Pharmacotherapy of Tobacco Use Disorder

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Tobacco use is the leading cause of preventable mortality worldwide (1). Over one-half of all persistent smokers will eventually die of a tobacco-related disease (1). The primary addictive substance in tobacco is nicotine. Cigarette smoking facilitates the rapid absorption of nicotine via pulmonary circulation into the brain within seconds. Nicotine binds to α4β2 nAChRs (nAChRs) and causes the release of dopamine, norepinephrine, serotonin, beta-endorphins, and other neurotransmitters. These nAChRs are pentameric in nature and are made up of α and β subunits. The α subunit occurs in nine different isoforms (α2–α10), while the β subunit occurs in three different isoforms (β2–β4). Nicotinic receptors containing the α4 and β2 subunits (α4β2 nAChRs) are the most prevalent in the brain and are thought to play the largest role in nicotine’s reinforcing effects (2). Repeated exposure to nicotine causes upregulation of α4β2 nicotinic acetylcholine receptors, leading to an increase in their numbers, which subsequently reinforces the addiction (3). Although debate regarding the mechanism of upregulation continues to exist, proposed mechanisms include conformation changes of low-affinity receptors to high-affinity states, as well as decreased cell surface receptor degradation secondary to nicotine exposure (4).

The reinforcing effects of nicotine are primarily tied to its stimulatory effect on the mesoaccumbens dopamine pathway, which consists of dopamine projects from the ventral tegmental area (VTA) to the nucleus accumbens (NAcc). Nicotine’s action at α4β2 nAChRs in the VTA is thought to be the primary role behind nicotine’s reinforcing effects; however, other subtypes, such as α6 nAChRs heavily located in the VTA and NAcc, are important as well. The α7 nAChRs are also important, as they are thought to play a role in regulating nicotine intake (25). Tobacco dependence also has a genetic component. Two single-nucleotide polymorphisms in CHRNA4 (the gene coding for the α4 subunit of nAChRs) are biologically functional and associated with tobacco dependence phenotypes (5).

Pharmacotherapies are effective treatments for tobacco dependence and are recommended by the United States Public Health Service to be provided in conjunction with behavioral therapy (6) (Tables 1 and 2). Nicotine replacement therapy, such as the nicotine patch, acts mainly at the α4β2 nAChRs, while bupropion is an antagonist at α4β2 nAChRs, as well as a full agonist at α7 nAChRs (2). The present article focuses primarily on first-line pharmacotherapies for tobacco dependence (7).

NICOTINE REPLACEMENT THERAPY

All nicotine replacement therapy products are recommended as first-line agents to treat tobacco dependence (6, 7) (Table 1). Nicotine replacement therapies deliver nicotine via oral or nasal mucosa, thus reducing the severity of withdrawal symptoms and cravings associated with tobacco use cessation (6, 7). A Cochrane meta-analysis of 150 trials demonstrated that nicotine replacement therapy increases long-term smoking abstinence compared with placebo or controls without nicotine replacement therapy (relative risk=1.60; 95% confidence interval [CI]=1.53–1.68) (7).

Nicotine Gum
Nicotine gum is available over the counter in 2-mg or 4-mg dose forms and increases smoking abstinence rates at 12 months compared with a control intervention (relative risk=1.43; 95% CI=1.31–1.56; 32 studies) (7). As monotherapy, standard dosing for highly dependent smokers is 4 mg, as this dose showed higher abstinence rates compared with the 2-mg dose (4, 5). Nicotine gum side effects include hiccups, gastrointestinal upset, and jaw discomfort associated with chewing (7).

Nicotine Lozenges
Nicotine lozenges are available over the counter in 2-mg or 4-mg dose forms, and a meta-analysis demonstrated their efficacy in increasing abstinence rates at 6 months compared with placebo (relative risk=1.90; 95% CI=1.36–2.67; four trials) (7). Lozenges provide at liberty dosing in response to cravings and release 25% more nicotine than an equal dose of gum. The lozenge is placed in the buccal cavity, allowing for nicotine absorption through the oral mucosa. It may be preferable to gum for patients with oral problems (8).

Nicotine Patches
Nicotine patches are available over the counter in various formulations and dosing schedules (i.e., 15 mg/16 hours; 7 mg, 14 mg, and 21 mg/24 hours). The nicotine patch is neither designed to alleviate acute cravings nor replace the behavioral activities of smoking in comparison to other types of nicotine replacement therapy (6). Nicotine patches provide slow, transdermal nicotine delivery over 16–24 hours and have been shown to significantly increase sustained 12-month abstinence rates (relative risk=1.51; 95% CI=1.35–1.70; 21 trials), with the most common side effect being mild skin irritation at the application site (7). Highest dose should be started in individuals smoking 10 or more cigarettes per day (3). In a preference trial comparing nicotine
replacement therapy products, smokers preferred nicotine patches the most (8).

**Nasal Sprays**
Nasal sprays are available through prescription and deliver nicotine through nasopharyngeal mucosa. One spray through each nostril constitutes a dose. Patients can initially use 1 or 2 doses/hour but should not exceed 5 doses/hour or 40 doses/day (9). Nasal sprays deliver nicotine faster than gum, patches, or inhalers but less rapidly than cigarettes (9). Nasal sprays increase smoking abstinence at 6 months greater than placebo (relative risk=2.02; 95% CI=1.49–2.73; four trials) (7). Side effects include rhinorrhea and nasal irritation (7).

**Nicotine Inhalers**
Nicotine inhalers require a prescription and deliver nicotine into the oropharynx where it is absorbed across the buccal mucosa (7). It addresses the sensory and ritualistic aspects of smoking behavior (10). Nicotine inhalers increase long-term abstinence compared with placebo (relative risk=1.90; 95% CI=1.36–2.67; four trials) (11). The most common side effects reported are oropharyngeal irritation and cough (7).

No nicotine replacement therapy product delivers an equivalent dose of nicotine as quickly as cigarette smoking (7). Consequently, they have a limited ability to consistently and effectively counter the addictive appeal of smoking in tobacco-dependent individuals (7).

Evidence recommends combination use of nicotine replacement therapy products that provide both continuous and at-liberty dosing (6, 7).

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**TABLE 1. First-Line Pharmacotherapies of Tobacco Dependence**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Usual Dose</th>
<th>Side Effects</th>
<th>Cautions</th>
<th>Drug-Drug Interactions</th>
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</thead>
<tbody>
<tr>
<td>Nicotine gum (over the counter)</td>
<td>Intermediate nicotine absorption, nicotine delivery through oral mucosa, full agonist, reduces cravings and withdrawal</td>
<td>2 mg or 4 mg</td>
<td>Hiccups, gastrointestinal side effects, jaw discomfort</td>
<td>Pregnancy or breastfeeding; history of systemic rash with nicotine replacement therapy; less than 18 years of age; temporomandibular joint disease; dental or oral problem</td>
<td>None</td>
</tr>
<tr>
<td>Nicotine lozenge (over the counter)</td>
<td>Intermediate nicotine absorption, nicotine delivery through oral mucosa, full agonist, reduces cravings and withdrawal</td>
<td>2 mg or 4 mg</td>
<td>Hiccups, oropharyngeal irritation, dry lips, oral ulcers</td>
<td>Pregnancy or breastfeeding; history of systemic rash with nicotine replacement therapy; less than 18 years of age</td>
<td>None</td>
</tr>
<tr>
<td>Nicotine patch (over the counter)</td>
<td>Slow nicotine absorption; nicotine delivery through skin full agonist; reduces cravings and withdrawal</td>
<td>7 mg, 14 mg, or 21 mg/24 hours</td>
<td>Mild skin irritation, nightmares</td>
<td>Pregnancy or breastfeeding; history of systemic rash with nicotine replacement therapy; less than 18 years of age; certain skin conditions</td>
<td>None</td>
</tr>
<tr>
<td>Nasal spray (prescription)</td>
<td>Fast nicotine absorption; rapidly reduces cravings and nicotine withdrawal</td>
<td>1 or 2 doses/hour but should not be &gt;5 doses/ hour or 40 doses/day</td>
<td>Mild irritation in nasal mucosa</td>
<td>Pregnancy or breastfeeding; history of systemic rash with nicotine replacement therapy; less than 18 years of age; skin conditions; rhinitis; nasal polyps; sinusitis</td>
<td>None</td>
</tr>
<tr>
<td>Nicotine Inhaler (prescription)</td>
<td>Intermediate nicotine absorption; nicotine delivery through oral mucosa, full agonist; reduces cravings and withdrawal</td>
<td>6 to 16 cartridges/day</td>
<td>Oropharyngeal irritation, cough</td>
<td>Pregnancy or breastfeeding; history of systemic rash with nicotine replacement therapy; less than 18 years of age; hypersensitivity to menthol</td>
<td>None</td>
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PHARMACOTHERAPY NOT CONTAINING NICOTINE

Bupropion Sustained-Release

Bupropion sustained-release is the first non-nicotine prescription drug to be Food and Drug Administration (FDA) approved as a first-line agent for tobacco dependence (6). Bupropion mediates its effect on the brain’s reward centers through norepinephrine and dopamine reuptake inhibition, as well as through competitive inhibition on nAChRs (12). A network meta-analysis showed that bupropion significantly increased the odds of quitting as monotherapy (odds ratio=1.82; 95% CI=1.60–2.06) and demonstrated comparable efficacy with nicotine replacement therapy (13). There was no significant difference in abstinence based on gender or dosing bupropion at 150 mg or 300 mg (relative risk=1.08, 95% CI=0.93–1.26) (14). Bupropion has been shown to decrease withdrawal symptoms, cigarette craving, and improve mood during smoking cessation (15). Additionally, bupropion has benefits in limiting postcessation weight gain at the end of treatment (mean weight loss=–1.12 kg; 95% CI=–1.47 to –0.77 kg), although results beyond 6 months did not demonstrate persistence of effect (16). Bupropion was found to be safe and effective in smoking cessation in patients with schizophrenia (17). The “target quit date” is typically set on the eighth day of bupropion treatment when the bupropion level reaches a steady-state concentration.

Common side effects include insomnia and dry mouth (14). Bupropion should be used with caution in patients with liver disease or renal impairment and is contraindicated in those with a history of seizure, eating disorders, or head trauma with loss of consciousness or those using medications that lower seizure threshold (6). Bupropion was associated with a seizure rate of 1:1500 but had no excess neuropsychiatric or cardiovascular events compared with placebo across all trials (13).

<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>Bupropion sustained-release</td>
<td>Norepinephrine and dopamine reuptake inhibition; competitive inhibition of nAChR; reduces nicotine craving; withdrawal, and reinforcement</td>
<td>150 mg twice daily</td>
<td>Insomnia, dry mouth</td>
<td>Liver disease, renal impairments; seizure disorder in personal and/or family history or with concomitant medications that lower seizure threshold; eating disorders; head trauma with loss of consciousness; pregnancy or breast feeding; less than 18 years of age; taking medications for Parkinson’s disease; history of depressive disorders, bipolar disorders, or schizophrenia; prior adverse reaction with bupropion</td>
<td>Increase risk of seizure with tramadol; can increase tricyclic antidepressant levels Can be fatal with monoamine oxidase inhibitors via CYP 2D6 inhibition; can interfere with analgesic actions of codeine; can increase plasma levels of some beta-blockers and atomoxetine; can increase concentrations of thioridazine and cause cardiac arrhythmias</td>
</tr>
<tr>
<td>Varenicline</td>
<td>Partial agonist at α4β2 nAChR; mitigates nicotine craving; withdrawal, and reinforcement</td>
<td>Dose titrated to 1 mg twice daily</td>
<td>Mild nausea, insomnia, nightmares, constipation, possible neuropsychiatric changes (behavioral changes, depressed mood, self-injurious thoughts or behaviors, “boxed warning”); cardiovascular side effects, decreased tolerance to alcohol; rare risk of seizure</td>
<td>Pregnancy or breast feeding; less than 18 years of age; history of depressive disorders, bipolar disorders, or schizophrenia; prior adverse reaction with varenicline</td>
<td>Does not inhibit hepatic enzymes or renal transport proteins; is not hepatically metabolized—unlikely to be affected by other drugs</td>
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TABLE 2. Pharmacotherapies for Tobacco Dependence Not Approved by the Food and Drug Administration

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Study Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine</td>
<td>Alpha2-adrenergic receptor agonist</td>
<td>Small benefit for smoking cessation</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Tricyclic antidepressant</td>
<td>Demonstrated efficacy for long-term abstinence (&gt;6 months) but no statistical-</td>
</tr>
<tr>
<td>Cytisine</td>
<td>Nicotine receptor partial agonist</td>
<td>ly significant benefits in adding nortriptyline to nicotine replacement therapy.</td>
</tr>
<tr>
<td>Mecamylamine</td>
<td>Ganglionic blocker and noncompetitive antagonist of a4b2 nAChRs</td>
<td>Nicotine patch in combination with transdermal mecamylamine patch or placebo.</td>
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* For further details, see Elrashidi and Ebbert (25).
At the time this article was accepted for publication, Dr. Sinha was a fellow in addictive disorders at the Mayo Clinic, Rochester, Minn. Dr. Shah is a child and adolescent psychiatry fellow at the Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, Tex.

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REFERENCES