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Tobacco use treatment in primary care patients with psychiatric illness

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Abstract

The prevalence of smoking is higher in patients with psychiatric illness compared to the general population. Smoking causes chronic illnesses which lead to premature mortality in those with psychiatric illness, is associated with greater burden of psychiatric symptoms, and contributes to the social isolation experienced by individuals with psychiatric disorders. Most patients with psychiatric illness present initially to primary care rather than specialty care settings, and some patients receive care exclusively in the primary care setting. Therefore, family physicians and other primary care clinicians have an important role in the recognition and treatment of tobacco use disorders in patients with psychiatric illnesses. In this article we review common myths associated with smoking and psychiatric illness, techniques in implementing evidence-based tobacco use treatments, the evidence base for tobacco use treatment for patients with specific psychiatric diagnoses, and factors to consider in treating tobacco use disorders in patients with psychiatric illness.

Background

Tobacco use is common among patients with psychiatric disorders (1). While smoking prevalence in the general adult population is 20%, almost one-half of patients with bipolar disorder and two-thirds of patients with schizophrenia seen in clinical settings smoke (2), and the decline in smoking prevalence in the United States that has occurred in the general population has not occurred in the population with psychiatric illness (3) Furthermore, tobacco use disorders occur in one-third to one-half of patients with common psychiatric illnesses such as major depressive disorder, post-traumatic stress disorder, or one of three anxiety disorders (generalized anxiety disorder, social anxiety disorder and panic disorder) (4). Smokers with psychiatric illness also consume more cigarettes per day compared to smokers without psychiatric illness (5). Consequently, between 31–44% of all cigarettes in

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the United States are smoked by individuals with psychiatric illnesses which occur in about 20% of the population annually (4, 6).

Chronic diseases caused by smoking such as hypertension and chronic obstructive pulmonary disease are more common among patients with psychiatric illness compared to those without psychiatric disorders (7, 8). Additionally, such chronic illnesses generally occur earlier in life in these patients, leading to a greater degree of illness -related disability and impairment (9). Unfortunately, the life expectancy of people with psychiatric illnesses such as schizophrenia and bipolar disorder is approximately 10–20 years lower than the general population, largely due to premature deaths from smoking-related illnesses (10–12).

The disparity in tobacco use between individuals with and without psychiatric illness is present in primary care settings as well. In one study, primary care patients with psychiatric disorders were twice as likely to be current smokers(41.1% v s. 19.5%, p=0.002) compared to those without psychiatric illness (13). Family physicians are well-positioned to initiate tobacco use treatment for patients with psychiatric illness since most of these patients initially present in primary care settings (14). Furthermore, national efforts by the Centers for Disease Control and Prevention encouraging smokers to ask their doctors about smoking will likely lead to more patients initiating discussions with primary care doctors about their cigarette use (15). Many patients with common psychiatric conditions such as depression are treated by primary care physicians without referral to specialty mental health care providers, and patients who smoke generally prefer receiving tobacco use treatment in their primary care clinic (16). Based on patients' service utilization and preferences, the primary care setting may be the only opportunity many patients with psychiatric illness have to receive tobacco use treatment.

Despite the known negative consequences of smoking, clinicians often feel uncomfortable addressing tobacco use in patients generally, and this is particularly true when patients have psychiatric diagnoses (12). Primary care physicians' efforts to treat tobacco use in patients with psychiatric illness can be enhanced by dispelling common myths and misperceptions about why patients with psychiatric disorders smoke, and by improving knowledge of evidence based treatment options.

This article is a narrative review of the treatment of tobacco use disorders in primary care patients with psychiatric illnesses. We identified relevant articles for this paper by searching PubMed, the Cochrane database and GoogleScholar. We also searched the reference list of key articles for additional, relevant reports. We will not cover the research examining tobacco use treatment in patients with substance use disorders due to our intent to focus on other psychiatric illnesses such as depression and bipolar disorder.

Myths about Psychiatric Illness and Smoking

Prochaska described five myths associated with clinicians' reluctance to provide tobacco use treatment to patients with psychiatric illness (17). First is that patients with psychiatric illness smoke for "necessary self-medication" (17). Six studies prospectively measured associations between smoking and psychiatric symptom severity over at least 6 months in patients with bipolar disorder or schizophrenia who smoked compared to patients who did

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not smoke(18). Five studies showed that those who smoked cigarettes experienced higher symptom burden, as evidenced by more frequent suicidal thoughts (19), higher severity of negative symptoms of schizophrenia (20) and bipolar disorder symptoms (21), higher rates of alcohol and cannabis use (21, 22), and spending a greater number of days in a psychiatric hospital (21). These findings are consistent with evidence showing that use of other addictive substances, such as alcohol, is associated with higher psychiatric symptom burden, greater treatment resistance and greater risk of relapse in patients with co-occurring psychiatric illness substance use (23).

The second myth is that “people with mental illness are not interested in quitting smoking.” Smokers with psychiatric illness are just as likely as smokers without psychiatric illness to express interest in quitting smoking (17). For example, among over 500 current smokers with bipolar disorder, approximately three-quarters reported wanting to quit smoking, consistent with the general population rate (24). Additionally, patients with bipolar disorder had a median number of prior quit attempts of four, suggesting that individuals remained interested in quitting despite prior unsuccessful attempts.

Prochaska’s third listed myth is that “mentally ill people cannot quit smoking” (17). Several systematic reviews and meta-analyses (1, 25–29)have shown that patients with psychiatric illness when treated with appropriate tobacco use treatments can achieve abstinence from cigarettes at a rate only slightly lower than patients without psychiatric illness (5).

The fourth myth describes the belief that “quitting smoking interferes with recovery from mental illness” (17). Research suggests that smoking cessation does not interfere with psychiatric illness treatment, and may actually improve treatment outcomes (17,28). For example, McFall, et al. (30)showed that initiating tobacco use treatment concurrently with posttraumatic stress disorder(PTSD) treatments was associated with greater prolonged abstinence and no worsening in symptoms of PTSD. Additionally, smokers with baseline anxiety or depressive disorder who continued smoking were more likely to have major depression (OR 1.97, 95% CI: 1.003–3.85) or a substance use disorder (OR 2.51, 95% CI: 1.13–5.56) at 3 year follow-up compared to individuals who quit smoking (31).

The final myth is that smoking cessation is a low priority for patients with psychiatric symptoms. Clinicians treating patients with psychiatric illness often encounter competing demands such as co-occurring general medical, substance use, and psychosocial problems. However, for patients with psychiatric illness, smoking causes chronic illnesses and premature mortality(32), contributes to social isolation and financial stress (5), is associated with poor nutrition (33), and is associated with higher psychiatric symptom burden (18). As such, clinicians should consider smoking and its consequences as high priority clinical problems

General treatment principles

The U.S. Public Health Service (USPHS)clinical practice guideline by Fiore, et al. (34) comprehensively describes the evidence and proven techniques for clinical management of tobacco use disorders. Two subsequent review articles describe updates in evidence-based clinical practice (35,36). Much of the discussion below draws from these key resources. The

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principles of smoking cessation apply equally to the treatment of smokers with and without psychiatric illness. We will briefly review 5 categories of tobacco use treatment principles and practice: addressing nicotine withdrawal, case identification and counseling, enhancing motivation to quit, medications for smoking cessation, and telephone quit lines.

Nicotine withdrawal

Abrupt cessation or reduction in nicotine consumption results in a withdrawal syndrome characterized by irritability, sleep problems, dysphoria, lowered frustration tolerance, impaired concentration, restlessness, increased appetite, lowered heart rate and cigarette craving(37). These symptoms may last up to 4 weeks, with most patients experiencing a higher intensity of symptoms during the first week of abstinence (38). Primary care physicians can help patients understand the nicotine withdrawal syndrome, and offer treatment with nicotine replacement therapy, other approved cessation medications, and/or behavioral coping strategies to alleviate the discomfort caused by nicotine withdrawal (38).

Nicotine withdrawal symptoms can mimic symptoms of patients' primary psychiatric illnesses such as major depression and generalized anxiety disorder (36). Because nicotine withdrawal symptoms are lessened with exposure to nicotine (i.e. when smoking a cigarette), many patients and clinicians believe that cigarettes treat psychiatric symptoms when in fact resuming smoking is only lessening the symptoms of nicotine withdrawal (12, 37). Additionally, patients with psychiatric illnesses may experience more severe nicotine withdrawal symptoms. Since greater severity of nicotine withdrawal symptoms is associated with smoking relapse, it is important to help patients accurately recognize nicotine withdrawal symptoms, and to offer treatments for nicotine withdrawal (34, 36, 39, 40).

Case identification and Counseling

Almost three-quarters of smokers attend at least one primary care appointment per year (35). Enhancing recognition of smokers in primary care is important so that effective treatments can be initiated for patients who are motivated to quit smoking, and strategies to increase motivation can be employed for patients who are not ready to quit (35). The 2008 USPHS clinical practice guideline (34) recommends using the 5 A's technique for case identification and treatment (**A**sk about tobacco use; **A**dvise to quit; **A**ssess willingness to make a quit attempt; **A**ssist in a quit attempt; **A**rrange follow-up). One way to incorporate the 5 A's into clinical practice is to ask each patient about smoking during vital sign measurement and record smoking status as a vital sign (41). The primary care clinician will then be able to implement the remaining 4 A's for those patients answering "yes" to the question about current tobacco use.

A large effectiveness trial involving 2,325 patients in nine primary care clinics showed that clinicians in routine practice tended to use only the first two A's (Ask and Advise) more often than all 5 A's(42). However, patients receiving treatment using the 5 A's were more likely to quit smoking (OR = 1.82, 95% CI: 1.16–2.86 for counseling; OR=2.23, 95% CI: 1.56–3.2 for pharmacotherapy), arguing for the importance of utilizing all 5 components.

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Enhancing motivation to quit

Approximately 30% of smokers report not being interested in quitting smoking (43), and patients who say they want to stop smoking often have mixed feelings about making a quit attempt (35). Thus, enhancing motivation to quit is a critical part of tobacco use treatment and can be done using motivational interviewing. Motivational interviewing (MI) is an evidence-based approach used to address patients' ambivalence about behavior change. Expressing empathy, developing discrepancy, rolling with resistance and supporting self-efficacy are key strategies in motivational interviewing (34). MI has been shown to be effective in treating tobacco dependence both alone and in combination with medication. A Cochrane Review (44) showed that MI significantly increased 6 month abstinence from smoking compared to usual care or brief advice (RR 1.27, 95% CI: 1.14, 1.42).

In addition to MI, the 2008 USPHS clinical practice guideline (34) recommends using the 5 R's technique to enhance motivation, whereby patients are asked to identify the personal **R**elevance of quitting smoking, the short and long-term **R**isks of continued smoking, the **R**ewards of quitting smoking, and the anticipated **R**oadblocks to quitting. The clinician should **R**epeat these techniques each time the smoker is seen in the clinic, until he or she has successfully quit(34).

Smoking cessation medications

All patients should be encouraged to use counseling and pharmacotherapy since the combination is more effective than either intervention alone(34). Seven first-line pharmacological agents have been approved by the FDA for tobacco use treatment, including two non-nicotine medications (bupropion and varenicline)and five forms of nicotine replacement (patch, gum, lozenge, nasal spray, and inhaler) (34–36). Two second - line agents (clonidine and nortriptyline) have evidence supporting their effectiveness in tobacco use treatment, but do not have FDA indications(34). Patients' odds of achieving abstinence are approximately doubled when using any of these seven medications during a quit attempt (34–36). Adding counseling to medication treatment increases abstinence rates by approximately 50% over medication treatment alone (34).

Three preparations of nicotine replacement (patch, gum, lozenge) are sold over the counter, and two preparations are prescription-only (inhaler and nasal spray) (36). Patients using any of the nicotine replacement products, including over-the-counter products, should be counseled on appropriate use since many misperceptions about nicotine replacement exist. The transdermal patch delivers nicotine slowly over 24 hours and must be replaced daily. Heavy smokers may require more than one patch to achieve relief from nicotine withdrawal and often benefit from combining the patch with a faster-onset and shorter-duration form of nicotine replacement (the nicotine gum, lozenge, inhaler or nasal spray) which are generally dosed several times daily. Combination treatment with the nicotine patch plus nicotine lozenge, where the patch is applied daily and the lozenge is used as-needed, resulted in the highest abstinence rates compared to four other treatment options in two trials (45, 46).

In a randomized controlled trial that largely excluded individuals with psychiatric illness, the combination of varenicline and bupropion was superior to varenicline alone in producing

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prolonged abstinence rates at 12 and 26 weeks but not at 52 weeks (47). A recent analysis of 17 clinical trials involving over 8000 patients showed that use of varencline was not associated with adverse neuropsychiatric events (48), though a black box warning from 2009 advises clinicians to assess patients for adverse neuropsychiatric events in patients receiving varenicline. Additional information on each of the seven FDA-approved medications is shown in Table 1.

Tobacco Quitlines

Telephone quitlines provide effective treatment for tobacco dependence. Current state quitlines (1-800-QUIT-NOW) connect individuals with counselors who deliver phone-based interventions and assist callers with finding local clinicians who can provide tobacco use treatment (49). Additionally, many states offer fax referral systems for clinicians to refer patients directly to a quitline, and some states also offer nicotine replacement therapy. A large trial of 3282 smokers showed that quitlines delivering a protocol-based smoking cessation intervention of up to seven phone sessions approximately doubled quitrates (6 month abstinence 11.7% vs. 5.2%)compared to quit lines delivering self-help materials and information about smoking (50). One study showed that quitline callers with major depression could achieve abstinence at two months, though a lower percentage of callers with depression achieved two month abstinence compared to callers without depression (18.5% vs. 28.4%) (51).

Tobacco use treatment inpatients with psychiatric illness

Major depression

Early studies showed that while patients with depression receiving treatment for tobacco dependence could successfully quit smoking, the incidence of depressive symptoms or a depressive episode was increased in patients who achieved cessation (52–55). Until recently, many clinicians hesitated to offer tobacco use treatment to patients with major depression due to concerns that cessation would cause a depressive episode.

Current evidence shows that patients with depression should be offered tobacco use treatment since smoking may actually worsen depressive symptoms. Longitudinal studies have shown that smoking increases the risk of depressive symptoms (56) and the incidence of mood and anxiety disorders (57), that current heavy smoking is strongly associated with current depression (58), and that current smoking strongly predicts depression recurrence (59). Additionally, a trial of tobacco use treatment in patients with current depression showed that depressive symptoms were not worse in patients who successfully quit smoking compared to those who continued to smoke (60, 61). Another study showed that smokers who did not successfully quit smoking experienced higher severity of depression symptoms compared to those who successfully quit (62). A recent randomized, clinical trial (n=525) showed that 12 weeks of treatment with varenicline in adults with past or current treated major depression doubled the odds of quitting during 52 weeks of follow-up, and that no worsening of depression, anxiety, suicidal ideation or other neuropsychiatric occurred in the varenicline or placebo groups (63).

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A Cochrane Review (64) showed that use of bupropion increase d long-term cessation in smokers with past depression, and that adding a mood-management intervention to standard tobacco use treatment further increased abstinence rates in patients with current depression.

Anxiety disorders and PTSD

Smoking during adolescence was associated with the onset of adulthood anxiety disorders in a large epidemiologic study (65). Consistent with this finding, the prevalence of current smoking among adults with anxiety disorders is approximately 35–45%, nearly double that of the general population (4). Despite the bidirectional association between anxiety disorders and smoking, few clinical trials have tested tobacco use treatment in patients with anxiety disorders (28).

As noted earlier, the intervention tested by McFall, et al. (30) doubled the rate of 12-month prolonged abstinence (OR 2.26, 95% CI: 1.3–3.91) in veteran smokers with PTSD. This was achieved using a well-tolerated combination of educational and behavioral skills sessions and medications, including varenicline, bupropion, and nicotine replacement therapy.

Bipolar disorder and Schizophrenia

Although approximately half of patients with bipolar disorder smoke, few trials have assessed tobacco use treatment in this population (2, 66). Two small (n=5 for both studies), randomized controlled trials of tobacco use treatment in patients with bipolar disorder showed that bupropion (67) and varenicline (68) did not worsen psychiatric symptoms. Additionally, the total number of cigarettes smoked per day was reduced in the varenicline group compared to placebo (68), and both patients randomized to bupropion stopped smoking (67). A subsequent proof-of-concept study by Heffner, et al. (69) showed that a mood management intervention plus nicotine patch resulted in 2 of 9 patients achieving tobacco abstinence, and 7 of 9 patients achieving at least 50% reduction in daily cigarette consumption over 8 weeks. A recent, large clinical trial of 203 patients with either bipolar disorder or schizophrenia showed that varenicline is efficacious for tobacco use treatment and presents no safety risks in this population (70).

A Cochrane Review (71) showed that in seven trials, bupropion, compared to placebo, was associated with a 3-fold higher cessation rate at the end of the trials (RR 3.03, 95% CI: 1.69, 5.42), a result that endured for 6 months in 5 of the trials (RR 2.78, 95% CI: 1.02–7.58) (71). Varenicline use was also associated with significantly higher cessation rates compared to placebo in 2 trials with 137 patients (RR 4.74, 95% CI: 1.34, 16.71) (71). Psychiatric symptoms were not worsened in patients receiving bupropion or varenicline (26, 71). Although individual trials have shown increased cessation rates for patients with schizophrenia who used nicotine replacement, the Cochrane Review analysis did not find evidence of a significant benefit (71).

Other Considerations

Electronic cigarettes have received much attention recently, and one randomized trial suggests that use of electronic cigarettes may lead to abstinence rates similar to that seen with transdermal nicotine replacement (72). However, concerns exist about the safety,

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regulation, content, and marketing of electronic cigarettes, mixed evidence regarding use of e-cigarettes as a cessation aid, high levels of dual use with tobacco cigarettes, and the potential “renormalization” of smoking through advertising and public use of electronic cigarettes (73).

There are several special considerations in the treatment of tobacco use in patients with psychiatric illness (Table 2). The aromatic hydrocarbons in tobacco smoke induce the CYP P450 enzymes that metabolize several psychotropic medications such as clozapine, olanzapine and haloperidol (74). Thus current smokers typically need higher doses of some psychotropic medications to attain therapeutic levels, and dosages should be reduced after smoking cessation to avoid potential adverse medication side effects. Additionally, treating tobacco use requires persistent efforts by clinicians since most patients require more than one quit attempt to achieve abstinence, whether they have psychiatric disorders or not(1). However, every quit attempt provides opportunities for learning how to quit, and subsequent tries are more likely to succeed.

Case Example

A 30 y/o woman with depression and asthma presents to a primary care clinic for an annual exam. On vital sign measurement, the medical assistant asks the patient if she smokes cigarettes, and the patient answers “yes, a pack a day” and that she is “on the fence about quitting.” The primary care physician determines that the patient is currently experiencing mild depressive symptoms evidenced by a Patient Health Questionnaire-9 score of 8, and moderate asthma symptoms evidenced by exercise intolerance and daily cough. In addition to continuing treatment for asthma and depression, the primary care physician advises the patient to quit smoking, explaining that smoking may be associated with her chronic depressive and asthma symptoms. The physician then assesses the patient’s willingness to make a quit attempt. Despite mixed feelings about quitting, the patient states that she does want to make a quit attempt, and says that her main reason for coming to the clinic was “to get help quitting”. The physician counsel the patient briefly, encouraging her and reinforcing the message that quitting smoking is the best thing she can do for her health, prescribes varenicline with instructions and precautions, and helps her set a quit date for one week later. The physician then refers the patient to the state quitline for telephone support, and arranges for the patient to return to the clinic in 10 days for follow-up.

Conclusion

Tobacco dependence occurs frequently in patients with psychiatric illness causing chronic illnesses resulting in reduced life expectancy. Smoking is also associated with psychiatric symptoms in a substantial portion of patients with psychiatric illness, and although the nicotine withdrawal syndrome may mimic psychiatric symptoms, withdrawal can be alleviated by behavioral and pharmacological modalities. Effective tobacco dependence treatments are available for patients with psychiatric illness. Reframing tobacco use treatment as a way to reduce overall psychiatric symptom burden and improve the general health of patients with psychiatric illness may help clinicians make tobacco use treatment a higher priority in the care of patients with psychiatric illness.

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Table 1

FDA-Approved Medications for Smoking Cessation

	Nicotine Replacement Therapy (NRT) Formulations					Bupropion SR	Varenicline
	Gum	**Lozenge**	**Transdermal Patch**	**Nasal Spray**	**Oral Inhaler**		
Product	**Nicorette**[*], **Generic** OTC 2 mg, 4 mg	**Nicorette Lozenge,**[*] **Nicorette Mini Lozenge,**[*] **Generic** OTC 2 mg, 4 mg	**NicoDerm CQ**[*], **Generic** OTC (NicoDerm CQ, generic) Rx (generic) 7 mg, 14 mg, 21 mg (24-hour release)	**Nicotrol NS**[†] Rx Metered spray 0.5 mg nicotine in 50 mcL aqueous nicotine solution	**Nicotrol Inhaler**[†] Rx 10 mg cartridge delivers 4 mg inhaled nicotine vapor	**Zyban**[*], **Generic** Rx 150 mg sustained-release tablet	**Chantix**[†] Rx 0.5 mg, 1 mg tablet
Precautions	• Precautions for all NRT formulations • Recent (≤ 2 weeks) myocardial infarction • Serious underlying arrhythmias • Serious or worsening angina pectoris • Pregnancy[‡] (category D) and breastfeeding • Adolescents (<18 years) • Precautions specific to certain NRT formulations • *Gum*: Temporomandibular joint disease • *Nasal spray*: Underlying chronic nasal disorders (rhinitis, nasal polyps, sinusitis); Severe reactive airway disease • *Oral inhaler*: Bronchospastic disease					• Medications or medical conditions known to lower the seizure threshold • Severe hepatic cirrhosis • Pregnancy[‡] (category C) and breastfeeding • Adolescents (<18 years) **Warning:** • Black-boxed warning for neuropsychiatric symptoms[§] **Contraindications:** • Seizure disorder • Diagnosis of bulimia or anorexia nervosa • MAO inhibitor therapy in previous 14 days	• Severe renal impairment (dosage adjustment is necessary) • Pregnancy[‡] (category C) and breastfeeding • Adolescents (<18 years) **Warning:** • Black-boxed warning for neuropsychiatric symptoms[4]
Dosing	*1st cigarette ≤30 minutes after waking:* 4 mg *1st cigarette >30 minutes after waking:* 2 mg Weeks 1–6: 1 piece q 1–2 hours Weeks 7–9: 1 piece q 2–4 hours	*1st cigarette ≤30 minutes after waking:* 4 mg *1st cigarette >30 minutes after waking:* 2 mg Weeks 1–6: 1 lozenge q 1–2 hours Weeks 7–9: 1 lozenge q 2–4 hours	*>10 cigarettes/day:* 21 mg/day × 4 weeks (generic) 6 weeks (NicoDerm CQ) 14 mg/day × 2 weeks 7 mg/day × 2 weeks *≤ 10 cigarettes/day:* 14 mg/day × 6 weeks 7 mg/day × 2 weeks	1–2 doses/hour (8–40 doses/day) One dose = 2 sprays (one in **each** nostril); each spray delivers 0.5 mg of nicotine to the nasal mucosa • Maximum	6–16 cartridges/day Individualize dosing; initially use 1 cartridge q 1–2 hours • Best effects with continuous puffing for 20 minutes	150 mg po q AM × 3 days, then 150 mg po bid • Do not exceed 300 mg/day • Begin therapy 1–2 weeks **prior** to quit date	Days 1–3: 0.5 mg po q AM Days 4–7: 0.5 mg po bid Weeks 2–12: 1 mg po bid • Begin therapy 1 week **prior** to quit

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	Nicotine Replacement Therapy (NRT) Formulations					Bupropion SR	Varenicline
	Gum	**Lozenge**	**Transdermal Patch**	**Nasal Spray**	**Oral Inhaler**		
	Weeks 10–12: 1 piece q 4–8 hours • Maximum, 24 pieces/day • Chew each piece slowly • Park between cheek and gum when peppery or tingling sensation appears (~15–30 chews) • Resume chewing when tingle fades • Repeat chew/park steps until most of the nicotine is gone (generally 30 min) • Park in different areas of mouth • No food or beverages 15 minutes before or during use • Duration: up to 12 weeks	Weeks 10–12: 1 lozenge q 4–8 hours • Maximum, 20 lozenges/day • Allow to dissolve slowly (20–30 minutes for standard; 10 minutes for mini) • Nicotine release may cause a warm, tingling sensation • Do not chew or swallow • Occasionally rotate to different areas of the mouth • No food or beverages 15 minutes before or during use • Duration: up to 12 weeks	• May wear patch for 16 hours if patient experiences sleep disturbances (remove at bedtime) • Duration: 8–10 weeks	– 5 doses/ hour or – 40 doses/day • For best results, initially use at least 8 doses/day • Do not sniff, swallow, or inhale through the nose as the spray is being administered • Duration: 3–6 months	• Initially use at least 6 cartridges/day • Nicotine in cartridge is depleted after 20 minutes of active puffing • Inhale into back of throat or puff in short breaths • Do NOT inhale into the lungs (like a cigarette) but “puff” as if lighting a pipe • Open cartridge retains potency for 24 hours • No food or beverages 15 minutes before or during use • Duration: 3–6 months	• Allow at least 8 hours between doses • Avoid bedtime dosing to minimize insomnia • Dose tapering is not necessary • Duration: 7–12 weeks, with maintenance up to 6 months in selected patients	date; alternatively, the patient can begin therapy and then quit smoking between days 8–35 of treatment • Take dose after eating and with a full glass of water • Dose tapering is not necessary • Dosing adjustment is necessary for patients with severe renal impairment • Duration: 12 weeks; an additional 12-week course may be used in selected patients
Adverse Effects	• Mouth/jaw soreness • Hiccups • Dyspepsia • Hypersalivation • Effects associated with incorrect chewing technique: – Lightheadedness – Nausea/vomiting – Throat and mouth irritation	• Nausea • Hiccups • Cough • Heartburn • Headache • Flatulence • Insomnia	• Local skin reactions (erythema, pruritus, burning) • Headache • Sleep disturbances (insomnia, abnormal/vivid dreams); associated with nocturnal nicotine absorption	• Nasal and/or throat irritation (hot, peppery, or burning sensation) • Rhinitis • Tearing • Sneezing • Cough • Headache	• Mouth and/or throat irritation • Cough • Headache • Rhinitis • Dyspepsia • Hiccups	• Insomnia • Dry mouth • Nervousness/ difficulty concentrating • Rash • Constipation • Seizures (risk is 0.1%) • Neuropsychiatric symptoms (rare; see Precautions)	• Nausea • Sleep disturbances (insomnia, abnormal/vivid dreams) • Constipation • Flatulence • Vomiting • Neuropsychiatric symptoms (rare; see Precautions)
Advantages	• Might satisfy oral cravings • Might delay weight gain	• Might satisfy oral cravings	• Provides consistent nicotine levels over 24 hours	• Patients can titrate therapy to rapidly manage	• Patients can titrate therapy to manage withdrawal symptoms	• Easy to use; oral formulation might be associated with	• Easy to use; oral formulation might be associated with

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	Nicotine Replacement Therapy (NRT) Formulations					Bupropion SR	Varenicline
	Gum	**Lozenge**	**Transdermal Patch**	**Nasal Spray**	**Oral Inhaler**		
	• Patients can titrate therapy to manage withdrawal symptoms • Variety of flavors are available	• Might delay weight gain • Easy to use and conceal • Patients can titrate therapy to manage withdrawal symptoms • Variety of flavors are available	• Easy to use and conceal • Once daily dosing associated with fewer compliance problems • FDA-approved for use in combination with bupropion SR	withdrawal symptoms	• Mimics hand-to-mouth ritual of smoking (could also be perceived as a disadvantage)	fewer compliance problems • Might delay weight gain • Can be used safely with NRT; FDA-approved for use in combination with nicotine transdermal patch • Might be beneficial in patients with depression	fewer compliance problems • Offers a new mechanism of action for patients who have failed other agents
Disadvantages	• Need for frequent dosing can compromise compliance • Might be problematic for patients with significant dental work • Patients must use proper chewing technique to minimize adverse effects • Gum chewing may not be socially acceptable	• Need for frequent dosing can compromise compliance • Gastrointestinal side effects (nausea, hiccups, heartburn) might be bothersome	• Patients cannot titrate the dose to acutely manage withdrawal symptoms • Allergic reactions to adhesive might occur • Patients with dermatologic conditions should not use the patch	• Need for frequent dosing can compromise compliance • Nasal/throat irritation may be bothersome • Patients must wait 5 minutes before driving or operating heavy machinery • Patients with chronic nasal disorders or severe reactive airway disease should not use the spray	• Need for frequent dosing can compromise compliance • Initial throat or mouth irritation can be bothersome • Cartridges should not be stored in very warm conditions or used in very cold conditions • Patients with underlying bronchospastic disease must use with caution	• Seizure risk is increased • Several contraindications and precautions preclude use in some patients (see Precautions) • Patients should be monitored for potential neuropsychiatric symptoms[§] (see Precautions)	• May induce nausea in up to one third of patients • Patients should be monitored for potential neuropsychiatric symptoms[4] (see Precautions)
Cost/day[‖]	2 mg or 4 mg: $1.90–$5.48 (9 pieces)	2 mg or 4 mg: $3.05–$4.10 (9 pieces)	$1.52–$3.40 (1 patch)	$4.32 (8 doses)	$7.74 (6 cartridges)	$2.54–$6.22 (2 tablets)	$6.54 (2 tablets)

Abbreviations: MAO, monoamine oxidase; NRT, nicotine replacement therapy; OTC, over-the-counter (non-prescription product); Rx, prescription product.

[*] Marketed by GlaxoSmithKline.

[†] Marketed by Pfizer.

[‡] The USPHS Clinical Practice Guideline (37) states that pregnant smokers should be encouraged to quit without medication based on insufficient evidence of effectiveness and theoretical concerns with safety. Pregnant smokers should be offered behavioral counseling interventions that exceed minimal advice to quit.

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[§] In July 2009, the FDA mandated that the prescribing information for all bupropion- and varenicline-containing products include a black-boxed warning highlighting the risk of serious neuropsychiatric symptoms, including changes in behavior, hostility, agitation, depressed mood, suicidal thoughts and behavior, and attempted suicide. Clinicians should advise patients to stop taking varenicline or bupropion SR and contact a healthcare provider immediately if they experience agitation, depressed mood, and any changes in behavior that are not typical of nicotine withdrawal, or if they experience suicidal thoughts or behavior. If treatment is stopped due to neuropsychiatric symptoms, patients should be monitored until the symptoms resolve.

[||] Wholesale acquisition cost from Red Book Online. Thomson Reuters, July 2013. **This Table was adapted with permission from The Regents of the University of California, RxforChange (**http://rxforchange.ucsf.edu/**)**

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Table 2

Special considerations when treating smoking in patients with psychiatric illness

Consideration	Comment
Tobacco smoke – medication interactions	Tobacco smoke, but not nicotine, induces the metabolism of several psychotropic medications through the CYP1A2 enzyme. Medication doses for some psychotropic medications will need to be reduced if the patient achieves abstinence from smoking
Nicotine withdrawal	Symptoms of nicotine withdrawal such as irritability, sleep problems, fatigue, impaired concentration, and appetite changes may mimic symptoms of psychiatric illness. Nicotine withdrawal can be alleviated with nicotine replacement therapy or with varenicline to some extent.
Persistence	Successful smoking cessation requires persistent efforts since most patients require more than one quit attempt. Every quit attempt provides opportunities for learning how to quit, and patients are more likely to succeed with each subsequent try.
Caffeine – tobacco smoke interaction	Tobacco smoke also induces the metabolism of caffeine. Smoking cessation occurring without a reduction in caffeine intake may lead to symptoms of caffeine toxicity including anxiety, restlessness, sleep problems and irritability, which can mimic symptoms of psychiatric illness.