Pharmacotherapy of Tobacco Cessation

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Disclosure

“I have no relevant financial relationships to disclose as part of this lecture”

Objectives

• Explain the pharmacological effects of nicotine and the impact of tobacco use on an individual’s health as well as costs to society

• Compare and contrast the available pharmacotherapies for smoking cessation.

• Formulate a treatment plan for a tobacco user using preferred pharmacotherapies for tobacco cessation.
Tobacco Use

• Tobacco use is the single greatest cause of preventable disease and premature death in the United States

• Smoking kills more people than alcohol, AIDS, car accidents, illegal drugs, murders and suicides combined

• 50% of all smokers will die prematurely

• Tobacco use costs the American economy over $100 billion per year in healthcare costs and lost work time

Tobacco Use Consequences

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Lung, bronchial, laryngeal, oral cavity, and pharyngeal, esophageal, stomach, pancreatic, kidney, renal pelvis, urinary bladder, cervical, acute myelogenous leukemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary Health</td>
<td>COPD, CO poisoning, pneumothorax, asthma exacerbation, bronchitis, emphysema</td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>Stroke, heart attack, hypertension, peripheral vascular disease, abdominal aortic aneurysm, platelet adhesion</td>
</tr>
</tbody>
</table>

Tobacco Use Consequences (continued)

<table>
<thead>
<tr>
<th>Cosmetic Changes</th>
<th>Premature skin aging, bad breath, stained teeth and fingers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reproductive Health</td>
<td>Impotence, infertility, ectopic pregnancy, spontaneous abortion, preterm delivery</td>
</tr>
<tr>
<td>Fetal Health</td>
<td>Stillbirth and neonatal deaths, preterm birth, low birth weight, lung development problems, SIDS</td>
</tr>
<tr>
<td>Oral Health</td>
<td>Oral lesions, gingivitis, loss of bone in jaw, leukoplakia</td>
</tr>
<tr>
<td>Other</td>
<td>Otitis Media, cataracts, age-related macular degeneration, osteoporosis, memory loss and Alzheimer’s</td>
</tr>
</tbody>
</table>
Health Benefits of Quitting

- Circulation improves
- Walking becomes easier
- Lung function increases up to 30%
- Lung cilia regain normal function
- Excess risk of CHD decreases to half that of a continuing smoker
- Risk of stroke is reduced to that of people who have never smoked
- Lung cancer death rate drops to half that of a continuing smoker
- Risk of all other cancer decreases

After 15 years: Risk of CHD is similar to that of people who have never smoked.

Cigarette Contents

Nicotine (Nicotiana tabacum)
- The addictive substance in tobacco products
- Reaches brain within 10-20 seconds of inhalation
- Natural liquid alkaloid
- Colorless, volatile base pKa = 8.0
- 1 mg of nicotine per cigarette

Hukkanen et al., 2005; Hibbeln Ryan E, Goodman & Gilmore's Chapter 11
Nicotine: Absorption

- Absorption is pH dependent
  - Poorly absorbed in acidic media
  - Well absorbed in alkaline media
- Buccal
  - pH inside the mouth is 7.0
  - Significant absorption of pipes, cigars, spit tobacco, oral nicotine products
- Skin
  - Readily absorbed through intact skin

Hukkanen et al. 2005; Hibbs Ryan E, Goodman & Gillman’s Chapter 11

Nicotine: Absorption (cont.)

- Gastrointestinal Tract
  - Nicotine is well absorbed in the small intestine but has low bioavailability (20-45%) due to first-pass hepatic metabolism
- Lungs
  - Nicotine is rapidly absorbed across respiratory epithelium
    - Lung pH = 7.4
    - Large alveolar surface area
    - Extensive capillary system in lung

Hukkanen et al. 2005; Hibbs Ryan E, Goodman & Gillman’s Chapter 11

Nicotine: Distribution

- Nicotine reaches the brain within 10-20 seconds

Nicotine: Metabolism

- Metabolized by the liver
  - CYP2A6
- Primarily metabolized to cotinine
  - ~70-80% cotinine
  - ~10% other metabolites
- Daily intake of nicotine can be estimated from plasma cotinine levels (pCL)
  - Daily dose nicotine (mg) = pCL x 0.08

Hukkanen et al. 2005; Hibbs Ryan E, Goodman & Gillman’s Chapter 11

Nicotine: Excretion

- Products of nicotine metabolism are primarily excreted through the kidneys
  - pH dependent (increases with acidic pH)
- Half life
  - Nicotine t1/2 = 2 hours
  - Cotinine t1/2 = 16 hours

Nicotine: Physiological Effects

<table>
<thead>
<tr>
<th>Central Nervous System</th>
<th>Pleasure, Reward, Arousal, Improved Concentration, Anxiety Relief</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Increased heart rate, cardiac output, and blood pressure; vasoconstriction of coronary arteries</td>
</tr>
<tr>
<td>Other</td>
<td>Appetite suppression, increased metabolic rate, skeletal muscle relaxation</td>
</tr>
</tbody>
</table>


Nicotine Withdrawal

- Begins a few hours after last dose
- Usually peaks in a few days to one week
- Lasts ~4 weeks
- “Cravings” will last longer than 4 weeks
  - 50% of former smokers report cravings at 6 months


Nicotine Withdrawal

- Anxiety
- Irritability
- Insomnia
- Increased Appetite
- Difficulty Concentrating
- Depressed Mood
- Drowsiness
- Restlessness
- Decreased Heart Rate
- Cravings

Assessing Nicotine Dependence

- **Fagerstrom Test for Nicotine Dependence (FTND)**
  - Last revised in 1991
  - 6 questions
  - Responses assigned points
  - Points range from 0-10
  - 5 points or greater indicates substantial nicotine dependence
  - Most common research method of nicotine dependence
  - Also used in clinical practice


Clinical Practice Guidelines

- Update released in May 2008
- Sponsored by U.S. Department of Health and Human Services
- Designed for all tobacco users

PDF version via URL: http://www.surgeongeneral.gov/tobacco/

Clinical Practice Guidelines

- Chapter 1: Overview and Methods
- Chapter 2: Assessment of Tobacco Use
- Chapter 3: Clinical Interventions for Tobacco Use and Dependence
- Chapter 4: Intensive Interventions for Tobacco Use and Dependence
- Chapter 5: Systems Interventions
- Chapter 6: Evidence and Recommendations
- Chapter 7: Specific Populations and Other Topics
**How to Approach a Patient**

Ask → Advise → Assess → Assist → Arrange

“The 5 A’s”

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**The 5 A’s: Ask**

- Ask about tobacco use
  - At every visit
  - Ex: “Do you ever smoke or use any type of tobacco?”
  - Ex: “Condition X is often worsened by smoking, do you or does anyone in your household smoke?”

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**The 5 A’s: Advise**

- Advise tobacco users to quit
  - Use clear, strong, and personalized statements
    - **Clear:** “There are new treatments and medications available to help you quit.”
    - **Strong:** “As your ____, I want you to understand that quitting is the most important thing you can do to improve your health.”
    - **Personalized:** “Continuing to smoke makes your asthma worse and quitting will help dramatically.”
The 5 A’s: **Assess**

- Assess readiness to make a quit attempt
  - “Are you willing to give quitting another try?”
  - “Are you ready to set a quit date within the next 30 days?”

- If patient is willing to quit
  - Provide intensive treatment if acceptable to patient (counseling and pharmacotherapy)

- If patient is not ready to quit
  - Express empathy
  - Use motivational interviewing interventions

The 5 A’s: **Assist**

- Assist with the quit attempt
  - The best intervention is a combination of counseling and medication
  - Advise patient to set a quit date within the next 2-4 weeks
  - Build on past quit experience (if any)
  - Nicotine Replacement Therapy

The 5 A’s: **Arrange**

- Arrange follow up care
- Evaluate relapse prevention skills
- Evaluate progress
Tobacco Cessation Aids

• Nonprescription Products
  – Transdermal Patches (NRT)
  – Nicotine Gum (NRT)
  – Nicotine Lozenges (NRT)

• Prescription Products
  – Nicotine Nasal Spray (NRT)
  – Nicotine Inhaler (NRT)
  – Bupropion
  – Varenicline

The above are the 7 first-line therapies for tobacco cessation.

Nicotine Replacement Therapy: Transdermal Patches

• Use
  – Apply as soon as awaken on quit day
  – Apply to clean, relatively hairless skin between the neck and the waist
  – Rotate site every 24 hours
  – Taper over time
  – Do not cut

• Abstinence rate 23.4% vs placebo


Nicotine Replacement Therapy: Transdermal Patches

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Cautions</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>First 4 weeks:</td>
<td>Pregnancy</td>
<td>Skin Reactions</td>
</tr>
<tr>
<td>21mg patches</td>
<td>• Unstable angina</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Next 2 weeks:</td>
<td>• Serious arrhythmias</td>
<td>Vivid dreams</td>
</tr>
<tr>
<td>14mg patches</td>
<td>• 2 weeks post MI</td>
<td></td>
</tr>
<tr>
<td>Next 2 weeks:</td>
<td>• 7mg patches</td>
<td></td>
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<tr>
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http://www.plymouthhypnosis.com/patch-nicotine-gum-chantix-wellbutrin/
Nicotine Replacement Therapy

Nicotine Gum

• Use
  – Chew and “park”
    • For 30 minutes or until taste dissipates
  – Avoid eating or drinking for 15 minutes before or during chewing
  – Chew the gum on a fixed schedule (at least one piece every 1-2 hours) for at least 1-3 months

Dosage Cautions Adverse Effects

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<tr>
<th>Dosage</th>
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<tr>
<td>4mg if smoke &gt; 25 cigarettes per day</td>
<td>Recent MI</td>
<td>Dyspepsia</td>
</tr>
<tr>
<td>2mg if smoke &lt; 25 cigarettes per day</td>
<td>Serious arrhythmias</td>
<td>Hiccups</td>
</tr>
<tr>
<td>At least one piece every 1-2 hours</td>
<td>Unstable angina</td>
<td>Mouth and jaw soreness</td>
</tr>
<tr>
<td>Max: 24 pieces/day</td>
<td>Pregnancy</td>
<td>Increased saliva</td>
</tr>
<tr>
<td>Duration: 12 weeks</td>
<td></td>
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</tbody>
</table>

Nicotine Replacement Therapy

Nicotine Lozenges

• Use
  – Dissolve in mouth over 30 minutes
    • Don’t chew or swallow
    • Occasionally rotate to different areas of the mouth
  – Nicotine release may cause a warm, tingling sensation
    • 25% higher blood nicotine levels than gum
  – Avoid eating or drinking 15 minutes before or during chewing
  – Use 9-15 lozenges/day for 6 weeks than taper over next 6 weeks

Nicotine Replacement Therapy

**Nicotine Lozenges**

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<th>Dosage</th>
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<td>• 4mg if time to first cigarette is &lt; 30 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 2mg if time to first cigarette is &gt; 30 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• At least one lozenge every 1-2 hours during first 6 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Maximum: 20 lozenges per day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Duration: 12 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Recent MI</td>
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</tr>
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</tr>
<tr>
<td>• Unstable angina</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cough</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Hiccups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Dyspepsia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Flatulence</td>
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</tbody>
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Nicotine Replacement Therapy

**Nicotine Nasal Spray**

• Prescription only

• Directions for use:
  – Press in circles on sides of bottle and pull to remove cap
  – Prime the pump (before first use)
  – Blow nose
  – Tilt head back slightly and insert tip of bottle into nostril as far as comfortable
  – Breathe through mouth and spray once in each nostril
  – Wait 2-3 minutes before blowing nose
  – Wait 5 minutes before driving or operating heavy machinery
  – Avoid contact with skin, eyes, and mouth
    • If contact occurs, rinse with water immediately

Nicotine Replacement Therapy

**Nicotine Nasal Spray**

**Dosage**
- 1-2 doses per hour (1 dose = 1 spray in each nostril)
- Min: 8 doses per day
- Max: 40 doses per day or 5 doses per hour

**Cautions**
- Recent MI
- Serious arrhythmias
- Angina
- Pregnancy
- Chronic nasal disorders
- Severe reactive airway disease

**Adverse Effects**
- Nasal/Throat irritation
- Rhinitis
- Tearing
- Sneezing
- Cough
- Headache

**Nicotine Replacement Therapy**

**Nicotine Inhaler**

**Dosage**
- Initially 1 cartridge every 1-2 hours (each cartridge delivers a total of 4mg nicotine over 80 inhalations)
- 6-16 cartridges per day
- Duration of therapy is 3-6 months

**Cautions**
- Recent MI
- Serious arrhythmias
- Angina
- Pregnancy
- Bronchospastic disease

**Adverse Effects**
- Mouth/Throat irritation
- Cough
- Headache
- Rhinitis
- Dyspepsia
- Hiccups

**Use**
- Inhale into back of throat or puff in short breaths
- Avoid eating or drinking 15 minutes before or during use
- Nicotine in cartridges is depleted after about 20 minutes of active puffing
  - Cartridge does not have to be used all at once
  - Open cartridge retains potency for 24 hours

Bupropion

• MOA: dopaminergic and norepinephrine effects

• Zyban®, Wellbutrin SR®, Bupropion SR®

• Therapy begins 1-2 weeks before quit date

Dosage

• 150mg daily for 3 days, then twice daily
• Therapy begins 1-2 weeks before quit date
• Duration 7-12 weeks
• Avoid bedtime dosing to minimize insomnia

Cautions

• Medications that lower seizure threshold
• Severe liver disease
• Pregnancy
• Contraindicated within 14 days of use of MAOI inhibitor

Adverse Effects

• Insomnia
• Dry mouth
• Nervousness
• Rash
• Constipation
• Seizures

Contraindications

• Diagnosis of bulimia or anorexia nervosa
• Seizure disorders
• Current use of bupropion
• Recent abrupt discontinuation of alcohol or benzodiazepines
• MAOI therapy within 14 days
• Electrolyte abnormalities
Varenicline

- MOA: Partial agonist/antagonist at $\alpha_4\beta_2$ nicotine receptor
- Chantix®
- Therapy begins 1 week prior to quit date

Varenicline Dosage Cautions Adverse Effects

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Cautions</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 1-3 0.5 mg daily</td>
<td>Severe renal impairment</td>
<td>Nausea</td>
</tr>
<tr>
<td>Days 4-7 0.5 mg twice daily</td>
<td>Psychiatric disorders</td>
<td>Insomnia/Vivid dreams</td>
</tr>
<tr>
<td>Should initiate 1 week prior to quit date</td>
<td></td>
<td>Constipation</td>
</tr>
<tr>
<td>12–24 weeks or longer</td>
<td></td>
<td>Neuropsychiatric symptoms</td>
</tr>
</tbody>
</table>

Second Line Therapies

- Clonidine
  - Antihypertensive (prescription only) agent that has demonstrated efficacy at controlling withdrawal symptoms
  - Initial dosing is typically 0.10mg BID PO
    - Doses range widely across clinical trials
    - Initiate 3 days before quit date
    - Duration studied ranges from 3-10 weeks
  - Side Effects:
    - Dry mouth, drowsiness, dizziness, sedation, and constipation
    - Lowers blood pressure
    - Reboud hypertension with non tapered discontinuation

Second Line Therapies (cont.)

- Nortriptyline
  - Antidepressant (prescription only) medication with demonstrated efficacy equal to NRT
  - Initiate at 25mg/day, increasing gradually to a target dose of 75-100 mg/day
    - Duration of treatment used in smoking cessation trials is 12 weeks, however, may extend treatment for up to 6 months
    - Therapy is initiated 10-28 days before the quit date to allow nortriptyline to reach steady state at the target dose
  - Side effects:
    - Sedation, dry mouth, blurred vision, urinary retention, lightheadedness, and shaky hands

Combination Therapy

- Continuous NRT + Short-term NRT
- NRT + Bupropion
- Varenicline is not a candidate for combination therapy
- Effective for patients with:
  - High level of dependence
  - History of relapse
  - Breakthrough cravings
  - Failed attempt at monotherapy

Nicotine Vaccine

- NicVax®
  - Concept:
    - Inject components of nicotine molecule into bloodstream
    - Body perceives these as foreign (antigen) and produces antibodies
    - Antibodies bind to nicotine from smoke
  - Need up to 6 injections
  - Unclear how long duration of effect will be
  - Can’t combine NRT with vaccine model
  - Clinicaltrials.gov
Alternative Therapies

- Hypnosis
- Acupuncture
- SMART shot
- Herbal products – Chamomile
- Zero Nicotine
- Cigarrest
- E-cigarette

Factors in Choosing Therapy

- Efficacy
- Medical Comorbidity
- Adverse effects
- Previous experience
  - Patient and provider
- Patient preference
- Potential drug interactions
- Cost/access

There is no algorithm for choosing a tobacco cessation aid.

Patient Case

Mr. Smith is a 72 year old man who comes to you to ask about buying a tobacco cessation product. He wants to try an over-the-counter product because he doesn’t like taking prescription medications. He is ready to quit and is currently smoking 1 and ½ packs per day. The time to his first cigarette is 10 minutes within awakening. His FTND score is a 7.
Patient Case

• What options are available for Mr. Smith?

• What questions should you ask Mr. Smith before initiating any NRT?

• Is Mr. Smith a candidate for combination therapy?

Patient Case

• What dose of each NRT should Mr. Smith be started on if he chooses?

• Upon further questioning you discover Mr. Smith has dentures. What is your final recommendation for Mr. Smith?

References

Thank you for your attention!

Questions: email at ksando@cop.ufl.edu