MEDICATIONS for CESSATION

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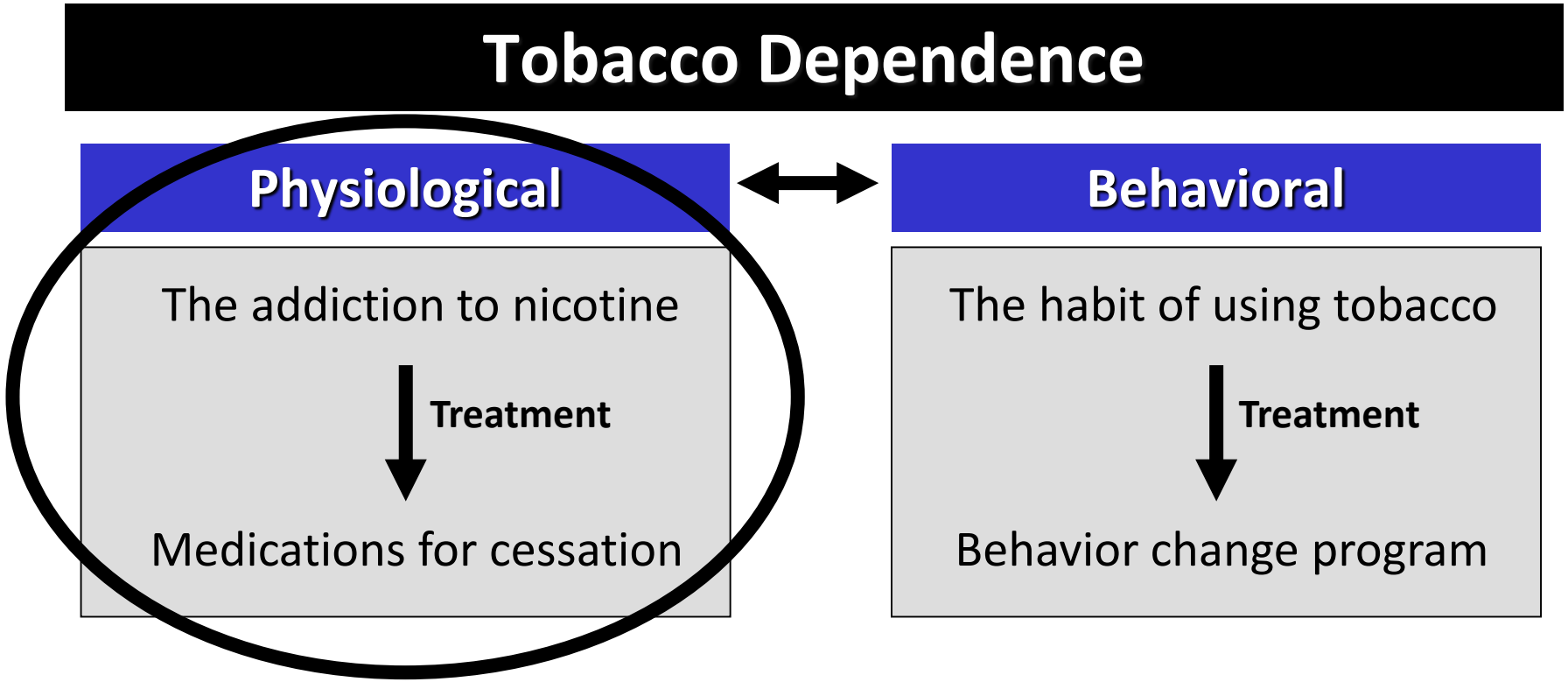
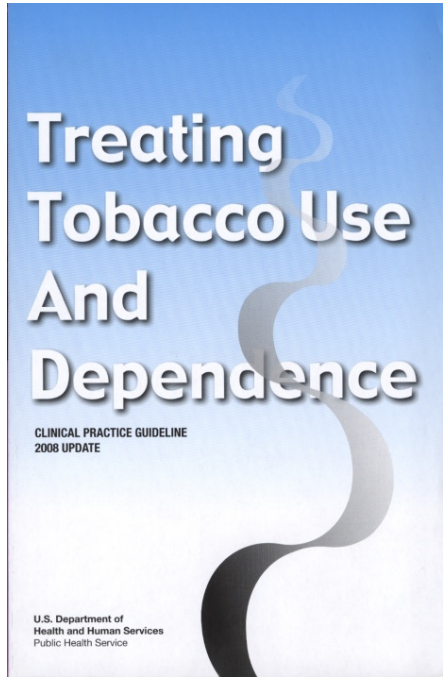
TOBACCO DEPENDENCE: A 2-PART PROBLEM



Treatment should address the physiological **and** the behavioral aspects of dependence.

PHARMACOTHERAPY

"Clinicians should encourage all patients attempting to quit to use effective medications for tobacco dependence treatment, except where contraindicated or for specific populations* for which there is insufficient evidence of effectiveness."



** Includes pregnant women, smokeless tobacco users, light smokers, and adolescents.*

Medications significantly improve success rates.

Fiore et al. (2008). *Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline.* Rockville, MD: USDHHS, PHS, May 2008.

PHARMACOTHERAPY: Use in SPECIAL POPULATIONS

Pharmacotherapy is **not** recommended for:

- Pregnant smokers
  - Insufficient evidence of effectiveness
- Smokeless tobacco users
  - No FDA indication for smokeless tobacco cessation
- Individuals smoking fewer than 10 cigarettes per day
- Adolescents
  - Nonprescription sales of nicotine replacement therapy (NRT) products (i.e., patch, gum, lozenge) are restricted to adults ≥18 years of age
  - NRT use in minors requires a prescription

Recommended treatment is behavioral counseling.

FDA-APPROVED MEDICATIONS for CESSATION

Nicotine polacrilex gum*

- Nicorette (OTC)
- Generic nicotine gum (OTC)

Nicotine lozenge*

- Nicorette (OTC)
- Generic nicotine lozenge (OTC)

Nicotine transdermal patch*

- Habitrol (OTC)
- NicoDerm CQ (OTC)
- Generic nicotine patches (OTC)

Nicotine inhaler *

- Nicotrol (Rx)

Nicotine nasal spray *

- Nicotrol NS (Rx)

Bupropion SR

- Generic (Rx)

Varenicline

- Chantix (Rx)

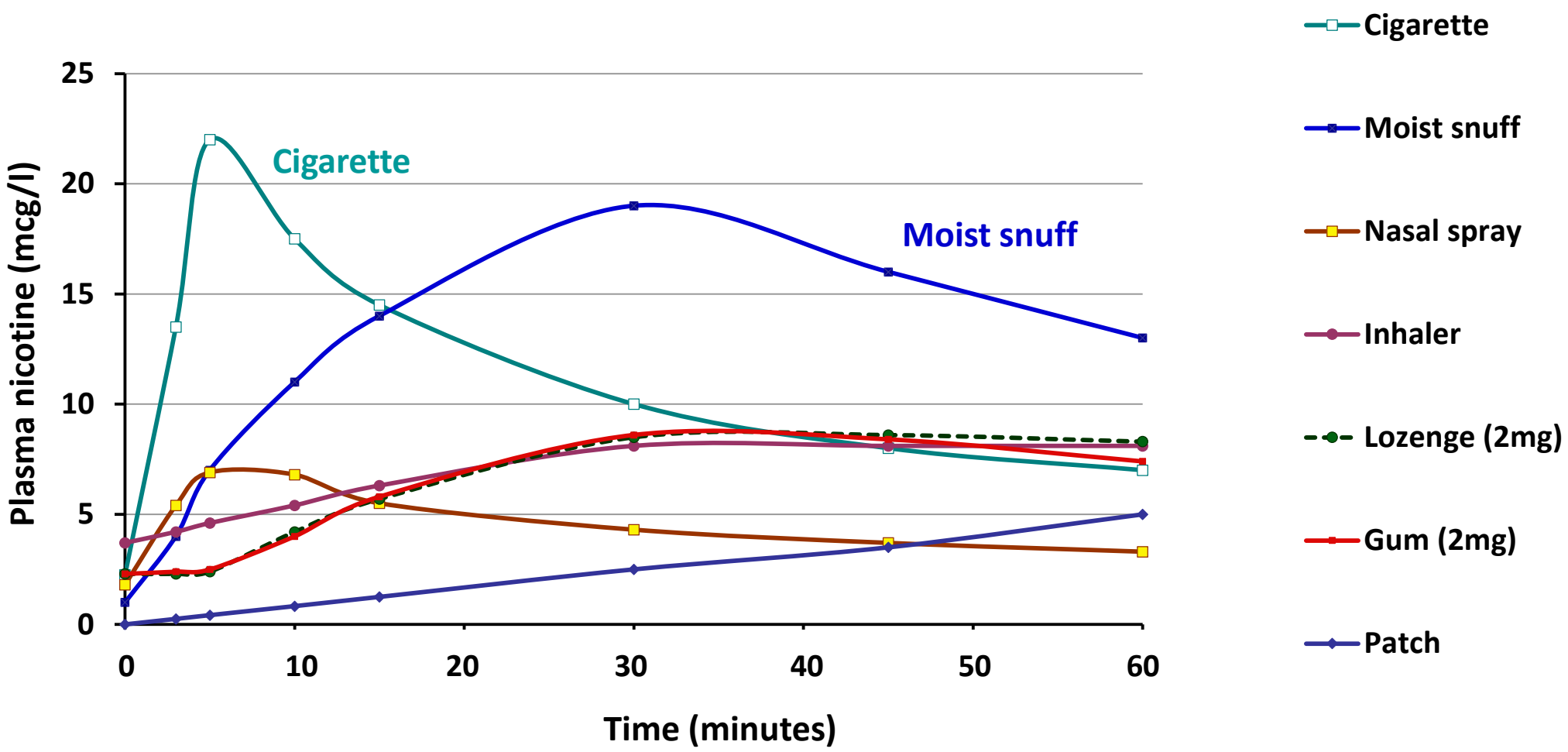
* Nicotine replacement therapy (NRT) products.

NICOTINE REPLACEMENT THERAPY (NRT) RATIONALE for USE

- Reduces physical withdrawal from nicotine
- Eliminates the immediate, reinforcing effects of nicotine that is rapidly absorbed via tobacco smoke
- Allows patient to focus on behavioral and psychological aspects of tobacco cessation

NRT products approximately doubles quit rates.

PLASMA NICOTINE CONCENTRATIONS for NICOTINE-CONTAINING PRODUCTS



NRT: PRECAUTIONS

- Patients with underlying cardiovascular disease
  - Recent myocardial infarction (within past 2 weeks)
  - Serious arrhythmias
  - Serious or worsening angina

NRT products may be appropriate for these patients if they are under medical supervision.

NICOTINE GUM
Nicorette; generics

- Resin complex
  - Nicotine
  - Polacrilin
- Sugar-free chewing gum base

- Contains buffering agents to enhance buccal absorption of nicotine
- Available: 2 mg, 4 mg; original, cinnamon, fruit, and mint (various) flavors

NICOTINE LOZENGE

Nicorette Lozenge, Nicorette Mini Lozenge; generics

- Nicotine polacrilex formulation
  - Delivers ~25% more nicotine than equivalent gum dose
- Sugar-free mint, cherry flavors
- Contains buffering agents to enhance buccal absorption of nicotine
- Available: 2 mg, 4 mg

NICOTINE GUM & LOZENGE: DOSING

Dose based on the "time to first cigarette" (TTFC) as an indicator of nicotine dependence

Use the 2 mg gum/lozenge:

If first cigarette of the day is smoked more than 30 minutes after waking

Use the 4 mg gum/lozenge:

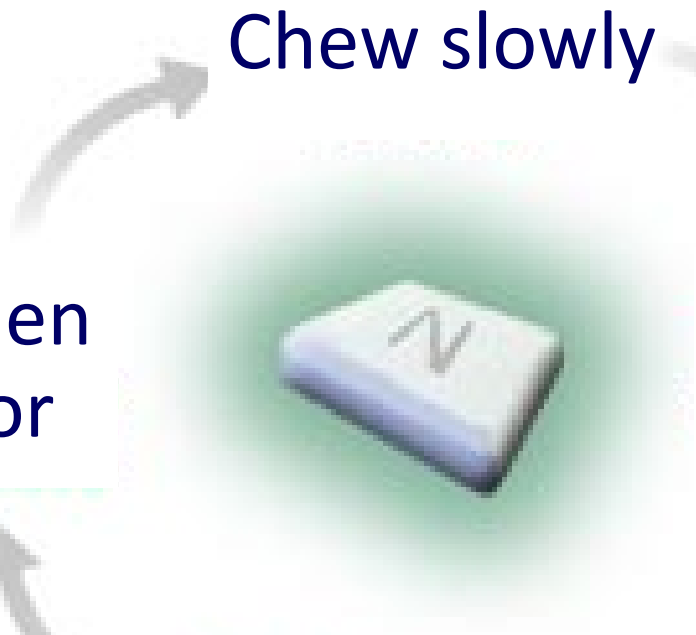
If first cigarette of the day is smoked within 30 minutes of waking

NICOTINE GUM & LOZENGE: DOSING (cont'd)

Recommended Usage Schedule		
Weeks 1–6	**Weeks 7–9**	**Weeks 10–12**
1 piece q 1–2 h	**1 piece q 2–4 h**	**1 piece q 4–8 h**

Do not use more than 24 pieces of GUM or 20 LOZENGES per day.

NICOTINE GUM: DIRECTIONS FOR USE



Chew slowly

Stop chewing at first sign of peppery taste or tingling sensation

Park between cheek & gum

Chew again when peppery taste or tingle fades

NICOTINE LOZENGE: DIRECTIONS for USE

- Place in mouth and allow to dissolve slowly (nicotine release may cause warm, tingling sensation)
- Do not chew or swallow
- Occasionally rotate to different areas of the mouth
- Lozenges will dissolve completely in about 20–30 minutes

NICOTINE GUM/LOZENGE: ADDITIONAL PATIENT EDUCATION

- To improve chances of quitting, use at least nine pieces daily during the first 6 weeks
- The gum/lozenge will *not* provide the same rapid satisfaction that smoking provides
- The effectiveness of the nicotine gum/lozenge may be reduced by some foods and beverages:
  - Coffee
  - Juices
  - Wine
  - Soft drinks

Do NOT eat or drink for 15 minutes BEFORE or while using the nicotine gum or lozenge.

NICOTINE GUM/LOZENGE: ADD'L PATIENT EDUCATION (cont'd)

- Chewing the lozenge or using incorrect gum chewing technique can cause excessive and rapid release of nicotine, resulting in:
  - Lightheadedness/dizziness
  - Nausea and vomiting
  - Hiccups
  - Irritation of throat and mouth

NICOTINE GUM/LOZENGE: ADD'L PATIENT EDUCATION (cont'd)

- Adverse effects of nicotine gum and lozenge:
  - Mouth and throat irritation
  - Hiccups
  - Gastrointestinal complaints (dyspepsia, nausea)
- Adverse effects associated with nicotine gum:
  - Jaw muscle ache
  - May stick to dental work

NICOTINE GUM/LOZENGE: SUMMARY

ADVANTAGES

- Might serve as an oral substitute for tobacco
- Might delay weight gain
- Can be titrated to manage withdrawal symptoms
- Can be used in combination with other agents to manage situational urges
- Relatively inexpensive

DISADVANTAGES

- Need for frequent dosing can compromise adherence
- Gastrointestinal adverse effects (nausea, hiccups, and dyspepsia) may be bothersome
- Specific to nicotine gum:
  - Might be problematic for patients with significant dental work
  - Proper chewing technique is necessary for effectiveness and to minimize adverse effects
  - Chewing might not be acceptable or desirable for some patients

TRANSDERMAL NICOTINE PATCH

Habitrol; NicoDerm CQ; generic

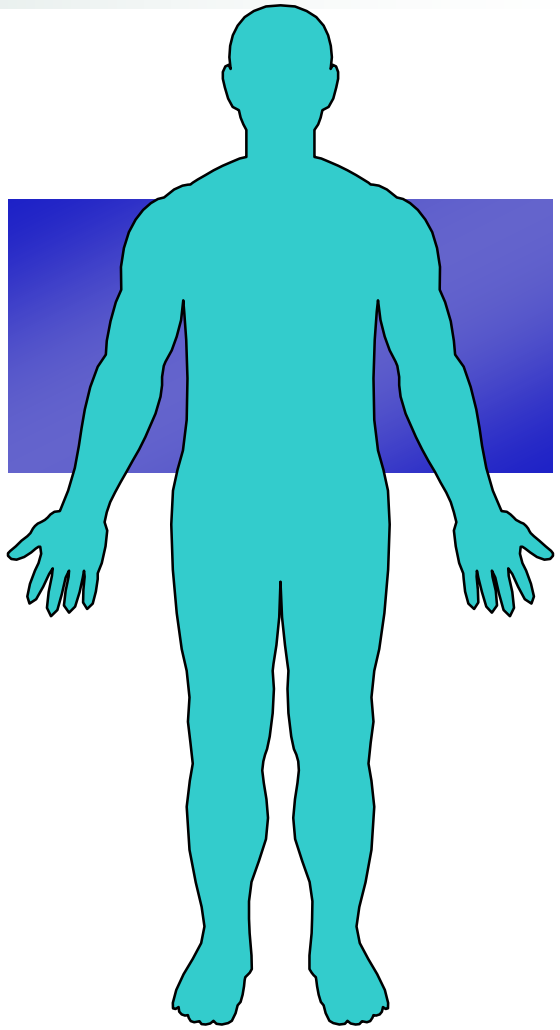
- Continuous (24-hour) nicotine delivery system
- Nicotine is well absorbed across the skin
- Transdermal delivery to systemic circulation avoids hepatic first-pass metabolism
- Plasma nicotine levels are lower and fluctuate less than with smoking

TRANSDERMAL NICOTINE PATCH: DOSING

Product	Light Smoker	Heavy Smoker
NicoDerm CQ	**≤10 cigarettes/day** Step 2 (14 mg x 6 weeks) Step 3 (7 mg x 2 weeks)	**>10 cigarettes/day** Step 1 (21 mg x 6 weeks) Step 2 (14 mg x 2 weeks) Step 3 (7 mg x 2 weeks)
Habitrol **Generic**	**≤10 cigarettes/day** Step 2 (14 mg x 6 weeks) Step 3 (7 mg x 2 weeks)	**>10 cigarettes/day** Step 1 (21 mg x 4 weeks) Step 2 (14 mg x 2 weeks) Step 3 (7 mg x 2 weeks)

TRANSDERMAL NICOTINE PATCH: DIRECTIONS for USE

- Choose an area of skin on the upper body or upper outer part of the arm
- Make sure skin is clean, dry, hairless, and not irritated
- Apply patch to different area each day
- Do not use same area again for at least 1 week



TRANSDERMAL NICOTINE PATCH: DIRECTIONS for USE (cont'd)

- Wash hands: Nicotine on hands can get into eyes or nose and cause stinging or redness
- Do not leave patch on skin for more than 24 hours—doing so may lead to skin irritation
- Adhesive remaining on skin may be removed with rubbing alcohol or acetone
- Dispose of used patch by folding it onto itself, completely covering adhesive area

TRANSDERMAL NICOTINE PATCH: ADDITIONAL PATIENT EDUCATION

- Water will not harm the nicotine patch if it is applied correctly; patients may bathe, swim, shower, or exercise while wearing the patch
- Do *not* cut patches to adjust dose
  - Can unpredictably effect nicotine delivery
  - Patch may be less effective
- Keep new and used patches out of the reach of children and pets
- Remove patch before MRI procedures

TRANSDERMAL NICOTINE PATCH: ADD'L PATIENT EDUCATION (cont'd)

Common adverse effects include:

- Irritation at the patch application site (generally within the first hour)
  - Mild itching
  - Burning
  - Tingling
- Sleep disturbances
  - Abnormal or vivid dreams
  - Insomnia

TRANSDERMAL NICOTINE PATCH: ADD'L PATIENT EDUCATION (cont'd)

- After patch removal, skin may appear red for 24 hours
  - If skin stays red more than 4 days or if it swells or a rash appears, contact health care provider—do not apply new patch
- Local skin reactions (redness, burning, itching)
  - Usually caused by adhesive
  - Up to 50% of patients experience this reaction
  - Fewer than 5% of patients discontinue therapy
  - Avoid use in patients with dermatologic conditions (e.g., psoriasis, eczema, atopic dermatitis)

TRANSDERMAL NICOTINE PATCH: SUMMARY

ADVANTAGES

- Once-daily dosing associated with fewer adherence problems
- Of all NRT products, its use is least obvious to others
- Can be used in combination with other agents; delivers consistent nicotine levels over 24 hrs
- Relatively inexpensive

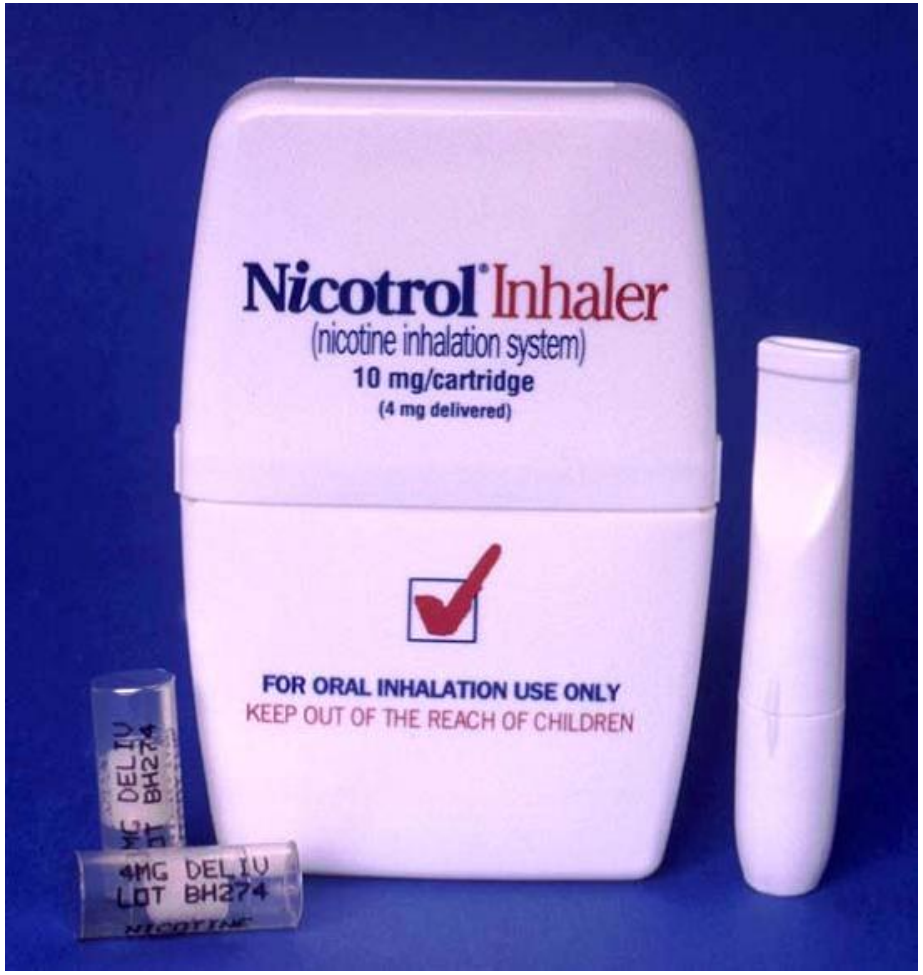
DISADVANTAGES

- When used as monotherapy, cannot be titrated to acutely manage withdrawal symptoms
- Not recommended for use by patients with dermatologic conditions (e.g., psoriasis, eczema, atopic dermatitis)

NICOTINE INHALER

Nicotrol Inhaler

- Nicotine inhalation system consists of:
  - Mouthpiece
  - Cartridge with porous plug containing 10 mg nicotine and 1 mg menthol
- Delivers 4 mg nicotine vapor, absorbed across buccal mucosa



NICOTINE INHALER: DOSING

- Initial treatment (up to 12 weeks)
  - Start with at least 6 cartridges/day during the first 3–6 weeks of treatment
  - Increase prn to maximum of 16 cartridges/day
  - In general, use 1 cartridge every 1–2 hours
- Gradually reduce daily dosage over the following 6–12 weeks
- Recommended maximum duration of therapy is 6 months

NICOTINE INHALER: DIRECTIONS for USE (cont'd)

- Press nicotine cartridge firmly into bottom of mouthpiece until it pops into place

- Line up the markings on the mouthpiece again and push the two pieces back together so they fit tightly
- Twist the top to misalign marks and secure unit

NICOTINE INHALER: SUMMARY

ADVANTAGES

- Might serve as an oral substitute for tobacco
- Can be titrated to manage withdrawal symptoms
- Mimics the hand-to-mouth ritual of smoking
- Can be used in combination with other agents to manage situational urges

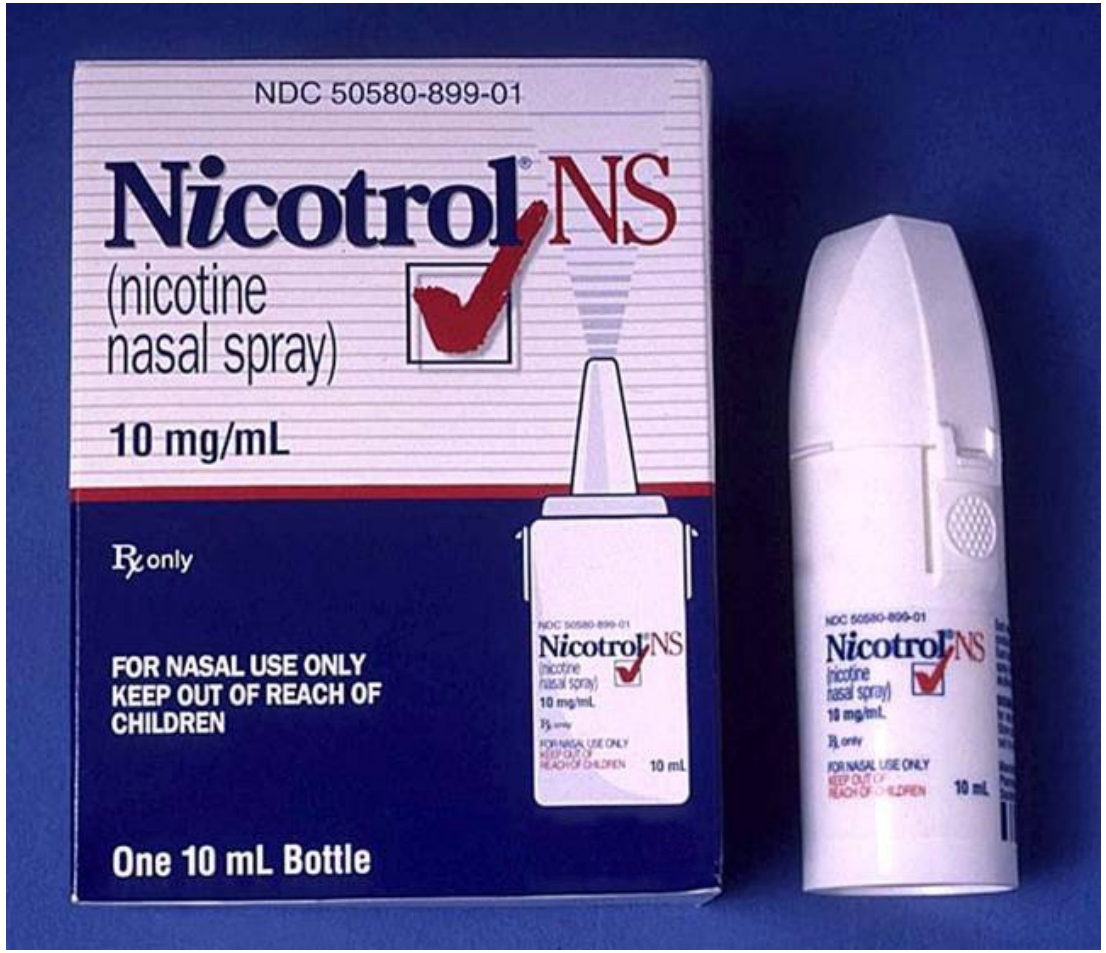
DISADVANTAGES

- Need for frequent dosing can compromise adherence
- Cartridges might be less effective in cold environments (≤60°F)
- Cost of treatment

NICOTINE NASAL SPRAY

Nicotrol NS

- Aqueous solution of nicotine in a 10-ml spray bottle
- Each metered dose actuation delivers
  - 50 mcL spray
  - 0.5 mg nicotine
- ~100 doses/bottle
- Rapid absorption across nasal mucosa



NICOTINE NASAL SPRAY: SUMMARY

ADVANTAGES

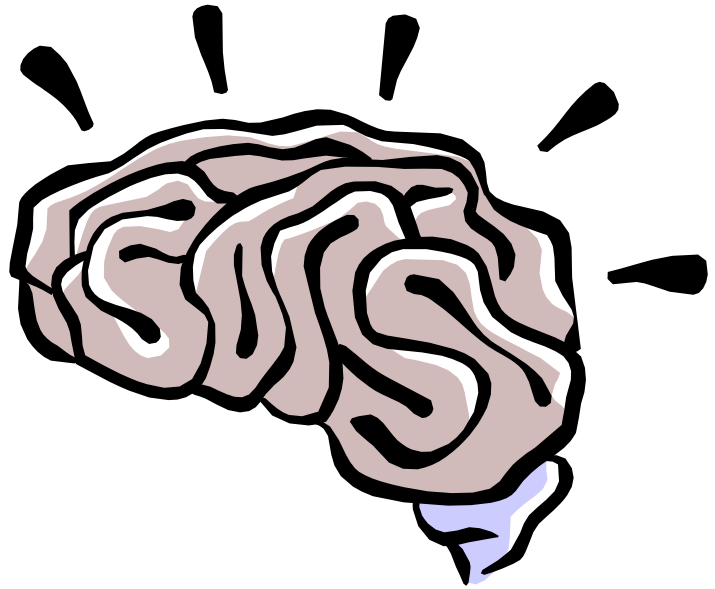
- Can be titrated to rapidly manage withdrawal symptoms
- Can be used in combination with other agents to manage situational urges

DISADVANTAGES

- Need for frequent dosing can compromise adherence
- Nasal administration might not be acceptable/desirable for some patients; nasal irritation often problematic
- Not recommended for use by patients with chronic nasal disorders or severe reactive airway disease
- Cost of treatment

BUPROPION SR Generics

- Non-nicotine cessation aid
- Mechanism of action: atypical antidepressant thought to affect levels of various brain neurotransmitters
  - Dopamine
  - Norepinephrine
- Clinical effects
  - ↓ craving for cigarettes
  - ↓ symptoms of nicotine withdrawal



BUPROPION: CONTRAINDICATIONS

- Seizure disorder
- Current or prior diagnosis of bulimia or anorexia nervosa
- Abrupt discontinuation of alcohol, benzodiazepines, barbiturates and antiepileptic drugs
- Use of MAO inhibitors (within 14 days of initiating or discontinuing therapy)

BUPROPION: WARNINGS and PRECAUTIONS

Use with caution in the following populations:

- Patients with an elevated risk for seizures, including:
  - Severe head injury
  - Concomitant use of medications that lower the seizure threshold (e.g., other bupropion products, antipsychotics, tricyclic antidepressants, theophylline)
  - Severe hepatic impairment
- Patients with underlying neuropsychiatric conditions

For a comprehensive listing of warnings and precautions, refer to the manufacturer's prescribing information.

BUPROPION SR: DOSING

To ensure therapeutic plasma levels of the drug are achieved, begin therapy 1 to 2 weeks PRIOR to the quit date.

Initial treatment

- 150 mg po q AM for 3 days

Then…

- 150 mg po bid for 7–12 weeks
- Doses must be administered at least 8 hours apart
- Tapering not necessary when discontinuing therapy

BUPROPION: ADVERSE EFFECTS

Common adverse effects include the following:

- Insomnia (avoid bedtime dosing)
- Dry mouth
- Nausea

Less common but reported effects:

- Anxiety/difficulty concentrating
- Constipation
- Tremor
- Skin rash

BUPROPION SR: SUMMARY

ADVANTAGES

- Oral dosing is simple and associated with fewer adherence problems
- Might delay weight gain
- Bupropion might be beneficial in patients with depression
- Can be used in combination with NRT agents
- Relatively inexpensive

DISADVANTAGES

- Seizure risk is increased
- Several contraindications and precautions preclude use in some patients
- Patients should be monitored for neuropsychiatric symptoms

VARENICLINE
Chantix

- Nonnicotine cessation aid
- Partial nicotinic receptor agonist
- Oral formulation

VARENICLINE: MECHANISM of ACTION

- Binds with high affinity and selectivity at $\alpha_4\beta_2$ neuronal nicotinic acetylcholine receptors
  - Stimulates low-level agonist activity
  - Competitively inhibits binding of nicotine
- Clinical effects
  - ↓ symptoms of nicotine withdrawal
  - Blocks dopaminergic stimulation responsible for reinforcement & reward associated with smoking

VARENICLINE: WARNINGS and PRECAUTIONS (cont'd)

In some patients, use of varenicline has been associated with:

- Seizures
- Enhanced effects of alcohol
- Accidental injury
- Cardiovascular events
- Somnambulism
- Angioedema and hypersensitivity reactions
- Serious skin reactions

These are rare events and most have not been causally linked to varenicline use.

VARENICLINE: STANDARD DOSING

Patients should begin therapy 1 week PRIOR to their quit date. The dose is gradually increased to minimize treatment-related nausea and insomnia.

Initial dose titration

Treatment Day	Dose
Day 1 to day 3 	0.5 mg qd
Day 4 to day 7 	0.5 mg bid
Day 8 to end of treatment* 	1 mg bid

* Up to 12 weeks

VARENICLINE: ADVERSE EFFECTS

Common adverse effects include the following:

- Nausea
- Insomnia
- Abnormal dreams
- Headache

Less common adverse effects:

- Gastrointestinal (flatulence, constipation)
- Taste alteration

VARENICLINE: ADDITIONAL PATIENT EDUCATION

- Doses should be taken after eating, with a full glass of water
- Nausea and insomnia are usually temporary side effects
  - If symptoms persist, notify your health care provider
- May experience vivid, unusual or strange dreams during treatment
- Use caution driving, drinking alcohol, and operating machinery until effects of quitting smoking with varenicline are known

VARENICLINE: SUMMARY

ADVANTAGES

- Oral dosing is simple and associated with fewer adherence problems
- Offers a different mechanism of action for persons who have failed other agents
- Most effective agent for cessation when used as monotherapy

DISADVANTAGES

- Cost of treatment
- Patients should be monitored for potential neuropsychiatric symptoms

VARENICLINE and BUPROPION SR: Safety

The "EAGLES study": FDA-mandated clinical trial

- 8,144 participants (4,116 with a psychiatric disorder)
- 140 multinational centers
- 24-week, double-blind; active and placebo-controlled:
  - **Varenicline:** standard dosing, 12 wks
  - **Bupropion SR:** standard dosing, 12 wks
  - **Nicotine patch:** 21 mg/day with standard taper, 12 wks
  - **Placebo:** 12 wks
- All arms: 13 counseling visits, 11 telephone calls
- Follow-up through 24 wks; outcome = continuous abstinence

"EAGLES" = Evaluating Adverse Events in a Global Smoking Cessation Study

Anthenelli RM et al. Lancet 2016;387:2508-2520.

The "EAGLES" STUDY: SAFETY DATA (Weeks 9-24)

Incidence of Moderate or Severe Neuropsychiatric Adverse Events

Patient cohort	Varenicline	Bupropion SR	Nicotine patch	Placebo
Non-psychiatric	1.3%	2.2%	2.5%	2.4%
Psychiatric	6.5%	6.7%	5.2%	4.9%

No significant differences in neuropsychiatric events by treatment arm

Anthenelli RM et al. Lancet 2016;387:2508-2520.

THE "EAGLES" STUDY: EFFICACY DATA (Weeks 9-24)

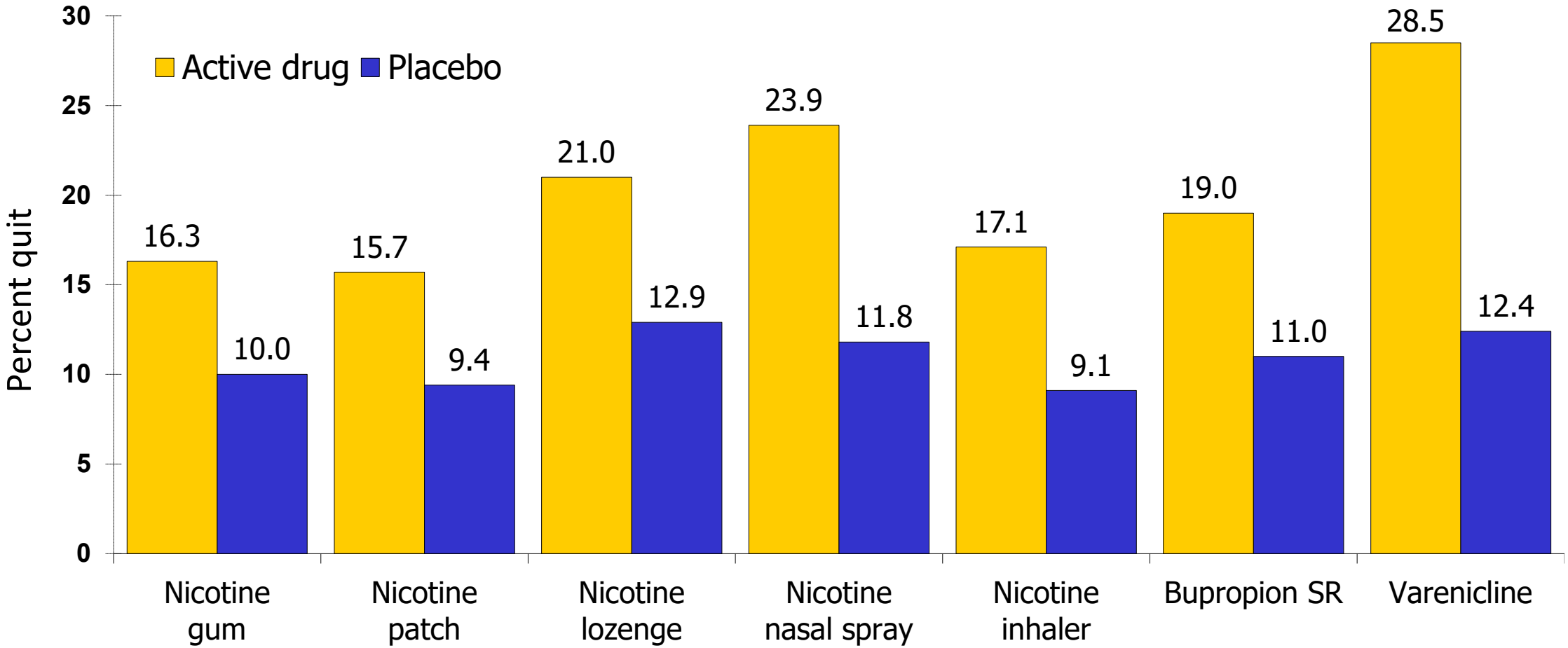
Continuous abstinence

Patient cohort	Varenicline	Bupropion SR	Nicotine patch	Placebo
Non-psychiatric	25.5%	18.8%	18.5%	10.5%
Psychiatric	18.3%	13.7%	13.0%	8.3%

Highest efficacy with varenicline

Anthenelli RM et al. Lancet 2016;387:2508-2520.

LONG-TERM (≥6 month) QUIT RATES for AVAILABLE CESSATION MEDICATIONS



Data adapted from Cahill et al. (2016); Hartmann-Boyce et al. (2018); Howes et al. (2020). *Cochrane Database Syst Rev.*

COMBINATION PHARMACOTHERAPY

Combination NRT [first-line, recommended treatment approach]

- Long-acting formulation (patch)
  - Produces relatively constant levels of nicotine

PLUS

- Short-acting formulation (gum, inhaler, lozenge, nasal spray)
  - Allows for acute dose titration as needed for nicotine withdrawal symptoms

Other combinations [evidence less compelling]

- Bupropion + NRT
- Varenicline + NRT
- Varenicline + bupropion SR

TREATMENT OPTIONS

Multiple Treatment Comparison Meta-Analysis

Comparison	Odds ratio (95% CI)
Nicotine gum vs Placebo	**1.7** (1.5–1.9)
Bupropion SR vs Placebo	**1.9** (1.6–2.1)
Nicotine patch vs Placebo	**1.9** (1.7–2.1)
Other NRT* vs Placebo	**2.0** (1.8–2.4)
Combination NRT vs Placebo	**2.7** (2.1–3.7)
Varenicline vs Placebo	**2.9** (2.4–3.5)

*Includes nicotine nasal spray, lozenge, and inhaler

Strong evidence that combination NRT and varenicline are more effective than bupropion SR or NRT monotherapy

Cahill et al. (2013). *Cochrane Database Syst Rev* 5:CD009329.

COMBINATION NRT: TREATMENT REGIMENS

- **Nicotine patch**
  Dose: 21 mg/day x 4–6 weeks → 14 mg/day x 2 weeks → 7 mg/day x 2 weeks

PLUS

- **Nicotine gum or lozenge** (2 mg/4 mg; based on TTFC)
  Dose: Use 1 piece q 1–2 hours as needed

OR

- **Nicotine inhaler** (10 mg cartridge; delivers 4 mg nicotine vapor)
  Dose: Use 1 cartridge q 1–2 hours as needed

OR

- **Nicotine nasal spray** (0.5 mg/spray)
  Dose: Use 1 spray in each nostril q 1–2 hours as needed

ESSENTIAL QUESTION for SELECTION of NRT PRODUCT(s)*

"Would it be a challenge for you to take a medication frequently throughout the day (e.g., a minimum of 8 or 9 times)?"

- With the exception of the nicotine patch, all NRT formulations require frequent dosing throughout the day.
- If patient is unable to adhere to the recommended dosing, these products should be ruled out as monotherapy because they will be ineffective.

* Product-specific screening—e.g., for warnings, precautions, and personal preferences—is also essential.

“Drugs don’t work…

…in patients who don’t take them.”

C. Everett Koop, M.D., former U.S. Surgeon General

Medication adherence should be addressed at each encounter.

ADHERENCE IS KEY to QUITTING

- Promote adherence with prescribed regimens
  - Select the correct strength of medication
  - Use daily (according to a fixed schedule, NOT as needed)
  - Complete the recommended duration of therapy
- Consider telling the patient:
  - “If used correctly, the medicines will make you more comfortable while quitting.”
  - “Medicines work best when taken regularly, to **prevent** withdrawal symptoms before they occur. If you wait until you’re already craving a cigarette, it will be too late. The medicines don’t work as fast as inhaled nicotine from a cigarette.”

At each encounter, assess withdrawal and adjust treatment as needed.

DRUG INTERACTIONS WITH SMOKING

- Clinically significant interactions result from the **combustion products** of tobacco smoke, not from nicotine.
- Constituents in tobacco smoke (e.g., polycyclic aromatic hydrocarbons) may **enhance the metabolism of other drugs,** resulting in an altered pharmacologic response.
  - Changes in smoking status might **alter the clinical response** to the treatment of a wide variety of conditions.
  - Drug interactions with smoking should be considered when patients **start smoking, quit smoking, or markedly alter their levels of smoking.**

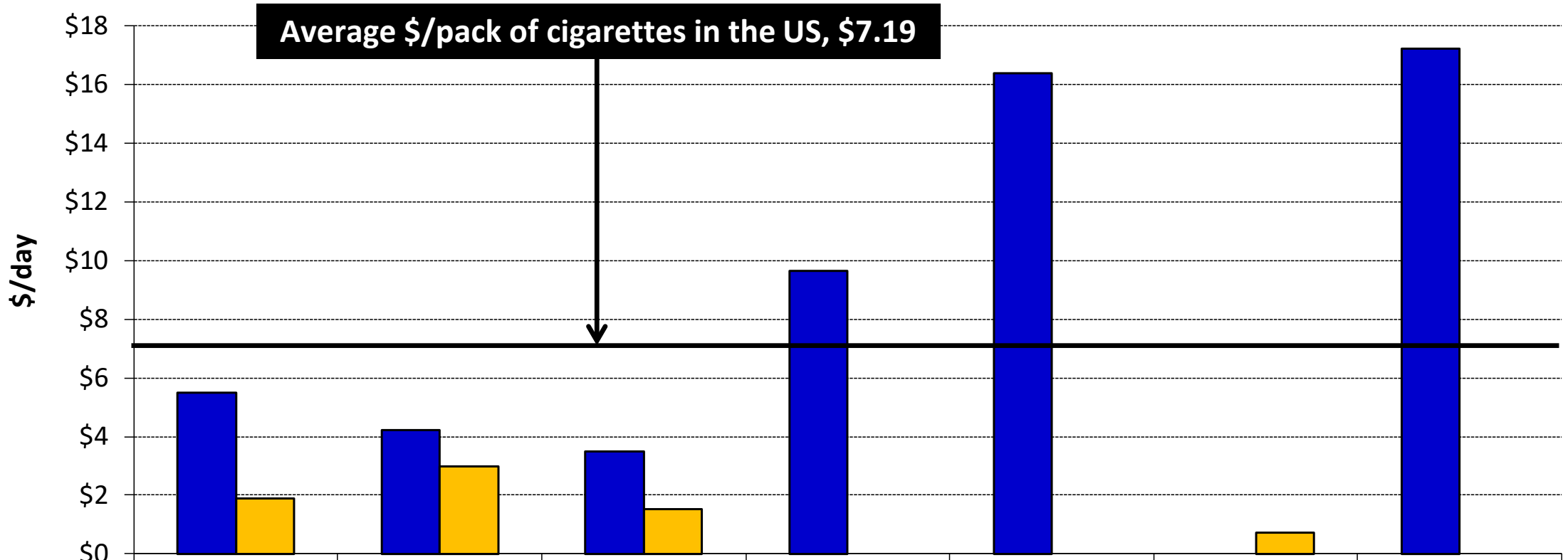
PHARMACOKINETIC DRUG INTERACTIONS with SMOKING

Drugs that may have a *decreased effect* due to induction of CYP1A2:

- Bendamustine
- Caffeine
- Clozapine
- Erlotinib
- Fluvoxamine
- Irinotecan
- Haloperidol
- Olanzapine
- Pirfenidone
- Riociguat
- Ropinirole
- Tasimelteon
- Theophylline

Smoking cessation will reverse these effects.

COMPARATIVE DAILY COSTS of PHARMACOTHERAPY



	Gum	Lozenge	Patch	Nasal spray	Inhaler	Bupropion SR	Varenicline
Trade	$5.49	$4.23	$3.49	$9.64	$16.38		$17.20
Generic	$1.90	$2.97	$1.52			$0.72	

*Wholesale acquisition cost from Red Book Online. Thomson Reuters, January 2021.

SUMMARY

- To maximize success, interventions should include behavioral counseling and one or more medications
- Encourage the use of effective medications by all patients attempting to quit smoking
  - Exceptions include medical contraindications or specific populations for which there is insufficient evidence of effectiveness
- First-line medications that reliably increase long-term smoking cessation rates:
  - Bupropion SR
  - Nicotine replacement therapy (as monotherapy or combination therapy)
  - Varenicline
- Varenicline and combination NRT demonstrate the highest efficacy

For Additional Information contact:

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