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Drugs for Tobacco Dependence

Tobacco dependence remains the primary preventable cause of death in the United States. It is a chronic disorder that often requires pharmacologic therapy, but counseling may be equally effective and can add to the effectiveness of any treatment for this indication.\(^1,2\) Abrupt cessation of smoking appears to be as effective as gradual reduction.\(^3\)

NICOTINE — All FDA-approved nicotine replacement therapies (NRTs) deliver nicotine to nicotinic receptors in the central nervous system (CNS) in a lower dose and at a substantially slower rate than tobacco cigarettes. They increase smoking cessation rates by 50-70% and, in the short term, may decrease weight gain associated with smoking cessation.\(^4,5\) Nicotine undergoes first-pass metabolism, which limits its effectiveness in oral pill formulations. Nicotine gum, lozenges, and patches are available without a prescription in the US for persons \(\geq\) 18 years old; these products appear to be as effective as those that require a prescription (nicotine oral inhaler and nasal spray). Used as monotherapy, a rapid-onset NRT such as a gum, lozenge, nasal spray, or oral inhaler should be taken on a regular schedule to prevent nicotine withdrawal symptoms. Combining the nicotine patch with a rapid-onset formulation (combination NRT) is more effective than monotherapy.

Transdermal — Nicotine patches require 6-8 hours to achieve peak serum concentrations. They deliver nicotine to the CNS more slowly than any other NRT.

Oral — Nicotine from a gum, lozenge, or oral inhaler is absorbed through the buccal mucosa. Serum nicotine concentrations peak in 20-60 minutes. If oral nicotine is swallowed, first-pass metabolism decreases its bioavailability.

Nasal Spray — Nicotine from nasal spray, the fastest-acting of all NRTs (but still much slower than cigarettes), achieves a peak CNS concentration in 5-20 minutes. Patients report that relief of nicotine withdrawal symptoms is faster with the nasal spray than with other NRT formulations. Because it can irritate the throat and nasal mucosa, the nasal spray should not be used for more than 3 months.

Adverse Effects — The transdermal nicotine patch is generally well tolerated, but some patients discontinue it because of insomnia, vivid dreams, or pruritus at the application site. Removing the patch at bedtime can minimize or eliminate vivid dreams and other sleep disturbances. The nicotine oral inhaler can cause minor mouth and throat irritation and cough; tolerance to the irritating effects usually develops within one or two days. Nicotine gum can cause flatulence, indigestion, nausea, unpleasant taste, hiccups, and a sore mouth, throat, and jaw. Nicotine lozenges can cause mouth irritation, heartburn, hiccups, and nausea. Nicotine nasal spray causes transient burning and stinging of the nasal mucosa, throat irritation, flushing, coughing, sneezing, lacrimation, rhinorrhea, and nausea; these symptoms are a common cause of drug discontinuation.

Drug Interactions — NRTs are metabolized by CYP2A6, but do not inhibit or induce CYP enzymes to a clinically significant extent. Tobacco smoke, not nicotine itself, induces CYP1A2, CYP2E1, and some uridine diphosphate-glucuronosyltransferases (UGTs); it may increase the metabolism and decrease the efficacy of
### Table 1. Some Drugs for Treatment of Tobacco Dependence

<table>
<thead>
<tr>
<th>Drug</th>
<th>Some Available Formulations</th>
<th>Usual Adult Maintenance Dosage</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nicotinic Receptor Agonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine transdermal patch – generic Nicoderm CQ (Sanofi)</td>
<td>7, 14, 21 mg/24 hr patches</td>
<td>1 patch/d&lt;sup&gt;4&lt;/sup&gt;</td>
<td>$40.70&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nicotine nasal spray – Nicotrol NS (Pfizer)</td>
<td>200 sprays/10 mL bottle (0.5 mg/spray)</td>
<td>1 dose (2 sprays) 8-40x/d (max 5 doses/h)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>304.90&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nicotine oral inhaler – Nicotrol (Pfizer)</td>
<td>10 mg cartridges</td>
<td>4-16 cartridges/d (max 16 cartridges/d)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>290.40&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nicotine polacrilex gum – generic Nicorette Gum (GSK)</td>
<td>2, 4 mg/piece</td>
<td>8-24 pieces/d&lt;sup&gt;4&lt;/sup&gt;</td>
<td>77.20</td>
</tr>
<tr>
<td>Nicotine polacrilex lozenge – generic Nicorette Lozenge (GSK)&lt;sup&gt;11&lt;/sup&gt;</td>
<td>2, 4 mg/lozenge</td>
<td>8-20 lozenges/d&lt;sup&gt;4,10&lt;/sup&gt;</td>
<td>72.00</td>
</tr>
<tr>
<td><strong>Dopaminergic-Noradrenergic Reuptake Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion SR – generic Wellbutrin SR (GSK)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>100, 150, 200 mg SR tabs&lt;sup&gt;12&lt;/sup&gt;</td>
<td>150 mg bid&lt;sup&gt;12&lt;/sup&gt;</td>
<td>27.00</td>
</tr>
<tr>
<td>Zyban (GSK)</td>
<td>150 mg SR tabs</td>
<td></td>
<td>236.00</td>
</tr>
<tr>
<td><strong>Nicotinic Receptor Partial Agonist</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Varenicline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Drug Formulations</strong></td>
<td><strong>Maintenance Dosage</strong></td>
<td><strong>Cost</strong></td>
<td></td>
</tr>
<tr>
<td>Varenicline tartrate – Chantix (Pfizer)</td>
<td>0.5, 1 mg tabs</td>
<td>1 mg bid&lt;sup&gt;18&lt;/sup&gt;</td>
<td>157.50</td>
</tr>
</tbody>
</table>

1. Dosage reduction may be needed for hepatic or renal impairment.
2. Approximate WAC for 30 days’ treatment at the lowest usual maintenance dosage. WAC = wholesaler acquisition cost, or manufacturer’s published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. February 5, 2016. Reprinted with permission by First Databank, Inc. All rights reserved. ©2016. www.fdbhealth.com/policies/drug-pricing-policy.
3. Available over the counter (OTC) for persons ≥18 years old. Patients should not eat or drink within 15 minutes of using a gum or lozenge.
4. See specific label for instructions for dose titration.
5. Cost for 28 transdermal patches.
6. One spray per nostril. Maximum of 40 doses/day. Should not be used for ≥3 months.
7. Cost of 4 10-mL bottles.
8. Cost of 168 10-mg cartridges; each cartridge delivers 4 mg of nicotine.
9. A second piece of gum can be used within one hour. Continuously chewing one piece after another is not recommended.
10. Maximum of 5 lozenges in 6 hours or 20 lozenges/day. Do not use more than one lozenge at a time or continuously use one after another.
11. Also available in a mini-lozenge.
12. Only the generic 150-mg SR tablets are FDA-approved for this indication.
13. Initial dosage is 150 mg once/d for 3 days.
14. Not FDA-approved for this indication.
15. Initial dosage is 0.5 mg once/d for 3 days, then bid for 4-7 days.

**Drugs** that are substrates of these pathways such as clozapine (Clozaril, and others), theophylline (Theo-Dur, and others), and propranolol. Dosages of these drugs may need to be reduced when patients stop smoking.

**BUPROPION** – Used mainly for treatment of depression, bupropion also has some nicotinic-receptor-blocking activity. A sustained-release (SR) formulation of bupropion is FDA-approved for treatment of tobacco dependence (marketed as Zyban). Bupropion SR should be started 7-14 days before the target quit date to allow for adequate steady-state serum concentrations. Immediate-release bupropion (Wellbutrin, and generics) has also been used (off-label) to treat tobacco dependence.

**Effectiveness** – Bupropion has doubled smoking cessation rates compared to placebo in short-term trials. It has been as effective as NRT in increasing smoking cessation rates and decreasing weight gain.<sup>8</sup>

**Adverse Effects** – Bupropion is generally well tolerated. The most common adverse effects in clinical trials were insomnia and dry mouth. Headache, nausea, and anxiety can also occur.<sup>9</sup> Bupropion SR has been associated with a seizure incidence of 0.1%; patients with a history of seizure, stroke, brain tumor, brain surgery, or severe head injury should not take bupropion.

**Drug Interactions** – Bupropion is primarily metabolized by CYP2B6 to hydroxybupropion, its most active metabolite. Drugs that are inhibitors or inducers of CYP2B6 may interact with bupropion. Bupropion and hydroxybupropion inhibit CYP2D6; many antidepressants, antipsychotics, beta-blockers, and type 1C antiarrhythmics are CYP2D6 substrates and should be used with caution in patients taking bupropion.<sup>6</sup> Use of bupropion with a monoamine oxidase (MAO) inhibitor or within 2 weeks of stopping one is contraindicated.

**VARENICLINE** – Varenicline tartrate (Chantix), a nicotinic receptor partial agonist, is FDA-approved for smoking cessation.<sup>10</sup> It binds selectively to α<sub>4</sub>β<sub>2</sub> nicotinic acetylcholine receptors, relieving cravings and withdrawal symptoms during abstinence. Varenicline binds to the α<sub>4</sub>β<sub>2</sub> receptor with greater affinity than nicotine, reducing the reward of smoking. Varenicline should be started 7 days before the target quit date to allow for adequate steady-state serum concentrations.
**Effectiveness** – Randomized controlled trials, including both short-term trials and some for up to one year, have found varenicline to be more effective than NRT monotherapy or bupropion and as effective as combination NRT (nicotine patch plus a rapid-onset NRT) in increasing smoking cessation rates. In one randomized, open-label trial in 1086 smokers, smoking cessation rates with varenicline, combination NRT, and a nicotine patch alone were similar at 26 and 52 weeks, possibly due to a relatively low level of dependence among participating smokers.13

**Adverse Effects** – Varenicline was generally well tolerated in clinical trials. The most common adverse effects were nausea, sleep disturbances, abnormal dreams, headache, constipation, vomiting, flatulence, and xerostomia. Neuropsychiatric symptoms, exacerbations of pre-existing psychiatric illness, suicidal behavior, and an increased rate of cardiovascular events have been associated with varenicline use in observational studies, but a retrospective cohort study in almost 165,000 patients found no increased risk of any cardiovascular or neuropsychiatric event with varenicline compared to NRT or bupropion. Varenicline has increased smoking cessation rates in patients with psychiatric illnesses, with no significant psychiatric adverse effects. Recent analyses of clinical trials have found no increase in suicidal behavior in patients treated with varenicline compared to those treated with NRT, bupropion, or placebo.17

**Drug Interactions** – Varenicline has no clinically significant drug interactions. Coadministration of varenicline and transdermal nicotine does not affect nicotine pharmacokinetics, but nausea, headache, vomiting, dizziness, dyspepsia, and fatigue may occur more frequently with combined use than with transdermal nicotine alone.

**COMBINATIONS** – Use of ≥2 medications has generally been more effective than monotherapy in treating tobacco dependence. In one trial, 127 smokers with comorbid conditions were randomly assigned to receive a nicotine patch alone or in combination with a nicotine oral inhaler and bupropion for 10 weeks; abstinence rates at 26 weeks were 35% with the combination compared to 19% with the patch alone. A randomized, placebo-controlled trial in 446 smokers that included a 12-week treatment period and a 12-week follow-up found that varenicline plus a nicotine patch was significantly more effective than varenicline alone in achieving continuous abstinence at 12 weeks (55.4% vs 40.9%) and 24 weeks (49.0% vs 32.6%) and point-prevalence abstinence at 6 months (65.1% vs 46.7%). In another trial, a combination of varenicline and bupropion SR was significantly more effective than varenicline alone in achieving prolonged abstinence among 506 smokers at 12 weeks (53.0% vs 43.2%) and 26 weeks (36.6% vs 27.6%), but not at 52 weeks.20

**DURATION OF TREATMENT** – Longer-duration pharmacotherapy may improve smoking cessation rates. Most patients should receive a minimum of 3-6 months of effective therapy. In general, the dosage of NRTs should be tapered at the end of treatment; bupropion SR and varenicline can usually be discontinued without a gradual dosage reduction, but some clinicians recommend a taper.

**ELECTRONIC CIGARETTES** – Electronic cigarettes, also called e-cigarettes, are advertised as a safer, more convenient, and socially acceptable alternative to tobacco cigarettes. They have not been approved by the FDA as smoking cessation aids. E-cigarettes are battery-operated devices that typically contain a heating element (atomizer) and a reservoir of liquid (usually nicotine dissolved in propylene glycol and/or glycerin). When the user inhales or activates the device with a button, the liquid nicotine is vaporized into a visible mist.

**Clinical Studies** – In a clinical trial in adult smokers not intending to quit, 300 participants were randomized to e-cigarettes containing 5.4 or 7.2 mg of nicotine or no nicotine. At 12 weeks, complete abstinence from tobacco cigarettes had occurred in 14% of participants using a nicotine-containing e-cigarette and in 4% of those using the nicotine-free device.22

A randomized trial in 657 smokers who wanted to quit compared a 16-mg nicotine e-cigarette, a 21-mg nicotine patch, and a placebo e-cigarette. The percentage of patients who achieved abstinence from tobacco cigarettes at 6 months was not significantly higher with the nicotine e-cigarette (7.3%) than with the nicotine patch (5.8%) or placebo device (4.1%).23

A meta-analysis of 38 trials of smokers who used e-cigarettes, including some in smokers who wanted to quit and others in smokers in general, found that those who used e-cigarettes were actually 28% less likely to quit smoking tobacco cigarettes than smokers who did not use e-cigarettes.24

**Adverse Effects** – There is no evidence to date that short-term use of e-cigarettes has serious adverse effects. The most common adverse effects reported during clinical trials of e-cigarettes were mouth and...
throat irritation and dry cough. Lipoid pneumonia has been reported. In non-smokers, repeated exposure to nicotine in e-cigarettes could lead to nicotine dependence.

**Toxic Substances** – An FDA analysis of 2 different brands of e-cigarette cartridges found that they contained a number of impurities including polycyclic aromatic hydrocarbons and tobacco-specific nitrosamines, which are carcinogenic. The vapor from e-cigarettes has been found to contain levels of potentially toxic and carcinogenic substances that are lower than those found in cigarette smoke, but higher than those in ambient air.

**PREGNANCY** – Counseling is the preferred treatment for pregnant women who smoke. Nicotine is classified as category D (positive evidence of risk) for use during pregnancy. However, using NRT during pregnancy is probably safer for the fetus than smoking, which increases the incidence of low birth weight deliveries and is associated with peri- and post-natal complications. NRT can increase smoking cessation rates in late pregnancy by about 40% and, in one trial that followed infants after birth, it improved developmental outcomes. Bupropion and varenicline are classified as category C (no adequate studies in pregnant women; fetal toxicity in animals) for use during pregnancy.
