National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Smoking Cessation

Version 1.2016 — September 16, 2016

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

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus.

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NCCN Guidelines Version 1.2016 Updates Smoking Cessation

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Updates in Version 1.2016 of the NCCN Guidelines for Smoking Cessation from Version 2.2015 include:

INTRO

- First bullet revised: "*Evidence-based motivational strategies and* behavior therapy."
- Clinical recommendations, first bullet: clarified that the most effective approach is combining pharmacologic and behavior therapy.
- Bullet added: "Smoking cessation should be offered as part of oncology treatment and continued throughout the entire oncology care continuum, including during end-of-life care. An emphasis should be put on patient preferences and values when considering the best approach to fostering smoking cessation during end-of-life care."

SC-1

- Footnote "a" revised: "*Recommendations in this guideline apply to cessation of cigarette smoking.* ~~For the purposes of this guideline, "smoking" refers to cigarette use.~~ *Patients with cancer should be encouraged to discontinue the use of all combustible products* (eg, cigars, hookah, marijuana) and smokeless tobacco products. For information about e-cigarettes, see Principles of Alternative Approaches to Smoking Cessation (SC-A).*"*

SC-2

- This page has been significantly reorganized.
- Evaluation of nicotine dependency, first sub-bullet revised: "How much do you *currently* smoke per day, *and what is the maximum you ever smoked in a day?*
- Management for patients ready to quit within 4 weeks:
  - Second bullet revised: "Set quit date *as soon as possible* ~~preferably within 2 weeks.~~"
  - Third bullet revised: "*Encourage smoking cessation as soon as possible if cancer surgery is planned.* ~~Advise patients to set quit date 2 or more weeks prior to planned surgery as continued smoking increases risk of complications.~~"
- Management for patients not ready to quit within 4 weeks, second bullet revised: "Set a future quit date *and encourage immediate initiation of pharmacotherapy for targeted reduction of* ~~Consider reducing~~ cigarettes per day ~~using NRT or varenicline~~ with a goal of cessation in the near future."

SC-2 (continued)

- Footnote "j" added: "Longer periods of smoking cessation confer better surgical outcomes but should not delay appropriate timing of cancer resection. See Principles of Smoking Cessation and Cancer Surgery (SC-D)."

SC-3

- Evaluation, first bullet revised: "Evaluate ~~patient for~~ *and document patient risk factors* for smoking relapse."
- The definitions of high risk (≥1 risk factors) and low risk (0 risk factors) have been clarified.
- Under management:
  - First bullet added: "*Behavior therapy, including counseling on relapse risk factors and prevention."*
  - Second bullet revised: *"*~~For patients concerned about ability to maintain abstinence, suggest~~ *Consider NRT as clinically indicated to maintain abstinence* ~~and behavior therapy.~~"
- Clarified recommendations after re-evaluation of smoking status/risk of relapse.
- Footnote "m" revised: "*Refer to specialist for management of psyciatric comorbidities.* ~~Evaluate patient for psychiatric comorbidities and refer to specialist if indicated.~~"

SC-4

- Recommendations have been significantly revised.
- Footnote "r" added: "A minimum of 4 sessions of individual/group therapy in 12 weeks is preferred, but at least brief counseling is required. See Principles of Behavior Therapy (SC-E)." (Also for SC-5)
- Added line to footnote "t": "Varenicline should be avoided for patients with brain metastases due to seizure risk."
- Footnote "u" added: "Nicotine withdrawal symptoms typically peak within 1–2 weeks of quitting. Encourage continued therapy through brief slips. Patients who do not quit immediately may quit at some later point after withrawal symptoms subside." (Also for SC-5)
- Footnote "v" added: "Adjust pharmacotherapy dose or behavior therapy frequency for undesirable side effects, or if high risk of relapse is suspected." (Also for SC-5)

Continued

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NCCN Guidelines Version 1.2016 Updates Smoking Cessation

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Updates in Version 1.2016 of the NCCN Guidelines for Smoking Cessation from Version 2.2015 include:

SC-5
- This page has been added to expand the recommendations for those who relapse or continue smoking after primary therapy.
- Footnote "w" added: "Decision to switch therapy should be based on patient preference, toxicity, and/or a change in clinical status (eg, upcoming surgery)."

SC-A
- New section added: "Principles of Alternative Approaches to Smoking Cessation."

SC-B (1 of 2)
- Bendamustine added as one of the drugs for which metabolism is known to be affected by smoking.

SC-B (2 of 2)
- References updated.

SC-C
- Additional resources and references for patients and health professionals have been added.

SC-D
- New section added: "Principles of Smoking Cessation and Cancer Surgery."

SC-E
- Principles of Behavioral Strategies significantly revised and reorganized.

SC-F (1 of 2)
- Principles of smoking cessation pharmacotherapy significantly revised.
- The following options have been removed:
  - Varenicline + combination NRT
  - Varenicline + bupropion ± NRT
  - Nortriptyline (tricyclic antidepressant)
  - Clonidine (antihypertensive, alpha-2 adrenergic receptor agonist)
- Bupropion added as a subsequent therapy option (category 2B).
- Footnote "b" added: "Varenicline and bupropion should be avoided for patients with brain metastases due to seizure risk."

SC-F (2 of 2)
- Drug warnings/contraindications:
  - Added for varenicline: "Nausea is a common side effect of varenicline and may need to be managed for patients with cancer, especially during chemotherapy."
  - Added for varenicline: "Contraindicated for patients with brain metastases due to seizure risk."
  - Revised for both varenicline and bupropion: "*Although these side effects are uncommon,* providers should monitor for the development or worsening of serious neuropsychiatric issues *(ie, depression and suicidal ideation/behavior)*, including those without a previous history, and discontinue use if these signs occur."
- Bullet added: "A recent multicenter RCT examined the neuropsychiatric safety of varenicline and bupropion in 2 cohorts of patients: those with diagnosed psychiatric disorders (n=4074) and those without (n=3984). Rates of neuropsychiatric adverse events in individuals receiving varenicline or bupropion were not significantly increased relative to those receiving nicotine patches or placebo in either cohort." Reference: Anthenelli RM, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. Lancet 2016;387:2507-2520.

MS-1
- The Discussion section has been updated to reflect the changes in the algorithm.

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GENERAL PRINCIPLES OF THE SMOKING CESSATION GUIDELINES

These guidelines are focused on smoking cessation recommendations for patients with cancer. There are health benefits to smoking cessation even after a cancer diagnosis, regardless of stage or prognosis, namely improvement in cancer treatment outcomes, disease recurrence, and secondary cancers. It is never too late for patients with cancer to stop smoking cigarettes. Smoking and nicotine addiction is a chronic relapsing disorder. Patients may slip or relapse, which is expected and can be managed. Smokers with cancer often demonstrate high-level nicotine dependence. The NCCN Panel recommends that treatment plans for all smokers with cancer include the following:

- **Evidence-based motivational strategies and behavior therapy, and**
- **Evidence-based pharmacotherapy, and**
- **Close follow-up with retreatment as needed.**

Clinical Recommendations:

- **Combining pharmacologic therapy and behavior therapy is the most effective approach and leads to the best results for smoking cessation.**
  - **The two most effective pharmacotherapy agents are combination nicotine replacement therapy (NRT) and varenicline.**
  - **High-intensity behavior therapy with multiple counseling sessions is most effective, but at least a minimum of brief counseling is highly recommended.**
- **Smoking status should be documented 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 utilized.**
- **Smoking relapse and brief slips are common. Providers should discuss this and provide guidance and support to encourage continued smoking cessation attempts. Smoking slips are not necessarily an indication to try an alternative method. It may take more than one quit attempt with the same therapy to achieve long-term cessation.**
- **Smoking cessation should be offered as part of oncology treatment and continued throughout the entire oncology care continuum, including during end-of-life care. An emphasis should be put on patient preferences and values when considering the best approach to fostering smoking cessation during end-of-life care.**

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EVALUATION AND ASSESSMENT OF PATIENT SMOKING[a]

INITIAL EVALUATION[b]

STATUS

Assess current cigarette smoking status of all patients with cancer:[b,c,d]
- **Have you ever smoked cigarettes?**
- **Do you currently smoke cigarettes or have you smoked in the last 30 days?**

Current smoker and/or those who have smoked within the last 30 days → **See Assessment of Current Smokers (SC-2)**

Former smoker or recently quit (>30 days since patient last smoked) → **See Assessment of Former Smokers (SC-3)**

Never smoked or long-term former smoker → **Encourage patient to remain smoke-free**

[a]Recommendations in this guideline apply to cessation of cigarette smoking. Patients with cancer should be encouraged to discontinue the use of all combustible products (eg, cigars, hookah, marijuana) and smokeless tobacco products. For information about e-cigarettes, see Principles of Alternative Approaches to Smoking Cessation (SC-A).

[b]Initial evaluation and assessment of patient smoking may be completed by any member of the health care team, including physicians, nurses, medical assistants, health educators, or other dedicated staff.

[c]Smoking status should be documented in the patient health record and assessment should be repeated at every visit (less often for patients with remote smoking histories).

[d]Smoking cessation should be offered to all smokers with cancer regardless of cancer prognosis. See Smoking-Associated Risks for Patients With Cancer (SC-B).

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CURRENT SMOKERS AND THOSE WHO HAVE SMOKED WITHIN LAST 30 DAYS

EVALUATION

Assess and document in the patient health record:

- **Nicotine dependency:**
  - How much do you currently smoke per day, and what is the maximum you ever smoked in a day?
  - How soon do you smoke after you wake up in the morning?
  - Do you use any other type(s) of tobacco/nicotine products and if so, how much? (eg, pipes, cigars, snuff, e-cigarettes)
- **History of quit attempts:**
  - What is the longest period you have gone without smoking?
  - When was your last quit attempt?
  - Did you use anything to help you quit in the past? If so, what?
    - ◊ Unaided
    - ◊ Medications[e] (eg, varenicline, bupropion, NRT)
    - ◊ Support group
    - ◊ Behavior therapy
    - ◊ Quitlines, websites, smart phone applications, or other media
    - ◊ E-cigarettes[f]
    - ◊ Other
  - Why were previous quit attempts unsuccessful? (eg, side effects, cost, continued cravings, did not work)
- **Patient readiness to quit[g,h]**

→ **Engage patients in motivational dialog about smoking cessation[g]**
- **Review risks of smoking and benefits of quitting (See SC-B)**
- **Provide patient education resources (See SC-C)**

MANAGEMENT

Ready to quit within 4 weeks[g]
- **Establish personalized quit plan based on:**
  - **Nicotine dependency and prior quit attempts[i]**
  - **Smoking cessation therapy options (see SC-4)**
- **Set quit date as soon as possible.**
- **Encourage smoking cessation as soon as possible if cancer surgery is planned.[j]**
- **Discuss risk of relapse.[k]**

→ **Begin smoking cessation treatment (See SC-4)**

Not ready to quit within 4 weeks[g]
- **Assess and address barriers and concerns of patient.**
- **Set a future quit date and encourage immediate initiation of pharmacotherapy for targeted reduction of cigarettes per day with a goal of cessation in the near future.[h,l]**

→ **Reassess readiness to quit at each visit**

[e]Document type and dose of medications used during previous quit attempts.
[f]There is currently insufficient evidence to support the use of electronic nicotine delivery systems (e-cigarettes) in smoking cessation for patients with cancer.
[g]Physicians and members of the health care team should discuss potential benefits of quitting with each patient. Readiness to quit is to be determined by both physician and patient.
[h]Making an immediate quit attempt is recommended but smoking reduction may be considered with a goal of cessation at a future quit date (ie, 1–3 mo).
[i]Adjustments to therapy length, intensity, and surveillance may be considered, as clinically indicated, for patients with high nicotine dependency and/or prior unsuccessful quit attempts.
[j]Longer periods of smoking cessation confer better surgical outcomes but should not delay appropriate timing of cancer resection. See Principles of Smoking Cessation and Cancer Surgery (SC-D).
[k]Providers should discuss risk of relapse and smoking slips and provide guidance and support to encourage continued smoking cessation attempts. See Principles of Behavioral Strategies (SC-E).
[l]See Principles of Smoking Cessation Pharmacotherapy (SC-F).

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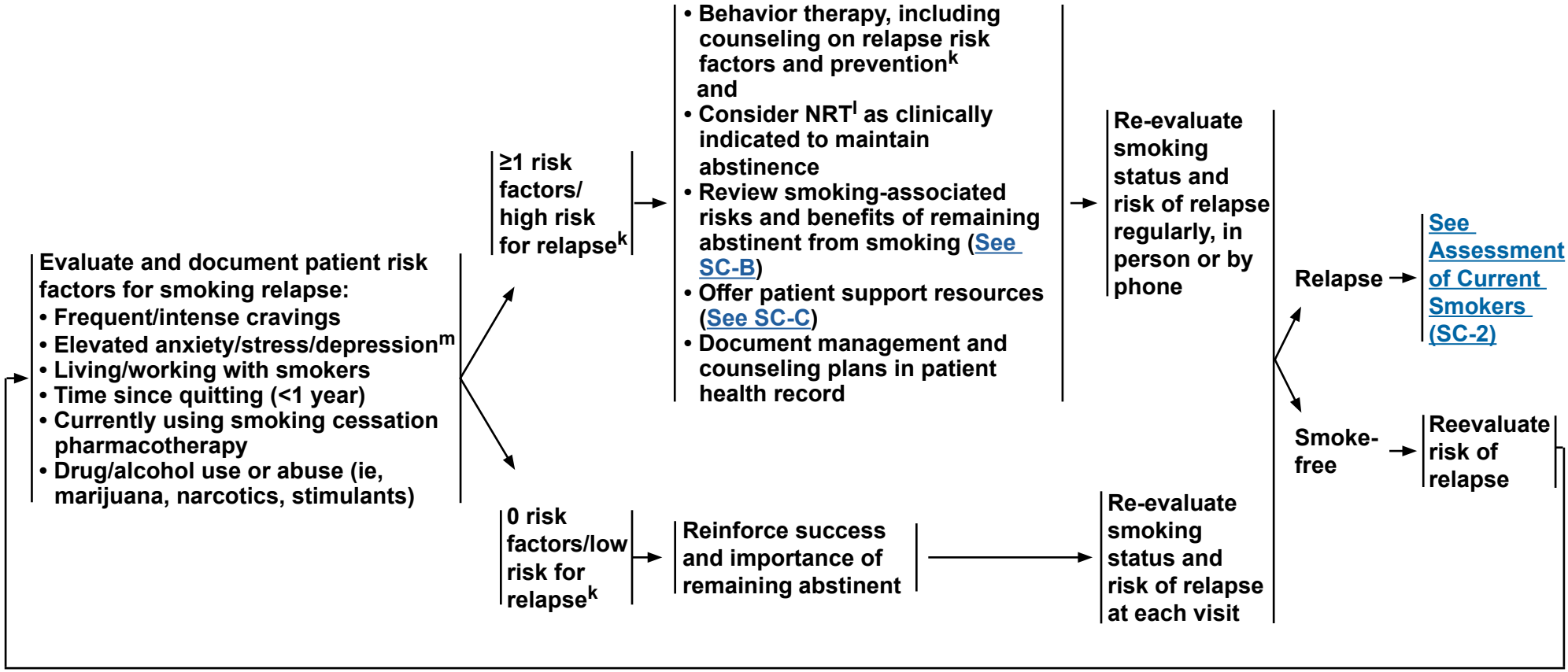
FORMER SMOKERS AND RECENT QUITTERS (>30 Days Since Last Smoked)



[k]Providers should discuss risk of relapse and smoking slips and provide guidance and support to encourage continued smoking cessation attempts. See Principles of Behavioral Strategies (SC-E).
[l]See Principles of Smoking Cessation Pharmacotherapy (SC-F).
[m]Refer to specialist for management of psychiatric comorbidities.

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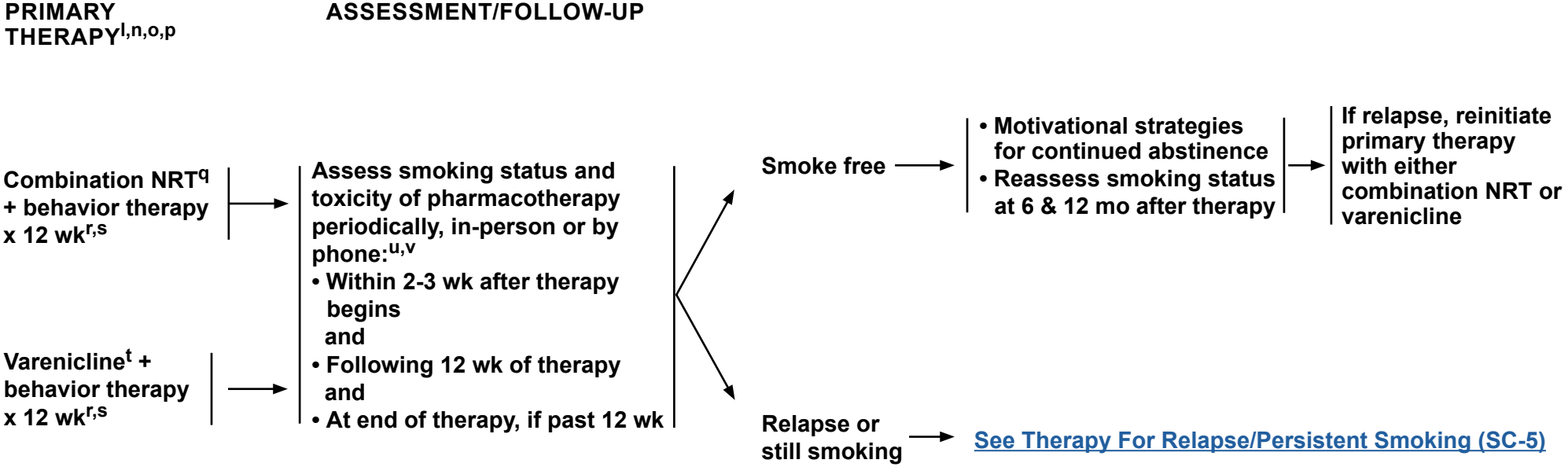
GENERAL APPROACH TO SMOKING CESSATION DURING CANCER TREATMENT



[l] See Principles of Smoking Cessation Pharmacotherapy (SC-F).
[n] See Principles of Behavior Therapy (SC-E).
[o] Efficacy data are lacking for the use of e-cigarettes and alternative therapies (eg, hypnosis, acupuncture, nutritional supplements). Use of evidence-based cessation methods should be encouraged to avoid delay in achieving smoking abstinence. See Principles of Alternative Approaches to Smoking Cessation (SC-A).
[p] The use of marijuana, or other substances associated with smoking relapse, is discouraged for those attempting to quit smoking.
[q] Combination NRT= Nicotine patch + short-acting NRT (gum/lozenge/inhaler/nasal spray).
[r] A minimum of 4 sessions of individual/group therapy in 12 weeks is preferred, but at least brief counseling is required. See Principles of Behavior Therapy (SC-E).
[s] Therapy may be extended to promote continued cessation (ie, 6 mo–1 y) while attempting to avoid longer periods of time if possible.
[t] Nausea is a common side effect of varenicline and may need to be managed for patients with cancer, especially during chemotherapy. Varenicline should be avoided for patients with brain metastases due to seizure risk.
[u] Nicotine withdrawal symptoms typically peak within 1–2 weeks of quitting. Encourage continued therapy through brief slips. Patients who do not quit immediately may quit at some later point after withrawal symptoms subside.
[v] Adjust pharmacotherapy dose or behavior therapy frequency for undesirable side effects, or if high risk of relapse is suspected.

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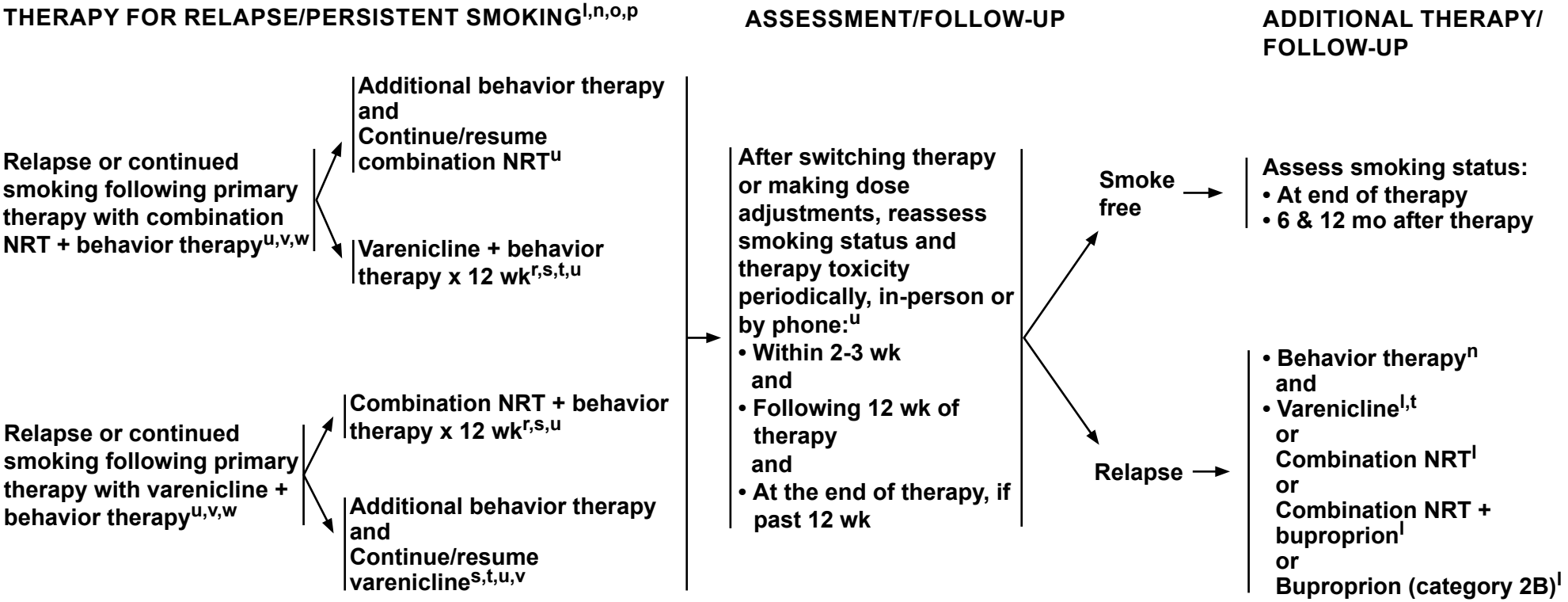
GENERAL APPROACH TO SMOKING CESSATION DURING CANCER TREATMENT



[l] See Principles of Smoking Cessation Pharmacotherapy (SC-F).

[n] See Principles of Behavior Therapy (SC-E).

[o] Efficacy data are lacking for the use of e-cigarettes and alternative therapies (eg, hypnosis, acupuncture, nutritional supplements). Use of evidence-based cessation methods should be encouraged to avoid delay in achieving smoking abstinence. See Principles of Alternative Approaches to Smoking Cessation (SC-A).

[p] The use of marijuana, or other substances associated with smoking relapse, is discouraged for those attempting to quit smoking.

[r] A minimum of 4 sessions of individual/group therapy in 12 weeks is preferred, but at least brief counseling is required. See Principles of Behavior Therapy (SC-E).

[s] Therapy may be extended to promote continued cessation (ie, 6 months– 1 year) while attempting to avoid longer periods of time if possible.

[t] Nausea is a common side effect of varenicline and may need to be managed for patients with cancer, especially during chemotherapy. Varenicline should be avoided for patients with brain metastases due to seizure risk.

[u] Nicotine withdrawal symptoms typically peak within 1–2 weeks of quitting. Encourage continued therapy through brief slips. Patients who do not quit immediately may quit at some later point after withrawal symptoms subside.

[v] Adjust pharmacotherapy dose or behavior therapy frequency for undesirable side effects, or if high risk of relapse is suspected.

[w] Decision to switch therapy should be based on patient preference, toxicity, and/or a change in clinical status (eg, upcoming surgery).

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PRINCIPLES OF ALTERNATIVE APPROACHES TO SMOKING CESSATION

- **Offer motivational and behavioral support to all patients attempting to quit smoking, regardless of what smoking cessation method(s) is/are being used. See Principles of Behavioral Strategies (SC-E)**
- **Continue to work with patients who are already using alternative approaches. Encourage the use of evidence-based cessation methods to avoid delays in achieving abstinence.**
- **Relapse and smoking slips are common. Remind patients that repeated attempts with evidence-based methods are frequently needed to achieve longer-term abstinence.**

Electronic Nicotine Delivery Systems (ENDS) or "E-Cigarettes"

- **ENDS are not FDA-approved smoking cessation devices.**
- **There is currently insufficient evidence to support the use of e-cigarettes in smoking cessation, both alone and/or in combination with evidence-based smoking cessation methods. There is also insufficient evidence regarding the safety and efficacy of e-cigarette use in patients with cancer.**
  - **The American Heart Association, AACR, and ASCO recognize the potential for ENDS to alter existing smoking behaviors, as well as the lack of definitive data regarding associated benefits and harms.[1,2] However, ENDS are not recommended by these associations because of the insufficient data on efficacy and safety.**
  - **According to the US Preventative Services Task Force (USPSTF), "Current evidence is insufficient to recommend electronic nicotine delivery systems (ENDS) for tobacco cessation in adults, including pregnant women. The USPSTF recommends that clinicians direct patients who smoke tobacco to other cessation interventions with established effectiveness and safety."[3]**

Other Alternative Methods

- **There is currently insufficient evidence to support the use of alternative methods (eg, hypnosis, acupuncture, nutritional supplements), when used alone and in combination with standard smoking cessation methods.[4,5]**
- **Prior unsuccessful quit attempts with conventional therapies do not justify the use of unproven alternative cessation methods, because multiple attempts with evidence-based methods may be necessary to achieve abstinence.**
- **There are very limited, low-quality data regarding the efficacy of exercise-based interventions.[6]**

[1]Brandon TH, Goniewicz ML, Hanna NH, et al. Electronic nicotine delivery systems: a policy statement from the American Association for Cancer Research and the American Society of Clinical Oncology. J Clin Oncol 2015;33:952-963.
[2]Bhatnagar A, Whitsel LP, Ribisl KM, et al. Electronic cigarettes: a policy statement from the American Heart Association. Circulation 2014;130:1418-1436.
[3]Final Update Summary: Tobacco Smoking Cessation in Adults, Including Pregnant Women: Behavioral and Pharmacotherapy Interventions. U.S. Preventive Services Task Force. September 2015. http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/tobacco-use-in-adults-and-pregnant-women-counseling-and-interventions1?ds=1&s=tobacco
[4]Barnes J, Dong CY, McRobbie H, et al. Hypnotherapy for smoking cessation. Cochrane Database Syst Rev 2010:CD001008.
[5]White AR, Rampes H, Liu JP, et al. Acupuncture and related interventions for smoking cessation. Cochrane Database Syst Rev 2014;1:CD000009.
[6]Ussher MH, Taylor AH, Faulkner GE. Exercise interventions for smoking cessation. Cochrane Database Syst Rev 2014;8:CD002295.

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SMOKING-ASSOCIATED RISKS FOR PATIENTS WITH CANCER (1 of 2)

- The 2014 Surgeon General's Report[1] stated that:
  - Sufficient evidence exists to support a causal relationship between smoking and adverse health outcomes, increased all-cause mortality and cancer-specific mortality, and increased risk for secondary primary cancers.
  - Existing evidence is suggestive of a link between smoking and increased risk of cancer recurrence, poor treatment response, and increased treatment-related toxicity.
- Providers should:
  - Inform patients of the potential benefits of smoking cessation, including improved survival, treatment outcomes, and health-related quality of life, as well as decreased treatment-related toxicity, drug side effects, and surgical complications.
  - Educate patients on the specific risks of smoking during treatment for their particular cancer.
  - Encourage smoking cessation as far in advance as possible before initiating cancer treatment.
  - Consider patient smoking status, prior to initiating treatment, when making decisions regarding treatment selection, dosage, and timing of initiation.

Treatment-Specific Risks (see Discussion for additional information)

- Smoking can impact the metabolism of chemotherapy and targeted therapy.
  - Smoking effects on cytochrome P450 enzymes may include altered drug clearance time and plasma concentration, potentially impacting the efficacy of certain drugs for patients who smoke. Providers should consider whether patients are at risk for altered drug metabolism due to smoking and determine if medication or dose adjustments may be required. Drugs whose metabolisms are known to be affected include erlotinib, irinotecan, and bendamustine.[2-6]
- Smoking increases risk of radiation therapy (RT)-associated treatment complications during RT and may decrease treatment response.[7-9]
- Smoking is associated with increased rates of postoperative complications and mortality after cancer surgery.
  - Compared with nonsmokers, patients who smoke may experience decreased health-related quality of life after cancer surgery (eg, dyspnea, fatigue, pain).[10-12]
  - Smoking may impair wound healing following surgery for cancer.[13,14]
  - Increased infection rates, pulmonary complications, and longer postoperative hospital stays are more commonly observed in patients who smoke.[15]
  - Postoperative mortality rates are higher among patients who smoke.[16]

Potential Nicotine Effects on Cancer and Cardiovascular Risks (see Discussion for additional information)

- Blood nicotine levels from NRT, including combination NRT, are significantly less than from smoking cigarettes. Therefore, providers and smokers should not be dissuaded from using NRT to foster quitting and long-term cessation. The use of combination NRT as one type of pharmacotherapy is recommended.
- There is insufficient evidence that NRT causes cancer in humans.[17-21]
- While myocardial infarction has rarely been reported in NRT users, there is insufficient evidence that NRT increases the risk of myocardial infarction or cardiovascular disease.

References on next page

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SMOKING-ASSOCIATED RISKS FOR PATIENTS WITH CANCER (2 of 2)

REFERENCES

[1]The Health Consequences of Smoking-50 Years of Progress: A Report of the Surgeon General. Atlanta (GA); 2014. Available at: http://www.surgeongeneral.gov/library/reports/50-years-of-progress/. Accessed September 9, 2016.

[2]Li H, Shi Q. Drugs and diseases interacting with cigarette smoking in US prescription drug labeling. Clin Pharmacokinet 2015;54:493-501.

[3]O'Malley M, King AN, Conte M, et al. Effects of cigarette smoking on metabolism and effectiveness of systemic therapy for lung cancer. J Thorac Oncol 2014;9:917-926.

[4]Hamilton M, Wolf JL, Rusk J, et al. Effects of smoking on the pharmacokinetics of erlotinib. Clin Cancer Res 2006;12:2166-2171.

[5]van der Bol JM, Mathijssen RH, Loos WJ, et al. Cigarette smoking and irinotecan treatment: pharmacokinetic interaction and effects on neutropenia. J Clin Oncol 2007;25:2719-2726.

[6]Darwish M, Bond M, Hellriegel E, et al. Pharmacokinetic and pharmacodynamic profile of bendamustine and its metabolites. Cancer Chemotherapy and Pharmacology. 2015;75(6):1143-1154. doi:10.1007/s00280-015-2727-6.

[7]Eifel PJ, Jhingran A, Bodurka DC, et al. Correlation of smoking history and other patient characteristics with major complications of pelvic radiation therapy for cervical cancer. J Clin Oncol 2002;20:3651-3657.

[8]Browman GP, Wong G, Hodson I, et al. Influence of cigarette smoking on the efficacy of radiation therapy in head and neck cancer. N Engl J Med 1993;328:159-163.

[9]Zevallos JP, Mallen MJ, Lam CY, et al. Complications of radiotherapy in laryngopharyngeal cancer: effects of a prospective smoking cessation program. Cancer 2009;115:4636-4644.

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SMOKING CESSATION RESOURCES FOR HEALTH CARE PROVIDERS AND PATIENTS (1 of 2)

Quitlines/Online Support/Mobile Apps	
American Indian Commercial Tobacco Program	• 1.855.372.0037 • Enroll online- https://americanindian.quitlogix.org
American Lung Association	• 1.800.LUNGUSA (1.800.586.4872) • Live Help (Online Chat)- http://www.lung.org/about-us/lung-helpline.html
Asian Smokers' Quitline	Mandarin/Cantonese: 1.800.838.8917; Korean: 1.800.556.5564; Vietnamese: 1.800.778.8440
National Cancer Institute (NCI)	• 1.877.448.7848 • Live Help (Online Chat)- https://livehelp.cancer.gov/app/chat/chat_launch
National Network of Tobacco Cessation Quitlines	English: 1.800.QUIT.NOW (1.800.784.8669) Spanish: 1.855.DÉJELO.YA (1.855.335.3569)
Smokefree.gov	• SmokefreeTXT (Text messaging support)- http://smokefree.gov/smokefreetxt ▸ SmokefreeMOM: http://smokefree.gov/smokefreemom ▸ SmokefreeVET: http://smokefree.gov/vet ▸ SmokefreeESPANOL: http://espanol.smokefree.gov/smokefreetxt-espanol • Smokefree Apps (for smartphones)- http://smokefree.gov/apps-quitstart
TRICARE (For military service members and their families)	• Quitlines: North: 1.866.459.8766; South: 1.877.414.9949; West: 1.888.713.4597 • http://www.tricare.mil/HealthWellness/Tobacco.aspx
Quit Tobacco: UCANQUIT2.org	• Live chat with quit coach: http://www.ucanquit2.org • SmokefreeMIL text message support: http://www.ucanquit2.org/en/HowToQuit/SmokefreeMIL.aspx
General Information Online	
American Heart Association	http://www.heart.org/HEARTORG/GettingHealthy/QuitSmoking/Quit-Smoking_UCM_001085_SubHomePage.jsp
American Lung Association	http://www.lung.org/stop-smoking/
Centers for Disease Control and Prevention (CDC)	http://www.cdc.gov/tobacco/quit_smoking/how_to_quit/resources/index.htm
NCI	http://www.cancer.gov/cancertopics/tobacco/smoking
SmokeFree.gov	http://smokefree.gov
Smoking Cessation Programs	
American Lung Association	http://www.lung.org/stop-smoking/how-to-quit/freedom-from-smoking/
Ex: A New Way To Think About Quitting Smoking	http://www.becomeanex.org/

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SMOKING CESSATION RESOURCES FOR HEALTH CARE PROVIDERS AND PATIENTS (2 OF 2)

Guides to Quitting	
American Cancer Society (ACS)	http://www.cancer.org/healthy/stayawayfromtobacco/guidetoquittingsmoking/index
NCI: "Clearing the Air: Quit Smoking Today"	http://smokefree.gov/sites/default/files/pdf/clearing-the-air-accessible.pdf
NCI: "Clear Horizons: A Quit-Smoking Guide for People 50 and Older"	http://smokefree.gov/sites/default/files/pdf/clear-horizons-accessible.pdf
Additional Resources for Health Professionals	
American Academy of Family Physicians (AAFP)	Ask and Act Smoking Cessation Program http://www.aafp.org/about/initiatives/ask-act.html
American Association for Cancer Research (AACR)	http://www.aacr.org/AdvocacyPolicy/GovernmentAffairs/Documents/AACRStatement_TobaccoUseCancerPatients_2013_CCR___f3f578.pdf
American College of Chest Physicians (ACCP)	Tobacco dependence treatment toolkit: http://tobaccodependence.chestnet.org/
American Society of Clinical Oncology (ASCO)	http://www.asco.org/practice-guidelines/cancer-care-initiatives/prevention-survivorship/tobacco-cessation-control
Association for the Treatment of Tobacco Use and Dependence (ATTUD)/Council for Tobacco Treatment Training Programs (CTTTP)	• http://www.attud.org/ • Accredited training programs: http://ctttp.org/accredited-programs/
NCCN Guidelines for Lung Cancer Screening	http://www.nccn.org/professionals/physician_gls/pdf/lung_screening.pdf
NCCN Guidelines for Survivorship	http://www.nccn.org/professionals/physician_gls/pdf/survivorship.pdf
NCI- Physician Data Query: "Smoking In Cancer Care"	http://www.cancer.gov/cancertopics/pdq/supportivecare/smokingcessation/HealthProfessional
RxForChange: Clinician-Assisted Tobacco Cessation	http://rxforchange.ucsf.edu/
Smokefree.gov	http://smokefree.gov/health-care-professionals
Treatobacco.net	http://www.treatobacco.net/en/index.php
U.S. Department of Health and Human Services- Surgeon General Reports	http://www.surgeongeneral.gov/priorities/tobacco

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PRINCIPLES OF SMOKING CESSATION AND CANCER SURGERY

- **Smoking increases the risk of pulmonary complications, surgical site infection, and poor wound healing in patients undergoing surgery. See Smoking Associated Risks for Patients With Cancer (SC-B)**
- **Access to cancer surgery should not be restricted for smokers, although smoking cessation may be deemed mandatory for some elective non-cancer surgery (ie, reconstructive procedures).**
- **Smokers who have planned cancer surgery should be encouraged to quit smoking as soon as possible.**
- **Longer periods of smoking cessation confer better surgical outcomes but should not delay appropriate timing for cancer resection.**
- **Elective procedures, such as plastic surgery reconstruction, may benefit from delaying surgery for 60–90 days after smoking cessation.**

- **Preoperative pharmacotherapy options are consistent with the smoking cessation options for all patients with cancer who smoke. See Primary Therapy (SC-4). Primary therapy options for preoperative smoking cessation include:**
  - **Combination NRT + behavior therapy**
    - **There is no clear evidence that NRT degrades the wound healing benefits of smoking cessation. NRT offers benefits over continued smoking.**
    - **NRT is a valuable adjunct to perioperative smoking cessation.**

  or
  - **Varenicline + behavior therapy**

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PRINCIPLES OF BEHAVIORAL STRATEGIES (1 of 2)

- **Pharmacotherapy is most effective when combined with behavior therapy.[1] Population-level studies of smoking cessation treatment modalities indicate that counseling by a smoking cessation specialist plus medication results in a significant improvement in cessation rates relative to no counseling or medication (OR = 3.25; CI, 2.05–5.15).[2] In addition to the benefits of enhancing motivation and knowledge of the addiction process, behavior therapy assists patients with medication use and strategies since adherence to tobacco treatment medication recommendations is often inadequate. Therefore, pharmacotherapy alone without some form of counseling may not be better than unaided cessation.**
- **Through behavior therapy, smokers are provided with problem-solving skills, support, and encouragement. Behavior therapy, tailored somewhat to the patient's nicotine dependence and previous quit attempts, provides strategies for:**
  - **Coping with nicotine withdraw symptoms (Note: Symptoms typically peak within 1–2 weeks after quitting and then subside.)**
  - **Identifying smoking triggers**
  - **Coping with stressful and difficult situations in which smoking is likely**
  - **Avoiding high-risk situations**
  - **Addressing other patient-specific barriers to and facilitators of smoking behavior change.**
- **Motivational counseling is beneficial for all patients, including those unwilling to quit.[2-4]**
  - **Motivational counseling includes exploring the smoker's feelings, beliefs, ideas, and values in order to identify areas for change towards willingness to quit. Provide reasons, ideas, and needs for cessation, with encouragement. It is important to be directive with a smoker, while using an empathic approach to help the smoker understand his/her reasons for smoking and build his/her confidence to quit.**
  - **The four general principles to follow are:**
    (1) Express empathy,
    (2) Develop discrepancy,
    (3) Roll with resistance, and
    (4) Support self-efficacy.[3]
- **In smokers with cancer, there is a high incidence of depression, anxiety, and stress, all of which are common causes of relapse. It may be optimal to enroll patients in a behavior therapy program with specific interventions designed to ameliorate these conditions and other cancer-related relapse challenges. This may require referral to specialized smoking cessation programs that have staff trained to treat mental health disorders, or referral to behavior therapists who have expertise in treating comorbid substance dependence and mental health disorders.**
- **Specialized treatment centers may consider providing smoking cessation therapy targeted specifically to patients with cancer (eg, individual therapy and group support that focuses on challenges specific to cancer survival and treatment) with access to counselors or group leaders experienced in the treatment of patients with cancer.**

References on next page

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PRINCIPLES OF BEHAVIORAL STRATEGIES (2 of 2)

Behavior Therapy/Counseling Recommendations:

- **Four or more sessions during each 12-week course of pharmacotherapy. The first session is recommened within the first 2–3 weeks.**
  - **Duration: 10–30+ minutes per session; Research suggests that longer, more frequent sessions are linked to higher success rates.**
  - **Brief advice, at minimum, should be delivered. Brief advice of about 3 minutes by physicians or other health care providers results in a small but important increase in quit rates.[2]**
- **Individual or group therapy, in-person and/or by phone, in coordination with a smoking cessation clinic, if available.**
  - **For those in active cancer treatment, behavior therapy can occur during scheduled oncology visits to avoid the need for additional appointments.**
  - **Refer to a smoking cessation quitline, in addition to providing brief counseling from a health care provider, if face-to-face or group intervention is not available. See Smoking Cessation Resources (SC-C).**
- **Performed by a tobacco treatment specialist or a dedicated staff member (ie, nurse, medical assistant, health educator) trained in smoking cessation motivational and behavior strategies.**
- **Therapy should include skills training, social support, and motivational interviewing with print- or web-based patient education materials.**
- **For more information on behavior therapy for smoking cessation, see Discussion.**

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PRINCIPLES OF SMOKING CESSATION PHARMACOTHERAPY (1 of 2)

- **Smoking cessation is important for improving clinical outcomes for patients with cancer. Therefore, the included agents and methodologies should be made available to all patients with cancer who smoke.**
- **A minimum of 12 weeks of combination NRT or varenicline[a] is recommended for the initial quit attempt. Therapy may be extended to promote continued cessation (ie, 6 months–1 year) while attempting to avoid longer periods of time if possible.**
  - **Follow-up is recommended (in-person or by phone) within 2 weeks after starting pharmacotherapy, but can be extended to within 3 weeks to coordinate with regularly scheduled oncology appointments, as needed. Additional periodic follow-up during therapy (at a minimum of 12 wk intervals), and after completion of therapy.**
  - **Nicotine withdrawal symptoms typically peak within 1–2 weeks of quitting and then subside. Encourage continued therapy through brief slips. Patients who do not quit immediately may quit at some later point after withrawal symptoms subside.**
  - **Pharmacotherapy dose adjustments may be considered, as clinically indicated.**
- **Track attempts at smoking reduction. If reduction efforts stall, or reaching total abstinence seems unlikely, consider switching to a different pharmacotherapy.**
- **As patients progress through multiple lines of treatment, behavior therapy should be progressively intensified with referral to specialty care (eg, psychiatrist, psychologist) as indicated.**

Preferred Primary Therapy Options	• **Combination NRT: Nicotine patch + short-acting NRT for cravings (lozenge/gum/inhaler/nasal spray) or** • **Varenicline[a,b]** • **Patients who continue to smoke or experience relapse may continue or resume the initial pharmacotherapy, or switch to the other primary therapy option before trying the subsequent therapy options.**
Subsequent Therapy Options*	• **Combination NRT + bupropion[b]** • **Bupropion[b] (category 2B)**

***Additional pharmacotherapy options are currently being evaluated. See Discussion for details.**

Continued on next page

[a]Nausea is a common side effect of varenicline and may need to be managed for patients with cancer, especially during chemotherapy.
[b]Varenicline and bupropion should be avoided for patients with brain metastases due to seizure risk.

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PRINCIPLES OF SMOKING CESSATION PHARMACOTHERAPY (2 of 2)
Standard Pharmacotherapy Dosing Information

	Standard Dose[c]	Duration	Drug Warnings and Contraindications[e,f]
Combination NRT (preferred)	• 21 mg patch + short-acting NRT • If 21 mg patch is not effective, consider increasing to 35 or 42 mg patch	12 wk[d]	Blood nicotine levels from NRT, including combination NRT, are significantly less than from smoking cigarettes. NRT is well tolerated and nicotine toxicity is rare and transient, even when used with smoking.
Varenicline (preferred)	• Initiate dosing 1–2 wk prior to quitting • Days 1–3: 0.5 mg orally, once daily • Days 4–7: 0.5 mg orally, twice daily • Week 2–12: 1 mg orally, twice daily, if tolerated	12 wk[d]	• Nausea is a common side effect of varenicline and may need to be managed for patients with cancer, especially during chemotherapy. • Although these side effects are uncommon, providers should monitor for the development or worsening of serious neuropsychiatric issues (ie, depression and suicidal ideation/behavior), including those without a previous history, and discontinue use if these signs occur. See Manufacturer Black Box Warning, and weigh the substantial benefits of immediate smoking cessation versus risks of increased hostility, depression, or suicidal behavior.1 • Contraindicated for patients with brain metastases due to seizure risk.
Bupropion ± NRT (category 2B for bupropion alone)	• Initiate dosing 1–2 wk prior to quitting • Days 1–3: 150 mg orally, once daily ▸ Adjust dose for hepatic insufficiency. • Day 4–12 wk: 150 mg orally, twice daily, if tolerated • Maximum 300 mg per day	7–12 wk[d]	• Although these side effects are uncommon, providers should monitor for the development or worsening of serious neuropsychiatric issues (ie, depression and suicidal ideation/behavior), including those without a previous history, and discontinue use if these signs occur. See Manufacturer Black Box Warning, and weigh the substantial benefits of immediate smoking cessation versus risks of increased hostility, depression, or suicidal behavior.[2] • Burpropion is contraindicated for patients with seizure risks (ie, stroke, brain metastases), those taking MAO inhibitors (increased risk of hypertensive reactions) or tamoxifen, or those with closed-angle glaucoma.

Side Effects

- **In most circumstances, the side effects related to preferred smoking cessation medications are minimal and are considered an acceptable risk compared to smoking. Serious side effects are extremely rare. Refer to manufacturer inserts for exhaustive lists of potential side effects and warnings.[e,f]**
- **A recent multicenter RCT examined the neuropsychiatric safety of varenicline and bupropion in 2 cohorts of patients: those with diagnosed psychiatric disorders (n=4074) and those without (n=3984). Rates of neuropsychiatric adverse events in individuals receiving varenicline or bupropion were not significantly increased relative to those receiving nicotine patches or placebo in either cohort.[g]**

[c] Dose adjustments may be considered, if clinically indicated.
[d] Therapy may be extended to promote continued cessation (ie, 6 months–1 year) while attempting to avoid longer periods of time if possible.
[e] National Institutes of Health. Varenicline (Chantix) drug label and full prescribing information. Available at: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d52bc40b-db7b-4243-888c-9ee95bbc6545 Accessed September 9, 2016.
[f] National Institutes of Health. Bupropion hydrochloride (Zyban) Drug label and full prescribing information. Available at: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a3327c31-d987-40ec-b3b5-097bbf2f4f8c Accessed September 9, 2016.
[g] Anthenelli RM, Benowitz NL, West R, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. Lancet 2016;387:2507-2520.

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Discussion

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.

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Overview

An estimated 42.1 million adults in the United States currently smoke cigarettes, accounting for approximately 18% of the adult population.[1] Cigarette smoking results in over 480,000 premature deaths yearly, and 1 in every 5 deaths are smoking-related.[2] Tobacco smoking has been implicated in causing cancers of mouth, lips, nose, sinuses, larynx, pharynx, esophagus, stomach, pancreas, kidney, bladder, uterus, cervix, colon/rectum, ovary, and myeloid leukemia.[3] Moreover, tobacco use causes at least 30% of all cancer deaths.[3]

These guidelines emphasize the importance of smoking cessation in all patients with cancer and seek to establish evidence-based, standard-of-care recommendations tailored to the unique needs and concerns of patients with cancer. The recommendations contained herein describe interventions for cessation of cigarette smoking. However, the panel recommends that patients with cancer be encouraged to discontinue use of all combustible products (eg, cigars, hookah, marijuana) as well as smokeless tobacco products.

In a 2014 report from the Surgeon General, “The Health Consequences of Smoking—50 Years of Progress”, a comprehensive review of the evidence revealed the following important findings for patients with cancer and cancer survivors:[2]

- Sufficient evidence exists to infer a causal relationship between cigarette smoking and adverse health outcomes, increased all-cause mortality (ACM), and cancer-specific mortality.
- Sufficient evidence exists to infer a causal relationship between cigarette smoking and second primary cancer.
- Evidence is suggestive of a causal relationship between cigarette smoking and risk of recurrence, poorer response to treatment, and increased treatment-related toxicity.

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 prevalence of continued smoking among those who have received a cancer diagnosis has been examined in recent studies. The rate of smoking post-diagnosis varies widely by cancer type and with other factors such as gender, race, and age.

Smoking Prevalence in Patients with Cancer

Using data from the National Health and Nutrition Examination Survey (NHANES), of the 566 cancer survivors who regularly smoked prior to their diagnosis, 64% continued to smoke post-diagnosis. Those identified at higher risk for continued smoking included female, younger, and Hispanic individuals.[4] In the Cancer Care Outcomes Research and Surveillance (CanCORS) cohort of patients with lung (n = 2456) and colorectal (n = 3063) cancers, 90% of patients with lung cancers and 55% of patients with colorectal cancer reported a history of smoking. At diagnosis, 39% of those with lung and 14% of those with colorectal cancer were current smokers, and of these individuals 14% of patients with lung and 9% of patient with colorectal cancer continued to smoke at 5 months post-diagnosis.[5]

Smoking often persists beyond cancer treatment and well into survivorship. In a population-based study using the Behavioral Risk Factor Surveillance System, survivors of tobacco-related cancers had a smoking prevalence of 27% compared with 16% and 18% for other cancer survivors and those without a history of cancer, respectively.[6] Based on prospectively collected data from 772 individuals with cancer in the Cancer Prevention Study-II Nutrition Cohort, persistent smoking was observed in 68.7% and 57% of the cohort at 2- and 4-years post-

diagnosis, respectively.[7] One study revealed smoking prevalence to be highest among survivors of bladder, lung, and ovarian cancers.[8] Other studies have found high prevalence of continued smoking in survivors of cervical cancers.[9]

Health Care Community Response

Given the adverse health effects and prevalence of smoking in patients with cancer and survivors, several leading national organizations have called upon the oncology community for improved smoking cessation efforts. In 2013, the American Association for Cancer Research (AACR) released a policy statement calling for provision of evidence-based smoking cessation assistance to all patients with cancer, outlining the following objectives:

- "Universal assessment and documentation of tobacco use by cancer patients in all clinical settings;
- Development of universal standards for measurement of tobacco use and exposure in clinical and research settings;
- Incorporation of evidence-based tobacco interventions into review criteria used by research and health care quality and accreditation bodies; and
- Recognition and support of the value of tobacco cessation interventions by health systems, payers, and research funders through provision of appropriate incentives for infrastructure development and intervention delivery."[10]

Additionally, in a recent policy statement update, the American Society for Clinical Oncology (ASCO) called upon oncology professionals to treat tobacco dependence as aggressively and compassionately as cancer and to advocate for the wide availability of tobacco cessation services.[11]

However, despite general consensus on the importance of smoking cessation, particularly for patients with cancer, many cancer centers and oncology practices report that they fall short of providing consistent, high-quality smoking cessation services. In a survey of 58 National Cancer Institute (NCI)-designated cancer centers, 20% reported offering no smoking cessation services for their patients, 38% did not routinely provide tobacco education materials to patients, and only half reported that they effectively identified tobacco use in their patients.[12] The AACR Task Force on Tobacco and Cancer found that few cancer care institutions utilize systematic and consistent mechanisms to foster cessation among patients with cancer.[10]

Several studies have linked increased patient satisfaction to the delivery of smoking cessation advice or intervention.[13,14] Data from large surveys of oncologists practicing in academic medical centers, non-academic hospitals, and oncology practices depict generally high rates of smoking assessment and providing initial advice to quit.[15-18] However, smoking assessment rates were weaker outside of the academic/university setting (ie, for those practicing in a hospital-based, nonacademic, or private setting).[18] Regardless of work setting, only 30% to 44% of respondents reported discussing specific interventions or providing subsequent follow-up. Moreover, the majority of respondents report inadequate training and/or a lack of confidence in ability to provide effective smoking cessation counseling and intervention.[15-18] A dearth of smoking assessment and documentation has also been demonstrated in oncology trials.[19,20]

Issues regarding insurance coverage and provider reimbursement for smoking cessation assessment, counseling, and cessation aids have also presented a challenge for the oncology community in the past. However, implementation of the Affordable Care Act has led to changes designed to increase access to smoking cessation interventions.[21]

Barriers to Smoking Cessation in Oncology Patients

Although over 68.8% of current smokers in the United States express a desire to quit and 52.5% report making a quit attempt within the past year, only 6.2% report recent smoking cessation.[22] In the general population, individuals who smoke report a number of different barriers to quitting, including stress; dependence; home, work, and social environmental factors; and lack of resources and support for quitting.[23] Importantly, patients and providers in the oncology setting face additional life challenges that can amplify the magnitude of these barriers.

In a population-based analysis of individuals recently diagnosed with cancer who actively smoked, health professional-provided cessation counseling was provided to only 52% of individuals in the past 12 months.[24] Surveys of oncology providers have identified common themes among barriers to smoking cessation for patients with cancer. Inadequate provider training and lack of time are often cited by oncology providers as barriers to successful intervention.[16] Providers have also cited patient-related factors such as inability to quit, lack of motivation, or resistance to treatment.[15,16] However, pain, second-hand smoke exposure, guilt over smoking, fear of stigmatization, and fatalism regarding disease also represent obstacles unique to oncology patients, particularly those with advanced disease.[25-30]

Notably, clinical trial research on smoking cessation for patients with cancer is limited, particularly for patients thought to have non-tobacco-related cancers. Barriers that limit or prevent enrollment in smoking cessation trials include smoking rate, medical history, contraindicated medications, lack of interest, and language barriers.[31]

Given the complexity of smoking cessation interventions for patients with cancer, there is a great need for resources that provide guidance on smoking cessation specifically for this patient population. The inaugural NCCN Guidelines for Smoking Cessation have been created to establish a standard of care for smoking cessation in patients with cancer. The NCCN Guidelines panel has developed these guidelines in order to facilitate implementation of this standard, to allow for quality control monitoring, to fill a gap among existing treatment guidelines, and ultimately, to improve the health and outcomes for patients with cancer.

Literature Search Criteria and Guidelines Update Methodology

Prior to the development of this inaugural version of the NCCN Guidelines® for Smoking Cessation, an electronic search of the PubMed database was performed to obtain key literature in smoking cessation for patients with cancer, published from August 2014 through November 2015, using the following search terms: smoking cessation[Title/Abstract]) AND (cancer[Title/Abstract] OR oncology[Title/Abstract]. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[32]

The search results were narrowed by selecting studies in humans published in English. The PubMed search resulted in 216 citations and their potential relevance was examined. The data from key PubMed articles selected by the panel for review during the NCCN Guidelines update meeting as well as articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN webpage.

General Principles of the Smoking Cessation Guidelines

The recommendations in these guidelines apply to cessation of cigarette smoking for patients with cancer; however, the panel strongly recommends that patients also discontinue use of all combustible products, including cigars, hookah, marijuana, as well as smokeless tobacco products. Smoking cessation has health benefits even after a cancer diagnosis, regardless of stage or prognosis—namely improvement in cancer treatment outcomes, disease recurrence, and secondary cancers. Importantly, a diagnosis of cancer may present a teachable moment and valuable opportunity for providers to encourage smoking cessation.[7,33,34] It is the view of the NCCN Guidelines panel that it is never too late for patients with cancer at any stage to stop smoking cigarettes.

Because smokers with cancer often demonstrate high-level nicotine dependence, the panel recommends a multimodal approach to cessation therapy. The NCCN Panel recommends that treatment plans for all smokers with cancer include the following 3 tenets: evidence-based motivational strategies and behavior therapy (counseling), which can be brief; evidence-based pharmacotherapy; and 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 smoking cessation. The two most effective pharmacotherapies are combination nicotine replacement therapy (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.[35-38]

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 utilized.

The panel emphasizes that smoking relapse and brief slips are common. Providers should discuss this with patients and provide guidance and support to encourage continued smoking cessation attempts despite slips. 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.

Finally, smoking cessation interventions should be offered and continued throughout the oncology care continuum, including during end-of-life care. Emphasis on patient preferences and values is important when considering the best approach to fostering smoking cessation in that setting.

Smoking-Associated Risks for Patients with Cancer

Exposing cancer cells to cigarette smoke has been shown to promote a more malignant phenotype through its effects on angiogenesis and cell proliferation, migration, invasion, and survival. For a review of the preclinical data, see Sobus and Warren (2014).[39] These data have been corroborated by clinical studies. Per the Surgeon General's Report, *The Health Consequences of Smoking—50 Years of Progress*[2], sufficient evidence exists to support a causal relationship between smoking and adverse health outcomes, increased ACM and cancer-specific mortality, and increased risk for secondary primary cancers. Additionally, existing

evidence is suggestive of a link between smoking and increased risk of cancer recurrence, poor treatment response, and increased treatment-related toxicity.

NCCN recommends that providers should inform patients of the potential benefits of smoking cessation, including improved survival, treatment outcomes, and health-related quality of life, as well as decreased treatment-related toxicity, drug side effects, and surgical complications. Patients should receive education on the specific risks of smoking during treatment for their particular cancer and should be encouraged to stop smoking as far in advance as possible before initiating cancer treatment. Prior to initiating treatment, when making decisions regarding treatment selection, dosage, and timing of initiation, providers should consider patient smoking status and potential smoking-related effects.

Overall Survival and Mortality

Smoking has been linked not only to the development of disease in tobacco-related cancers, but also to prognosis upon diagnosis and risk of death during treatment. Evidence suggests that current smoking increases risk of death and negatively impacts survival for patients with cancer in a variety of disease sites, including bladder,[40-42] breast,[43,44] cervix,[45,46] colon/rectum,[47,48] endometrium,[49] esophagus,[50,51] head and neck,[52-54] kidney,[55,56] lung,[57-60] ovarian,[61] pancreas,[62] and prostate,[63] as well as hematologic malignancies.[64]

Prospective studies of smoking at cancer diagnosis offer insight into the negative effects of smoking on overall survival (OS), disease-specific mortality (DSM), and ACM. In the 2014 Surgeon General's report, a comprehensive review of the data assessing smoking and ACM in patients with cancer revealed that 87% of the studies (139/159) indicated increased risk, while 62% of all studies (99/159) demonstrated a statistically significant risk increase.[2] Additionally over half of the reviewed studies found at least a 50% increase in risk of death.[2] Additionally, among the studies examining OS in patients with cancer who smoke, 77% (48/62) were indicative of shortened survival, with 42% (26/62) revealing statistical significance.[2] Finally, smoking in patients with cancer was associated with higher DSM in 79% of studies reviewed (46/58), with a statistically significant link between cancer-related mortality and patients' smoking status in 59% (34/59).[2]

Risk of Recurrence or Secondary Primary Tumor

A number of studies have linked cigarette smoking and heightened risk of recurrence (ie, recurrent cancer in the same anatomic location as the original primary cancer). The 2014 Surgeon General's Report identified a positive association between smoking and risk of recurrence in 82% of the reviewed studies (42/51), with 53% of studies revealing significantly increased risk.[2] Among the studies that compared relative risk (RR) of recurrence between never smokers, former smokers, and current smokers, the median RR was 1.42 and 1.15 for current and former smokers, respectively.[2]

Disease sites with data linking current patient smoking to increased risk of recurrence include the anus,[65] bladder,[40,66,67] breast,[68] lung,[57] stomach,[69] and prostate.[63,70-72]

Studies have also examined the impact of continued smoking in patients with cancer on the risk of second primary tumor formation. The 2014 Surgeon General's Report identified a positive association between smoking and risk of second primary tumor in all studies examined (n = 26). The association was strongest when considering the effects of smoking on RR of developing a smoking-related second primary cancer (eg, lung cancer). Among 5 studies classifying smoking status into "never," "former," and "current," the median elevated RR of a

second primary tumor was 1.20 and 2.20 for former and current smokers, respectively. Data from a large retrospective series and pooled data analyses have continued to provide support for smoking and increased risk of second primary malignancy, especially smoking-associated cancers.[73,74] Additionally, data also suggest that smoking interacts synergistically with radiation therapy (RT) to elevate the risk of second primary cancers.[2,75,76]

Smoking-Related Effects on Treatment Efficacy, Side Effects, and Outcomes

A majority of the existing data establishes and supports the detrimental impact of persistent smoking during cancer treatment. In a 2014 report from the Surgeon General, 80% of the evaluated studies (66/82) demonstrated a statistically significant association between active smoking and increased anticancer treatment-related toxicity.[2] Smoking has implications across the spectrum of cancer treatment, including surgical outcomes, RT efficacy and toxicity, chemotherapy metabolism and side effects, and overall symptom burden. This discussion also addresses the developing evidence base for the benefits of smoking cessation after receiving a cancer diagnosis.

Smoking-Associated Risks

Surgery

Smoking has been shown to negatively impact outcomes from cancer surgery, affecting postoperative complications, quality of life, length of hospital stay, and mortality risk.

In lung cancer, studies show that smoking impacts the success of surgical resection, decreases postoperative quality of life, and increases persistent dyspnea and thoracic pain at 12 months postoperatively.[77,78] Analysis of data from 7990 patients who had primary resections for lung cancer (Society of Thoracic Surgeons General Thoracic Surgery Database) revealed increased risk of hospital death and pulmonary complications associated with smoking.[79]

The adverse effects of smoking on postoperative outcomes was examined in more than 20,000 patients with gastrointestinal (n = 12,432), lung (n = 4490), and urinary tract cancers (n = 3491) using the Veteran's Health Administration Surgical Quality Improvement Program (VASQIP) database for 2002 through 2008.[80] Surgical complications examined included surgical site infections, vascular complications (venous thromboembolism, stroke/cerebrovascular accident, myocardial infarction), and composite pulmonary outcomes (CPO: pneumonia, failure to wean from ventilator >48 hours or re-intubation for cardio-respiratory failure). Across all three cohorts, never smokers had fewer complications than former and current smokers. Compared with prior smokers, current smokers in the gastrointestinal cancer cohort had higher postoperative rates of pneumonia, failure to wean from ventilator, reintubation, and CPO. In the lung cancer cohort, current smokers had higher rates of pneumonia, failure to wean from the ventilator, reintubation, CPO, and return to surgery compared with former smokers. Current smoking status was associated with an increased length of hospital stay across all cancer sites when compared with never smokers; never smokers and prior smokers did not differ on this measure.

Postsurgical outcomes (ie, incisional infections, infectious and major complications, and mortality at 30 days) were compared between cohorts of never smokers, former smokers, and current smokers using data from over 26,000 patients with colorectal cancer in the American College of Surgeon's National Surgical Quality Improvement Program database (2005–2010). Postoperative morbidity and mortality rates were higher among current smokers and a significant dose-dependent

effect was observed when stratifying risk of major complications by pack-years of smoking.[81]

In patients undergoing hematopoietic stem cell transplantation to treat acute leukemias, pulmonary complications and longer postoperative hospital stays were more commonly observed in patients who smoked.[82]

Smoking can also impair wound healing and predispose patients to surgical complications for those undergoing reconstructive surgeries after cancer treatment. Among patients with breast cancer who underwent transverse rectus abdominis myocutaneous (TRAM) flap breast reconstruction surgery, smoking was associated with significantly higher risk of flap complications and delayed healing,[83,84] and evidence suggested that complication risk was reduced by smoking cessation of at least 4 weeks prior to surgery.[83] In patients with stage III or IV squamous cell carcinoma of the head and neck, serum cotinine concentration was dose-dependently linked to increased risk of wound complications following reconstructive head and neck surgery.[85]

Radiation

Studies have shown that prior smoking and active smoking during RT may decrease treatment response and increase complication rates, particularly for patients with head and neck cancers, but also in cervical, lung, breast, or prostate cancers.

In patients with head and neck cancer receiving RT, current smokers had poorer rates of locoregional control.[53,86] In another cohort, patients with head and neck cancer who continued to smoke during RT had lower rates of complete response and worse survival times than nonsmokers or those who quit prior to treatment.[87] Continued smoking during RT in patients with head and neck cancer has also been shown to increase the rates of treatment-related complications. In patients with laryngopharyngeal cancers, smoking during treatment was associated with significantly elevated incidence of osteoradionecrosis and hospitalization during treatment.[88] Another study demonstrated a significantly greater decline in several health-related quality-of-life measures in patients who continued to smoke during therapy compared with patients who quit beforehand.[89]

Among 3,489 patients receiving RT as part of treatment for stage I or II cervical cancer, heavy smoking (defined as at least 1 pack/day) was the strongest independent factor in predicting long-term major bladder, rectal, or small bowel complications, with even light/moderate smoking (less than 1 pack/day) predisposing patients to small bowel complications.[90] In another study of 565 patients with cervical cancer who were receiving primary RT, patients who smoked during treatment had lower cure rates, higher frequency of RT side effects, and higher rates of severe, irreversible complications.[91]

Smoking during RT for non-small-cell lung cancer was associated with significantly decreased locoregional control.[92] Active smoking may also decrease the efficacy of RT for prostate cancers and increase the prevalence of long-lasting treatment related effects on the bowel and anal sphincter.[93-95] Concurrent smoking and RT increased the risk of cardiovascular disease in 4414 10-year survivors of breast cancer.[96]

Chemotherapy/Systemic Therapy

Data on the impact of smoking on chemotherapy are much more limited than that for surgery and RT, in part because smoking quantity during treatment is often left out of the medical record.[19] Many of the purported effects of smoking during chemotherapy are extrapolated from what is known about the impact of chemotherapy and smoking as individual factors of health. Smoking has the potential to exacerbate the risk of

anticancer drug-related pulmonary and cardiac toxicities such as cardiomyopathy and pulmonary fibrosis.[97] Combining neoplastic agents with radiation while smoking may lead to further toxicity. Additionally, cancer drug side effects such as weight loss, cachexia, and fatigue may also be increased by smoking during treatment.[97,98]

Many systemic anticancer agents result in some degree of immune suppression/compromise, and smoking during chemotherapy may further compromise immune function in an already vulnerable patient population.[19,97] Preclinical and clinical studies suggest that smoking and nicotine exposure can be detrimental to the function of both the adaptive[99-102] and innate immune system.[103-107] Similarly, cigarette smoking may increase the incidence of infection, particularly for smoking-related infectious diseases such as pneumonia and influenza.[108]

Preclinical studies also suggest a potential link between nicotine exposure from smoking and the development of chemoresistance, [109-113] although no clinical data are currently available to support these findings.

Smoking can also impact the metabolism of certain cytotoxic chemotherapies and other systemic therapy. Smoking effects on cytochrome P450 enzymes may alter drug clearance time and plasma concentration, potentially impacting the efficacy of certain drugs for patients who smoke.[114] Providers should consider whether patients are at risk for altered drug metabolism due to smoking and determine if medication or dose adjustments may be required.

Drugs with metabolisms that are known to be affected include erlotinib and irinotecan. Rapid drug clearance has been observed in smokers who were receiving erlotinib therapy, such that higher doses may be required to achieve equivalent systemic exposure to standard dosing in nonsmokers.[115,116] Similarly, smoking increases the clearance time of irinotecan, potentially lessening systemic exposure.[115,117] Given the narrow therapeutic index of systemic therapy for lung cancer, small changes in drug exposure due to smoking could affect treatment efficacy and patient outcomes.[115] Bendamustine metabolism is also likely to be impacted by smoking, resulting in decreased drug plasma concentration and increased concentration of its active metabolites.[118,119] However, smoking does not appear to alter the pharmacokinetic properties of taxane chemotherapeutics (eg, docetaxel, paclitaxel) despite its paradoxical protective effects on drug-induced neutropenia and leukopenia.[120]

Symptom Burden

In a study of 947 patients who were undergoing chemotherapy and/or RT, smoking during treatment was linked to a higher overall burden of symptoms commonly experienced among patients with cancer. In analyses that controlled for age, gender, race, education, occupation, treatment, cancer site, and Karnofsky performance score, current smokers had a significantly higher symptom burden compared with nonsmokers, both during treatment and 6-months afterwards.[121] Active smoking in patients with advanced lung cancer was associated with greater symptom burden on diagnosis and poorer health-related quality of life post-diagnosis. [122] Additional studies suggest that current smokers with cancer may experience more severe or frequent pain than nonsmoking counterparts.[123-126]

Benefits of Smoking Cessation for Patients with a Cancer Diagnosis

For many smokers, the benefits of smoking cessation can be appreciated immediately through reduced blood carbon monoxide levels, decreased irritative respiratory symptoms (eg, cough, shortness of breath), and improved lung function. In the long term, cessation is

associated with reduced risk of smoking-related disease, development of malignancy, and smoking-related mortality.[127] Although the deleterious effects of smoking after a cancer diagnosis are well documented and understood, research on the benefits of cessation post-diagnosis is much more limited.[10,128] For patients with cancer, the potential benefits and risk reductions associated with cessation are of critical importance.

Studies have begun to assess the impact of smoking cessation at or near the time of a cancer diagnosis by comparing outcomes of patients who continue to smoke during cancer treatment to those who quit prior to treatment ("recent quitters"). Studies generally show that recent quitters have survival outcomes intermediate to that of never-smokers and current-smokers, suggesting a measurable benefit of cessation post-diagnosis. The data to support this survival pattern are derived primarily from cohorts of patients with lung or head and neck cancers,[57,59,87,129-131] but similar patterns have been observed for other disease sites.[59,132]

A prospective longitudinal study examined the impact of smoking at diagnosis in 5185 patients with cancer across 13 disease sites over the course of at least 12 years.[59] In this study, recent quitters were examined as a specific subset of former smokers who quit within 1 year of the study's structured smoking assessment, allowing for comparisons to individuals who actively smoked during cancer treatment. For disease sites with larger recent quit cohorts (ie, lung, head /neck cancers), recent quitters had lower overall mortality risk compared with continued smokers (current smoker vs. recent quitter: lung cancer HR = 1.38–1.42; head/neck cancer HR = 2.11–2.15).[59] Similarly, a systematic review and meta-analysis of 10 observational studies pointed to a 5-year survival benefit for patients with lung cancer who quit smoking compared to patients who continued smoking (70% vs. 33%).[57] In a comprehensive cancer center study that controlled for disease characteristics, smoking history, and patient demographics, 250 patients with lung cancer who quit smoking had statistically improved survival time of 9 months over those who continued to smoke through treatment and beyond.[133]

Smoking cessation is linked to reduced risk of recurrence and second primary tumor formation. Data from patients with lung and head and neck cancers showed that rates of second primary cancers were lower for patients who quit smoking than for those who continued to smoke after diagnosis.[130,134,135] In a cohort of patients with colon cancer, active smokers were at significantly greater risk for baseline metastasis, but interestingly, rates among former smokers and never smokers were similar and significantly less in comparison.[136]

Cessation at or near cancer diagnosis appears to reduce treatment-related complications compared to patients who continued smoking. In patients undergoing lung cancer resection, preoperative cessation mitigated the risk of pulmonary complications and in-hospital mortality. Risk-adjusted odds ratios for mortality and pulmonary complications decreased as preoperative cessation time increased from 14 days to 1 month, to 1 to 12 months, and to more than 12 months.[79] A retrospective study of 188 patients undergoing reconstructive surgery after treatment for head and neck cancer revealed that preoperative smoking cessation of at least 3 weeks led to lower incidence of wound healing complications than patients who continued smoking.[137]

Cessation has been shown to lead to improvements in various measures of general health and wellbeing for patients with cancer. Smoking cessation improved performance status at 6 and 12 months post-lung cancer diagnosis over that of continued smokers when adjusting for disease stage, patient demographics, therapy, and

comorbidity.[138] Additionally, patients with cancer who quit smoking benefited from lower rates of smoking-related cardiovascular and pulmonary disease.[139]

Evaluation and Assessment of Patient Smoking

These guidelines highlight the importance of evaluating and assessing smoking status and history in patients with cancer. In a recent policy statement, the AACR emphasized 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.[10] The NCI-AACR Cancer Patient Tobacco Use Assessment Task Force recently published proposed core and extension items to be used for the assessment of tobacco use in patients with cancer enrolled in research trials.[140] However, 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 clinical trials.[12,20]

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).[19,20] 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 a comprehensive cancer center, a smoking assessment questionnaire was integrated into the electronic health record (EHR) in order to automatically identify and refer appropriate candidates for onsite cessation services. The smoking assessment items incorporated into the EHR 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/what other types of tobacco products were used. For former smokers, 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 employed.[141] The study revealed that just 3 assessment questions made it possible to efficiently and accurately identify the vast majority (over 98%) of current smokers or those at risk for smoking relapse.

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. To do so, the panel recommends the providers initially ascertain: 1) whether the patient has ever smoked, and if so, then initially and at regular intervals; 2) whether the patient is a current smoker; and 3) whether the patient has smoked within the past 30 days. All information 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 current smokers (patient smoked within the last 30 days) and recent quitters/former smokers (greater than 30 days since patient last smoked) are included. For never smokers or longer-term former smokers, providers should urge patients to remain smoke-free, providing them with the benefits for remaining smoke-free.

Assessing Smokers

In patients who are current smokers (or those who have smoked in the last 30 days), providers should assess nicotine dependency to understand the chances for success and risk of relapse, and document the findings in the patient’s health record. To assess nicotine

dependency, providers should query patients regarding the amount of cigarettes smoked per day, how soon the patient smokes after waking up in the morning, whether the patient uses other forms of tobacco (eg, pipes, cigars, snuff, e-cigarettes), and if so, what quantity. The Fagerstrom Test for Nicotine Dependence is an alternative standardized tool for assessing nicotine dependence.[142] However, the panel has opted to recommend a more streamlined assessment for use in the oncology setting.

In order to best tailor treatment, providers should also gather information regarding the patient's history of quit attempts and why they were or weren't successful. Specifically, providers should ascertain the longest period of abstinence achieved, the date of the most recent quit attempt, what cessation aids were employed, 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; quit-lines, websites, smart phone applications, or other media aids; etc. The patient's perspective on why these aids were unsuccessful—such as medication side effects, continued cravings, or inefficacy—are important pieces of information.

Patient readiness to quit within the next month should be determined. Providers are encouraged to engage patients in a motivation dialog about smoking and to ensure patients are aware of the disease-specific risks of smoking and benefits of quitting. Educational resources should be provided. The panel recommends that clinicians provide patients with reasons, ideas, and needs 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, 3) roll with resistance, and 4) support self-efficacy.[143,144] For a summary of the methods and data on MI for smoking cessation, see the *Principles of Behavior Therapy* section below.

If patients are not ready to quit within the next month, 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 and/or consider smoking reduction with the goal of cessation in the near future. The panel encourages immediate initiation of pharmacotherapy for targeted smoking reduction with a goal of cessation in the near future. A meta-analysis of 10 randomized trials in 3760 patients with cancer found quit rates to be comparable when comparing abrupt cessation to gradual smoking reduction.[145,146] 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.[147] At each visit, providers should reassess readiness to quit and engage in motivational dialog as indicated.

Assessing Former Smokers/Recent Quitters

To evaluate patients who recently quit at least 30 days prior, providers should assess and document the patient's risk of relapse. The panel suggests the following characteristics to identify patients at high risk for relapse: frequent/intense cravings; elevated anxiety, stress, or depression; cohabitating or working with smokers; quitting within the past year; use of ongoing smoking cessation treatment; and drug/alcohol use or abuse. 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, refer patients with anxiety and/or depression to a specialist to manage psychiatric comorbidities.

Management of patients who demonstrate an elevated risk of relapse includes behavior therapy with counseling on relapse risk factors and relapse prevention. Short-acting NRT can be considered to promote maintenance of abstinence. Providers should review smoking-associated risks for patients with cancer as well as 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. Risk of relapse should be reevaluated at subsequent visits.

It is important to regularly reevaluate patients' smoking status and risk of relapse, which can be accomplished in person or by phone. If relapse occurs, patients should be evaluated per the recommendations for current smokers. Additionally, providers should remain aware that patient self-report of smoking status may underestimate the rate of active smoking among patients with cancer, as is evidenced by research comparing self-reported and objective measures.[148-150] Patients who remain smoke free should regularly undergo reevaluation with documentation of any risk factor changes.

Smoking Cessation During Cancer Treatment

Devising a Treatment Plan

Following assessments, providers should establish a personalized quit plan for each patient that takes into account the patient's nicotine dependency, prior quit attempts and any cessation aids used, and smoking cessation therapy options. Providers should work with patients to set a quit date as soon as possible. Risk of relapse and smoking slips should be discussed with the patient along with reassurance and support for continued cessation efforts should slips occur.

Smoking Cessation and Cancer Surgery

Smoking has been shown to increase the risk of pulmonary complications, surgical site infection, and poor wound healing in patients undergoing surgery. For an overview of the data, see section on *Smoking-Related Effects on Treatment Efficacy, Side Effects, and Outcomes* in this Discussion. Study findings generally support the benefits of preoperative smoking cessation, which has been shown to reduce postoperative morbidity in patients undergoing surgery for various cancer types.[79,151,152]

For patients with planned cancer surgery, cessation should occur as far in advance as is feasible. Although longer periods of preoperative smoking cessation may confer better surgical outcomes,[153] the panel emphasizes that patient smoking should not delay appropriate timing for cancer resection, and access to cancer surgery should not be restricted based on smoking status. Preoperative smoking cessation interventions that combine pharmacotherapy with behavioral therapy may be most effective.[154-157] NRT at the normal doses has not been shown to negatively affect acute wound healing,[158-160] and therefore functions as a valuable adjunct to perioperative smoking cessation.

Elective procedures, such as plastic surgery reconstruction, may benefit from delaying surgery for a period of time after smoking cessation. At this time, consensus on an optimal time period of preoperative cessation has not been demonstrated through the existing literature.[153] Providing surgery-specific resources and advice for smoking cessation may facilitate smoking reduction or cessation in patients undergoing elective (non-cancer) surgery.[161,162]

Preferred Primary Therapy Options

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.[163-165]

Preferred primary therapy options in these guidelines are 1) combination NRT (combined long- and short-acting NRT); or 2) varenicline (typical initial duration of 12 weeks). The combination NRT approach includes the use of nicotine patch plus a short-acting NRT (eg, for break-through craving) such as nicotine gum, lozenge, inhaler, or nasal spray. As a general principle, the panel recommends trying both preferred primary therapy approaches (combination NRT and varenicline) before proceeding to any of the subsequent pharmacotherapy options. See section below on *Treatment for Persistent Smoking or Relapse* for additional details. Pharmacotherapy regimens should always be paired with behavioral counseling.

Providers should note that nausea is a common side effect of varenicline and may need to be managed in patients with cancer who are receiving chemotherapy. Additionally, varenicline (and bupropion) should be avoided in patients with brain metastases due to increased seizure risk. For discussion of the evidence for individual pharmacotherapeutic regimens, see section below on *Principles of Pharmacotherapy*.

Follow-up

Assessment of smoking status and toxicity of pharmacotherapy should be performed within 2-3 weeks of initiating therapy and on a periodic basis moving forward, but no more than 12-week intervals, including within about 12 weeks following completion of pharmacotherapy. Nicotine withdrawal symptoms typically peak within 1 to 2 weeks of cessation before subsiding. Initial follow-up within 2 weeks of initiating smoking cessation therapy is important in order to assess efficacy and toxicity of pharmacotherapy. Providers should encourage continued treatment adherence through brief slips, with adjustments to dose or behavior therapy frequency as indicated. Undesirable side 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 health care team during oncology visits. Alternatives include phone contact. During follow-up, providers should assess risk of relapse and, as indicated, consider adjusting the dose and or type of pharmacotherapeutic. 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. For pharmacotherapy courses exceeding 12 weeks duration, assessment should be repeated at the end of the course of therapy.

If patients remain smoke free, additional follow-up should take place at 6 and 12 months, either in person or by phone. Motivational strategies should be employed to promote continued abstinence. Patients who experience smoking relapse can be considered for second-line therapy.

Treatment for Persistent Smoking or Relapse

For patients who continue to smoke or experience relapse, the panel recommends continuation of initial pharmacotherapy or switching to the alternate preferred option (combination NRT or varenicline). Regimens should always be paired with continued behavior therapy. Both preferred primary therapy approaches (combination NRT and

varenicline) should be tried before proceeding to any of the subsequent pharmacotherapy options.

Subsequent options for pharmacotherapy include combination NRT with bupropion or bupropion alone (category 2B). Bupropion should be avoided in patients with brain metastases due to increased seizure risk. For further relapse, extended duration of pharmacotherapy can be considered. Additional or more intensive behavior therapy is also an option.

After switching therapy or adjusting the dose of an existing regimen, follow-up should occur within 2 weeks, after 12 weeks, and at the end of therapy if extended beyond that point. Smoking status should be re-evaluated at the end of each course of prescribed pharmacotherapy, with additional follow-up at 6 and 12 months after successful quitting.

Principles of Pharmacotherapy

General

A minimum of 12 weeks of combination NRT or varenicline is recommended for the initial quit attempt. Duration of therapy can be extended to promote continued cessation, but providers should attempt to avoid unnecessarily long treatment duration when possible. Research suggests that longer courses of certain cessation regimens may be associated with higher rates of 7-day point-prevalence abstinence.[166]

Follow-up is recommended 2 weeks after starting pharmacotherapy but can be extended to 3 weeks to coordinate with scheduled oncology appointments. For relapse or continued 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 cessation medications are minimal and are considered an acceptable risk compared to smoking. A review of post-marketing case reports on adverse neuropsychiatric effects from smoking cessation medications have generated some safety concerns in the past,[167] but recent large-scale analyses of the data support the safety of these regimens.[168,169] Although serious side effects of primary cessation 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 and improve medication adherence.[170]

Below, data from various clinical trials are discussed. Included in this discussion are findings from a 2013 Cochrane network meta-analysis that included data on pharmacologic interventions across 267 individual studies in 101,804 participants.[171] The authors characterized positive treatment outcome as continuous or prolonged abstinence at least 6 months from the start of smoking cessation therapy. Harm outcomes were measured by the incidence of serious adverse events associated with treatment.

Primary Therapy Options

For patients with cancer, the guidelines recommend primary therapy with either combination NRT or varenicline. If smoking persists 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 should be used before trying any subsequent therapy options. The efficacy and safety data on preferred primary regimens are summarized below.

Combination Nicotine Replacement Therapy

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 fast-acting NRT offers the greatest potential benefits for smokers.[154,171-173] Cochrane network meta-analysis data published in 2013 support the superiority of combination NRT over single forms of NRT such as nicotine patch (odds ratio [OR] 1.43; 95% confidence interval [CI], 1.08–1.91), nicotine gum (OR 1.63; 95% CI, 1.21–2.2), and various other forms that collectively include inhaler, lozenge, spray, or tablets (OR 1.34; 95% CI, 1.0–1.8).[171] All forms of NRT were superior to placebo, but smokers using combination NRT were almost three times as likely to succeed (OR 2.73; 95% CI, 2.07–3.65).[171] Compared with single forms of NRT, combination NRT using a patch plus short-acting NRT improved the odds of quitting (OR 1.34; 95% CI, 1.18–1.51).[171,174]

The success of NRT may be contingent on 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. The addition of behavior therapy to NRT increased the odds of success nearly three-fold.[163]

Safety

The safety of combination NRT for use in humans has been demonstrated and benefits are considered to outweigh potential risks.[175] Importantly, providers should be aware that blood nicotine levels from NRT, including combination NRT, are significantly less than that from smoking cigarettes.[176-178] Therefore, providers and smokers should not be dissuaded from using NRT to foster quitting and long-term cessation. Recent reviews of the data suggest that NRT is not linked to increased serious cardiovascular adverse events when used for smoking cessation.[179] While myocardial infarction has rarely been reported in NRT users, there is insufficient evidence that NRT increases the risk of myocardial infarction or cardiovascular disease.[174,180] Data from large case series have not shown elevated risk with the use of NRT in patients with acute coronary syndromes.[181,182]

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.[183] Some *in vitro* data suggested that nicotine increased the malignant potential of small cell lung cancer cells[184]; induced chemoresistance in models using lung cancer cells[109-111] and nasal epithelial cells[112]; and promoted chemoresistance and metastasis in pancreatic cancer cell and mouse models.[113] However, other studies suggested no effects of physiological levels nicotine exposure on tumorigenesis in mouse lung cancer models.[185,186] Moreover, there is insufficient evidence that NRT causes cancer in humans.[185-189] Evaluation of data from 3320 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.[188]

Varenicline

Efficacy

Varenicline is a non-nicotinic partial agonist of the alpha4beta2 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.[190]

Systematic reviews/meta-analyses have identified varenicline as the most effective single pharmacotherapy option for smoking cessation.[171,191,192] Cochrane network meta-analysis data report that varenicline increases the odds of smoking cessation by almost three-fold compared with placebo (OR 2.88; 95% CI, 2.40–3.47).[171] 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).[171] 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.[171]

Results recently published from the double-blind EAGLES RCT (n = 8144) revealed that varenicline-treated patients achieved higher abstinence rates than patients receiving placebo (OR 3.61; 95% CI, 3.07–4.24), nicotine patch (OR 1.68; 95% CI, 1.46–1.93), and bupropion (OR 1.75, 95% CI, 1.52–2.01).[193] A recent study investigated the efficacy of varenicline specifically for patients with cancer, revealing 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 affect over time.[194]

Varenicline may also be efficacious for smoking reduction. A clinical trial enrolling 1510 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.[195] Therefore, this agent provides an alternative for patients who cannot or will not attempt abrupt cessation. A clinical trial in 1236 smokers showed that an additional 12 weeks of varenicline maintenance therapy helped to sustain continued abstinence in those who successfully quit during initial treatment.[196]

One study examined whether varenicline dose increases would boost treatment efficacy in patients who had a low or no response to standard dosing. A double-blind, randomized controlled trial (RCT) of 503 smokers found no evidence to suggest that gradual dose titration beyond the standard 2-mg dose (up to a maximum 5 mg/d) lessened frequency of urges and nicotine withdrawal symptoms, or increased cessation rates.[197] However, nausea and vomiting were increased in the treatment group receiving more than 2 mg/d. Additionally, another RCT showed that varenicline was effective and well-tolerated for retreating patients who had previously received this agent (n = 498).[198]

A recent RCT (n = 1246) examined whether a biomarker of nicotine clearance (nicotine metabolite ratio, NMR) was predictive of nicotine patch versus varenicline efficacy in "slow" versus "normal" metabolizers of nicotine. The findings showed that varenicline was more effective than nicotine patch in normal metabolizers, but varenicline superiority was not observed among slow metabolizers, suggesting the possibility in the future to optimize treatment selection based on this biomarker.[199]

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% to 29%, 14%, and 10% to 13%, respectively.[200,201]

Concerns regarding neuropsychiatric adverse effects of varenicline have been extensively investigated in smokers with comorbid mental illness.[171] Despite reviews of case reports that raised concern,[167] 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.[169] Another trial showed that varenicline increased smoking cessation rates without exacerbating anxiety and depression symptoms in adults with stably treated current or past depression.[202] Results were recently published from a large double-blind RCT (EAGLES trial) that enrolled 2 cohorts: individuals with psychiatric disorders (n = 4116) and those without psychiatric disorders (n = 4028). No significant increase in neuropsychiatric events was observed for varenicline relative to nicotine patch or placebo. Varenicline was associated with significantly higher abstinence rates than bupropion plus nicotine patch, as well as placebo.[193]

Cardiovascular risks have also been examined. Importantly, recent systematic reviews and meta-analyses of RCT data have not identified a significant link between varenicline and increased risk of serious cardiovascular adverse events.[171,179,203,204] However, the cardiovascular safety of varenicline has remained a topic of interest and concern.[205-207]

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 = 6557), neither varenicline nor bupropion posed an elevated risk of cardiovascular or neuropsychiatric (depression, self-harm) events compared with NRT.[208] 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 is a concern with varenicline therapy.[209,210] In patients with brain metastases who have a history or elevated risk of seizure, varenicline should be avoided.

Subsequent Therapy Options

Recommended subsequent therapy options in these guidelines include combination NRT with bupropion or bupropion alone (category 2B). Currently, other regimens are not recommended in this treatment setting. However, the panel acknowledges ongoing evaluation of alternative regimens (eg, varenicline plus combination NRT, varenicline plus bupropion, nortriptyline, or clonidine). The panel regularly reviews the evidence base for alternative regimens when updating these guidelines. The data for various regimens are summarized below.

Recommended Regimens

Bupropion + NRT

A large trial in the United Kingdom (n = 1071) examined the efficacy of NRT alone, bupropion alone, and NRT plus bupropion.[211] All participants received 7 weeks of behavior therapy support in addition to the pharmacologic interventions. Abstinence rates at 6-months 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 ($\chi^2 = 2.86$, $P = .091$).

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.[212] 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.[213] A 2014 meta-analysis of 12 trials examining this combination revealed a nonsignificant trend in improved cessation with the addition of NRT to bupropion.[214]

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 acetylcholingeric receptors. A 2014 Cochrane review of 44 trials examined bupropion efficacy, revealing an RR of 1.62 (95% CI, 1.49–1.76).[214] Recent results from the EAGLES trial (n = 8144) revealed that patients receiving bupropion achieved superior abstinence rates compared with placebo (OR 2.07; 95% CI, 1.75–2.45).[193] Efficacy was similar to 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.[211,215] Additionally, longer duration of bupropion treatment may help to prevent relapse in those who have successfully quit.[216]

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.[214] In patients with brain metastases who have a history or elevated risk of seizure, bupropion should be avoided.

Neuropsychiatric effects have also been identified as a safety concern with bupropion, although to a lesser extent than varenicline.[167] However, recent 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.[171,217] In the EAGLES trial, no significant increase in neuropsychiatric events was observed for bupropion relative to nicotine patch or placebo.[193]

Similarly, regarding risk of serious adverse cardiovascular effects, recent meta-analyses do not show elevated risk as a result of bupropion use for smoking cessation.[171,179,214]

Other Regimens

Several other pharmacotherapy regimens for smoking cessation have been studied in clinical trials but are not recommended by the panel at this time based on the existing data. Data from these studies are summarized below for information purposes.

Varenicline + NRT

A study in 435 smokers found that the addition of nicotine patch to varenicline therapy significantly increased the cessation rates at the end of treatment (12 weeks), 24 weeks, and at 6-month follow-up.[218] 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 smokers did not find enhanced cessation rates at 12 and 24 weeks follow-up among individuals receiving a combination of varenicline and nicotine patch, versus varenicline alone.[219] 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 NRT to

varenicline increased abstinence rates at 1, 4, or 12 weeks after the targeted quit date, and no between-group differences in adverse effects were found.[220]

Varenicline + Bupropion

In an RCT of smokers 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.[221] This observation was more pronounced among male smokers and those with a high level of nicotine dependency. Although no significant differences in side effects were observed between varenicline and 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. Another study of varenicline plus bupropion therapy versus varenicline alone (n = 316) demonstrated that combination therapy increased prolonged abstinence but did not affect 7-day point prevalence at 12 and 26 weeks follow-up, and no significant differences were observed between the groups at 52 weeks.[222] 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.

Nortriptyline and Clonidine

Studies have also suggested some efficacy of off-label use of nortriptyline, a tricyclic antidepressant, as well as the antihypertensive agent clonidine.

A Cochrane network review identified 6 trials comparing nortriptyline with placebo, finding a pooled RR of 2.03 (95% CI, 1.48–2.78).[102,133] However, as an adjunct to NRT, clear cut benefits were not observed.[171,223]

Clonidine is recommended as a third-line smoking cessation option. Although several studies have produced data in favor of clonidine as a cessation aid versus placebo, not all study data reveal a statistically significant effect. Additionally, clonidine's benefits can be counteracted by dose dependent increases in drug side effects. A 2013 Cochrane network review of data from 6 studies resulted in a pooled RR of 1.63 (95% CI, 1.22–2.18).[102]

Principles of Behavior Therapy

General Principles

The 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.[164,165,175]

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.[13,14] A 2012 systematic review of 41 studies provided support for the efficacy of this approach.[164] 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.[163] Additionally, a 2016 meta-analysis of data from 1239 patients with head and neck cancer showed improved smoking cessation rates with the addition of counseling to usual care (NRT).[224]

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 motivational and behavior strategies for smoking cessation.

As a general principle, more intensive behavior therapy is preferred over brief advice or counseling.[165] The evidence supports a measurable dose-response effect of behavior therapy with more numerous and/or longer sessions delivering improved outcomes. The panel defines intensive behavioral therapy as at least 4 sessions within 12 weeks (in person; group or individual) lasting at least 10 minutes but typically 30 minutes or longer. As patients progress through multiple lines of pharmacotherapy, behavior therapy should be progressively intensified with referral to specialty care (eg, psychiatrist, psychologist) as indicated. Studies have also demonstrated additional benefit for relapse prevention of extending behavioral therapy for six months or more.[225-227] Importantly, if intensive therapy is not feasible, brief counseling should still be given. Studies have demonstrated a small but significant benefit of counseling lasting only a few minutes.[35-38]

The most successful behavior therapy strategies employ practical counseling, which addresses problem solving and skills training, as well as social support and MI (see section on *Motivational Interviewing* below) as elements of the treatment plan.[144,175] Optimally, behavior therapy plans should take into account a patient's nicotine dependence levels, previous quit attempts, and cessation aids utilized. In doing so, patients can be equipped with tailored strategies to cope with nicotine withdrawal symptoms, environmental smoking triggers, and stressful situations. For instance, the addition of a cognitive behavior therapy program designed to improve stress management improved cessation rates over controls receiving standard smoking cessation therapy.[228]

Providers should prepare patients for nicotine withdrawal symptoms, which typically peak at several days to 2 weeks post-cessation before gradually subsiding.[229-231]

A number of modalities can be employed to deliver behavior therapy to patients. Counseling can take place in a variety of settings such as in person, remotely by telephone,[232] or through web-based interventions.[233] Effective in-person counseling can occur as an individual session or in the group therapy setting.[234,235] Additionally, print materials[236] and mobile telephone "apps"[237-239] can be used to deliver behavior therapy. However, providers should be aware that media-based behavioral interventions, particularly those using mobile telephones, may vary in the degree to which they comply with clinical practice guidelines.[240]

A recent study investigated preferences for the provision of smoking cessation information among Canadian patients with cancer. 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%). Younger patients (≤45 years) were more likely to prefer cessation advice via telephone, while older patients preferred print materials.[241] Selection of a particular modality or modalities should be guided by patient preference, medical history, and resource availability.

For patients who are unable to quit, referral to a smoking cessation clinic 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.[35-37] Additionally, quitlines can provide essential behavioral support in the absence of in-person counseling resources.[232] For instance, the addition of combination NRT to quitline counseling improved cessation outcomes.[242]

Tailoring Behavior Therapy for Patients with Cancer

As resources allow, specialized treatment centers should provide tailored smoking cessation therapy programs that address the unique needs of patients with cancer. For patients in active cancer treatment, behavior therapy can be provided during scheduled oncology visits to obviate the need for additional appointments. 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.

The prevalence of mental disorders or serious emotional issues in patients with cancer is high, with several large studies reporting rates between 30% and 40%.[243-245] 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. 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 to specialized smoking cessation programs may be necessary so that these patients have access to staff trained to treat co-morbid substance dependence and mental health disorders.

Motivational Interviewing

MI is beneficial for all patients, including those who are currently ambivalent or unwilling to quit. MI is typically performed by a provider trained in strategic questioning and listening, and uses a series of directive and nondirective approaches.[143,144] Through this approach to counseling, the provider seeks to understand the patient's values (eg, health, parenting, fitness) and highlights discrepancies between these values and continued smoking. Direct advice is given but is tied specifically to the patient's previously-stated values and supports the patient's autonomy to decide whether or not they want to quit. In MI, self-efficacy is emphasized by asking about and acknowledging the patient's strengths to make change.

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.[246] 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 less than 20 minutes had demonstrated efficacy.[246] A recent systematic review summarized the evidence to support MI for behavioral change, including smoking cessation, in patients with cancer.[247]

In order to promote willingness to quit smoking, the US Preventive Services Task Force (USPSTF) recommends a model of MI that employs the "5 R's" of relevance, risks, rewards, roadblocks, and repetition.[175] 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 alternative smoking cessation treatment approaches. Particular attention has been paid to the discussion of e-cigarettes for smoking cessation given increasing popularity and widespread use. 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 support the use of alternative therapies alone or in combination with standard smoking cessation methods 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 relapse are common, and prior unsuccessful quit attempts with conventional therapies do not justify the use of unproven alternative cessation methods. When discussing alternative therapies, providers should counsel patients on potential interactions with evidence-based cessation methods and/or cancer treatments.

Electronic Cigarettes/Electronic Nicotine Delivery Systems

The popularity of electronic cigarettes, "e-cigarettes," and their various derivatives is a recent phenomenon, and, as such, the available literature is new and relatively limited, particularly within specific subpopulations such as patients with cancer. Electronic nicotine delivery systems (ENDS) are not FDA-approved smoking cessation devices. At the present time, the panel does not recommend use of e-cigarettes, and instead known effective methods for smoking cessation should be offered. Below, we discuss the current data and expert opinions on e-cigarettes for smoking cessation.

Several healthcare organizations have released similar policy statements concerning ENDS, highlighting the urgent need for research on the safety of these devices and efficacy as a cessation aid. The American Heart Association, AACR, and ASCO recognize the potential for ENDS to alter existing smoking behaviors, as well as the lack of definitive data regarding associated benefits and harms.[248,249] Experts in the field generally acknowledge that ENDS may offer an attractive approach for smoking reduction and/or cessation in certain populations. However, these policy statements also highlight the unknown potential for ENDS to affect nicotine addiction, combustible tobacco product use, and renormalization of smoking behaviors.

In the September 2015 Final Recommendation Summary, the USPSTF concluded "that the current evidence is insufficient to recommend ENDS for tobacco cessation. The USPSTF recommends that clinicians direct patients who smoke tobacco to other cessation interventions with established effectiveness and safety".[250]

One study examined e-cigarette use in 1074 patients with cancer who enrolled in a tobacco treatment program at a comprehensive cancer center.[251] The study revealed a marked increase in e-cigarette use from 10.6% to 38.5% between 2012 and 2013. E-cigarette users, most often patients 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), e-cigarette users were no more likely to have quit than non-users (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.

High-quality data on e-cigarette use for smoking cessation are limited. In the largest RCT to date, 657 individuals were randomized to receive nicotine e-cigarettes, placebo e-cigarettes, or nicotine patch. Abstinence rates were unexpectedly low across all groups, with no statistically significant differences in biochemically verified smoking abstinence between treatment groups at 6 months.[252]

Systematic reviews have summarized the data from the general population to determine the potential efficacy of e-cigarettes as a

smoking cessation aid, noting a limited overall pool of data and heterogeneous measures. More individuals reduced cigarette consumption with nicotine e-cigarette vs. placebo (RR 1.31; 95% CI, 1.02–1.68), and one study suggested that nicotine e-cigarettes improved reduction over nicotine patch (RR 1.41; 95% CI 1.20–1.670).[253] Across all 13 studies examined, no serious adverse events were reported.[253] Similarly, a 2015 systematic review and meta-analysis of data from 1242 participants suggested that nicotine-containing e-cigarettes were more effective cessation aids than non-nicotine-containing e-cigarettes (RR 2.29; 95% CI, 1.05–4.97).[254] E-cigarette use over a minimum of 6 months was associated with an 18% reported smoking cessation rate (effect size 0.20; 95% CI, 0.11–0.28), and e-cigarette use was also associated with smoking reduction.[254]

A large cross-sectional study of 5863 adults in the United Kingdom assessed the “real-world effectiveness” of e-cigarettes for smoking cessation compared to NRT and unaided quitting, revealing that e-cigarette users were more likely to report abstinence 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).[255] These observations persisted when adjusting for measures of nicotine dependence across the cohorts.

However, e-cigarette use did not decrease cigarette smoking in a cross-sectional study in 106 patients with head and neck cancers seeking to quit. Non-users of e-cigarettes had a significantly greater rate of cessation compared with e-cigarette users (72% vs. 39%; P =.0057).[256]

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.[257]

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.[258] 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.[259,260] 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.

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