ARTICLE TITLE: Tobacco Use and Cessation for Cancer Survivors: An Overview for Clinicians

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After reading the article “Tobacco Use and Cessation for Cancer Survivors: An Overview for Clinicians,” the learner should be able to:
1. Discuss the benefits of smoking cessation for cancer survivors during and after active treatment.
2. Describe current clinical recommendations for behavioral therapy and pharmacotherapy for nicotine dependence or tobacco use disorder, as well as situations in which these recommendations might be tailored for cancer survivors during and after treatment.

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Tobacco Use and Cessation for Cancer Survivors: An Overview for Clinicians

Maher Karam-Hage, MD; Paul M. Cinciripini, PhD; Ellen R. Gritz, PhD

Introduction

The early detection of cancer, due to improved diagnostic modalities, and the development of more effective treatments have contributed to the increase in the overall cancer survival rate. The overall 5-year survival rate for all cancers rose from 49% in 1975 to 1977 to approximately 68% in 2002 through 2008 according to the most recent available data. This increase in survival rates highlights the importance of caring for survivors, but also suggests further work is needed in cancer prevention, particularly for modifiable risk factors like smoking. Smoking accounts for at least 30% of all cancer deaths and nearly 90% of lung cancer deaths. Almost 62% of all patients recently diagnosed with cancer are reportedly current smokers, recent quitters (quit within the last 12 months), or former smokers, with the highest percentages of current smokers, recent quitters, or former smokers noted among patients with lung or head and neck cancer. Smoking cessation and relapse prevention represent an important opportunity to improve cancer survival rates, reduce the risk of cancer treatment complications, and improve the quality of life of patients with and survivors of cancer.

Approximately 30% of all cancer deaths in the United States are caused by tobacco use and smoking. Cancers of eighteen sites have been causally linked to smoking, the most common of which are the lung, head and neck, bladder, and esophagus. While quit rates and quit attempt rates are relatively high shortly after a cancer diagnosis, the recidivism rates are also high. Therefore, screening, treating, and preventing relapse to tobacco use is imperative among patients with and survivors of cancer. To date, research has consistently shown that a combination of pharmacologic and behavioral interventions is needed to achieve the highest smoking cessation rates, with a recent emphasis on individualized treatment as a most promising approach. Challenges in health care systems, including the lack of appropriate resources and provider training, have slowed the progress in addition to important clinical considerations relevant to the treatment of tobacco dependence (eg, a high degree of comorbidity with psychiatric disorders and other substance use disorders). However, continued tobacco use has been shown to limit the effectiveness of major cancer treatments and to increase the risk of complications and of developing secondary cancers. The authors recommend that oncology providers screen all patients for tobacco use and refer users to specialized treatment when available. Alternatively, oncology clinicians can provide basic advice on tobacco use cessation and pharmacotherapy and/or referral to outside resources (eg, quitlines). Herein, the authors summarize the current knowledge on tobacco use and its treatment, with a focus on the related available evidence for patients with and survivors of cancer.

Keywords: tobacco, survivorship, treatment, prevention

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After a continuous decrease in smoking rates over several decades, the overall smoking prevalence in the United States has remained nearly constant for the past several years despite the widespread knowledge that smoking and tobacco use cause cancer as well as cardiovascular, pulmonary, and several other deadly diseases. Close to a 500,000 Americans die each year from smoking-related illnesses. In one national survey in 2010, an estimated 69.6 million Americans aged 12 years or older were current users of a tobacco product (ie, had used tobacco within the past month), confirming that tobacco is one of the most widely used substances in the United States. Among these tobacco users, 58.3 million (23.0% of the population aged older than 12 years) were current cigarette smokers, 13.2 million (5.2%) smoked cigars, 8.9 million (3.5%) used smokeless tobacco, and 2 million (0.8%) smoked pipes. Conversely, the most recent yearly report of the Centers for Disease Control and Prevention estimates that 42.1 million individuals, or 18% of all adults (aged 18 years or older), in the United States are still smoking cigarettes and that cigarette smoking is more common among men (20.5%) than women (15.8%). Other national surveys estimate that 70% of smokers in the United States say they want to quit and 50% have tried to quit at least once in the preceding year. Unfortunately, almost all (95%) of those who tried to quit on their own relapse, usually within the first week. This attests to the chronic relapsing nature of nicotine dependence and difficult-to-reverse brain neuroadaptations that take place as a function of years of nicotine exposure.

Among patients with lung, head and neck, and bladder cancer as well as survivors, prognosis, tumor site, and the impact of cancer treatment itself seem to influence smoking cessation rates. A poorer prognosis does not usually motivate patients to quit, but a cancer site that is clearly attributable to smoking does, especially if patients have a favorable survivorship prognosis. In addition, the nature of the cancer treatment required affects the ability to smoke (eg, the need to avoid smoking before surgery or a hospitalization that would limit patients’ ability to smoke). Nevertheless, in the long run, there do not seem to be significant differences between smoking rates in survivors of cancer and the general population. In one survey, almost 20% of survivors of cancer reported being current smokers, with a high rate of 43% of survivors aged younger than 40 years reporting current smoking. The overall prevalence of current smoking among survivors of cancer is approximately 23% during the first year after diagnosis. After that period, abstinence from smoking drops gradually, suggesting that the first year after diagnosis is a crucial time for relapse prevention interventions. The pool of individuals who could be helped by such interventions may be even larger since some current smokers may be among those who self-identify as “recent quitters” but could be identified as current smokers using biologic measures (such as cotinine or carbon monoxide measure) for confirmation of abstinence. Indeed, self-reports of tobacco use (smoking) status in one study among patients with head and neck cancer was shown to be underestimated in comparison with rates obtained using biologic corroboration of smoking status. In another study, patients recently diagnosed with cancer who self-identified as “recent quitters” were 12 times more likely to have their report be discordant with cotinine verification (34.5% discordant) than those who reported being “former smokers” (2.8% discordant).

Remarkably, apart from disease site and stage, abstinence from smoking is the strongest predictor of survival in patients with cancer who have ever smoked. As a group, current smokers, former smokers, and recent quitters have poorer survival outcomes than never-smokers. In a cohort of 5185 patients with cancer at one institution, smoking at the time of cancer diagnosis was found to be associated with higher 5-year overall and disease-specific mortality rates than those of recent quitters, former smokers, and never-smokers. In that study, with a minimum of 12 years of follow-up but without biochemical verification, current smokers had a higher overall mortality risk compared with recent quitters (hazard ratio [HR], 1.17; 95% confidence interval [95% CI], 1.03–1.32), former smokers (HR, 1.29; 95% CI, 1.17–1.42), and never-smokers (HR, 1.38; 95% CI, 1.23–1.54) in the cohort. Furthermore, current smokers had a higher disease-specific mortality risk than former smokers (HR, 1.23; 95% CI, 1.09–1.39) and never-smokers (HR, 1.18; 95% CI, 1.03–1.36).

In recent years, screening for tobacco use in cancer settings has been emphasized, and although progress has been made, more system-wide changes need to occur to reach universal screening. In addition, the provision of tobacco cessation treatment for identified tobacco users is still not widely available. In a recent survey of oncology providers, fewer than one-half of tobacco users were offered tobacco cessation treatment. This gap is an area of cancer care that requires improvement because it can bring both long-term (survival) as well as short-term benefit to the patient in terms of improved treatment outcomes. Multiple retrospective studies have been performed on the impact of continued smoking on cancer treatment; although some had small sample sizes, all were found to demonstrate the deleterious impact of continuing to smoke in patients with cancer. These retrospective studies have focused mostly on smoking-related cancers such as lung, head and neck, esophagus, hematologic (leukemia), bladder, colon, and breast cancers. Other prospective studies that were also performed to show the impact of continued smoking on cancer treatment have produced similar findings in patients with cancers of the head and neck, oropharynx, lung, prostate, and breast. Collectively, these studies support the notion that tobacco cessation improves treatment outcomes in
patients with cancer and highlight the importance of providing tobacco cessation services to both patients and survivors. Not to do so can have negative clinical implications because patients who continue to smoke during the course of their cancer treatment have higher risks of complications, developing secondary cancers, and death. A wide body of literature supports the role of tobacco in carcinogenesis and, as detailed above, the impact of tobacco on cancer treatment.

The impact of continuing to smoke on survivorship is also grim. In a review of 10 studies, Parsons et al found that those who continue to smoke after a diagnosis of early-stage lung cancer almost double their risk of death. In a study of 611 patients with small cell lung cancer, the risk of all second cancers (mostly non-small cell cancers of the lung) was increased by 3.5-fold (relative risk [RR], 3.5; 95% CI, 2.8-4.3) compared with the general population. This translated to 327 excess cancers per 10,000 person-years among those patients who had any smoking history (former smokers, recent quitters, or current smokers). Furthermore, the risk of a second lung cancer was also increased (RR, 13; 95% CI, 9.4-17) in those patients (compared with never-smokers) who received chest radiation, whereas the risk of second lung cancer increased to a lesser extent (RR, 7; 95% CI, 2.9-13) among those patients if they did not receive chest radiation. An interaction between chest radiation and continued smoking resulted in the highest risk (RR, 21; 95% CI, 13-32). In addition, in other studies, patients with cancer who were active smokers during cancer treatment had lower response rates to radiation therapy compared with former smokers and recent quitters who stopped smoking before starting treatment. Common side effects of radiation such as oral mucositis, xerostomia, weight loss, and fatigue were reported to be exacerbated by cigarette smoking. Smoking also affects the hepatic metabolism of many chemotherapeutic agents, thereby often decreasing the response to chemotherapy and increasing the rates of complications. Continued smoking also increases the risk of complications in patients who require surgical intervention. In a meta-analysis on the topic, several endpoints were evaluated separately. In 19 unique studies comprising 7616 individual patients, cigarette smoking was found to increase the risk of tissue and wound necrosis, with an odds ratio (OR) of 3.61 (95% CI, 2.78-4.68). The endpoint of healing delay and dehiscence was evaluated in 18 studies comprising 26,297 patients, with an OR of 2.86 (95% CI, 2.78-4.68) reported. Surgical site infection was an endpoint in 51 unique studies comprising over 400,000 patients, with an OR of 2.12 (95% CI, 1.56-2.88); furthermore, in plastic surgery tissue, ischemia and impairments in wound healing are related to continued tobacco use versus abstinence.

In addition to higher morbidity and mortality rates, survivors of cancer who are former smokers/recent quitters or current smokers score lower on quality-of-life indices than survivors who have never smoked. Moreover, in 2 studies of survivors of lung cancer and one study performed in survivors of head and neck cancer, those who quit smoking prior to their cancer diagnosis (recent quitters and former smokers) were likely to perform better on quality-of-life indices than survivors who continued smoking or those who quit smoking after their cancer diagnosis. Survivors who continued to smoke generally also had poorer physical health, self-perception of their general health, emotional and social functioning, and vitality compared with survivors who were never-smokers or former smokers.

A causal relationship between smoking and the diagnosed cancer seems to help motivate patients to quit smoking. Smokers with certain cancers clearly related to smoking, such as lung or head and neck cancer, reportedly often quit smoking as an immediate response to their diagnosis and are even more likely to quit when told that their cancer is related to smoking; however, the recidivism rates remain high. Although the concept of addiction (compulsive use of tobacco despite adverse consequences) has not been studied in patients with cancer, addiction is thought of as a universal concept of a brain disorder that affects patients with cancer similarly to how any other chronic disease would (eg, hypertension, asthma, or type 2 diabetes). Like addiction, these chronic diseases have behavioral and biological components and require pharmacological treatment and lifestyle changes to manage the disease or sustain remission. Therefore, clinicians are urged to be on the lookout for delayed relapses. In addition, they should address smoking behavior and history on an ongoing basis by conceptualizing smoking (repeated tobacco use) as a chronic and relapsing disorder in contrast to the way acute disorders (eg, infectious disease) are viewed, and by anticipating and normalizing setbacks.

In the area of tobacco cessation, there are only a few well-designed prospective studies focused on patients with cancer, with approximately one-half concentrating on nurse-delivered interventions. A recent meta-analysis on the topic concluded that heavy smokers and those in the perioperative period did benefit from a cessation intervention, although the authors reported that, overall, providing smoking cessation interventions to patients with cancer did not seem to improve cessation rates. This may be due to a lack of homogeneity among the pooled studies because they had different measures for smoking and abstinence and included different types of cancer sites and cancer patient populations (outpatients only or inpatients only).

**Methods**

**Literature Search**

We conducted a PubMed search for the key words survivorship + cancer + tobacco use + smoking cessation, which
generated a list of over 200 publications. We then cross-checked pertinent references and reviewed all available abstracts to obtain those of interest for the background section and to collect data on prospective clinical trials or retrospective reviews comparing the effects of tobacco cessation and continued use after cancer diagnosis on cancer treatment outcomes.

Clinical Assessment
To treat a tobacco use disorder (formerly called tobacco addiction or nicotine dependence), clinicians must be aware of its presence. Systematic screening for tobacco use has been recommended for many years. In early 2013, as part of a “meaningful use” of electronic health records, the US government began mandating systematic screening and showing provider ability to access the tobacco use status of patients aged 13 years or older. This is required for more than 50% of admitted patients in phase 1, with 80% or more required in phase 2. Furthermore, screening for tobacco use presents an opportunity for oncology clinicians to talk with patients about cessation and encourage or persuade them to pursue a tobacco cessation treatment referral. Specific scales for nicotine dependence exist, including the Fagerstrom Test for Nicotine Dependence (FTND), which is the most recognized and frequently used tool to identify classic nicotine dependence or tobacco use disorder (also known as “nicotine addiction”). The FTND is a short and practical tool and is particularly useful for clinicians; a score of only 3 out of 10 is enough to consider someone to be nicotine-dependent. Administering only the first item of the test can be a quick screening for nicotine dependence: if a patient smokes within 5 minutes of waking in the morning, they automatically receive an affirmative score of at least 3 (regardless of how many cigarettes he or she smokes in a day). Alternatively, smoking more than 10 cigarettes per day and smoking the first cigarette within 30 minutes of waking would result in a score of at least 3 and thus also indicate dependence on nicotine. A quicker screening question to define a lifetime smoker is whether the individual has smoked more than 100 cigarettes in their lifetime. To determine daily smoking, the question asked is: Do you smoke one or more cigarettes per day? A comprehensive screening questionnaire would need to have at least one question to cover the use of other forms of tobacco and nicotine such as cigars, smokeless tobacco, and electronic cigarettes.

As mentioned above, an important component of assessment is biologic confirmation; carbon monoxide breathalyzers and testing for cotinine in saliva or urine are easy measures to implement. Self-reports of smoking status usually have a high correlation with biomarkers, except in patients who perceive a stigma associated with smoking, some because they are dealing with chronic diseases related to tobacco and are under pressure to quit to improve their health or lower their risks (eg, pregnant women, patients with coronary disease, and patients with cancer). Patients with cancer in particular are under pressure (both internal and external) to quit using tobacco, especially when their cancer is tobacco related. Advising patients ahead of time about the procedure of verification of abstinence via cotinine or carbon monoxide testing (eg, before a surgical procedure) may provide them with an accountability check that will motivate them to stay tobacco free after they quit or to seek help if they are not able to quit on their own.

Subpopulations With a High Prevalence of Tobacco Use
Smoking and tobacco use are more frequent in certain populations than in others. Smoking is more common among those with lower educational attainment (25% of those with less than a high school degree and 45% of those with a General Education Development degree are smokers) and among those with lower socioeconomic status (29% of those living under the federal poverty level are smokers). Even more dramatic is that one of 3 individuals with a mental health disorder is a current smoker (33%) in contrast to one of 5 (20%) in the general population. In a nationally representative sample, current smokers diagnosed with a mental disorder within the past month accounted for 44% of all cigarettes consumed (smoked) in the United States. In that study, having a current or past psychiatric disorder was found to effectively double the likelihood of being a smoker. This evidence that smoking is closely linked to psychiatric comorbidities, including substance use disorders, suggests a shared biologic pathway that may underlie a vulnerability to these disorders. This hypothesis is supported by several studies that have reported a positive correlation between smoking and psychiatric disorders, including alcohol or other substance use disorders. For example, the prevalence of lifetime alcohol and/or other drug use disorders in the adult smoker population is more than twice the reported rates in the general population, with an estimated 23% to 30% of smokers having lifetime alcohol or other substance use disorders. The fact that smokers have an elevated risk of a first onset of major depression, panic disorder, or generalized anxiety disorder adds further support to the idea of a common link between smoking (with or without nicotine dependence) and mental health disorders.

The co-occurrence of these mental health disorders and tobacco use disorder supports the importance of screening and treating mental health disorders among smokers; patients with or survivors of cancer are no different. Although the data are limited, treating co-occurring psychiatric disorders has the potential of increasing cancer
patients’ resilience, their ability to face cancer, and arguably their ability to maintain abstinence after quitting tobacco. Accordingly, it was reported that patients with lower depression scores and patients with lower tumor stages were more confident about their ability to quit smoking than those with higher depression scores and those with more advanced tumor stages.

Treatment Principles
In 2008, when the US Department of Health and Human Services treatment guidelines for tobacco cessation were last updated, 10 specific recommendations for treatment were formulated as a quick guide to the overall principles. While some patients may quit on their own or require minimal advice to quit, it is essential to keep in mind that the treatment of tobacco use in many patients with cancer may require a more intensive and comprehensive approach. This can be accomplished by addressing the biological, psychological, and social aspects of a tobacco use disorder. In other words, supportive and cognitive behavioral therapies combined with pharmacologic treatments are needed to provide the best possible chance for a patient with or survivor of cancer to quit smoking. Unfortunately, very few smoking cessation studies have been conducted in the cancer setting, and their focus is usually on the delivery of the behavioral intervention rather than the effectiveness of a specific therapy or pharmacotherapy. Likewise, patients with cancer are usually excluded from pharmacologic smoking cessation trials, mostly owing to concerns about the patients’ ability to participate in and complete a trial and the difficulty of determining whether any emerging side effects are due to the cancer or cancer treatment or to a smoking cessation medication. Nevertheless, smoking cessation medications are expected to be as effective in patients with and survivors of cancer as they are in patients without cancer or a history of cancer, with proper precautions for relapse prevention.

Pharmacological Interventions
The first-line smoking cessation medications that are approved by the US Food and Drug Administration (FDA) are bupropion (commercially known as Wellbutrin or Zyban [GlaxoSmithKline, Research Triangle Park, NC]), varenicline (known as Chantix in the United States and as Champix in other countries [Pfizer Inc, New York, NY]), and 5 forms of nicotine replacement therapies (NRTs). Other medications that are not approved by the FDA but are used off-label for smoking cessation are clonidine and nortriptyline. However, they are considered second-line because they have more potential for side effects. For a detailed comparison of the differential efficacies of mono-therapies and combination therapies, refer to Table 1, as published in the clinical treatment guideline of 2008. Topiramate is another medication that holds promise for both alcohol and tobacco use disorders and is being studied in clinical trials to test its efficacy in treating co-occurring alcohol and nicotine use disorders. Topiramate is currently available in the United States for other indications (seizures and migraine headaches).

In addition to medications, vaccines against nicotine have been proposed, and several are on the horizon. Although the initial trials of one of the nicotine vaccines revealed some benefits for smoking cessation and relapse prevention, these benefits were not sustained in a later, multisite trial. A recent study incorporating imaging techniques with a different type of vaccine had encouraging results. However, more research is needed to determine the efficacy and magnitude of the benefit from nicotine vaccines and whether they should be used for treatment or for relapse prevention.

Bupropion
Bupropion has both antidepressant and smoking cessation benefits, and is efficacious for smoking cessation in smokers at the usual therapeutic dose of 150 or 300 mg per day independent of whether or not they are depressed. Bupropion has been studied extensively for smoking cessation; as of 2014, there had been 65 smoking cessation trials conducted with bupropion. It was used as a monotherapy and compared with a placebo in 44 of those trials, with over 13,000 patients exposed and an efficacy risk ratio (or relative risk) of 1.62 (95% CI, 1.49-1.76) of continuous abstinence at 6 months. The RR of 1.62 is based on an assumed risk of 115 per 1000 for a control (placebo) and a risk of 187 (95% CI, 172-201) per 1000 for bupropion (RR is an important statistic that is being used increasingly because it refers to the probability of abstinence on the active treatment divided by the probability of abstinence on the control). The side effects of this first-line medication (eg, dry mouth, insomnia, and tremors) are usually mild, and most patients are able to tolerate them. Among the contraindications for and precautions against using bupropion are prior seizures, head trauma, being underweight, or having a current eating disorder (the risk of seizures with a daily dose of bupropion of between 150 and 300 mg/day is similar to that of other antidepressants at about one in 1000; however, risk increases with increased daily dose). This medication has the added advantage of improving the mood and energy levels of individuals experiencing a depressed mood or low energy, which also seems to be true for patients with cancer. In addition, bupropion reduces the usual appetite increase and weight gain that follows smoking cessation; however, this may not be desirable for survivors of cancer who lose weight during cancer treatment.
Another reported advantage is its positive impact on sexual functioning when used as an antidepressant in some patients, although bupropion has not been tested for this specific symptom among patients with cancer and survivors, despite this dysfunction being a major problem in some survivors of cancer.

Varenicline

Varenicline is the latest marketed non–nicotine-based smoking cessation medication; it was approved in 2006 in the United States. As a partial agonist (or mixed agonist/antagonist in older terminology), varenicline is thought to diminish smoking abstinence and nicotine withdrawal symptoms while lowering the rewarding effect of smoking. Pooled analyses from several controlled trials have shown that varenicline resulted in cessation rates that were approximately 2 times higher than bupropion and 3 times higher than a placebo.

Two recent Cochrane reviews of tobacco use disorder treatments, one on psychopharmacologic treatment and the other on partial agonists (varenicline, cytisine, and dianicline) of the nicotine receptor, encompassed a large number of studies. Two of those studies reported that the nicotine partial agonist cytisine (a natural product) is more effective for smoking cessation than a placebo (pooled RR, 3.98). Another trial found that dianicline (a synthetic product similar to varenicline) was not more effective than a placebo (RR, 1.2). In the same review, continuous or sustained abstinence at 6 months or longer for varenicline at the standard dosage compared with a placebo in 14 trials had a

| Medication                | Number of Arms | Estimated OR (95% CI) | Estimated Abstinence Rate (95% CI), % |
|---------------------------|----------------|-----------------------|--------------------------------------|
| Placebo                   | 80             | 1.0                   | 13.8                                 |

**Monotherapies**

- Varenicline (2 mg/d) 5 3.1 (2.5-3.8) 33.2 (28.9-37.8)
- Nicotine nasal spray 4 2.3 (1.7-3.0) 26.7 (21.5-32.7)
- High-dose nicotine patch (>25 mg) (included both standard or long-term duration) 4 2.3 (1.7-3.0) 26.5 (21.3-32.5)
- Long-term nicotine gum (>14 wk) 6 2.2 (1.5-3.2) 26.1 (19.7-33.6)
- Varenicline (1 mg/d) 3 2.1 (1.5-3.0) 25.4 (19.6-32.2)
- Nicotine inhaler 6 2.1 (1.5-2.9) 24.8 (19.1-31.6)
- Clonidine 3 2.1 (1.2-3.7) 25.0 (15.7-37.3)
- Bupropion SR 26 2.0 (1.8-2.2) 24.2 (22.2-26.4)
- Nicotine patch (6-14 wk) 32 1.9 (1.7-2.2) 23.4 (21.3-25.8)
- Long-term nicotine patch (>14 wk) 10 1.9 (1.7-2.3) 23.7 (21.0-26.6)
- Nortriptyline 5 1.8 (1.3-2.6) 22.5 (16.8-29.4)
- Nicotine gum (6-14 wk) 15 1.5 (1.2-1.7) 19.0 (16.5-21.9)

**Combination therapies**

- Patch (long-term; >14 wk) plus ad lib NRT (gum or spray) 3 3.6 (2.5-5.2) 36.5 (28.6-45.3)
- Patch plus bupropion SR 3 2.5 (1.9-3.4) 28.9 (23.5-35.1)
- Patch plus nortriptyline 2 2.3 (1.3-4.2) 27.3 (17.2-40.4)
- Patch plus inhaler 2 2.2 (1.3-3.6) 25.8 (17.4-36.5)
- Patch plus second-generation antidepressants (paroxetine, venlafaxine) 3 2.0 (1.2-3.4) 24.3 (16.1-35.0)

**Medications not shown to be effective**

- Selective serotonin reuptake inhibitors 3 1.0 (0.7-1.4) 13.7 (10.2-18.0)
- Naltrexone 2 0.5 (0.2-1.2) 7.3 (3.1-16.2)

OR indicates odds ratio; 95% CI, 95% confidence interval; SR, sustained release; NRT, nicotine replacement therapy. Adapted from Fiore MC, Jaen CR, Baker TB, et al. Treating Tobacco Use and Dependence: 2008 Update, Clinical Practice Guideline. Rockville, MD: US Department of Health and Human Services, Public Health Service; 2008.
pooled RR of 2.27 (95% CI, 2.02–2.55 [N = 6166], excluding one trial evaluating long-term safety). Varenicline at lower or variable doses was also shown to be effective in 4 trials, with an RR of 2.09 (95% CI, 1.56–2.78 [N = 1272]). The pooled RR for varenicline versus bupropion in 3 trials after 1 year of treatment was 1.52 (95% CI, 1.22–1.88 [N = 1622]). The RR for varenicline compared with that of NRT for point prevalence abstinence at 24 weeks of treatment in 2 trials was 1.13 (95% CI, 0.94–1.35 [N = 778]). Of interest, a lower dosage of varenicline (1 mg/day) in 4 trials seemed to reduce the number and severity of adverse effects while having only slightly lower efficacy, with an RR of 2.09 (95% CI, 1.56–2.78 [N = 1272]). Although 2 small trials are reported in patients with and survivors of cancer treated with varenicline successfully, the finding that a low dosage of varenicline causes fewer severe side effects is particularly important to keep in mind when prescribing it in the oncology setting due to the fact that cancer patients and survivors can be more susceptible to side effects, possibly owing to their exposure to invasive treatments (eg, surgery, chemotherapy, and radiation therapy).

Among the commonly reported side effects of varenicline are nausea, flatulence, and vivid dreams; conversely, neuropsychiatric side effects from varenicline (eg, irritability, depression, anxiety, and rarely, suicidal ideation) are thought to be less commonly reported among the general population than among patients who have active or a history of psychiatric disorders. In the postmarketing phase of varenicline, the FDA received a large number of reports regarding this medication via the tool for voluntary reporting of adverse events, “MedWatch.” These reported events consisted mainly of difficulty with coordination, depressive symptoms, aggression, irritability, and more rarely suicidal ideation. Since these reports are voluntary with no confirmation or standardization, it is impossible to determine the relationship between these events and smoking, smoking cessation, or the medication itself; all 3 of these factors, alone or in combination, have the potential to cause the reported neuropsychiatric side effects. Nicotine dependence and withdrawal are independently associated with suicidal ideation, suicide attempts, and completed suicide, as shown in large studies controlling for psychiatric illness and alcohol use. Furthermore, nicotine dependence has the third-highest population-attributable fraction for suicide attempts of any psychiatric disorder, after major depressive disorder and borderline personality disorder, even higher than that of posttraumatic stress disorder. Recently, a very large Veterans Health Administration data analysis showed that tobacco use disorder is associated with an increased rate of suicides in patients seeking treatment, independent of having a psychiatric disorder.

Several recent reports, including a pooled analysis of original studies of volunteers without psychiatric disorders, do not support the notion that varenicline leads to more neuropsychiatric events than other smoking cessation medications or controls. An observational study from England, based on 80,660 smokers, found no evidence of increased risk of depression, suicidal thoughts, or self-harm during smoking cessation attempts with varenicline compared with NRT or bupropion. In a US Department of Defense study based on 23,956 veterans who were current smokers, varenicline and the nicotine patch did not lead to significantly different rates of psychiatric hospitalization during a smoking cessation attempt. Two reanalyses of existing databases did not show an increase in neuropsychiatric events with varenicline compared with placebo, mostly in patients without a psychiatric history or psychiatric symptoms, and varenicline seemed to reduce the impact of nicotine withdrawal and the occurrence of neuropsychiatric events (eg, depression and anxiety). Furthermore, 3 recently published reports based on prospective and controlled studies have shown varenicline to have a beneficial effect on nicotine withdrawal syndrome and no effect on neuropsychiatric symptoms. One study from our group showed that varenicline ameliorated negative affect and reduced depressive symptoms regardless of quit status when compared with bupropion and a placebo in community volunteers without current psychiatric disorders. The second study did not find a difference in depressive symptoms between patients who quit smoking while receiving varenicline and those who quit while receiving a placebo, regardless of whether they had a history of or current depression. The third study, done in stable patients with schizophrenia in a multisite controlled trial, resulted in lower abstinence with varenicline than in the general population, at 19% versus 5% for placebo, but with no difference noted in the exacerbation of psychotic symptoms. Finally, another large multisite study, called Study Evaluating The Safety and Efficacy of Varenicline and Bupropion for Smoking Cessation in Subjects With and Without a History of Psychiatric Disorder (EAGLES), is currently under way. EAGLES is an international multisite study with 8 arms into which 8000 participants currently are being randomized. The study will assess varenicline, bupropion, and nicotine patches as aids to smoking cessation treatment and to characterize the neuropsychiatric safety profiles of these medications in individuals with and without an established diagnosis of major psychiatric disorders. The study is expected to be completed by October 2016 and should provide more definitive answers to the questions of possible differential exacerbation of neuropsychiatric symptoms when quitting smoking with varenicline in comparison with bupropion, the nicotine patch, or placebo.

Finally, varenicline seems to have other beneficial effects for certain patients; for example, it may help those who are both heavy drinkers and smokers to decrease their alcohol...
Nicotine replacement therapies

NRTs are available in various forms. A steady level of nicotine delivery from an NRT is usually achieved by applying a transdermal nicotine patch. An episodic form of NRT can be achieved by using the oral or nasal mucosa as the medium of absorption of nicotine; oral mucosa-absorbed NRTs are currently available in the form of gum, lozenges, or a buccal inhaler, and NRT absorbed by nasal mucosa is available as a spray. A recent Cochrane review identified 150 trials of NRTs, 117 of which had over 50,000 participants contributing to the primary comparison between any type of NRT and a placebo or non-NRT control group. The RR of abstinence for any form of NRT relative to a control was 1.60 (95% CI, 1.53-1.68), which corresponds to a risk of 161 (95% CI, 154-169) per 1000, in contrast to an assumed 100 of 1000 for a control (placebo). The pooled RRs for each NRT type were as follows: 1.49 (95% CI, 1.40-1.60; 55 trials) for nicotine gum, 1.64 (95% CI, 1.52-1.78; 43 trials) for a nicotine patch, 1.95 (95% CI, 1.61-2.36, 6 trials) for oral tablets/lozenges, 1.90 (95% CI, 1.36-2.67; 4 trials) for a nicotine inhaler, and 2.02 (95% CI, 1.49-2.73; 4 trials) for nicotine nasal spray. Furthermore, combining a nicotine patch with a rapid-delivery (episodic) form of NRT was found to be more effective than a single type of NRT (RR, 1.34; 95% CI, 1.18-1.51 [9 trials]). It is important to keep in mind that in all NRTs, the active ingredient, nicotine, is administered to the patient at a much lower dose and at a much slower rate than what cigarettes deliver to the lungs; this lower dose is intended to progressively wean the brain off nicotine instead of abruptly halting nicotine use. Another benefit of NRTs is that they deliver only nicotine and none of the more than 7000 toxic and 60 carcinogenic substances that the body is exposed to through smoking tobacco. These methods of nicotine replacement help limit craving and withdrawal symptoms and usually do not present any serious side effects since patients already have much higher levels of nicotine in their system from their tobacco use.

Currently, it is recommended that NRT be initiated while a patient is still smoking to help them cut back on their level of smoking and increase their self-efficacy and belief in their ability to quit; then, the patient can proceed to complete cessation. The original recommendations, from several decades ago, were to start using the NRTs (only the patch and gum were available then) on the first quit day and stop using them if a relapse occurred because of the fear of overdosing on nicotine and increasing the risk for cardiovascular events. This fear was not substantiated in later studies; in fact, the currently available data show that using an NRT during a short lapse (less than 1 day of smoking after having quit) may reduce the chances of complete relapse (returning to smoking). The efficacy of NRTs can be affected by an individual's level of nicotine dependence and rate of nicotine metabolism; those who have greater nicotine dependence and/or a higher rate of nicotine metabolism are thought to have less robust responses to NRTs.

Some studies have shown that the combination of an NRT such as a nicotine patch plus an episodic NRT (eg, gum or lozenge) has odds of abstinence similar to those observed for varenicline, but there have not been yet any blinded, head-to-head comparisons of varenicline and NRT combinations.

Alternative pharmacologic treatments

Recent trends in the literature point toward a combination approach as being more effective than monotherapy (ie, using several first-line medications together in targeting tobacco cessation). Among the various possible combinations, some have been shown to be more effective than others, including nicotine lozenges plus bupropion or nicotine lozenges plus a nicotine patch. Those 2 combinations were superior when compared with each of those agents taken as monotherapy. Another potential combination is varenicline plus bupropion, which has shown some preliminary positive evidence in a small open-label trial and recently in a blinded, placebo-controlled trial it was found to have marginal effectiveness for regular smokers but a more robust effect for heavy smokers. Our group recently concluded another randomized placebo-controlled clinical trial testing the efficacy of that combination; however, our preliminary results are not conclusive.

Clinicians can consider second-line agents (nortriptyline or clonidine) in the case of side effects from first-line medications (varenicline, NRTs, or bupropion) or in patients unable to achieve cessation with first-line agents who are willing to consider another pharmacotherapy. Nortriptyline and clonidine are available in generic form, and they are used “off-label” because they have not received...
FDA approval for treating tobacco use or for smoking cessation. Nevertheless, these second-line medications have been shown to be at least twice as effective as a placebo for smoking cessation; however, the drawbacks that limit their use are their significant side effect profiles, in particular the potential lethality of a nortriptyline overdose. In the first author’s experience with patients with and survivors of cancer, nortriptyline also was found to have desirable effects as an antidepressant, antianxiety, appetite-stimulating, sleep-inducing, and pain-attenuating medication.

Clonidine also has some particular advantages in certain patients with cancer and survivors, especially those who have uncontrolled high blood pressure, anxiety, or insomnia, as clonidine has a favorable profile for all of these symptoms. A drawback for its use, however, is the potential lack of adherence to its dosing schedule: it needs to be taken 3 times a day, owing to its short half-life.

Finally, in the most recent multiple tobacco cessation treatment comparison meta-analysis to date, Mills et al identified 146 randomized controlled trials for smoking cessation: 65 studies used standard doses of the nicotine patch (less than 22 mg), 6 studies used a high-dose NRT patch (greater than 22 mg), 5 studies used high-dose versus standard-dose NRT patches, 5 studies used combination NRT versus inert controls, 6 studies used combination NRT versus single-form NRT (patch), 48 studies used bupropion, and 11 studies used varenicline (Table 2). This multiple treatment comparison found that all therapies offered treatment benefits at most time points compared with the controls. Furthermore, varenicline was associated with statistically significant improvements in smoking abstinence compared with all the other interventions at all the time points.

### Behavioral Interventions

The standard for behavioral interventions for tobacco and smoking cessation consists of face-to-face or telephone-based individual counseling along with medications. The Public Health Service 2008 guideline concludes that the combination of behavioral and pharmacological interventions doubles abstinence rates compared with either type of intervention alone. Furthermore, in the guideline, specific

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**TABLE 2. Multiple Treatment Comparison, Meta-Analysis of Pharmacotherapies**

| Control vs | SHORT-TERM RR (95% CI) | 12-MONTH RR (95% CI) |
|------------|-------------------------|---------------------|
| Standard nicotine patch NRT (<22 mg) | 1.48 (1.30-1.69) | 1.52 (1.43-1.61) |
| High-dose nicotine patch NRT (>22 mg) | 1.69 (1.32-2.11) | 1.73 (1.62-1.84) |
| Combination NRT | 1.34 (0.96-1.84) | 1.68 (1.30-2.08) |
| Bupropion | 1.40 (1.22-1.60) | 1.7 (1.58-1.83) |
| Varenicline | 2.39 (1.96-2.88) | 2.19 (1.94-2.44) |

| Standard-dose nicotine patch therapy (<22 mg) vs | SHORT-TERM RR (95% CI) | 12-MONTH RR (95% CI) |
|-----------------------------------------------|-------------------------|---------------------|
| High-dose nicotine patch NRT (>22 mg) | 1.15 (0.91-1.43) | 1.14 (1.07-1.21) |
| Combination NRT | 0.91 (0.62-1.29) | 1.10 (0.85-1.37) |
| Bupropion | 0.94 (0.77-1.15) | 1.12 (1.02-1.22) |
| Varenicline | 1.43 (1.26-1.60) | 1.65 (1.29-2.07) |

| High-dose nicotine patch therapy (>22 mg) vs | SHORT-TERM RR (95% CI) | 12-MONTH RR (95% CI) |
|-----------------------------------------------|-------------------------|---------------------|
| Combination NRT | 0.78 (0.50-1.20) | 0.97 (0.73-1.23) |
| Bupropion | 0.81 (0.6-1.09) | 0.98 (0.88-1.09) |
| Varenicline | 1.47 (1.06-2.01) | 1.29 (1.12-1.46) |

| Combination NRT vs | SHORT-TERM RR (95% CI) | 12-MONTH RR (95% CI) |
|-----------------------------------------------|-------------------------|---------------------|
| Bupropion | 1.04 (0.72-1.45) | 1.01 (0.79-1.25) |
| Varenicline | 1.78 (1.25-2.41) | 1.28 (1.02-1.53) |

| Bupropion vs | SHORT-TERM RR (95% CI) | 12-MONTH RR (95% CI) |
|-----------------------------------------------|-------------------------|---------------------|
| Varenicline | 1.61 (1.32-1.93) | 1.29 (1.12-1.45) |

RR indicates relative risk; 95% CI, 95% confidence interval; NRT, nicotine replacement therapy. For efficacy: RRs >1 favor the row-defining treatment. Adapted from Mills EJ, Wu P, Lockhart I, Thorlund K, Puhan M, Ebbert JO. Comparisons of high-dose and combination nicotine replacement therapy, varenicline, and bupropion for smoking cessation: a systematic review and multiple treatment meta-analysis. Ann Med. 2012;44:588-597.
therapeutic techniques have been shown to be superior with regard to abstinence rates compared with no contact (ie, untreated control condition). These categories are: 1) providing practical counseling such as problem solving, skills training, and stress management, according to 104 trials with an OR of 1.5 (95% CI, 1.3–1.8) and an abstinence rate of 16.2% (95% CI, 14–18.5); 2) providing support during a smoker’s direct contact with a clinician (intratreatment social support), according to 50 trials with an OR of 1.3 (95% CI, 1.1–1.6) and an abstinence rate of 14.4 (95% CI, 12.3–16.5); 3) intervening to increase social support in the smoker’s environment (extratreatment social support), according to 19 trials with an OR of 1.5 (95% CI, 1.1–2.1) and an abstinence rate of 16.2% (95% CI, 11.8–20.6); and 4) using aversive smoking procedures (eg, rapid smoking and rapid puffing, a procedure that is not typically used), according to 19 trials with an OR of 2.0 (95% CI, 1.1–3.5) and an abstinence rate of 19.9% (95% CI, 11.2–29.0). Any type and amount of therapy, including “minimal counseling” support of 1 to 3 minutes, is better than none, according to 12 trials with an OR of 1.4 (95% CI, 1.1–1.8) and an abstinence rate of 14.4% (95% CI, 11.3–17.5).80

Furthermore, a dose-dependent response has also been reported for behavioral therapies, with incremental benefits from increases in the number of sessions for up to 8 sessions. The same incremental benefit was observed for the total length of all sessions, with 90 minutes total as an upper limit. In a recent Cochrane review of behavioral interventions for smoking cessation, 38 studies met the inclusion criteria, with over 15,000 participants in the relevant arms. There was evidence of a small but statistically significant benefit from more intensive support (RR, 1.16; 95% CI, 1.09–1.24) for abstinence at the longest follow-up. All but 2 of the included studies provided 4 or more sessions of support. Most trials used NRT as the pharmacotherapy. In subgroup analyses, studies that provided at least 4 sessions of personal contact for the intervention and no personal contact for the control had slightly larger effects (RR, 1.25; 95% CI, 1.08–1.45 [6 trials]), as did studies in which all intervention counseling was conducted via telephone (RR, 1.28; 95% CI, 1.17–1.41 [6 trials]).185 In a recent review of combined behavioral and pharmacological interventions, based on 40 studies, there was good evidence for an advantage in using combination pharmacotherapy and behavioral treatment in comparison with usual care or brief advice or less intensive behavioral support (RR, 1.82; 95% CI, 1.66–2.00). The relative effect of an intervention did not differ according to whether smokers were required to be motivated to make a quit attempt. A weak but consistent effect was noted supporting larger effects for studies using more versus fewer sessions but that was not considered to be clear evidence that increasing the total duration of contact increased the effect. However, there was more evidence of a dose-response relationship among studies in which treatment uptake was high.186 Finally, group therapy for smoking cessation has been suggested to be more effective than nonintervention in the 2008 Public Health Service guideline for treating tobacco use and dependence, according to 52 studies with an OR of 1.3 (95% CI, 1.1–1.6) and an abstinence rate of 13.9% (95% CI, 11.6–16.1).80 Group therapy has also been reported to be more effective than individual therapy in real-life settings.187

Tailoring these therapies for patients with cancer and survivors in various oncology settings (eg, inpatient, perioperative period, or outpatient) has been suggested; however, a lack of provider training is a major obstacle for delivering these therapies in the cancer setting. For the general health care provider in an oncology setting, mastering and delivering specialized techniques may not be feasible. Nevertheless, by providing simple support and empathy, the oncology practitioner can make a difference, as these basic behavioral interventions can be powerful vehicles. The alternative approach is to refer those patients to specialized treatment programs, but those are only gradually becoming available in comprehensive cancer centers.

Alternative Sources of Help

Two alternatives to the interventions described so far are available for both patients and clinicians, especially those with time constraints: quitlines and self-help materials. Quitlines are convenient for individuals with limited or no resources or with travel limitations and are useful for clinicians in private practice who do not have the expertise or capability to treat tobacco use. Both telephone-based and Internet-based quitlines have been shown to improve smoking cessation rates and often allow clinicians to offer referrals to specialized providers. In a recent review of 77 trials among smokers who contacted helplines, quit rates were higher for groups randomized to receive multiple sessions of proactive counseling (for cessation at longest follow-up: RR, 1.37; 95% CI, 1.26–1.50 [9 studies with 24,000 participants]).189 There was mixed evidence about whether increasing the number of calls altered quit rates, but most trials used more than 2 calls. Three studies comparing different counseling approaches during a single quitline contact did not detect significant differences. Of 3 studies that tested the provision of access to a hotline, 2 detected a significant benefit and one did not. Telephone counseling not initiated by calls to helplines also increased quitting (RR, 1.27; 95% CI, 1.20–1.36 [51 studies with 30,000 participants]). In a meta-regression controlling for other factors, the effect was estimated to be slightly larger for participants to whom more calls were offered and in trials that specifically recruited smokers motivated to try to quit. The relative extra benefit of counseling was smaller...
when it was provided in addition to pharmacotherapy (usually NRT) than when it was provided in addition to only self-help material or a brief intervention.189

Quitlines are available in all US states through a national number (1-800-QUIT-NOW), which redirects callers to the quitline for their particular state or locality if a specific state-funded and state-tailored program is available. Furthermore, in some states, access to a quitline provides access to tobacco cessation medications. The National Cancer Institute (NCI) has dedicated some resources to tobacco cessation, including a commonly used booklet titled “Clearing the Air” and the NCI quitline (1-877-44U-QUIT or 1-877-448-7848). The NCI’s quitline provides telephone counseling with important elements such as creating a quit plan, handling withdrawal symptoms, setting a quit date, and using pharmaceutical options.

Self-help materials have also been found to be effective in smoking cessation for some patients,190 especially certain Internet-based self-help interventions that have gained recent attention and proven to be more practical and effective than control conditions.191-195 An important resource that can be accessed through the Internet at no out-of-pocket cost is the smokefree.gov Web site. This Web site contains information on behavioral and pharmaceutical management of smoking cessation. It also incorporates a “Smokefree TXT” imbedded in the Web site, for which patients can sign up to receive text messages to help them quit smoking. Another useful feature on the Web site is its LiveHelp Chat Service and instant messaging that patients can use. Finally, newer applications for smart phones are now available in online stores, in an attempt to provide support to those trying to quit.

Recommended System Changes
The Public Health Service tobacco treatment guideline was developed in 1996, updated in 2000, and updated again in 2008 in a continuous effort to provide a structured and standardized guideline to clinicians for behavioral and pharmacological treatments in addition to system changes that need to be put in place.80 The main pillars of screening and interventions for tobacco use and dependence are summarized in the “5 A’s” model, which is recommended in the 2008 Public Health Service guideline. The 5 A’s are a simple, common tool for clinicians to help their patients quit smoking through the steps of “Ask, Advise, Assess, Assist, and Arrange.”196 Furthermore, the guidelines recommend proper documentation of medical and psychiatric histories; assessing smoking status as part of vital sign checkups; and, if feasible, obtaining biologic confirmation of abstinence from tobacco as part of any routine clinical intake.197 Another major recommendation in the 2008 Public Health Service guideline was the use of electronic health records to provide across-the-board screening for tobacco use (current or past) and effective referrals to treatment.198,199

Tailoring Cessation Treatments for Patients With Cancer
Patients with cancer who have never smoked, are former smokers, or have recently quit smoking have an approximately 2-fold increase in the 5-year overall likelihood of survival from cancer.200 In one study, patients undergoing bone marrow transplant who were not current smokers spent 50% less time in the hospital than their counterparts who continued to smoke.201 Former smokers and recent quitters also have better treatment outcomes and quality of life after treatment than current smokers. In one study in 105 patients with head and neck cancer, a comparison of 12-month quality-of-life scores between current smokers and former smokers or recent quitters indicated that, in general, current smokers reported a lower quality of life.73 In a study of 114 patients with head and neck cancer, continued smoking had a significantly negative influence on 20 of 33 quality-of-life scales.202 Fortunately, patients with cancer show higher motivation to quit smoking than the general population of smokers.16,20,203-205 Clinicians can seize this opportunity and provide the needed support to patients with cancer and survivors in their attempts to quit smoking, as recommended by the Centers for Disease Control and Prevention.206,207

Suggesting and promoting smoking cessation interventions (eg, a specific medication) for patients with cancer can be done once a thorough knowledge of the oncologic treatment (including the consequences and possible side effects) is achieved so the contraindications for each of the available smoking cessation medications can be considered and avoided. In the vast majority of situations, any of the 3 classes of smoking cessation medication can be used readily depending on patient preference, with a few exceptions in which precaution is needed. The best example would be nausea that occurs with chemotherapy, which prescribing varenicline can exacerbate.208 Other examples are NRTs (gum or lozenge), which may be irritating to a patient’s oral mucosa,209 in particular if fragile after head and neck radiation or certain chemotherapies, and bupropion, which can inactivate tamoxifen by blocking its metabolism into its active metabolites.210 In addition, attention must be given to the presence of psychiatric comorbidities (eg, depression, anxiety, and alcohol dependence) because a lack of proper psychiatric symptom relief can interfere with both the pharmacologic treatments for tobacco use disorder and the adjuvant cancer treatments.89,211

The above evidence to date supports the need for a tailored individual treatment plan to treat tobacco use among patients with cancer that would encompass smoking.
cessation advice and medications. Although studies of the effectiveness of tobacco cessation interventions specifically in patients with cancer are currently limited and in some cases have conflicting results, a few studies have been conducted that show physician-to-patient advice on smoking cessation as an intervention to be more effective than no such advice (control) in patients with cancer.207,212,213 Other interventions involving nurse-delivered advice to patients with cancer as one-on-one sessions have also resulted in successful outcomes in smoking cessation.214,215 With that stated, the gold standard for patients with cancer and survivors remains the same as that for the general population: a combination of medication and psychosocial therapies to increase the chances of quitting smoking and staying abstinent.109

Lastly, clinicians must be firm when setting specific expectations for patients to quit smoking before receiving treatment (especially for heavy smokers and those smokers about to undergo surgery or radiation therapy); as mentioned earlier in this article, the evidence of benefit from smoking cessation under those circumstances has been established.78 At the same time, clinicians need to be tactful and sensitive to avoid appearing to blame or instill guilt in these patients, because it has been shown that patients with cancer are often already blaming themselves for their diagnosis upon receiving a cancer diagnosis, especially if their cancer is tobacco related.216

The Tobacco Treatment Program at The University of Texas MD Anderson Cancer Center

The Tobacco Treatment Program (TTP) at The University of Texas MD Anderson Cancer Center is a comprehensive program that was initiated in 2006; it was built based on the 2000 Public Health Service tobacco treatment guideline and later the updated 2008 Public Health Service guideline.80 The central philosophy of treatment at the TTP is “meeting patients where they are” in terms of motivation to quit and tailoring each patient’s pharmacologic treatment to his or her particular situation and needs. To achieve this level of individualized care, we assess patients through a variety of approaches. We conduct an in-person interview covering their smoking history, previous attempts to quit, and methods used, as well as a detailed psychosocial history including issues surrounding their current cancer treatment. We also obtain an expired air carbon monoxide sample as corroboration of smoking and as a way for clinicians and patients to track their progress throughout the smoking cessation process.

Patients also complete a battery of self-administered assessment tools consisting of: 1) the Patient Health Questionnaire217; 2) the Center of Epidemiological Studies Depression scale218; 3) the Sleep Problems Questionnaire219; (4) the FTND81; 5) the Wisconsin Smoking Withdrawal Scale220; 6) the Positive and Negative Affect Schedule221; and 7) the Alcohol Use Disorders Identification Test.221,222 The results of these assessments and the psychosocial interview are shared with one of our medical providers (a physician assistant, an advanced practice nurse, or a medical doctor), who then evaluates the findings to determine the optimal tobacco cessation medication for each patient. The behavioral and pharmacological approaches are tailored as an individual-based smoking cessation plan.

The behavioral counseling consists of 20-minute to 30-minute sessions (6–8 sessions in total) delivered weekly or every 2 weeks by a tobacco specialist (master’s degree or higher) and spanning a 10-week period. Additional sessions can be provided if needed. Follow-up may be conducted in person or by telephone at the patient’s preference or convenience. Approximately 60% of the follow-up visits are done by telephone. During active treatment, highly specialized tailoring and adjustment of medications is made for those who do not quit within their first few weeks of the program, including the use of medication in combinations; novel medications; and, when indicated, increases in dosage above the usual dosages of first-line medications, done under close supervision. The entire program is free of charge to patients at The University of Texas MD Anderson Cancer Center and is paid for by Tobacco Settlement Funds to the state of Texas.223

Since its inception in January 2006 through the end of August 2013, the TTP served 4670 new patients and conducted 48,033 follow-up appointments. In 2012, we instituted a system-wide referral system using the proactive identification of all smokers and recent quitters using the electronic health record. On an annual basis, this has resulted in our program receiving over 5000 automatic referrals. Approximately 1100 individuals per year enter a face-to-face treatment option, and we estimate that about 300 individuals per year will enter a new telephone-only treatment option (similar to the face-to-face option but medication is provided by an outside physician); 3000 individuals will elect to receive an initial motivational call, educational materials, and at least one follow-up telephone call (many of these participants are recent quitters who opt for less contact); and around 1000 individuals, who we are unable to contact within a week of referral, will receive only the educational materials, although they may elect to participate at later time.

In 2011, we analyzed our 6-month follow-up data from our first cohort of patients (those who had at least one in-person appointment) from the start of the TTP in 2006 until the end of 2010. The 6-month abstinence rate (7-day point prevalence at 6 months after the end of treatment) among those who we were able to reach (respondent-only) was 46% abstinent (N = 1291 individuals; response rate, 74%). However, when an intention-to-treat model was used (including all patients treated at baseline and assuming that all those
lost to follow-up have resumed smoking), the 6-month abstinence rate (7-day point prevalence at 6 months after the end of treatment) dropped to 34% (N = 1670 individuals). In either case, these rates compare favorably with the abstinence rates of the best treatments available in the general population\(^ {184,224}\) as well as those for chronic illness.\(^ {225}\) Also of interest is our finding that individuals who did not quit reduced their daily cigarette consumption by about 44% from baseline to the end of treatment (from a mean of 16 cigarettes per day [standard deviation, 12.2 cigarettes] to a mean of 9 cigarettes per day [standard deviation, 9.1 cigarettes]; N = 1034) and by about 38% from baseline to 6 months after the end of treatment (from a mean of 16 to 10 cigarettes per day; N = 663) (unpublished data). We attribute these relatively high rates of abstinence from tobacco and reduction in its use to our individualized and intensive approach in both medications and psychosocial support. Another important element contributing to our higher quit rates is likely the fact of the individual having a diagnosis of cancer, which is a teachable moment that has a major influence on propelling patients to make a quit attempt.\(^ {226}\)

Conclusions

Tobacco use causes 30% of cancer deaths, complicates the treatment course, and adversely affects survival rates from cancer. These deaths can be prevented or greatly reduced by screening for and treating tobacco use disorder, in particular in the oncology setting. There are multiple medications and therapy techniques that are most effective when used in combination. Patients with and survivors of cancer are likely to be more dependent on nicotine than the average smoker (unpublished data) and therefore may require more intensive approaches, including the use of multiple medications along with counseling. Most studies on the impact of smoking and tobacco use on medical outcomes in patients with cancer show a deleterious effect, although the majority of those are retrospective studies. Therefore, there is a need for rigorous prospective trials to clarify the magnitude of the problem, and studies are needed to develop and test specific clinical algorithms to improve tobacco treatment among patients with and survivors of cancer. In the meantime, all clinicians are urged to identify tobacco use, provide treatment whenever possible, and use other public resources when internal ones are not available (eg, quitlines, Web sites, etc). A cultural shift is required for oncology providers to focus on screening for and treating tobacco use or referring tobacco users to treatment. Effective resource allocation and specialized treatment programs can be expected to maximize the success of such interventions.

References

1. Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States, 2000. JAMA. 2004;291: 1238-1245.

2. Centers for Disease Control and Prevention (CDC). Smoking-attributable mortality, years of potential life lost, and productivity losses—United States, 2000-2004. MMWR Mortal Mortal Wkly Rep. 2008;57:1226-1228.

3. Centers for Disease Control and Prevention (CDC). Cigarette smoking-attributable morbidity—United States, 2000. MMWR Mortal Mortal Wkly Rep. 2003;52:842-844.

4. Warren GW, Kasa KA, Reid ME, Cummings KM, Marshall JR. Smoking at diagnosis and survival in cancer patients. Int J Cancer. 2013;132:401-410.

5. US Department of Health and Human Services. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Atlanta, GA: Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.

6. Pappone LJ, Mustian KM, Morrow GR, et al. The effect of cigarette smoking on cancer treatment-related side effects. Oncologist. 2011;16:1784-1792.

7. Baldyuck B, Sardari Nia P, Cogen A, et al. The effect of smoking cessation on quality of life after lung cancer surgery. Eur J Cardiothorac Surg. 2011;40:1432-1437.

8. Substance Abuse and Mental Health Services Administration. Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings, HHS Pub. No. (SMA) 11-458. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2011.

9. US Department of Health and Human Services. How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2010.

10. Substance Abuse and Mental Health Services Administration. Results from the 2011 National Survey on Drug Use and Health: Summary of National Findings. HHS Pub. No. (SMA) 12-4713. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2012.

11. Agaku IT, King BA, Dubé SR; Centers for Disease Control and Prevention (CDC). Current cigarette smoking among adults—United States, 2005-2012. MMWR Morb Mortal Wkly Rep. 2014;63:29-34.

12. Centers for Disease Control and Prevention (CDC). Quitting smoking among adults—United States, 2001-2010. MMWR Morb Mortal Wkly Rep. 2011;60:1513-1519.

13. National Institute on Drug Abuse, National Institutes of Health. Tobacco Addiction. drugabuse.gov/publications/research-reports/tobacco-addiction. Accessed April 17, 2014.

14. Gritz ER, Nisenbaum R, Elashoff R, Holmes EC. Smoking behavior following diagnosis in patients with stage I nonsmall cell lung cancer. Cancer Causes Control. 1991;2:105-112.

15. Ostroff J, Garland J, Moadel A, et al. Cigarette smoking patterns in patients after treatment of bladder cancer. J Cancer Educ. 2000;15:86-90.

16. Ostroff JS, Jacobsen PB, Moadel AB, et al. Prevalence and predictors of continued tobacco use after treatment of patients with head and neck cancer. Cancer. 1995;75:569-576.

17. Sanderson CL, Patten CA, Ebbert JO, et al. Tobacco use outcomes among patients with lung cancer treated for nicotine dependence. J Clin Oncol. 2002;20:3461-3469.

18. Coups EJ, Ostroff JS. A population-based estimate of the prevalence of behavioral risk factors among adult cancer survivors and noncancer controls. Prev Med. 2005; 40:702-711.

19. Bellizzi KM, Rowland JH, Jeffery DD, McNeel T. Health behaviors of cancer survivors: examining opportunities for cancer control intervention. J Clin Oncol. 2005; 23:8884-8893.

20. Walker MS, Vidrine DJ, Gritz ER, et al. Smoking relapse during the first year after treatment for early-stage non-small-cell
lungenkrebs. Cancer Epidemiol Biomarkers Prev. 2006;15:2370-2377.
21. Warren GW, Arnold SM, Valentino JP, et al. Accuracy of self-reported tobacco assessments in a head and neck cancer treatment population. Radiother Oncol. 2012;103:45-48.
22. Morales NA, Romano MA, Michael CK, et al. Accuracy of self-reported tobacco use in newly diagnosed cancer patients. Cancer Causes Control. 2013;24:1223-1230.
23. Duffy SA, Ronis DL, McLean S, et al. Pre-treatment health behaviors predict survival among patients with head and neck squamous cell carcinoma. J Clin Oncol. 2009;27:1969-1975.
24. Gritz ER, Dresler C, Sarna L. Smoking, the missing drug interaction in clinical trials: ignoring the obvious. Cancer Epidemiol Biomarkers Prev. 2005;14:2287-2293.
25. Rabius V, Karam-Hage M, Blalock JA, Chaturvedi AK. Meaningful use provides a meaningful opportunity. Cancer. 2014;120:464-468.
26. Blumenthal D, Tavenner M. The “meaningful use” regulation for electronic health records. N Engl J Med. 2010;363:501-504.
27. Warren GW, Marshall JR, Cummings KM, et al. Addressing tobacco use in patients with cancer: a survey of an American Society of Clinical Oncology members. J Oncol Pract. 2013;9:258-262.
28. Gritz ER, Toll BA, Warren GW. Tobacco use in the oncology setting: advancing clinical practice and research. Cancer Epidemiol Biomarkers Prev. 2014;23:3-9.
29. Videtic GM, Stitt LW, Dar AR, et al. Continued cigarette smoking by patients receiving concurrent chemoradiation for limited-stage small-cell lung cancer is associated with decreased survival. J Clin Oncol. 2003;21:1544-1549.
30. Nguyen SK, Masson-Cote L, Fortin A, Dagnault A. Influence of smoking status on treatment outcomes after post-operative radiation therapy for non-small-cell lung cancer. Radiother Oncol. 2010;96:89-93.
31. Rades D, Setter C, Schild SE, Dunst J. Effect of smoking during radiotherapy, respiratory insufficiency, and hemoglobin levels on outcome in patients irradiated for non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2008;71:1134-1142.
32. Tammemagi CM, Neslund-Dudas C, Simoff M, Kvale P. Smoking and lung cancer survival: the role of comorbidity and treatment. Chest. 2004;125:27-37.
33. Garces VI, Yang P, Parkinson J, et al. The relationship between cigarette smoking and quality of life after lung cancer diagnosis. Chest. 2004;126:1733-1741.
34. Fox JL, Rosenzweig KE, Ostroff JS. The effect of smoking status on survival following radiation therapy for non-small-cell lung cancer. Lung Cancer. 2004;44:287-293.
35. Nordquist LT, Simon GR, Cantor A, Alberts WM, Bepler G. Improved survival in never-smokers vs current smokers with primary adenocarcinoma of the lung. Chest. 2004;126:347-351.
36. Kreuzer M, Bofetta P, Whitley E, et al. Gender differences in lung cancer risk by smoking: a multicentre case-control study in Germany and Italy. Br J Cancer. 2000;82:227-233.
37. Risch HA, Howe GR, Jain M, Burch JD, Holowaty EJ, Miller AB. Are female smokers at higher risk for lung cancer than male smokers? Am J Epidemiol. 1993;138:281-293.
38. Hinds JD, Wang HY, Stembermann G, Lee J, Kolonel LN. Smoking history and lung cancer survival in women. J Natl Cancer Inst. 1982;68:395-399.
39. Johnston-Early A, Cohen MH, Minna JD, et al. Smoking abstinence and small cell lung cancer survival. JAMA. 1980;244:2175-2177.
40. Chen AM, Chen LM, Vaughan A, et al. Tobacco smoking during radiation therapy for head-and-neck cancer is associated with unfavorable outcome. Int J Radiat Oncol Biol Phys. 2011;79:414-419.
41. Fortin A, Wang CS, Vigneault E. Influence of smoking status and alcohol drinking behaviors on treatment outcomes of patients with squamous cell carcinomas of the head and neck. Int J Radiat Oncol Biol Phys. 2004;60:106-110.
42. Marin VP, Pytynia KB, Langstein HN, Dahlstrom KR, Wei Q, Sturgis EM. Serum cotinine concentration and wound complications in head and neck reconstruction. Plast Reconstr Surg. 2008;121:451-457.
43. Pytynia KB, Grant JR, Ezel CJ, Roberts DB, Wei Q, Sturgis EM. Matched-pair analysis of survival of never smokers and ever smokers with squamous cell carcinoma of the head and neck. J Clin Oncol. 2004;22:3981-3988.
44. Rugg T, Saunders MJ, Dische S. Smoking and mucosal reactions to radiotherapy. Br J Radiol. 1990;63:554-556.
45. Stevens MH, Gardner JW, Parkin JL, Thompson JS. Effect of smoking on human natural killer cell activity. Cancer Epidemiol Biomarkers Prev. 2001;10:823-829.
46. Chelghoum Y, Danaila C, Belhabri A, et al. Influence of cigarette smoking on the presentation and histology of non-small cell lung cancer patients. Eur J Cancer. 2004;40:2546-2551.
47. Archimbaud E, Maupas J, Lecluzes-Allemand C, Fiore D, Viala JI. Influence of cigarette smoking on the presentation and course of acute myeloid leukemia. Ann Oncol. 2002;13:1621-1627.
48. Hormuzdi AR, Alavi A, Hanauer SB, et al. Smoking and the risk of cutaneous melanoma: a case-control study. JAMA. 2002;288:2060-2065.
49. Schuermans JP, Danaila C, Belhabri A, et al. Smoking and the risk of osteosarcoma: a population-based case-control study. Cancer. 1999;86:2373-2345.
50. Daniell HW. Increased lymph node metastases at mastectomy for breast cancer associated with host obesity, cigarette smoking, age, and large tumor size. Cancer. 1998;62:429-435.
51. Daniell HW. Estrogen receptors, breast cancer, and smoking. N Engl J Med. 1980;302:1478.
52. Lee CY, Choi W, Ramakrishnan R, et al. Longitudinal study of smoking patterns in relation to the development of smoking-related secondary primary tumors in patients with upper aerodigestive tract malignancies. Cancer. 2004;101:2837-2842.
53. Khuri FR, Kim ES, Lee JJ, et al. The impact of smoking status, disease stage, and index tumor site on second primary tumor incidence and tumor recurrence in the Head and Neck Retinoid Chemoprevention Trial. Cancer Epidemiol Biomarkers Prev. 2001;10:823-829.
54. Brown G, Sturgis EM, Boyd CR, et al. Influence of cigarette smoking on the efficacy of radiotherapy in head and neck cancer. N Engl J Med. 1993;328:159-163.
55. Brown G, Mohide EA, Willan A, et al. Association between smoking during radiotherapy and prognosis in head and neck cancer: a follow-up study. Head Neck. 2002;24:1031-1037.
56. Garces YL, Schroeder DR, Nirelli LM, et al. Tobacco use outcomes among patients with head and neck carcinoma treated for nicotine dependence: a matched-pair analysis. Cancer. 2004;101:116-124.
57. Hoff CM, Grau C, Overgaard J. Effect of smoking on oxygen delivery and outcome in patients treated with radiotherapy for head and neck squamous cell carcinoma: a prospective study. Radiother Oncol. 2012;103:38-44.
58. Gillison ML, Zhang Q, Jordan R, et al. Tobacco smoking and increased risk of death and progression for patients with p16-positive and p16-negative oropharyngeal cancer. J Clin Oncol. 2012;30:2102-2111.
59. Chen J, Qi Y, Wampfler JA, et al. Effect of cigarette smoking on quality of life in small cell lung cancer patients. Eur J Cancer. 2012;48:1593-1601.
60. Kenfield SA, Stampfer MJ, Chan JM, Giovannucci E. Smoking and prostate cancer survival and recurrence. JAMA. 2011;305:2548-2555.
61. Holmes MD, Murin S, Chen WY, Kroenke CH, Spiegelman D, Colditz GA. Smoking and survival after breast cancer diagnosis. Int J Cancer. 2007;120:2672-2677.
62. Toll BA, Brandon TH, Gritz ER, Warren GW, Herbst RS; AACR Subcommittee on Tobacco and Cancer. Assessing tobacco use by cancer patients and facilitating cessation: an American Association for Cancer Research policy statement. Clin Cancer Res. 2013;19:1941-1948.
63. Parsons A, Daley A, Begh R, Aveyard P. Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: systematic review of observational studies with meta-analysis. BMJ. 2010;340:b5569.
64. Tucker MA, Murray N, Shaw EG, et al. Second primary cancers related to smoking and treatment of small-cell lung can-
cer. Lung Cancer Working Cadre. J Natl Cancer Inst. 1997;89:1782-1788.
68. Gritz E, Lam CY, Vidrine DJ, Fingeret MC. Cancer prevention: tobacco dependence and its treatment. In: DeVita VT, Lawrence TS, Rosenberg SA, DePinho RA, Weinberg RA, eds. Cancer: Principles and Practice of Oncology. Vol 2. 8th ed. Philadelphia: Lippincott Williams & Williams; 2008:593-608.
69. Dresler CM, Gritz ER. Smoking, smoking cessation and the oncologist. Lung Cancer. 2003;43:135-150.
70. Sorensen LT, Horby J, Friis E, Pilgaard B, Jorgensen T. Smoking as a risk factor for wound healing and infection in breast cancer surgery. Eur J Surg Oncol. 2002;28:815-820.
71. Krueger JK, Rohrich RJ. Clearing the smoke: the scientific rationale for tobacco abstinence with plastic surgery. Plast Reconstr Surg. 2001;108:1063-1073.
72. Duffy SA, Terrell JE, Valenstein M, Ronis DL, Copeland LA, Connors M. Effect of smoking, alcohol, and depression on the quality of life of head and neck cancer patients. Gen Hosp Psychiatry. 2002;24:140-147.
73. Gritz ER, Carmack CL, de Moor C, et al. First year after head and neck cancer: quality of life. J Clin Oncol. 1999;17:352-360.
74. Volkow ND, Wang GJ, Fowler JS, Tomasi D, Teling F, Baler R. Addiction: decreased reward sensitivity and increased expectation sensitivity conspire to overwhelm the brain's control circuit. Bioessays. 2010;32:748-755.
75. Steinberg MB, Greenhaus S, Schmelzer AC, et al. Triple-combination pharmacotherapy for medically ill smokers: a randomized trial. Ann Intern Med. 2009;151:74-82.
76. McBride CM, Emmons KM, Lipkus IM. Understanding the potential of teachable moments: the case of smoking cessation. Health Educ Res. 2003;18:156-170.
77. Cooley ME, Wang Q, Johnson BE, et al. Factors associated with smoking abstinence among smokers and recent-quitters with lung and head and neck cancer. Lung Cancer. 2012;76:144-149.
78. Nayan S, Gupta MK, Strychowyk JE, Sommer DD. Smoking cessation interventions and cessation rates in the oncology population: an updated systematic review and meta-analysis. Otolaryngol Head Neck Surg. 2013;149:200-211.
79. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th revised ed. Washington, DC: American Psychiatric Association; 2000.
80. Fiore MC, Jaen CR, Baker TB, et al. Treating Tobacco Use and Dependence: 2008 Update, Clinical Practice Guideline. Rockville, MD: US Department of Health and Human Services, Public Health Service; 2008.
81. Payne TJ, Smith PO, McCracken LM, McSherry WC, Anthony MM. Assessing nicotine dependence: a comparison of the Fagerstrom Tolerance Questionnaire (FTQ) with the Fagerstrom Test for Nicotine Dependence (FTND) in a clinical sample. Addict Behav. 1994;19:307-317.
82. Pomerleau CS, Pomerleau OF, Majchrzak MJ, Kloska DD, Malakuti R. Relationship between nicotine tolerance questionnaire scores and plasma cotinine. Addict Behav. 1990;15:73-80.
83. Centers for Disease Control and Prevention (CDC). Smoking among adults-United States, 1992, and changes in the definition of current cigarette smoking. MMWR Morb Mortal Wkly Rep. 1994;43:342-346.
84. Yeager DS, Krosnick JA. The validity of self-reported nicotine product use in the 2001-2008 National Health and Nutrition Examination Survey. Med Care. 2010;48:1128-1132.
85. Curry LE, Richardson A, Xiao H, Niaura RS. Nondisclosure of smoking status to health care providers among current and former smokers in the United States. Health Educ Behav. 2013;40:266-273.
86. Shipton D, Tappin DM, Vadiveloo T, Crossley JA, Aitken DA, Chalmers J. Reliability of self-reported smoking status by pregnant women for estimating smoking prevalence: a retrospective, cross sectional study. BMJ. 2009;339:b4347.
87. Pell JP, Haw SJ, Cobbe SM, et al. Validity of self-reported smoking status: comparison of patients admitted to hospital with acute coronary syndrome and the general population. Nicotine Tob Res. 2008;10:861-866.
88. Martinez ME, Reid M, Jiang R, Einspahr J, Alberts DS. Accuracy of self-reported smoking status among participants in a chemoprevention trial. Prev Med. 2004;38:492-497.
89. Gritz ER, Fingeret MC, Vidrine DJ, Lazev AB, Mehta NV, Reece GP. Successes and failures of the teachable moment: smoking cessation in cancer patients. Cancer. 2006;106:17-27.
90. Centers for Disease Control. Adult Smoking: Focusing on People with Mental Illness. cdc.gov/vitalsigns. Accessed April 14, 2017.
91. Schroeder SA, Morris CD. Confronting a neglected epidemic: tobacco cessation for persons with mental illnesses and substance abuse problems. Annu Rev Public Health. 2010;31:297-314.
92. Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: a population-based prevalence study. JAMA. 2000;284:2606-2610.
93. Barkley RA, Fischer M, Edelbrock CS, Smallish L. The adolescent outcome of boys and their brothers. A 25-year follow-up study. Arch Gen Psychiatry. 1990;47:546-557.
94. Borland BL, Heckman HK. Hyperactive boys and their brothers. A 25-year follow-up study. Arch Gen Psychiatry. 1990;29:546-557.
95. Breslau N, Johnson EO, Hiripi E, Kessler RC. Nicotine dependence in the United States: prevalence, trends, and smoking persistence. Arch Gen Psychiatry. 2001;58:810-816.
96. Covey LS, Hughes DC, Glassman AH, Blazer DG, George LK. Ever-smoking, stance abuse problems. cdc.gov/vitalsigns. Accessed April 14, 2017.
97. Glassman AH, Helzer JE, Covey LS, et al. Smoking, smoking cessation, and major depression. JAMA. 1990;264:1546-1549.
98. Hartough CS, Lambert NM. Pattern and progression of drug use among hyperactive children and controls: a prospective short-term longitudinal study. J Child Psychol Psychiatry. 1987;28:543-553.
99. Williams JM, Ziedonis D. Addressing tobacco among individuals with a mental illness or an addiction. Addict Behav. 2004;29:1067-1083.
100. Batel P, Pessone F, Maître C, Rueff B. Relationship between alcohol and tobacco dependence among alcoholics who smoke. Addiction. 1995;90:977-980.
101. Breslau N. Psychiatric comorbidity of smoking and nicotine dependence. Behav Genet. 1995;25:95-101.
102. Breslau N, Peterson EL, Schultz LR, Chilcoat HD, Andreski P. Major depression and stages of smoking: a longitudinal investigation. Arch Gen Psychiatry. 1998;55:161-166.
103. Breslau N, Klein DF. Smoking and panic attacks: an epidemiologic investigation. Arch Gen Psychiatry. 1999;56:1141-1147.
104. Brown DC. Smoking cessation in pregnancy. Can Fam Physician. 1996;42:102-105.
105. Johnson RA, Hoffmann JP. Adolescent cigarette smoking in U.S. racial/ethnic subgroups: findings from the National Educational Longitudinal Study. J Health Soc Behav. 2000;41:392-407.
106. Kendler KS, Neale MC, Maclean CJ, Heath AC, Eaves LJ, Kessler RC. Smoking and major depression: a casual analysis. Arch Gen Psychiatry. 1993;50:36-43.
107. Blacket JA, Minnik JA, Karam-Hage M, Gritz ER, Robinson JD, Cinciripini PM. The effect of mood, anxiety and alcohol use disorders on smoking cessation in cancer patients. J Cognitive Psychother. 2011;25:82-90.
108. Martinez E, Tatum KL, Weber DM, et al. Issues related to implementing a smoking cessation clinical trial for cancer patients. Cancer Causes Control. 2009;20:97-104.
109. Nayan S, Gupta MK, Sommer DD. Evaluating smoking cessation interventions and cessation rates in cancer patients: a systematic review and meta-analysis. ISRN Oncol. 2011;2011:849023.
110. Oncken C, Arias AJ, Feinn R, et al. Topiramate for smoking cessation: a randomized, placebo-controlled pilot study. Nicotine Tob Res. 2014;16:288-296.
111. Johnson BA, Rosenthal N, Capece JA, et al. Topiramate for treating alcohol dependence: a randomized controlled trial. JAMA. 2007;298:1641-1651.
112. US National Institutes of Health. High and Low Dose Topiramate for the Treatment of Alcohol-Dependent Smokers. clinicaltrials.gov/ct2/show/NCT01182766?term=high+and+low+dose+topiramate&rank=1. Accessed April 17, 2014.
113. Nabi Biopharmaceuticals. Nabi Biopharmaceuticals Announces Results of Second NicVAX(R) Phase IIb/III Study. corporate-ir.net/phoenix.zhtml?c=100445&p=irol-newsArticle&ID=1626882. Accessed April 17, 2014.
114. Esterlis I, Hannestad JO, Perkins E, et al. Effect of a nicotine vaccine on nicotine binding to beta2&-nicotinic acetylcholine receptors in vivo in human tobacco smokers. *Am J Psychiatry*. 2013;170:399-407.

115. Raupach T, Hoogsteder PHJ, Onno CP. Nicotine receptor antagonists to assist with smoking cessation: current status of research. *Drugs*. 2012;72:e1-e16.

116. Tonstad S, Heggen E, Giljam H, et al. Nicotine[R], a nicotine vaccine, for relapse prevention: a phase II, randomized, placebo-controlled, multicenter clinical trial. *Nicotine Tob Res*. 2013;15:1492-1501.

117. Hughes JR, Stead LF, Hartmann-Boyce J, Cullik K, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev*. 2014;1:CD000031.

118. Beckham JC. Smoking and anxiety in combat veterans with chronic posttraumatic stress disorder: a review. *J Psychoactive Drugs*. 1999;31:103-110.

119. Evins AE, Cather C, Deckersbach T, et al. Nicotine receptor antagonists for smoking cessation. *Cochrane Database Syst Rev*. 2012:4;CD006103.

120. Hughes JR, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev*. 2012;4:CD009329.

121. Cullum JL, Wojciechowski AE, Pelletier G, et al. Evaluation of an intervention to enhance the delivery of smoking cessation services to patients with cancer. *J Cancer Educ*. 2011;26:577-582.

122. Taylor MJ, Rudkin L, Bullemor-Day P, et al. A randomized, double-blind, placebo-controlled trial of bupropion sustained-release for smoking cessation in schizoaffective disorder. *J Clin Psychopharmacol*. 2005;25:218-225.

123. Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev*. 2007;1:CD000031.

124. Cullum JL, Wojciechowski AE, Pelletier G, Simpson JS. Bupropion sustained release treatment reduces fatigue in cancer patients. *Can J Psychiatry*. 2004;49:139-144.

125. Mooney ME, Sofouglu M. Bupropion for the treatment of nicotine withdrawal and craving. *Exp Rev Neurother*. 2006;6:965-981.

126. Segraves RT, Kavoussi R, Hughes AR, et al. Evaluation of sexual functioning in drug treatment outpatients: a double-blind, comparison of sustained-release bupropion and sertraline treatment. *J Clin Psychopharmacol*. 2000;20:122-128.

127. Taylor MJ, Rudkin L, Buller-Day P, Labin J, Chukwujekwu C, Hawton K. Strategies for managing sexual dysfunction induced by antidepressant medication. *Cochrane Database Syst Rev*. 2013;5:CD003582.

128. Sadovsky R, Basson R, Krychman M, et al. Cancer and sexual problems. *J Sex Med*. 2010;7(1 pt 2):349-375.

129. Gonzales D, Rennard SI, Nides M, et al; Varenicline Phase 3 Study Group. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA*. 2006;296:56-63.

130. Hertzberg MA, Moore SD, Feldman ME, Beckham JC. A preliminary study of bupropion sustained-release for smoking cessation in patients with chronic posttraumatic stress disorder. *J Clin Psychopharmacol*. 2001;21:94-98.

131. Breslau N, Schultz LR, Johnson EO, Peterson EL, Davis GC. Smoking and the risk of suicidal behavior: a prospective study of a community sample. *Arch Gen Psychiatry*. 2005;62:328-334.

132. Donald M, Dower J, Correa-Velez I, Jones M. Risk and protective factors for medically serious suicide attempts: a comparison of hospital-based with population-based samples of young adults. *Aust N Z J Psychiatry*. 2006;40:87-96.

133. Kessler RC, Borges G, Sampson N, Miller M, Nock MK. The association between alcohol, cigarettes and coffee and the risk of suicide. *Addiction*. 2000;95:1699-1704.

134. Tonstad S, Davies S, Flammer M, et al. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev*. 2012;4:CD009329.

135. Taylor MJ, Rudkin L, Bullemor-Day P, et al. A randomized, double-blind, placebo-controlled trial of varenicline, an alpha 4 beta 2 nicotinic receptor partial agonist, vs placebo or sustained-release bupropion, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA*. 2006;296:56-63.

136. Montoya DE, Robinson J, Sareen J, Bolton JM. The relation between nicotine dependence and suicide attempts in the general population. *Can J Psychiatry*. 2011;56:161-170.

137. Hughes JR, Stead LF, Hartmann-Boyce J, Cullik K, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev*. 2014;1:CD000031.

138. Raupach T, Hoogsteder PHJ, Onno CP. Nicotine receptor antagonists for smoking cessation. *Cochrane Database Syst Rev*. 2012;4:CD006103.

139. Tanskanen A, Tuomilehto J, Viinamaki H, M. Nicotine dependence vs. daily smoking and placebo for smoking cessation. *Cochrane Database Syst Rev*. 2012:5:CD009329.

140. Bohnert KM, Ilgen MA, McCarthy JF, Ignacio RV, Blow FC, Ganz DJ. Tobacco use disorder and the risk of suicide mortality. *Addiction*. 2013;109:155-162.

141. Tonstad S, Davies S, Flammer M, et al. Nicotine and Tobacco. 2006.

142. Hughes JR, Stead LF, Hartmann-Boyce J, Cullik K, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev*. 2014;1:CD000031.

143. Miller M, Hemenway D, Bell NS, Yore MM, Amoroso PJ. Cigarette smoking and suicide: a prospective study of 300,000 military active-duty soldiers. *Am J Epidemiol*. 2000;151:1060-1063.

144. Gonzales D, Rennard SI, Nides M, et al; Varenicline Phase 3 Study Group. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA*. 2006;296:56-63.

145. Williams JM, Anthenelli RM, Morris CD, et al. A randomized, double-blind, placebo-controlled study of the safety and efficacy of varenicline for smoking cessation in patients with schizophrenia or schizoaffective disorder. *J Clin Psychiatry*. 2012;73:654-660.
208. Jimenez-Ruiz C, Berlin I, Hering T. Varenicline: a novel pharmacotherapy for smoking cessation. *Drugs*. 2009;69:1319-1338.

209. Wallstrom M, Sand L, Nilsson F, Hirsch JM. The long-term effect of nicotine on the oral mucosa. *Addiction*. 1999;94:417-423.

210. Desmarais JE, Looper KJ. Interactions between tamoxifen and antidepressants via cytochrome P450 2D6. *J Clin Psychiatry*. 2009;70:1688-1697.

211. Duffy SA, Ronis DL, Valenstein M, et al. A tailored smoking, alcohol, and depression intervention for head and neck cancer patients. *Cancer Epidemiol Biomarkers Prev*. 2006;15:2203-2208.

212. Gritz ER, Carr CR, Rapkin D, et al. Predictors of long-term smoking cessation in head and neck cancer patients. *Cancer Epidemiol Biomarkers Prev*. 1993;2:261-270.

213. Schnoll RA, Rothman RL, Wient DB, et al. A randomized pilot study of cognitive-behavioral therapy versus basic health education for smoking cessation among cancer patients. *Ann Behav Med*. 2005;30:1-11.

214. Griebel B, Wewers ME, Baker CA. The effectiveness of a nurse-managed minimal smoking-cessation intervention among hospitalized patients with cancer. *Oncol Nurs Forum*. 1998;25:897-902.

215. Wewers ME, Bowen JM, Stanislaw AE, Desimone VB. A nurse-delivered smoking cessation intervention among hospitalized postoperative patients—fluence of a smoking-related diagnosis: a pilot study. *Heart Lung*. 1994;23:151-156.

216. Gritz ER, Fingeret MC, Vidrine DJ. Tobacco control in the oncology setting. In: Brawley OW, Khuri FR, Rock C, eds. ASCO Cancer Prevention Curriculum. Alexandria, VA: American Society of Clinical Oncology; 2007.

217. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *JAMA*. 1999;282:1737-1744.

218. Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977;1:385-401.

219. Jenkins CD, Stanton BA, Niemczyk SJ, Rose RM. A scale for the estimation of sleep problems in clinical research. *J Clin Epidemiol*. 1988;41:313-321.

220. Welsch SK, Smith SS, Wetter DW, Jorenby DE, Fiore MC, Baker TB. Development and validation of the Wisconsin Smoking Withdrawal Scale. *Exp Clin Psychopharmacol*. 1999;7:354-361.

221. Babor TF, de la Fuente JR, Saunders JB, Grant M. AUDIT. The Alcohol Use Disorders Identification Test. Guidelines for Use in Primary Healthcare. Geneva, Switzerland: World Health Organization; 1992:1-30.

222. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol*. 1988;54:1063-1070.

223. Texas Department of State Health Services Mental Health and Substance Abuse Division, Tobacco Prevention and Control Program. Texas Tobacco Settlement Information. dshs.state.tx.us/tobacco/settlement.shtm. Accessed April 17, 2014.

224. Kotz D, Brown J, West R. 'Real-world' effectiveness of smoking cessation treatments: a population study. *Addiction*. 2014;109:491-499.

225. Rigotti NA, Pipe AL, Benowitz NL, Arteaga C, Garza D, Tonstad S. Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease: a randomized trial. *Circulation*. 2010;121:221-229.

226. Gritz ER, Vidrine DJ, Fingeret MC. Smoking cessation a critical component of medical management in chronic disease populations. *Am J Prev Med*. 2007;33(suppl 6):S414-S422.