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Curr Psychiatry Rep. Author manuscript; available in PMC 2011 October 1.

Published in final edited form as:
Curr Psychiatry Rep. 2010 October ; 12(5): 433–440. doi:10.1007/s11920-010-0134-6.

Comparison of Available Treatments for Tobacco Addiction

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Abstract

Cigarette smoking is a major public health problem that causes more than 5 million deaths annually worldwide. Cigarette smoking is especially common among individuals with psychiatric comorbidity, including individuals with primary psychiatric disorders and other addictions. Effective behavioral and pharmacologic treatments for smoking cessation are available. Behavioral treatments including brief (< 3 minutes) counseling by physicians are effective. Seven first-line pharmacologic treatments are currently available: five nicotine replacement therapies, bupropion, and varenicline. In addition, clonidine and nortriptyline are second-line treatments for smoking cessation. These treatments increase the chances of quitting smoking by two- to threefold, supporting their use in smokers who are motivated to quit. However, effective treatments for many subpopulations, including smokers with psychiatric comorbidities as well as adolescent, pregnant, or postpartum smokers, remain to be developed and represent an important challenge.

Keywords

Nicotine; Nicotine pharmacotherapy; Special populations; Tobacco use disorder; Clinical trials; Smoking cessation

Introduction

Cigarette smoking is the main cause of preventable death in developed countries, with an estimated 435,000 premature deaths in the United States and 5 million deaths worldwide. The economic and health care costs of tobacco use in the United States exceed 400 billion dollars annually. Although about 19.8% of US adults are smokers [1], the lowest rate ever recorded, cigarette smoking is especially common among individuals with psychiatric comorbidity. In fact, about 44% of the cigarettes sold in this country are purchased by those with psychiatric comorbidity, who represent 22% of the population [2]. Thus, smokers with psychiatric comorbidity carry a disproportionately heavy burden of health risks caused by cigarette smoking.

Quitting smoking is associated with immediate health benefits irrespective of age or presence of smoking-related diseases. As recently reviewed by the US Public Health Service *Clinical Practice Guideline Treating Tobacco Use and Dependence*, effective behavioral and pharmacologic treatments for smoking cessation are available [3••]. Although less effective

Disclosure No potential conflicts of interest relevant to this article were reported.

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than one would desire, currently available treatments increase the chances of quitting smoking by two- to threefold, supporting their use in smokers who are motivated to quit. However, effective treatments of many subpopulations, including smokers with psychiatric comorbidities as well as adolescent, pregnant or postpartum smokers, remain to be developed and represent an important challenge. The goal of this article is to review the recent advances in the treatment of tobacco addiction. Although the focus is on the pharmacotherapies, behavioral treatment is also summarized.

Neurobiology of Nicotine Addiction

Nicotine, the main addictive chemical in tobacco smoke, is essential in continued and compulsive tobacco use. Pure nicotine, given intravenously, is self-administered by rodents and primates [4] as well as by smokers [5•]. Nicotine's effects are mediated by the nicotinic-type acetylcholine receptors (nAChRs), which belong to the ligand-gated ion channel family [6]. nAChRs are pentameric combinations of 12 subunits (α2–α10 and β2–β4). The two most commonly expressed nAChRs in the brain are α4β2nAChRand α7nAChR types. Activation of nAChRs facilitates the release of several neurotransmitters in the brain, including dopamine (DA), serotonin, noradrenaline, acetylcholine, γ-aminobutyric acid (GABA), and glutamate [7]. Especially critical to the rewarding effects of nicotine is DA release in the nucleus accumbens, which is mediated by α4β2nAChRs. The nucleus accumbens also contains GABAergic and glutamatergic synapses, which inhibit and stimulate nicotine-induced DA release, respectively. nAChRs desensitize following prolonged exposure to nicotine [8]. The nAChR subtypes controlling GABA release, (mainly non-α7 type) desensitize faster relative to those controlling glutamate release (mainly α7 type) [9]. This unequal desensitization may result in reduced GABA release relative to glutamate following prolonged nicotine exposure, as in cigarette smoking. A relative deficiency of GABA over glutamate may lead to an enhanced DA release in the nucleus accumbens, and this may be a crucial mechanism in the development and maintenance of nicotine dependence [9].

Behavioral Treatments

In clinical settings, health care professionals typically spend limited time on tobacco addiction due to large time demands imposed on the clinician. However, even a 3-minute counseling session by a physician can increase the likelihood of prolonged abstinence (OR, 1.3) compared with no counseling. A recent meta-analysis of 50 randomized behavioral treatments for smoking cessation concluded that telephone counseling, group treatment, and individual treatments all seem to increase the chances of quitting smoking [10]. Longer counseling time (> 10 minutes) doubles the abstinence rates compared with brief (< 3 minutes) counseling (OR, 2.3 vs 1.3). Behavioral therapies for smoking cessation require specially trained counselors and are not commonly implemented in clinical settings.

For all clinicians, including those who practice in mental health settings, a minimum intervention for tobacco addiction should include several steps. First, presence of past or current smoking should be viewed as a "vital sign" assessed each time a patient comes in for a visit. Second, all smokers should be advised to quit smoking in a clear, strong, and personalized manner. Third, smokers who are interested in quitting smoking should be provided assistance, including a quit date, counseling, and/or pharmacotherapy. These recommendations are consistent with the "5 A's" strategy (Ask about tobacco use; Advise to quit smoking; Assess willingness to make a quit attempt; Assist the quit attempt with counseling and pharmacotherapy; and Arrange follow-up).

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Pharmacologic Treatments for Tobacco Addiction

Seven medications are currently US Food and Drug Administration (FDA) approved for smoking cessation: five nicotine replacement therapies (NRTs), bupropion, and varenicline. In addition, clonidine and nortriptyline are effective for smoking cessation but are not FDA approved for this indication.

Nicotine Replacement Therapy

In the US market, five NRT products are currently available: nicotine patch, nicotine chewing gum, nicotine lozenge, nicotine nasal spray, and nicotine vapor inhaler. Nicotine gum, patch, and lozenge are available as over-the-counter (OTC) products, whereas nasal spray and vapor inhaler are available by prescription only. Although initially thought to be a "substitution" treatment, similar to methadone treatment for opioid addiction, the NRTs have limited efficacy in reducing nicotine reinforcement in clinically used doses. The NRTs are effective in relieving tobacco withdrawal and making abstinence easier in smokers trying to quit. NRTs approximately double the success rate of quitting smoking relative to placebo [3••]. NRTs can be classified as short-acting (gum, lozenge, inhaler, and spray) and longer-acting (patch) products. Short-acting NRT products are especially effective in acute management of tobacco withdrawal and craving. An important consideration for NRT treatment is titration of the dose based on the smoker's nicotine intake, determined roughly by the number of cigarettes smoked per day (CPD).

Nicotine Patch

The nicotine patch delivers nicotine transdermally at a relatively steady rate. The steady-state nicotine levels with patch treatment are about half those obtained through smoking [11]. The nicotine patch is currently available in 16- or 24-hour delivery systems. The 24-hour delivery system is available in 7-, 14-, or 21-mg doses. Smokers who use more than 10 CPD begin with a 21-mg/d nicotine patch for the first 6 weeks and switch to 14 mg/d on weeks 7 and 8, and to 7 mg/d on weeks 9 and 10 [12]. Neither longer term (> 14 weeks) nor a higher dose (> 21 mg/d) of nicotine patch improves efficacy over the standard treatment. However, highly dependent smokers may benefit from higher nicotine doses and longer treatment duration. The advantages of the nicotine patch include ease of administration, few side effects (skin irritation, nausea, vomiting, sweating, mood and sleep disturbances), and once-daily dosing, all of which may lead to better compliance. Nicotine patches, however, do not seem to be effective against craving episodes [3••].

Nicotine Gum

Nicotine polacrilex gum is available OTC in 2- or 4-mg doses. With nicotine gum administration, nicotine is absorbed through buccal mucosa, reaching peak plasma nicotine concentrations within 15 to 30 minutes, as compared with 1 to 2 minutes after smoking. Smokers who are heavily dependent (> 25 CPD) are suggested to start with the 4-mg pieces [12]. The initial dose recommended is one piece every 1 to 2 hours in the first 6 weeks, one piece every 2 to 4 hours between weeks 7 and 9, and one piece every 4 to 8 hours between weeks 10 and 12 [12]. The main side effects of gum include nausea, burping, hiccups, and jaw fatigue. Acidic beverages such as coffee and juices should be avoided before and after the use of nicotine gum because they decrease the absorption of nicotine.

Nicotine Lozenge

Similar to nicotine gum, the lozenge is available OTC in 2- or 4-mg doses of nicotine. The 4-mg dose is preferred for highly dependent smokers (ie, smoke their first cigarette < 30 minutes after waking up) [12]. Compared with the same dose of nicotine gum, the lozenge delivers

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about 25% more nicotine, as some nicotine is retained in the gum, and the lozenge is dissolved completely [13]. Nicotine lozenges may be particularly well-suited for smokers who wear dentures, have temporomandibular joint pain, or prefer not to chew gum.

Nicotine Nasal Spray

Nicotine nasal spray delivers nicotine faster than the other NRTs by directly delivering it to the nasal cavity. The nasal spray comes in a multidose container with a pump that delivers 0.5 mg of nicotine per 50-μL squirt [12]. The dose of nasal spray varies depending on the individual level of dependence and severity of symptoms [14]. The usual recommended dose is 1 to 2 doses/h for 8 weeks, with a minimum of 8 doses/d and a maximum of 40 doses/d [12], with tapering occurring between 9 and 14 weeks. Individuals who use nasal spray are more than twice as likely to have long-term abstinence from cigarette smoking as compared with placebo treatment. Nasal spray may cause nasal burning, itching, and irritation, and adherence rates tend to be lower than those for other forms of NRT [15].

Nicotine Inhaler

The nicotine inhaler contains a vaporized cartridge of nicotine placed in a plastic container with the mouthpiece similar to that used in the treatment of asthma. The nicotine aerosol is inhaled and absorbed through the buccal mucosa rather than through the lungs, as in smoking [12]. The nicotine comes in individualized 10-mg cartridges, of which 4 mg are delivered and 2 mg are absorbed [12]. However, puffs are highly variable and dependent on factors such as consistency of delivery between puffs as well as air temperature. The nicotine inhaler can cause local irritation, such as a burning sensation in the throat, coughing, sneezing, dizziness, nausea, and indigestion. These side effects may compromise compliance with heavy use and may reduce the efficacy of an inhaler [16].

Sustained-Release Bupropion

Bupropion, an atypical antidepressant, is approved for treatment of smoking cessation. In preclinical studies, bupropion reduced nicotine's rewarding effects and attenuated nicotine withdrawal symptoms [17]. Its mechanism of action is thought to be mediated by its ability to block the reuptake of norepinephrine and DA in the mesolimbic system and nucleus accumbens, a key area for nicotine reinforcement. Additionally, bupropion antagonizes brain nicotinic receptors and blocks the reinforcing effects of nicotine [17]. Following oral administration, bupropion is metabolized extensively in the liver and excreted through the kidneys with a half-life of about 21 hours [12]. The recommended treatment with bupropion begins about 1 week prior to the quit date to build up a steady-state plasma level at the time of quit attempt. The initial dose is 150 mg for 3 days, and then 150 mg twice daily, with a recommended duration of treatment of 7 to 12 weeks, which may be extended to 12 months to prevent relapse and dependence during the individual's nicotine withdrawal phase [18]. A meta-analysis of 36 trials indicated that bupropion is an effective single pharmacotherapy for smoking cessation (OR, 1.5–1.9) [19]. Common side effects of bupropion are dry mouth, insomnia, tremor, skin rash, headache, and urticaria. Bupropion may also lower seizure threshold and cause seizures, especially in those with increased risks (head trauma, structural brain lesions, use of other drugs or medications reducing seizure threshold, or eating disorders). There is a black box warning for depression, suicidal ideation, suicide attempt, and completed suicide for patients taking bupropion for smoking cessation. Patients taking bupropion should be closely monitored and advised to contact health care providers immediately if they notice emergence of these symptoms.

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Varenicline

Varenicline is a partial agonist for the α4β2 subtype of nAChRs, which are associated with the addictive effects of nicotine [20]. Varenicline is also a full agonist at the α7 nAChR. In smokers, varenicline attenuates the subjective rewarding responses and heart rate increases induced by intravenous nicotine [21•]. Varenicline also improves tobacco withdrawal symptoms, mood, and cognitive performance in abstinent smokers. All these effects may contribute to varenicline's efficacy for smoking cessation. A review of clinical trial results indicates that varenicline increases the chances of a successful quit attempt two- to threefold over placebo [3••]. The initial dose of varenicline is 0.5 mg/d for 3 days, followed by 1-mg/d dose given in two divided daily doses for 4 days. On day 8, the target quit date, the varenicline dose is increased to 1 mg twice per day [3••]. The recommended duration of treatment is a total of 12 weeks. The most common side effects of varenicline are nausea, vomiting, flatulence, and vivid dreams. In a recent study, flexible-dosing strategy for varenicline was investigated in which smokers could choose between 0.5-mg/d to 1-mg twice-daily dose. Varenicline's long elimination half-life, 19 to 24 hours, allows once-daily dosing. In that study, the average dose was 1.3 mg/d, and smokers achieved 40% abstinence rates [22]. Flexible dosing may be an important clinical strategy to minimize the adverse effects while maintaining efficacy.

Postmarketing reporting indicated that varenicline treatment was associated with suicidal thoughts, agitation, depressed mood, aggressive and erratic behavior, and excessive drowsiness. In response to these reports, the FDA issued an updated public health advisory to warn providers to carefully monitor any significant mood and/or behavioral changes in patients and recommended that patients contact their physician should these mood and/or behavioral changes develop. The FDA has also added a black box warning to the varenicline package insert about neuropsychiatric symptoms and exacerbations of preexisting psychiatric illness associated with its use.

Nortriptyline

Nortriptyline, a tricyclic antidepressant, has been found to be effective for smoking cessation. The underlying mechanism of nortriptyline's efficacy for smoking cessation might be through norepinephrine reuptake inhibition in central synapses or through nAChR antagonism. In clinical trials for smoking cessation, the dose of nortriptyline was 75 to 100 mg/d, and the length of treatment was 8 to 12 weeks [23,24]. Compared with placebo, nortriptyline approximately doubles the rates of smoking abstinence. Nortriptyline is not FDA approved for smoking cessation and is recommended only as a second-line treatment. Nortriptyline has multiple adverse effects related to its blockage of muscarinic cholinergic receptors (dry mouth, blurred vision, constipation, and urinary retention), H1 histamine receptors (sedation, drowsiness, weight gain), and α1-adrenergic receptors (orthostatic hypotension).

Clonidine

Clonidine, an antihypertensive agent, reduces central sympathetic activity by stimulating the α2-adrenergic receptors. Clonidine is not FDA approved for smoking cessation and is a second-line option. It effectively suppresses the acute symptoms of nicotine withdrawal, such as tension, irritability, anxiety, cravings, and restlessness [25]. A Cochrane review of six clinical trials found clonidine, oral or transdermal, more effective than placebo, with twofold higher abstinence rates [26]. Interestingly, clonidine seems to be more effective in female smokers, although women generally respond less favorably to smoking cessation treatments [27]. The side effects of clonidine, especially sedation, fatigue, orthostatic hypotension, dizziness, and dry mouth, limit its widespread use.

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Comparative Efficacy of Pharmacotherapies

Among smoking cessation pharmacotherapies, varenicline has shown the greatest efficacy, with an OR of 3.1 (95% CI, 2.5–3.8) at 6 months post-quit [3••]. For other first-line treatments, the OR ranges from 1.5 (95% CI, 1.2–1.7) for nicotine gum to 2.3 (95% CI, 1.7–3.0) for nasal spray [3••]. Only a few studies have focused on head-to-head comparison of the smoking cessation pharmacotherapies. A recent clinical trial of five smoking cessation pharmacotherapies (nicotine lozenge, nicotine patch, sustained-release bupropion, nicotine patch + nicotine lozenge, or bupropion + nicotine lozenge) found that only the combination of nicotine patch plus nicotine lozenge significantly improved smoking cessation at 6 months post-quit [28•]. These findings are consistent with a recent meta-analysis in which two combination treatments were especially effective: 1) nicotine patch (> 14 weeks) and one NRT (gum or spray) when needed had an OR of 3.6 (95% CI, 2.5–5.2) and 2) nicotine patch and bupropion SR (OR, 2.5 [95% CI, 1.9–3.4]) [3••]. Combination therapy, as opposed to some of the other first-line monotherapies, is particularly useful among treatment-resistant patients [29].

Special Populations

Psychiatric Comorbidity

Individuals with psychiatric comorbidity, including those with other addictions, compared with those without comorbidity, consume more cigarettes, are more dependent on tobacco, and are less likely to quit smoking [30••]. High rates of smoking have been observed in individuals with schizophrenia (44%–88%), depression (40%–60%), bipolar disorder (55%–70%), and panic disorder (19%–56%). Similarly, higher rates of smoking have been observed especially in those with cocaine (80%), methamphetamine (> 90%), opioid (> 80%), and alcohol use (70%–80%) disorders. The high rates of heavy smoking likely contribute to reduced life expectancy by 20 to 25 years in those with chronic psychiatric disorders in the United States compared with the general population [31].

Depression—An important clinical question is whether quitting smoking will lead to recurrence of a depressive episode in smokers with a history of major depressive disorder. Within 1 year of a quit attempt, 24% and 14% of smokers with and without a history of major depression, respectively, experienced a depressive episode [32]. Another study found that among smokers who were receiving treatment for current depression, smoking cessation was not associated with worsening of depressive symptoms [33]. In smokers with a past history of recurrent depression, antidepressant medications—sustained-release bupropion or nortriptyline—combined with cognitive-behavioral therapy improved the long-term success rate of smoking cessation [33]. These medications are equally effective in smokers without a history of depression.

Schizophrenia—Schizophrenic smokers present unique challenges. In addition to their high rates of smoking, schizophrenia patients are more dependent on tobacco, extract more nicotine from each cigarette, and have about 50% lower smoking cessation rates than regular smokers. Two recent small clinical trials suggest that a combination of sustained-release bupropion and NRT may be beneficial in achieving smoking abstinence in schizophrenic smokers [34,35]. However, very high rates of relapse during taper and after treatment discontinuation suggest that schizophrenic smokers may benefit from combination behavioral and pharmacotherapies longer than the usual 12-week treatments [34].

Addictive disorders—Smokers who receive treatments for other addictions represent a unique opportunity to target both tobacco and other addictions. Unfortunately, there are several barriers to integrating a smoking cessation component into an addiction program, including

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provider education and awareness and the concern that smoking abstinence will interfere with abstinence from other drugs [30••]. In fact, a meta-analysis of 19 studies that provided smoking cessation treatments during addictions treatment or following at least 1 year of clean time showed that smoking cessation treatment did not interfere with nontobacco addiction outcomes but rather improved smoking cessation rates [36]. The timing of smoking cessation treatment in relation to addiction treatment may be important. One study reported that concurrent alcohol and tobacco addiction treatment was associated with worse outcomes for alcohol dependence than the delayed tobacco addiction treatment group [37].

Among substance users, methadone-maintained opioid users are highly resistant to smoking cessation treatments, including NRT or bupropion [38]. In a recent study, varenicline had reduced rates of smoking in opioid-addicted smokers maintained on methadone [39]. These initial promising findings need to be confirmed in larger clinical trials.

Pregnancy

In the United States, 13.1% of women smoke during pregnancy [40], reflecting the fact that about 45% of women are able to quit during pregnancy. However, among women who quit smoking during pregnancy, 40% to 52% relapse within 2 weeks and 70% to 80% resume smoking within 1 year of childbirth [41]. In addition to the health risk associated with smoking in postpartum women, second-hand exposure is also a significant health risk for newborns, including increased risk for respiratory and ear infections, sudden infant death syndrome, behavioral dysfunction, and cognitive impairment [42].

For pregnant smokers, both pharmacologic and behavioral treatments have been under investigation. Among pharmacotherapies, NRTs seem to be safe and increase birth weight [43•]. However, the efficacy of NRTs or other first-line medications remains to be determined in pregnant and postpartum smokers [43•]. For behavioral treatments, the challenge is to address commonly observed depression and stress that may impede smoking cessation effects of pregnancy or the postpartum period [44]. Although there are some promising findings with intense behavioral treatments for pregnant smokers, their implementation to clinical practice may need further work.

Adolescents

Every day, about 4000 individuals younger than 18 years of age smoke their first cigarette, with one third becoming daily smokers. Given that more than 80% of dependent smokers start smoking before the age of 18, tobacco addiction can be regarded as a childhood disorder extending into adulthood [45]. Accumulating evidence suggests that adolescence may be a period of greater vulnerability to nicotine addiction. Smokers who initiate smoking during adolescence, compared with those who initiate smoking later, smoke more cigarettes per day, are less likely to quit, and have an increased risk of relapse [46]. Unfortunately, only 4% of 12- to 19-year-old smokers successfully quit smoking each year [3••]. The efficacy of NRT or sustained-release bupropion has not been demonstrated in adolescent smokers [3••]. Behavioral treatments, including cognitive-behavioral therapy, motivation enhancement, social influence, as well as school and classroom modalities, have shown promise [47].

Conclusions

The past two decades have seen important advances in the development of effective behavioral and pharmacologic treatments for smoking cessation treatment. Initial results show that varenicline as well as combination treatments with the nicotine patch or sustained-release bupropion in combination with short-acting NRTs seem to be more effective than other pharmacotherapies [3••]. The clinician should also consider the side effect profiles of these

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medications, especially varenicline or bupropion, before making treatment decisions. However, many smokers are not helped by these treatments. These treatment-resistant subpopulations include, but are not limited to, adolescent smokers; pregnant and postpartum smokers; smokers with psychiatric comorbidities (including those with schizophrenia, major depression, and bipolar disorder); as well as those with cocaine, opioid, and alcohol addictions. These subpopulations represent a significant percentage of smokers. For example, smokers with psychiatric comorbidity within the past 12 months represent about 32% of all smokers in the United States [48]. Although clinicians' hesitation to address smoking or offer treatments, especially in special subpopulations, has been cited as a roadblock for effective treatment of tobacco addiction [30••], a great need also exists for more effective treatments of tobacco addiction. Most smoking cessation trials exclude smokers with a psychiatric or medical comorbidity or pregnant or teenage smokers. Unfortunately, the results from these clinical trials are used to determine the safety and efficacy of individual treatments that may not match their real life efficacy in clinical settings. For a more effective tobacco addiction treatment, we need to develop safe and effective medications for special populations as well. Similarly, development of behavioral treatments that can address the needs of special populations as well as the individual smoker are desperately needed. Not having effective pharmacologic or behavioral treatments available for the needs of individual smokers should not deter clinicians from addressing tobacco addiction of their patients. Clinicians should at least provide the minimum intervention summarized by the "5 A's" strategy. As commented by Hughes [49], helping patients to quit smoking is the "single most important thing one can do to improve their health."

Acknowledgments

This research was supported by the Veterans Administration Mental Illness Research, Education, and Clinical Center and National Institute on Drug Abuse grants K02 DA021304 (to Dr. Sofuoglu) and K12 DA00167 (to Dr. Herman)

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