Smoking Cessation Pharmacotherapy

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Objectives

- Discuss the prevalence of tobacco use in the United States (U.S.)
- Describe the health risks associated with smoking
- Describe the health benefits of smoking cessation
- Define smoking cessation
- Recognize the 5 “A’s” to promote smoking cessation
- Highlight the role of nicotine replacement therapy in smoking cessation
- Identify the use of other pharmacotherapies in smoking cessation

Prevalence of Tobacco Use

- In 2014, nearly 17 of every 100 U.S. adults 18 years or older (16.8%) or an estimated 40 million adults in the U.S., smoked cigarettes
- Each year there are 480,000 deaths attributed to smoking in the U.S
- Largest avoidable source of mortality

Disclosure

- The author of this presentation has nothing to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.
Prevalence of Tobacco Use

- Each day 4,000 minors, ages 12 to 17, smoke their first cigarette
- Approximately 1,200 children and adolescents become daily cigarette smokers
- More than 16 million Americans live with a smoking-related disease

Second Hand Smoke

- Smoke that has been exhaled, or breathed out, from burning tobacco products, such as:
  - Cigarettes
  - Cigars
  - Pipes

Second Hand Smoke

- Accounts for approximately 2,500,000 deaths in nonsmokers
- Results in nearly 34,000 heart disease deaths each year
- Associated with more than 7,300 lung cancer-related deaths each year
Costs of Tobacco Use

- $96 billion dollars per year in direct medical expenses
- $156 billion dollars lost in work wages
- $193 billion dollars in annual health-related economic losses
- $300 billion dollars in total economic cost of smoking

Health Consequences of Smoking
Health Consequences of Smoking

Chronic Diseases
- Stroke
- Blindness
- Gum infection

Cancers
- Head or Neck
- Lung
- Leukemia
- Stomach
- Kidney
- Pancreas
- Colon

Cancers
- Bladder
- Cervix

Assessment Tools for Tobacco Dependence

- Fagerstrom Tolerance Questionnaire (FTQ)
- Fagerstrom Test for Nicotine Dependence (FTND)
- Diagnostic and Statistical Manual (DSM)
- Cigarette Dependence Scale (CDS)
- Nicotine Dependence Syndrome Scale (NDSS)
- Wisconsin Inventory of Smoking Dependence Motives (WISDM)

Tobacco Dependence

- Smoking within 30 minutes of awakening
- Smoking more than 20 cigarettes per day
- Awaking at night to smoke

Nicotine Addiction

American Psychiatric Association, (2019). Diagnostic and Statistical Manual for Mental Disorders – V
Nicotine Withdrawal Symptoms

- Anxiety
- Craving
- Cognitive and attention deficits
- Depression
- Decreased heart rate
- Increased appetite or weight gain
- Irritability, frustration, anger
- Sleep disturbances

5 A's Model for Treating Tobacco Use and Dependence

- ASK
- ADVISE
- ASSESS
- ASSIST
- ARRANGE

Tobacco Dependence

- 70% of adult tobacco users report wanting to quit each year
- 44% of adult tobacco users report they try to quit each year
- Only 4-7% of tobacco users who attempt to quit are successful

Methods for Enhancing Motivation to Quit The 5 R's

- Relevance: What's the most important reason for you to consider quitting?
- Risks: What are the negative things you think about smoking?
- Rewards: What are the benefits you may have if you stop smoking?
- Roadblocks: What barriers do you have to quitting tobacco?
- Repetition: Many people need 7 to 10 attempts before they are successful

Fiore et al. (2008). Treating Tobacco Use and Dependence
**Who Should Receive Treatment?**

- All tobacco users trying to quit, except:
  - Contraindication to pharmacotherapy
  - Specific populations with insufficient evidence of effectiveness
    - Adolescents
    - Light smokers (<10 cigarettes a day)
    - Pregnant women
    - Smokeless tobacco users

**Considerations for Treatment Selection**

- Adverse effects
- Cost
- Patient characteristics
  - History of depression
  - Weight gain concerns
  - Breastfeeding
- Patient preference
- Precautions and contraindications
- Previous patient experience
Pharmacotherapy

First Line Agents

- FDA-approved
  - Nicotine Replacement Therapy (NRT)
    - Nicotine Transdermal Patch (OTC)
    - Nicotine Gum (OTC)
    - Nicotine Lozenge (OTC)
    - Nicotine Inhaler (Rx)
    - Nicotine Nasal Spray (Rx)
  - Bupropion SR (Zyban®, Wellbutrin SR®) (Rx)
  - Varenicline (Chantix®) (Rx)

Second Line Agents

- Non FDA-approved
  - Clonidine (Catapres®, Catapres-TTS®)
  - Nortriptyline (Pamelor®)

Fiore et al. (2008). Treating Tobacco Use and Dependence


Nicotine Replacement Therapy (NRT)

- **Options**
  - Patch
  - Gum, Inhaler, Lozenge
  - Nasal Spray

- **Absorption**
  - Slow
  - Intermediate
  - Fast

Nicotine Containing Products Plasma Concentrations

- **Cigarette**
- **Nicotine pouch**
- **Nasal spray**
- **Inhaler**
- **Lozenge (4mg)**
- **Gum (4mg)**
- **Patch**

NRT Precautions

- Recent MI (within 2 weeks)
- Serious underlying arrhythmias
- Serious or worsening angina pectoris
- Pregnancy category D
- Breastfeeding
- Adolescents (<18 years)

Efficacy of NRT

- All NRT forms increase quit rates at 6-12 months by 50-70% compared to placebo
- No significant difference between NRT forms
  - 4mg gum is more effective in highly dependent smokers
  - Higher dose patches do not show additional benefit
- The intensity of additional advice and support does not increase the effectiveness of NRT
- A combination of NRT products is more effective than one product alone
Nicotine Transdermal Patch (NicoDerm CQ®, etc.)

<table>
<thead>
<tr>
<th>Product</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>NicoDerm CQ® or generic</td>
<td>Local skin reactions</td>
</tr>
<tr>
<td>7mg, 14mg, 21mg (24-hour release)</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Sleep disturbances</td>
</tr>
</tbody>
</table>

Dosing Counseling Points

If >10 cigarettes/day:
- 21 mg/day x 4-6 weeks
- 14 mg/day x 2 weeks
- 7 mg/day x 2 weeks

If <10 cigarettes/day:
- 14 mg/day x 6 weeks
- 7 mg/day x 2 weeks
- 4 weeks, then 2 weeks, then 2 weeks

Advantages
- Once daily dosing improves adherence
- Less visible
- Can be used in combination with other agents
- Delivers consistent nicotine levels over 24 hours

Disadvantages
- Cannot be titrated to acutely manage withdrawal symptoms
- Not recommended for use in patients with dermatologic conditions (e.g., psoriasis, eczema, atopic dermatitis)
- Allergic reactions to adhesive

Nicotine Gum (Nicorette®, etc.)

<table>
<thead>
<tr>
<th>Product</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicorette® or generic</td>
<td>Dyspepsia</td>
</tr>
<tr>
<td>2mg, 4mg</td>
<td>Sore mouth</td>
</tr>
<tr>
<td>Original, cinnamon, fruit, and mint flavors</td>
<td>Hiccups</td>
</tr>
<tr>
<td></td>
<td>Jaw ache</td>
</tr>
<tr>
<td></td>
<td>Hypersalivation</td>
</tr>
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### Nicotine Gum (Nicorette®, etc.)

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Counseling Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 25 cigarettes/day: 2mg</td>
<td>- Chew each piece slowly&lt;br&gt;- Park between cheek and gum when peppery or tingling sensation appears (~15-30 chews)&lt;br&gt;- Resume chewing when tingling fades&lt;br&gt;- Park in different areas of mouth&lt;br&gt;- Avoid acidic beverages 15 minutes before and after chewing</td>
</tr>
<tr>
<td>≥ 25 cigarettes/day: 4mg</td>
<td>- 1 gum every 1-2 hours x 6 weeks&lt;br&gt;- 1 gum every 2-4 hours x 2 weeks&lt;br&gt;- 1 gum every 4-8 hours x 3 weeks&lt;br&gt;- Maximum 24 pieces/day&lt;br&gt;- Use up to 12 weeks</td>
</tr>
</tbody>
</table>

### Advantages
- Oral substitute for tobacco<br>- Titrated to manage withdrawal symptoms<br>- Used in combination with other agents to manage craving<br>- Variations in flavors

### Disadvantages
- Frequent dosing can compromise adherence<br>- Proper chewing technique is necessary for effectiveness and to minimize adverse effects

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### Nicotine Lozenge (Commit®, Nicorette®)

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Counseling Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st cigarette &lt; 30 minutes after waking: 4mg&lt;br&gt;1st cigarette &gt; 30 minutes after waking: 2mg</td>
<td>- Allow to dissolve slowly (20–30 minutes)&lt;br&gt;- Nicotine release may cause a warm, tingling sensation&lt;br&gt;- Do not chew or swallow&lt;br&gt;- Rotate to different areas of the mouth&lt;br&gt;- No food or beverages 15 minutes before or during use&lt;br&gt;- Used for at least 12 weeks</td>
</tr>
</tbody>
</table>

### Adverse Effects
- Nausea<br>- Sore throat<br>- Hiccups<br>- Heartburn<br>- Headache<br>- Flatulence<br>- Insomnia

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### Product Adverse Effects
- Commit® or generic<br>2mg, 4mg<br>Cherry or mint flavor<br>- Nausea<br>- Sore throat<br>- Hiccups<br>- Heartburn<br>- Headache<br>- Flatulence<br>- Insomnia
### Nicotine Lozenge (Commit®, Nicorette®)

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can serve as an oral substitute for tobacco</td>
<td>Frequent dosing can compromise adherence</td>
</tr>
<tr>
<td>Can be titrated to manage withdrawal symptoms</td>
<td>Gastrointestinal side effects</td>
</tr>
<tr>
<td>Can be used in combination with other agents to manage craving</td>
<td></td>
</tr>
</tbody>
</table>


### Nicotine Inhaler (Nicotrol Inhaler®)

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can be titrated to manage withdrawal symptoms</td>
<td>Frequent dosing can compromise adherence</td>
</tr>
<tr>
<td>Mimics hand-to-mouth ritual of smoking</td>
<td>Cartridges might be less effective in cold environments</td>
</tr>
<tr>
<td>Can be used in combination with other agents to manage cravings</td>
<td>Throat and mouth irritation</td>
</tr>
<tr>
<td></td>
<td>Caution in patients with bronchospastic disease</td>
</tr>
</tbody>
</table>


### Nicotine Inhaler (Nicotrol Inhaler®)

<table>
<thead>
<tr>
<th>Product</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotrol Inhaler® or generic</td>
<td>Local irritation of mouth and throat</td>
</tr>
<tr>
<td>10 mg cartridge delivers 4mg inhaled nicotine vapor</td>
<td>Cough</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
</tr>
<tr>
<td></td>
<td>Rhinitis</td>
</tr>
</tbody>
</table>

### Dosing

- 6–16 cartridges/day
- Individualize dosing
- Initially use 1 cartridge every 1–2 hours
- Use for up to 6 months

### Counseling Points

- Continuous puffing for 20 minutes
- Nicotine is depleted after 20 minutes of active puffing
- Inhale into back of throat or puff in short breaths
- Do NOT inhale into the lungs (like a cigarette) but “puff” as if using a pipe
- Open cartridge retains potency for up to 24 hours
- No food or beverages 15 minutes before or during use

Nicotine Nasal Spray (Nicotrol NS®)

**Product**
- Nicotrol NS® or generic
- Metered spray 10mg/ml aqueous nicotine solution

**Adverse Effects**
- Nasal irritation
- Nasal congestion
- Transient changes in taste and smell
- Headache
- Cough
- Sneezing

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

**Disadvantages**
- Frequent dosing can compromise adherence
- Development of dependence
- Patients with chronic nasal disorders or reactive airway disease should not use spray
- Nose and throat irritation

**Dosing**
- 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
- Maximum: 5 doses/hour or 40 doses/day
- Use up to 3-6 months

**Counseling Points**
- Prime prior to use
- Tilt head back slightly
- Do not sniff, swallow, or inhale through the nose as spray is being administered
- Wait 2 to 3 minutes before blowing nose

Bupropion SR (Zyban®)

- Atypical antidepressant which inhibits dopamine and norepinephrine reuptake and possibly acts as a nicotinic antagonist

**Contraindications**
- Seizure disorder
- Current or prior diagnosis of bulimia/anorexia
- Abrupt discontinuation of alcohol or sedatives/benzodiazepines
- MAO inhibitors in preceding 14 days


Bupropion SR (Zyban®)

- **Precautions**
  - Hepatic impairment
  - Concomitant therapy with medications/conditions known to lower the seizure threshold
  - History of seizure
  - Pregnancy category C
  - **BLACK-BOXED WARNING** for neuropsychiatric symptoms

**Efficacy of Bupropion SR (Zyban®)**

- Combining bupropion SR with an NRT has been shown to increase short-term smoking abstinence rates
- Combination of bupropion SR and nicotine patch have shown no significant increase for long-term (>6months) abstinence rates compared to nicotine patch alone

**Bupropion SR (Zyban®)**

<table>
<thead>
<tr>
<th>Product</th>
<th>Adverse Effects</th>
</tr>
</thead>
</table>
| Zyban® or bupropion SR 150mg (sustained-release tablet) | Insomnia
- Dry mouth
- Nervousness/difficulty concentrating
- Nausea
- Dizziness
- Constipation |

**Dosing Counseling Points**

- 150 mg every morning x 3 days, then 150 mg twice a day
- Do not exceed 300 mg/day
- Begin therapy 1–2 weeks prior to quit date
- Allow at least 8 hours between doses
- Avoid bedtime dosing to minimize insomnia
Bupropion SR (Zyban®)

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Twice daily oral dosing is associated with fewer adherence problems</td>
<td>• Increased seizure risk</td>
</tr>
<tr>
<td>• Might delay weight gain</td>
<td>• Several contraindications and precautions</td>
</tr>
<tr>
<td>• Beneficial in patients with depression</td>
<td>• Patients should be monitored for potential neuropsychiatric symptoms</td>
</tr>
<tr>
<td>• Can be used in combination with NRT agents</td>
<td></td>
</tr>
</tbody>
</table>

Advantages: Twice daily oral dosing is associated with fewer adherence problems, might delay weight gain, beneficial in patients with depression, can be used in combination with NRT agents.

Disadvantages: Increased seizure risk, several contraindications and precautions, patients should be monitored for potential neuropsychiatric symptoms.


Fiore et al. (2008). Treating Tobacco Use and Dependence

Zyban® (Summary of Product Characteristics). 2009. GlaxoSmithKline

Efficacy of Varenicline (Chantix®)

• Existing data indicates that varenicline is more effective than bupropion and some forms of NRT in achieving abstinence, and is recommended for use as a first line therapy.


Varenicline (Chantix®)

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Varenicline (Chantix®)

- **Precautions**
  - Use with caution and lower dosage in patients with CrCl <30 mL/min or those on dialysis
  - Pregnancy category C
  - Cardiovascular events
  - **BLACK BOX WARNING** for neuropsychiatric symptoms
- **Contraindications**
  - Hypersensitivity to varenicline

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**Dosing**

- Day 1-3: 0.5mg daily
- Day 4-7: 0.5mg twice daily
- Day 8-end of treatment: 1mg twice a day

**Counseling Points**

- Take after eating with full glass of water to decrease nausea
- Take second pill at dinner rather than bedtime to reduce insomnia

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**Product Adverse Effects**

<table>
<thead>
<tr>
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<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chantix® 0.5mg and 1mg</td>
<td>Nausea, Sleep disturbance, Vivid/strange dreams, Headaches, Constipation, Vomiting, Neuropsychiatric symptoms</td>
</tr>
</tbody>
</table>

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**Advantages**

- Twice daily oral dosing is associated with fewer adherence problems
- Different mechanism of action for patients who have failed other agents

**Disadvantages**

- Should be taken with food or a full glass of water to reduce the incidence of nausea
- Requires monitoring for potential neuropsychiatric and cardiovascular symptoms
Efficacy of varenicline combined with nicotine replacement therapy vs. varenicline alone for smoking cessation

**Title**

- Primary outcome was the 4-week abstinence rates from smoking for weeks 9 through 12 of treatment
- Secondary outcome included point prevalence abstinence at 6 months, continuous abstinence rate from weeks 9 through 24, and adverse events

**Methods**

- Randomized, blinded, placebo-controlled clinical trial with a 12-week treatment period and 12-week follow-up
- Four hundred forty-six generally healthy smokers were randomized (1:1); 435 were included in the efficacy and safety analyses

**Results**

- Combination treatment was associated with a higher continuous abstinence rate at 12 weeks (55.4% vs 40.9%) and 24 weeks (49.0% vs 32.6%) and point prevalence abstinence rate at 6 months (65.1% vs 46.7%)

**Conclusion**

- Varenicline in combination with NRT was more effective than varenicline alone at achieving tobacco abstinence at 12 weeks (end of treatment) and at 6 months

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**Clonidine (Catapres®, Catapres-TTS®)**

**Mechanism of Action**

- Stimulates alpha-2 adrenoreceptors in the brainstem and reduces sympathetic outflow

**Precautions**

- Rebound hypertension
- Pregnancy category C

**Adverse Effects**

- Dry mouth
- Drowsiness
- Dizziness
- Sedation
- Constipation

**Dosing**

- Begin 3 days before quit date or on the quit date
- Tablet: 0.15-0.75 mg daily
- Patch: 0.1-0.2 mg per 24 hours (via appropriate strength patch applied once every 7 days)

**Counseling Points**

- Apply patch to hairless location between the neck and waist
- Do not discontinue therapy abruptly
Nortriptyline (Pamelor®)

### Mechanism of Action
- Blocks reuptake of norepinephrine and serotonin
- Use with caution in cardiovascular disease
- Avoid co-administration with MAOIs
- Pregnancy category D

### Precautions
- Risk of arrhythmias
- Use with caution in cardiovascular disease
- Avoid co-administration with MAOIs

### Adverse Effects
- Sedation
- Dry mouth
- Blurred vision
- Urinary retention
- Lightheadedness
- Shaky hands

### Dosing Counseling Points
- Begin 10-28 days before quit date
- Initially 25 mg daily, gradually increase to 75-100 mg daily
- Do not discontinue abruptly because of withdrawal effects

### Efficacy of Nortriptyline (Pamelor®)
- Conflicting data exist regarding increased efficacy with combination therapy using nortriptyline and NRT compared to monotherapy

### Combination Therapy
- Combination of NRT
  - Long-acting formulation (patch) + short-acting formulation (gum, inhaler, nasal spray)
  - Bupropion SR + nicotine patch
  - Bupropion SR + varenicline
  - Varenicline + NRT
Combination Therapy

- Increased abstinence rates
- Enhanced relief of withdrawal effects
- Considered in highest risk of relapse
  - Previously failed monotherapy
  - Smokers with high nicotine-dependence
  - Heavy smokers (i.e. 20 cigarettes or more per day)
- Additional cost must be considered

Pharmacotherapy Use in Pregnancy

- Insufficient evidence for recommendations in pregnant smokers
- Category C: varenicline, bupropion SR
- Category D: nicotine replacement therapy
- Behavioral interventions are the preferred treatment
Pharmacotherapy: Other Special Populations

• Pharmacotherapy is NOT recommended for:
  – Smokeless tobacco users
  – Smoking fewer than 10 cigarettes per day
  – Adolescents
    • OTC sales are restricted to adults 18 years or older
    • Nicotine replacement therapy use in minors require a prescription

Role of the Pharmacist

• Assist in the selection of OTC products
• Counsel on proper use of smoking cessation medications
• Assist physicians with evidence based recommendations
• Monitor drug interactions with smoking and smoking cessation therapy

Role of the Pharmacist

• Ask about tobacco use
• Advise patient to quit
• Explain the risks and complications of tobacco use
• Promote and encourage smoking cessation
• Referral to a formal cessation program
• Encourage and provide support

Questions

References

• Stead LF et al. Nicotine replacement therapy for smoking cessation. Cochrane Review 2012; issue 11
• Elbirt JD, Hays JT, Hurt RD. Combination pharmacotherapy for stopping smoking: what advantage does it offer? Drugs 2010; 70(8): 643-659
• Bullen C et al. Electronic cigarettes for smoking cessation: a randomised controlled trial. Lancet Sep 7 2013

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