

## STEP One: ASK about Tobacco Use

### ➤ Suggested Dialogue

- ✓ Do you ever smoke or use any type of tobacco?
  - I take time to talk with all of my patients about tobacco use—because it's important.
- ✓ Medication X often is used for conditions linked with or caused by smoking. Do you, or does someone in your household smoke?
- ✓ Condition X often is caused or worsened by exposure to tobacco smoke. Do you, or does someone in your household smoke?

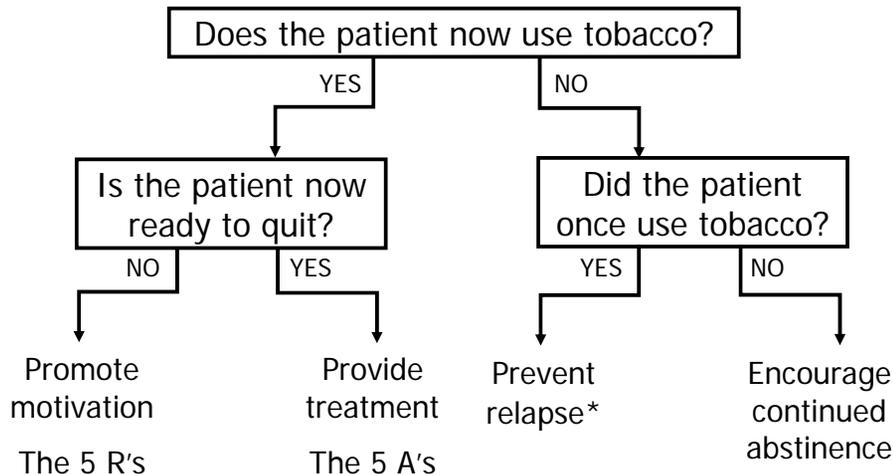
## STEP Two: Strongly ADVISE to Quit

It is important to be sensitive, because patients might be defensive of their smoking. Project empathy in your voice; be understanding, not reprimanding.

### ➤ Suggested Dialogue

- It's important that you quit as soon as possible, and I can help you.
- I realize that quitting is difficult. It is the most important thing you can do to protect your health now and in the future. I have training to help my patients quit, and when you are ready I will work with you to design a specialized treatment plan.

## STEP Three: ASSESS Readiness to Quit



\* Relapse prevention interventions not necessary if patient has not used tobacco for many years and is not at risk for re-initiation.

Fiore MC, Bailey WC, Cohen SJ, et al. *Treating Tobacco Use and Dependence. Clinical Practice Guideline.* Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, 2000.

## STEP Four: ASSIST with Quitting



### ✓ Assess Tobacco Use History

- Current use: type(s) of tobacco used, brand, amount
- Past use:
  - Duration of tobacco use
  - Changes in levels of use recently
- Past quit attempts:
  - Number of attempts, date of most recent attempt, duration
  - Methods used previously—What did or didn't work? Why or why not?
  - Prior medication administration, dose, compliance, duration of treatment
  - Reasons for relapse

### ✓ Discuss Key Issues (for the upcoming or current quit attempt)

- Reasons/motivation for wanting to quit (or avoid relapse)
- Confidence in ability to quit (or avoid relapse)
- Triggers for tobacco use
- Routines and situations associated with tobacco use
- Stress-related tobacco use
- Social support for quitting
- Concerns about weight gain
- Concerns about withdrawal symptoms

### ✓ Facilitate Quitting Process

- Discuss methods for quitting: pros and cons of the different methods
- Set a quit date: more than 2–3 days away but less than 2 weeks away
- Recommend Tobacco Use Log
- Discuss coping strategies (cognitive, behavioral)
- Discuss withdrawal symptoms
- Discuss concept of “slip” versus relapse
- Provide medication counseling: compliance, proper use, with demonstration
- Offer to assist throughout the quit attempt

### ✓ Evaluate the Quit Attempt (at follow-up)

- Status of attempt
- “Slips” and relapse
- Medication compliance and plans for discontinuation

## STEP Five: ARRANGE Follow-up Counseling

- ✓ Monitor patients' progress throughout the quit attempt. Follow-up contact should occur during the first week after quitting. A second follow-up contact is recommended in the first month. Additional contacts should be scheduled as needed. Counseling contacts can occur face-to-face, by telephone, or by e-mail. Keep patient progress notes.
- ✓ Address temptations and triggers; discuss relapse prevention strategies.
- ✓ Congratulate patients for continued success.



## DRUG INTERACTIONS WITH SMOKING

Many interactions between tobacco smoke and medications have been identified. Note that in most cases it is the tobacco smoke—not the nicotine—that causes these drug interactions. Tobacco smoke may interact with medications through pharmacokinetic (PK) or pharmacodynamic (PD) mechanisms. PK interactions affect the absorption, distribution, metabolism, or elimination of other drugs, potentially causing an altered pharmacologic response. The majority of PK interactions with smoking are the result of induction of hepatic cytochrome P450 enzymes (primarily CYP1A2). PD interactions alter the expected response or actions of other drugs. The amount of tobacco smoking needed to have an effect has not been established and the assumption is that any smoker is susceptible to the same degree of interaction. The most clinically significant interactions are depicted in the shaded rows.

DRUG/CLASS	MECHANISM OF INTERACTION AND EFFECTS
<b>Pharmacokinetic Interactions</b>	
Alprazolam (Xanax)	<ul style="list-style-type: none"> <li>Conflicting data on significance of a PK interaction. Possible ↓ plasma concentrations (up to 50%); ↓ half-life (35%).</li> </ul>
Caffeine	<ul style="list-style-type: none"> <li>↑ Metabolism (induction of CYP1A2); ↑ clearance (56%).</li> <li>Likely ↑ caffeine levels after cessation.</li> </ul>
Chlorpromazine (Thorazine)	<ul style="list-style-type: none"> <li>↓ Area under the curve (AUC) (36%) and serum concentrations (24%).</li> <li>↓ Sedation and hypotension possible in smokers; smokers may need ↑ dosages.</li> </ul>
Clozapine (Clozaril)	<ul style="list-style-type: none"> <li>↑ Metabolism (induction of CYP1A2); ↓ plasma concentrations (18%).</li> </ul>
Flecainide (Tambocor)	<ul style="list-style-type: none"> <li>↑ Clearance (61%); ↓ trough serum concentrations (25%).</li> <li>Smokers may need ↑ dosages.</li> </ul>
Fluvoxamine (Luvox)	<ul style="list-style-type: none"> <li>↑ Metabolism (induction of CYP1A2); ↑ clearance (24%); ↓ AUC (31%); ↓ plasma concentrations (32%).</li> <li>Dosage modifications not routinely recommended but smokers may need ↑ dosages.</li> </ul>
Haloperidol (Haldol)	<ul style="list-style-type: none"> <li>↑ Clearance (44%); ↓ serum concentrations (70%).</li> </ul>
Heparin	<ul style="list-style-type: none"> <li>Mechanism unknown but ↑ clearance and ↓ half-life are observed. Smoking has prothrombotic effects.</li> <li>Smokers may need ↑ dosages due to PK and PD interactions.</li> </ul>
Insulin, subcutaneous	<ul style="list-style-type: none"> <li>Possible ↓ insulin absorption secondary to peripheral vasoconstriction; smoking may cause release of endogenous substances that cause insulin resistance.</li> <li>PK &amp; PD interactions likely not clinically significant; smokers may need ↑ dosages.</li> </ul>
Insulin, inhaled (Exubera)	<ul style="list-style-type: none"> <li>Systemic exposure is greatly increased in smokers; greater maximal insulin concentrations (3–5 fold) and faster (by 20–30 minutes); ↑AUC 2–3 fold</li> <li>Contraindicated in smokers and those who have discontinued smoking for less than 6 months.</li> </ul>
Mexiletine (Mexitol)	<ul style="list-style-type: none"> <li>↑ Clearance (25%; via oxidation and glucuronidation); ↓ half-life (36%).</li> </ul>
Olanzapine (Zyprexa)	<ul style="list-style-type: none"> <li>↑ Metabolism (induction of CYP1A2); ↑ clearance (98%); ↓ serum concentrations (12%).</li> <li>Dosage modifications not routinely recommended but smokers may require ↑ dosages.</li> </ul>
Propranolol (Inderal)	<ul style="list-style-type: none"> <li>↑ Clearance (77%; via side chain oxidation and glucuronidation)</li> </ul>
Tacrine (Cognex)	<ul style="list-style-type: none"> <li>↑ Metabolism (induction of CYP1A2); ↓ half-life (50%); serum concentrations three-fold lower.</li> <li>Smokers may need ↑ dosages.</li> </ul>
Theophylline (Theo Dur, etc.)	<ul style="list-style-type: none"> <li>↑ Metabolism (induction of CYP1A2); ↑ clearance (58–100%); ↓ half-life (63%).</li> <li>Levels should be monitored if smoking is initiated, discontinued, or changed.</li> <li>↑ Clearance with second-hand smoke exposure.</li> <li>Maintenance doses are considerably higher in smokers.</li> </ul>
Tricyclic antidepressants (e.g., imipramine, nortriptyline)	<ul style="list-style-type: none"> <li>Possible interaction with tricyclic antidepressants in the direction of ↓ blood levels, but the clinical importance is not established.</li> </ul>
<b>Pharmacodynamic Interactions</b>	
Benzodiazepines (diazepam, chlordiazepoxide)	<ul style="list-style-type: none"> <li>↓ Sedation and drowsiness, possibly caused by nicotine stimulation of central nervous system.</li> </ul>
Beta-blockers	<ul style="list-style-type: none"> <li>Less effective antihypertensive and heart rate control effects; might be caused by nicotine-mediated sympathetic activation.</li> <li>Smokers may need ↑ dosages.</li> </ul>
Corticosteroids, inhaled	<ul style="list-style-type: none"> <li>Asthmatic smokers may have less of a response to inhaled corticosteroids.</li> </ul>
Hormonal contraceptives	<ul style="list-style-type: none"> <li>↑ Risk of cardiovascular adverse effects (e.g., stroke, myocardial infarction, thromboembolism) in women who smoke and use oral contraceptives.</li> <li>↑ Risk with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women age 35 and older.</li> </ul>
Opioids (propoxyphene, pentazocine)	<ul style="list-style-type: none"> <li>↓ Analgesic effect; smoking may ↑ the metabolism of propoxyphene (15–20%) and pentazocine (40%). Mechanism unknown.</li> <li>Smokers may need ↑ opioid dosages for pain relief.</li> </ul>

Adapted from Zevin S, Benowitz NL. Drug interactions with tobacco smoking. *Clin Pharmacokinet* 1999;36:425–438.



# PHARMACOLOGIC PRODUCT GUIDE: FDA-APPROVED MEDICATIONS

NICOTINE REPLACEMENT THERAPY (NRT) FORMULATIONS						BUPROPION SR	VARENICLINE	
GUM		LOZENGE	TRANSDERMAL PREPARATIONS <sup>1</sup>		NASAL SPRAY			ORAL INHALER
PRODUCT	Nicorette <sup>2</sup> , Generic OTC 2 mg, 4 mg; original, FreshMint <sup>2</sup> , Fruit Chill <sup>2</sup> mint, orange <sup>2</sup>	Commit <sup>2</sup> , Generic OTC 2 mg, 4 mg mint	Nicoderm CQ <sup>2</sup> OTC 24-hour release 7 mg, 14 mg, 21 mg	Generic Patch OTC/Rx (formerly Habitrol) 24-hour release 7 mg, 14 mg, 21 mg	Nicotrol NS <sup>3</sup> Rx Metered spray 0.5 mg nicotine in 50 µL aqueous nicotine solution	Nicotrol Inhaler <sup>3</sup> Rx 10 mg cartridge delivers 4 mg inhaled nicotine vapor	Zyban <sup>2</sup> , Generic Rx 150 mg sustained-release tablet	Chantix <sup>3</sup> Rx 0.5 mg, 1 mg tablet
PRECAUTIONS	<ul style="list-style-type: none"> <li>▪ Pregnancy (Category D)</li> <li>▪ Recent (≤ 2 weeks) myocardial infarction</li> <li>▪ Serious underlying arrhythmias</li> <li>▪ Serious or worsening angina pectoris</li> <li>▪ Temporomandibular joint disease</li> </ul>	<ul style="list-style-type: none"> <li>▪ Pregnancy (Category D)</li> <li>▪ Recent (≤ 2 weeks) myocardial infarction</li> <li>▪ Serious underlying arrhythmias</li> <li>▪ Serious or worsening angina pectoris</li> </ul>	<ul style="list-style-type: none"> <li>▪ Pregnancy (Category D)</li> <li>▪ Recent (≤ 2 weeks) myocardial infarction</li> <li>▪ Serious underlying arrhythmias</li> <li>▪ Serious or worsening angina pectoris</li> </ul>	<ul style="list-style-type: none"> <li>▪ Pregnancy (Category D)</li> <li>▪ Recent (≤ 2 weeks) myocardial infarction</li> <li>▪ Serious underlying arrhythmias</li> <li>▪ Serious or worsening angina pectoris</li> <li>▪ Underlying chronic nasal disorders (rhinitis, nasal polyps, sinusitis)</li> <li>▪ Severe reactive airway disease</li> </ul>	<ul style="list-style-type: none"> <li>▪ Pregnancy (Category D)</li> <li>▪ Recent (≤ 2 weeks) myocardial infarction</li> <li>▪ Serious underlying arrhythmias</li> <li>▪ Serious or worsening angina pectoris</li> <li>▪ Bronchospastic disease</li> </ul>	<ul style="list-style-type: none"> <li>▪ Pregnancy (Category C)</li> <li>▪ Concomitant therapy with medications or medical conditions known to lower the seizure threshold</li> <li>▪ Severe hepatic cirrhosis</li> </ul> <p><b>Contraindications:</b></p> <ul style="list-style-type: none"> <li>▪ Seizure disorder</li> <li>▪ Concomitant bupropion (e.g., Wellbutrin) therapy</li> <li>▪ Current or prior diagnosis of bulimia or anorexia nervosa</li> <li>▪ Simultaneous abrupt discontinuation of alcohol or sedatives (including benzodiazepines)</li> <li>▪ MAO inhibitor therapy in previous 14 days</li> </ul>	<ul style="list-style-type: none"> <li>▪ Pregnancy (Category C)</li> <li>▪ Severe renal impairment (dosage adjustment is necessary)</li> </ul>	
DOSING	<p>≥25 cigarettes/day: 4 mg &lt;25 cigarettes/day: 2 mg</p> <p>Week 1–6: 1 piece q 1–2 hours</p> <p>Week 7–9: 1 piece q 2–4 hours</p> <p>Week 10–12: 1 piece q 4–8 hours</p> <ul style="list-style-type: none"> <li>▪ Maximum, 24 pieces/day</li> <li>▪ Chew each piece slowly</li> <li>▪ Park between cheek and gum when peppery or tingling sensation appears (~15–30 chews)</li> <li>▪ Resume chewing when taste or tingle fades</li> <li>▪ Repeat chew/park steps until most of the nicotine is gone (taste or tingle does not return; generally 30 min)</li> <li>▪ Park in different areas of mouth</li> <li>▪ No food or beverages 15 min before or during use</li> <li>▪ Duration: up to 12 weeks</li> </ul>	<p>1<sup>st</sup> cigarette ≤30 minutes after waking: 4 mg 1<sup>st</sup> cigarette &gt;30 minutes after waking: 2 mg</p> <p>Week 1–6: 1 lozenge q 1–2 hours</p> <p>Week 7–9: 1 lozenge q 2–4 hours</p> <p>Week 10–12: 1 lozenge q 4–8 hours</p> <ul style="list-style-type: none"> <li>▪ Maximum, 20 lozenges/day</li> <li>▪ Allow to dissolve slowly (20–30 minutes)</li> <li>▪ Nicotine release may cause a warm, tingling sensation</li> <li>▪ Do not chew or swallow</li> <li>▪ Occasionally rotate to different areas of the mouth</li> <li>▪ No food or beverages 15 minutes before or during use</li> <li>▪ Duration: up to 12 weeks</li> </ul>	<p>&gt;10 cigarettes/day: 21 mg/day x 6 weeks 14 mg/day x 2 weeks 7 mg/day x 2 weeks</p> <p>≤10 cigarettes/day: 14 mg/day x 6 weeks 7 mg/day x 2 weeks</p> <ul style="list-style-type: none"> <li>▪ May wear patch for 16 hours if patient experiences sleep disturbances (remove at bedtime)</li> <li>▪ Duration: 8–10 weeks</li> </ul>	<p>&gt;10 cigarettes/day: 21 mg/day x 4 weeks 14 mg/day x 2 weeks 7 mg/day x 2 weeks</p> <p>≤10 cigarettes/day: 14 mg/day x 6 weeks 7 mg/day x 2 weeks</p> <ul style="list-style-type: none"> <li>▪ May wear patch for 16 hours if patient experiences sleep disturbances (remove at bedtime)</li> <li>▪ Duration: 8 weeks</li> </ul>	<p>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</p> <ul style="list-style-type: none"> <li>▪ Maximum – 5 doses/hour – 40 doses/day</li> <li>▪ For best results, initially use at least 8 doses/day</li> <li>▪ Patients should not sniff, swallow, or inhale through the nose as the spray is being administered</li> <li>▪ Duration: 3–6 months</li> </ul>	<p>6–16 cartridges/day; individualized dosing</p> <ul style="list-style-type: none"> <li>▪ Initially, use at least 6 cartridges/day</li> <li>▪ Best effects with continuous puffing for 20 minutes</li> <li>▪ Nicotine in cartridge is depleted after 20 minutes of active puffing</li> <li>▪ Patient should inhale into back of throat or puff in short breaths</li> <li>▪ Do NOT inhale into the lungs (like a cigarette) but “puff” as if lighting a pipe</li> <li>▪ Open cartridge retains potency for 24 hours</li> <li>▪ Duration: up to 6 months</li> </ul>	<p>150 mg po q AM x 3 days, then increase to 150 mg po bid</p> <ul style="list-style-type: none"> <li>▪ Do not exceed 300 mg/day</li> <li>▪ Treatment should be initiated while patient is still smoking</li> <li>▪ Set quit date 1–2 weeks after initiation of therapy</li> <li>▪ Allow at least 8 hours between doses</li> <li>▪ Avoid bedtime dosing to minimize insomnia</li> <li>▪ Dose tapering is not necessary</li> <li>▪ Can be used safely with NRT</li> <li>▪ Duration: 7–12 weeks, with maintenance up to 6 months in selected patients</li> </ul>	<p>Days 1–3: 0.5 mg po q AM</p> <p>Days 4–7: 0.5 mg po bid</p> <p>Weeks 2–12: 1 mg po bid</p> <ul style="list-style-type: none"> <li>▪ Patients should begin therapy 1 week prior to quit date</li> <li>▪ Take dose after eating with a full glass of water</li> <li>▪ Dose tapering is not necessary</li> <li>▪ Nausea and insomnia are side effects that are usually temporary</li> <li>▪ Duration: 12 weeks; an additional 12 week course may be used in selected patients</li> </ul>

NICOTINE REPLACEMENT THERAPY (NRT) FORMULATIONS								
	GUM	LOZENGE	TRANSDERMAL PREPARATIONS		NASAL SPRAY	ORAL INHALER	BUPROPION SR	VARENICLINE
			NICODERM CQ	GENERIC PATCH				
ADVERSE EFFECTS	<ul style="list-style-type: none"> <li>▪ Mouth/jaw soreness</li> <li>▪ Hiccups</li> <li>▪ Dyspepsia</li> <li>▪ Hypersalivation</li> <li>▪ Effects associated with incorrect chewing technique: <ul style="list-style-type: none"> <li>– Lightheadedness</li> <li>– Nausea/vomiting</li> <li>– Throat and mouth irritation</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>▪ Nausea</li> <li>▪ Hiccups</li> <li>▪ Cough</li> <li>▪ Heartburn</li> <li>▪ Headache</li> <li>▪ Flatulence</li> <li>▪ Insomnia</li> </ul>	<ul style="list-style-type: none"> <li>▪ Local skin reactions (erythema, pruritus, burning)</li> <li>▪ Headache</li> <li>▪ Sleep disturbances (insomnia) or abnormal/vivid dreams (associated with nocturnal nicotine absorption)</li> </ul>		<ul style="list-style-type: none"> <li>▪ Nasal and/or throat irritation (hot, peppery, or burning sensation)</li> <li>▪ Rhinitis</li> <li>▪ Tearing</li> <li>▪ Sneezing</li> <li>▪ Cough</li> <li>▪ Headache</li> </ul>	<ul style="list-style-type: none"> <li>▪ Mouth and/or throat irritation</li> <li>▪ Unpleasant taste</li> <li>▪ Cough</li> <li>▪ Rhinitis</li> <li>▪ Dyspepsia</li> <li>▪ Hiccups</li> <li>▪ Headache</li> </ul>	<ul style="list-style-type: none"> <li>▪ Insomnia</li> <li>▪ Dry mouth</li> <li>▪ Nervousness/difficulty concentrating</li> <li>▪ Rash</li> <li>▪ Constipation</li> <li>▪ Seizures (risk is 1/1,000 [0.1%])</li> </ul>	<ul style="list-style-type: none"> <li>▪ Nausea</li> <li>▪ Sleep disturbances (insomnia, abnormal dreams)</li> <li>▪ Constipation</li> <li>▪ Flatulence</li> <li>▪ Vomiting</li> </ul>
ADVANTAGES	<ul style="list-style-type: none"> <li>▪ Gum use might satisfy oral cravings</li> <li>▪ Gum use may delay weight gain</li> <li>▪ Patients can titrate therapy to manage withdrawal symptoms</li> </ul>	<ul style="list-style-type: none"> <li>▪ Lozenge use might satisfy oral cravings</li> <li>▪ Patients can titrate therapy to manage withdrawal symptoms</li> </ul>	<ul style="list-style-type: none"> <li>▪ Provides consistent nicotine levels over 24 hours</li> <li>▪ Easy to use and conceal</li> <li>▪ Once-a-day dosing associated with fewer compliance problems</li> </ul>		<ul style="list-style-type: none"> <li>▪ Patients can titrate therapy to manage withdrawal symptoms</li> </ul>	<ul style="list-style-type: none"> <li>▪ Patients can titrate therapy to manage withdrawal symptoms</li> <li>▪ Mimics hand-to-mouth ritual of smoking</li> </ul>	<ul style="list-style-type: none"> <li>▪ Easy to use; oral formulation might be associated with fewer compliance problems</li> <li>▪ Can be used with NRT</li> <li>▪ Might be beneficial in patients with depression</li> </ul>	<ul style="list-style-type: none"> <li>▪ Easy to use; oral formulation might be associated with fewer compliance problems</li> <li>▪ Offers a new mechanism of action for patients who have failed other agents</li> </ul>
DISADVANTAGES	<ul style="list-style-type: none"> <li>▪ Gum chewing may not be socially acceptable</li> <li>▪ Gum is difficult to use with dentures</li> <li>▪ Patients must use proper chewing technique to minimize adverse effects</li> </ul>	<ul style="list-style-type: none"> <li>▪ Gastrointestinal side effects (nausea, hiccups, heartburn) might be bothersome</li> </ul>	<ul style="list-style-type: none"> <li>▪ Patients cannot titrate the dose</li> <li>▪ Allergic reactions to adhesive might occur</li> <li>▪ Patients with dermatologic conditions should not use the patch</li> </ul>		<ul style="list-style-type: none"> <li>▪ Nasal/throat irritation may be bothersome</li> <li>▪ Dependence can result</li> <li>▪ Patients must wait 5 minutes before driving or operating heavy machinery</li> <li>▪ Patients with chronic nasal disorders or severe reactive airway disease should not use the spray</li> </ul>	<ul style="list-style-type: none"> <li>▪ Initial throat or mouth irritation can be bothersome</li> <li>▪ Cartridges should not be stored in very warm conditions or used in very cold conditions</li> <li>▪ Patients with underlying bronchospastic disease must use the inhaler with caution</li> </ul>	<ul style="list-style-type: none"> <li>▪ Seizure risk is increased</li> <li>▪ Several contraindications and precautions preclude use (see PRECAUTIONS, above)</li> </ul>	<ul style="list-style-type: none"> <li>▪ May induce nausea in up to one third of patients</li> <li>▪ Post-marketing surveillance data not yet available</li> </ul>
WEB-SITE	www.nicorette.com	www.commitlozenge.com	www.nicodermcq.com	www.habitrol.com	www.nicotrol.com	www.nicotrol.com	---	www.chantix.com
COST/DAY <sup>4</sup>	2 mg: \$2.53–\$5.16 (9 pieces) 4 mg: \$3.18–\$5.81 (9 pieces)	2 mg: \$4.98 (9 pieces) 4 mg: \$5.31 (9 pieces)	\$3.39–\$3.93 (1 patch)	\$2.10–\$2.94 (1 patch)	\$3.67 (8 doses)	\$5.25–\$6.07 (6 cartridges)	\$3.62–\$5.24 (2 tablets)	\$4.00–\$4.22 (2 tablets)

<sup>1</sup> Transdermal patch formulations previously marketed, but no longer available: Nicotrol 5 mg, 10 mg, 15 mg delivered over 16 hours (Pfizer) and generic patch (formerly Prostep) 11 mg and 22 mg delivered over 24 hours.

<sup>2</sup> Marketed by GlaxoSmithKline.

<sup>3</sup> Marketed by Pfizer.

<sup>4</sup> Average wholesale price from 2006 Drug Topics Redbook. Montvale, NJ: Medical Economics Company, Inc., August 2006.

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

**For complete prescribing information, please refer to the manufacturers' package inserts.**

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