

# Welcome

Please stand by. We will begin shortly.

## Beyond the Basics: Pharmacotherapy for Smoking Cessation

Monday, March 14, 2016 · 1pm ET (120 minutes)



# Disclosure

Dr. Robin L. Corelli, Dr. Karen S. Hudmon, and Catherine Saucedo have disclosed no financial interest/arrangement or affiliation with any commercial companies who have provided products or services relating to their presentation or commercial support for this continuing medical education activity.

# Moderator



## Catherine Saucedo

- Deputy Director,  
Smoking Cessation Leadership  
Center, University of California,  
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# Thank you to our funders



Robert Wood Johnson Foundation



**truth initiative**  
INSPIRING TOBACCO-FREE LIVES



**National Behavioral Health Network**  
*For Tobacco & Cancer Control*

# Housekeeping

- All participants will be in **listen only mode**.
- Please **make sure your speakers are on** and adjust the volume accordingly.
- If you do not have speakers, please request the dial-in via the chat box.
- **This webinar is being recorded** and will be available on SCLC's website, along with the slides.
- **Use the chat box to send questions** at any time for the presenters.

# Today's Speaker



**UCSF** School of Pharmacy  
Department of Clinical Pharmacy

## **Robin L. Corelli, PharmD**

- Professor of Clinical Pharmacy,  
Department of Clinical Pharmacy,  
School of Pharmacy, University of  
California, San Francisco

# Today's Speaker



## **Karen S. Hudmon, DrPH, MS, RPh**

- Professor of Pharmacy Practice and Associate Head for Operations, Department of Pharmacy Practice, College of Pharmacy, Purdue University



# BEYOND the BASICS:

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## Pharmacotherapy for Smoking Cessation

Robin Corelli, PharmD  
UCSF School of Pharmacy

Karen Hudmon, DrPH, MS, RPh  
Purdue University College of Pharmacy



# LEARNING OBJECTIVES

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- Identify patients who are candidates for **combination therapy** and, after consideration of patient-specific factors, design a treatment regimen (drugs, dosages, routes, and duration of therapy).
- Identify patients who are candidates for **high-dose pharmacotherapy** and recommend a treatment regimen (drug, dose, route, and duration of therapy).



## LEARNING OBJECTIVES, cont'd

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- Identify patients who are candidates for **extended-duration pharmacotherapy** and recommend a treatment plan (drug, dose, route and duration of therapy).
- Determine situations for which use of **nicotine replacement therapy prior to the quit date** might be beneficial and recommend a treatment regimen (drug, dose, route, and duration of therapy)



# FDA-APPROVED MEDICATIONS for SMOKING CESSATION:

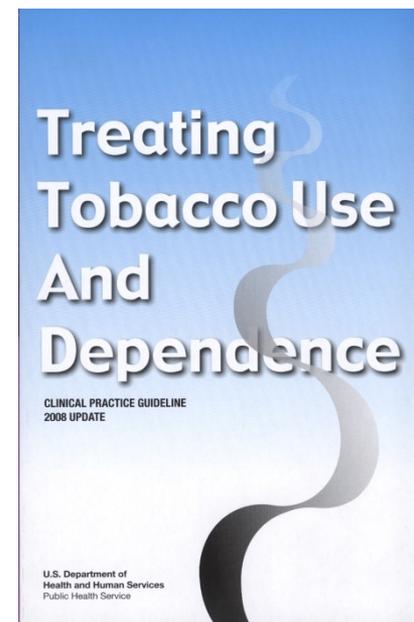
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A brief review



# 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.



# PHARMACOLOGIC METHODS: FIRST-LINE THERAPIES

## **Nicotine gum**

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

## **Nicotine lozenge**

- Commit (OTC)
- Generic nicotine lozenge (OTC)

## **Transdermal nicotine patch**

- NicoDerm CQ (OTC)
- Generic nicotine patches (OTC, Rx)

## **Nicotine nasal spray**

- Nicotrol NS (Rx)

## **Nicotine oral inhaler**

- Nicotrol (Rx)

## **Bupropion SR tablets**

- Zyban (Rx)
- Generic (Rx)

## **Varenicline tablets**

- Chantix (Rx)

*OTC = over-the-counter / no prescription needed*

These are the only medications approved by the Food and Drug Administration (FDA) for smoking cessation.



# NICOTINE GUM and LOZENGE

**Available:** 2 mg, 4 mg; various flavors

## Pros:

- Oral substitute for tobacco
- Can be titrated to manage withdrawal symptoms
- Can be used in combination with other agents to manage situational urges

## Cons:

- Need for frequent dosing can compromise adherence
- Might be problematic with significant dental work
- Proper chewing technique is necessary for gum
- Gum chewing might not be acceptable/desirable





# TRANSDERMAL NICOTINE PATCH

**Available:** 21 mg, 14 mg, 7 mg

## Pros:

- Once-daily dosing
- Can be used in combination with other agents; delivers consistent nicotine levels over 24 hours

## Cons:

- Cannot be titrated to acutely manage withdrawal symptoms
- Not recommended for use with dermatologic conditions





# NICOTINE NASAL SPRAY

**Available:** 10ml bottle; 0.5 mg per spray

## Pros:

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

## Cons:

- Need for frequent dosing can compromise adherence
- Nasal administration; nasal irritation often problematic
- Not recommended for use with chronic nasal disorders or severe reactive airway disease





# NICOTINE ORAL INHALER

**Available:** 10mg cartridge delivers 4mg inhaled vapor for absorption across buccal mucosa

## Pros:

- Oral substitute for tobacco
- Can be titrated to manage withdrawal symptoms
- Mimics hand-to-mouth ritual of smoking
- Can be used in combination with other agents to manage situational urges

## Cons:

- Need for frequent dosing can compromise adherence
- Cartridges might be less effective in cold environments ( $\leq 60^{\circ}\text{F}$ )





# BUPROPION SR

**Available:** 150 mg tablets

## **Pros:**

- Twice-daily dosing
- Might be beneficial in patients with depression
- Can be used in combination with NRT

## **Cons:**

- Seizure risk is increased
- Several contraindications and precautions
- Patients must be monitored for potential neuropsychiatric symptoms





# VARENICLINE

**Available:** 0.5 and 1.0 mg tablets

## Pros:

- Twice-daily dosing
- Offers a different mechanism of action

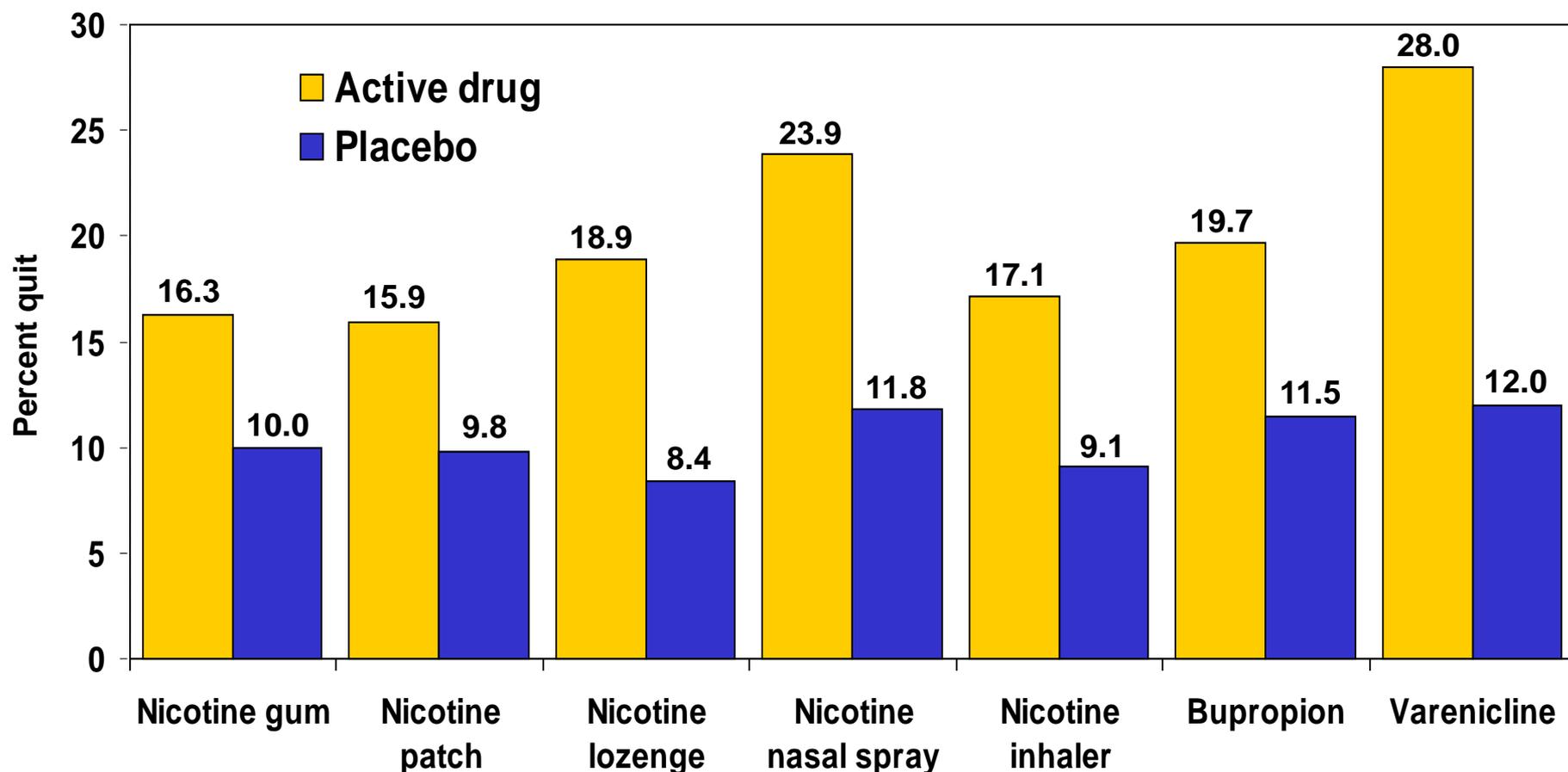
## Cons:

- Should be taken with food or full glass of water
- Patients must be monitored for potential neuropsychiatric symptoms





# LONG-TERM ( $\geq 6$ month) QUIT RATES for AVAILABLE CESSATION MEDICATIONS



Data adapted from Cahill et al. (2012). *Cochrane Database Syst Rev*; Stead et al. (2012). *Cochrane Database Syst Rev*; Hughes et al. (2014). *Cochrane Database Syst Rev*



# IDENTIFY KEY ISSUES to STREAMLINE PRODUCT SELECTION\*

- Do you prefer a prescription or non-prescription medication?
- Would it be a challenge for you to take a medication frequently throughout the day, e.g., a minimum of 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.

**Asking these two questions will reduce the time required for product selection.**

\* Product-specific screening, for warnings/precautions/contraindications and personal preferences, is also essential.



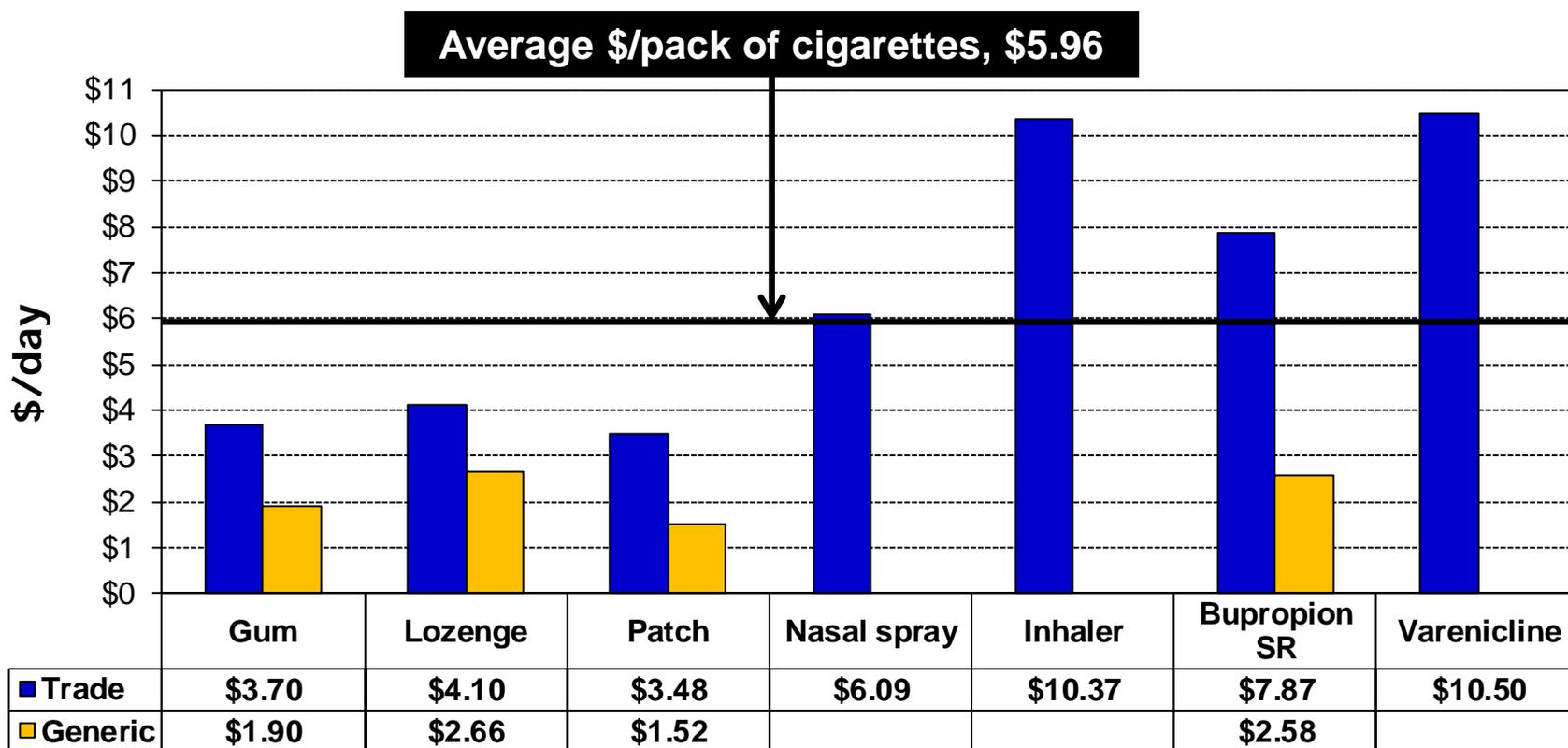
# ADHERENCE IS KEY to QUITTING

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- Promote adherence with prescribed regimens.
- Use according to dosing schedule, NOT as needed.
- Consider telling the patient:
  - “When you use a cessation product it is important to read all the directions thoroughly before using the product. The products work best in alleviating withdrawal symptoms when used correctly, and according to the recommended dosing schedule.”



# COMPARATIVE DAILY COSTS of PHARMACOTHERAPY



Cigarette costs: Campaign for Tobacco-Free Kids. (2016). "State Cigarette Excise Tax Rates & Rankings."  
Drug costs: Red Book Online. (2016, January). New York, NY: Thomson Reuters.



# TOBACCO DEPENDENCE: A 2-PART PROBLEM

## Tobacco Dependence

### Physiological

The addiction to nicotine



Treatment

Medications for cessation

### Behavioral

The habit of using tobacco



Treatment

Behavior change program



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

## STEP One: ASK about Tobacco Use

### ➤ Suggested Dialogue

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

## STEP Two: ADVISE to Quit

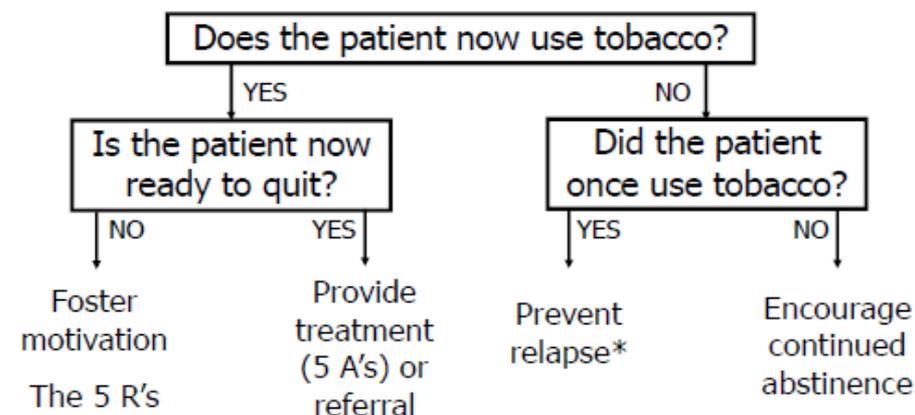
### ➤ Suggested Dialogue

- Quitting 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 would be more than happy to work with you to design a treatment plan.
- Prior to imparting advice, consider asking the patient for permission to do so – e.g., "May I tell you why this concerns me?" [then elaborate on patient-specific concerns]

## STEP Three: ASSESS Readiness to Quit

### ➤ Suggested Dialogue

- For current tobacco users: What are your thoughts about quitting? Might you consider quitting sometime in the next month?



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

Fiore MC, Jaén CR, Baker TB, et al. *Treating Tobacco Use and Dependence: 2008 Update*. Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. May 2008.

## STEP Four: ASSIST with Quitting



### ✓ Assess Tobacco Use History

- Current use: type(s) of tobacco used, 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, adherence, 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
- 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: ideally, 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: adherence, 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 strategies to prevent relapse.
- ✓ Congratulate patients for continued success.

## STEP One: ASK about Tobacco Use

### ➤ Suggested Dialogue

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

## STEP Two: ADVISE to Quit

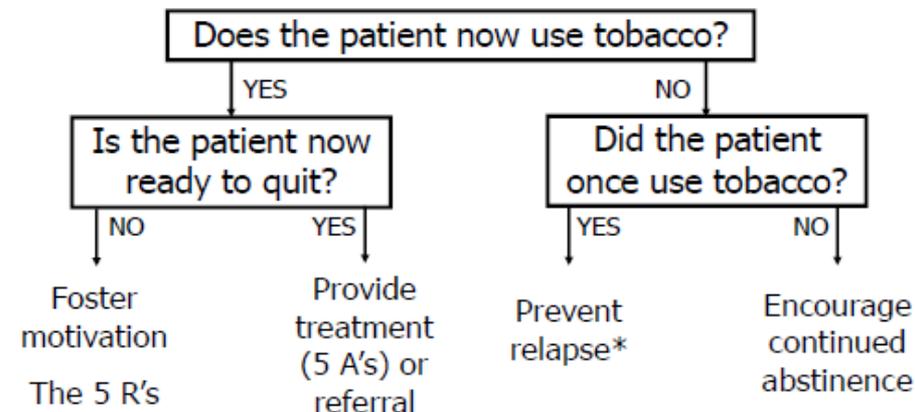
### ➤ Suggested Dialogue

- Quitting 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 would be more than happy to work with you to design a treatment plan.
- Prior to imparting advice, consider asking the patient for permission to do so – e.g., "May I tell you why this concerns me?" [then elaborate on patient-specific concerns]

## STEP Three: ASSESS Readiness to Quit

### ➤ Suggested Dialogue

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## STEP Four: ASSIST with Quitting



- ✓ **Assess Tobacco Use History**
  - Current use: type(s) of tobacco used, 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, adherence, 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
  - 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: ideally, less than 2 weeks away
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  - Discuss coping strategies (cognitive, behavioral)
  - Discuss withdrawal symptoms
  - Discuss concept of "slip" versus relapse
  - Provide medication counseling: adherence, proper use, with demonstration
  - Offer to assist throughout the quit attempt
- ✓ **Evaluate the Quit Attempt** (at follow-up)
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- ✓ 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 strategies to prevent relapse.
- ✓ Congratulate patients for continued success.



# CLINICAL CASES

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# CASE PRESENTATIONS

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- Brief description of case provided
- What questions do you want to ask?
- Questions are asked; immediate responses provided
- Audience poll for recommended therapy regimen
- Data and discussion of treatment options
- Audience re-poll for recommended therapy regimen



# CASE A: PETER

- Peter, 59 yo male with HTN, hyperlipidemia, depression, chronic rhinitis
- Current medications:
  - Valsartan 80mg QAM for HTN
  - Atorvastatin 40mg QAM for hyperlipidemia
  - Bupropion XL 300 QAM for depression
  - Flonase (50mcg/spray), 1 spray in each nostril QAM for rhinitis
- Wants to quit in the next month; has joined a smoking cessation group program at work

**What questions do you want to ask Peter?**



## SUMMARY, CASE A: PETER

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Peter, 59 yo, HTN, hyperlipidemia, depression, chronic rhinitis, enrolled in a group program and interested in using medication(s) for this quit attempt

### **Key points to consider for medication selection:**

- Failed prior quit attempts with monotherapy
- Concerns about adherence with complex regimens
- Currently taking bupropion XL 300 QD for depression
- Refuses nicotine gum
- Chronic rhinitis



# WHICH REGIMEN is MOST APPROPRIATE for PETER?

- (1) Combination NRT
- (2) Pre-quit NRT
- (3) High-dose nicotine patch
- (4) High-dose bupropion



# OPTION #1: Combination NRT

Regimens with sufficient evidence to be 'recommended' as first-line

## ■ Combination NRT

Long-acting formulation (patch)

- Produces relatively constant levels of nicotine

**PLUS**

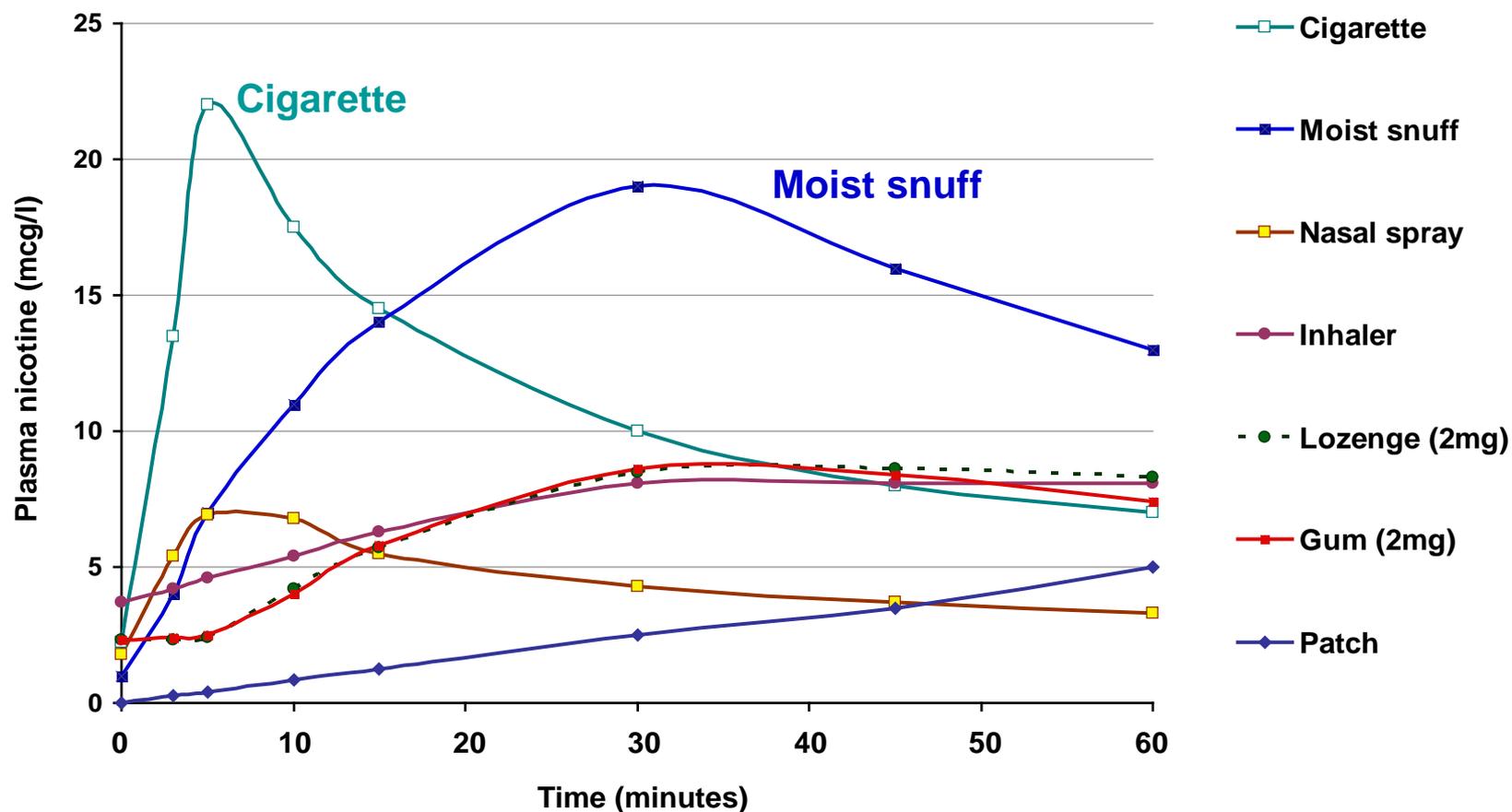
Short-acting formulation (gum, lozenge<sup>\*</sup>, inhaler, nasal spray)

- Allows for acute dose titration as needed for nicotine withdrawal symptoms

*\*No combination data with lozenge when CPG published*



# Plasma Nicotine Concentrations for Nicotine-Containing Products





# OPTION #1: Combination NRT (cont'd)

## Multiple Treatment Comparison Meta-Analysis

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

\*Includes nicotine nasal spray, lozenge and inhaler



# OPTION #1: Combination NRT (cont'd)

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- Summary of RCTs (n=10; >7,100 pts)
  - Baseline characteristics of study subjects
    - Motivated to quit smoking
    - Heavier smokers (mean, 24 CPG; range, 20-27)
    - H/O multiple, failed quit attempts (mean, 4)
    - Moderate-high level of nicotine dependence (FTND scale)
  - Substantial evidence that combination NRT is safe and has better long-term quit rates than NRT monotherapy



# Combination NRT: Recommended Treatment Regimens

- **Nicotine patch**

- Dose: 21mg/day x 4-6w → 14mg/day x 2w → 7mg/day x 2w

**PLUS**

- **Nicotine gum or lozenge** (2mg/4mg; based on TTFC)

- Dose: Use 1 piece q 1-2 hours as needed (*use at least 4-5/day*)

**OR**

- **Nicotine inhaler** (10mg cartridge; delivers 4mg nicotine vapor)

- Dose: Use 1 cartridge q 1-2 hours as needed

**OR**

- **Nicotine nasal spray** (0.5mg/spray)

- Dose: Use 1 spray in each nostril q 1-2 hours as needed



# Combination NRT: Recommendation for Peter?

## ■ Nicotine patch

- Dose: 21mg/day x 4-6w → 14mg/day x 2w → 7mg/day x 2w

**PLUS**

## ■ Nicotine ~~gum~~ or lozenge (2mg/~~4~~mg; based on TTFC)

- Dose: Use 1 piece q 1-2 hours as needed (*use at least 4-5/day*)

**OR**

## ■ Nicotine inhaler (10mg cartridge; delivers 4mg nicotine vapor)

- Dose: Use 1 cartridge q 1-2 hours as needed

**OR**

## ■ Nicotine ~~nasal~~ spray (0.5mg/spray)

- Dose: Use 1 spray in each nostril q 1-2 hours as needed

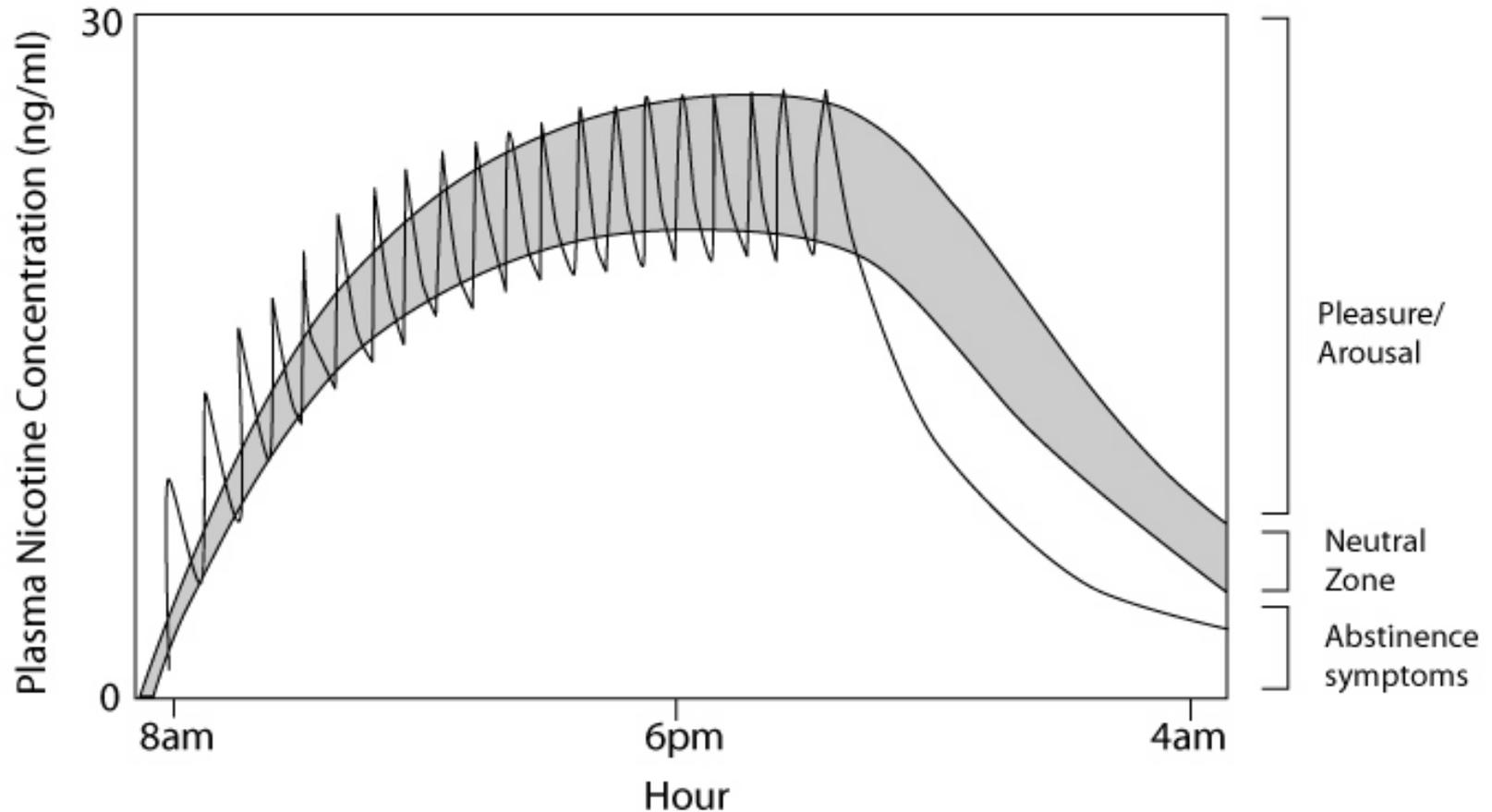


## OPTION #2: Pre-Quit NRT

- Use of NRT before the quit date (e.g., while smoking)
- Rationale
  - Smoking while using NRT might reduce the reinforcing effects of inhaled nicotine from cigarette smoking
  - Abrupt cessation and medication initiation problematic
    - Early exposure to NRT can: (1) allow for dosage adjustment; (2) familiarity with the product; (3) gain confidence as quit date approaches
- Concerns
  - Concomitant use of NRT and smoking will lead to nicotine toxicity



# NICOTINE ADDICTION CYCLE



## Original Investigation

# Precessation treatment with nicotine patch significantly increases abstinence rates relative to conventional treatment

*Jed E. Rose, Joseph E. Herskovic, Frederique M. Behm, & Eric C. Westman*

## Abstract

**Introduction:** Previous studies have reported that smoking abstinence rates are increased when nicotine skin patch treatment is initiated prior to the target quit smoking date, as compared with conventional treatment beginning on the quit date. We hypothesized that smoking in the presence of continuous levels of nicotine would attenuate the reinforcing effects of cigarette smoking and lead to a decline in dependence on inhaled nicotine, thus facilitating cessation.

## Introduction

Nearly 25% of the U.S. population continue to smoke despite the well-known health risks of tobacco smoking (Grant, Hasin, Chou, Stinson, & Dawson, 2004). Although self-help strategies alone marginally affect quit rates, individual and combined pharmacotherapies as well as counseling can significantly increase the likelihood of success for a given quit attempt (Ranney, Melvin, Lux, McClain, & Lohr, 2006). Behavioral counseling, however, is rarely sought by smokers attempting to quit, and therefore, more attention has been directed to the development



# OPTION #2: Pre-Quit NRT (cont'd)

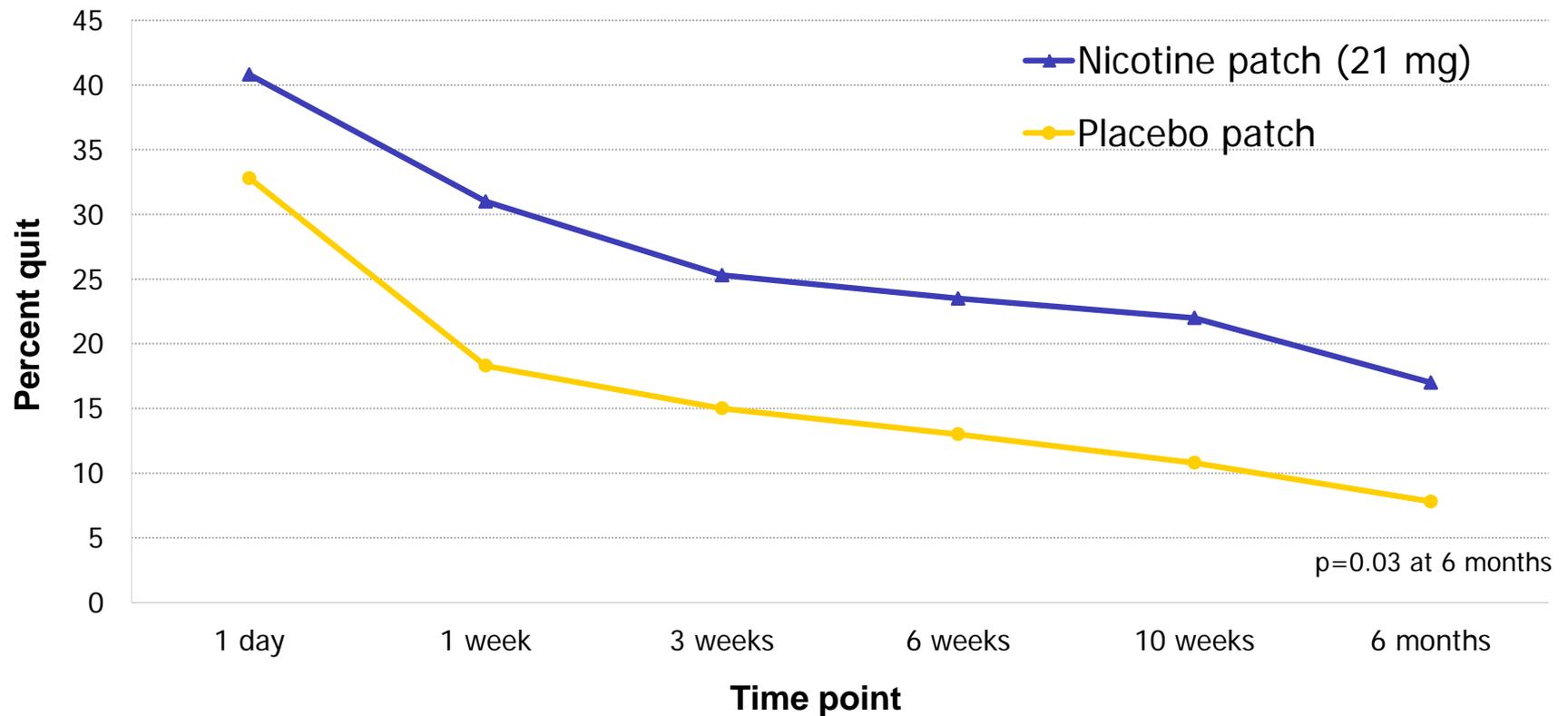
- Randomized, double-blind, placebo controlled (n=400)
- Participants—baseline characteristics (mean)
  - Age: 42 years
  - CPD: 23; mean duration, 23 years
- Procedure:
  - Treatment phase (2 weeks):
    - Pre-quit date 21mg nicotine patch or placebo patch
  - Study phase (10 weeks):
    - Nicotine patch (21mg x 6wk → 14mg x 2wk → 7mg x 2wk)
  - Follow-up through 6 months



# Rose et al., 2009

## Pre-Quit NRT

### Effect of pre-cessation nicotine patch use on long-term abstinence rates





# OPTION #2: Pre-Quit NRT (cont'd)

- Summary of RCTs (n=8\*; >2,700 pts)
  - Baseline characteristics of study subjects
    - Motivated to quit smoking
    - Heavier smokers (mean, 25 CPG; range, 19-30)
    - High level of nicotine dependence (FTND scale)
  - Pooled results show a modest but non-significant increase in quit rates with pre-quit NRT (RR 1.18, 95% CI 0.98-1.41)
  - Analysis of nicotine patch trials only suggests a more pronounced response (RR 1.34, 95% CI 1.08-1.65)

\*NRT included patch (6 studies), lozenge (1 study), gum (1 study)



# OPTION #3: High-Dose Nicotine Patch

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- Definition: nicotine patch doses  $>22\text{mg/day}$
- Rationale:
  - In general, people who smoke heavily require higher doses of nicotine replacement
    - Plasma levels of nicotine with standard dose NRT are generally much lower than those achieved by smoking
    - Higher nicotine replacement doses may be necessary to effectively attenuate withdrawal symptoms
  - The FDA-labeled patch dose is the same for ALL patients smoking  $>10$  CPD—regardless of baseline smoking patterns



# OPTION #3: High-Dose Nicotine Patch (cont'd)

- Summary of RCTs (n=8; >5,100 pts)
  - Patch (44mg vs 22mg)
    - Pooled results show a modest but non-significant increase in quit rates with high dose NRT (RR 1.08, 95% CI 0.89-1.32)
  - Patch (25mg vs 15mg)
    - Pooled results show a modest increase in quit rates with high-dose NRT (RR 1.19, 95% CI 1.00-1.41)
  - Pooling all studies suggests only marginal evidence of a small benefit from high-dose vs conventional-dose nicotine patch therapy (RR 1.14, CI 1.01-1.29)



# OPTION #4: High-Dose Bupropion

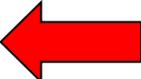
- Use of dosages exceeding 300mg/day

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Usual Dosage

Treatment with ZYBAN should be initiated **before** the patient's planned quit day, **while the patient is still smoking**, because it takes approximately 1 week of treatment to achieve steady-state blood levels of bupropion. The patient should set a "target quit date" within the first 2 weeks of treatment with ZYBAN.

Dosing: To minimize the risk of seizure:

- Begin dosing with one 150-mg tablet per day for 3 days.
- Increase dose to 300 mg/day given as one 150-mg tablet twice each day with an interval of at least 8 hours between each dose.
- Do not exceed 300 mg/day. 



# OPTION #4: High-Dose Bupropion (cont'd)

## 5.3 Seizure

ZYBAN can cause seizure. The risk of seizure is dose-related. The dose of ZYBAN should not exceed 300 mg per day [*see Dosage and Administration (2.1)*]. Discontinue ZYBAN and do not restart treatment if the patient experiences a seizure.

Incidence of Seizure with Bupropion Use: Doses for smoking cessation should not exceed 300 mg per day. The seizure rate associated with doses of sustained-release bupropion in depressed patients up to 300 mg per day is approximately 0.1% (1/1,000) and increases to approximately 0.4% (4/1000) at doses up to 400 mg per day.

The risk of seizure can be reduced if the dose of ZYBAN for smoking cessation does not exceed 300 mg per day, given as 150 mg twice daily, and titration rate is gradual.



## CASE A: Follow-up with Peter

- Peter initiated combination NRT (patch + lozenge prn)
- At 3 months follow-up, he has reduced the patch dose to 7mg daily, with prn nicotine lozenge
  - 2mg; 3-5 doses/day for situational cravings
  - Around other smokers, during periods of high stress
- Expresses fear of relapse:
  - "I'm afraid I'll start smoking again when I stop using the patch. What should I do?"
  - "Can I stay on these medicines longer than what it says on the box?"

**Is Peter a candidate for extended-duration therapy?**



# Extended Duration NRT

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- Use of NRT beyond the conventional FDA-labeled duration of therapy (8-12 weeks)
- Rationale
  - For most quitters, nicotine withdrawal symptoms resolve 2-4 weeks after quitting; however, some patients experience prolonged withdrawal with strong cravings for tobacco
    - Extended duration/maintenance NRT might provide additional benefit
    - Continued access to treatment can prevent a 'slip' from progressing to relapse

Original Investigation

# Long-term Nicotine Replacement Therapy A Randomized Clinical Trial

Robert A. Schnoll, PhD; Patricia M. Goelz, MPH; Anna Veluz-Wilkins, MA; Sonja Blazekovic, BA;  
Lindsay Powers, MA; Frank T. Leone, MD; Peter Gariti, PhD; E. Paul Wileyto, PhD; Brian Hitsman, PhD

**IMPORTANCE** The US Food and Drug Administration adopted labeling for nicotine patches to allow use beyond the standard 8 weeks. This decision was based in part on data showing increased efficacy for 24 weeks of treatment. Few studies have examined whether the use of nicotine patches beyond 24 weeks provides additional therapeutic benefit.

**OBJECTIVE** To compare 8 (standard), 24 (extended), and 52 (maintenance) weeks of nicotine patch treatment for promoting tobacco abstinence.



# Extended Duration NRT (cont'd)

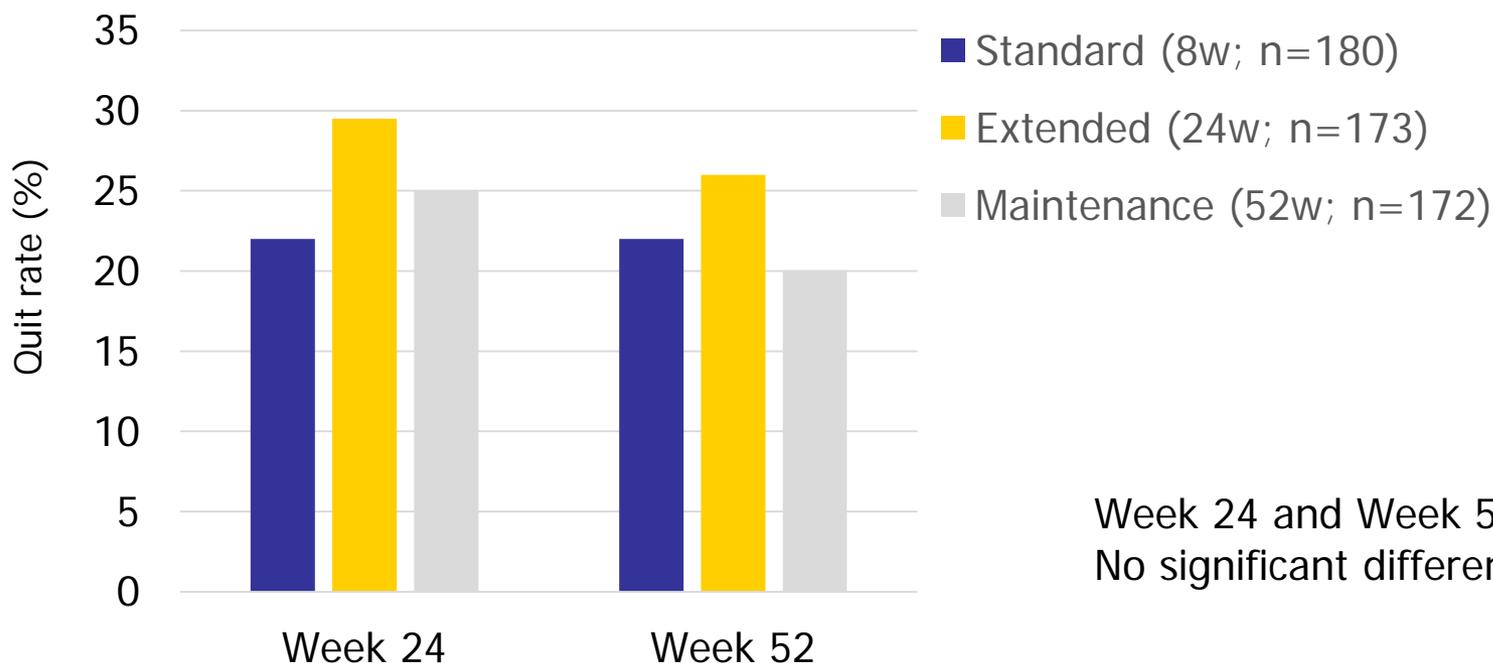
- Randomized, trial (n=525) comparing standard, extended and maintenance nicotine patch therapy for tobacco cessation
- Participants—baseline characteristics (mean)
  - Age: 46 years
  - CPD: 17; mean duration, 29 years
  - Moderate level of nicotine dependence (FTND scale)
- Intervention
  - Nicotine patch 21mg/day x 8, 24, or 52 weeks (no taper)
  - Twelve behavioral counseling sessions (initial in-person --> follow-up provided by telephone quitline)
  - Follow-up through 52 weeks



# Schnoll et al, 2015

## Extended Duration NRT

### 7-day point prevalence abstinence rates by treatment arm



Week 24 and Week 52:  
No significant differences.

Adherence with patch therapy was low across all treatment arms:  
Standard (38%); Extended (47%); Maintenance (32%)



## Extended Duration NRT (cont'd)

- Summary of RCTs (n=3; >3,950 pts)
  - Variable treatment durations (24, 28, 52 weeks)
  - No trial demonstrated statistically significant improvements for long-term cessation compared to standard duration
  - Adherence rates were low
  - Currently, evidence is weak; further research needed with emphasis on adherence to treatment



# OTC NRT Labeling Changes: Nicotine gum, lozenge, & patch

## Previous

- Do not use if you continue to smoke, chew tobacco, use snuff, or use other nicotine containing products
- Stop smoking completely when you begin using [*NRT product*]
- Stop using [*NRT product*] at the end of [a specified # of weeks]. If you still feel the need to use [*NRT product*], talk to your doctor

## Current

- None; “do not use” statement is deleted
- Begin using [*NRT product*] on your quit day
- If you feel you need to use [*NRT product*] for a longer period to keep from smoking, talk to your health care provider



# OTC NRT Labeling Changes: Nicotine gum, lozenge, & patch (cont'd)

## How Nicorette Works

### Quit Your Way

How Nicorette Works

## NOW, QUIT ON YOUR OWN TERMS.

There are as many ways to quit smoking as there are smokers.  
Here are new, FDA-approved ways to help you stop smoking.

🔔 **START** even if you can't  
immediately stop smoking

🔔 **SLIP UP** and still  
stay on track

🔔 **STICK** with it, even if you  
need more time to quit

<http://www.nicorette.com/how-nicorette-works/quit-your-way>

Accessed 08/14/14

## Drug Facts

### Active ingredient (in each lozenge)

Nicotine polacrilex, 2mg ..... Stop smoking aid

### Purpose

**Use** • reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking

### Warnings

If you are pregnant or breast-feeding, only use this medicine on the advice of your health care provider. Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.

### Do not use

- if you continue to smoke, chew tobacco, use snuff, or use a nicotine patch or other nicotine containing product

### Ask a doctor before use if you have

- a sodium-restricted diet
- heart disease, recent heart attack, or irregular heartbeat. Nicotine can increase your heart rate.
- high blood pressure not controlled with medication. Nicotine can increase your blood pressure.
- stomach ulcer or diabetes

### Ask a doctor or pharmacist before use if you are

- using a non-nicotine stop smoking drug
- taking prescription medicine for depression or asthma. Your prescription dose may need to be adjusted.

### Stop use and ask a doctor if

- mouth problems occur
- persistent indigestion or severe sore throat occurs
- irregular heartbeat or palpitations occur
- you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat

**Keep out of reach of children and pets.** Nicotine lozenges may have enough nicotine to make children and pets sick. If you need to remove the lozenge, wrap it in paper and throw away in the trash. In case of overdose, get medical help or contact a Poison Control Center right away.

## Directions

- if you are under 18 years of age, ask a doctor before use
- before using this product, read the enclosed User's Guide for complete directions and other important information
- stop smoking completely when you begin using the lozenge
- if you smoke your first cigarette within 30 minutes of waking up, use 4mg nicotine lozenge
- if you smoke your first cigarette more than 30 minutes after waking up, use 2mg nicotine lozenge according to the following 12 week schedule:

Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to 12
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours

## Drug Facts

### Active ingredient (in each lozenge)

Nicotine polacrilex, 2 mg ..... Stop smoking aid

### Purpose

**Use** • reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking

### Warnings

If you are pregnant or breast-feeding, only use this medicine on the advice of your health care provider. Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.

### Ask a doctor before use if you have

- heart disease, recent heart attack, or irregular heartbeat. Nicotine can increase your heart rate.
- high blood pressure not controlled with medication. Nicotine can increase your blood pressure.
- stomach ulcer or diabetes

### Ask a doctor or pharmacist before use if you are

- using a non-nicotine stop smoking drug
- taking prescription medicine for depression or asthma. Your prescription dose may need to be adjusted.

### Stop use and ask a doctor if

- mouth problems occur
- persistent indigestion or severe sore throat occurs
- irregular heartbeat or palpitations occur
- you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat
- you have symptoms of an allergic reaction (such as difficulty breathing or rash)

**Keep out of reach of children and pets.** Nicotine lozenges may have enough nicotine to make children and pets sick. If you need to remove the lozenge, wrap it in paper and throw away in the trash. In case of overdose, get medical help or contact a Poison Control Center right away.

## Drug Facts

### Active ingredient (in each lozenge)

Nicotine polacriflex, 2mg ..... Stop smoking aid

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**Use** • reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking

### Warnings

If you are pregnant or breast-feeding, only use this medicine on the advice of your health care provider. Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.

### Do not use

- if you continue to smoke, chew tobacco, use snuff, or use a nicotine patch or other nicotine containing product

### Ask a doctor before use if you have

- a sodium-restricted diet
- heart disease, recent heart attack, or irregular heartbeat. Nicotine can increase your heart rate.
- high blood pressure not controlled with medication. Nicotine can increase your blood pressure.
- stomach ulcer or diabetes

### Ask a doctor or pharmacist before use if you are

- using a non-nicotine stop smoking drug
- taking prescription medicine for depression or asthma. Your prescription dose may need to be adjusted.

### Stop use and ask a doctor if

- mouth problems occur
- persistent indigestion or severe sore throat occurs
- irregular heartbeat or palpitations occur
- you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat

**Keep out of reach of children and pets.** Nicotine lozenges may have enough nicotine to make children and pets sick. If you need to remove the lozenge, wrap it in paper and throw away in the trash. In case of overdose, get medical help or contact a Poison Control Center right away.

### Directions

- if you are under 18 years of age, ask a doctor before use
- before using this product, read the enclosed User's Guide for complete directions and other important information
- stop smoking completely when you begin using the lozenge
- if you smoke your first cigarette within 30 minutes of waking up, use 4mg nicotine lozenge
- if you smoke your first cigarette more than 30 minutes after waking up, use 2mg nicotine lozenge according to the following 12 week schedule:

Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to 12
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours

## Drug Facts (continued)

### Directions

- if you are under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you.
- before using this product, read the enclosed User's Guide for complete directions and other important information
- begin using the lozenge on your quit day
- if you smoke your first cigarette within 30 minutes of waking up, use 4 mg nicotine lozenge
- if you smoke your first cigarette more than 30 minutes after waking up, use 2 mg nicotine lozenge according to the following 12 week schedule:

Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to 12
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours

- nicotine lozenge is a medicine and must be used a certain way to get the best results
- place the lozenge in your mouth and allow the lozenge to slowly dissolve. Minimize swallowing. **Do not chew or swallow lozenge.**
- you may feel a warm or tingling sensation
- occasionally move the lozenge from one side of your mouth to the other until completely dissolved
- do not eat or drink 15 minutes before using or while the lozenge is in your mouth
- to improve your chances of quitting, use at least 9 lozenges per day for the first 6 weeks
- do not use more than one lozenge at a time or continuously use one lozenge after another since this may cause you hiccups, heartburn, nausea or other side effects
- **do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day.**
- it is important to complete treatment. If you feel you need to use the lozenge for a longer period to keep from smoking, talk to your health care provider.

### Other information

- each lozenge contains: sodium, 5 mg
- store at 20 - 25°C (68 - 77°F)
- keep vial tightly closed and protect from light

**Inactive ingredients** acesulfame potassium, calcium polycarbophil, flavors, magnesium stearate, mannitol, potassium bicarbonate, sodium alginate, sodium carbonate, xanthan gum

**Questions or comments?** call toll-free 1-888-569-1743 (English/Spanish) weekdays (9:00 am - 4:30 pm ET)

## Drug Facts (continued)

- nicotine lozenge is a medicine and must be used a certain way to get the best results
- place the lozenge in your mouth and allow the lozenge to slowly dissolve (about 20 - 30 minutes). Minimize swallowing. **Do not chew or swallow lozenge.**
- you may feel a warm or tingling sensation
- occasionally move the lozenge from one side of your mouth to the other until completely dissolved (about 20 - 30 minutes)
- do not eat or drink 15 minutes before using or while the lozenge is in your mouth
- to improve your chances of quitting, use at least 9 lozenges per day for the first 6 weeks
- do not use more than one lozenge at a time or continuously use one lozenge after another since this may cause you hiccups, heartburn, nausea or other side effects
- **do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day.**
- stop using the nicotine lozenge at the end of 12 weeks. If you still feel the need to use nicotine lozenges, talk to your doctor.

### Other information

- each lozenge contains: sodium, 18mg
- store at 20 - 25°C (68 - 77°F)
- keep POPPAC tightly closed and protect from light

**Inactive ingredients** acesulfame potassium, butylhydroxy toluene, calcium polycarboxophil, flavor, magnesium stearate, maltodextrin, mannitol, potassium bicarbonate, sodium alginate, sodium carbonate, xanthan gum

### Questions or comments?

call toll-free 1-888-569-1743 (English/Spanish) weekdays (9:00 am - 4:30 pm ET)

## Drug Facts (continued)

### Directions

- if you are under 18 years of age, ask a doctor before use. **No studies have been done to show if this product will work for you.**
- before using this product, read the enclosed User's Guide for complete directions and other important information
- begin using the lozenge on your quit day
- **if you smoke your first cigarette within 30 minutes of waking up,** use 4 mg nicotine lozenge
- **if you smoke your first cigarette more than 30 minutes after waking up,** use 2 mg nicotine lozenge according to the following 12 week schedule:

Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to 12
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours

- **nicotine lozenge is a medicine and must be used a certain way to get the best results**
- place the lozenge in your mouth and allow the lozenge to slowly dissolve. Minimize swallowing. **Do not chew or swallow lozenge.**
- you may feel a warm or tingling sensation
- occasionally move the lozenge from one side of your mouth to the other until completely dissolved
- do not eat or drink 15 minutes before using or while the lozenge is in your mouth
- to improve your chances of quitting, use at least 9 lozenges per day for the first 6 weeks
- do not use more than one lozenge at a time or continuously use one lozenge after another since this may cause you hiccups, heartburn, nausea or other side effects
- **do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day.**
- it is important to complete treatment. If you feel you need to use the lozenge for a longer period to keep from smoking, talk to your health care provider.

### Other information

- each lozenge contains: sodium, 5 mg
- store at 20 - 25°C (68 - 77°F)
- keep vial tightly closed and protect from light

**Inactive ingredients** acesulfame potassium, calcium polycarboxophil, flavors, magnesium stearate, mannitol, potassium bicarbonate, sodium alginate, sodium carbonate, xanthan gum

**Questions or comments?** call toll-free 1-888-569-1743 (English/Spanish) weekdays (9:00 am - 4:30 pm ET)



# WHICH REGIMEN is MOST APPROPRIATE for PETER?

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- (1) Combination NRT
- (2) Pre-quit NRT
- (3) High-dose NRT
- (4) High-dose bupropion



# Summary of Therapy Options: Peter

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## **SUFFICIENT EVIDENCE to RECOMMEND:**

- Combination NRT

## **INSUFFICIENT EVIDENCE to RECOMMEND:**

- Pre-quit NRT
- High-dose NRT
- Extended duration NRT

## **SUFFICIENT EVIDENCE to NOT RECOMMEND:**

- High-dose bupropion



## CASE B: SUZANNE

---

Suzanne, 45 yo, s/p ankle injury sustained while skiing (otherwise healthy); her orthopedic surgeon has refused to perform a ligament reconstruction procedure if she is smoking due to potential for poor surgical outcomes.

Current medications: ibuprofen 400mg prn

She is here today for assistance with quitting.

**What questions do you want to ask Suzanne?**



## SUMMARY, CASE B: SUZANNE

Suzanne, 45 yo, s/p ankle injury sustained while skiing (otherwise healthy); her orthopedic surgeon has refused to perform a ligament reconstruction procedure if she is smoking

### **Key points to consider for medication selection:**

- High dependence level (30 cig/day)
- Prior attempts:
  - Zyban; refuses retrial due to side effects
  - Nicotine patch; severe withdrawal, relapse after 1 week
  - Varenicline; well tolerated and effective for short-term (3 wks); experienced withdrawal sx during treatment
- Concerns about adherence with complex regimens



# WHICH REGIMEN is MOST APPROPRIATE for SUZANNE?

- (1) Varenicline, standard dosing
- (2) Varenicline, standard dosing with up to 35-day preloading
- (3) High-dose varenicline
- (4) Varenicline, standard dosing + NRT
- (5) Combination NRT



# OPTION #1:

## Varenicline, standard dosing

### Rationale:

- Re-initiation success rates (6 mo):
  - Nicotine patch, up to 6.4% with NRT\*
  - Bupropion, 12%\*\*
  - Varenicline, unknown
- Prior attempt:
  - Adherence with regimen? Behavioral counseling?

\* Gourlay et al. (1995). BMJ 311;363-366

\* Hughes et al. (2000). J Addict Dis. 19;95-100.

\* Tønnesen et al. (1993). Addiction 88;533-539.

\*\* Gonzales et al. (2001). Clin Pharmacol Ther 69;438-444.

# Retreatment With Varenicline for Smoking Cessation in Smokers Who Have Previously Taken Varenicline: A Randomized, Placebo-Controlled Trial

D Gonzales<sup>1</sup>, P Hajek<sup>2</sup>, L Pliamm<sup>3</sup>, K Nackaerts<sup>4</sup>, L-J Tseng<sup>5</sup>, TD McRae<sup>5</sup> and J Treadow<sup>5</sup>

The efficacy and safety of retreatment with varenicline in smokers attempting to quit were evaluated in this randomized, double-blind, placebo-controlled, multicenter trial (Australia, Belgium, Canada, the Czech Republic, France, Germany, the United Kingdom, and the United States). Participants were generally healthy adult smokers ( $\geq 10$  cigarettes/day) with  $\geq 1$  prior quit attempt ( $\geq 2$  weeks) using varenicline and no quit attempts in  $\leq 3$  months; they were randomly assigned (1:1) to 12 weeks' varenicline ( $n = 251$ ) or placebo ( $n = 247$ ) treatment, with individual counseling, plus 40 weeks' nontreatment follow-up. The primary efficacy end point was the carbon monoxide-confirmed ( $\leq 10$  ppm) continuous abstinence rate for weeks 9–12, which was 45.0% (varenicline;  $n = 249$ ) vs. 11.8% (placebo;  $n = 245$ ; odds ratio: 7.08; 95% confidence interval: 4.34, 11.55;  $P < 0.0001$ ). Common varenicline group adverse events were nausea, abnormal dreams, and headache, with no reported suicidal behavior. Varenicline is efficacious and well tolerated in smokers who have previously taken it. Abstinence rates are comparable with rates reported for varenicline-naive smokers.



# Gonzales et al., 2014

## Retreatment with Varenicline

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- RCT; varenicline (n=251) vs placebo (n=247)
- Healthy, adult smokers; at least 10 cig/day
- Mean, 20 cig/day x 30 yrs
- At least 1 prior quit attempt; at least 2 wks on drug using varenicline (none in past 3 months)
- 74% reported 3+ prior quit attempts



# Gonzales et al., 2014 (cont'd)

## Retreatment with Varenicline

- Compliance: Received any dose of drug for >80% of planned number of days in study
  - 78%, varenicline; 71%, placebo
- Among >80% compliant (weeks 9-12) at 3 mo:
  - 56.4%, varenicline; 15.4%, placebo [OR, 8.99]
- CAR at 6 mo:
  - 20.1%, varenicline; 3.3%, placebo [OR, 9.00]



## OPTION #2:

Varenicline, standard dosing with preloading

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### Rationale:

- Mechanism of action,  $\alpha 4\beta 2$  nicotinic receptor partial agonist:
  - Alleviates withdrawal (dopamine reward pathway)
  - Reduces reward/pleasure associated with smoking (blocks nicotine at receptor sites)
  - Reduction in smoking prior to quit date
- Oct 2014 update: Package insert permits preloading up to 35 days prior to quit date (1 week is standard)

# Use of Varenicline for 4 Weeks Before Quitting Smoking

## *Decrease in Ad Lib Smoking and Increase in Smoking Cessation Rates*

Peter Hajek, PhD; Hayden J. McRobbie, PhD; Katie E. Myers, MSc, CPsychol;  
John Stapleton, MSc; Al-Rehan Dhanji, MBBS, MRCS

**Background:** The use of varenicline tartrate alleviates postquit withdrawal discomfort, but it also seems to reduce the “reward” associated with smoking. The current treatment schedule, which commences 1 week before quitting, relies primarily on the first mechanism. We set out to determine whether increasing the prequit medication period renders cigarettes less satisfying and facilitates quitting.

**Methods:** One hundred one smokers attending a stop-smoking clinic in London, United Kingdom, were randomly allocated to receive varenicline for 4 weeks before

with 36.7% of participants reducing their cotinine concentrations by more than 50% (reducers). Varenicline preloading did not affect postquit withdrawal symptoms, but it increased 12-week abstinence rates (47.2% in the varenicline arm vs 20.8% in the placebo arm,  $P = .005$ ). The effect was particularly strong among the reducers in the varenicline arm (66.7% in reducers vs 22.6% in nonreducers,  $P = .002$ ). Varenicline preloading was well tolerated.

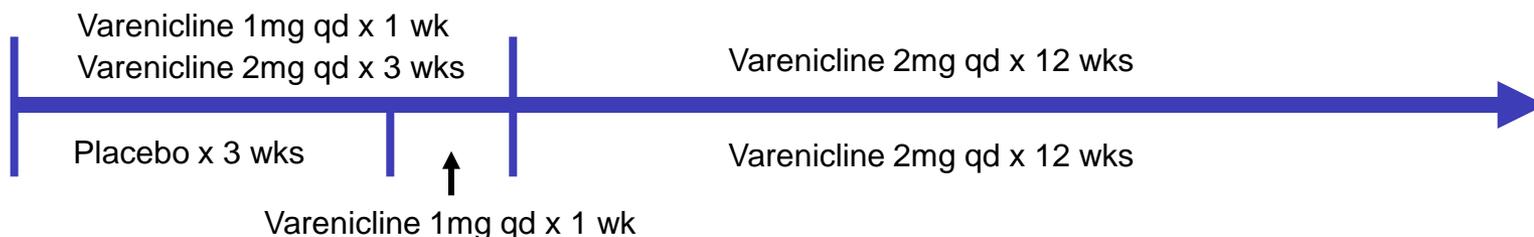
**Conclusions:** Although several issues remain to be clarified, varenicline preloading can generate a substantial re-



# Hajek et al., 2011

## Varenicline, standard dosing with preloading

- ~58% male; age, 45 yo; 19 cig/day; 17 yo at initiation; no psychiatric or other serious illnesses
- Treatment sessions at BL, wk 3, wk 4, and weekly up to wk 8
- Smoke ad libitum until week 4, then quit

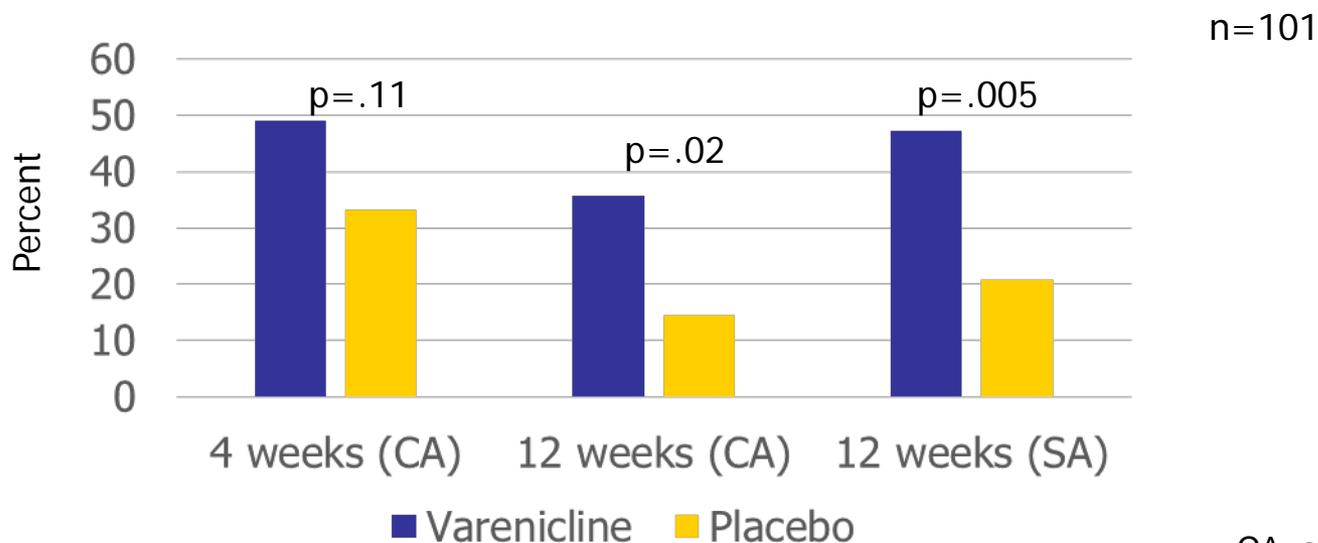




# Hajek et al., 2011

## Varenicline, standard dosing with preloading

- Pre-quit: Significant between-group differences in reductions in smoking, CO, and cotinine
  - Reduced enjoyment of smoking and urges to smoke



CA=continuous abstinence  
SA=sustained abstinence,  $\leq 5$  cig



# OPTION #3:

## High-dose varenicline

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### Rationale:

- Dose-response observed for 1mg (doubles) and 2mg (triples) vs placebo at 6 mo
- Patients with limited response (no reduction in cotinine) to standard varenicline dose during first 4 wks of preloading tx had poorer outcomes (Hajek et al. 2011)
  - Might benefit from higher dosages
- Primary concern: side effect profile

# Increasing the Dose of Varenicline in Patients Who Do Not Respond to the Standard Dose

Carlos A. Jiménez-Ruiz, MD, PhD; Malena Barrios, MD; Sandra Peña, MD; Ana Cicero, MD; Marisa Mayayo, BSN; Maribel Cristóbal, BSN; and Lidia Perera, BSN

## Abstract

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Varenicline is a partial agonist of  $\alpha 4\beta 2$  nicotinic acetylcholine receptors. It is effective at dosages of 2 mg/d for 12 weeks, but not for all smokers. It is possible that increasing the dose can increase the drug efficacy. We reviewed the clinical records of consecutive smokers who had been treated in 2 smoking cessation services with varenicline at doses of 3 mg/d. In all cases, the treatment program consisted of a combination of behavioral therapy and drug treatment. Varenicline was prescribed at a standard dosage for 8 weeks. After 8 weeks of treatment, the dose was increased to 3 mg/d if patients tolerated varenicline well and continued smoking or, in spite of not smoking, if they experienced severe withdrawal symptoms. The sample included 73 patients, of whom 52 continued to smoke at 8 weeks and 21 stopped smoking but reported severe



# Jimenez-Ruiz et al., 2013

## Increasing the Dose of Varenicline

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- Observational study of highly-dependent smokers
  - Standard varenicline dose x 8 wks
  - Increased to 1.0mg TID in 73 patients who continued smoking (n=52) or had severe withdrawal (n=21)
  - CAR: 40% and 48%, respectively, wks 9-24
  - 30% mild adverse events; 2 D/C, nausea/vomiting
- Limited adverse events; high success in this population
- No comparison group

Original Investigation

# Increasing Varenicline Dose in Smokers Who Do Not Respond to the Standard Dosage A Randomized Clinical Trial

Peter Hajek, PhD; Hayden McRobbie, MB, ChB, PhD; Katherine Myers Smith, DPsych;  
Anna Phillips, BSc; Danielle Cornwall, MSc; Al-Rehan Dhanji, MB, BS

**IMPORTANCE** Standard varenicline tartrate dosing was formulated to avoid adverse effects (primarily nausea), but some patients may be underdosed. To our knowledge, no evidence-based guidance exists for physicians considering increasing varenicline dose if there is no response to the standard dosage.



# Hajek et al., 2015

## Increasing Varenicline Dose

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- Double-blind RCT (n=200)
  - Varenicline (2mg/day), 3 wks pre-quit
  - No reduced satisfaction from smoking; <50% reduction in cigarette consumption
  - Increased by 0.5mg/BID on days 12, 15, and 18; up to max of 5mg/day
- **No effect** on withdrawal sx or cessation (3 mo) in low responders to standard dosage
  - 26.0% hi-dose; 23.0% standard dose
  - More nausea and vomiting in hi-dose arm



## OPTION #4:

Varenicline, standard dosing + NRT

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### **Rationale:**

- Monotherapy efficacy has much room for improvement
- Combination therapy, in general, has been shown to be more effective than monotherapy
- Complementary mechanisms of action not fully understood

**RESEARCH ARTICLE**

**Open Access**

# Is a combination of varenicline and nicotine patch more effective in helping smokers quit than varenicline alone? A randomised controlled trial

Peter Hajek<sup>1</sup>, Katie Myers Smith<sup>1</sup>, Al-Rehan Dhanji<sup>2</sup> and Hayden McRobbie<sup>1\*</sup>

## Abstract

**Background:** Nicotine replacement therapy (NRT) and varenicline are both effective in helping smokers quit. There is growing interest in combining the two treatments to improve treatment outcomes, but no experimental data exist on whether this is efficacious. This double-blind randomised controlled trial was designed to evaluate whether adding nicotine patches to varenicline improves withdrawal relief and short-term abstinence rates.

**Methods:** 117 participants seeking help to stop smoking were randomly allocated to varenicline plus placebo patch or varenicline plus nicotine patch (15 mg/16 hour). Varenicline use commenced one week prior to the target quit date (TQD), patch use started on the TQD. Ratings of urges to smoke and cigarette withdrawal symptoms were collected weekly over 4 weeks post-TQD. Medication use and smoking status were established at 1, 4 and 12 weeks. Participants lost to follow-up were included as continuing smokers.

**Results:** 92% of participants used both medications during the first week after the TQD. The combination treatment generated no increase in nausea or other adverse effects. It had no overall effect on urges to smoke or on other withdrawal symptoms. The combination treatment did not improve biochemically validated abstinence



# Hajek et al., 2013

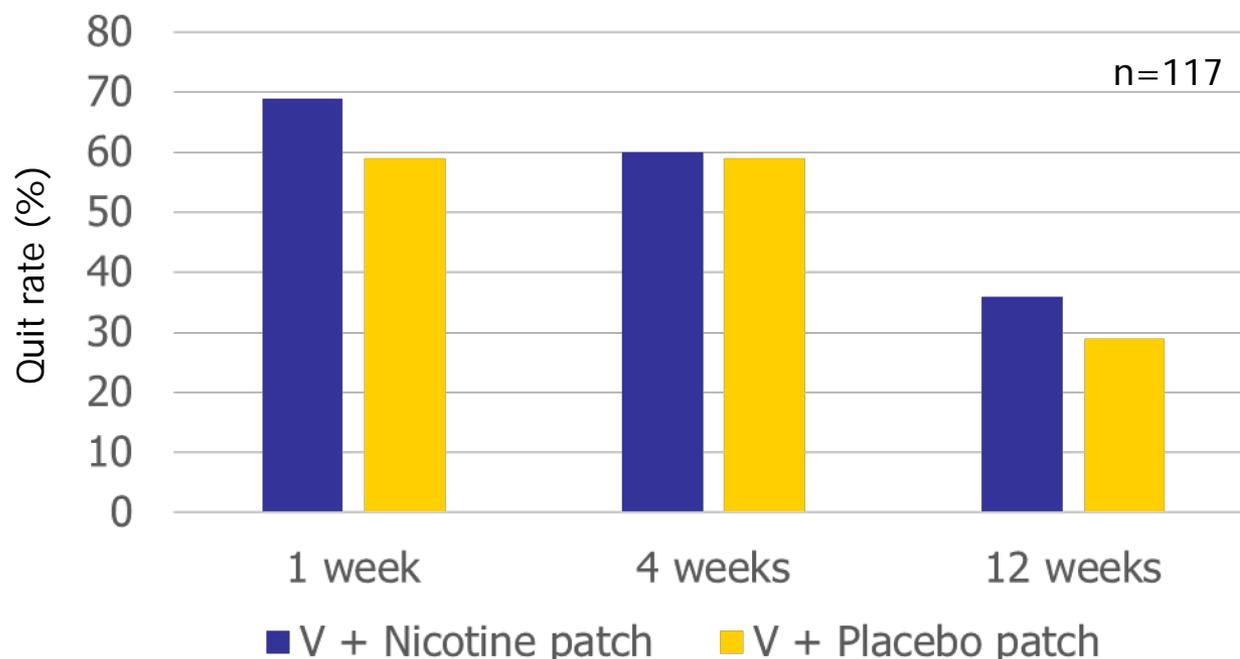
## Varenicline, standard dosing + NRT

- Double-blind RCT (n=117)
  - Varenicline: 0.5mg QD days 1-3; 0.5mg BID days 4-7; 1mg BID day 8 to end of treatment (12 weeks)
  - 15mg/16hr nicotine patch or placebo patch x 4 weeks
  - 67% male; age, 44-45; 17-18 cigarettes/day; 17-18 at initiation; 2.8 prior quit attempts



# Hajek et al., 2013

## Varenicline, standard dosing + NRT



Nonsignificant at all time points; weeks 1 and 4 biochemical verification, week 12 self-report. High adherence at week 1; at week 4, ~20% nonadherence with patch and ~10% nonadherence with varenicline. At 12 weeks, ~75% nonadherence with varenicline (similar across both groups at all time points).

Original Investigation

# Efficacy of Varenicline Combined With Nicotine Replacement Therapy vs Varenicline Alone for Smoking Cessation

## A Randomized Clinical Trial

Coenraad F. N. Koegelenberg, MD, PhD; Firdows Noor, MD; Eric D. Bateman, MD, PhD; Richard N. van Zyl-Smit, MD, PhD; Axel Bruning, MD; John A. O'Brien, MD; Clifford Smith, MD; Mohamed S. Abdool-Gaffar, MD; Shaunagh Emanuel, MD; Tonya M. Esterhuizen, MSc; Elvis M. Irusen, MD, PhD

**IMPORTANCE** Behavioral approaches and pharmacotherapy are of proven benefit in assisting smokers to quit, but it is unclear whether combining nicotine replacement therapy (NRT) with varenicline to improve abstinence is effective and safe.

**OBJECTIVE** To evaluate the efficacy and safety of combining varenicline and a nicotine patch vs varenicline alone in smoking cessation.

**DESIGN, SETTING, AND PARTICIPANTS** Randomized, blinded, placebo-controlled clinical trial with a 12-week treatment period and a further 12-week follow-up conducted in 7 centers in South Africa from April 2011 to October 2012. Four hundred forty-six generally healthy smokers were randomized (1:1); 435 were included in the efficacy and safety analyses.

 [Related article page 180](#)

 [Supplemental content at jama.com](#)



# Koegelenberg et al., 2014

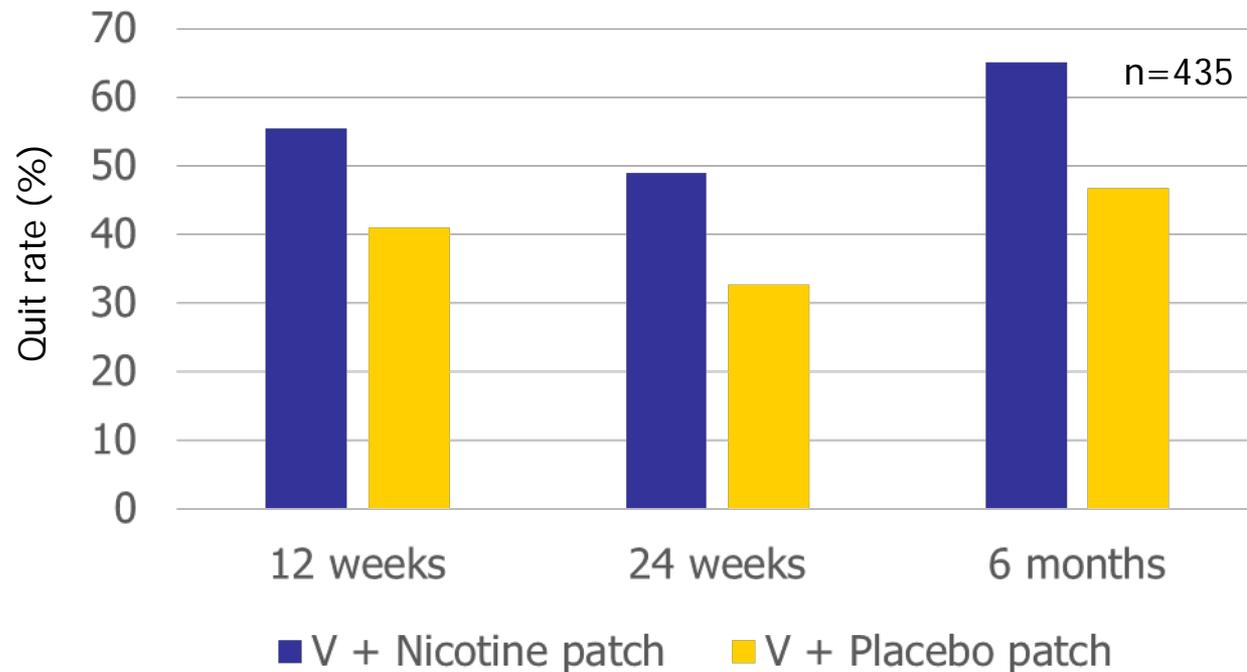
## Varenicline, standard dosing + NRT

- Blinded RCT (n=435)
  - Varenicline: 0.5mg QD days 1-3; 0.5mg BID days 4-7; 1mg BID day 8 to end of week 12; tapered last week (14 weeks)
  - 15mg/16hr nicotine patch or placebo patch started 2 weeks prior to quit date (14 weeks)
  - 38% male; age, 46; 16 cigarettes/day; 26 yrs smoked; 1-2 prior quit attempts



# Koegelenberg et al., 2014

## Varenicline, standard dosing + NRT



Significant at all time points.  
Weeks 12 and 24 are 4-wk continuous abstinence.  
Six months is 7-day point prevalence abstinence.  
Biochemical verification via exhaled carbon monoxide.  
High adherence (>75% of participants) with both medications.



# OPTION #5: Combination NRT

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## **Rationale:**

- Failed nicotine patch monotherapy due to extreme withdrawal
- Combination NRT therapy has been shown to be more effective than NRT monotherapy



# WHICH REGIMEN is MOST APPROPRIATE for SUZANNE?

- (1) Varenicline, standard dosing
- (2) Varenicline, standard dosing with up to 35-day preloading
- (3) High-dose varenicline
- (4) Varenicline, standard dosing + NRT
- (5) Combination NRT



# Summary of Therapy Options: SUZANNE

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## **SUFFICIENT EVIDENCE to RECOMMEND:**

- Varenicline, standard dosing
- Varenicline, standard dosing with preloading
- Combination NRT

## **INSUFFICIENT EVIDENCE to RECOMMEND:**

- Varenicline, standard dosing + NRT [conflicting data]
- High-dose varenicline



# DOSING for SUZANNE

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## **SUFFICIENT EVIDENCE to RECOMMEND:**

- Varenicline, standard dosing
  - 0.5mg QD days 1-3; 0.5mg BID days 4-7; 1mg BID day 8 to end of treatment (12 weeks)
- Varenicline, standard dosing with preloading up to 35 days
  - 0.5mg BID days 1-7; 1mg BID through end of treatment
- Combination NRT

## **INSUFFICIENT EVIDENCE to RECOMMEND:**

- Varenicline, standard dosing + NRT
- High-dose varenicline (generally 3mg QD)



“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  
assessed at each encounter.**



# TOOLS

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## STEP One: ASK about Tobacco Use

### ➤ Suggested Dialogue

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

## STEP Two: ADVISE to Quit

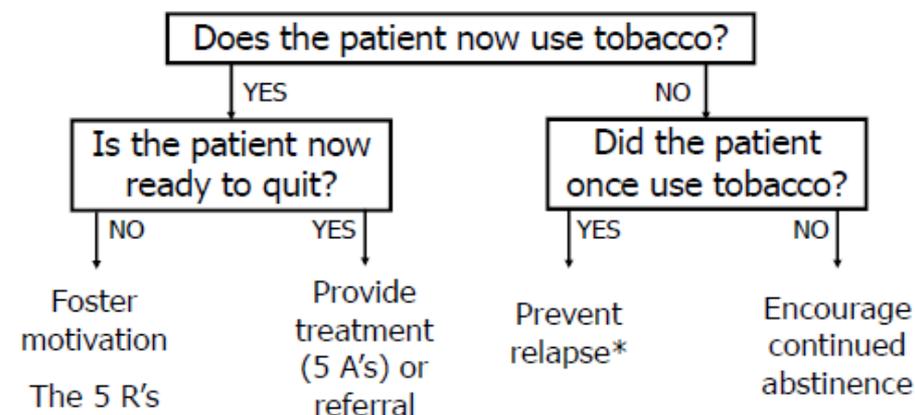
### ➤ Suggested Dialogue

- Quitting 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 would be more than happy to work with you to design a treatment plan.
- Prior to imparting advice, consider asking the patient for permission to do so – e.g., "May I tell you why this concerns me?" [then elaborate on patient-specific concerns]

## STEP Three: ASSESS Readiness to Quit

### ➤ Suggested Dialogue

- For current tobacco users: What are your thoughts about quitting? Might you consider quitting sometime in the next month?



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

Fiore MC, Jaén CR, Baker TB, et al. *Treating Tobacco Use and Dependence: 2008 Update*. Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. May 2008.

## STEP Four: ASSIST with Quitting



### ✓ Assess Tobacco Use History

- Current use: type(s) of tobacco used, 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, adherence, 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
- 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: ideally, 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: adherence, 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 strategies to prevent relapse.
- ✓ Congratulate patients for continued success.



# PHARMACOLOGIC PRODUCT GUIDE: FDA-APPROVED MEDICATIONS FOR SMOKING CESSATION

		NICOTINE REPLACEMENT THERAPY (NRT) FORMULATIONS				BUPROPION SR	VARENICLINE
		GUM	LOZENGE	TRANSDERMAL PATCH	NASAL SPRAY	ORAL INHALER	
PRODUCT	<p>Nicorette<sup>1</sup>, ZONNIC<sup>2</sup>, Generic OTC 2 mg, 4 mg original, cinnamon, fruit, mint</p>	<p>Nicorette Lozenge,<sup>1</sup> Nicorette Mini Lozenge,<sup>1</sup> Generic OTC 2 mg, 4 mg; cherry, mint</p>	<p>NicoDerm CQ<sup>1</sup>, Generic OTC (NicoDerm CQ, generic) Rx (generic) 7 mg, 14 mg, 21 mg (24-hr release)</p>	<p>Nicotrol NS<sup>3</sup> Rx Metered spray 10 mg/mL aqueous solution</p>	<p>Nicotrol Inhaler<sup>3</sup> Rx 10 mg cartridge delivers 4 mg inhaled vapor</p>	<p>Zyban<sup>1</sup>, Generic Rx 150 mg sustained-release tablet</p>	<p>Chantix<sup>3</sup> Rx 0.5 mg, 1 mg tablet</p>
PRECAUTIONS	<ul style="list-style-type: none"> <li>Recent (<math>\leq 2</math> weeks) myocardial infarction</li> <li>Serious underlying arrhythmias</li> <li>Serious or worsening angina pectoris</li> <li>Temporomandibular joint disease</li> <li>Pregnancy<sup>4</sup> and breastfeeding</li> <li>Adolescents (&lt;18 years)</li> </ul>	<ul style="list-style-type: none"> <li>Recent (<math>\leq 2</math> weeks) myocardial infarction</li> <li>Serious underlying arrhythmias</li> <li>Serious or worsening angina pectoris</li> <li>Pregnancy<sup>4</sup> and breastfeeding</li> <li>Adolescents (&lt;18 years)</li> </ul>	<ul style="list-style-type: none"> <li>Recent (<math>\leq 2</math> weeks) myocardial infarction</li> <li>Serious underlying arrhythmias</li> <li>Serious or worsening angina pectoris</li> <li>Pregnancy<sup>4</sup> (Rx formulations, category D) and breastfeeding</li> <li>Adolescents (&lt;18 years)</li> </ul>	<ul style="list-style-type: none"> <li>Recent (<math>\leq 2</math> 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> <li>Pregnancy<sup>4</sup> (category D) and breastfeeding</li> <li>Adolescents (&lt;18 years)</li> </ul>	<ul style="list-style-type: none"> <li>Recent (<math>\leq 2</math> weeks) myocardial infarction</li> <li>Serious underlying arrhythmias</li> <li>Serious or worsening angina pectoris</li> <li>Bronchospastic disease</li> <li>Pregnancy<sup>4</sup> (category D) and breastfeeding</li> <li>Adolescents (&lt;18 years)</li> </ul>	<ul style="list-style-type: none"> <li>Concomitant therapy with medications/conditions known to lower the seizure threshold</li> <li>Hepatic impairment</li> <li>Pregnancy<sup>4</sup> (category C) and breastfeeding</li> <li>Adolescents (&lt;18 years)</li> </ul> <p><b>Warning:</b></p> <ul style="list-style-type: none"> <li>BLACK-BOXED WARNING for neuropsychiatric symptoms<sup>5</sup></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/benzodiazepines</li> <li>MAO inhibitors in preceding 14 days; concurrent use of reversible MAO inhibitors (e.g., linezolid, methylene blue)</li> </ul>	<ul style="list-style-type: none"> <li>Severe renal impairment (dosage adjustment is necessary)</li> <li>Pregnancy<sup>4</sup> (category C) and breastfeeding</li> <li>Adolescents (&lt;18 years)</li> </ul> <p><b>Warning:</b></p> <ul style="list-style-type: none"> <li>BLACK-BOXED WARNING for neuropsychiatric symptoms<sup>5</sup></li> </ul>
DOSING	<p><i>1<sup>st</sup> cigarette <math>\leq 30</math> minutes after waking:</i> 4 mg <i>1<sup>st</sup> cigarette &gt;30 minutes after waking:</i> 2 mg</p> <p>Weeks 1–6: 1 piece q 1–2 hours Weeks 7–9: 1 piece q 2–4 hours Weeks 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 tingle fades</li> <li>Repeat chew/park steps until most of the nicotine is gone (tingle does not return; generally 30 min)</li> <li>Park in different areas of mouth</li> <li>No food or beverages 15 minutes before or during use</li> </ul>	<p><i>1<sup>st</sup> cigarette <math>\leq 30</math> minutes after waking:</i> 4 mg <i>1<sup>st</sup> cigarette &gt;30 minutes after waking:</i> 2 mg</p> <p>Weeks 1–6: 1 lozenge q 1–2 hours Weeks 7–9: 1 lozenge q 2–4 hours Weeks 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 for standard; 10 minutes for mini)</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><i>&gt;10 cigarettes/day:</i> 21 mg/day x 4–6 weeks 14 mg/day x 2 weeks 7 mg/day x 2 weeks</p> <p><i><math>\leq 10</math> cigarettes/day:</i> 14 mg/day x 6 weeks 7 mg/day x 2 weeks</p> <ul style="list-style-type: none"> <li>Rotate patch application site daily; do not apply a new patch to the same skin site for at least one week</li> <li>May wear patch for 16 hours if patient experiences sleep disturbances (remove at bedtime)</li> <li>Duration: 8–10 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 or – 40 doses/day</li> <li>For best results, initially use at least 8 doses/day</li> <li>Do 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 Individualize dosing; initially use 1 cartridge q 1–2 hours</p> <ul style="list-style-type: none"> <li>Best effects with continuous puffing for 20 minutes</li> <li>Initially use at least 6 cartridges/day</li> <li>Nicotine in cartridge is depleted after 20 minutes of active puffing</li> <li>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>No food or beverages 15 minutes before or during use</li> <li>Duration: 3–6 months</li> </ul>	<p>150 mg po q AM x 3 days, then 150 mg po bid</p> <ul style="list-style-type: none"> <li>Do not exceed 300 mg/day</li> <li>Begin therapy 1–2 weeks prior to quit date</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>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 Days 4–7: 0.5 mg po bid Weeks 2–12: 1 mg po bid</p> <ul style="list-style-type: none"> <li>Begin therapy 1 week prior to quit date</li> <li>Take dose after eating and with a full glass of water</li> <li>Dose tapering is not necessary</li> <li>Dosing adjustment is necessary for patients with severe renal impairment</li> <li>Duration: 12 weeks; an additional 12-week course may be used in selected patients</li> </ul>

NICOTINE REPLACEMENT THERAPY (NRT) FORMULATIONS							BUPROPION SR	VARENICLINE
	GUM	LOZENGE	TRANSDERMAL PATCH	NASAL SPRAY	ORAL INHALER			
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, 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>Cough</li> <li>Headache</li> <li>Rhinitis</li> <li>Dyspepsia</li> <li>Hiccups</li> </ul>	<ul style="list-style-type: none"> <li>Insomnia</li> <li>Dry mouth</li> <li>Nervousness/difficulty concentrating</li> <li>Nausea</li> <li>Dizziness</li> <li>Constipation</li> <li>Rash</li> <li>Seizures (risk is 0.1%)</li> <li>Neuropsychiatric symptoms (rare; see PRECAUTIONS)</li> </ul>	<ul style="list-style-type: none"> <li>Nausea</li> <li>Sleep disturbances (insomnia, abnormal/vivid dreams)</li> <li>Constipation</li> <li>Flatulence</li> <li>Vomiting</li> <li>Neuropsychiatric symptoms (rare; see PRECAUTIONS)</li> </ul>	
ADVANTAGES	<ul style="list-style-type: none"> <li>Might serve as an oral substitute for tobacco</li> <li>Might delay weight gain</li> <li>Can be titrated to manage withdrawal symptoms</li> <li>Can be used in combination with other agents to manage situational urges</li> </ul>	<ul style="list-style-type: none"> <li>Might serve as an oral substitute for tobacco</li> <li>Might delay weight gain</li> <li>Can be titrated to manage withdrawal symptoms</li> <li>Can be used in combination with other agents to manage situational urges</li> </ul>	<ul style="list-style-type: none"> <li>Once-daily dosing associated with fewer adherence problems</li> <li>Of all NRT products, its use is least obvious to others</li> <li>Can be used in combination with other agents; delivers consistent nicotine levels over 24 hours</li> </ul>	<ul style="list-style-type: none"> <li>Can be titrated to rapidly manage withdrawal symptoms</li> <li>Can be used in combination with other agents to manage situational urges</li> </ul>	<ul style="list-style-type: none"> <li>Might serve as an oral substitute for tobacco</li> <li>Can be titrated to manage withdrawal symptoms</li> <li>Mimics hand-to-mouth ritual of smoking</li> <li>Can be used in combination with other agents to manage situational urges</li> </ul>	<ul style="list-style-type: none"> <li>Twice-daily oral dosing is simple and associated with fewer adherence problems</li> <li>Might delay weight gain</li> <li>Might be beneficial in patients with depression</li> <li>Can be used in combination with NRT agents</li> </ul>	<ul style="list-style-type: none"> <li>Twice-daily oral dosing is simple and associated with fewer adherence problems</li> <li>Offers a different mechanism of action for patients who have failed other agents</li> </ul>	
DISADVANTAGES	<ul style="list-style-type: none"> <li>Need for frequent dosing can compromise adherence</li> <li>Might be problematic for patients with significant dental work</li> <li>Proper chewing technique is necessary for effectiveness and to minimize adverse effects</li> <li>Gum chewing might not be acceptable or desirable for some patients</li> </ul>	<ul style="list-style-type: none"> <li>Need for frequent dosing can compromise adherence</li> <li>Gastrointestinal side effects (nausea, hiccups, heartburn) might be bothersome</li> </ul>	<ul style="list-style-type: none"> <li>When used as monotherapy, cannot be titrated to acutely manage withdrawal symptoms</li> <li>Not recommended for use by patients with dermatologic conditions (e.g., psoriasis, eczema, atopic dermatitis)</li> </ul>	<ul style="list-style-type: none"> <li>Need for frequent dosing can compromise adherence</li> <li>Nasal administration might not be acceptable or desirable for some patients; nasal irritation often problematic</li> <li>Not recommended for use by patients with chronic nasal disorders or severe reactive airway disease</li> </ul>	<ul style="list-style-type: none"> <li>Need for frequent dosing can compromise adherence</li> <li>Cartridges might be less effective in cold environments (<math>\leq 60^{\circ}\text{F}</math>)</li> </ul>	<ul style="list-style-type: none"> <li>Seizure risk is increased</li> <li>Several contraindications and precautions preclude use in some patients (see PRECAUTIONS)</li> <li>Patients should be monitored for potential neuropsychiatric symptoms<sup>5</sup> (see PRECAUTIONS)</li> </ul>	<ul style="list-style-type: none"> <li>Should be taken with food or a full glass of water to reduce the incidence of nausea</li> <li>Patients should be monitored for potential neuropsychiatric symptoms<sup>5</sup> (see PRECAUTIONS)</li> </ul>	
COST/DAY <sup>6</sup>	2 mg or 4 mg: \$1.90–\$3.70 (9 pieces)	2 mg or 4 mg: \$2.66–\$4.10 (9 pieces)	\$1.52–\$3.48 (1 patch)	\$6.09 (8 doses)	\$10.37 (6 cartridges)	\$2.58–\$7.87 (2 tablets)	\$10.50 (2 tablets)	

<sup>1</sup> Marketed by GlaxoSmithKline.

<sup>2</sup> Marketed by Nicovum USA (a subsidiary of Reynolds American, Inc.)

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

<sup>4</sup> The U.S. Clinical Practice Guideline states that pregnant smokers should be encouraged to quit without medication based on insufficient evidence of effectiveness and theoretical concerns with safety. Pregnant smokers should be offered behavioral counseling interventions that exceed minimal advice to quit.

<sup>5</sup> In July 2009, the FDA mandated that the prescribing information for all bupropion- and varenicline-containing products include a black-boxed warning highlighting the risk of serious neuropsychiatric symptoms, including changes in behavior, hostility, agitation, depressed mood, suicidal thoughts and behavior, and attempted suicide. Clinicians should advise patients to stop taking varenicline or bupropion SR and contact a health care provider immediately if they experience agitation, depressed mood, or any changes in behavior that are not typical of nicotine withdrawal, or if they experience suicidal thoughts or behavior. If treatment is stopped due to neuropsychiatric symptoms, patients should be monitored until the symptoms resolve.

<sup>6</sup> Wholesale acquisition cost from Red Book Online. Thomson Reuters, January 2016.

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

For complete prescribing information and a comprehensive listing of warnings and precautions, please refer to the manufacturers' package inserts.



# DRUG INTERACTIONS WITH TOBACCO SMOKE

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 interacts with medications through pharmacokinetic (PK) and 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). Smokers may require higher doses of medications that are CYP1A2 substrates. Upon cessation, dose reductions might be needed. 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, but possible ↓ plasma concentrations (up to 50%); ↓ half-life (35%).</li> </ul>
Bendamustine (Treanda®)	<ul style="list-style-type: none"> <li>▪ Metabolized by CYP1A2. Manufacturer recommends using with caution in smokers due to likely ↓ bendamustine concentrations, with ↑ concentrations of its two active metabolites.</li> </ul>
Caffeine	<ul style="list-style-type: none"> <li>▪ ↑ Metabolism (induction of CYP1A2); ↑ clearance (56%). Caffeine levels likely ↑ after cessation.</li> </ul>
Chlorpromazine (Thorazine®)	<ul style="list-style-type: none"> <li>▪ ↓ Area under the curve (AUC) (by 36%) and serum concentrations (by 24%).</li> <li>▪ ↓ Sedation and hypotension possible in smokers; smokers may require ↑ dosages.</li> </ul>
Clopidogrel (Plavix®)	<ul style="list-style-type: none"> <li>▪ ↑ Metabolism (induction of CYP1A2) of clopidogrel to its active metabolite.</li> <li>▪ Clopidogrel's effects are enhanced in smokers (≥10 cigarettes/day): significant ↑ platelet inhibition, ↓ platelet aggregation; while improved clinical outcomes have been shown, may also ↑ risk of bleeding.</li> </ul>
Clozapine (Clozaril®)	<ul style="list-style-type: none"> <li>▪ ↑ Metabolism (induction of CYP1A2); ↓ plasma concentrations (by 18%).</li> <li>▪ ↑ Levels upon cessation may occur; closely monitor drug levels and reduce dose as required to avoid toxicity.</li> </ul>
Erlotinib (Tarceva®)	<ul style="list-style-type: none"> <li>▪ ↑ Clearance (24%); ↓ trough serum concentrations (2-fold).</li> </ul>



# Rx for Change

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## **Teaching materials and tools:**

<http://rxforchange.ucsf.edu>

## **Continuing education programs:**

<https://ce.pharmacy.purdue.edu/content/intro-tobacco-cessation>

# Questions and Answers



- Submit questions via the **chat box**

# Contact SCLC for technical assistance

**CME/CEUs of up to 2.0 credits are available to all attendees of this live session. Instructions will be emailed after the webinar.**



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# 2016 *Tips* Campaign



[www.cdc.gov/tips](http://www.cdc.gov/tips)

# CME/CEU Statement

## **Accreditation:**

The University of California, San Francisco (UCSF) School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

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**Social Workers:** This course meets the qualifications for 2.0 hours of continuing education credit for MFTs and/or LCSWs as required by the California Board of Behavioral Sciences. If you a social worker in another state, you should check with your state board for approval of this credit.