

Treatment Guidelines

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Tobacco dependence is a chronic illness that may require pharmacological treatment (MC Fiore et al, *JAMA* 2000; 283:3244; DPL Sachs in JE Hodgkin et al, eds, *Pulmonary Rehabilitation: Guidelines to Success*, 3rd ed, Philadelphia; Lippincott Williams & Wilkins, 2000, page 261).

NICOTINE-RECEPTOR AGONISTS — All of the nicotine-delivery systems listed in the table on page 66 deliver the drug to the CNS in a lower dose and at a substantially slower rate than tobacco cigarettes. All of these products roughly double smoking cessation rates (C Silagy et al, *Cochrane Database Syst Rev* 2002; 4:CD000146). Nicotine gum, lozenges and patches are available without a prescription. These non-prescription products appear to be as effective as those that require a prescription (P Hajek et al, *Arch Intern Med* 1999; 159:2033; JR Hughes et al, *Tob Control* 2003; 12:21).

Transdermal nicotine – Nicotine patches deliver nicotine to the CNS more slowly than any other nicotine delivery system, taking 6-8 hours to reach peak serum levels. Patches from different manufacturers have somewhat different pharmacokinetic profiles; in one study comparing two 21-mg, 24-hour patches, one produced higher peak serum concentrations in a shorter time and had a larger AUC (RV Fant et al, *Pharmacol Biochem Behav* 2000; 67:479). Higher doses of transdermal nicotine appear to be more effective than lower doses (Transdermal Nicotine Study Group, *JAMA* 1991;

266:3133; JR Hughes et al, *Nicotine Tob Res* 1999; 1:169).

Oral Nicotine – Nicotine polacrilex gum, nicotine polacrilex lozenges and the nicotine oral inhaler are intermediate in CNS delivery speed; serum nicotine levels reach a peak in 20-30 minutes. The nicotine lozenge, although available in 2- and 4-mg doses like the gum, actually provides more nicotine because the lozenge dissolves completely, delivering the entire dose (S Shiffman et al, *Arch Intern Med* 2002; 162:1267). If nicotine from gum or lozenges is swallowed, first-pass metabolism decreases its bioavailability.

Nicotine Nasal Spray – By far the fastest of all nicotine formulations (but still much slower than cigarettes), nicotine nasal spray delivers a peak level to the CNS in 5 minutes. Patients using the nasal spray notice faster relief of nicotine withdrawal symptoms than with other nicotine delivery systems. Dependence and prolonged use of the nasal spray have been reported (NG Schneider et al, *Clin Pharmacokinet* 1996; 31:65). Used with a nicotine patch to provide a steady-state plasma level, the nasal spray can be helpful for sudden urges or crises. In a 6-year, randomized, double-blind, placebo-controlled study, combination use of the nicotine patch for 5 months with the nasal spray *ad libitum* for 1 year increased smoking cessation rates after 1 year, compared to the nicotine patch used alone (27% vs. 11%). Five years later the rates were 16% vs. 9% (T Blondal et al, *BMJ* 1999; 318:285).

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Drugs for Tobacco Dependence

Drug	Preparations	Daily adult maintenance	Cost ¹	Frequent adverse effects	FDA Approved ²
NICOTINIC-RECEPTOR AGONISTS					
Nicotine oral inhaler <i>Nicotrol Inhaler</i> (Pharmacia)	4-mg cartridges	6-16 cartridges	\$163.20	Mouth and throat irritation; cough; rhinitis	Yes
Nicotine nasal spray <i>Nicotrol NS</i> (Pharmacia)	0.5 mg/spray; 1 dose = 2 sprays	8-40 mg in 8-40 doses	102.00	Burning and stinging of the nasal mucosa; minor throat irritation; cough; sneeze; increased lacrimation; rhinorrhea; nausea	Yes
Nicotine polacrilex gum ³ generic price	2 mg/piece ⁴ 4 mg/piece ⁴	8-24 pieces 8-24 pieces	89.04 100.20	Indigestion; nausea; flatulence; unpleasant taste; hiccups; sore mouth; sore throat; sore jaw	Yes
<i>Nicorette</i> (GlaxoSmithKline)			139.95 ⁵ 149.95 ⁵		Yes
Nicotine polacrilex lozenge ³ <i>Commit</i> (GlaxoSmithKline)	2 mg/lozenge ⁶ 4 mg/lozenge ⁶	9-20 lozenges 9-20 lozenges	149.96 ⁵ 149.96 ⁵	Heartburn; hiccup; nausea; headache	Yes
Nicotine transdermal ³ generic price	21 mg/24 hr patch ⁷ 14 mg/24 hr patch ⁷ 7 mg/24 hr patch ⁷	1 patch	198.58 188.72 188.37	Pruritus at patch site; insomnia; vivid dreams; ~2.5% incidence of cutaneous hypersensitivity reaction	Yes
<i>NicoDerm CQ</i> (GlaxoSmithKline)	21 mg/24 hr patch ⁷ 14 mg/24 hr patch ⁷ 7 mg/24 hr patch ⁷		102.84 ⁵ 102.84 ⁵ 102.84 ⁵		Yes
<i>Nicotrol</i> (Pharmacia)	15 mg/16 hr patch ⁸ 10 mg/16 hr patch ⁸ 5 mg/16 hr patch ⁸		107.12 ⁵ 107.12 ⁵ 107.12 ⁵		Yes
DOPAMINERGIC-NORADRENERGIC RE-UPTAKE INHIBITORS					
Bupropion <i>Wellbutrin SR</i> (GlaxoSmithKline)	100-mg tablet sustained-release 150-mg tablet sustained-release	150-300 mg in 1-2 doses	— 57.93	Insomnia; dry mouth; headache; anxiety; constipation; dizziness; seizure rate ≤1/1000	No
<i>Zyban</i> (GlaxoSmithKline)	150-mg tablet sustained-release		57.93		Yes
ALPHA₂-ADRENERGIC AGONISTS					
Clonidine – generic price	0.1-mg tablet 0.2-mg tablet 0.3-mg tablet	0.1-0.3 mg in 2-3 doses	6.48 4.76 4.66	Dry mouth; decreased heart rate; decreased systolic blood pressure; decreased diastolic blood pressure; drowsiness; dizziness; postural hypotension; nausea; vomiting	No
<i>Catapres</i> (Boehringer Ingelheim)	0.1-mg tablet 0.2-mg tablet 0.3-mg tablet		26.16 20.01 16.74		No
<i>Catapres-TTS</i> (Boehringer Ingelheim)	0.1-mg patch 0.2-mg patch 0.3-mg patch	1 patch/week	51.38 86.50 120.00	<u>With transdermal only</u> - Pruritis; erythema; edema; vesicles; blisters at application site	No
NORADRENERGIC-SEROTONERGIC RE-UPTAKE INHIBITOR					
Nortriptyline – generic price	25-mg tablet 75-mg tablet	75-100 mg in 3-4 doses	77.49 74.19	Rash; weight gain; xerostomia; tremor; constipation; blurred vision; impotence; decreased libido; urinary retention; tachycardia; can be fatal in overdose	No
<i>Aventyl</i> (Eli Lilly)	25-mg tablet		94.54		No
<i>Pamelor</i> (Novartis)	25-mg tablet 75-mg tablet		170.62 163.37		No
<ol style="list-style-type: none"> 1. Cost for 30 days' treatment at the lowest dosage, according to AWP listings in <i>Drug Topics Red Book 2002</i> and <i>May 2003 Update</i>. 2. For treatment of tobacco dependence. 3. Available without a prescription. 4. Use the 2-mg strength if <25 cigarettes are smoked per day; 4-mg strength if >25 cigarettes per day. 5. Cost for 30 days' treatment at the lowest dosage, according to drugstore.com, May 5, 2003. 6. Use the 2-mg strength if first cigarette is smoked >30 minutes after waking; 4-mg strength if within 30 minutes after waking. 7. Begin with the 21-mg strength if >10 cigarettes are smoked per day; 14-mg strength if <10 cigarettes per day; 7-mg strength used for tapering. 8. Start with the 15-mg strength, then taper to 10 mg and 5 mg. 					

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Cardiac Safety – Most studies of the cardiac safety of nicotine replacement therapy have been with nicotine patches. Transdermal nicotine does not activate clotting, increase thrombogenesis or cause myocardial infarction (NL Benowitz and SG Gourlay, *J Am Coll Cardiol* 1997; 29:1422). A randomized, double-blind, placebo-controlled trial in more than 500 patients with high-risk cardiac disease found that transdermal nicotine, even with continued cigarette use, did not increase the incidence of death, myocardial infarction or arrhythmia (AM Joseph et al, *N Engl J Med* 1996; 335:1792). One study found that patients with known coronary artery disease showed improvement in exercise-induced myocardial ischemia with transdermal nicotine, even when they continued to smoke (JJ Mahmarian et al, *J Am Coll Cardiol* 1997; 30:125).

Use in Pregnancy – Nicotine is classified by the FDA as a pregnancy category D drug, which implies substantial risk to the fetus. However, taking nicotine during pregnancy is probably safer than smoking, which increases the incidence of low birth weight deliveries, and pregnant women are often highly motivated to stop smoking. One randomized trial in 250 pregnant smokers found that mean birth weight was 186g higher among patients who used a nicotine patch during pregnancy (K Wisborg et al, *Obstet Gynecol* 2000; 96:967).

Adverse Effects – **Transdermal** nicotine is generally well tolerated but some patients discontinue therapy because of pruritus at the patch site, insomnia or vivid dreams. Patients who experience skin irritation with one brand of nicotine patch may be able to tolerate a different brand. Instructing the patient to remove the patch at bedtime usually minimizes or eliminates vivid dreams and other sleep disturbances. Nicotine **nasal spray** causes transient burning and stinging of the nasal mucosa, throat irritation, coughing, sneezing, lacrimation, rhinorrhea and nausea, usually lasting only a few seconds, and diminishing after about a week. The nicotine **oral inhaler** may cause minor mouth and throat irritation and cough; tolerance to the irritating effects usually occurs within a day or two. Nicotine **gum** can cause flatulence, indigestion, nausea, unpleasant taste, hiccups and a sore mouth, throat and jaw. A small percentage of patients may become dependent on the gum and continue to use it. Nicotine **lozenges** may cause heartburn, hiccup and nausea due to swallowed nicotine.

DOPAMINERGIC-NORADRENERGIC RE-UPTAKE INHIBITORS — Bupropion is the only drug available in this class and the only non-nicotine drug approved by the FDA for smoking cessation. The FDA has only approved bupropion SR marketed as *Zyban* for this indication; it is also marketed for depression as *Wellbutrin SR*. Immediate-release bupropion available both as a generic and as *Wellbutrin* has also

been effective for smoking cessation (LH Ferry et al, *Circulation* 1992; 86:1671; LH Ferry et al, *J Addict Dis* 1994; 13:9A). Bupropion should be started 7-14 days before stopping smoking to allow for adequate CNS steady-state levels. Typically, patients start with 150 mg each morning for three days, then increase to 150 mg b.i.d.

Effectiveness – The effectiveness of bupropion for smoking cessation is not affected by the presence or absence of co-morbid depression. In a randomized, double-blind trial in 615 smokers, smoking cessation rates at the end of 7 weeks were 44% with bupropion SR 300 mg, 39% with 150 mg, 29% with 100 mg, and 19% with placebo. One year later, cessation rates were 23% (300 mg), 23% (150 mg), 20% (100 mg), and 12% with placebo (RD Hurt et al, *N Engl J Med* 1997; 337:1195).

In a randomized, double-blind trial in 893 smokers using 300 mg of bupropion SR and/or transdermal nicotine, 21 mg/24 hours, nonsmoking rates after 4 weeks were 67% (bupropion + nicotine), 60% (bupropion alone), 48% (nicotine alone) and 34% with placebo. Abstinence rates at 12 months were 36% (combination), 30% (bupropion), 16% (patch) and 16% (placebo) (DE Jorenby et al, *N Engl J Med* 1999; 340:685).

A study in a lower socioeconomic group found that among 600 patients randomized to a 7-week course of bupropion SR 150 mg b.i.d. or placebo, active treatment nearly doubled the end-of-treatment nonsmoking rate (36% vs. 19%) and increased the rate after 4½ months off treatment (21% vs. 14%) (JS Ahluwalia et al, *JAMA* 2002; 288:468).

Adverse Effects – Bupropion is thought to increase the risk of seizures, but the slow-release form has a lower risk. *Wellbutrin SR* has been associated with a seizure incidence of 0.1%. Among more than 2,000 patients who took the drug in clinical trials for smoking cessation, there were no seizures, but these patients were screened for seizure risk before enrollment in the study. Patients with a history of seizure, stroke, brain tumor, brain surgery or serious closed head injury should not receive bupropion. The risk of seizures may also be increased with bupropion use in patients with anorexia-bulimia. The most common adverse effects in clinical trials were insomnia (35% with the 300-mg bupropion dose vs. 21% with placebo) and dry mouth (13% vs. 5%). Other commonly reported effects included headache, nausea and anxiety (JT Hays and JO Ebbert, *CNS Drugs* 2003; 17:71).

ALPHA₂-ADRENERGIC AGONISTS — Although not approved for this indication by the FDA, the anti-hypertensive drug clonidine, available both as tablets (*Catapres*, and others) and in a patch formulation (*Catapres TTS*), has been used as a second-line treatment

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for patients who cannot tolerate or refuse to use nicotine or bupropion. Clinical trial data have been mixed, but a meta-analysis concluded that clonidine was effective ([LS Covey and AH Glassman, Br J Addict 1991; 86:991](#)). Dosages for tobacco dependence treatment are similar to those used for treatment of hypertension; the starting dose should be 0.1 mg per day, increasing slowly to the highest tolerated dose, usually about 0.3 mg per day. The main adverse effects are dry mouth, sedation, dizziness and hypotension. The transdermal formulation has caused local reactions at the application site.

NORADRENERGIC-SEROTONERGIC RE-UPTAKE INHIBITORS — The tricyclic antidepressant nortriptyline (*Pamelor*, and others) has improved smoking cessation rates compared to placebo ([AV Prochazka et al, Arch Intern Med 1998; 158:2035](#); [CL da Costa et al, Chest 2002; 122:403](#)). As with bupropion, the effectiveness of nortriptyline for this indication appears to be unrelated to its antidepressant effect. Adverse effects, similar to those seen when nortriptyline is used for treatment of depression, include sedation, dry mouth, blurred vision, urinary retention, lightheadedness and tremor. Therapy must be started 10-28 days before stopping smoking to allow nortriptyline to reach steady-state levels in the CNS. Dosage generally should be started at 25 mg per day, and increased slowly to a maximum of 75-100 mg per day.

COMBINATIONS — Any combination of bupropion SR and nicotine drugs can be used. Two different nicotine preparations used together have been more effective and as safe as any single drug ([M Kornitzer et al, Prev Med 1995; 24:41](#); [P Puska et al, Tob Control 1995; 4:231](#); [CT Sweeney et al, CNS Drugs 2001; 15:453](#)).

DURATION OF USE — Only one randomized, double-blind, placebo-controlled trial has evaluated two different treatment durations, and only for transdermal nicotine; in this study, 22 weeks was no more effective than 8 weeks ([P Tønnesen et al, Eur Respir J 1999;](#)

[13:238](#)). Most Medical Letter consultants believe, nevertheless, that patients who want to stop smoking should receive at least 3 to 6 months of nicotine, bupropion or both. Generally, the dosage of nicotine is gradually reduced at the end of treatment. Bupropion SR can simply be discontinued.

COUNSELING — The effectiveness of all of these drugs is enhanced by counseling. The longer the physician counseling time and the greater the number of office visits, the better the smoking abstinence rates.

DRUG INTERACTIONS — Tobacco smoke, which includes more than just nicotine, increases the metabolism and can decrease the effect of many drugs (*The Medical Letter Handbook of Adverse Drug Interactions* 2003, page 497). Doses of these drugs may need to be lowered when patients stop smoking, even though they are taking nicotine.

CONCLUSION — Use of a nicotine patch, inhaler, nasal spray, gum or lozenge, or bupropion SR, either alone or in combination, can help patients stop smoking. All of these drugs are about equally effective and generally well tolerated. Nicotine patches have the best compliance record and can be removed at night to prevent insomnia; their disadvantage is that they cannot be used for emergency relief of withdrawal symptoms. Some patients benefit from the combination of a patch with oral nicotine or the nicotine nasal spray. Use of more than one nicotine product at the same time has been safe. The optimum duration of treatment is not clear; 3-6 months is probably the minimum, and many patients need 12 months or longer.

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