

## Appendix 14.5 Smoking Cessation Medications

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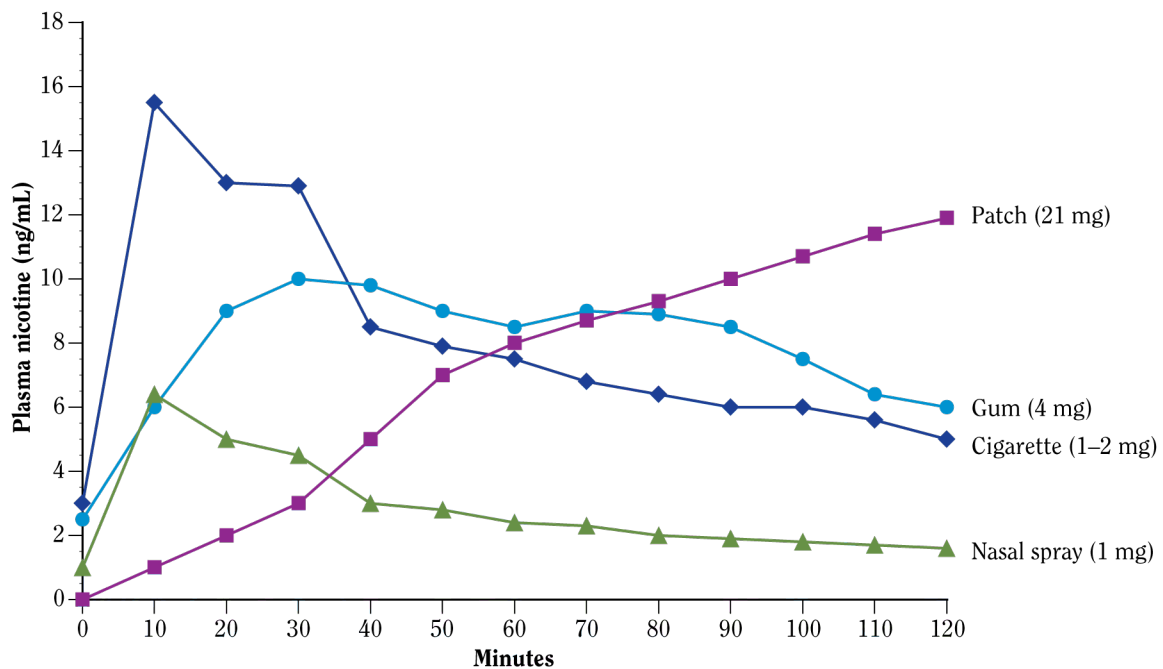
# Smoking Cessation Medications

Smoking cessation medications can aid smoking cessation by alleviating nicotine withdrawal symptoms. All five U.S. Food and Drug Administration (FDA)-approved formulations of nicotine replacement therapy (NRT) deliver nicotine without burning tobacco. Of these five products, three are available without a prescription in the United States (skin patch, gum, and lozenge) and two require a prescription (oral inhaler and nasal spray). The nicotine in NRT products is absorbed through the skin (patch), oral mucosa (gum, lozenge, and inhaler), or nasal mucosa (nasal spray). Because nicotine in the NRT is not absorbed through the lower respiratory tract, no NRT product approaches the rapid arterial delivery of a cigarette. Thus, NRT products have low addictive potential. Unfortunately, widespread misconceptions still exist about NRT, and many smokers still mistakenly believe that these

products are addictive or cause cancer and heart disease (Shiffman et al. 2008).

The different pharmacodynamic characteristics of the available NRT products provide a rationale for combining nicotine products with the goal of heightening efficacy for smoking cessation (Figure 14.5.1). The patch features a slow (2–3 hour) onset with steady levels over a 16- or 24-hour period (depending on preparation), which provides long-term relief of withdrawal symptoms. The patch is the simplest to use of the NRT products and, therefore, has the best patient adherence. The disadvantage of its steady nicotine delivery is the inability of users to self-titrate their nicotine levels in the way they had while they were smoking (i.e., by ad-lib smoking to avoid withdrawal symptoms). Thus, individuals are not able to respond to cigarette cravings by self-administering

**Figure 14.5.1 Plasma nicotine levels after a smoker has smoked a cigarette, received nicotine nasal spray, begun chewing nicotine gum, or applied a nicotine patch**



Source: Modified from Garrett et al. 2001.

Note: The amount of nicotine in each product is shown in parentheses. The pattern produced by the nicotine lozenge and nicotine inhaler resemble that of nicotine gum. **mg** = milligram; **mL** = milliliter; **ng** = nanogram.

nicotine unless they concomitantly use another short-acting NRT preparation.

The remaining four NRT products feature a more rapid onset, but shorter duration of action, requiring repeated administration to maintain patient comfort (i.e., stable nicotine blood levels) and relief from withdrawal symptoms. The nasal spray has the most rapid onset of action (5–10 minutes to peak nicotine blood levels), but spraying nicotine onto the nasal mucosa can be irritating, thus limiting its repeated use. Nicotine in gum, lozenge, and oral inhaler is absorbed through the oropharynx and reaches peak blood levels 20–30 minutes after administration. Using any of these shorter-acting products, individuals can regulate nicotine in their blood levels by adjusting administration throughout the day. However, users may fail to administer the products often enough to achieve reliable levels of relief from withdrawal via stable nicotine blood levels. Furthermore, with the exception of the lozenge, the short-acting products require training for proper use, which is another barrier to initial patient acceptance and adherence.

The 2008 Public Health Service Clinical Guidelines recommends combinations of short- and long-acting NRT products (Fiore et al. 2008), which is not only safe and more comfortable for individuals, but is also more effective than using a single NRT product (Piper et al. 2009; Smith et al. 2009; Stead et al. 2012). Additional evidence supports other novel methods of administering NRT, which can improve quit rates, including prolonging treatment well beyond the standard 8–12-week duration (e.g., 6–12 months) (Steinberg et al. 2009; Schnoll et al. 2010). Cautious use of NRT for prolonged duration may be particularly important for individuals who are concerned that they will relapse upon discontinuing use, although evidence to date for this strategy is limited (Carpenter et al. 2013). Other strategies include continuing to use NRT after a slip (e.g., smoking a cigarette). Some studies found better efficacy when NRT is started 2 weeks before the quit day, rather than on the quit day as traditionally recommended, although this practice has not been uniformly associated with improved quit rates (Lindson and Aveyard 2011; Stead et al. 2012). A 2013 review of strategies to enhance the efficacy of NRT examined randomized trials reporting outcomes of at least 6 months in which the dose and duration of NRT use was manipulated, or for which NRT was used for a novel purpose (e.g., relapse prevention) (Carpenter et al. 2013). This review concluded that combination NRT use (nine studies examined) is the most promising of the novel strategies. Other strategies, including the use of pre-quit NRT (nine studies examined), offer potential utility, but require more evidence before they can be definitively and widely recommended. For example,

in the six studies in which participants were randomized to high-dose NRT versus medium- or low-dose, results varied widely. However, two of the four studies testing a higher dose patch (42 or 44 milligrams) against a standard dose patch found greater rates of cessation at 6 months. Similarly, six of the eight studies assessing use of NRT for relapse prevention reported increased cessation at 6 months.

There is some evidence that providing NRT to smokers who want to cut down, but not to quit immediately, influences some of them to quit smoking long-term (Moore et al. 2009). Approximately 30% of smokers surveyed indicated that they do not want to quit in the next year, and addressing tobacco use in this population is particularly challenging. Using NRT to aid in cutting down has been shown to double quit rates at 1 year, although the absolute quit rates remain low (7%) even in the treatment group (Wang et al. 2008). On a population level, however, this doubling translates into several million former smokers. The United Kingdom has incorporated the gradual reduction strategy into their national tobacco control efforts since 2010 and has licensed NRT for combination use. These restrictions reflect early concerns about causing nicotine overdose or sustaining dependence that have subsequently been proven to be unfounded. The restrictions can dissuade clinicians and smokers, alike, from obtaining the maximum possible benefit of NRT. FDA has heard public comment and is currently reviewing its recommendations for use of NRT (USFDA 2012a). More than 150 randomized trials with long-term cessation outcomes, involving over 50,000 individuals, have definitively demonstrated the efficacy of all forms of NRT for quitting smoking (50–70% increase compared to placebo).

## Safety of NRT

Nicotine is an adrenergic drug that increases heart rate and blood pressure after acute administration and, therefore, increases myocardial oxygen demand. The rate of increase of pulse and blood pressure is related to the rate of nicotine absorption, which is less for NRT products than for smoking cigarettes. NRT use is associated with a variety of mildly adverse side effects (Mills et al. 2010). An increase in myocardial workload could theoretically be harmful for a smoker with coronary heart disease, whose ability to increase oxygen supply is limited by the presence of coronary atheromata. The risk should be lower for an individual using NRT than it is for an individual smoking cigarettes. No increase in cardiovascular events or mortality was found in several double-blind randomized controlled trials of NRT for smoking cessation among

individuals with stable cardiovascular disease (Stead et al. 2012). Patients in these studies are at least 2 weeks after a cardiovascular event. In one study of smokers with stable coronary heart disease, the extent of exercise-induced myocardial ischemia on exercise thallium-201 single-photon emission computed tomography was compared with individual smokers who either smoked or used nicotine patches prior to the stress test. The extent of exercise-induced ischemia was far less after NRT use, than after smoking, and not significantly different from the no-drug control condition (Mahmorian et al. 1997).

Data on the safety of NRT immediately after an acute coronary event, such as myocardial infarction (MI) is lacking; but NRT is used in practice by some cardiologists in hospitals to treat nicotine withdrawal symptoms, which could independently increase myocardial workload. The rationale for using NRT for smoking cessation following acute MI is that the risk of cardiovascular mortality is greater for someone who resumes smoking than the potential risk of using NRT after MI.

## Bupropion

### Efficacy

Bupropion is an atypical antidepressant that increases dopamine levels in central nervous system mesolimbic pathways, which are also activated by other drugs of dependence. The mechanism of bupropion to increase smoking cessation rates is independent of its antidepressant effects (Fiore et al. 2008; Hughes et al. 2014). There is some evidence that adding bupropion to NRT increases long-term cessation (Fiore et al. 2008) and this combination is used in practice (see Table 14.4.1 in Appendix 14.4) (Barnes et al. 2010).

### Safety of bupropion

The most serious safety concern with the use of bupropion is an increased risk of seizure, which occurred in 0.1% of smokers using bupropion in smoking cessation clinical trials (Hughes et al. 2014). It is contraindicated in smokers with an existing seizure disorder and those who are at an increased risk of seizure. An additional concern about potential psychiatric side effects emerged in 2009 after FDA reviewed the case reports it had received about behavioral changes associated with the use of all smoking cessation medications. FDA required the addition of a boxed warning about this association to the product label for bupropion (USFDA 2009) (See section on varenicline safety for full details).

## Varenicline

### Efficacy

Varenicline is a selective partial agonist at the  $\alpha 4\beta 2$  nicotinic receptor subtype, which is one of the main receptor subtypes mediating human nicotine dependence. As a partial agonist, varenicline has dual actions. It serves to relieve nicotine withdrawal symptoms by actively stimulating the receptor, while simultaneously blocking the reinforcement of smoking by preventing nicotine from binding to the receptor. In 14 placebo-controlled randomized trials, varenicline has demonstrated efficacy for smoking cessation (Cahill et al 2011). In 3 head-to-head trials, varenicline proved to be more efficacious than bupropion for long-term cessation (Gonzales et al. 2006; Jorenby et al. 2006; Nides et al, 2006). Varenicline was also marginally more efficacious than NRT monotherapy (the nicotine patch) for long-term cessation in a single open-label randomized trial (Aubin et al. 2008). In a case series of over 400 individuals with and without mental illness, who were monitored before and after using varenicline or NRT (in combination with group behavioral therapy) to quit smoking, varenicline was more effective 4 weeks after the quit date (Stapleton et al. 2008). A recent randomized trial has shown that the combination of varenicline and NRT can be more effective (Ebbert et al. 2009a; Brose 2013; Hajek et al. 2013).

The efficacy of varenicline might also be enhanced by combining it with bupropion or NRT. Recent evidence suggest that adding bupropion to varenicline plus intensive smoking cessation counseling can enhance prolonged abstinence (Cinciripini et al 2013). There is theoretical rationale for the combination, because the two drugs have different mechanisms of action, and a preliminary study found it to be feasible and acceptable in a clinical population (Ebbert et al. 2009b). In a case series, NRT was started concomitantly with varenicline in order to achieve relief of withdrawal during the loading period, followed by gradual reduction of NRT over time, and this combination was found to be tolerable (Ebbert et al. 2009b). Whether adding NRT to varenicline will further increase the efficacy of varenicline has not been formally tested. One pilot randomized controlled double-blind study tested the efficacy of varenicline to prompt quit attempts among smokers who were not ready to quit in the next month. Varenicline reduced the number of cigarettes smoked, but did not definitively increase quit attempts in this population (Hughes et al. 2011a). Another study found that varenicline was efficacious when used with a flexible quit date between weeks 2–5 after varenicline use started (Hughes et al. 2011b).

### **Safety of varenicline: psychiatric side effects**

Postmarketing case reports submitted to FDA describing behavior changes in smokers taking varenicline prompted concerns about the safety of varenicline. In 2009, FDA undertook a comprehensive review of its case reports for all smoking cessation drugs and reported that varenicline and bupropion were “associated with reports of changes in behavior such as hostility, agitation, depressed mood, and suicidal thoughts or actions” (USFDA 2009). The manufacturers of bupropion and varenicline were required to add boxed warnings to the labels of these medications. Warnings were not required for NRT. Case reports, alone, cannot define the true association of bupropion or varenicline with behavioral changes. Stopping smoking, by itself, produces nicotine withdrawal symptoms that may include irritability, anxiety, and depressed mood. From case-report data, it is not possible to distinguish whether the cause of withdrawal-like symptoms was a side effect of the drug or nicotine withdrawal itself. In 2010, a pooled analysis of 10 randomized double-blind placebo-controlled varenicline trials, which in total enrolled over 3,000 smokers, did not detect an excess of psychiatric side effects in participants who had taken varenicline (Tonstad et al. 2010). However, the studies included in this analysis systematically excluded smokers who might be more vulnerable to developing these side effects when taking varenicline, such as people with depression and other mental illness (Tonstad et al. 2010). In two subsequent trials of varenicline for smoking cessation in people with schizophrenia (total of 240 smokers enrolled), the medication was well tolerated (Pachas et al. 2012; Williams et al. 2012).

Analyzing data from electronic health records is another strategy for evaluating the potential risk of varenicline. Two analyses of electronic health record databases have found no difference in psychiatric side effects in smokers, who were prescribed varenicline for smoking cessation, as compared with smokers prescribed a different drug such as NRT. The first, a retrospective analysis of the U.K. General Practice Research Database examined the risk of suicides, suicidal thoughts or attempts, and new antidepressant prescriptions in patients starting varenicline, compared to NRT or bupropion. It found no difference in the frequency of these outcomes between smokers starting varenicline, bupropion, or NRT (Gunnell et al. 2009). A second retrospective cohort study compared the rates of neuropsychiatric hospitalizations in new users of varenicline to new users of NRT patch in the U.S. Military Health System database. There was no increase in the rate

of neuropsychiatric hospitalizations in patients treated with varenicline, compared to NRT patch, when followed for 30 days (propensity-score matched HR = 1.14; 95% CI, 0.56–2.34) or 60 days (Meyer et al. 2013). A large case series of individuals, including those with mental illness, undergoing behavioral treatment combined with either NRT or varenicline, found no evidence for exacerbation of psychiatric symptoms (Stapleton et al. 2008). The limitations of these observational studies include the relatively small number of psychiatric events as well as the possibility of residual confounding (e.g., confounding by indication, if individuals at heightened risk of psychiatric side effects were preferentially steered away from varenicline or bupropion, and toward NRT, by their provider).

A large double-blind randomized controlled trial, mandated by FDA, is being conducted to better evaluate the risk of varenicline and bupropion in people with mental illness (USFDA 2011c). Results from this trial are expected in 2017. In the meantime, FDA stated in a 2011 communication, “the Agency continues to believe that varenicline’s benefits outweigh the risks and the current warnings in the Chantix drug label are appropriate” (USFDA 2011c).

### **Safety of varenicline: cardiovascular disease risk**

A small absolute risk and absolute risk difference in cardiovascular events among people taking varenicline versus placebo was reported by a 2011 meta-analysis of varenicline randomized controlled trials (Singh et al. 2011). Methodologic limitations of the meta-analysis include concerns about the low quality of several included studies, the uncertainty surrounding the calculation for the number needed to harm, and the fact that an independent examination of these data, which used a random-effects analysis, failed to find an increased risk of cardiovascular disease events among smokers who took varenicline (Brophy 2011; Hays 2011). FDA issued a Drug Safety Communication about varenicline due to concerns that the drug may increase the risk of cardiovascular events in patients with existing cardiovascular disease (USFDA 2011a) and updated drug labels to reflect new safety and efficacy information (USFDA 2011b). A subsequent meta-analysis found no significant association between varenicline and an increased risk of cardiovascular events (Prochaska and Hilton 2012). These studies did not find an increased risk of cardiovascular-related mortality or all-cause mortality with varenicline; the cardiovascular disease risk in question pertained specifically to

cardiovascular events.

A subsequent FDA Safety Communication released in December 2012 reported the results of another meta-analysis that included data from 7,002 patients (4,190 Chantix and 2,812 placebo) who were enrolled in 15 Pfizer-sponsored, randomized, double-blind, placebo-controlled clinical trials of 12 or more weeks treatment duration (USFDA 2012b). The analysis assessed the frequency of a composite cardiovascular outcome that included cardiovascular-related death, nonfatal MI, and nonfatal stroke. The incidence of the endpoint was low (Chantix 0.31% vs. placebo 0.21%) in the trials included in the

meta-analysis. The adjusted hazard ratio associated with Chantix use was 1.95 (95% CI, 0.79–4.82) and nonsignificant. However, even with this large sample, the statistical power for finding a significant difference was low because the overall number of adverse cardiovascular events was low. FDA's recommendation to health care professionals was "to weigh the risks of Chantix against the benefits of its use. It is important to note that smoking is a major risk factor for cardiovascular disease, and Chantix is effective in helping patients to quit smoking and abstain from it for as long as one year. The health benefits of quitting smoking are immediate and substantial" (USFDA 2012b).



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