrently with a CYP2B6 inhibitor such as bupropion. Bupropion reduces the seizure threshold, and meta-analyses of trial data have found a 0.1% seizure risk among those receiving the drug for smoking cessation. In patients with a seizure disorder (eg, patients with brain metastases who have a history or elevated risk of seizure), bupropion should be avoided. Bupropion is a norepinephrine-dopamine reuptake inhibitor; central nervous system toxicity may occur when used concurrently with other dopaminergic drugs.

Neuropsychiatric effects have also been identified as a safety concern with bupropion, although to a lesser extent than with varenicline. However, systematic reviews of the data have found that serious neuropsychiatric adverse events were rarely associated with bupropion prescribed for smoking cessation, including studies of bupropion in patients with mental illness. In the EAGLES trial, no significant increase in neuropsychiatric events was observed for bupropion relative to nicotine patch or placebo.

Regarding risk of serious adverse cardiovascular effects, meta-analyses do not show elevated risk as a result of bupropion use for smoking cessation. Dose adjustments/reductions are indicated in the event of renal or hepatic impairment.

Varenicline + Bupropion

In an RCT of individuals who smoke who demonstrated an inadequate response to front-line nicotine patch treatment (n=222), combination therapy with varenicline and bupropion appeared to be more efficacious than varenicline alone as a second-line therapy option. This observation was more pronounced among males and those with a high level of nicotine dependency. Although no significant differences in side effects were observed between varenicline + bupropion versus varenicline alone, dose reductions were required for 11.5% and 24.8% of patients, respectively. Common side effects were vivid dreams, change in taste perception, thirst, insomnia, and irritability. In a follow-up to this study, males who smoke (n=174) were randomized to receive combination varenicline + bupropion or varenicline alone. As in the previous study, the combination therapy was more efficacious than varenicline alone in those with a higher baseline level of nicotine dependence (n=63; OR, 3.14; 95% CI, 1.11–8.92; P [one-tailed]=.016). Another study of varenicline + bupropion demonstrated that combination therapy increased prolonged abstinence but did not affect 7-day point prevalence at 12- and 26-week follow-up, and no significant differences were observed between the groups at 52 weeks. In this study, anxiety (7.2% vs 3.1%; P=.04) and depressive symptoms (3.6% vs 0.8%; P=.03) occurred more frequently in patients receiving combination therapy versus varenicline alone. In an RCT (n=385), the addition of bupropion to varenicline did not improve prolonged abstinence at 12 months compared with varenicline alone, although both regimens were superior to placebo. The diversity in populations used for these studies makes it difficult to draw conclusions about the efficacy of combination varenicline + bupropion, and this regimen is not commonly used as a first-line approach.

Principles of Behavioral Treatment of Smoking

General Principles

The NCCN Guidelines provide the following guiding principles on behavior therapy, which have been developed in consideration of the existing evidence base,
clinical practice guidelines, and expert consensus (see SC-E 1 and SC-E 2, pages 306 and 307). The panel recommends a combination of behavior therapy with pharmacotherapy for best outcomes. In fact, studies suggest that counseling for smoking cessation may enhance patient satisfaction. A 2012 systematic review of 41 studies provided support for the efficacy of this approach. The “real-world effectiveness” of adding a behavior therapy component to smoking cessation therapy was further supported by a large population study published in 2014. Additionally, a 2016 meta-analysis of data from 1,239 patients with head and neck cancer showed improved smoking cessation rates with the addition of counseling to usual care (NRT). Behavior therapy may enhance motivation and support optimal medication strategies and adherence to pharmacotherapy. When possible, therapy should be provided by a tobacco treatment specialist or dedicated staff member (ie, nurse, medical assistant, health educator) with training in evidence-based treatment of smoking.

As a general principle, the panel recommends more intensive and sustained behavior therapy over brief advice or counseling. The evidence supports a measurable dose-response effect of behavior therapy with more numerous and/or longer sessions delivering improved cessation rates. A recent RCT including 303 patients with cancer who also smoke cigarettes showed that those randomized to receive intensive treatment (free FDA-approved cessation medication and 4 weekly telephone counseling sessions, followed by 4 biweekly telephone sessions and 3 monthly booster sessions) were more likely to have quit smoking at 6-month follow-up (biochemically confirmed) than patients who received standard treatment (medication advice and 4 weekly telephone counseling sessions; 35% vs 17%, respectively; OR, 2.15; 95% CI, 1.14–4.05; \( P = .02 \)). Among patients in the intensive treatment group, completion of more counseling sessions, but not medication use, was significantly associated with likelihood of quitting.

The panel recommends that the first counseling session occur within 3 weeks of cessation, but preferably within 1 week as most people who smoke relapse during this period. The panel defines intensive behavior therapy as at least 4 sessions of at least 10 minutes (in person and/or by phone/telehealth; group or individual), ideally. As described previously, longer, more frequent sessions are associated with higher abstinence rates. If intensive therapy is not feasible, brief counseling of about 3 minutes should still be given. Studies have shown a small but significant increase in smoking abstinence rates with brief counseling lasting only a few minutes. As patients progress through multiple lines of pharmacotherapy, behavior therapy should be progressively intensified with referral to specialty care (eg, tobacco treatment specialist, psychologist) as indicated. Studies have also shown additional benefit for relapse prevention of extending behavior therapy for 6 months or more.

The most successful behavior therapy strategies use practical counseling in which patients learn coping skills and receive support and education. Optimally, behavior therapy plans should consider a patient’s nicotine dependence level, previous quit attempts, and cessation aids used. With this approach, patients can be equipped with tailored strategies to cope with nicotine withdrawal symptoms, environmental smoking triggers (eg, coffee, alcohol, social situations), and stressful situations. For instance, the addition of a cognitive behavior therapy program designed to improve stress management improved cessation rates over control patients receiving standard smoking cessation therapy. The presence of other household members who smoke is a predictor of relapse or sustained smoking and there is no risk-free level of secondhand smoke exposure among those who don’t smoke for causing lung cancer, heart disease, and acute respiratory effects. Therefore, individuals in the patient’s household who smoke should also be encouraged to abstain from smoking to benefit the patient. Providers should prepare patients for nicotine withdrawal symptoms and cravings, which typically peak 48–72 hours after quitting and last about 2–3 weeks before gradually subsiding.

A number of modalities can be used to deliver behavior therapy to patients. Counseling can occur in a variety of settings such as in person, remotely by phone or telehealth, or through web-based interventions. Effective in-person counseling can occur as an individual session or in the group therapy setting. Additionally, print materials and mobile telephone “apps” can be used to deliver behavior therapy. However, providers should be aware that media-based behavioral interventions, particularly those using mobile telephones, might vary in the degree to which they comply with clinical practice guidelines. Digital resources such as the NCI’s smokefree.gov provide free, evidence-based cessation support through mobile-optimized websites, text messaging programs, and 2 mobile applications. A study revealed that approximately 7 to 8 million people accessed smokefree.gov resources in 2018 alone and that people do take advantage of the full range of technology tools.

A study investigating preferences for the provision of smoking cessation information among Canadian patients with cancer showed that patients most often preferred print materials (45%), followed by telephone support (39%), speaking with a clinician (29%), website-based information (15%), and support groups (11%). Patients ≥45 years were more likely to prefer cessation advice via telephone, while patients ≥46 years preferred print materials. Selection of a particular modality or modalities should be guided by patient preference, medical history, and resource availability.
A meta-analysis including 21 RCTs targeting smoking cessation in cancer survivors showed larger effects with interventions delivered by nurses, compared with interventions delivered by others (eg, research team, doctor, educator, counselor/therapist).155

For patients who are unable to quit, referral to a smoking cessation specialist is encouraged when available. If specialized resources are limited, effective behavior counseling can still be provided. For instance, brief counseling by providers has been shown to generate a small but important increase in quit rates.19–21 Additionally, quitlines can provide essential behavioral support in the absence of in-person counseling resources.22 For instance, the addition of combination NRT to quitline counseling improved cessation outcomes.166

Additional Considerations for Patients With Cancer

As resources allow, specialized treatment centers should provide tailored treatment of smoking that address the unique needs of patients with cancer, or refer to external resources (eg, quitlines) that provide such specialized services. For patients in active cancer treatment, behavior therapy can be provided during scheduled oncology visits to obviate the need for additional appointments. Interventions initiated during hospital stays have also been successful. Intensive behavioral interventions provided during hospitalization, with at least a month of subsequent follow-up on discharge, increased smoking cessation rates.138 Beneficial services might include individual and group therapy focusing on the challenges specific to cancer treatment and survival, which would ideally be provided by clinicians experienced in working with patients with cancer. One study suggested age-based differences in preferences for smoking cessation resources.164

The prevalence of psychiatric disorders or serious emotional concerns in patients with cancer is high, with several large studies reporting rates between 30% and 40%.167–169 The high rates of anxiety, depression, and stress can present a significant challenge for patients with cancer who attempt to quit smoking in the face of these common smoking/relapse triggers. Providers should routinely assess for these symptoms among those who smoke throughout treatment of smoking. Patients with cancer, particularly those experiencing psychiatric comorbidity, may benefit significantly from behavior therapy programs tailored to manage cancer-related issues that predispose patients to relapse. Referral for appropriate evaluation and treatment as needed or to specialized smoking treatment programs may be necessary so that these patients have access to staff trained to treat psychiatric and/or substance use disorders.

Motivational Enhancement

All patients with and survivors of cancer should be encouraged to quit smoking. Strategies to enhance motivation to quit are beneficial for all patients, including those who are currently ambivalent or unwilling to quit. MI is one evidence-based approach to foster motivation to quit in which a clinician offers empathy as the patient explores ambivalence regarding quitting smoking. Clinicians reflect, validate, and summarize patient emotions and concerns and help patients identify discrepancies between smoking and core values/goals (eg, health, parenting) and support patient confidence to achieve and maintain abstinence.36,37,170

A 2015 Cochrane database review of 28 studies examined the efficacy of MI for smoking cessation, revealing a modest but significant increase in chance of quitting with MI versus brief advice or usual care.171 MI by a primary care physician appeared to be somewhat more successful than that administered by counselors, although both were effective. Notably, one-time short MI sessions of <20 minutes had demonstrated efficacy.171 One systematic review summarized the evidence to support MI for behavioral change, including smoking cessation, in patients with cancer.172

To promote willingness to quit smoking, the US Preventive Services Task Force recommends a model of MI that employs the “5 R’s” of the personal relevance of quitting; personal risks of continuing smoking; personal rewards of quitting; identifying roadblocks to quitting; and repeating the message at every contact.57 This model encourages that motivational information be relevant to the individual patient, and that clinicians and patients work together to identify personalized risks of smoking and potential rewards of cessation. By having the patient identify perceived roadblocks to quitting, providers can suggest tailored treatments to address patient-reported concerns. Finally, this model recommends repetition of MI at each patient visit, coupled with reminders that repeated quit attempts may be necessary to achieve long-term cessation.

Alternative Treatment Approaches

The panel has reviewed the available evidence for several alternative smoking cessation treatment approaches (see SC-A, page 305). With any approach, it is critical to continue to provide motivational and behavioral support to all patients during quit attempts, regardless of what smoking cessation methods are being used. At the current time, e-cigarettes are not an FDA-approved method for smoking treatment, but the potential of e-cigarettes as a smoking cessation aid continues to be considered by the panel. Particular attention has been paid to the discussion of e-cigarettes for smoking treatment given increasing popularity and widespread use, and not fostering dual use with cigarettes. Limited data are available on the safety and efficacy of these approaches, specifically for patients with cancer; data have been drawn primarily from studies in the general population.
The panel has found insufficient evidence to recommend the use of alternative therapies alone or in combination with standard smoking treatment approaches, and use of alternative therapies is not recommended. The guidelines recommend that patients use evidence-based cessation methods to avoid any delay in achieving smoking abstinence. Smoking slips and relapses are common, and prior unsuccessful quit attempts with conventional therapies do not justify the use of unproven alternative approaches. When discussing alternative therapies, providers should counsel patients on potential interactions with evidence-based cessation methods and/or cancer treatments.

E-Cigarettes/Vaping
The popularity of electronic cigarettes, also known as e-cigarettes or vaping, is a recent phenomenon, and, as such, the available literature is new and relatively limited, particularly within specific subpopulations such as patients with cancer. As stated previously, e-cigarettes are currently not FDA-approved for the treatment of smoking. The FDA may authorize the sale of select electronic nicotine delivery system products as modified-risk tobacco products. The next section discusses the current data and expert opinions on e-cigarettes for smoking cessation.

Several health care organizations have released similar policy statements concerning e-cigarettes, highlighting the urgent need for research on the safety of these devices and efficacy as a cessation aid. The American Heart Association, American Cancer Society, AACR, and ASCO recognize the potential for e-cigarettes to alter existing smoking behaviors, as well as the lack of definitive data regarding associated benefits and harms. Experts in the field generally acknowledge that e-cigarettes may offer an attractive approach for smoking cessation in certain populations. However, these policy statements also highlight the unknown potential for e-cigarettes to affect nicotine dependence, combustible tobacco product use, and renormalization of smoking behaviors. Concurrent use of both e-cigarettes and combustible cigarettes is strongly discouraged by the American Cancer Society. In their 2021 statement, the US Preventive Services Task Force concluded that the current evidence is insufficient to recommend e-cigarettes for tobacco cessation and that smoking treatment efforts should continue to focus on behavioral counseling and pharmacotherapy. Dual use of smoking cigarettes and e-cigarettes is associated with high exposure to tobacco toxicants.

Efficacy and Effectiveness in the General Population
In the first head-to-head comparison, an RCT (n=886) compared e-cigarettes to NRT (combination NRT allowed), paired with at least 4 weeks of behavioral support. Abstinence rates at 1 year were 18% and 9.9% for e-cigarettes and NRT, respectively (RR, 1.83; 95% CI, 1.30–2.58; P<.001).

However, prolonged e-cigarette use extended beyond the initial treatment period, particularly among abstainers, with unclear health implications. In a real-world setting, people who smoke who reported dual use of e-cigarettes were more likely to report abstinence at 6 months, but this pattern was no longer present at 12 or 18 months. A 2022 Cochrane review found better abstinence from smoking rates with nicotine e-cigarettes, compared with NRT, with high certainty (RR, 1.63; 95% CI, 1.30–2.04). However, this difference is most likely due to dose; specifically, e-cigarette use provides an on-demand continuous supply of nicotine, with some doses equivalent to that for cigarette smoking.

Initiation of e-cigarette use may lead to long-term use and the continued dual use of both e-cigarettes and cigarettes, which has greater health risk concerns. Although individuals using e-cigarettes alone or NRT alone had lower levels of toxins than those using combustible cigarettes only, toxicant exposure was greatest among dual users of e-cigarette and combustible cigarettes. A prospective cohort study compared e-cigarette use, tobacco use, and dual use with longer-term follow-up. At 24 months, users of only e-cigarettes were more likely to remain abstinent from other tobacco products than users of only tobacco or users of both e-cigarettes and tobacco (abstinence rates of 61.1%, 23.1%, and 26.0%, respectively). Analyzes of adults who used e-cigarettes and enrolled in the Population Assessment of Tobacco and Health Study (n=2,835), an ongoing longitudinal cohort study, showed that 48.8% had quit both e-cigarettes and combustible cigarettes over a 1-year period (2013–2014 and 2014–2015), while 11.4% decreased their frequency of e-cigarette use. However, it is important to note that there are now more potent e-cigarette products available. Therefore, these results may not be generalizable to the present day. The same study showed that, among baseline dual users (n=2,036), 87.8% reported continued smoking of combustible cigarettes at the time of follow-up assessment. Among those who smoked solely e-cigarettes at baseline (n=869), 43.4% continued to smoke e-cigarettes after 1 year, while 30.9% had quit smoking e-cigarettes. Nondaily e-cigarette use at baseline was associated with discontinued e-cigarette use at the time of follow-up assessment. However, daily users of e-cigarettes at baseline were more likely to report having quit combustible cigarettes after 1 year, compared with nondaily users. Similar associations were found in a large cohort study of individuals who smoke initially not using e-cigarettes and with no plans to ever quit smoking. Abstinence rates of cigarettes after 12 months were higher in those who used e-cigarettes daily, compared with those who did not (28.0% vs 5.8%, respectively; OR, 8.11; 95% CI, 3.14–20.97). However, nondaily e-cigarette use was not associated with abstinence from cigarettes (OR, 0.53; 95% CI, 0.08–3.35).

Several systematic reviews and meta-analyses have reported somewhat divergent findings. A meta-analysis
of 20 controlled studies (2 trials, 15 cohort studies, and 3 cross-sectional studies) by Kalkhoran and Glantz\(^\text{186}\) (2016) calculated that individuals using e-cigarettes were 28% less likely to achieve smoking cessation (OR, 0.72; 95% CI, 0.57–0.91). Similarly, a 2020 systematic review including 13 studies suggested that e-cigarettes were not significantly associated with increased smoking cessation among individuals who smoke cigarettes.\(^\text{187}\) Two additional meta-analyses published in 2016 concluded that, based on low- or very-low-quality evidence, e-cigarettes may be helpful for smoking reduction and possibly cessation for some who smoke.\(^\text{188,189}\) A more recent and comprehensive Cochrane review published in 2021, which included 61 total studies, showed that quitting cigarettes for 6 months or longer was more likely in those who used nicotine-containing e-cigarettes, compared with NRT (4 studies with moderate certainty; RR, 1.53; 95% CI, 1.21–1.93), nicotine-free e-cigarettes (5 studies with moderate certainty; RR, 1.94; 95% CI, 1.21–3.13), and behavioral or no treatment (6 studies with very low certainty; RR, 2.61; 95% CI, 1.44–4.74).\(^\text{190}\)

A large cross-sectional survey of 5,863 adults in the United Kingdom assessed the “real-world effectiveness” of e-cigarettes for smoking cessation compared with NRT and unaided quitting, revealing that users of e-cigarettes were more likely to self-report abstinence from cigarettes compared with the other cohorts (e-cigarettes vs NRT: OR, 2.23; 95% CI, 1.70–2.93; e-cigarettes vs no aid: OR, 1.38; 95% CI, 1.08–1.76).\(^\text{191}\) However, it is important to note that e-cigarettes in the United Kingdom are different than those in the United States, which lags in product regulation in the real-world marketplace.

Federal, state, and local health departments investigated e-cigarette or vaping use–associated lung injury (EVALI). EVALI is associated with respiratory, constitutional, and gastrointestinal symptoms,\(^\text{192}\) with about half of patients experiencing EVALI requiring intensive care for respiratory failure.\(^\text{193}\) Factors correlated with EVALI-associated death include age ≥35 years, obesity, and the presence of a chronic medical condition (ie, chronic respiratory disease and cardiac disease).\(^\text{194}\) An analysis of bronchoalveolar lavage fluid in 51 patients with EVALI and 99 patients without EVALI (including patients who never smoke, patients who smoke combustible cigarettes, and patients who smoke e-cigarettes) showed that vitamin E acetate was found in 94% of patients with EVALI and in none of the comparators, making it the likely causative agent.\(^\text{195}\) Vitamin E acetate is often added to THC (the active ingredient in marijuana) vaping liquids as a diluting or thickening agent. Limonene and coconut oil were found in the bronchoalveolar lavage fluid of 2 patients with EVALI (1 patient each), but no other potentially toxic substances (eg, plant oil, petroleum distillates) were found. The reporting structure for these events has been officially closed.

### Studies in Patients With Cancer

One study examined e-cigarette use in 1,074 patients with cancer who enrolled in a tobacco treatment program at a comprehensive cancer center.\(^\text{196}\) The study revealed a marked increase in e-cigarette use from 10.6% to 38.5% between 2012 and 2013. Patients who use e-cigarettes, most often diagnosed with thoracic or head and neck cancers, were more nicotine dependent and had greater numbers of prior quit attempts. At follow-up (6–12 months after intake), patients who use e-cigarettes were no more likely to have quit than patients who did not use e-cigarettes (OR, 1.0; 95% CI, 0.5–1.7), calling into question the potential benefits of e-cigarettes as a cessation agent for patients with cancer. Two cross-sectional studies of cancer survivors in the United States showed that e-cigarette use was highest among patients who currently smoke cigarettes, compared with patients who formerly smoked or who never smoked cigarettes.\(^\text{197,198}\) Two other cross-sectional studies including cancer survivors showed that e-cigarette use was associated with current cigarette smoking.\(^\text{199,200}\) Collectively, these studies highlight the importance of screening and addressing e-cigarette use by patients with cancer and cancer survivors.

E-cigarette use did not decrease cigarette smoking in a cross-sectional study in 106 patients with head and neck cancers seeking to quit. Nonusers of e-cigarettes had a significantly greater rate of cessation compared with patients who use e-cigarettes (72% vs 39%; \(P=0.0057\)).\(^\text{201}\) Another cross-sectional study surveyed 121 patients with cancer who were currently using e-cigarettes.\(^\text{202}\) Eighty-one percent of these surveyed patients who use e-cigarettes reported smoking cessation as their motivation for initiating e-cigarette use, but 51% also reported dual use of combustible cigarettes with e-cigarettes. Additionally, more than 70% reported that they had not discussed their e-cigarette use with their oncology care providers.

### NCCN Recommendations

At the current time, e-cigarettes are not an FDA-approved method for smoking treatment. It is not yet clear how factors such as real-world use or the addition of behavior therapy may influence the efficacy, safety, and effectiveness of e-cigarettes. Patients should be counseled toward the use of evidence-based smoking treatment approaches. For patients who choose to use e-cigarettes for smoking cessation, despite recommendations to use evidence-based methods, encourage smoking abstinence even if this is by the use of e-cigarettes, and continue behavioral counseling, given the harm to one’s health that is associated with smoking combustible cigarettes. For dual users of e-cigarettes and combustible cigarettes, complete smoking cessation is recommended given increased health risk concerns. When the patient develops more confidence about not smoking, cessation of e-cigarettes...
should be encouraged, but not at the risk of relapse to smoking combustible products.

Other Alternative Approaches

Very limited data exist to support exercise-based interventions; small study size, inadequate controls, and insufficient exercise intensity limit the ability to make conclusions based on the existing evidence.\textsuperscript{203} Sufficient efficacy data are also lacking to support the use of alternative therapies such as acupuncture, hypnosis, and nutritional supplements. A 2014 systematic review of the data on acupuncture, acupressure, and laser therapy revealed no consistent, bias-free evidence to support these methods for smoking cessation, although pooled evidence was suggestive of possible short-term benefits.\textsuperscript{204} Acupuncture was less effective than NRT and there was no evidence to support electrostimulation for smoking cessation. Similarly, systematic reviews of the data on hypnosis for smoking cessation revealed inadequate high-quality evidence to support this approach.\textsuperscript{205-206} Claims of efficacy data for hypnosis from several studies were not substantiated by the review of RCT data. Controlled studies are needed to provide higher quality evidence on these interventions, both in the general population and among patients with cancer.

Conclusion

A significant number of patients with cancer continue to smoke cigarettes during treatment and beyond. Patients should be encouraged to achieve and maintain abstinence from all combustible and smokeless tobacco products, as well as to avoid smoke exposure with household members. Evidence shows that smoking cessation is associated with improvements in cancer treatment outcomes, primary cancer recurrence, and secondary cancers. The NCCN Guidelines for Smoking Cessation highlight the importance of evaluating and assessing smoking status and history in patients with cancer, because documentation is suboptimal in care settings, cancer registries, and clinical trials. Smoking treatment should include the following: evidence-based motivational strategies and behavior therapy (counseling), which may be brief; evidence-based pharmacotherapy; and close follow-up with retreatment as needed. The optimal smoking cessation approach combines pharmacologic therapy (combination NRT and varenicline) and behavior therapy. At the current time, e-cigarettes are not an FDA-approved method for smoking treatment. For patients who use e-cigarettes exclusively for smoking cessation, despite recommendations to use evidence-based methods, smoking abstinence and behavioral counseling should be encouraged. As the patient becomes more confident about quitting smoking, encourage cessation of e-cigarettes, but not at the risk of relapse to smoking combustible products. For dual users of e-cigarettes and combustible cigarettes, complete smoking cessation is recommended given increased health risk concerns.

References


## Individual Disclosures for the NCCN Smoking Cessation Panel

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<td>Donna Edmondson, MSN, CRNP</td>
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<td>Joy Feliciano, MD</td>
<td>AstraZeneca Pharmaceuticals LP; Bristol-Myers Squibb Company; Pfizer Inc.; and Regeneron Pharmaceuticals</td>
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<td>Brian Hitsman, PhD</td>
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<td>Karen S. Hudmon, DrPH, MS, BS</td>
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<td>Michael T. Jaklitsch, MD</td>
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<td>Judith Prochaska, PhD, MPH</td>
<td>Achieve Life Sciences</td>
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<td>Peter G. Shields, MD</td>
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<td>Jamie L. Studts, PhD</td>
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The NCCN Guidelines Staff have no conflicts to disclose.

*The following individuals have disclosures relating to employment/governing board, patent, equity, or royalty:

- Michael K. Ong, MD, PhD: Greater Los Angeles Veteran Research and Education Foundation; State of California Tobacco Education and Research Oversight Committee; and UpToDate

- Laura Bierut, MD: Dr. Inventor on a patent “Markers for Addiction” (US 20070258698)