Objectives

1. Describe the pharmacokinetics of nicotine to aid providers in treating TB patients who use tobacco.
2. List the types of nonprescription and prescription Nicotine Replacement Therapy products for tobacco cessation to aid in treating TB patients who use tobacco.
3. List and describe the types of Non nicotine pharmacotherapy products for tobacco cessation to aid in treating TB patients who use tobacco.
4. List 3 different tobacco cessation medication combinations that can be used to aid in treating TB patients who use tobacco.
Pharmacokinetics of Nicotine

What is Nicotine

- Chemical in tobacco that keeps users addicted
- Structurally similar to other addictive substances
  - Mimics Acetylcholine
- One of the few natural alkaloids that exist in a liquid state
  - Clear, volatile and turns brown on exposure to air.
  - Has the smell of tobacco
Nicotine in Tobacco

The amount of nicotine in tobacco products is not specified by manufacturers

- Standardized smoking machine tests can determine nicotine yield in brands

Differs by parts of the plant

- higher stalk positions = higher nicotine concentration
- lower stalk positions; ribs and stems of the leaves = lowest nicotine concentration

Combining different varieties of tobacco and different parts of the plant is a way to change the nicotine concentration of commercial tobacco

Effects of Nicotine

- Development of tolerance
- Acute toxicity
- Increased heart rate
- Increased blood pressure
Pharmacokinetics

- Absorption
- Distribution
- Metabolism
- Excretion

Absorption

Absorption across biological membranes depends on pH.

- Weak base
- Ionized vs Non-ionized

When tobacco smoke reaches the small airways and alveoli of the lung, the nicotine is rapidly absorbed

- Surface area of alveoli and small airways

Concentrations of nicotine in blood rise quickly during cigarette smoking and peak at its completion

Smokeless tobacco

- Absorption through mucous membranes
**Distribution**

- Tissues rapidly uptake nicotine once inhaled
- Organs with highest affinity for nicotine: liver, kidney, spleen, lung
  - Lowest is adipose tissue
- Nicotine accumulates in breast milk
  - Crosses the placental barrier easily
- Inhaled: Delivers nicotine rapidly to the pulmonary venous circulation, then to the left ventricle of the heart and to the systemic arterial circulation and brain.
  - The lag time between a puff of a cigarette and nicotine reaching the brain is 10–20 seconds
  - Rapid onset of effect provides optimal reinforcement for development of drug dependence

**Metabolism**

- Primary metabolites of nicotine:
  - Cotinine
  - Nicotine-N-oxide
- Metabolized by the liver
  - Lung metabolizes some nicotine
Excretion

Nicotine is excreted by glomerular filtration and tubular secretion within the kidney

- Urinary pH and urine flow rate effects reabsorption of nicotine

Half life is ~2 hours

Pharmacodynamics

- The relationship between nicotine levels in the body and their effects on behavior and physiological function
  - Dose-Response relationship
  - Level of tolerance
Drug Interactions With Tobacco Cessation Medication

Significant Pharmacokinetic Interactions with Smoking Cessation

- **Caffeine** – increased metabolism & clearance
- **Theophylline** (Theo Dur, etc.) – increased metabolism & clearance, decreased half-life; also, increased clearance with 2nd hand smoke
- **Insulin** requirements may drop notably within 1 day of quitting
- **Warfarin** requirements drop with smoking cessation – may need up to a 12% decrease of dosage
- **Blood pressure and/or antidepressant drugs** may also need to be adjusted
Significant Pharmacokinetic Interactions with Smoking

- **Clozapine** (Clozaril) – increased metabolism & decreased plasma concentrations
- **Olanzapine** (Zyprexa) – increased metabolism & clearance, decreased serum concentrations
- **Fluvoxamine** (Luvox) – increased metabolism & clearance, decreased plasma and area-under-curve concentrations
- **Tacrine** (Cognex) – increased metabolism, decreased half-life and serum concentrations

Significant Pharmacodynamic Interactions with Smoking

- **Inhaled corticosteroids** – asthmatic smokers may have a reduced response to these
- **Hormonal contraceptives** – increased risk of adverse cardiovascular effects (e.g., MI, stroke, thromboembolism)
  - This risk increases with age (especially 35 + YOA) and heavier smoking (15+ cig./day)
- **Beta-blockers** – less effective antihypertensive and heart rate control effects
Interactions with TB drugs

- No *significant* interactions
- *Buproprion* might have an interaction with linezolid
- *Cycloserine* and *bupropion* can both cause seizures-monitor the patient closely for any seizure activity
- Potential interaction with the *quinolones*

Overall, smoking cessation products have been used with TB patients and didn’t have a problem with drug interactions

Addiction Cycle
Withdrawal Symptoms

- Tingling in hands/feet
- Sweating
- Nausea
- Headaches
- Coughing/Sore throat
- Insomnia
- Difficulty concentrating
- Irritability
- Weight gain

Nicotine Withdrawal Timeline

- Your Last Cigarette → 4 hours in → 10 hours in → 1 day in
- 1 week smoke-free → 3 days → 2.5 days in → 2 days in
Nicotine Replacement Therapy

There are 7 first-line medications available:
- 5 nicotine (NRT) and 2 non-nicotine (NNP)

- **Prescription ONLY**
  - Nicotine Inhaler
  - Nicotine Nasal Spray
  - Bupropion SR (Wellbutrin, Zyban)
  - Varenicline (Chantix)

- **OTC**
  - Nicotine Patches
  - Nicotine Gum
  - Nicotine Lozenges
**NRT Timeline**

- **1984**: Prescription NRT gum (2 mg) was first smoking cessation aid to be approved by the FDA.
- **1992**: Prescription NRT patch was approved.
- **1993**: Prescription NRT gum (4 mg) was approved.
- **1996**: Both gum and patch were approved for OTC use.
- **1998**: Prescription nicotine nasal spray was approved.
- **2002**: OTC NRT lozenges (2 mg & 4 mg) were approved.

**NNP Timeline**

- **1997**: Bupropion (Zyban) becomes the first non-nicotine smoking cessation aid.
- **2006**: Varenicline (Chantix) is the next non-nicotine aid FDA approved.
- **2009**: Black Box warning added.
- **2016**: Black Box warning removed.

Black Box warning added 2009

Bupropion (Zyban) becomes the first non-nicotine smoking cessation aid in 1997

Varenicline (Chantix) is the next non-nicotine aid FDA approved in 2006

Black Box warning removed 2016
Average Daily Costs of NRT/NNP

2013 average cost/pack of cigarettes, $5.98**

<table>
<thead>
<tr>
<th>Product</th>
<th>Trade 2013</th>
<th>Generic 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gum Lozenge</td>
<td>$5.49</td>
<td>$1.99</td>
</tr>
<tr>
<td>Patch</td>
<td>$4.14</td>
<td>$2.66</td>
</tr>
<tr>
<td>Inhaler</td>
<td>$2.10</td>
<td>$1.52</td>
</tr>
<tr>
<td>Nasal spray</td>
<td>$3.97</td>
<td>$2.72</td>
</tr>
<tr>
<td>Bupropion SR</td>
<td>$4.76</td>
<td>$0.00</td>
</tr>
<tr>
<td>Varenicline</td>
<td>$7.53</td>
<td>$2.10</td>
</tr>
</tbody>
</table>

**From Campaign for Tobacco Free Kids, avg. pack cost 2013 update.

Nicotine Content in Tobacco Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Nicotine content</th>
<th>Suggested Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarettes</td>
<td>1.1mg to 1.8mg per cigarette</td>
<td>21mg patch ODT x 210 days plus NRT gum or NRT lozenge (6mg/2mg). Gradual decrease patch dose monthly (PACT manual to track?). May add Buproprion if no contraindications.</td>
</tr>
<tr>
<td>Cigar</td>
<td>3.3mg average</td>
<td>Patch and Short Acting NRT (6mg/2mg) based on 10 of cigarettes per day. May add Buproprion if no contraindications.</td>
</tr>
<tr>
<td>Mini-cigar (i.e. Swisher or Dark Horse)</td>
<td>3.8mg per mini-cigar = 7.6mg/pack</td>
<td>2mg to 21mg (depending on # smoked) plus Short Acting NRT (6mg/2mg). May add Buproprion if no contraindications.</td>
</tr>
<tr>
<td>Pipe</td>
<td>5.2mg average per bowl</td>
<td>Patch and Short Acting NRT (6mg/2mg) based on 5 of bowls smoked per day. May add Buproprion if no contraindications.</td>
</tr>
<tr>
<td>Chewing/Slipping can (i.e. Slims, Copenhagen)</td>
<td>3.9mg per can of chewing</td>
<td>2.2mg Patch and Short Acting NRT (6mg/2mg). May add Buproprion if no contraindications.</td>
</tr>
<tr>
<td>Loose-leaf pouch (i.e. Redman)</td>
<td>2.4mg per pouch</td>
<td>2.2mg Patch and Short Acting NRT (6mg/2mg). May add Buproprion if no contraindications.</td>
</tr>
<tr>
<td>Hookah (water pipe)</td>
<td>45-60 minute session ~ approximately one pack of cigarettes in nicotine and tar content</td>
<td>21mg Patch and Short Acting NRT (6mg/2mg). May add Buproprion if no contraindications.</td>
</tr>
<tr>
<td>Hand-rolled cigarettes imported from India</td>
<td>8 mg nicotine or less as much nicotine as a regular cigarette</td>
<td>Patch and Short Acting NRT (6mg/2mg) based on # of cigarettes smoked per day. May add Buproprion if no contraindications.</td>
</tr>
<tr>
<td>Keezek (clonie cigarette)</td>
<td>Little research available; increased risk of acute lung injury, especially with asthma or respiratory infections</td>
<td>Short Acting NRT (6mg/2mg) based on # of Keezek’s per day. May add Buproprion if no contraindications.</td>
</tr>
</tbody>
</table>

References available on request.

Southeastern National TB Center
Why NRT/NNP?

• More pharmacologic options increase treatment-assisted quit attempts

• Adding NRT/NNP to behavioral therapy greatly improves outcomes, often doubling success rates

• The World Health Organization added NRT to its list of “essential medicines” in March, 2009

NRT/NNP: To Use or Not?

<table>
<thead>
<tr>
<th>USE</th>
<th>Talk to doctor first if...</th>
</tr>
</thead>
<tbody>
<tr>
<td>• It works — roughly doubling success rates</td>
<td>• Recent MI or arrhythmia</td>
</tr>
<tr>
<td>• Reduces severity of withdrawal symptoms</td>
<td>• Current pregnancy</td>
</tr>
<tr>
<td>• Helps the patient feel more comfortable while they abstain</td>
<td>• Under 18</td>
</tr>
<tr>
<td>• It is very safe</td>
<td>• Bupropion – seizure disorder, eating disorder, MAO use</td>
</tr>
<tr>
<td>▪ Patient isn’t getting any “new drug”, just the same one at lower dose, in a less addictive form, over a relatively short period of time</td>
<td>• Concurrent medications</td>
</tr>
<tr>
<td></td>
<td>• Monitor psychiatric illness</td>
</tr>
<tr>
<td></td>
<td>• Varenicline – kidney disease</td>
</tr>
</tbody>
</table>
Plasma Nicotine Concentrations for Nicotine-Containing Products

From Rx for Change, “Aids for Cessation” Power Point; http://rxforchange.ucsf.edu, accessed 07/01/2014
Tobacco Treatment Medication Dosing Chart

• Suggests 3 months minimum length of treatment for all medications
• NRT/NNP use cautioned in:
  • Pregnant women
  • Persons with unstable coronary syndrome (esp. heart attack within the past 2 weeks)
  • Persons under the age of 18

• Chart for informational use only for patients and providers; consult professional publications or manufacturers for more details

NRT Usage: Nicotine Patch

3 patch strengths:
• 21mg
• 14mg
• 7mg
• <21mg*

*If smoking >10 cigarettes/day:
• 21mg for 4 – 6 weeks
• 14mg for 2 – 4 weeks
• 7mg for 2 – 4 weeks

If smoking ≤10 cigarettes/day:
• 14mg for 6 weeks
• 7mg for 2 weeks

* Product packaging slightly differs from chart
NRT Usage: Nicotine Patch

- Apply to clean, dry, hairless skin
- 1 patch every 24 hours – replace daily to prevent skin irritation
- Apply to different areas of upper body
- Wash hands after applying
- DO NOT cut the patch
- Skin irritation usually caused by the adhesive, not the nicotine

NRT Usage: Nicotine Patch

- Possible adverse reactions:
  - Vivid dreams/sleep disturbance
  - Mild skin reactions (e.g. burning, itching)
- Remove 1 – 2 hours before bed if sleep disturbance/vivid dreams occur; apply new patch in the morning
- Apply OTC cortisone cream or spray if rash occurs; put cream under patch and reaffix to skin with medical tape
- Contraindicated in people with severe eczema/skin disorders
NRT Usage: Nicotine Gum

**2 Strengths**
- 2mg
- 4 mg

If first cigarette within 30 minutes of waking up:
- 4 mg
- 1 piece every 1-2 hours

If first cigarette after 30 minutes:
- 2 mg
- 1 piece every 1-2 hours

NRT Usage: Nicotine Gum

- Possible adverse reactions include:
  - Mouth soreness
  - Hiccups
  - Indigestion
  - Jaw ache
  - Oral blistering (Sept. 2011 FDA packaging update)

- **Move gum around** to avoid mouth sores
- **Avoid chewing gum** too much to avoid jaw ache and indigestion
- **Caution** with peptic ulcers
- **Contraindicated with** TMJ disease or other jaw problems, dentures/other dental appliances or lack of teeth
NRT Usage: Nicotine Gum

1. Chew slowly
2. Park between cheek & gum
3. Chew again when the taste or tingle fades
4. Stop chewing when you notice a peppery taste or tingle

NRT Usage: Nicotine Lozenge

<table>
<thead>
<tr>
<th>Strengths</th>
<th>If first cigarette within 30 minutes of waking up:</th>
<th>If first cigarette after 30 minutes:</th>
</tr>
</thead>
</table>
| 2mg, 4mg  | • 4mg  
            • 1 piece every 1-2 hours                     | • 2mg  
            • 1 piece every 1-2 hours                     |

Southeastern National TB Center
NRT Usage: Nicotine Lozenge

- **Allow to dissolve slowly for 10-30 minutes**; move from side to side of mouth
- **DO NOT** chew
- **DO NOT** use lozenge if oral thrush or oral lesions are present
- **Caution** with peptic ulcers

- **Avoid drinking acidic drinks 15 minutes** prior to and during lozenge use
- **Possible adverse side effects:**
  - Headache
  - Insomnia
  - Nausea
  - Indigestion
  - Hiccups

Non-Nicotine Pharmacotherapy
NRT Usage: Nasal Spray

• 1 – 2 doses/hour
  - 1 dose = 1 spray/nostril
• Do not exceed 5 doses/hour or 40 doses/day
• Prime pump before first use
• Blow nose prior to application
• Insert bottle tip as far as comfortable, angling away from septum
• Do not sniff while spraying
• Used for heavier smokers, dippers
• Higher dependence potential compared to other NRT products
• Contraindications are rhinitis, sinusitis or nasal polyps

NRT Usage: Nasal Spray

• Possible adverse side effects (usually short term):
  - Nose, throat or eye irritation

• 94% experience these moderate to severe side effects within the first 2 days of starting the nasal spray:
  - Hot peppery feeling back of throat or nose
  - Sneezing
  - Coughing
  - Watery eyes
  - Runny nose
NRT Usage: Nicotine Inhaler

- For use in any type smoker, but generally not heavy smokers due to slower administration
- **10mg/cartridge:**
  - 1 cartridge = 200 puffs
- **Use 6 – 16 cartridges/day**
  - Pull top off, press cartridge in firmly until seal breaks; align marks on device to close
- **Not an actual inhaler** – nicotine is absorbed through oral lining
- To administer, use sipping or short puffing action
- **Satisfies handling habit** for some people

NRT Usage: Nicotine Inhaler

- Possible adverse reactions (usually short term):
  - Mouth/throat irritation
  - Cough
- **Do NOT inhale into lungs**
- **Contraindicated in people** with asthma and/or allergy to menthol
  - Menthol is one of the ingredients in the cartridges
NNP: Bupropion SR

- Also known as Zyban or Wellbutrin
- Produces mood elevating properties and actually caused weight loss in some study participants
- Actual mechanism that promotes smoking cessation is unclear
- Decreases withdrawal symptoms
- \textbf{Bupropion differs} from other antidepressants in biochemical action in the brain:
  - Targets dopamine and to some extent noradrenaline – it reduces their re-uptake
  - \textbf{Does not alter} serotonin re-uptake
  - Decreases craving for cigarettes

NNP: Bupropion SR

- Do not take bupropion with or within 14 days of discontinuing MAO inhibitor use – bupropion lowers seizure threshold
- FDA recommends to discontinue meds and contact healthcare provider if experiencing: agitation, hostility, atypical changes in behavior or thinking, suicidal thoughts or behavior
- \textbf{Possible adverse reactions include:}
  - Anxiety
  - Insomnia
  - Skin rash
  - Psychiatric symptoms
  - Depression
- \textbf{Off label use:} bupropion also used to treat ADD/ADHD
**NNP Usage: Bupropion SR**

- 150 mg per dose
- Begin 3 – 7 days prior to quit date; **starting 7 – 10 days prior reduces side effects:**
  - 150 mg/day for first week
  - 150 mg twice/day until end of treatment (minimum 3 months) – allow 8 hours between doses
- Can reduce to once/day if adverse side effects occur
- Contraindicated for people with seizure history/risk, history of eating disorders, or if using MAO inhibitors

**NNP Usage: Varenicline**

- Dose is 0.5 mg to 1 mg
- Begin 1 week before quit date

**Starter pack used to titrate from 0.5 mg daily to 1.0 mg twice/day:**
- 0.5 mg in morning only for 3 days
- 0.5 mg twice/day for 4 days
- 1mg twice/day until end of treatment (minimum 3 months)
- Can reduce to once/day if adverse side effects occur
- Take with food and water if possible
NNP: Varenicline (Chantix)

- **It is a partial agonist** (activator) selective for the $\alpha_4\beta_2$ nicotinic acetylcholine receptor subtype

- This partial activation is believed to **diminish nicotine withdrawal symptoms** by enhancing mesolimbic ("reward pathway") dopamine levels, but at a lower level than nicotine would produce

- **Approved by FDA for monotherapy**; further studies needed to evaluate combination therapy

---

NNP Usage: Varenicline

- **Possible adverse reactions include:**
  - Nausea
  - Headache
  - Sleep disturbance/unusual dreams
  - Possible psychiatric symptoms/depression

- **FDA recommends to discontinue meds and contact healthcare provider if experiencing:** agitation, hostility, atypical changes in behavior or thinking, suicidal thoughts or behavior

- **Also reported: serious allergic/inflammatory reaction**
  - Swelling of face, lips, tongue, throat, neck
  - Hives
  - Breathing difficulties
  - Blistering rash in mouth or on skin

- **REMEMBER:** allergic reactions can happen with any medication
Update: 2009 Varenicline Study

- October 2009 study in UK showed Varenicline side effects are comparable to other cessation medications
- Varenicline has best cessation rates of any NNP available and is generally well tolerated
- A two fold increase in risk of self harm cannot be ruled out due to the study parameters
- REMEMBER: depression and suicidal thoughts are also potential side effects of nicotine withdrawal

2009 FDA Update

- July, 2009--Varenicline (marketed as Chantix) and Bupropion (marketed as Zyban, Wellbutrin, and generics) received Boxed Warnings
- Highly publicized reports of depression, suicidal thoughts/attempts, unusual changes in behavior
- Monitor patients on these meds closely until symptoms resolve (during use and as needed after discontinuing use)
- Small percentage of patients experience serious adverse side effects
- Benefits still outweigh risks
2016 FDA Update

- EAGLES Trial published in The Lancet in April 2016
  - 8,144 participants between ages 18 and 75
  - Smoked more than ½ pack per day
  - Half with and half without psychiatric history
  - Neuropsychiatric symptoms with Varenicline just slightly more in psychiatric history
  - Benefit of Varenicline in smoking cessation outweighed the symptoms

2016 FDA Update

- FDA advisory board recommended that black box warning regarding neuropsychiatric symptoms be removed in September 2016
- Black Box warning was removed in December 2016
- Current recommendations
  - Clinicians should not prescribe Varenicline to smokers who have experienced suicidal ideation in the past year or those who are currently unstable regarding their mental health issues
  - If a smoker has a Mental Health provider, that provider should be consulted before initiating Varenicline

Combination Therapy

• Patch + NRT gum
• Patch + NRT lozenge
• Patch + Buproprion SR
• Patch + Inhaler

NRT for Other Tobacco Users
NRT Usage For Smokeless/Other Tobacco Users

• Clinical Practice Guideline does not recommend NRT for smokeless/other tobacco users due to lack of studies proving efficacy

• Suggested dosages on dosing chart based on cigarette equivalent of daily use

• Doses should then be self-titrated

NRT Usage For Smokeless Tobacco Users

• 1 can/week or more (equals up to 4 packs of cigarettes )
  • 21 mg patch 4 – 6 weeks, 14 mg 2 – 4 weeks, 7 mg 2 – 4 weeks
  • 4 mg gum or lozenge

• Less than 1 can/week
  • 14 mg patch 4 – 6 weeks, 7 mg 2 – 4 weeks
  • 2 mg gum or lozenge

• High Dose Nicotine Patch
  • 21mg, 42mg, 53 mg
Cigarette vs. Cigar

NRT Suggestions For Cigar Users

• **2 medium cigars/day or more** (equals about 12 strong cigarettes)
  - 21 mg patch 4 weeks, 14 mg 2 weeks, 7 mg 2 weeks
  - 4 mg gum or lozenge
  - Nicotine inhaler, 6 – 16 cartridges/day as needed

• **Less than 2 medium cigars/day**
  - 14 mg patch 2 weeks, 7 mg 2 weeks
  - 2 mg gum or lozenge
  - Nicotine inhaler, 6 – 10 cartridges/day as needed
  - **Little Cigars/One ppd** (one equals about four strong cigarettes)
  - 42mg to 21mg patch (depending on # smoked) plus
  - 4 mg gum or lozenge, depending on when first one is smoked
Department of Health & Human Services
Clinical Practice Guideline: 2008 Update

• Off label discussion:
  ➢ Using cessation medications in certain combinations is more effective

Clinical Practice Guideline:
2008 Statements

• Many current studies show combining therapies greatly increases success rates

• FDA has yet to approve most combination usages: it currently approves only NRT + bupropion

• Some researchers recommend continuing combination therapy for 3 – 6 months, or longer
Clinical Practice Guideline: 2008 Recommendations

- Suggested combinations (as tolerated):
  - Nicotine patch + nicotine gum or lozenge
  - Nicotine patch + nicotine nasal spray or inhaler (“puffer”)
  - Nicotine patch + Bupropion SR
- Not recommended to use NRT with Varenicline/Chantix (nicotine antagonist)
- If patient is using Wellbutrin, DO NOT prescribe Zyban/Buproprion SR & vice versa (same medication)

Which product is BEST for my patient?

- Double check current medications being taken
- Ensure no contraindicated diseases/symptoms exist
- Ask about past cessation attempts and medications used
- Ask if patient is willing to try something new or revisit NRT/NNP
Which product is **best** for my patient?

- **Method/ease of usage** can have impact on compliance

**Patient Compliance Rates for NRT:**
- Patch 82%
- Gum 38%
- Spray 15%
- Inhaler 11%

Compliance can be increased by following up, and checking in with patients!

Which product is **best** for my patient?

- **Usage rates in patients**
  - 5 – 20% of nicotine gum users continue use after 1 year or more
  - 43% of nicotine nasal spray users continue use at 1 year
  - Longer term use not typical with patch, inhaler and Zyban

*Note: recent studies have shown NO ADVERSE EVENTS with extended NRT/NNP use*
Mark Your Calendar

September 5:
Treating Tobacco Dependence in Special Populations