# Pharmacotherapy Considerations for Tobacco Cessation: Special Considerations with Neuroleptics

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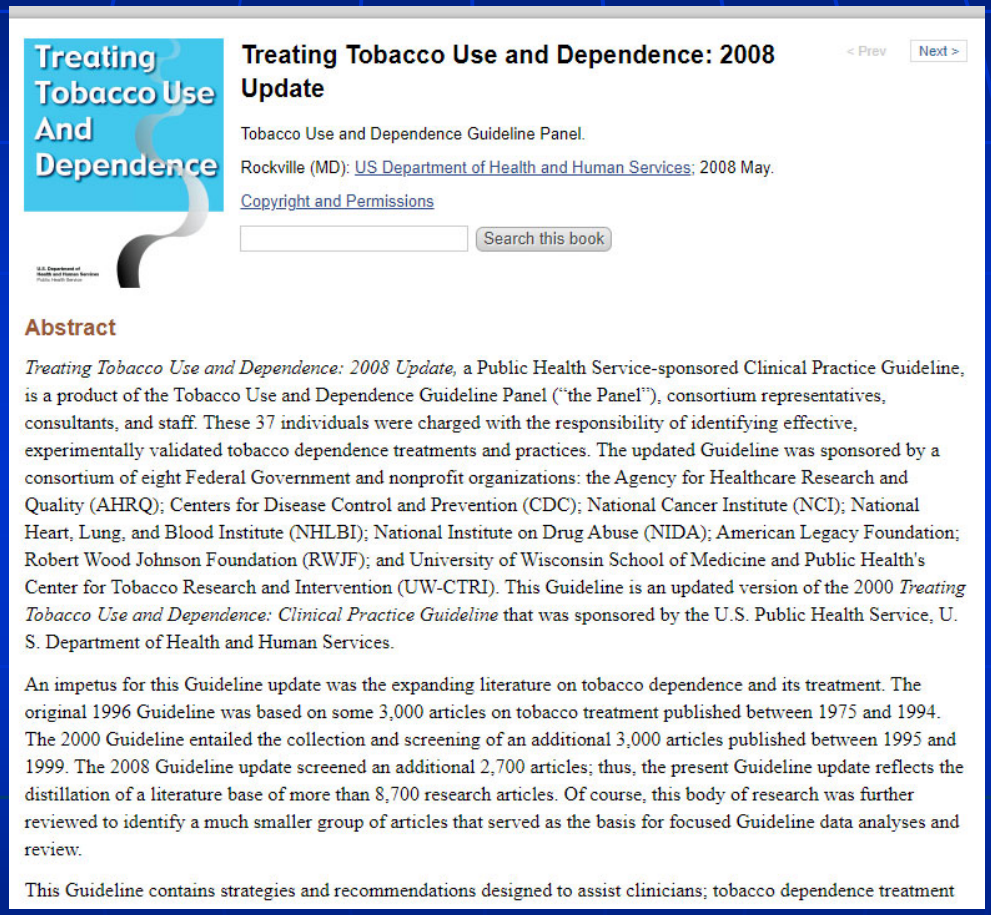
# Learning Objectives

| | |
|---|---|
| Describe | Describe the benefits of combining pharmacotherapy and counseling. |
| Provide | Provide information on correct use, efficacy, adverse events, contraindications, and patient education for all approved tobacco dependence medications. |
| Identify | Identify information that may impact pharmacotherapy decisions. |
| Discuss | Special considerations for patients taking neuroleptics |

# Guiding Document




**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.**

# 5-As Recommended

- Ask-every patient
- Advise- to quit
- Assess-willingness to make quit attempt
- Assist- in making quit attempt
- Arrange-follow-up

# Prescribing Considerations

- Thorough medical history
- Fagerstrom test
- Prior successful experience
- Support system
- Medication choices
- Education
  - Effectiveness
  - Method of action
  - Dosing
  - Side effects
  - Precautions

# Seven FDA-approved medications

Medications with Nicotine:

1. Gum
2. Inhaler
3. Lozenge
4. Nasal spray
5. Patch

- Non-nicotine medications:

6. Bupropion SR
7. Varenicline

All smokers trying to quit should be offered medication, except when contraindicated or for specific populations for which there is insufficient evidence of effectiveness (i.e., pregnant women, smokeless tobacco users, light smokers, and adolescents; see USPHS Guidelines, Chapter 7).

# Combining Counseling and Medication

- Combination of counseling and medication more effective than either medication or counseling alone.
- When feasible, both should be provided (Strength of Evidence = A, p. 101)

# Medication + Counseling

**Table 6.23. Meta-analysis (2008): Effectiveness of and estimated abstinence rates for the number of sessions of counseling in combination with medication vs. medication alone (n = 18 studies)[a]**

| Treatment | Number of arms | Estimated odds ratio (95% C.I.) | Estimated abstinence rate (95% C.I.) |
|---|---|---|---|
| 0–1 session plus medication | 13 | 1.0 | 21.8 |
| 2–3 sessions plus medication | 6 | 1.4 (1.1–1.8) | 28.0 (23.0–33.6) |
| 4–8 sessions plus medication | 19 | 1.3 (1.1–1.5) | 26.9 (24.3–29.7) |
| More than 8 sessions plus medication | 9 | 1.7 (1.3–2.2) | 32.5 (27.3–38.3) |

[a] Go to *www.surgeongeneral.gov/tobacco/gdlnrefs.htm* for the articles used in this meta-analysis.

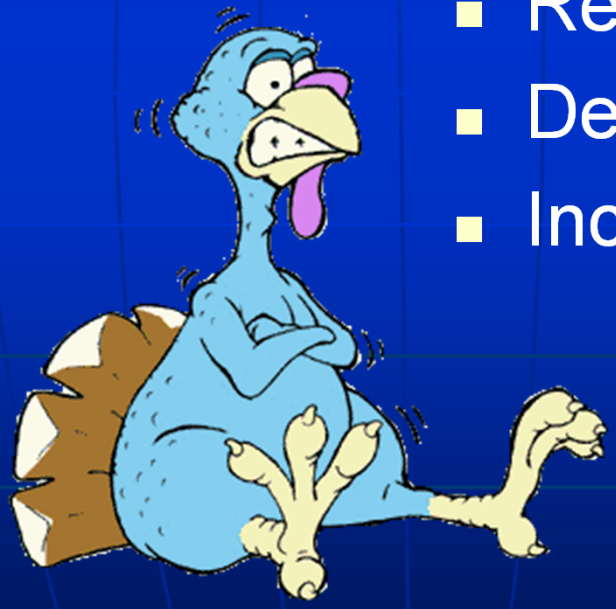
**Take away: Counseling increases odds of quitting and the more sessions attended, the greater the odds of quitting.**

# Initial Pharmacologic Dose

- Base initial dosing on current amount of tobacco used, previous quit attempts and severity of dependence, and patient preference/experience with medication
- Individualize the dose and duration to achieve:
  - Withdrawal symptom relief
  - Control of cravings/urges
  - Abstinence
- Adjust dose and determine length of Rx based on patient response and side effects
- Return visit or phone call at 1 or 2 wk intervals to monitor medication efficacy and side-effects

# Nicotine Withdrawal Symptoms

- Constant craving of cigarettes
- Insomnia
- Irritability
- Anxiety
- Frustration
- Anger
- Depression
- Difficulty concentrating
- Restlessness
- Decreased heart rate
- Increased appetite



# Withdrawal

- Peaks within 1–2 wks. after quitting, may persist for months.
- Factors that influence:
  - Time span
  - Frequency and the amount of usage
  - Physiology
  - Support
  - Knowledge

# Nicotine Replacement Therapy (NRT)

Over the counter

- Gum
- Lozenge
- Patch

Prescription only

- Nasal spray
- Inhaler

# NRT Mechanism of Action

- Replaces the nicotine from cigarettes
- Patch: nicotine being replaced has a much slower and longer-acting profile
  - Likely desensitizes and inactivates nicotinic receptors to reduce nicotine withdrawal
- Gum, spray, inhaler, lozenge: faster acting, but more short-lived

# NRT Rationale for use

- Improves success rates 2xs ↑ cold turkey
- Prevents nicotine withdrawal symptoms
- Allows time for patient to control psychological withdrawal
  - Behavioral modification necessary for psychological withdrawal

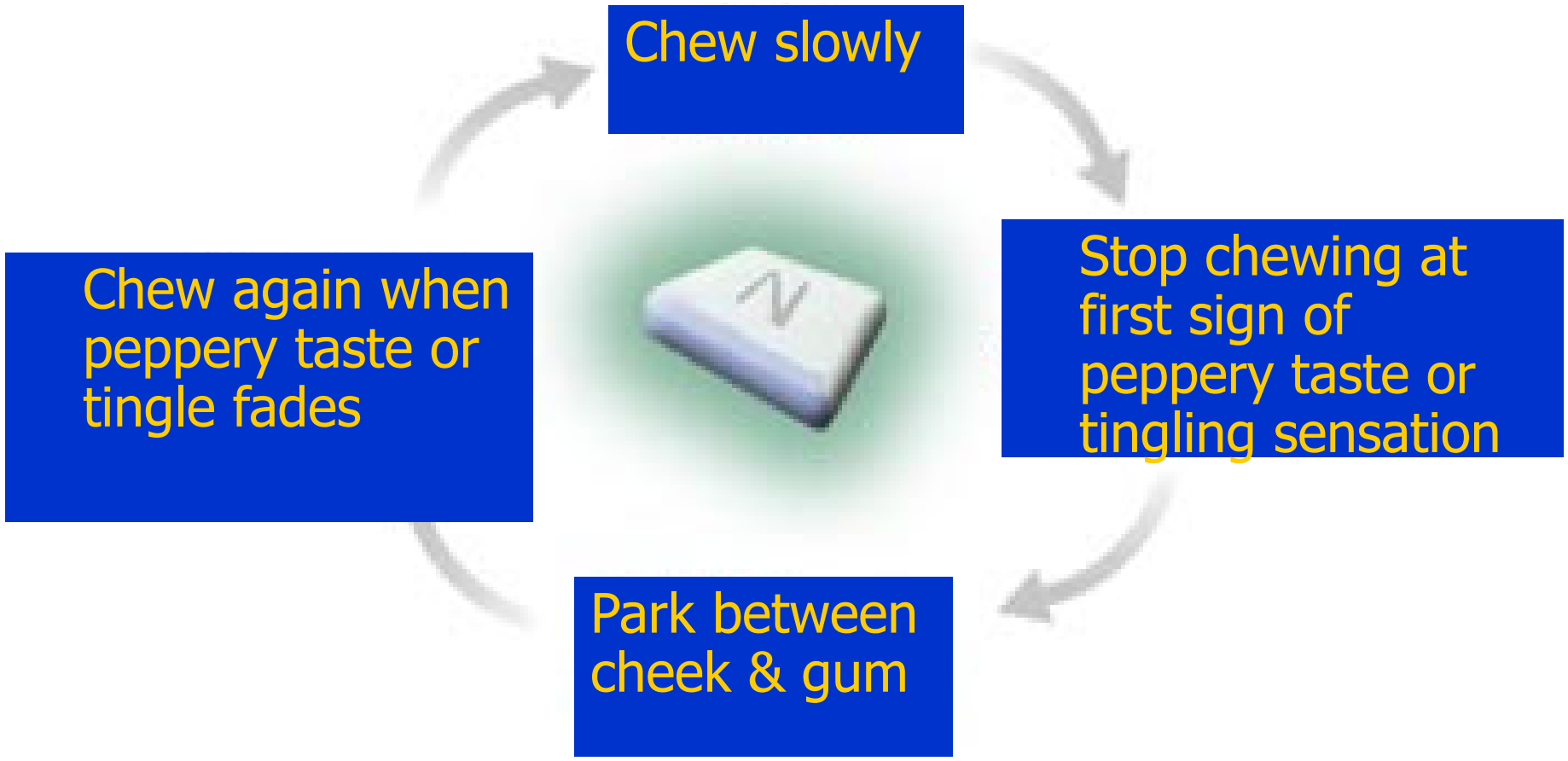
# NRT Precautions/contraindications

- MI within 4 weeks
- Life-threatening arrhythmias
- Severe or worsening angina
- Active TMJ (avoid gum)
- Hypersensitivity to nicotine
- Pregnancy
- Microvascular surgical procedures

# Nicotine Gum

- Length of treatment: <12 weeks, most useful in combination therapy with patch and/or Buproprion
- Dose: <24 pieces/day, start 1-piece q1-2h
  - **<24 cpd: 2 mg  (or if first cig > 30 min)**
  - **24+ cpd: 4 mg  (or if first cig < 30 min)**
- SE: dyspepsia, hiccups, mouth soreness; less frequent with proper technique. OTC antacids may help

# NICOTINE GUM: CHEWING TECHNIQUE SUMMARY



# NICOTINE GUM: ADDITIONAL PATIENT EDUCATION

- Use at least nine pieces of gum daily.
- Use as a fixed schedule -a piece every hour or two.
- Avoid acidic foods and beverages:
  - Coffee
  - Wine
  - Juices
  - Soft drinks

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

# Nicotine lozenge

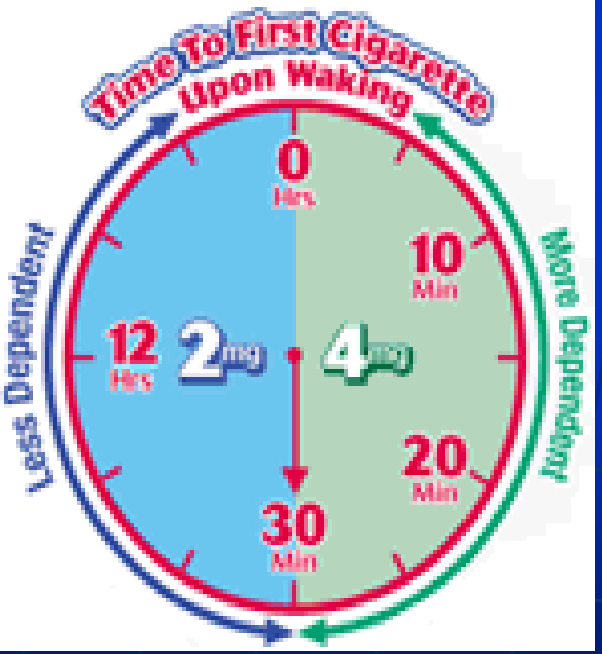
- NRT 2 mg & 4 mg
- Like hard candy, dissolves in mouth.
- Not chewed or swallowed
- 1 lozenge every 1-2 hours for the first six weeks; one lozenge every 2-4 hours during weeks 7-9; one lozenge every 4-8 hours during the final weeks 10-12.
- Minimum 9/day 1st 6 weeks;
- Maximum dosage: >5 within six hrs. or 20/day

# NICOTINE LOZENGE: DOSING

Dosage is based on the "time to first cigarette" as an indicator of nicotine addiction


**Use Commit Lozenge 2 mg:** if you smoke your first cigarette more than 30 minutes after waking up


**Use Commit Lozenge 4mg:** if you smoke your first cigarette of the day within 30 minutes of waking up



# LOZENGE DIRECTIONS for USE

- Use on regular schedule
- 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.
- Will dissolve completely ~20–30 minutes.

# Nicotine Nasal Spray Nicotrol NS®

- Quickest nicotine delivery
- Similar efficacy to patches and gum
- May be most beneficial to highly dependent smokers
- Metered dose pump 10mg/ml 10ml (200 sprays)

# Nicotine Nasal Spray

- Length of treatment: 3-6 months
- Dose: 10mg/ml provides 0.5 mg nicotine
  - 8-40 doses/day
  - 1-2 doses/hour
    - 1 dose = 1 spray each nostril
- SE: nasal irritation

# Nicotine Nasal Spray Patient Instructions

- Initially
  - nose and/or throat irritation
  - usually subside after 1st week of use
- Prime pump before first use and if not used for 24 hours
- Store at room temperature away from children and pets

# NICOTINE NASAL SPRAY: DIRECTIONS for USE

- Blow nose (if not clear)
- Tilt head back slightly and insert tip of bottle into nostril as far as comfortable
- Breathe through mouth, and spray once in each nostril
- Do not sniff or inhale while spraying
- Wait 2 min before blowing nose

# Nicotine Inhaler

**Dosage**

- Initial treatment
  - 6 cartridges/day increase prn to max 16 cartridges/day
  - min of 3 weeks, max 12 weeks
- Gradual dosage reduction
  - if needed over additional 12 weeks

- Absorbed through buccal membrane
- Satisfies hand-to-mouth smoking ritual
- Two-fold increase in quit rates at 12 months

# Nicotine Inhaler

- Length of treatment: 6 months
- Dose: 10mg cartridge provides 2-4 mg nicotine
  - Frequent continuous puffing over 20 minutes
- SE: mouth irritation, cough, rhinitis

# Nicotrol® Inhaler Patient Education

- Stop smoking before using the inhaler
- Use for 20 minutes each time
- Do not inhale into lungs like cigarette
  - Puff like lighting a pipe
- Each opened cartridge is good for 1 day
- Do not use for longer than 6 months

# Nicotine Patch Therapy
## Initial Dosing Guidelines

### Dosage Based on Baseline Cigarettes/Day

- <10 CPD 7-14 mg/d
- 10-20 CPD 14-21 mg/d
- 21-40 CPD 22-42 mg/d
- >40 CPD 42+ mg/d

# When do we start the patch?

- Begin on quit day
- New data shows efficacy of starting patch prior to quitting

Meta-analysis: OR for abstinence at 6 weeks 1.96; 6 months 2.17 for those who started patch prior to quit date

- Consider combination with short-acting NRT

**Shiffman S. Nicotine patch therapy prior to quitting smoking: a meta-analysis**
***Addiction* Vol. 103 Issue 4 Page 557-563, April 2008**

# Nicotine Transdermal Patches Patient Instructions

- Apply patch to a non-hairy, clean, dry area of the body, rotate sites
- Do not cut
- Replace patch daily
- Remove at bedtime & before MRI
- Dispose of properly
- May swim & shower
- What if patients are still smoking a month later?
  - Combine with gum, if under clinical care.

# Nicotine Transdermal Patches Adverse Effects

- Skin reactions
  - irritation, itching, burning
  - hydrocortisone 0.5% can relieve symptoms; rotate application sites
- Sleep disturbances
  - insomnia, vivid dreams, nightmares
  - Remove patch before sleep
- Headaches

# NICOTINE PATCH: SUMMARY

## ADVANTAGES

- Consistent nicotine levels.
- Easy to use and conceal.
- Fewer compliance issues.

## DISADVANTAGES

- Patients cannot titrate the dose.
- Allergic reactions to the adhesive may occur.
- Patients with some dermatologic conditions should not use the patch (severe psoriasis, for example)

# Nicotine Patch

- Length of treatment: 8 weeks (original FDA approval was for 6 months)
- Dose: 1 patch/day
  - Step down: 21mg/24h, 14mg/24h, 7mg/24h
- Place when wake up (usually)
- SE: local irritation

# Effectiveness of NRT
## Results from Cochrane Meta-Analysis

| Formulation | RR for Abstinence | # Clinical Trials in Meta-Analysis | 95% CI |
|---|---|---|---|
| Gum | 1.49 | 53 | 1.4-1.6 |
| Patch | 1.64 | 41 | 1.52-1.78 |
| Inhaler | 1.90 | 4 | 1.36-2.67 |
| Lozenge | 1.95 | 6 | 1.63-2.45 |
| Spray | 2.02 | 4 | 1.49-3.73 |

Overall RR of abstinence for any form of NRT vs. control = 1.60 (95% CI = 1.50-1.66)

RR = Risk Ratio for abstinence compared with control (placebo or no NRT)
CI = Confidence Interval

adapted from Stead LF et al. *Cochrane Database of Systematic Reviews* 2012

# Can NRT be used long-term?

- May be useful with persistent withdrawal sx, or those who have had frequent past relapse.
- A minority of ad lib short-acting NRT users continue > 6 months.
- No known health risk; low dependence risk.

# BUPROPION: 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

- Hx of seizure disorder
- Hx of head injury
- Patients taking
  - Wellbutrin, Wellbutrin SR, Wellbutrin XL
  - MAO inhibitors in preceding 14 days
- Current or prior diagnosis of anorexia or bulimia nervosa
- Undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines)
- Safe with SSRIs
- Attenuates weight gain
- May be more effective among women

# BUPROPION SR: DOSING

**Patients should begin therapy 1 to 2 weeks PRIOR to their quit date.**

**Initial treatment**

- 150 mg po q AM x 3 days

**Then…**

- 150 mg po bid, pm dose before 6 pm
- Duration, 7–52 weeks
- Approved for use up to 52 weeks
- Can be combined with all forms of NRT
- No taper needed

# BUPROPION:ADVERSE EFFECTS

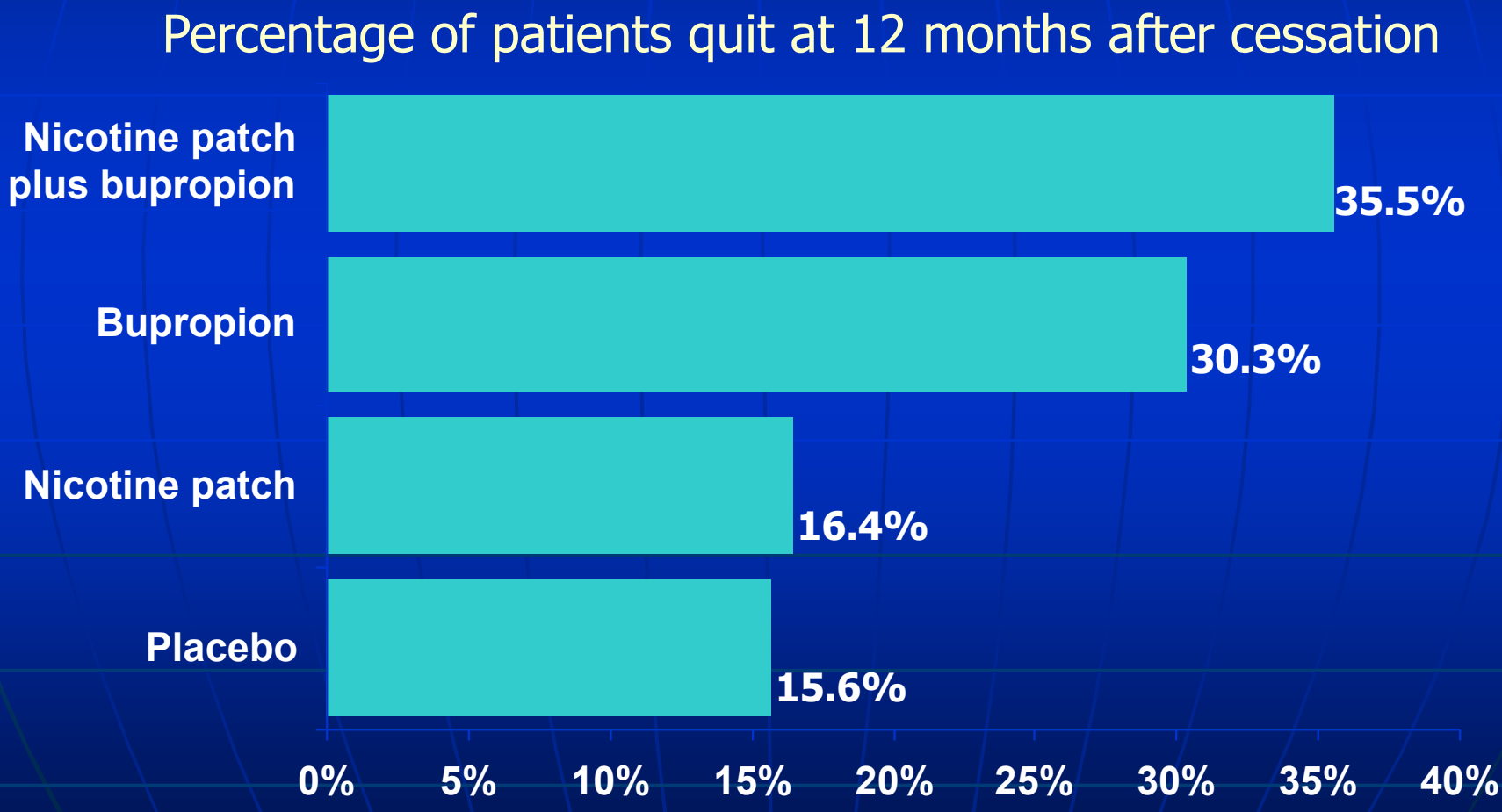
Common side effects include:

- Insomnia (if this occurs, avoid bedtime dosing—take 2nd dose in the afternoon, 8 hrs between doses)
- Dry mouth

Less common but reported:

- Tremor
- Skin rash

# Combination Therapy: Patch Plus Bupropion SR




Jorenby et al. *N Engl J Med* 1999;340(9):685–691.

# VARENICLINE Mechanism

- Competitively inhibits binding of nicotine
- Clinical effects
  - ↓ symptoms of nicotine withdrawal
  - Blocks dopaminergic stimulation responsible for reinforcement & reward associated with smoking

# VARENICLINE: DOSING

**Begin therapy 1 week PRIOR to quit date. Gradual dose increase to minimize nausea and insomnia.**

| | Treatment Day | Dose |
|---|---|---|
| *Initial dose titration* | 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

# Side Effects ≥ 10%

- Nausea
- Insomnia
- Headaches
- Abnormal Dreams
- Taste Aversion
- Behavioral and mood disturbance
- New FDA warning related to alcohol intolerance
- Dosage adjustment and monitoring severe renal dysfunction

# Side effects

- Most common SE is nausea
- Must take with food to avoid nausea
  - Dose reduction (drop to 0.5 mg bid) may help nausea
- Abnormal dreams most often subside; dose reduction may benefit
- Pt should report mood and behavior changes to clinician

# Varenicline (Chantix): FDA Alert February 1, 2008

Recommendations and Considerations for Healthcare Professionals

- Monitor all patients taking Chantix for serious neuropsychiatric symptoms
- Serious psychiatric illness (e.g., schizophrenia, bipolar, major depressive disorder) may worsen
- Consider these safety concerns and **alert patients about these risks**

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm106540.htm

# Newer Research: Varenicline and depression

Anthenelli et al multicenter study of smokers with stable or treated depression found no increase in anxiety or depression with varenicline.

Ann Intern Med. 2013 Sep 17;159(6):390-400

Thomas et al-a large prospective cohort study (>111K smokers) found that neither varenicline nor bupropion had greater depression or self-harm than NRT during treatment for cessation. BMJ. 2013 Oct 11;347-57

EAGLES study double-blind RCT. Found no significant increase in neuropsychiatric adverse events. Lancet 2016 387:10037

# Special Considerations

# Pharmacotherapy and Smokeless Tobacco Users

# Initial Dosing Guidelines: Smokeless Tobacco

| **Cans/Pouches/Week** | **Mg NRT/day** |
|---|---|
| > 3 | 42+ |
| 2-3 | 33-44 |
| 1-2 | 21-33 |
| < 1 | 11-22 |

# Recommended Treatment Approach for Smokeless Tobacco Users

1. Behavioral treatment
   - Oral examination by dentist/hygienist
   - +/- oral replacement products
2. Bupropion
   - 150 mg po twice a day
   - Continue for 3-6 months
3. Tailored nicotine patch therapy
   - +/- gum/lozenge for self-titration
   - ? Lozenge alone
4. Combinations of medications, or varenicline

# Alternative therapies

- Laser
- Acupuncture
- Hypnosis

No or very limited evidence for their effectiveness

# Pregnant Patients

- Non-pharmacologic treatment (counseling) preferred
- NRT products are all FDA Category D
- Use intermittent dose type NRT, or remove patch at night
- Bupropion is Category C--Pregnancy registry available
- Varenicline—no information available, FDA Category C—but not indicated during pregnancy—never tested. Case reports of accidental use in pregnancy show no problems.
- None of the medications are proven to have a long-term effect on smoking in pregnancy

# Treatment of pts using Neuroleptics

- High tobacco use >70%
- Standard approach e.g. 5 A's
- Best to offer cessation when sx managed
- Cessation:
  - May exacerbate symptoms
  - May affect pharmacokinetics of medications
- Monitor pt. closely
- More research needed for tailored approaches

# Summary

- Numerous pharmotherapy options
- Thorough history necessary
- Individualize medication choice & duration
- Combined with counseling is most effective
- More data needed in special populations

# Resources

- www.tobacco.org
- www.askandact.org (AAFP site)
- http://smokingcessationleadership.ucsf.edu Smoking Cessation Leadership Center
- http://www.treatobacco.net/en/index.html
- www.cdc.gov/tobacco
- http://www.smokefree.gov NCI site
- QuitNet www.quitnet.com