Chapter 15
Tobacco Cessation

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Contents

Chapter Overview Tobacco use is behind most preventable diseases with disabling consequences and death. These diseases are among the most serious, including cancer, cardiovascular diseases (brain strokes, cardiac infarcts, peripheral artery disease), and respiratory system diseases (emphysema, chronic infections). It is estimated that one-third of cancers are attributable to tobacco use and in theory can be prevented. Therefore, a comprehensive tobacco cessation program is a crucial element of successful survivorship and cancer prevention programs. Smoking cigarettes is the most common and deadliest method of consuming tobacco, and nicotine is the reinforcing substance in any tobacco use that with long-term exposure leads to dependence (addiction). Nicotine dependence involves biological, behavioral, and cognitive elements; an optimal approach to treatment

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for nicotine dependence should address each of these three dimensions. A comprehensive tobacco/smoking cessation program should include cognitive behavioral techniques, motivational interviewing approaches, and appropriate medications. Currently the medications approved by the US Food and Drug Administration for the treatment of nicotine dependence include nicotine replacement therapies, bupropion-SR (sustained release), and varenicline; these treatments can be used individually or in combination. Combining medications capitalizes on the synergy resulting from differing mechanisms of action.

Introduction

Cigarette smoking is the principal cause of preventable morbidity and mortality in the United States (US Centers for Disease Control and Prevention [CDC] 2010) and around the globe. In the United States alone, 443,000 deaths per year are attributable to cigarette smoking, according to the CDC; around the world, that number is estimated to be about six million deaths per year. Although tobacco use in general correlates with many cancers, cigarette smoking in particular is reported to be causally linked to at least 18 types of cancer. Smoking-related health care expenditures in the United States are estimated to be around $96 billion, and costs related to the accompanying loss in productivity are about $97 billion, resulting in an economic burden from smoking of about $193 billion per year (CDC 2012).

Approximately 12 million people are living with cancer in the United States (CDC 2012); lung cancer, ischemic heart disease, and chronic obstructive pulmonary disease constitute the three leading causes of smoking-attributable mortality. Smoking cigarettes accounts for the vast majority of tobacco use and addiction, as well as for the vast majority of nicotine dependence (for the purpose of this chapter we will use the term “tobacco addiction” interchangeably with “smoking cigarettes” or “nicotine dependence”). Therefore, treating tobacco addiction must be an essential component of any campaign to eradicate cancer, in particular because of the staggering statistics pointing to smoking as the cause of one out of every three deaths from cancer and as the cause of four out of five deaths from chronic obstructive pulmonary disease. Because the consequences of smoking take many years or decades to become apparent, declining smoking rates and increasing public health campaigns against tobacco will take years or even decades to make a dent in the current death toll.

Unfortunately, smoking cigarettes remains the leading cause of death in the United States even though cigarette use has declined substantially in United States and other industrialized nations. However, there is reason for hope, as evidenced by outcomes of public health programs in the state of California, where aggressive campaigns with provisions for treatment did ultimately decrease cigarette use, which is currently at around 15% in the state (CDC 2011). This is the second lowest

smoking rate in the nation, after Utah (13%). Interestingly, this decrease in smoking in California was followed by a substantial reduction in lung cancer incidence within 5 years and thereafter. For 2009 the incidence of new lung cancer cases/year was at 60 and 78 per 100,000 for California versus the US respectively, while in 1999 that incidence was at 75 and 93 cases per 100,000 for California versus the US respectively. This provides concrete evidence at the population level of the causal relationship between smoking and lung cancer and between quitting smoking and decreased lung cancer incidence.

Overall, despite several public health campaigns, one-fifth of the US population (<20%) currently smokes cigarettes. Unfortunately, smoking rates are substantially higher among certain groups; rates increase gradually with lower education levels and lower income levels. Yet 70% of smokers, when asked, say they would like to quit, and 40% of current smokers have made at least one quit attempt of at least 24 hours in the previous year, although only 6% manage to maintain abstinence from cigarettes when they quit without assistance (US Department of Health and Human Services 2000). Evidence shows that the difficulty in maintaining abstinence after quitting, whether assisted or not, is strongly related to affective and cognitive dysfunction, which may persist for some time after the initial cessation. In addition, cravings for cigarettes after cessation can result in a slip to smoking (less than 24 hours of smoking), and those slips often lead to full relapse to regular smoking.

Biological and Behavioral Determinants of Nicotine Dependence

The Reward Pathway

Cigarettes contain nicotine, a highly addicting substance. Like most drugs that are used for prolonged periods, nicotine can lead to dependence (traditionally referred to as addiction) because it acts on and stimulates specific receptors. Because nicotine receptors are spread in most areas of the brain, the administration of nicotine leads to a rapid increase in dopamine release within the nucleus accumbens and the ventral tegmental area (the two main areas of the reward pathway). This stimulation typically starts within 10 seconds of smoking a cigarette. It has been established that natural rewards such as food consumption, social affiliation, and sexual activity, which are linked to survival of the individual or species, also activate these two central areas of the reward pathway within the brain. The reward pathway has projections to many areas of the brain; of particular importance are the projections from the nucleus accumbens and ventral tegmental area to the prefrontal cortex, the amygdala, and the olfactory tubercle (Fig. 15.1). Several other brain systems (neurotransmitters and pathways) are thought to be involved in the process of developing

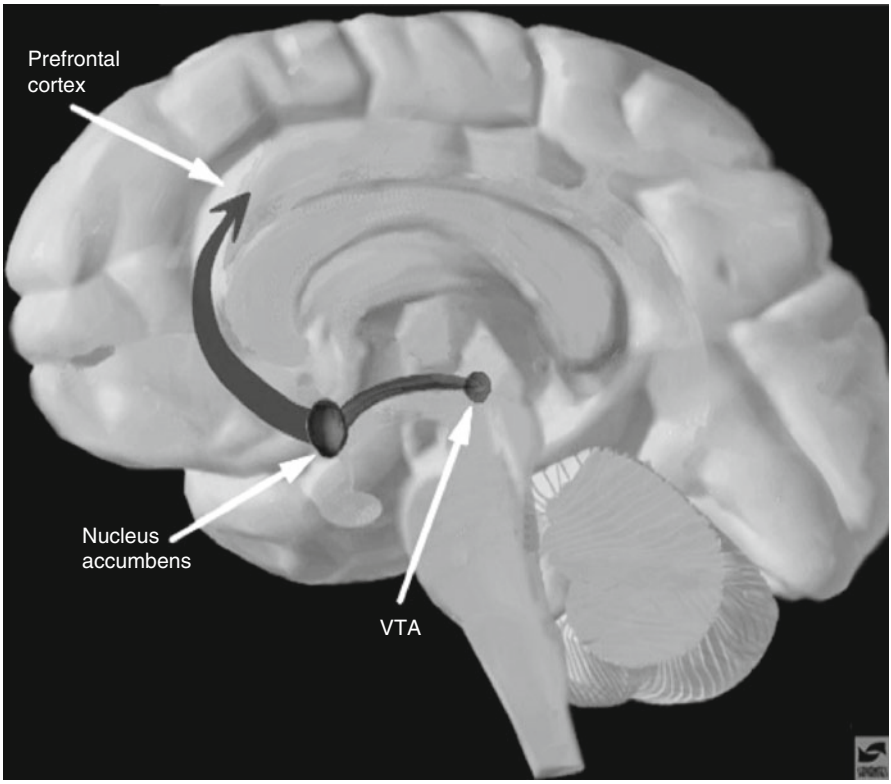

Fig. 15.1 The nucleus accumbens and ventral tegmental area (VTA) project to the prefrontal cortex as part of the reward pathway

dependence to a substance, although dopamine is referred to as the final or common neurotransmitter in the reward pathway.

Neuronal Adaptation

A pleasurable sensation from the activation of the reward pathway is associated with the acute use of a substance of abuse such as nicotine. However, repeated administration of a substance such as nicotine over months or years is likely to lead to increased tolerance, which in turn produces a state of withdrawal in the absence of the substance. Tolerance and withdrawal are the physiologic hallmarks of dependence and are thought to be the result of neuroadaptive effects occurring within the brain (Benowitz 2008). Interestingly, the chronic use of drugs of abuse and dependence (including nicotine) appears to result in a generalized decrease in dopaminergic neurotransmission. This decrease is likely to be a homeostatic response to the intermittent yet repetitive increases in dopamine induced by the frequent and sustained use of such drugs (Volkow et al. 2002).

Diagnosis of Nicotine Dependence

Because specific biological markers are absent, nicotine dependence is a clinical diagnosis. The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5; American Psychiatric Association 2013), employs universal criteria for all substance dependence, including nicotine use disorder (formerly nicotine dependence). According to DSM-5, a substance use disorder is diagnosed when the patient meets two or more of the 11 total criteria within a 12-month period. The DSM-5 criteria offer ease of use for the clinician because of the universality of the criteria to all substances of dependence. However, because of their universality, the DSM-5 criteria are not specific to tobacco and therefore do not capture many of the particular aspects of tobacco use and nicotine dependence. This nonspecific categorization has led to the development of specific scales to quantify nicotine dependence. Traditionally, the Fagerström Test of Nicotine Dependence has been used, although recently the Wisconsin Inventory of Smoking Dependence Motives has become more accepted as a more comprehensive scale.

Smoking and Psychiatric Comorbidities

Smoking rates among individuals with no mental illness, past-month mental illness, and lifetime mental illness have been reported to be 22%, 34%, and 41%, respectively. These rates indicate that having a current mental disorder effectively doubles the chances of being a smoker. Furthermore, in a nationally representative sample, smokers who had a mental disorder in the past month were reported to consume 44% of all cigarettes smoked (Lasser et al. 2000). Smoking seems to be closely linked with several psychiatric comorbidities, including dependence on other substances, suggesting a shared biological pathway between nicotine dependence and these other psychiatric conditions. Evidence of co-occurrence of mental illness with smoking also highlights the importance of screening and treating mental health disorders among smokers, whether the co-occurrence is causal or a simple correlation. Treating these comorbid mental disorders would at least reduce the impact of the disorders on patients' ability to quit smoking, and treating such disorders may increase patients' resilience against relapsing to cigarette use. This is of particular importance among patients who are in remission from cancer (survivors) who relapse to or continue to smoke and are unable to quit because they may still be recovering from the emotional toll of cancer, which often leads to clinical depression or anxiety disorders.

Treatment for Tobacco Use

To achieve maximum benefits, the treatment approach for tobacco use disorder (nicotine dependence) must be comprehensive, because the disease itself has multiple components. Similarly, the approach must be ongoing or longitudinal because

dependence is a chronic relapsing disorder. The essential components of a treatment program are psychosocial therapies and medications. Therapies such as cognitive behavioral therapy, motivational interviewing, skills building, and problem solving have been shown empirically to be effective.

First-line medications approved by the US Food and Drug administration (FDA) comprise three major categories: (1) nicotine replacement therapies (NRTs); (2) sustained-release bupropion (bupropion-SR), a nicotine receptor antagonist; and (3) varenicline (Chantix), a nicotine receptor partial agonist. The US Department of Health and Human Services updated the Clinical Practice Guideline for Treating Tobacco Use and Dependence (CPG-TTUD) in 2008 (Fiore et al. 2008). This guideline is evidence-based and is considered the standard of practice in providing treatment for tobacco and smoking cessation; it can be summarized in ten key recommendations (Table 15.1). Medications have a big impact on smoking cessation, reduction of cravings, and mitigation of nicotine withdrawal symptoms. NRTs, bupropion-SR, and varenicline are first-line therapies for nicotine dependence (Table 15.2), whereas nortriptyline (Pamelor) and clonidine (Catapres) are not approved by the FDA for this particular use and are considered second-line therapies owing to their side effect profiles.

Nicotine Replacement Therapies

NRTs were the first pharmacologic treatments to be offered for smoking cessation. In general, the quit rate among smokers who use an NRT is double that of smokers who do not use an NRT (Karam-Hage and Cinciripini 2007). The FDA has approved the following NRTs for smoking cessation: 16- or 24-hour prescription or over-the-counter patch, prescription nasal spray or buccal inhaler, and over-the-counter polacrilex gum, flavored gum, and flavored lozenges and mini-lozenges (Table 15.2).

In a review of 103 trials of NRTs, the overall odds ratio for maintaining abstinence from cigarette smoking when using a single NRT, compared with placebo, was 1.77 (95% confidence interval, 1.66–1.88; Silagy et al. 2004). However, combinations of NRTs, in particular combining the patch with an episodic NRT (gum, lozenge, inhaler, or nasal spray), seemed to be more effective than any single NRT and may be more effective than any other pharmacologic treatment available today. Silagy et al. (2004) concluded that (1) 8 weeks of patch therapy is as effective as longer courses of patch therapy, and there is no evidence that tapering off patch therapy is better than ending patch therapy abruptly; (2) wearing a patch only during waking hours (for 16 hours per day) is as effective as wearing a patch for 24 hours per day; (3) gum may be offered on a fixed-dose or as-needed basis; (4) highly dependent smokers (e.g., those who need to smoke within 30 minutes of waking) and those who have been unable to quit with the 2-mg dose gum need the 4-mg dose gum; and (5) the effectiveness of NRTs appears to be largely independent of the intensity of psychosocial therapeutic support provided to the smoker.

Table 15.1 Ten key recommendations for tobacco and smoking cessation treatment programs

The overarching goal of these recommendations is that clinicians strongly recommend the use of effective tobacco dependence counseling and medication treatments to their patients who use tobacco, and that health systems, insurers, and purchasers assist clinicians in making such effective treatments available.

1. Tobacco dependence is a chronic disease that often requires repeated intervention and multiple attempts to quit. Effective treatments exist, however, that can significantly increase rates of long-term abstinence.
2. It is essential that clinicians and health care delivery systems consistently identify and document tobacco use status and treat every tobacco user seen in a health care setting.
3. Tobacco dependence treatments are effective across a broad range of populations. Clinicians should encourage every patient willing to make a quit attempt to use the counseling treatments and medications in this Guideline.
4. Brief tobacco dependence treatment is effective. Clinicians should offer every patient who uses tobacco at least the brief treatments shown to be effective in this Guideline.
5. Individual, group, and telephone counseling are effective, and their effectiveness increases with treatment intensity. Two components of counseling are especially effective, and clinicians should use these when counseling patients making a quit attempt:

   Practical counseling (problem solving/skills training)

   Social support delivered as part of treatment
6. Numerous effective medications are available for tobacco dependence, and clinicians should encourage their use by all patients attempting to quit smoking—except when medically contraindicated or with specific populations for which there is insufficient evidence of effectiveness (i.e., pregnant women, smokeless tobacco users, light smokers, and adolescents).

   Seven first-line medications (five nicotine and two non-nicotine) reliably increase long-term abstinence: bupropion-SR, nicotine gum, nicotine inhaler, nicotine lozenge, nicotine nasal spray, nicotine patch, and varenicline.

   Clinicians also should consider the use of certain effective combinations of medications in this Guideline.
7. Counseling and medication are effective when used individually for treating tobacco dependence. The combination of counseling and medication, however, is more effective than either treatment alone. Thus, clinicians should encourage all individuals making a quit attempt to use both counseling and medication.
8. Telephone quitline counseling is effective with diverse populations and has broad reach. Therefore, both clinicians and health care delivery systems should ensure patient access to quitlines and promote quitline use.
9. If a tobacco user currently is unwilling to make a quit attempt, clinicians should use the motivational treatments shown in this Guideline to be effective in increasing future quit attempts.
10. Tobacco dependence treatments are both clinically effective and highly cost-effective relative to interventions for other clinical disorders. Providing coverage for these treatments increases quit rates. Insurers and purchasers should ensure that all insurance plans include the effective counseling and medication in this Guideline as covered benefits.

From the US Department of Health and Human Services Clinical Practice Guideline for Treating Tobacco Use and Dependence (Fiore et al. 2008)

Table 15.2 Dosage and availability of US Food and Drug Administration–approved pharmacologic agents for smoking cessation

Cessation agent	Dosage	Label indication and use	Availability in the United States	OR of efficacy (95% CI)
Nicotine gum	2 and 4 mg	2 mg for ≤25 cigarettes per day and 4 mg for >25 cigarettes per day; minimum 8 pieces per day, maximum 20 pieces per day	OTC; traditional, mint, and orange flavors; generic available	1.66 (1.52–1.81)[a]
Nicotine patch	21, 14, and 7 mg	≥10 cigarettes per day: 21 mg for 6 weeks, then 14 mg for 2 weeks, then 7 mg for 2 weeks	OTC; clear and skin color; generic available	1.81 (1.63–2.02)[a]
Nicotine nasal spray	10 mg/mL, 0.5 mg per squirt	2 squirts (1 dose) per hour, minimum 8 doses per day, maximum 40 doses per day	Prescription only, 100 mg per bottle; no generic	2.35 (1.63–3.38)[a]
Nicotine oral inhaler	10 mg per cartridge, 4 mg delivered	6–16 cartridges per day up to 12 weeks, then gradual reduction for 12 weeks	Prescription only, 168 cartridges per box; no generic	2.14 (1.44–3.18)[a]
Nicotine lozenges	2 and 4 mg	If first cigarette is ≤30 minutes after waking, use 4-mg lozenge; if >30 minutes, use 2-mg lozenge; minimum 8 lozenges per day, maximum 20 lozenges per day	OTC; mint and cherry flavors; no generic	2.05 (1.62–2.59)[a]
Bupropion-SR	100 and 150 mg	150 mg every morning for 3 days, then 150 mg twice daily for 3 months	Prescription only; generic available	1.94 (1.72–2.19)[b]
Varenicline	0.5 and 1 mg	0.5 mg every morning for 3 days, then 0.5 mg twice daily for 4 days, then 1 mg twice daily up to 3 months; if quit, another 3 months	Prescription only; no generic	High dose 3.09 (1.95–4.91)[c]; low dose 2.66 (1.72–4.11)[d]

Adapted from Karam-Hage and Cinciripini (2007)
OR indicates odds ratio, *CI* confidence interval, *OTC* over the counter
[a]OR for comparative efficacy of nicotine replacement therapies and control (placebo), as reviewed by Silagy et al. (2004)
[b]OR for overall bupropion-SR efficacy, as reviewed by Hughes et al. (2007)
[c]OR for varenicline efficacy compared with placebo; Gonzales et al. (2006)
[d]OR for varenicline efficacy compared with placebo; Jorenby et al. (2006)

Patient education and management of expectations are key aspects of the clinical visit before treatment begins. This is especially true for combination approaches, such as the simultaneous use of two NRTs, use of bupropion-SR plus an NRT, or use of bupropion-SR plus varenicline. Although NRTs carry a warning that patients should not use them while continuing to smoke, the use of any NRT, such as gums, inhalers, and patches, has been deemed safe even in patients who continue to smoke. In fact, studies have shown that the use of NRTs while continuing to smoke helped reduce the number of cigarettes smoked per day by as much as 50% among participants who were not motivated to quit, without any significant nicotine toxicity or major adverse events. NRTs have a minor side effect profile: the patch can cause local skin irritation, nausea, or headaches in some patients; oral NRTs may cause nausea, sore throat, or mouth sores in those receiving chemotherapy; and the nasal spray may cause nasal irritation (Physicians' Desk Reference 2013).

A trend in smoking cessation pharmacotherapy is the combination of NRTs or the combination of NRTs with bupropion-SR, which has a different mechanism of action. A recent large and well-designed placebo-controlled trial was conducted among volunteers recruited from the community (Piper et al. 2009). In that trial, three monotherapies (bupropion-SR, patch, and lozenge) and two combination therapies (bupropion-SR plus lozenge and patch plus lozenge) were compared; the patch and lozenge combination produced the greatest benefit relative to placebo for smoking cessation, and bupropion-SR plus lozenge came in as a close second best (Piper et al. 2009). An effectiveness trial by the same research group using the same monotherapies and combinations was conducted in a primary care patient population (Smith et al. 2009). The combination of bupropion-SR plus lozenge was superior to each monotherapy tested and resulted in a smoking abstinence rate of 30% at 6-month follow-up. In addition, the combination of the patch and lozenge was the second-best therapy tested and was superior to any of the monotherapies (Smith et al. 2009).

Bupropion-SR

In 1991 the FDA approved bupropion-SR, under the name Zyban, for the treatment of nicotine dependence, although it was originally approved as an antidepressant. Bupropion is considered an atypical antidepressant because it does not have a clearly known mechanism of action. However, its pharmacodynamic properties include inhibition of norepinephrine reuptake and, to some extent, dopamine reuptake. These inhibitory properties are thought to play a role in its mechanisms of action as an antidepressant and possibly as a treatment for nicotine dependence. In addition, bupropion was found to have some activity as a noncompetitive antagonist on high-affinity $\alpha4\beta2$ subnicotinic acetylcholinergic receptors. One of the drug's metabolites, (2S,3S)-hydroxybupropion, could have more powerful antagonist activity against $\alpha4\beta2$ receptors than bupropion itself. This

metabolite may also reduce nicotine reward, withdrawal symptoms, and cravings. Bupropion-SR therapy is typically started 1–2 weeks before the planned quit date at a dosage of 150 mg per day for 3–7 days; then it is increased to 150 mg twice per day.

Unfortunately, use of bupropion-SR is limited by its contraindication for patients with a family or personal history of seizure, a personal history of head trauma, or a history of bulimia and anorexia nervosa. The most commonly reported adverse events with use of bupropion-SR are anxiety, insomnia, dry mouth, and tremors; therefore, bupropion-SR should be used cautiously in patients who may already have these symptoms. Bupropion-SR is also relatively contraindicated in patients who have elevated liver enzyme levels (>3× the upper limit of normal) because it is metabolized extensively in the liver and its metabolites may accumulate and lead to toxic effects.

A recent meta-analysis based on 44 clinical trials that included more than 13,000 smokers showed that bupropion-SR was more effective than placebo in helping patients achieve long-term (6–12 months) abstinence from smoking (risk ratio, 1.62; 95% confidence interval, 1.49–1.76; Hughes et al. 2014). Bupropion-SR also has been shown to be effective in primary care settings and in several special clinical populations, such as patients with schizophrenia, patients with depression, veterans (Beckham 1999), and patients who have posttraumatic stress disorder (Hertzberg et al. 2001).

Bupropion-SR offers unique advantages for cancer survivors, especially those who have depression or attention deficit hyperactivity disorder, because it may alleviate the comorbid symptoms in addition to helping with smoking cessation. Another advantage of bupropion-SR is its potential attenuation of the weight gain associated with smoking cessation, an important issue for smokers who are obese, overweight, or afraid of gaining weight after quitting. Bupropion-SR also has a subtle positive effect on sexual dysfunction (through an unknown mechanism); this is an important advantage because smoking and cancer treatment are known to cause impotence and other sexual dysfunction.

Bupropion-SR has some side effects, most commonly dry mouth, insomnia, and hand tremors, and rarely seizures, depression, or suicidal ideation (Physicians' Desk Reference 2013).

Varenicline

Varenicline (Chantix in the United States, Champix in other countries) is the first pharmaceutically designed compound with partial agonist effects on nicotinic receptors to become available on the market. Varenicline is a selective partial agonist that occupies and stimulates α4β2 nicotinic cholinergic receptors; consequently, it stimulates dopamine release in the nucleus accumbens, although to a lesser extent (40–60% less) than nicotine itself. By binding competitively to nicotinic receptors throughout its relatively long half-life of 24 hours, varenicline

also displays antagonistic properties, in that it prevents the full stimulation of the nicotinic receptors that ensues when nicotine is co-administered. Because of these mixed properties, varenicline may provide relief from withdrawal symptoms, via its agonist effect, while blocking the rewarding effects of nicotine, via its antagonist effect (Gonzales et al. 2006).

Two initial randomized, double-blind clinical trials showed that varenicline (2 mg per day) is more effective for smoking cessation than placebo (odds ratio ≈ 3) and bupropion-SR (300 mg per day; odds ratio ≈ 2). The overall continuous smoking abstinence rates from the end of the 12-week treatment through 1-year follow-up were 21% for varenicline, 16% for bupropion-SR, and 8% for placebo in one study (Gonzales et al. 2006) and 23%, 14%, and 10%, respectively, in the other study (Jorenby et al. 2006). In a combined analysis of the two trials, treatment with varenicline resulted in significantly higher continuous smoking abstinence rates at 1 year than did treatment with placebo alone or bupropion-SR alone ($p < 0.05$ for both comparisons). In this pooled analysis, compared with placebo, varenicline nearly tripled the odds of a smoker quitting, even when a conservative definition (continued abstinence during the last 4 weeks of treatment with the medication) was used as the outcome measure (odds ratio, 3.09; 95% confidence interval, 1.95–4.91; $p < 0.001$).

In a randomized, double-blind continuation study of the same treatments, an additional 12 weeks of treatment with varenicline or placebo (for a total of 24 weeks of treatment) was administered to patients who had abstained from smoking at some point during the first 3 months of treatment with varenicline. In that trial, patients who received varenicline during the 12-week extension period reported significantly fewer cravings and diminished withdrawal symptoms throughout the trial, and 70% of them remained abstinent at the end of the 12-week extension period. In contrast, only 50% of patients who were randomized to receive a placebo during the 12-week extension period remained abstinent at the end of the study. Furthermore, the 1-year follow-up abstinence rate (i.e., 1 year after treatment was completed) in patients who had received 24 weeks of treatment with varenicline was twice that of patients who had received only 12 weeks of treatment with varenicline (25 and 12%, respectively; Tonstad et al. 2006).

The most commonly observed adverse effect of varenicline was nausea, which occurred in up to 30% of patients receiving the medication (approximately twice the rate of nausea observed in patients receiving a placebo); fortunately, the nausea was mild to moderate in most cases. Other commonly reported adverse events were flatulence and abnormal dreams. Recently, the FDA has received a large amount of MedWatch voluntary reports indicating an increased risk for neuropsychiatric events among people taking varenicline. Most of these events consisted of depressive symptoms, irritability, aggression, or suicidal ideation, as well as difficulty with motor coordination. As a result, the FDA mandated the inclusion of specific warnings about the possibility of occurrence of these symptoms on the medication label; it also recommended that patients stop the medication immediately and report to their health care providers if they develop such symptoms. The FDA has commissioned further analysis of existing data and mandated that the manufacturer conduct

postmarket prospective studies to clarify the relationship between these adverse effects and varenicline and the magnitude of such occurrences (FDA 2008).

For many patients, the prospect of trying a new treatment option (i.e., varenicline) could motivate them to try to quit smoking again, especially among those who have not succeeded in quitting with prior established smoking cessation medications. In addition, a combination strategy such as adding bupropion-SR to varenicline or vice versa may increase the efficacy of smoking cessation (Ebbert et al. 2009). The combination may also mitigate the emergence of depression and other neuropsychiatric symptoms (Karam-Hage et al. 2010); bupropion-SR is expected to counterbalance the neuropsychiatric side effects that may occur with varenicline.

A recent Cochrane review concluded that, at 6-month follow-up, treatment with varenicline at the standard dose (2 mg per day) more than doubled the chances of abstaining from smoking compared with treatment with placebo. Low-dose varenicline (1 mg per day) roughly doubled the chances of quitting compared with placebo and reduced the number and severity of side effects compared with the standard dose of varenicline. The number of patients who quit smoking after treatment with varenicline was higher than the number of patients who quit smoking after treatment with bupropion-SR. Interestingly, the Cochrane review also reported that two trials of nicotine patches did not show that varenicline had a clear benefit over the nicotine patch at 6-month follow-up (Cahill et al. 2011). Another important factor in an era of cost containment is the cost-effectiveness of a new treatment; the review indicated that varenicline seemed to be more cost-effective than bupropion-SR in most cost-effectiveness models studied.

Nonpharmacologic Treatments

Behavioral therapy delivered by physicians, psychologists, nurses, pharmacists, dentists, and other clinicians increases patients' smoking abstinence rates; this is especially true when "the 5 A's" are applied: Ask patients if they smoke, Advise them to quit, Assess motivation for change, Assist if they are willing to change, and Arrange for follow-up.

Sixty-four behavioral therapy studies met selection criteria for meta-analyses performed for the CPG-TTUD in 2000; these meta-analyses were needed to examine the effectiveness of interventions using various types of counseling and behavioral therapies. In these meta-analyses, four specific categories of counseling and behavioral therapy yielded statistically significant increases in smoking abstinence rates relative to no contact (i.e., untreated control conditions). These categories were (1) providing practical counseling such as problem solving, skills training, or stress management; (2) providing support during a smoker's direct contact with a clinician (intratreatment social support); (3) intervening to increase social support in the smoker's environment (extratreatment social support); and (4) using aversive smoking procedures (rapid smoking, rapid puffing, other smoking exposure). These recommendations remained the same for the updated CPG-TTUD in 2008 because no newer studies or therapies were available to warrant additional analysis.

Of interest is the finding that even minimal interventions lasting less than 3 minutes increased overall cigarette abstinence rates. Every smoker should be offered at least a minimal intervention, whether or not he or she is eventually referred to an intensive intervention. In addition, a strong dose-response relationship has been observed between the session length of person-to-person contact and successful treatment outcomes. Intensive interventions are more effective than less intensive interventions and should be used whenever possible. Person-to-person treatment delivered for four or more sessions appears especially effective in increasing cigarette abstinence rates. Therefore, if feasible, clinicians should strive to meet four or more times with individuals trying to quit smoking. In a meta-analysis for the CPG-TTUD of 2000 and 2008, incremental improvements in abstinence rates were observed with an increasing number of sessions and total duration of treatment. These incremental improvements were categorized into intervals: abstinence rate of 22% (odds ratio, 1) with one session, abstinence rate of 28% (odds ratio, 1.4) with 2–3 sessions, abstinence rate of 27% (odds ratio, 1.3) with 4–8 sessions, and abstinence rate of 33% (odds ratio, 1.7) with >8 sessions. Unfortunately, the vast majority of pharmacologic trials provide only minimal behavioral therapy of around 10 minutes' duration as the minimal standard to show efficacy of a medication, which seems to carry on to clinical practice by necessity owing to the pressures on clinical providers to deliver more services in less time.

Strategies to Treat Cancer Survivors Who Are Hard-Core Smokers

Despite exposure to the best treatments, about 60–65% of smokers do not manage to quit smoking after a single quit attempt, and less than a quarter of the 35–40% who do succeed are able to stay abstinent 1 year later (Fiore et al. 2008). This is probably due to a multitude of factors, including genetic predisposition to nicotine dependence, psychiatric comorbidities, and readiness to quit. These resilient smokers are often called "hard-core" smokers, because they did not respond to treatment and remain smoking even after major health events related to smoking, such as cancer. Among this group of hard-core smokers are many cancer survivors, some of whom may have quit temporarily out of fear and the shock of "having cancer" or in response to pressure from their doctors and family, only to return to smoking once they started to feel healthier. Therefore, it is not sufficient to provide cancer survivors with basic smoking cessation therapy and expect them to have the same response as the average smoker in the community. Despite lack of controlled trials, cancer survivors need intensive interventions, including both behavioral and pharmacologic approaches.

As mentioned above, the CPG-TTUD of 2008 shows clear evidence of a dose-response relationship in exposure to psychosocial interventions, in terms of both duration and frequency. A variety of techniques have been suggested and other novel approaches can be used to help hard-core smokers. Two types of combination pharmacotherapy have been used successfully: (1) combinations of different forms

of NRT with different pharmacokinetic profiles (e.g., nicotine patch + nicotine gum), and (2) combinations of treatments with different therapeutic targets, such as NRT + non-nicotine medications or two non-nicotine medications (e.g., bupropion-SR + NRT or bupropion-SR + varenicline; Ebbert et al. 2010).

The Tobacco Treatment Program at MD Anderson

The Tobacco Treatment Program (TTP) at MD Anderson is a fully integrated multidisciplinary program because it provides an integrated mental health and substance use treatment model. The TTP model consists of providing psychosocial treatment from counselors with master's degrees or PhDs and providing medical and psychiatric treatment from a physician assistant, nurse, and psychiatrist specializing in addiction treatment. The addiction psychiatrist provides the specialized expertise on treatment plans and treats mental health and other substance use disorders (in addition to nicotine dependence).

A common clinical dilemma faced by the TTP team is whether it is best to treat co-occurring disorders simultaneously, sequentially, or in any particular order. Unfortunately, the literature is scant, and some of it is conflicting with regard to this issue. Our treatment philosophy at the TTP is to provide individualized treatment for each patient. For patients who are interested and feel that they are able to initiate treatment for both disorders simultaneously, we help them to do so, whereas for others who are reluctant or not ready to quit smoking, we try to treat the comorbid conditions first, in hope of building therapeutic alliances and stabilizing patients' mood and affect. This approach almost always improves patients' self-esteem and self-efficacy while it builds a therapeutic alliance that prepares them to then tackle smoking cessation. Of note, self-efficacy has been found to be correlated at various levels with the ability to initiate and succeed at quitting smoking.

The MD Anderson TTP, which was launched in 2006, was modeled on the CPG-TTUD for 2000. Through the end of August 2013, the TTP had served 4,111 new patients and conducted about 35,000 follow-up appointments since its inception in January 2006. The TTP has served patients from more than 50 MD Anderson clinical departments.

The demographics and other common measures of our patient population have remained somewhat constant, as illustrated in Table 15.3 (showing both demographics over time and for the 2013 fiscal year specifically) and Table 15.4. It is noteworthy that a substantial number of our patients also present with one or more psychiatric diagnoses (Fig. 15.2). In 2011, we analyzed our 6-month follow-up data, on the basis of cohorts treated from the start of the program in 2006 until the end of 2010. The 6-month abstinence rate (7-day point prevalence at 6 months after the end of treatment) among those who were able to reach abstinence (respondent-only) was 46% (n = 1,291; response rate, 74%); however, when an intention-to-treat model is used (including all patients treated at baseline and assuming all those lost to follow-up have relapsed to smoking), the 6-month abstinent rate (7-day point prevalence at 6 months after the end of treatment) dropped to 34% (n = 1,670). Also of interest is

Table 15.3 MD Anderson Tobacco Treatment Program patient demographics for 2006–2013 and for fiscal year 2013 (FY13)

Characteristic	FY13 (%)	2006–2013 (%)
Ethnicity		
Black	10.7	10.3
Hispanic	5.2	5.2
Other	6.5	7.1
White	77.7	77.4
Sex		
Female	49.5	50.4
Male	50.5	49.6
Location		
Houston metro	61.0	57.7
Texas	25.2	26.3
Other state	12.4	15.0
Outside United States	1.3	1.0

Table 15.4 MD Anderson Tobacco Treatment Program patient clinical characteristics for fiscal year 2013

Characteristic	Mean	SD
Age (years)	56.1	11.6
Cigarettes per day	15.8	10.5
Drinks per day	1.9	3.5
Years smoked	33.3	13.9
Fagerström Test for Nicotine Dependence score	4.3	2.2
Center for Epidemiologic Studies-Depression score	14.0	11.5
Positive and Negative Affect Schedule scores		
Negative affect	20.7	8.4
Positive affect	30.3	7.6

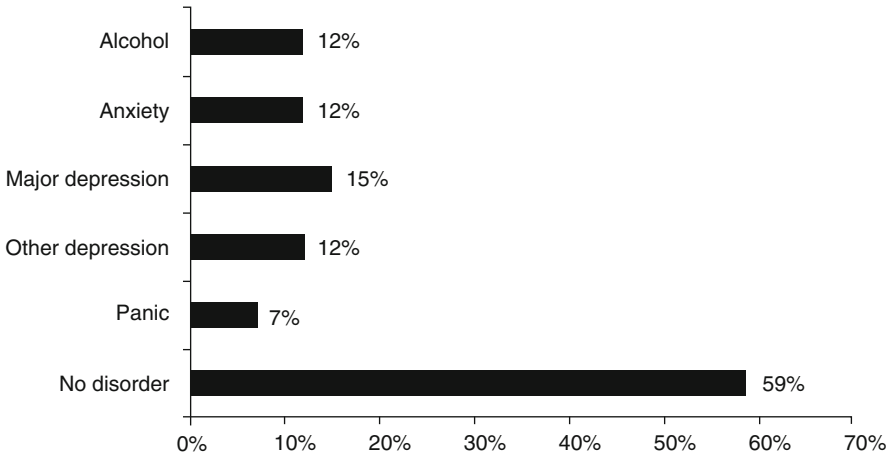

Fig. 15.2 Frequency of co-occurring psychiatric disorders among patients who visited the MD Anderson Tobacco Treatment Program in fiscal year 2013

our finding that non-quitters reduced their daily cigarette consumption by ~44% from baseline to the end of treatment (from 16 [standard deviation, 12.2] to nine [standard deviation, 9.1] cigarettes per day; n = 1,034) and by ~38% from baseline to 6 months after the end of treatment (from 16 to 10 cigarettes per day; n = 663). This reduction represents a significant change in behavior.

We pride ourselves with our program's success, measured by the 34–46% of patients who were abstinent from cigarettes at the 6-month follow-up point (7-day point prevalence of smoking abstinence rates). By comparison, the 4-week point prevalence smoking abstinence rates in a highly motivated population of healthy smokers were shown to range from 24% in patients treated with bupropion-SR to 35% in patients treated with varenicline, after 12 weeks of treatment (Gonzales et al. 2006; Jorenby et al. 2006).

Key Practice Points

- Tobacco use is responsible for more than 30% of cancer-related mortality and is the top cause of death in the United States. About 450,000 people in the United States and about five million globally die every year from tobacco-related illnesses.
- Nicotine is the addictive substance in tobacco; it stimulates nicotine receptors and consequently the reward areas of the brain.
- Behavioral and pharmacologic therapies successfully treat tobacco use; however, they work best when used together.
- Seven medications have been approved by the FDA for use as monotherapy for tobacco cessation.
- When used in certain combinations, medications can be a useful tool for tobacco cessation, especially among cancer survivors who are "hard-core" smokers.
- Minimal counseling can make a difference in smoking cessation rates; however, there is a dose-response rate in frequency and total amount of time dedicated to counseling smokers.
- Comprehensive cancer treatment needs to include tobacco cessation treatment, in particular to avoid treatment complications and disease recurrence among survivors.

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