



Nicotine Dependence and Tobacco Use Disorder Treatment

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According to the 2013–2014 National Adult Tobacco Survey (NATS), the prevalence of tobacco use in the United States during that time was 21.3% of adults age 18 and over [1]. About 17% of US adults consumed tobacco via cigarette smoking, which delivers a high amount of nicotine to the brain and the rest of the body [11]. Even though the prevalence of tobacco use and smoking has decreased compared to prior decades, millions of people who are actively smoking will eventually develop medical complications as a result of it. More recently, electronic cigarettes or e-cigarettes have skyrocketed in popularity, introducing a new vehicle for nicotine addiction, raising the specter of a reversal in decades-long efforts to reduce nicotine use, and creating a host of uncertain health effects for users given the paucity of available longitudinal evidence. In an effort to combat tobacco and nicotine addiction, many pharmacological treatments have been developed to treat tobacco use disorder and help facilitate smoking cessation. In this chapter, we will discuss the current treatment options available for tobacco use disorder and smoking cessation by incorporating clinical vignettes and highlighting research data that supports these treatments.

Aside from cigarette smoking, tobacco and nicotine can come in various other forms including cigars, pipes, water pipes (hookah), electronic cigarettes (e-cigs), and formulations developed for chewing, dipping, or snuffing [18]. However, smoking still remains the most popular method of nicotine consumption at this time. E-cigarettes and vaping have rapidly gained popularity since their appearance on the market more than a decade ago. According to the 2011–2018 National Youth Tobacco Survey (NYTS), e-cigarette use increased among high school students from 1.5% in 2011 to 20.8% in 2018 [4]. E-cigarettes are also regularly used as a smoking cessation tool, with some emerging evidence confirming that this can lead to prolonged abstinence from cigarettes for some [15]. Despite the rise in

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e-cigarettes' popularity and popular conceptions of vaping as a harm reduction strategy, health and safety data remain limited. E-cigarettes create known exposure to a number of other toxic compounds [19].

Regardless of the formulation, all tobacco-related products have nicotine, which is a naturally produced alkaloid found in the tobacco plant that acts as an agonist in the nicotinic cholinergic receptors of the autonomic ganglia and other areas of the central nervous system [18]. The effects of nicotine are dose-dependent and mediated by the release of several neurotransmitters including acetylcholine, beta-endorphins, dopamine, norepinephrine, serotonin, and adrenocorticotrophic hormone (ACTH). Stimulant effects of nicotine can include both vascular effects – such as peripheral vasoconstriction, hypertension, tachycardia, and increased cardiac output – and cognitive effects including increased alertness and insomnia. Nicotine also produces depressant effects, such as muscle relaxation and anxiety reduction. Withdrawal symptoms of nicotine include anxiety, poor concentration, irritability, and cravings for tobacco.

In addition to its short-term effects, nicotine has long-term effects associated with poor health outcomes, related to its delivery by tobacco products [18, 21]. About 400,000 people in the United States die prematurely as a result of smoking, which accounts for about one of every five deaths in the United States. Free radicals found in cigarettes and other tobacco products cause oxidative stress, inflammation, and DNA damage to the human body across multiple organ systems. The most common types of cancer associated with smoking include lung, head, neck, gastrointestinal, and cervical malignancies. Smoking also causes cardiovascular conditions including coronary artery disease, stroke, aortic aneurysms, and peripheral arterial disease, prompted by chemical products found in cigarettes that cause endothelial dysfunction, changes in lipid metabolism, increased myocardial oxygen demand, and prothrombic effects. Lung diseases, such as chronic obstructive pulmonary disease (COPD), are also commonly associated with smoking. When smoke enters the lungs, it causes inflammation, cilia destruction, and mucous gland hyperplasia resulting in pulmonary pathology. The reproductive system is also affected by smoking in both men and women. In pregnant women, smoking can lead to low birth weight, premature birth, ectopic pregnancy, teratogenic effects, and sudden infant death syndrome, while in men it causes erectile dysfunction. Additional effects from smoking include impaired immune functioning, increased infection risk, peptic ulcers, bone fractures, and diabetes-related complications.

The prevalence of tobacco use differs among various subgroups, reflecting both historical consumption patterns and socioeconomic and racial disparities. In 2015, the prevalence of cigarette smoking was 16.7% in men and 13.6% in women; decades ago many more men than women smoked, but this gap by sex has been gradually closing [14]. Smoking rates also differ by race, with American Indian/Alaska Natives having the highest prevalence of 21.9% and Asians having the lowest at 7.0%. Increased rates of smoking have been consistently noted in

communities with lower incomes, lower education levels, and higher unemployment, among many other socioeconomic correlates [10]. Those with mental illness or other substance use disorders have higher rates of cigarette smoking compared to the general population.

Due to addictive properties of nicotine, many individuals who smoke or consume tobacco, eventually develop tobacco use disorder. According to [5], in order to meet criteria for tobacco use disorder, a person must have a problematic pattern of tobacco use that leads to clinical impairment or distress within a 12-month period. The person must meet at least two criteria that are listed under that definition. Please see Table 10.1 for criteria listed by the DSM-5.

In terms of treatment, there are both pharmacologic and non-pharmacologic approaches to tobacco use disorder and smoking cessation. Most of the discussion of the rest of this chapter will focus on the evidence-based medication treatments currently available, which include nicotine replacement therapy (NRT), varenicline (also known as Chantix), and bupropion (also known as Wellbutrin). Please see Table 10.2 for a list of the medications as well as common doses for smoking cessation [21]. The following clinical cases will illustrate practical approaches to using these medications.

Table 10.1 DSM-5 criteria for tobacco use disorder

- A. A problematic pattern of tobacco use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:
1. Tobacco is often taken in larger amounts or over a longer period than was intended
 2. There is a persistent desire or unsuccessful efforts to cut down or control tobacco use
 3. A great deal of time is spent in activities necessary to obtain or use tobacco
 4. Craving, or a strong desire or urge to use tobacco
 5. Recurrent tobacco use resulting in a failure to fulfill major role obligations at work, school, or home
 6. Continued tobacco use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of tobacco (e.g., arguments with others about tobacco use)
 7. Important social, occupational, or recreational activities are given up or reduced because of tobacco use
 8. Recurrent tobacco use in situations in which it is physically hazardous (e.g., smoking in bed)
 9. Tobacco use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by tobacco
 10. Tolerance, as defined by either of the following:
 - (a) A need for markedly increased amounts of tobacco to achieve the desired effect
 - (b) A markedly diminished effect with continued use of the same amount of tobacco
 11. Withdrawal, as manifested by either of the following:
 - (a) The characteristic withdrawal syndrome for tobacco (refer to Criteria A and B of the criteria set for tobacco withdrawal)
 - (b) Tobacco (or a closely related substance, such as nicotine) is taken to relieve or avoid withdrawal symptoms

Table 10.2 Psychopharmacology of tobacco use disorders and dosing

Name of medication	Dosing
Varenicline (Chantix)	Dosing: 0.5 mg, 1 mg Frequency: 0.5 mg daily for days 1–3, then twice a day for days 4–7, then 1 mg twice a day starting day 8 and thereafter Note: start 1 week before quit date
Bupropion (Wellbutrin, Zyban)	Dosing: 150 mg of the sustained-release formulation Frequency: daily for days 1–3, then twice a day starting day 4 and thereafter Note: start 1 week before quit date
Nicotine replacement therapies	Transdermal patch: Doses: 7 mg, 14 mg, 21 mg Frequency: every 24 hours gum: Doses: 2 mg, 4 mg Frequency: every 1–2 h Lozenge: Doses: 2 mg, 4 mg Frequency: every 1–2 h Sublingual tablet: Doses: 2 mg, 4 mg Frequency: every 1–2 h Inhalation: Doses: 1 cartridge Frequency: continuously every 20 minutes but no more than 16 cartridges/day Nasal spray: Doses: 1 mg per dose (2 sprays) Frequency: 1–2 doses per hour

Clinical Cases

Dr. Ramos recently completed residency in psychiatry and started an addiction psychiatry fellowship. During her first week as a fellow, she discusses three cases with her attending related to tobacco use disorder and her proposed treatments. Her first case, Jonathan, is a 39-year-old man with a history of anxiety, who has never seen a therapist before and has never taken medication in the past because of “trouble swallowing pills.” Jonathan reports that he has been smoking about two packs a day and is interested in quitting. He is willing to try “anything,” including therapy and medication.

Her next case is Xavier, a 65-year-old man with a history of depression, previously on SSRIs but stopped due to sexual side effects. Lately he has been feeling more depressed with low energy, increased sleep, and weight gain. He attributes his low mood to the fact that he has failed to quit smoking in the past but is thinking of attempting to quit again. He has been smoking a pack of cigarettes a day almost every day for the last 20 years. He reports wanting to quit because recently he was diagnosed with coronary artery disease and hypertension. Xavier is now interested in medication that can help him in both smoking cessation and his depression.

Dr. Ramos's final patient is Nataly, a 20-year-old woman with a history of an eating disorder in the past and seizures. She began smoking half a pack of cigarettes a day two years ago when she turned 18 and started college. She has attempted to quit in the past by using nicotine gum and patch, but her attempts were unsuccessful. Lately, she has been vaping and using e-cigarettes, which help to reduce her cravings but at times she continues to smoke cigarettes, especially during her final examinations. Nataly is interested in trying another medication to help her quit before next month when school starts again.

Discussion

Dr. Ramos's patients are presenting with nicotine dependence and would benefit from treatment. Each of the available treatments has strengths and weaknesses, detailed in Table 10.3 [21, 24]. For each of these cases, there are specific factors in the history and presentation of these patients that might persuade a provider to choose one medication over another. For the rest of the chapter, we will discuss the current treatments available for tobacco use disorder and why Dr. Ramos might choose that particular treatment over the others.

Non-pharmacological Intervention

In our first case, Jonathan is interested in both therapy and medication. After a person stops smoking, there are many psychological factors that can lead someone to relapse including intermittent negative thoughts and emotions, multiple urges to smoke, decreased motivation, and self-efficacy about quitting. Therefore, there are a variety of interventions that have been shown to be effective in helping to prevent relapse of smoking and tobacco use [21]. Some of these non-pharmaceutical interventions include cognitive behavioral therapy (CBT), motivational interviewing, and acceptance and commitment therapy. These therapies can be individual or group based and vary in intensity. Nicotine Anonymous is another option, with hundreds of 12-step meetings available worldwide. They can also vary by mode of delivery, which can include delivery by a clinician, counselor, telephone, or computer. Most research supports their efficacy in increasing smoking cessation rates, but data comparing each of these modes is limited. However, data does show that effectiveness is dose-responsive, so higher amounts of exposure to these behavioral strategies yield longer periods of sustained cessation.

Nicotine Replacement Treatment

Another option for Jonathan is nicotine replacement therapy (NRT), which helps by reducing nicotine cravings in those that smoke or use tobacco. NRT comes in five forms including a transdermal patch, gum, lozenge, nasal spray, and inhaler [22].

Table 10.3 Comparison of different treatments in smoking cessation

Intervention	Advantages	Disadvantages
Psychosocial treatment only (brief provider interventions, individual psychological interventions, telephone support, Nicotine Anonymous, etc.)	Can address psychological factors and motivation to quit Brief interventions still effective Maximizes social support to help patient quit More effective than self-help	Does not address biological dependence, cravings, or withdrawal symptoms Less intensive interventions shown to be less effective
Nicotine replacement therapy	Low cost Different formulations chosen based on patient preference Has both short-acting and long-acting forms, which can help with withdrawal and craving symptoms Mimics hand to mouth ritual Few side effects	More frequent dosing for short-acting forms Irritation of the skin, mouth, or nose depending on formulation used Less effective than varenicline
Bupropion	Simple twice a day dosing No weight gain Can help with depression Can be combined with NRT	Adverse effects can include insomnia, anxiety, dry mouth Contraindicated in patients with history of eating disorder or seizures or concurrent use of monoamine oxidase inhibitors (MAOIs) Must monitor neuropsychiatric symptoms Less effective than varenicline
Varenicline	Simple dosing of twice a day Different mechanism of action for patient who have failed other treatments Most effective treatment	Adverse effects include nausea, vomiting, constipation, sleep disturbances Must monitor neuropsychiatric symptoms Limited data suggests cardiovascular effects

This is particularly convenient for someone like Jonathan, who doesn't like "swallowing pills." These formulations work by providing nicotine without the other hazardous chemicals found in cigarettes or tobacco. NRT provides lower doses of nicotine that normally last longer than nicotine found in cigarettes or tobacco. The nicotine patch provides the longest release of nicotine [22].

All forms of NRT increase rate of quitting by 50–60%, and efficacy is comparable among the different formulations [9]. However, based on research, combining the long-acting nicotine patch with a short-acting form is more effective than a single NRT agent. A Cochrane meta-analysis found that this combined approach made quitting 15–36% more likely. [16]. Therefore, Dr. Ramos may want to

prescribe Jonathan a long-acting patch with a short-acting form, such as nicotine gum, in hopes that this will be more effective in helping Jonathan quit smoking.

In general, NRT has a low side effect profile, including heart palpitations and chest pains, nausea and vomiting, insomnia, as well as irritation of the mouth and skin depending on route of administration [17]. Therefore, NRT is the safest pharmacological treatment to prescribe, particularly since most individuals prescribed NRT will already be habituated to these physiologic effects of nicotine.

Bupropion

Bupropion is an effective medication for smoking cessation and tobacco use disorder that is also a treatment for depression [8]. Therefore, Xavier might benefit from this medication as it would help both with his tobacco use disorder and his mood. The mechanism of this drug related to smoking cessation is not totally clear [23]. When nicotine crosses the blood-brain barrier, it causes a release of dopamine into the synaptic cleft of the dopaminergic, pleasure-seeking pathways of the brain. Similarly, bupropion blocks the reuptake of dopamine. Additionally, it is thought that dopamine deficiency in the nucleus accumbens leads to nicotine withdrawal when smoking is stopped. Therefore, bupropion might increase dopamine in the nucleus accumbens, which leads to attenuation of nicotine withdrawal symptoms. Bupropion is also a noncompetitive blocker of the postsynaptic acetylcholine nicotine receptor, which stops the reinforcing effect of nicotine use [23].

Bupropion appears to be an effective treatment of tobacco use disorder. A meta-analysis of 65 RCTs found that bupropion as a monotherapy significantly increased long-term cessation of 6 months or greater (RR = 1.62; 95% CI, 1.49–1.76) relative to placebo, which was comparable to NRT (RR = 0.96; 95% CI, 0.85–1.09) [13]. A Cochrane meta-analysis also found that both bupropion and NRT are comparable in efficacy [3].

Bupropion's most common side effects include headache, insomnia, dry mouth, and agitation [12]. However, one of the most notable adverse effects is seizures [12]. The risk of seizures depends both on dose and on preparation. The higher the dose, the higher the risk of developing seizures. Additionally, the sustained-release formulation has a lower risk of seizures compared to the immediate-release formulation. Therefore, seizure disorder is a major contraindication to use, as well as any other factors that predispose someone to seizures including discontinuation of alcohol or sedatives, arteriovenous malformations, severe headache injury, stroke, brain tumor, or any other significant central nervous system disease. Bupropion should also not be used in someone with a history of an eating disorder or bipolar disorder or who is on monoamine oxidase inhibitors [12]. Therefore bupropion would not be an appropriate medication to use in someone like Nataly, who has a history of an eating disorder and seizures.

The FDA requires all antidepressants to carry a boxed warning that antidepressants can increase risk of suicide in those under 25 years of age, including bupropion. However, suicidal behavior is less of a concern in smoking cessation. In

December 2016, data from a large clinical trial convinced the FDA that serious mood and suicidal behaviors were not as severe as previously thought of and the FDA removed the black box warning for smoking cessation [19]. The report still advises to use with caution and to monitor behavioral symptoms, especially in patients with co-occurring mood or psychotic disorders.

Varenicline

Another medication option for tobacco use disorder is varenicline, which may be an ideal option for Nataly. This drug works as a partial agonist of the alpha-4-beta-2 nicotinic acetylcholine receptor subtype (nACh) [20]. When the drug attaches to the receptor, it produces less effect of dopamine release than it would with nicotine. This leads to decreased nicotine addiction, and it also decreases the cravings and withdrawal syndrome associated with cessation of tobacco use.

Varenicline appears to be the most effective option for tobacco use disorder. A study assessing the effectiveness of varenicline in smokers who had no intention to quit in the next 30 days found that 32.1% of smokers were biochemically confirmed to have been continuously abstinent by weeks 15–24 after starting varenicline [6]. On the other hand, the placebo group only had an abstinence of 6.9% during that time period. Additionally, by weeks 21–52 after initiation of the trial, 27% of the varenicline group remained abstinent, compared to only 9% in the placebo group. A Cochrane review also found that varenicline is more effective than either NRT or bupropion [3]. The odds ratio of effectiveness compared to placebo was 1.84 (95% CI of 1.71–1.99) for NRT, 1.82 (95% CI 1.60–2.06) for bupropion, and 2.88 (95% CI 2.40–3.47) for varenicline.

The most common side effect of varenicline is nausea, which is seen in almost 30% of people taking it [7]. Other less common side effects include headache, insomnia, vivid dreams, constipation, and other gastrointestinal symptoms. In 2009, the US FDA required that varenicline carries a boxed warning that the drug should be stopped if there were any changes in behavior. This was done in response to post-marketing reports carried out by the FDA that found increased suicidality risk and suicidal behavior among people using varenicline for smoking cessation. However, many systematic reviews have been conducted that have found no increased suicide risk or neuropsychiatric side effects. In 2016, the FDA removed the black box warning as it did for bupropion, but the FDA continues to recommend monitoring patients for these side effects [19]. In June 2011, the US FDA also issued a safety announcement about varenicline potentially causing a small increase of cardiovascular adverse events in people with cardiovascular disease. This was based on a review that showed increased risk of cardiovascular events in people using varenicline compared to placebo. However, multiple reviews and meta-analyses afterward have found no increase in cardiovascular events associated with varenicline use [6]. Given that Xavier already has history of cardiovascular disease, it may be prudent to try a medication other than varenicline given possible risk of cardiovascular events.

A number of studies have also looked at combination therapies combining varenicline with other smoking cessation medications [2]. A study showed higher continuous abstinence in those who combined varenicline with a 15 mg nicotine patch compared to those who were on varenicline alone. However, another study found no difference. In another study that looked at varenicline plus bupropion, there were no differences found between the two groups in terms of abstinence. However, a subgroup analysis found significantly higher rates of abstinence in those who smoked more than 20 cigarettes per day [2]. Therefore, combining varenicline with bupropion might be another option for some patients.

Conclusion

Although prevalence rates for tobacco use disorder are decreasing around the world, millions of people worldwide continue to consume tobacco and are at increased risk of serious illness and death as a result of it. Providers must continue to discuss tobacco and nicotine use with their patients, keeping in mind the variety of potential nicotine delivery methods and the recent surge in popularity of e-cigarettes. A treatment plan including psychosocial and/or pharmacologic interventions for tobacco use disorder can be individually tailored to a patient's preferences and relevant additional information in the history that might make certain options a better fit than others.

Key Points

- Nicotine use remains a major cause of morbidity and mortality around the world, primarily because of its delivery through harmful tobacco products.
- Tobacco use disorder is a DSM-5 diagnosis that can be made based on an individual's pattern of problematic tobacco use.
- Both behavioral and pharmacological interventions on their own, or in combination, can be used to treat tobacco use disorder.
- Currently, there are three medication options to help with smoking cessation: nicotine replacement therapy, bupropion, and varenicline.
- The differences in these medications' required frequency, side effect profiles, contraindications, and effectiveness should all be considered when working with a patient to craft a plan for nicotine cessation.

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