Update on Pharmacotherapies for Smoking Cessation

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No Current Disclosures

- Past participation in both industry, NIH, and private foundation funded studies.
- Current Deputy Editor for the American Journal on Preventive Medicine (AJPM)

Objectives: participants should be able to:
- List the current trends in tobacco use in the U.S., especially cigarette smoking
- Prescribe pharmacotherapies for smoking cessation based on current recommendations
- Integrate behavioral therapies for smoking cessation
- Tailor smoking cessation therapies for special populations

Second most successful ad campaign, post WWII. Convinced women to smoke with returning veterans. What is the most successful ad? (answer at end of presentation)

“Cigarette smoking is the chief, single avoidable cause of death in our society and the most important public health issue of our time.”

- C. Everett Koop, M.D.
U.S. Surgeon General, 1981-1989

New Zealand Maori tribesman. What is their prevalence of male smokers? Answer: Over 70%
Recent Reports of the Surgeon General on Smoking

<table>
<thead>
<tr>
<th>Year</th>
<th>Report Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>The Health Consequences of Smoking—50 Years of Progress</td>
</tr>
<tr>
<td>2012</td>
<td>Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General</td>
</tr>
<tr>
<td>2010</td>
<td>How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking Attributable Disease</td>
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<td>2007</td>
<td>Children and Secondhand Smoke Exposure-Excerpts from The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General</td>
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<tr>
<td>2006</td>
<td>The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General</td>
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</table>

Each day, more than 3,200 youth (younger than 18 years of age) smoke their first cigarette and another 2,100 youth and young adults who are occasional smokers progress to become daily smokers.

The prevalence of current cigarette smoking among adults has declined from 42% in 1965 to 18% in 2012. However, more than 42 million Americans still smoke.

The burden of smoking-attributable disease and premature death and its high costs to the nation will continue for decades unless smoking prevalence is reduced more rapidly than the current trajectory.

2014 Report of the Surgeon General

Summary of Findings

- There is no safe level of exposure to tobacco smoke
- Damage from tobacco smoke is immediate
- Smoking longer means more damage
  - Risk is related to duration and level of exposure
- Cigarettes are designed for addiction.
- There is no safe cigarette
  - Lower emissions of specific toxicants in tobacco smoke is not associated with reduced risk

Preventable Causes of Death in the U.S.

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking-related cancers</td>
<td>6,587,000</td>
</tr>
<tr>
<td>Cardiovascular and metabolic diseases</td>
<td>7,787,000</td>
</tr>
<tr>
<td>Pulmonary diseases</td>
<td>3,804,000</td>
</tr>
<tr>
<td>Conditions related to pregnancy and birth</td>
<td>108,000</td>
</tr>
<tr>
<td>Residential fires</td>
<td>86,000</td>
</tr>
<tr>
<td>Lung cancers caused by exposure to secondhand smoke</td>
<td>263,000</td>
</tr>
<tr>
<td>Coronary heart disease caused by exposure to secondhand smoke</td>
<td>2,194,000</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>20,830,000</strong></td>
</tr>
</tbody>
</table>

Source: Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, unpublished data.

Prevalence of smoking among adults has declined from 42% in 1965 to 18% in 2012. However, more than 42 million Americans still smoke.

The burden of smoking-attributable disease and premature death and its high costs to the nation will continue for decades unless smoking prevalence is reduced more rapidly than the current trajectory.

The Health Consequences of Smoking—50 Years of Progress, Executive Summary, U.S. Department of Health and Human Services, 2014.

Preventable Causes of Death in the U.S.

- Smoking
- High blood pressure
- Overweight-obesity
- Inadequate physical activity and inactivity
- High blood sugar
- High LDL cholesterol
- High dietary salt

### SMOKING

<table>
<thead>
<tr>
<th>Rank</th>
<th>State</th>
<th>Share of Population who Smokes</th>
<th>Percent of Smokers Who Have Tried to Quit</th>
<th>Smoking Attributable Deaths per Year (per 100,000)</th>
<th>Costs Attributable to Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kentucky</td>
<td>28.20%</td>
<td>47.60%</td>
<td>378.10</td>
<td>$3.64 billion</td>
</tr>
<tr>
<td>17</td>
<td>Michigan</td>
<td>21.10%</td>
<td>55.60%</td>
<td>296.30</td>
<td>$7.20 billion</td>
</tr>
<tr>
<td>51</td>
<td>Utah</td>
<td>11.70%</td>
<td>53.70%</td>
<td>144.90</td>
<td>$0.62 billion</td>
</tr>
<tr>
<td>US</td>
<td></td>
<td>19.8%</td>
<td>47.7%</td>
<td>284.80</td>
<td>$194.45 billion</td>
</tr>
</tbody>
</table>

http://statehealth.newamerica.net/node/87?media=print

### FACT

69 percent of patients who smoke visit a physician during a year, yet only 48 percent of those patients report receiving advice about smoking from their physician.

Physicians are 1.5 times likely to direct their counseling efforts to those smokers who are less likely to attempt to quit smoking (heavier, older smokers).

St. Peter, Robert, Swadling, Peter, Cunningham Peter, & McGinnis, Alice
Counseling Patients to Quit Smoking: Missed Opportunities and the Need to Better Target Physician Counseling. Research Report No. 6 June 2002

50 year follow-up on British doctors who smoked, BMJ, 2004

- 50% of those who continue to smoke will die of tobacco-related causes
- Stopping before age 50 cuts the risk by ½
- Stopping before age 30 almost negates risk

http://www.countyhealthrankings.org/app/michigan/2013/measure/factors/map


### FACT

The prevalence of smoking in the Medicaid population is about twice that of population as a whole (45% of Medicaid patients vs. 22.8% of the adult population of the US in 2001.)


50% of those who continue to smoke will die of tobacco-related causes
- Stopping before age 50 cuts the risk by ½
- Stopping before age 30 almost negates risk
Nicotine Dependence

“As an addictive substance, nicotine, on a milligram for milligram basis, is 10 times more potent than heroin…”

Anyone see the movie, “The Insider”? What is it about?

RJR researchers who substantiated the biological basis of nicotine addiction.


Key Points of Nicotine Dependency

- Smoking on arising
- Unable to refrain when forbidden
- Difficulty in giving up “first AM cigarette”
- More than a pack per day
- Smoking more frequently in AM
- Smoking when ill

Nicotine Withdrawal Symptoms

- Craving to smoke
- Irritability
- Increasingly frequent waking from sleep
- Slowed heart rate
- Anxiety
- Impaired concentration
- Restlessness
- Drowsiness
- Impatience
- Confusion
- Increased hunger
- Impaired reaction time

Nicotine Replacement

- Indications
- Contraindications
  - Hypersensitivity
  - Severe arrhythmias
  - Recent acute MI
  - Caution in pregnancy

Advantages of Transdermal Nicotine

- Better compliance
- Fuller and more constant nicotine replacement
- No oral side-effects
- More acceptable to physicians
- Less dependence potential

Transdermal Nicotine Patch

<table>
<thead>
<tr>
<th>Smoker</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heavy (&gt;10 cig/day)</td>
<td>21 mg</td>
<td>8-12 weeks</td>
</tr>
<tr>
<td>Light or (≤10 cigs/day)</td>
<td>7-14 mg</td>
<td>8-12 weeks</td>
</tr>
<tr>
<td>&lt;100 # weight</td>
<td>7-14 mg</td>
<td>8-12 weeks</td>
</tr>
</tbody>
</table>

Nicotine Replacement Side Effects
(Transdermal nicotine versus placebo percentages)

- Insomnia/abnormal dreams (21% vs. 12%)
- Transient itching and burning (50% vs 20%)
- Erythema (14% vs 8%)
- Contact sensitization (2% vs 0%)
- Terminated due to side-effects (5% vs 2%)

Advantages of Nicotine Gum and Lozenges

- Patients can titrate dose
- Physicians can individualize dose
- Mimics oral behavior of smoking
- Can be used for relapse prevention

Nicotine Polacrilex (Gum & Lozenges)

- Nicotine absorbed through oral mucosa
- Gum
  - 2 mg and 4 mg
  - Chew gum slowly until it tingles, then park it between cheek and gum. When tingle disappears, repeat the process until most of the tingle is gone (about 30 minutes)
- Lozenges
  - 2mg and 4 mg
  - Dissolve slowly in mouth over 20-30 minutes. Occasionally move lozenge from one side of mouth to the other until completely dissolved.

Nicotine Polacrilex (Gum and Lozenges)

- Dosages
  - 1-2 pieces per hour vs prn
  - Controlled chewing
    - 2 mg if patient smokes fewer than 25 cigarettes/day
    - 4 mg if ≥25 cigarettes/day
  - 6 weeks plus 6 week taper

Nicotine Nasal Spray

- Rapid absorption may help nicotine craving
- Dosage - Nasal spray
  - 1-2 doses per hour for 3 months

Nicotine Inhaler

- Rod with nicotine plug providing nicotine vapor when puffed
- Absorption is buccal, not pulmonary
- Effect is similar to gum
Special Comments on NRT

- 2012 Cochrane review of 150 trials showed every type of NRT was associated with long-term cessation. No single type was more effective. Combining a short-acting form like the lozenge with a long-acting patch was more effective than either alone.
- No added benefit in using beyond 24 weeks (Schnoll et. al., JAMA Intern Med. 2015).
- Long-term adherence is better with the patch.

Bupropion (SR)-Wellbutrin or Zyban

- Dopaminergic and adrenergic
- Mechanism does not appear to be as an antidepressant
- May be used in conjunction with NRT
- Begin 150 mg in morning for 3 days, then twice daily for 4 days prior to quit date, then continue for 7-12 weeks

Bupropion (SR)

- Adverse events: dry mouth, insomnia, possible increase in seizures
- Contraindications: seizures, anorexia (eating disorders), heavy alcohol use, head trauma

2009 FDA Black Box warning on Buproprion SR

- Post market safety reports showing risk of neuropsychiatric symptoms, including suicidality.

Varenicline tartrate (Chantix)

- FDA approved 2006
- Acetylcholine receptor agonist-antagonist
- Better than placebo, at least as useful as bupropion
- 0.5 mg q D x 3 D then BID x 4 days then 1.0 mg BID oral dosing for 12 weeks total with one week run-in before quit date
- GI side effects most common
- Black box warning 2009—increased potential for suicidal behavior and depression

Varenicline special attributes:

- Considered a first-line agent.
- 2012 Cochrane review found varenicline to be more effective than buproprion SR but as effective as NRT.
- May be used for smoking reduction therapy for 24 weeks for those willing to ‘cut down but not quit’, nearly tripling cessation at 52 weeks (Ebbert et. al., JAMA.2015).
Mixed Safety Reports on Varenicline

- 2011 FDA large case-control study on adverse event reporting showed increased suicidality.
- Several follow-up studies and a meta-analysis failed to show an increased association with suicide (Thomas et al., BMJ, 2013 and 2015).
- Meta-analyses showing mixed outcomes on cardiovascular events (BMJ, 2012).

Recommendations on Varenicline in clinical practice:

- Review cardiac and psychiatric history
- Conduct a suicidality assessment
- Arrange close follow-up

Nortriptyline

- A tricyclic antidepressant.
- Not significantly different than buproprion SR in efficacy for smoking cessation (Hughes et al., Cochrane Review 2014).
- Not FDA approved.
- Not a first-line agent and potential cardiovascular effects.

Clonidine

- An alpha-2 adrenergic receptor agonist
- Second-line agent only.
- Not FDA approved.
- 2013 Cochrane meta-analysis showed more effective than placebo for smoking cessation but adverse effects of postural hypotension and sedation.

Pharmacotherapies More Effective with Counseling than alone

- 2008 US Public Health Service Guideline recommends counseling along with pharmacotherapies for smoking cessation for enhanced effectiveness (AJPM, 2008).
- Individual, group, telephone counseling were all effective.
- Team-based approaches were more effective than individual approaches.

Goals for Clinicians and Professional Organizations

To ensure that all members of the health care team and health professional organizations are directly, appropriately, and routinely involved in influencing patients and the public to avoid and discontinue the use of tobacco.

-National Cancer Institute
AHRQ Guidelines: Six Major Recommendations for Successful Treatment

1. Offer all smokers treatment at each office visit
2. Ask about and record tobacco-use status of every patient
3. Treatment of ≥3 minutes/visit is effective
4. More intensive treatment is more effective
5. Three most effective components are pharmacotherapy, clinician-delivered social support, and skills training
6. Modify health care system to routinely identify and intervene with all tobacco users at every visit


Tobacco-Use Intervention Services

Objectives for Clinicians

Increase to at least 75 percent the proportion of primary care and oral health care providers who routinely advise cessation and provide assistance and follow-up for all their tobacco-using patients.

Why You Should Ask in the Office

- 1-3 minute interventions by providers double quit rates
- Patients are 3-4 times more likely to attempt to quit if asked at a “sick” visit
- Patient quits with no assistance - 1 in 15 success; patient quits using all tools available - 1 in 3 success
- 7-10 smokers visit a doctor at least once/year and 80% want to quit
- If all providers asked at every visit, 1-2 million more people would quit - saving $2 billion

AAAAA: Ask
Ask Users Basic Questions

Tobacco Use as a Vital Sign in the Chart:

Blood pressure:_____________________
Pulse:_________ Weight:_________
Temperature:_____________________
Respiratory Rate:_________________
Tobacco Use: Current Former Never
(Circle One)

AAAAA: Arrange
Arrange Follow-up within one week of quit date
- Follow-up within one week (phone OK)
- Congratulate success
- If lapse occurred, ask for recommitment to total abstinence
- Offer self-help materials and other support resources and agencies.
- Remind the patient that a lapse can be a learning experience
- Identify problems encountered and anticipate challenges
First Visit:  AAAAA

- Ask all patients about tobacco
- Advise all users to stop
- Assess willingness to quit
- Assist interested patients in stopping
  - Help set a quit date
  - Provide self-help literature
  - Consider prescribing nicotine replacement
- Arrange patient follow-up services

For the patient who is not ready...

The 5 Rs of Motivational Intervention

- Relevance: “Do you understand why quitting smoking is relevant to you?”
- Risks: What do you think may happen if you continue to smoke?
- Rewards: What benefits can you think of if you quit smoking now?
- Roadblocks: “What things can you think of that would get in the way of your quitting smoking?”
- Repetition: “I'm going to remind you about quitting smoking next time you come in. Each time you try to quit, you have a better chance of succeeding.”

Motivational Interviewing

“A client centered, directive method for enhancing intrinsic motivation to change by exploring and resolving ambivalence”

For any number of reasons, 
people are ambivalent about change

Principles of Motivational Interviewing

1. Express empathy - acceptance of people as they are frees them to change whereas non-acceptance immobilizes the change process
2. Develop discrepancy - help patient perceive a mismatch between “where they are and where they want to be”
3. Roll with resistance - avoid imposing change; collaborative vs confrontational approach; de-escalate and avoid a negative interaction when occurs.
4. Support self-efficacy - strengths-based approach that seek to draw out patient’s belief that change is possible and highlight previous successes with positive change

Decisional Balance

<table>
<thead>
<tr>
<th>Benefits (pros)</th>
<th>Costs (cons)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Behavior (no change)</td>
<td>Status quo</td>
</tr>
<tr>
<td>New Behavior (making a change)</td>
<td>Change Talk</td>
</tr>
</tbody>
</table>

Defining Change Talk

Change Talk comes from the Motivational Interviewing literature. When we help patients, we are looking for and eliciting a more direct statement about plans for change; moving from “I might” or “I will think about it”, to direct plans to make changes. There are six types of change talk:

- **Desire**: “I like the idea of being a non-smoker/quitting”
- **Ability**: “I can…”
- **Reasons**: “I could more easily play with my kids if I stopped smoking”
- **Need**: “I really have to quit”
- **Commitment**: “I will…”
- **Taking Steps**: “This week I will…”

RRRR

**Relevance**

Encourage the patient to indicate why quitting is personally relevant

(may need to review e.g. frequent sore throats, PND, vulnerable family members, previous MI, cost, etc)

RRRR

**Risks**

Patient should identify negative consequences of tobacco use

- Acute risks—dyspnea, asthma
- Long-term risks—cardiovascular, cancer
- Environmental risks—children, spouse

RRRR

**Rewards**

Patient should identify rewards of cessation:

<table>
<thead>
<tr>
<th>Improved health</th>
<th>Self esteem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food tastes better</td>
<td>Home, care, breath smells better</td>
</tr>
<tr>
<td>Improved sense of smell</td>
<td>Reduced aging of skin</td>
</tr>
<tr>
<td>Save money</td>
<td>Set example for children</td>
</tr>
</tbody>
</table>

RRRR

**Roadblocks**

Patient’s perceived barriers to quitting

- Withdrawal symptoms
- Fear of failure
- Weight gain
- Lack of support
- Depression
- Enjoyment of tobacco

RRRR

**Roadblocks: Weight Gain**

Studies have shown that weight reduction dieting during an attempt to quit using tobacco decreases the chances that the individual will successfully quit.

Regular exercise may prevent some of the weight gain associated with smoking cessation.
**Roadblocks: Weight Gain**

Both nicotine replacement and bupropion may delay the weight gain associated with smoking cessation.

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**Repetition**

- The motivational intervention should be repeated every time an unmotivated patient visits the clinic setting.
- Tobacco users who have failed in their quit attempt should be told that most people make repeated quit attempts before they are successful.

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**Follow-up Visits**

**Prevent Relapse**

- Congratulate, encourage, and stress importance of remaining abstinent
- Review the benefits to be derived from cessation
- Review the patient’s success in quitting
- Inquire about problems encountered in maintaining abstinence and offer solutions
- Anticipate problems or threats to maintaining abstinence

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**Follow-up Visits**

**Prevent Relapse**

Discuss specific problems, such as:
- Weight gain
- Negative mood, depression
- Prolonged nicotine withdrawal
- Lack of support for cessation

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**Follow-up Visits**

**Relapse Rate Over Time**

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**Follow-up Visits**

**Smoking Cessation Rates**

*With and Without Follow-up*

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Special population approaches

- RCT on varenicline showed smokers diagnosed with schizophrenia and bipolar disorder prevented relapse for up to 52 weeks with abstinence rates of 60% vs. 19% in placebo group. No increase risk of psychiatric events (Evins et al., JAMA, 2014).
- 2014 Cochrane review found buproprion SR and nortriptyline to be the only effective anti-depressants for smoking cessation.

Special Populations

- No pharmacotherapies approved in pregnancy or found effective. Emphasize post-partum smoking cessation.
- Repeat attempts consider combination therapies such as short-acting with long-acting NRT, buproprion SR with NRT, Varenicline with patch for 24 weeks.
- Heavy smokers (>20 cigarettes/day) consider varenicline and buproprion SR combination.
- Hospitalized patients consider NRT with beside counseling and outpatient referral and follow-up.
- Complex patients with diabetes, hypertension, and COPD. It’s never too late to quit smoking (video of patient testimony). “The 20 year conversation that can change behavior.”

Follow-up Visits
Smoking Cessation
By Number of Follow-up Visits

<table>
<thead>
<tr>
<th>Number of Follow-up Visits</th>
<th>Patients Who Quit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
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</table>

Source: Wilson, DM et al., JAMA 1988

Most successful ad campaign