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

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Abstract

Around 30% of all cancer deaths in the United States are caused by tobacco use and smoking. Eighteen cancer sites have been causally linked to smoking, the most common of which are lung, head and neck, bladder and esophageal cancer. 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 cancer patients and survivors. 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 a most promising approach. Challenges in our 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, e.g. 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. We recommend that oncology providers screen all patients for tobacco use and refer users to specialized treatment where available. Alternatively, oncology clinicians can provide basic advice on tobacco use cessation and pharmacotherapy and/or referral to outside resources, e.g. quitlines. Here, we summarize the current knowledge on tobacco use and its treatment, with a focus on the related available evidence for cancer patients and cancer survivors.

Keywords

Tobacco; survivorship; treatment; prevention

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Background

The early detection of cancer, due to improved diagnostic modalities, and development of more effective treatments has contributed to the increase in the overall cancer survival rate. The overall 5-year survival rate for all cancers rose from 49% in 1975–1977 to about 68% in 2002–2008, according to the most recent available data.[1] 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.[1–3] Almost 62% of all recently diagnosed cancer patients are reportedly current smokers, recent quitters (quit within the last 12 months), or former smokers; with the highest proportions of current smokers, recent quitters, or former smokers in patients with lung or head and neck cancer.[4] Smoking cessation and relapse prevention represent an important opportunity to improve cancer survival rates,[5] reduce the risk of cancer treatment complications,[6] and improve the quality of life of cancer patients and survivors.[7]

After a continuous decrease in smoking rates over several decades, the overall smoking prevalence in the US 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.[8] Close to half a million Americans die each year from smoking-related illnesses.[9] In one national survey in 2010, an estimated 69.6 million Americans aged 12 years or older were current users of a tobacco product (i.e., had used tobacco in the past month), confirming that tobacco is one of the most widely used substances in the United States (US). Among these tobacco users, 58.3 million (23.0% of the population above the age of 12) 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.[10] On the other hand, the most recent yearly report of the Centers for Disease Control and Prevention (CDC) estimates that 42.1 million people, 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%).[11] Other national surveys estimate that 70% of smokers in the US say they want to quit and 50% have tried to quit at least once in the preceding year.[12] Unfortunately, almost all (95%) of those who tried to quit on their own relapse,[12] usually in 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.[13]

Among lung, head and neck, and bladder cancer patients as well as survivors, prognosis, tumor site, and the impact of cancer treatment itself seem to influence smoking cessation rates.[14–17] 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—for example, the need to avoid smoking before surgery or a hospitalization that would limit patients' ability to smoke. Still, in the long run, there do not seem to be significant differences between smoking rates in cancer survivors and the general population. In one survey, almost 20% of cancer survivors reported being current smokers, with a high rate of 43% of cancer survivors younger than 40 years reporting current

smoking.[18] The overall prevalence of current smoking among cancer survivors is around 23% during the first year after diagnosis.[19] After that period, abstinence from smoking drops gradually, suggesting that the first year after diagnosis is a crucial time for relapse prevention interventions.[20] 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 for confirmation of abstinence. Indeed, self-reports of tobacco use (smoking) status in one study with head and neck cancer patients was shown to be underestimated in comparison to rates obtained using biologic corroboration of smoking status.[21] In another study, recently diagnosed cancer patients 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).[22]

Remarkably, apart from disease site and stage, abstinence from smoking is the strongest predictor of survival in cancer patients who have ever smoked. As a group, current smokers, former smokers, and recent quitters have poorer survival outcomes than never smokers.[23] In a cohort of 5185 cancer patients 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 to recent quitters hazard ratio (HR) = 1.17, (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. Further, current smokers had a higher disease-specific mortality (DSM) risk than former HR = 1.23, (95% CI, 1.09–1.39) and never smokers HR = 1.18, (95% CI, 1.03–1.36).[4]

In recent years, screening for tobacco use in cancer settings has been emphasized,[24] while progress have been made, more system wide changes need to be done to reach universal screening.[25,26] In addition, the provision of tobacco cessation treatment for identified tobacco users is still not widely available. In a recent survey of oncology providers, less than half of tobacco users were offered tobacco cessation treatment.[27] This gap is an area of cancer care that requires improvement as it can bring both long term (survival) as well as short term benefit to the patient in terms of improved treatment outcomes.[28] Multiple retrospective studies have been done on the impact of continued smoking on cancer treatment; although some are of small sample sizes, all have shown the deleterious impact of continuing to smoke in cancer patients.[5] These retrospective studies have focused mostly on smoking-related cancers such as lung,[29,29–39] head and neck,[40–45] esophagus,[46] hematologic (leukemia),[47,48] bladder,[49,50] colon,[51] and breast cancers.[52–54] Other, prospective studies that were also done to show the impact of continued smoking on cancer treatment have produced similar findings in cancers of the head and neck,[23,43,55–60] oropharynx,[61] lungs,[7,62] prostate,[63] and breast.[64] Collectively, these studies support the notion that tobacco cessation improves treatment outcomes in cancer patients and highlight the importance of providing tobacco cessation services to cancer patients and survivors. Not to do so can have negative clinical implications as patients who continue to smoke during the course of their cancer treatment have higher risks of complications, of developing secondary cancers, and

of death.[65] A wide body of literature supports the role of tobacco in carcinogenesis[5] 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 people who continue to smoke after diagnosis of early-stage lung cancer almost double their risk of dying.[66] In a study of 611 small-cell lung cancer patients, the risk of all second cancers (mostly non–small-cell cancers of the lung) was increased by 3.5-fold [relative risk (RR) of 3.5 (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 (who were ex-smokers, recent quitters or current smoker). Further, the risk of a second lung cancer was also increased RR=13 (95% CI, 9.4–17), in those patient (compared with never smokers) who received chest radiation; while that risk of second lung cancer increased to a lesser extent RR=7 (95% CI, 2.9–13) those patients if did not receive chest radiation. An interaction between chest radiation and continued smoking resulted in the highest risk RR=21 (95% CI, 13–32).[67] In addition, in other studies cancer patients who were active smokers during cancer treatment had lower response rates to radiation therapy than former smokers and recent quitters who stopped smoking before starting treatment.[57,58] Common side effects of radiation such as oral mucositis, xerostomia, weight loss, and fatigue were reported as exacerbated by cigarette smoking.[68] Smoking also affects the liver metabolism of many chemotherapeutic agents, thereby often decreasing the response to chemotherapy and increasing the rates of complications.[69] Continued smoking also increases the risk of complications in patients who require surgical intervention. In a meta-analysis on the topic, several end points were separately evaluated. In 19 unique studies comprising 7616 unique patients, cigarette smoking was found to increase the risk of necrosis of wound and tissue, with an odds ratio (OR) of 3.61 (95% CI, 2.78–4.68). The end point 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). Surgical site infection was an end point in 51 unique studies comprising over 400,000 patients, with an OR of 2.12 (95% CI, 1.56–2.88)[70]; further, in plastic surgery tissue ischemia and wound-healing impairment are related to continued tobacco use versus abstinence.[71]

In addition to higher morbidity and mortality rates, cancer survivors who are former smokers/recent quitters or current smokers score lower on quality of life indices than survivors who have never smoked.[7,33] Moreover, in two studies of lung cancer survivors and one in head and neck survivors, 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 quit smoking after their cancer diagnosis.[33,72,73] Cancer survivors who continued to smoke generally also had poorer physical health, self-perception of their general health, emotional and social functioning, and vitality than survivors who were never smokers or former smokers.[33,72,73]

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[16]; however, the recidivism rates remain high.[20] Although the concept of addiction

(compulsive use of tobacco despite adverse consequences) has not been studied in cancer patients, addiction is thought of as a universal concept of a brain disorder[74] that affects cancer patients similarly as any other chronic disease would impact them, such as 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.[75] Therefore, clinicians are urged to be on the lookout for delayed relapses. And they should address smoking behavior and history on an ongoing basis by conceptualizing smoking (repeated tobacco use) as a chronic and relapsing disorder,[76] in contrast to the way acute disorders (e.g., 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 cancer patients, with about half concentrating on nurse delivered intervention.[77] 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 in the overall providing smoking cessation intervention to cancer patients did not seem to improve cessation rates. This may be due to lack of homogeneity among the pooled studies, as they had different measures for smoking and abstinence, they included different types of cancer site and cancer patient populations (out-patients only or inpatients only).[78]

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. Then, we 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. That is in 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.[79] Systematic screening for tobacco use has been recommended for many years.[80] 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 tobacco use status of 13 years old patients or older. This is required for more than 50% of admitted patients in phase I, then 80% or more is required in phase II.[26] Furthermore, screening for tobacco use opens 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 Fagerström Test for Nicotine Dependence (FTND), 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 nicotine

dependent.[81,82] 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: Have you smoked more than 100 cigarettes in your lifetime? And to determine daily smoking, the question is: Do you smoke one or more cigarettes per day?[83] 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 e-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[84] except in patients who perceive a stigma associated with smoking,[85] 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 (e.g., pregnant women,[86] patients with coronary disease,[87] and patients with cancer[88]). Cancer patients in particular are under pressure (both internal and external) to quit using tobacco, especially when their cancer is tobacco related.[89] Advising patients ahead of time about the procedure of verification of abstinence via cotinine or carbon monoxide testing (e.g., 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 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 high school and 45% of those with a (GED) are smokers), and among those with lower socioeconomic status (29% of those under the federal poverty level are smokers).[10] Even more dramatic is that one of three individuals with a mental health disorder is a current smoker (33%) in contrast to one of five (20%) in the general population.[90,91] 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 US.[92] 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.[92–99] 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%–30% of smokers having lifetime alcohol or other substance use disorders.[100,101] 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.[102–106]

The co-occurrence of these mental health disorders and tobacco use disorder supports the importance of screening and treating mental health disorders among smokers;[99] cancer patients or cancer survivors 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.[107] 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.[108]

Treatment Principles

When the US Department of Health and Human Services treatment guideline for tobacco cessation were last updated, in 2008, ten specific recommendations for treatment were formulated as a quick guide to the overall principles.[80] While some patients may quit on their own or require minimal advice to quit, it is essential to keep in mind that in the treatment of tobacco use in many cancer patients may require a more intensive and comprehensive approach.[25] 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 cancer patient or survivor to quit smoking.[109] 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, cancer patients 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 cancer patients and survivors as they are in patients without cancer or history of cancer, with proper precautions for any medical contraindications.

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), varenicline (known as Chantix in the US and as Champix in other countries), and five 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.[80] For a detailed comparison of the differential efficacies of monotherapies and combination therapies, refer to Table 1, as published in the clinical treatment guideline of 2008.[80] Topiramate is another medication that holds promise for both alcohol and tobacco use disorders[110,111] and is being studied in clinical trials[112] to test its efficacy in treating co-occurring alcohol and nicotine use disorders. Topiramate is currently available in the US under 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.[113] A recent study incorporating imaging techniques with a different type of vaccine had encouraging results.[114] 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.[114–116]

Bupropion—Bupropion has both antidepressant and smoking cessation benefits, although it 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) (RR) of 1.62 (95% CI, 1.49–1.76) of continuous abstinence at 6 months.[117] The RR of 1.62 is based on an assumed risk of 115 per 1000 for a control (placebo) and a risk of 187 (172–201) per 1000 for bupropion (RR is an important statistic that is being used increasingly, as RR refers to the probability of abstinence on the control divided by the probability of abstinence on the active treatment). The side effects of this first-line medication (e.g., 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 bupropion use of a daily dose between 150 and 300 mg/day is similar to other antidepressants at about one in 1000; however it is gets higher with increased daily dose).[117] This medication has the added advantages of improving the mood and energy levels of individuals experiencing a depressed mood or low energy,[118–121] which seems to be true for cancer patients as well.[122] In addition, bupropion reduces the usual appetite increase and weight gain that follows smoking cessation;[123] however, this may not be desirable for cancer survivors who lose weight during cancer treatment. Another reported advantage is its positive impact on sexual functioning when used as antidepressant in some patients,[124,125] although bupropion has not been tested for this specific symptom among cancer patients and survivors, despite it being a major problem in some cancer survivors.[126]

Varenicline—Varenicline is the latest marketed non–nicotine-based smoking cessation medication; it was approved in 2006 in the US. 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 about two times higher than bupropion did and three times higher than a placebo did.[127–129]

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 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 four trials, with an RR of 2.09 (95% CI, 1.56–2.78; N = 1272).[130] The pooled RR for varenicline versus bupropion in three 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 two trials was 1.13 (95% CI, 0.94–1.35; N = 778). Of interest, a lower dosage of varenicline (1mg/day) in four trials seemed to reduce the number and severity of adverse effects while having a slightly lower efficacy**,** with an RR of 2.09 (95% CI, 1.56–2.78; N = 1272).[131] Although two small trials are reported in cancer patients and survivors using Varenicline successfully,[132,133] the finding that a low dosage of varenicline causes fewer, less severe side effects is of particular importance to keep in mind when prescribing it in the oncology setting. That is because cancer patients and survivors can be more susceptible to side effects, possibly owing to their exposure to invasive treatments (e.g., surgery, chemotherapy, and radiation therapy).

Among the commonly reported side effects of varenicline are nausea, flatulence, and vivid dreams; on the other hand, neuropsychiatric side effects from varenicline (e.g., 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 post-marketing 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 ideations.[134] Since these reports are all 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 three 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.[135–144] 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.[145] 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.[146]

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 do.[147] 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.[148] 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.[149] Two re-analyses 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 (e.g., depression and anxiety).[150,151] Furthermore, three 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, 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.[152] The second study did not find a difference in depressive symptoms between people who quit smoking on varenicline and those who quit while on a placebo, regardless of whether they had a history of or current depression.[153] The third, done in stable patients with schizophrenia in a multisite controlled trial, resulted in lower abstinence with varenicline than in the general population, a 19% vs. 5% for placebo, but no difference in psychotic symptoms exacerbation.[154] 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 under way. EAGLES is an international multisite study with eight arms into which 8000 participants are being randomized. The study will assess varenicline, bupropion, and nicotine patch as aids to smoking cessation treatment and to characterize the neuropsychiatric safety profiles of these medications in subjects 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 to bupropion, the nicotine patch or placebo.[155]

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 consumption and aid their smoking cessation simultaneously.[156,157] While the evidence is not at the level of recommending varenicline as a standard of care for such patients, this finding is of particular importance because alcohol and tobacco use are common comorbid conditions and are causally linked to many head and neck cancers, and often, patients continue to use these two substances throughout cancer treatment and survivorship.

Another important factor in an era of cost containment is the cost-effectiveness of any new treatment; in a recent review, varenicline was clearly superior to bupropion in most of the cost-effectiveness models utilized.[158] In a study from the Netherlands, varenicline was found to be more cost-effective than nortriptyline, bupropion, or NRTs when efficacy was considered in the equation.[159]

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 100/1000 risk for a control (placebo).[160] 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; four trials) for a nicotine inhaler, and 2.02 (95% CI, 1.49–2.73; four 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; nine trials).[161] 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.[162]

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. This fear was not substantiated in later studies;[163,164] in fact, the currently available data show that using an NRT during a short lapse (less than a day of smoking after having quit) may reduce the chances of complete relapse (returning to smoking).[165] 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.[166–169]

Some studies have shown that the combination of an NRT such as a nicotine patch plus an episodic NRT (e.g., 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.[170]

Alternative Pharmacologic Treatments—Recent trends in the literature point towards a combination approach as more effective than monotherapy—that is, using several first-line medications together in targeting tobacco cessation.[171,172] 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 two combinations were superior when compared with each of those agents taken as monotherapy.[164,173–175] Another potential combination is varenicline plus bupropion, which has shown some

preliminary positive evidence in a small open-label trial,[176] and recently in a blinded, placebo-controlled trial it had marginal effectiveness for regular smokers but a more robust effect for heavy smokers.[177] Our group recently concluded another randomized placebo-controlled clinical trial testing the efficacy of that combination, however our preliminary results are not conclusive.[178]

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.[121,179,180] 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. Still, these second-line medications have been shown to be at least two times more effective than a placebo for smoking cessation;[181] 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 cancer patients and survivors, nortriptyline also has desirable effects as an antidepressant, antianxiety, appetite-stimulating, sleep–inducing, and pain-attenuating medication.[182]

Clonidine also has some particular advantages in certain cancer patients 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 three times a day, owing to its short half-life.[179,183]

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 (≤22 mg), six used a high-dose NRT patch (>22 mg), five used high-dose versus standard-dose NRT patches, five used combination NRT versus inert controls, six used combination NRT versus single-form NRT (patch), 48 used bupropion, and 11 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.[184]

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 PHS 2008 guideline concludes that the combination of behavioral and pharmacological interventions doubles abstinence rates compared with either type of intervention alone.[80] Further, in the guideline, specific therapeutic techniques have been shown to be superior in abstinence rates compared with no contact (i.e., 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 abstinence rate of 16.2% (95% CI, 14–18.5); (2) providing support during a smoker's direct contact with a clinician (intra-treatment social support), according to 50 trials with OR of 1.3 (95% CI, 1.1–1.6) and abstinence rate of 14.4 (95% CI, 121.3–16.5); (3) intervening to

increase social support in the smoker's environment (extra-treatment social support), according to 19 trials with OR of 1.5 (95% CI, 1.1–2.1) and abstinence rate of 16.2% (95% CI, 11.8–20.6); and (4) using aversive smoking procedures (e.g., rapid smoking and rapid puffing-a procedure that is not typically used), according to 19 trials with OR of 2.0 (95% CI, 1.1–3.5) and abstinence rate of 19.9% (95% CI, 11.2–29.0). Any type and amount of therapy, including "minimal counseling" support of 1–3 minutes, is better than none, according to 12 trials with an OR of 1.4 (95% CI, 1.1–1.8) and 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 eight 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 two of the included studies provided four or more sessions of support. Most trials used NRT as the pharmacotherapy. In subgroup analyses, studies that provided at least four 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; six trials), as did studies where all intervention counseling was via telephone (RR, 1.28; 95% CI, 1.17–1.41; six trials).[185] In a recent review of combined behavioral and pharmacological interventions, based on 40 studies there was good evidence for an advantage of using combination pharmacotherapy and behavioral treatment in comparison to 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 or not. A weak but consistent effect was noted supporting larger effects for studies using more versus less number of sessions but that was not 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 up-take was high.[186] Finally, group therapy for smoking cessation has been suggested to be more effective than non-intervention, in the 2008 Public Health Service (PHS) guideline for treating tobacco use and dependence, according to 52 studies with OR of 1.3 (95% CI, 1.1–1.6) and abstinence 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 cancer patients and survivors in various oncology settings (e.g., inpatient, peri-operative period or outpatient) has been suggested;[109] 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. Still, 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, as those are 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 useful for clinicians in private practice who do not have expertise or capability to treat tobacco use. Both telephone- and internet-based quitlines have been shown to improve smoking cessation rates[188] 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; nine studies with 24,000 participants).[189] There were mixed evidence about whether increasing the number of calls altered quit rates, but most trials used more than two calls. Three studies comparing different counseling approaches during a single quitline contact did not detect significant differences. Of three studies that tested the provision of access to a hotline, two 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 received self-help material or a brief intervention.[189]

Quitlines are available in all US states through a national number, the 1–800-QUIT-NOW line, which redirects callers to the quitline for their particular state or locality if a specific state-funded and -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 website. This website contains information on behavioral and pharmaceutical management of smoking cessation. It also incorporates a “Smokefree TXT” imbedded in the website, on which patients can sign up to receive text messages to help them quit smoking. Another useful feature on the website 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 attempts to provide support to those trying to quit.

Recommended System Changes

The PHS 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 are recommended in the 2008 PHS 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 PHS 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 Cancer Patients

Cancer patients who are former smokers, have never smoked, or have recently quit smoking have about a twofold 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 continuing-to-smoke counterparts.[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 head and neck patients, 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 lower quality of life.[73] In a study of 114 head and neck cancer patients, continued smoking had a significantly negative influence on 20 of 33 quality of life scales.[202] Fortunately, cancer patients 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 cancer patients and survivors in their attempts to quit smoking, as recommended by the CDC.[206,207]

Suggesting and promoting smoking cessation interventions (e.g., a specific medication) for cancer patients can be done once a thorough knowledge of the oncologic treatment (including the consequences and the possible side effects) is determined 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 three classes of smoking cessation medication can be used readily depending on patient preference, with a few exceptions where a 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 (e.g., depression, anxiety, and alcohol dependence), as 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 cancer patients, that would encompasses smoking cessation advice and medications. Although, studies of the effectiveness of tobacco cessation interventions specifically in cancer patients 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 cancer patients.[207,212,213] Other interventions involving nurse-delivered advice to cancer patients as one-on-one sessions have also resulted in successful outcomes in smoking cessation.[214,215] With that stated, the gold standard for cancer patients 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 get surgery or radiation therapy), as mentioned earlier in this paper, 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, as it has been shown that cancer patients 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 MD Anderson

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 PHS 2000 tobacco treatment guideline and later the updated PHS 2008 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 (CO) 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 Questionnaire (PHQ),[217] (2) the Center of Epidemiological Studies Depression (CES-D) scale,[218] (3) the Sleep Problems Questionnaire (SPQ),[219] (4) the Fagerström Test for Nicotine Dependence (FTND),[81] (5) the Wisconsin Smoking Withdrawal Scale (WSWS),[220] (6) the Positive and Negative Affect Schedule (PANAS),[221] and (7) the Alcohol Use Disorders Identification Test (AUDIT).[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 consist of 20–30 minutes sessions (6–8 in total), delivered weekly or every 2 weeks by a tobacco specialist (master degree or higher), 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. About 60% of the follow-up visits are done by phone. During the 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, where indicated, increases in dosage above the usual dosages of first-line medications, done under close supervision. The entire program is free of charge to MD Anderson patients 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 had served 4670 new patients and conducted 48,033 follow-up appointments. In 2012, we instituted a system wide referral system using proactive identification of all smokers and recent quitters using the EHR. On an annual basis this has resulted in our program receiving over 5000 automatic referrals. About 1100 per year enter a face to face treatment option; and we estimate that about 300 per year will enter a new phone only treatment option (similar to the face to face option but medication is provided by an outside physician); while 3000 will elect to receive an initial motivational call, educational materials and at least one follow-up phone call) many of these participants are recent quitters who opt for less contact); and around 1000, 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 whom we were able to reach (respondent-only) was 46% abstinent (N = 1,291; 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 relapsed to smoking), the 6-month abstinence rate (7-day point prevalence at 6 months after the end of treatment) dropped to 34% (N = 1,670). In either case these rates compare favorably to 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 non-quitters 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] to a mean of 9 cigarettes per day [SD= 9.1]; N = 1,034) 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; data not published). 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 situation of 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. Cancer patients and survivors are likely to be more dependent on nicotine than the average smoker (unpublished data)[227] 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 cancer patients 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 of cancer patients and survivors. In the meantime, all clinicians are urged to identify tobacco use, provide treatment wherever possible and utilize other public resources where internal ones are not available (e.g. quitlines, websites, 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.

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Reference List

1. Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States, 2000. JAMA. 2004; 291(10):1238–45. [PubMed: 15010446]
2. CDC. Smoking-attributable mortality, years of potential life lost, and productivity losses--United States, 2000–2004. MMWR Morb Mortal Wkly Rep. 2008; 57(45):1226–8. [PubMed: 19008791]
3. Centers for Disease Control and Prevention. Cigarette smoking-attibutable morbidity---United States, 2000. MMWR Morb Mortal Wkly Rep. 2003; 52(35):842–4. [PubMed: 12966360]
4. Warren GW, Kasza KA, Reid ME, Cummings KM, Marshall JR. Smoking at diagnosis and survival in cancer patients. Int J Cancer. 2013; 132(2):401–10. [PubMed: 22539012]
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. Peppone LJ, Mustian KM, Morrow GR, et al. The effect of cigarette smoking on cancer treatment-related side effects. Oncologist. 2011; 16(12):1784–92. [PubMed: 22135122]
7. Balduyck B, Sardari NP, Cogen A, et al. The effect of smoking cessation on quality of life after lung cancer surgery. Eur J Cardiothorac Surg. 2011; 40(6):1432–7. [PubMed: 21498082]
8. Substance Abuse and Mental Health Services Administration. Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings. Rockville, MD: Substance Abuse

and Mental Health Services Administration; 2011. Report No.: HHS Publication No. (SMA) 11–458

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: U.S. 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. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2012. Report No.: HHS Publication No. (SMA) 12–4713
11. Centers for Disease Control and Prevention. Current Cigarette Smoking Among Adults-United States, 2005–2012. Morbidity and Mortality Weekly Report. 2014; 63(02):29–34. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6302a2.htm. [PubMed: 24430098]
12. Centers for Disease Control and Prevention. Quitting Smoking Among Adults - United States, 2001–2010. Morbidity and Mortality Weekly Report. 2011; 60(44):1513–9. [PubMed: 22071589]
13. US Department of Health and Human Services. Tobacco Addiction. National Institute on Drug Abuse; 2012 Jul. http://www.drugabuse.gov/publications/research-reports/tobacco-addiction [Accessed October 4, 2013]
14. Gritz ER, Nisenbaum R, Elashoff R, Holmes EC. Smoking behavior following diagnosis in patients with Stage I non-small cell lung cancer. Cancer Causes and Control. 1991; 2:105–12. [PubMed: 1651777]
15. Ostroff J, Garland J, Moadel A, et al. Cigarette smoking patterns in patients after treatment of bladder cancer. Journal of Cancer Education. 2000; 15(2):86–90. [PubMed: 10879897]
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(2):569–76. [PubMed: 7812925]
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(16):3461–9. [PubMed: 12177107]
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(6):702–11. [PubMed: 15850868]
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(34):8884–93. [PubMed: 16314649]
20. Walker MS, Vidrine DJ, Gritz ER, et al. Smoking relapse during the first year after treatment for early-stage non-small-cell lung cancer. Cancer Epidem Biomar. 2006; 15(12):2370–7.
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(1):45–8. [PubMed: 22119370]
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(6):1223–30. [PubMed: 23553611]
23. Duffy SA, Ronis DL, McLean S, et al. Pretreatment health behaviors predict survival among patients with head and neck squamous cell carcinoma. J Clin Oncol. 2009; 27(12):1969–75. [PubMed: 19289626]
24. Gritz ER, Dresler C, Sarna L. Smoking, the missing drug interaction in clinical trials: ignoring the obvious. Cancer Epidem Biomar. 2005; 14(10):2287–93.
25. Rabius V, Karam-Hage M, Blalock JA, Cinciripini PM. Meaningful use “provides a meaningful opportunity”. Cancer. 2013; 20:464–8. [PubMed: 24496865]
26. Blumenthal D, Tavenner M. The “meaningful use” regulation for electronic health records. N Engl J Med. 2010; 363(6):501–4. [PubMed: 20647183]
27. Warren GW, Marshall JR, Cummings KM, et al. Addressing tobacco use in patients with cancer: a survey of american society of clinical oncology members. J Oncol Pract. 2013; 9(5):258–62. [PubMed: 23943904]

28. Gritz ER, Toll BA, Warren GW. Tobacco use in the oncology setting: advancing clinical practice and research. Cancer Epidemiol Biomarkers Prev. 2014; 23(1):3–9. [PubMed: 24420982]
29. Videtic GMM, Stitt LW, Dar AR, et al. Continued Cigarette Smoking by Patients Receiving Concurrent Chemoradiotherapy for Limited-Stage Small-Cell Lung Cancer Is Associated With Decreased Survival. Journal of Clinical Oncology. 2003; 21(8):1544. [PubMed: 12697879]
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(1):89–93. [PubMed: 20541274]
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(4):1134–42. [PubMed: 18258387]
32. Tammemagi CM, Neslund-Dudas C, Simoff M, Kvale P. Smoking and lung cancer survival: the role of comorbidity and treatment. Chest. 2004; 125(1):27–37. [PubMed: 14718417]
33. Garces YI, Yang P, Parkinson J, et al. The Relationship Between Cigarette Smoking and Quality of Life After Lung Cancer Diagnosis. Chest. 2004; 126(6):1733–41. [PubMed: 15596667]
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(3):287–93. [PubMed: 15140541]
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(2):347–51. [PubMed: 15302716]
36. Kreuzer M, Boffetta 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(1):227–33. [PubMed: 10638994]
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; 138:281–93. [PubMed: 8395141]
38. Hinds MW, Yang HY, Stemmermann G, Lee J, Kolonel LN. Smoking history and lung cancer survival in women. J Natl Cancer Inst. 1982; 68(3):395–9. [PubMed: 6950166]
39. Johnston-Early A, Cohen MH, Minna JD, et al. Smoking abstinence and small cell lung cancer survival. JAMA. 1980; 244:2175–9. [PubMed: 6252357]
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(2): 414–9. [PubMed: 20399030]
41. Fortin A, Wang CS, Vigneault E. Influence of smoking and alcohol drinking behaviors on treatment outcomes of patients with squamous cell carcinomas of the head and neck. Int J Radiat Oncol Biol Phys. 2009; 74(4):1062–9. [PubMed: 19036528]
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(2):451–7. [PubMed: 18300961]
43. Pytynia KB, Grant JR, Etzel 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(19):3981–8. [PubMed: 15459221]
44. Rugg T, Saunders MI, Dische S. Smoking and mucosal reactions to radiotherapy. Br J Radiol. 1990; 63:554–6. [PubMed: 2390690]
45. Stevens MH, Gardner JW, Parkin JL, Johnson LP. Head and neck cancer survival and lifestyle change. Arch Otolaryngol. 1983; 109:746–9. [PubMed: 6639443]
46. Shitara K, Matsuo K, Hatooka S, et al. Heavy smoking history interacts with chemoradiotherapy for esophageal cancer prognosis: a retrospective study. Cancer Sci. 2010; 101(4):1001–6. [PubMed: 20085588]
47. Chelghoum Y, Danaila C, Belhabri A, et al. Influence of cigarette smoking on the presentation and course of acute myeloid leukemia. Ann Oncol. 2002; 13(10):1621–7. [PubMed: 12377652]
48. Archimbaud E, Maupas J, Lecluze-Palazzolo C, Fiere D, Viala JJ. Influence of cigarette smoking on the presentation and course of chronic myelogenous leukemia. Cancer. 1989; 63(10):2060–5. [PubMed: 2702575]

49. Chen CH, Shun CT, Huang KH, et al. Stopping smoking might reduce tumour recurrence in nonmuscle-invasive bladder cancer. BJU Int. 2007; 100(2):281–6. [PubMed: 17419696]
50. Fleshner N, Garland J, Moadel A, et al. Influence of smoking status on the disease-related outcomes of patients with tobacco-associated superficial transitional cell carcinoma of the bladder. Cancer. 1999; 86(11):2337–45. [PubMed: 10590376]
51. Daniell HW. More advanced colonic cancer among smokers. Cancer. 1986; 58(3):784–7. [PubMed: 3731028]
52. Phillips B, Marshall E, Brown S, Thompson JS. Effect of smoking on human natural killer cell activity. Cancer. 1985; 56:2789–92. [PubMed: 4052953]
53. Daniell HW. Increased lymph node metastases at mastectomy for breast cancer associated with host obesity, cigarette smoking, age, and large tumor size. Cancer. 1988; 62(2):429–35. [PubMed: 3383142]
54. Daniell HW. Estrogen receptors, breast cancer, and smoking. N Engl J Med. 1980; 302(26):1478. [PubMed: 7374713]
55. Do KA, Johnson MM, Lee JJ, 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(12):2837–42. [PubMed: 15536619]
56. 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 Epidem Biomar. 1 A.D; 10(8):823–9.
57. Browman GP, Wong G, Hodson I, et al. Influence of cigarette smoking on the efficacy of radiation therapy in head and neck cancer. N Engl J Med. 1993; 328:159–63. [PubMed: 8417381]
58. Browman GP, 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(12):1031–7. [PubMed: 12454940]
59. Garces YI, 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(1): 116–24. [PubMed: 15221996]
60. 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(1):38–44. [PubMed: 22385797]
61. 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(17):2102–11. [PubMed: 22565003]
62. 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(11):1593–601. [PubMed: 22244802]
63. Kenfield SA, Stampfer MJ, Chan JM, Giovannucci E. Smoking and prostate cancer survival and recurrence. JAMA. 2011; 305(24):2548–55. [PubMed: 21693743]
64. Holmes MD, Murin S, Chen WY, Kroenke CH, Spiegelman D, Colditz GA. Smoking and survival after breast cancer diagnosis. Int J Cancer. 2007; 120(12):2672–7. [PubMed: 17278091]
65. Toll BA, Brandon TH, Gritz ER, Warren GW, Herbst RS. Assessing tobacco use by cancer patients and facilitating cessation: an American Association for Cancer Research policy statement. Clin Cancer Res. 2013; 19(8):1941–8. [PubMed: 23570694]
66. 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. [PubMed: 20093278]
67. Tucker MA, Murray N, Shaw EG, et al. Second primary cancers related to smoking and treatment of small-cell lung cancer. Lung Cancer Working Cadre. J Natl Cancer Inst. 1997; 89(23):1782–8. [PubMed: 9392619]
68. Gritz, E.; Lam, CY.; Vidrine, DJ.; Fingeret, MC. Cancer Prevention: Tobacco Dependence and Its Treatment. In: DeVita, VTLSR., editor. Cancer: Principles and Practice of Oncology. 8. Vol. 2. Philadelphia: Lippincott Williams & Williams; 2008. p. 593-608.
69. Dresler CM, Gritz ER. Smoking, smoking cessation and the oncologist. Lung Cancer. 2001; 34(3): 315–23. [PubMed: 11714528]

70. Sorensen LT, Horby J, Friis E, Pilsgaard B, Jorgensen T. Smoking as a risk factor for wound healing and infection in breast cancer surgery. European Journal of Surgical Oncology. 2002; 28(8):815–20. [PubMed: 12477471]
71. Krueger JK, Rohrich RJ. Clearing the smoke: the scientific rationale for tobacco abstention with plastic surgery. Plast Reconstr Surg. 2001; 108(4):1063–73. [PubMed: 11547174]
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. General Hospital Psychiatry. 2002; 24:140–7. [PubMed: 12062138]
73. Gritz ER, Carmack CL, de Moor C, et al. First Year After Head and Neck Cancer: Quality of Life. Journal of Clinical Oncology. 1999; 17(1):352. [PubMed: 10458254]
74. Volkow ND, Wang GJ, Fowler JS, Tomasi D, Telang F, Baler R. Addiction: Decreased reward sensitivity and increased expectation sensitivity conspire to overwhelm the brain's control circuit. Bioessays. 2010; 32(9):748–55. [PubMed: 20730946]
75. Steinberg MB, Greenhaus S, Schmelzer AC, et al. Triple-combination pharmacotherapy for medically ill smokers: a randomized trial. Ann Intern Med. 2009; 150(7):447–54. [PubMed: 19349630]
76. McBride CM, Emmons KM, Lipkus IM. Understanding the potential of teachable moments: the case of smoking cessation. Health Educ Res. 2003; 18(2):156–70. [PubMed: 12729175]
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(2):144–9. [PubMed: 22093155]
78. Nayan S, Gupta MK, Strychowsky 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(2):200–11. [PubMed: 23715685]
79. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4. Washington, D.C: American Psychiatric Association; 2000. Revised ed
80. Fiore, MC.; Jaen, CR.; Baker, TB., et al. Treating Tobacco Use and Dependence: 2008 Update, Clinical Practice Guideline. Rockville, MD: U. S. 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; 19:307–74. [PubMed: 7942248]
82. Pomerleau CS, Pomerleau OF, Majchrzak MJ, Kloska DD, Malakuti R. Relationship between Fagerstrom Tolerance Questionnaire scores and plasma cotinine. Addict Behav. 1990; 15:73–80. [PubMed: 2316414]
83. CDC. Cigarette smoking among adults - United States, 1992, and changes in the definition of current cigarette smoking. MMWR Morb Mortal Wkly Rep. 1994; 43(19):342–6. [PubMed: 8177192]
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(12):1128–32. [PubMed: 20940652]
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(3):266–73. [PubMed: 22984217]
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. [PubMed: 19875845]
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(5):861–6. [PubMed: 18569760]
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(4):492–7. [PubMed: 15020184]

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(1):17–27. [PubMed: 16311986]

90. Centers for Disease Control. [Accessed August 30, 2013] Adult smoking: focusing on people with mental illness. Vital Signs. 2013. www.cdc.gov/vitalsigns

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. [PubMed: 20001818]

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(20):2606–10. [PubMed: 11086367]

93. Barkley RA, Fischer M, Edelbrock CS, Smallish L. The adolescent outcome of hyperactive children diagnosed by research criteria: I. An 8-year prospective follow-up study. J Am Acad Child Adolesc Psychiatry. 1990; 29(4):546–57. [PubMed: 2387789]

94. Borland BL, Heckman HK. Hyperactive boys and their brothers. A 25-year follow-up study. Arch Gen Psychiatry. 1976; 33(6):669–75. [PubMed: 938190]

95. Breslau N, Johnson EO, Hiripi E, Kessler R. Nicotine dependence in the United States: prevalence, trends, and smoking persistence. Arch Gen Psychiatry. 2001; 58(9):810–6. [PubMed: 11545662]

96. Covey LS, Hughes DC, Glassman AH, Blazer DG, George LK. Ever-smoking, quitting, and psychiatric disorders: Evidence from the Durham, North Carolina, epidemiologic catchment area. Tobacco Control. 1994; 3:222–7.

97. Glassman AH, Helzer JE, Covey LS, et al. Smoking, smoking cessation, and major depression. JAMA. 1990; 264(12):1546–9. [PubMed: 2395194]

98. Hartsough CS, Lambert NM. Pattern and progression of drug use among hyperactives and controls: a prospective short-term longitudinal study. J Child Psychol Psychiatry. 1987; 28(4):543–53. [PubMed: 3654806]

99. Williams JM, Ziedonis D. Addressing tobacco among individuals with a mental illness or an addiction. Addict Behav. 2004; 29(6):1067–83. [PubMed: 15236808]

100. Batel P, Pessione F, Maitre C, Rueff B. Relationship between alcohol and tobacco dependencies among alcoholics who smoke. Addiction. 1995; 90(7):977–80. [PubMed: 7663320]

101. Breslau N. Psychiatric comorbidity of smoking and nicotine dependence. Behav Genet. 1995; 25(2):95–101. [PubMed: 7733862]

102. Breslau N, Peterson EL, Schultz LR, Chilcoat HD, Andreski P. Major depression and stages of smoking: A longitudinal investigation. Arch Gen Psychiatry. 1998; 55:161–6. [PubMed: 9477930]

103. Breslau N, Klein DF. Smoking and panic attacks: an epidemiologic investigation. Arch Gen Psychiatry. 1999; 56(12):1141–7. [PubMed: 10591292]

104. Brown DC. Smoking cessation in pregnancy. Can Fam Physician. 1996; 42:102–5. [PubMed: 8924801]

105. Johnson RA, Hoffmann JP. Adolescent cigarette smoking in U.S. racial/ethnic subgroups: findings from the National Education Longitudinal Study. J Health Soc Behav. 2000; 41(4):392–407. [PubMed: 11198564]

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(1):36–43. [PubMed: 8422220]

107. Blalock JA, Minnix 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. Journal of Cognitive Psychotherapy. 2011; 25(1):82–96.

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(1):97–104. [PubMed: 18758971]

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. [PubMed: 22091433]

110. Oncken C, Arias AJ, Feinn R, et al. Topiramate for smoking cessation: a randomized, placebo-controlled pilot study. Nicotine Tob Res. 2014; 16(3):288–96. [PubMed: 24057996]
111. Johnson BA, Rosenthal N, Capece JA, et al. Topiramate for treating alcohol dependence: A randomized controlled trial. JAMA. 2007; 298(14):1641–51. [PubMed: 17925516]
112. US National Institutes of Health. [Accessed September 18, 2013] High and Low Dose Topiramate for the Treatment of Alcohol-Dependent Smokers. Clinical Trials gov. 2013 Mar 7. http://clinicaltrials.gov/ct2/show/NCT01182766?term=high+and+low+dose+topiramate&rank=1
113. Nabi Biophamaceuticals. Nabi Biopharmceuticals Announces Results of Second NicVAX(R) Phase III Clinical Trial. Nabi Biopharmaceuticals; 2013 Jan. http://phx.corporate-ir.net/phoenix.zhtml?c=100445&p=irol-newsArticle_print&ID=1626882&highlight= [Accessed September 18, 2013]
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(4):399–407. [PubMed: 23429725]
115. Raupach T, Hoogsteder PHJ, Onno CP. Nicotine Vaccines to Assist with Smoking Cessation: Current Status of Research. Drugs. 2012; 72(4):e1–e16. [PubMed: 22356293]
116. Tonstad S, Heggen E, Giljam H, et al. Niccine(R), a Nicotine Vaccine, for Relapse Prevention: A Phase II, Randomized, Placebo-Controlled, Multicenter Clinical Trial. Nicotine Tob Res. 2013; 15(9):1492–501. [PubMed: 23471101]
117. Hughes JR, Stead LF, Hartmann-Boyce J, Cahill K, Lancaster T. Antidepressants for smoking cessation. Cochrane Database Syst Rev. 2014; 1:CD000031. [PubMed: 24402784]
118. Beckham JC. Smoking and anxiety in combat veterans with chronic posttraumatic stress disorder: a review. J Psychoactive Drugs. 1999; 31(2):103–10. [PubMed: 10437991]
119. Evins AE, Cather C, Deckersbach T, et al. A double-blind placebo-controlled trial of bupropion sustained-release for smoking cessation in schizophrenia. J Clin Psychopharmacol. 2005; 25(3): 218–25. [PubMed: 15876899]
120. 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(1):94–8. [PubMed: 11199956]
121. Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation. Cochrane Database Syst Rev. 2007; 1:CD000031. [PubMed: 17253443]
122. Cullum J, Wojciechowski A, Pelletier G, Simpson J. Bupropion sustained release treatment reduces fatigue in cancer patients. Canadian Journal of Psychiatry. 2004; 49/2:139–44.
123. Mooney ME, Sofuoglu M. Bupropion for the treatment of nicotine withdrawal and craving. Expert Review of Neurotherapeutics. 2006; 6(7):965–81. [PubMed: 16831112]
124. Segraves RT, Kavoussi R, Hughes AR, et al. Evaluation of sexual functioning in depressed outpatients: a double-blind comparison of sustained-release bupropion and sertraline treatment. J Clin Psychopharmacol. 2000; 20(2):122–8. [PubMed: 10770448]
125. Taylor MJ, Rudkin L, Bullemor-Day P, Lubin J, Chukwujekwu C, Hawton K. Strategies for managing sexual dysfunction induced by antidepressant medication. Cochrane Database Syst Rev. 2013; 5:CD003382. [PubMed: 23728643]
126. Sadovsky R, Basson R, Krychman M, et al. Cancer and sexual problems. J Sex Med. 2010; 7(1 Pt 2):349–73. [PubMed: 20092444]
127. Gonzales D, Rennard SI, Nides M, et al. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA. 2006; 296(1):47–55. [PubMed: 16820546]
128. Gonzales, DH.; Rennard, SI.; Billing, CB.; Reeves, K.; Watsky, E.; Gong, J. A pooled analysis of varenicline, an alpha 4 beta 2 nicotinic receptor partial agonist vs bupropion, and placebo for smoking cessation. 2006.
129. Jorenby DE, Hays JT, Rigotti NA, et al. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. JAMA. 2006; 296(1):56–63. [PubMed: 16820547]
130. Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev. 2012; 4:CD006103. [PubMed: 22513936]

131. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev. 2013; 5:CD009329. [PubMed: 23728690]

132. Gosselin MH, Mahoney MC, Cummings KM, et al. Evaluation of an intervention to enhance the delivery of smoking cessation services to patients with cancer. J Cancer Educ. 2011; 26(3):577–82. [PubMed: 21503842]

133. Park ER, Japuntich S, Temel J, et al. A smoking cessation intervention for thoracic surgery and oncology clinics: a pilot trial. J Thorac Oncol. 2011; 6(6):1059–65. [PubMed: 21512406]

134. US Food and Drug Administration. Public Health Advisory, Important Information on Chantix (varenicline). Rockville, MD: Department of Health and Human Services; 2008 Feb 1.

135. Beratis S, Lekka NP, Gabriel J. Smoking among suicide attempters. Compr Psychiatry. 1997; 38(2):74–9. [PubMed: 9056124]

136. 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(3):328–34. [PubMed: 15753246]

137. Bronisch T, Hofler M, Lieb R. Smoking predicts suicidality: findings from a prospective community study. J Affect Disord. 2008; 108(1–2):135–45. [PubMed: 18023879]

138. 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(1):87–96. [PubMed: 16403044]

139. Hawton K, Simkin S, Rue J, et al. Suicide in female nurses in England and Wales. Psychol Med. 2002; 32(2):239–50. [PubMed: 11866319]

140. Hintikka J, Koivumaa-honkanen H, Lehto SM, et al. Are factors associated with suicidal ideation true risk factors? A 3-year prospective follow-up study in a general population. Soc Psychiatry Psychiatr Epidemiol. 2009; 44(1):29–33. [PubMed: 18600285]

141. Kessler RC, Borges G, Sampson N, Miller M, Nock MK. The association between smoking and subsequent suicide-related outcomes in the National Comorbidity Survey panel sample. Mol Psychiatry. 2009; 14(12):1132–42. [PubMed: 18645572]

142. Martinez-Ortega JM, Jurado D, Gurpegui M. Nicotine dependence vs. daily smoking as a meaningful variable: implications for clinical and epidemiological psychiatric studies. Prog Neuropsychopharmacol Biol Psychiatry. 2008; 32(8):1972–7. [PubMed: 18854205]

143. Miller M, Hemenway D, Bell NS, Yore MM, Amoroso PJ. Cigarette smoking and suicide: a prospective study of 300,000 male active-duty Army soldiers. Am J Epidemiol. 2000; 151(11): 1060–3. [PubMed: 10873129]

144. Tanskanen A, Tuomilehto J, Viinamaki H, Vartiainen E, Lehtonen J, Puska P. Joint heavy use of alcohol, cigarettes and coffee and the risk of suicide. Addiction. 2000; 95(11):1699–704. [PubMed: 11219373]

145. Yaworski D, Robinson J, Sareen J, Bolton JM. The relation between nicotine dependence and suicide attempts in the general population. Can J Psychiatry. 2011; 56(3):161–70. [PubMed: 21443823]

146. Bohnert KM, Ilgen MA, McCarthy JF, Ignacio RV, Blow FC, Katz IR. Tobacco Use Disorder and the Risk of Suicide Mortality. Addiction. 2013; 109:155–62. [PubMed: 24134689]

147. Tonstad S, Davies S, Flammer M, Russ C, Hughes J. Psychiatric adverse events in randomized, double-blind, placebo-controlled clinical trials of varenicline: a pooled analysis. Drug Saf. 2010; 33(4):289–301. [PubMed: 20297861]

148. Gunnell D, Irvine D, Wise L, Davies C, Martin RM. Varenicline and suicidal behaviour: a cohort study based on data from the General Practice Research Database. BMJ. 2009; 339:b3805. [PubMed: 19797344]

149. Meyer TE, Taylor LG, Xie S, et al. Neuropsychiatric events in varenicline and nicotine replacement patch users in the Military Health System. Addiction. 2013; 108(1):203–10. [PubMed: 22812921]

150. Foulds J, Russ C, Yu CR, et al. Effect of Varenicline on Individual Nicotine Withdrawal Symptoms: A Combined Analysis of Eight Randomized, Placebo-Controlled Trials. Nicotine Tob Res. 2013; 170:1460–7.

151. Gibbons RD, Mann JJ. Varenicline, Smoking Cessation, and Neuropsychiatric Adverse Events. Am J Psychiatry. 2013
152. Cinciripini PM, Robinson JD, Karam-Hage M, et al. The effects of varenicline and bupropion-SR plus intensive counseling on prolonged abstinence from smoking, depression, negative affect and other symptoms of nicotine withdrawal. JAMA Psychiatry. 2013; 70(5):522–33. [PubMed: 23536105]
153. Anthenelli RM, Morris C, Ramey TS, et al. Effects of varenicline on smoking cessation in adults with stably treated current or past major depression: a randomized trial. Ann Intern Med. 2013; 159(6):390–400. [PubMed: 24042367]
154. Williams JM, Anthenelli RM, Morris CD, et al. A randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of varenicline for smoking cessation in patients with schizophrenia or schizoaffective disorder. J Clin Psychiatry. 2012; 73(5):654–60. [PubMed: 22697191]
155. US National Institutes of Health. [Accessed September 19, 2013] Study evaluating the safety and efficacy of bupropion for smoking cessation in subjects with and without a history of psychiatric disorders. ClinicalTrials gov. 2013 Sep 12. http://clinicaltrials.gov/ct2/show/NCT01456936
156. Mitchell JM, Teague CH, Kayser AS, Bartlett SE, Fields HL. Varenicline decreases alcohol consumption in heavy-drinking smokers. Psychopharmacology (Berl). 2012; 223:299–306. [PubMed: 22547331]
157. Nocente R, Vitali M, Balducci G, Enea D, Kranzler HR, Ceccanti M. Varenicline and neuronal nicotinic acetylcholine receptors: a new approach to the treatment of co-occurring alcohol and nicotine addiction? Am J Addict. 2013; 22(5):453–9. [PubMed: 23952890]
158. Mahmoudi M, Coleman CI, Sobieraj DM. Systematic review of the cost-effectiveness of varenicline vs. bupropion for smoking cessation. Int J Clin Pract. 2012; 66(2):171–82. [PubMed: 22257042]
159. Hoogendoorn M, Welsing P, Rutten-van Molken MP. Cost-effectiveness of varenicline compared with bupropion, NRT, and nortriptyline for smoking cessation in the Netherlands. Curr Med Res Opin. 2008; 24(1):51–61. [PubMed: 18021492]
160. Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev. 2004; 3:CD000146. [PubMed: 15266423]
161. Stead LF, Perera R, Bullen C, et al. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev. 2012; 11:CD000146. [PubMed: 23152200]
162. Le HJ. Role of nicotine pharmacokinetics in nicotine addiction and nicotine replacement therapy: a review. Int J Tuberc Lung Dis. 2003; 7(9):811–9. [PubMed: 12971663]
163. Cryan JF, Bruijnzeel SW, Skjei KL, Markou A. Bupropion enhances brain reward function and reverses the affective and somatic aspects of nicotine withdrawal in the rat. Psychopharmacology (Berl). 2003; 168:347–58. [PubMed: 12698231]
164. Kozlowski LT, Giovino GA, Edwards B, et al. Advice on using over-the-counter nicotine replacement therapy-patch, gum or lozenge-to quit smoking. Addict Behav. 2007; 32(10):2140–50. [PubMed: 17360126]
165. Shiffman S, Mason KM, Henningfield JE. Tobacco dependence treatments: review and prospectus. Annu Rev Public Health. 1998; 19:335–58. [PubMed: 9611623]
166. Garvey, AJ.; Kinnunen, T.; Doherty, K.; Vokonas, PS. Effects of nicotine gum on smokers differing in level of dependence. Washington, D.C: 1996.
167. McClure JB, Swan GE. Tailoring nicotine replacement therapy: rationale and potential approaches. CNS Drugs. 2006; 20(4):281–91. [PubMed: 16599646]
168. Shiffman S, Dresler CM, Hajek P, Gilburt SJ, Targett DA, Strahs KR. Efficacy of a nicotine lozenge for smoking cessation. Archives of Internal Medicine. 2002; 162(11):1267–76. [PubMed: 12038945]
169. Benowitz NL, Hukkanen J, Jacob P III. Nicotine chemistry, metabolism, kinetics and biomarkers. Handb Exp Pharmacol. 2009; (192):29–60. [PubMed: 19184645]
170. Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev. 2011; 2(February CD006103):1–87.

171. Loh WY, Piper ME, Schlam TR, et al. Should all smokers use combination smoking cessation pharmacotherapy? Using novel analytic methods to detect differential treatment effects over 8 weeks of pharmacotherapy. Nicotine Tob Res. 2012; 14(2):131–41. [PubMed: 22180577]

172. Shah SD, Wilken LA, Winkler SR, Lin SJ. Systematic review and meta-analysis of combination therapy for smoking cessation. Journal of the American Pharmacists Association. 2008; 48(5): 659–65. [PubMed: 18826906]

173. Piper ME, Smith SS, Schlam TR, et al. A randomized placebo-controlled clinical trial of 5 smoking cessation pharmacotherapies. Arch Gen Psychiatry. 2009; 66(11):1253–62. [PubMed: 19884613]

174. Shenassa E, Graham A, Burdzovic J, Buka S. Psychometric properties of the Wisconsin Inventory of Smoking Dependence Motives (WISDM-68): A replication extension. Nicotine Tob Res. 2010; 11(8):1002–10. [PubMed: 19542518]

175. Smith SS, McCarthy DE, Japuntich SJ, et al. Comparative effectiveness of 5 smoking cessation pharmacotherapies in primary care clinics. Arch Intern Med. 2009; 169(22):2148–55. [PubMed: 20008701]

176. Ebbert JO, Croghan IT, Sood A, Schroeder DR, Hays JT, Hurt RD. Varenicline and bupropion sustained release combination therapy for smoking cessation. Nicotine Tob Res. 2009; 11(3): 234–9. [PubMed: 19246427]

177. Ebbert JO, Hatsukami DK, Croghan IT, et al. Combination varenicline and bupropion SR for tobacco-dependence treatment in cigarette smokers: a randomized trial. JAMA. 2014; 311(2): 155–63. [PubMed: 24399554]

178. US National Institutes of Health. [Accessed September 20, 2013] Studies for bupropion and varenicline. ClinicalTrials gov. 2013 Aug. http://clinicaltrials.gov/ct2/results?term=bupropion+and+varenicline&pg=1

179. Gourlay SG, Stead LF, Benowitz NL. Clonidine for smoking cessation. Cochrane Database Syst Rev. 2004; 3:CD000058. [PubMed: 15266422]

180. Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation. Cochrane Database Syst Rev. 2003; (2):CD000031. [PubMed: 12804385]

181. Hughes JR, Stead LF, Lancaster T. Nortriptyline for smoking cessation: a review. Nicotine Tob Res. 2005; 7(4):491–9. [PubMed: 16085520]

182. Dhippayom T, Chaiyakunapruk N, Jongchansittho T. Safety of nortriptyline at equivalent therapeutic doses for smoking cessation: a systematic review and meta-analysis. Drug Saf. 2011; 34(3):199–210. [PubMed: 21332244]

183. Gourlay S, Forbes A, Marriner T, Kutin J, McNeil JA. A placebo-controlled study of three clonidine doses for smoking cessation. Clin Pharmacol Ther. 1994; 55:64–9. [PubMed: 8299319]

184. 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(6):588–97. [PubMed: 22860882]

185. Stead LF, Lancaster T. Behavioural interventions as adjuncts to pharmacotherapy for smoking cessation. Cochrane Database Syst Rev. 2012; 12:CD009670. [PubMed: 23235680]

186. Stead, LF.; Lancaser, T. [Accessed October 7, 2013] Does a combination of smoking cessation medication and behavioural support help smokers to stop?. Cochrane Reviews. 2012 Dec 12. http://summaries.cochrane.org/CD008286/does-a-combination-of-smoking-cessation-medication-and-behavioural-support-help-smokers-to-stop

187. Brose LS, West R, McDermott MS, Fidler JA, Croghan E, McEwen A. What makes for an effective stop-smoking service? Thorax. 2011; 66(10):924–6. [PubMed: 21709164]

188. Stead LF, Perera R, Lancaster T. Telephone counselling for smoking cessation. Cochrane Database Syst Rev. 2006; (3):CD002850. [PubMed: 16855992]

189. Stead LF, Hartmann-Boyce J, Perera R, Lancaster T. Telephone counselling for smoking cessation. Cochrane Database Syst Rev. 2013; 8:CD002850. [PubMed: 23934971]

190. Lancaster T, Stead LF. Self-help interventions for smoking cessation. Cochrane Database Syst Rev. 2005; 3(3):CD001118. [PubMed: 16034855]

191. Civljak M, Sheikh A, Stead LF, Car J. Internet-based interventions for smoking cessation - Updated 2010. Cochrane Database Syst Rev. 2010; 9
192. Graham AL, Cobb NK, Papandonatos GD, et al. A randomized trial of Internet and telephone treatment for smoking cessation. Arch Intern Med. 2011; 171(1):46. [PubMed: 21220660]
193. Rabius V, Pike KJ, Wiatrek D, McAlister AL. Comparing internet assistance for smoking cessation: 13-month follow-up of a six-arm randomized controlled trial. J Med Internet Res. 2008; 10(5):e45. [PubMed: 19033146]
194. Swartz LHG, Noell JW, Schroeder SW, Ary DV. A randomised control study of a fully automated internet based smoking cessation programme. Tobacco Control. 2006; 15(1):7–12. [PubMed: 16436397]
195. Walters ST, Wright JA, Shegog R. A review of computer and Internet-based interventions for smoking behavior. Addict Behav. 2006; 31(2):264–77. [PubMed: 15950392]
196. Fiore, MC.; Bailey, WC.; Cohen, SJ., et al. Treating tobacco use and dependence. Clinical practice guideline. Rockville, MD: U.S. Department of Health and Human Services; 2000.
197. Fiore MC, Jorenby DE, Schensky AE, Smith SS, Bauer RR, Baker TB. Smoking stutus as the new vital sign: Effect on assessment and intervention in patients who smoke. Mayo Clinic Proceedings. 1995; 70:209–13. [PubMed: 7861807]
198. Lindholm C, Adsit R, Bain P, et al. A demonstration project for using the electronic health record to identify and treat tobacco users. Wisc Med J. 2010; 109(6):335–340. Ref Type: Abstract.
199. Rigotti NA. Integrating comprehensive tobacco treatment into the evolving US health care system: it's time to act: comment on "A randomized trial of Internet and telephone treatment for smoking cessation". Arch Intern Med. 2011; 171(1):53–5. [PubMed: 21220661]
200. American Cancer Society. Facts and Figures 2013. Atlanta, GA: American Cancer Society; 2013.
201. Ehlers SL, Gastineau DA, Patten CA, et al. The impact of smoking on outcomes among patients undergoing hematopoietic SCT for the treatment of acute leukemia. Bone Marrow Transplant. 2011; 46(2):285–90. [PubMed: 20479707]
202. Jensen K, Jensen AB, Grau C. Smoking has a negative impact upon health related quality of life after treatment for head and neck cancer. Oral Oncol. 2007; 43(2):187–92. [PubMed: 16860590]
203. CDC. Tobacco use among adults - United States, 2005. MMWR Morb Mortal Wkly Rep. 2006; 55:1145. [PubMed: 17065979]
204. Gritz ER. Smoking and smoking cessation in cancer patients. Br J Addiction. 1991; 86:549–54.
205. Lippman SM, Lee JJ, Karp DD, et al. Randomized phase III intergroup trial of isotretinoin to prevent second primary tumors in stage I non-small-cell lung cancer. National Cancer Institute. 2001; 93(8):605–18.
206. CDC. Cigarette smoking among adults and trends in smoking - United States 2008. MMWR Morb Mortal Wkly Rep. 2009; 58(44):1227–1232. [PubMed: 19910909]
207. Gritz, ER.; Lam, CY.; Vidrine, DJ.; Fingeret, MC. Tobacco Dependence and Its Treatment. In: DeVita, VT.; Lawrence, TD.; Rosenberg, SA., editors. Cancer: Principles and Practice of Oncology. 9. Philadelphia: Lippincott Williams & Wilkins; 2012. p. 529-42.
208. Jimenez-Ruiz C, Berlin I, Hering T. Varenicline: a novel pharmacotherapy for smoking cessation. Drugs. 2009; 69(10):1319–38. [PubMed: 19583451]
209. Wallstrom M, Sand L, Nilsson F, Hirsch JM. The long-term effect of nicotine on the oral mucosa. Addiction. 1999; 94(3):417–23. [PubMed: 10605870]
210. Desmarais JE, Looper KJ. Interactions between tamoxifen and antidepressants via cytochrome P450 2D6. J Clin Psychiatry. 2009; 70(12):1688–97. [PubMed: 20141708]
211. Duffy SA, Ronis DL, Valenstein M, et al. A tailored smoking, alcohol, and depression intervention for head and neck cancer patients. Cancer Epidem Biomar. 2006; 15(11):2203–8.
212. Gritz ER, Carr CR, Rapkin D, et al. Predictors of long-term smoking cessation in head and neck cancer patients. Cancer Epidem Biomar. 1993; 2:261–70.
213. Schnoll RA, Rothman RL, Wielt 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):1–11. [PubMed: 16097900]

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

215. Wewers ME, Bowen JM, Stanislaw AE, Desimone VB. A nurse-delivered smoking cessation intervention among hospitalized postoperative patients--influence of a smoking-related diagnosis: a pilot study. Heart Lung. 1994; 23(2):151. [PubMed: 8206773]

216. Gritz, ER.; Fingeret, MC.; Vidrine, DJ. Tobacco Control in the oncology setting. In: Brawley, OW.; Khuri, FR.; Rock, C., editors. ASCO Cancer Prevention Curriculum. Alexandria, VA: 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(18):1737–44. [PubMed: 10568646]

218. Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. Appl Psychol Meas. 1977; 1(3):385–401.

219. Jenkins CD, Stanton BA, Niemcryk SJ, Rose RM. A scale for the estimation of sleep problems in clinical research. J Clin Epidemiol. 1988; 41(4):313–21. [PubMed: 3351539]

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(4): 354–61. [PubMed: 10609970]

221. Babor, TF.; de la Fuente, JR.; Saunders, JB.; Grant, M. Guidelines for use in primary healthcare. Vol. 92. Geneva, Switzerland: World Health Organization; 1992. AUDIT. The Alcohol Use Disorders Identification Test; p. 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; 54:1063–70. [PubMed: 3397865]

223. Tobacco Prevention and Control Program. Texas Tobacco Settlement Information. DSHS Mental Health and Substance Abuse Division; 2011. http://www.dshs.state.tx.us/tobacco/settlement.shtm [Accessed March 16, 2014]

224. Kotz D, Brown J, West R. 'Real-world' effectiveness of smoking cessation treatments: a population study. Addiction. 2014; 109(3):491–9. [PubMed: 24372901]

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(2):221–9. [PubMed: 20048210]

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(6 Suppl):S414–S422. [PubMed: 18021917]

227. Mallen, MJ.; Karam-Hage, M.; Blalock, JA.; Cinciripini, PM. A Comprehensive Tobacco-Cessation Treatment for Cancer Patients: Preliminary Outcome Findings. 2008.

Table #1

Meta-analysis (2008)*: Effectiveness and abstinence rates for various medications and medication combinations compared to placebo at 6-months post-quit (n=83 studies)

Medication	Number of arms	Estimated odds ratio (95% C.I.)	Estimated % abstinence rate (95% C.I.)
Placebo	80	1.0	13.8
Monotherapies			
Varenicline (2 mg/day)	5	3.1 (2.5 – 3.8)	33.2 (28.9 – 37.8)
Nicotine Nasal Spray	4	2.3 (1.7 – 3.0)	26.7 (21.5 – 32.7)
High-Dose Nicotine Patch (> 25 mg) (These included both standard or long- term duration)	4	2.3 (1.7– 3.0)	26.5 (21.3 – 32.5)
Long-Term Nicotine Gum (> 14 weeks)	6	2.2 (1.5 – 3.2)	26.1 (19.7 – 33.6)
Varenicline (1 mg/day)	3	2.1 (1.5 – 3.0)	25.4 (19. 6 – 32.2)
Nicotine Inhaler	6	2.1 (1.5 – 2.9)	24.8 (19.1 – 31.6)
Clonidine	3	2.1 (1.2 – 3.7)	25.0 (15.7 – 37.3)
Bupropion SR	26	2.0 (1.8 – 2.2)	24.2 (22.2 – 26.4)
Nicotine Patch (6–14 weeks)	32	1.9 (1.7 – 2.2)	23.4 (21.3 – 25.8)
Long-Term Nicotine Patch (> 14 weeks)	10	1.9 (1.7 – 2.3)	23.7 (21.0 – 26.6)
Nortriptyline	5	1.8 (1.3 – 2.6)	22.5 (16.8 – 29.4)
Nicotine Gum (6–14 weeks)	15	1.5 (1.2 – 1.7)	19.0 (16.5 – 21.9)
Combination Therapies			
Patch (long-term; > 14 weeks) + *ad lib* NRT (gum or spray)	3	3.6 (2.5 – 5.2)	36.5 (28.6 – 45.3)
Patch + Bupropion SR	3	2.5 (1.9 – 3.4)	28.9 (23.5 – 35.1)
Patch + Nortriptyline	2	2.3 (1.3 – 4.2)	27.3 (17.2 – 40.4)
Patch + Inhaler	2	2.2 (1.3 – 3.6)	25.8 (17.4 – 36.5)
Patch + Second generation antidepressants (paroxetine, venlafaxine)	3	2.0 (1.2 – 3.4)	24.3 (16.1 – 35.0)
Medications not shown to be effective			
Selective Serotonin Re-uptake inhibitors	3	1.0 (0.7 – 1.4)	13.7 (10.2 – 18.0)
Naltrexone	2	0.5 (0.2 – 1.2)	7.3 (3.1 – 16.2)

*Adapted from Clinical Practice Guideline PHS 2008

Table #2

Multiple Treatment Comparison, Meta-Analysis of Pharmacotherapies

	Short-term RR (95% CI)	12-Month RR (95% CI)
Control versus		
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) versus		
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) versus		
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 versus		
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 versus		
Varenicline	1.61 (1.32 – 1.93)	1.29 (1.12 – 1.45)

For efficacy: RRs higher than 1 favor the row-defining treatment.

Adapted *with permission* from: Mills et al. Annals of Medicine, 2012;4: 588–597