Pharmacotherapy for the Treatment of Tobacco Use Disorder

For groups with participants from a wide range of settings review the known settings and find ways to address how the TTS may address pharmacotherapy differently in each setting.
Objectives

Describe and apply evidence-based medicine principles to pharmacological treatment for nicotine dependence

Understand the anticipated effects of the different forms of pharmacologic treatment in select medical conditions

List additional special concerns and issues that affect the choice of pharmacologic treatment

KEY POINTS

• Have participants name the 7 FDA approved medications
• Have them name the recommended dosages
• Information about use of medications (dosing, tips) is included in Basic Skills for Working with Smokers. If your population needs more specific information, you may want to integrate the discussion into case studies.

Nicotine Replacement Products
Nicotine Patch: 21mg, 14mg, 7mg
Nicotine lozenges 2mg, 4mg
Nicotine gum 2mg, 4mg
Nicotine inhaler 10mg cartridges
Nicotine Nasal Spray 1mg/dose; 0.5 mg/spray

Bupropion
150mg daily x 3, then 150mg BID x 12 weeks. Recommend an additional 12 weeks if abstinent for a total of 6 months

Varenicline
0.5 mg Daily x3, 0.5mg BID x 4, then 1mg BID x 12 weeks. Recommend additional 12 weeks if abstinent for a total of 6 months.

Over the counter (OTC)
Nicotine patch, gum, lozenge (some insurances will cover if prescribed).

By prescription
Nicotine inhaler and nicotine nasal spray
Bupropion
Varenicline

The Who and Why of Pharmacotherapy for Smoking

WHO? All smokers who are trying to quit

WHY? Use of pharmacotherapy *more than doubles* long term quit rates

Pharmacotherapy + counseling increases success

KEYPOINTS:

• Smokers who quit cold turkey (no pharmacotherapy) have a 5-15% (avg 7%) chance of long term success
• In general, pharmacotherapy more than *doubles* the chances of success
• Furthermore, adding counseling to meds (the “Gold Standard”) will increase potential for success even more
• Smokers <10 CPD were not included in clinical trials therefore recommendations have only included those smoking 10 or more cigs/day
• Consider today’s changing landscape of smoking restrictions. The manner in which many smoke has changed i.e., many “relight” (e.g. reporting smoking 5 cigs/day but smoking 10-12 x/day). Re-lighters smoke differently in than they tend to have deeper and more complete inhalations each time they smoke.
• Using TFC (time to first cig/use) may be more helpful indicator of degree of dependence. Those who smoke within the first 30 mins. upon waking being more heavily dependent and therefore need more pharmacotherapy rather than less

REFERENCES: FAGERSTOM (FTC); Stead, 2012.
**Monotherapy**
- Seven first-line medications
- Two second-line medications

**Combination therapy**
- Patch + Other NRT
- Bupropion + NRT (patch, gum, lozenge, etc.)
- Varenicline + (NRT or Bupropion)
  - *Controversial*

**KEYPOINTS:**

- Published studies suggest that all 7 first line meds are effective, with varenicline being most effective and combination therapy being more effective than solo NRT
- Combination therapy is rapidly becoming a standard of treatment
- The patch combines well with the short-acting forms especially gum, lozenge, or inhaler
- Bupropion has also been shown to increase quit rates combined with NRT (reference “Triple Therapy” Bupropion, Patch, Lozenges)
- Varenicline has been shown to be safe to combine with NRT but it does increase rate of nausea. Further well run studies are needed to determine place in treatment. Because both NRT and varenicline work on the same receptors, there is a question of whether additive benefit is plausible. May have some place in long time/heavy smokers with lots of receptor upregulation. Note: The studies using combination therapy were with a 15 mg patch.
- Single study shows some benefit of combining bupropion and varenicline, particularly in smokers who are considered more highly addicted. This was associated with increased anxiety and depression though. Will need more research before it is generally recommended

**REFERENCES:** Steinberg, 2009; Ebbert, 2014; Kozlowski, 2007; Schnieder, 2001; Shiffman, 2005; Sweeney, 2005; Koegelenberg, 2014
Initial labelling was from an abundance of caution. There were further recommendations that labels be amended to include recommendations for combination therapy, but that has not been put into action.

When the PHS update was published in 2008 it included strong evidence to support combining medications – Patch plus short acting NRT especially

In 2013 the FDA responded to a citizens request from organizations like SRNT and ATTUD to change the labeling on NRT

The nicotine gum and patch products were originally approved through the new drug application (NDA) process between 1984 and 1992. Both the gum and the patch were initially available by prescription only; these products were switched from prescription to OTC status between 1996 and 2002. The nicotine lozenge and mini-lozenge were approved directly for OTC use in 2002 and 2009, respectively.

Over that 20 plus year period, additional evidence from studies and use in practice have shown that patients may benefit from tapering down cigarettes, combination NRT and longer duration of use, all of which we will discuss today.

In order to make the changes, the drug companies did have to submit an application for a label change to the FDA.
FDA Consumer Update: NRT Labeling

These recommendations now:

- Allow potential for use of more than one form of NRT
- Eliminate the precaution about smoking while using NRT
- Note that use longer than 12 weeks is safe to do so in most cases

• These recommendations now:
  • Allow for the use of more than one form of NRT → does not specifically recommend for or against; this is a good option for counseling. That being said, the patch does say not to wear more than 1 patch at a time. Again, this is a good option for counseling and explanation for nicotine levels attained from tobacco products.
  • Eliminate the precaution about smoking while using NRT
  • Note that use longer than 12 weeks is safe to do so in most cases.
  • Ask “What does this tell you about the safety of NRT?”
First Line Medications

<table>
<thead>
<tr>
<th>Nicotine Replacement</th>
<th>Non-nicotine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patch</td>
<td>Bupropion SR</td>
</tr>
<tr>
<td>Gum</td>
<td>Varenicline</td>
</tr>
<tr>
<td>Lozenge</td>
<td></td>
</tr>
<tr>
<td>Inhaler</td>
<td></td>
</tr>
<tr>
<td>Nasal Spray</td>
<td></td>
</tr>
</tbody>
</table>

List each product briefly. Remind group that basic dosing information for each product was covered in Basic Skills.
Let’s briefly review how each of the types of medication work.
Nicotine Replacement Therapy: Mechanism of Action

- Provides ‘medicinal’ or ‘clean’ nicotine
- Reduces withdrawal symptoms and craving
- May provide some positive effects of nicotine:
  - Desirable mood
  - Improved attention
- Replaces oral/handling aspects of habit (inhaler, gum, lozenge, nasal spray)

KEYPOINTS:

- Cigarettes use the best drug delivery system in our body (i.e., our lungs). Reaches the brain/reward pathway within 8 seconds.
- NRT is slower, does not access the reward pathway in the same manner.
- NRT will reduce both withdrawal symptoms and cravings which will allow the smoker to focus on changing behavior without the intense distraction of symptoms.

REFERENCES: Stead, 2012
**Bupropion SR: Mechanism of Action**

- **Brand names:** Wellbutrin SR (BID) Wellbutrin XL (once daily), Zyban, Buproban and Budeprion
- Sustained release forms (SR): Less variation in blood levels and less toxicity
- **Mechanism of action for tobacco cessation:** unknown
- Weak inhibitor of uptake of dopamine (DA) and norepinephrine (NE)
- Benefit likely related to the reduction in NE and DA during withdrawal
- PET scans show that brain cells known to be involved in drug craving do NOT activate in response to cigarette-related cues when in the presence of bupropion*

**KEYPOINTS:**

- Bupropion was originally just approved and used in the treatment of depression. When used for depression its brand name was Wellbutrin.
- It began being studied as a smoking cessation tool when those on the Wellbutrin reported decreased desire to smoke.
- In 1997 it was approved for use in treating tobacco dependence and marketed under the brand name Zyban.
- It is now available in the generic form, Bupropion.
- Mechanism of action not completely understood but believed to be related to the smoker’s level of dopamine. Interestingly, bupropion is now being used as part of a drug combination for binge eating disorder further supporting the theory that it has some effect on reward/addiction pathway.

**REFERENCES:**
- *Arthur Brody and colleagues; published online in the April 2004 issue of Psychiatry Research: Neuroimaging.
- Zyban Package Insert. GSK. 2017

**REFERENCES:** Brody, 2004; Hurt, 1997; Lerman, 2004
Varenicline: Mechanism of Action

Varenicline acts as a partial agonist/antagonist on the nicotinic acetylcholine receptors:
- Providing some nicotine effects to ease the withdrawal symptoms and
- Blocking the effects of nicotine from cigarettes if they resume smoking

KEYPOINTS:

- Designer drug (developed solely for the purpose of tobacco dependence treatment).
- Approved by FDA in 2006.
- Both a nicotine agonist and an antagonist.
- Decreases withdrawal symptoms.
- Decreases cravings.

REFERENCES: Aubin, 2008; Gonzales, 2006; Jorenby, 2006
Selecting Medications
Evidence-Based Medicine

**Evidence-Based Medicine (EBM):**
conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients

**Practice of EBM:** integrating individual clinical expertise with the best available external clinical evidence from systematic research

**KEYPOINTS:**

- Evidence based medicine means to:
  1. Understand the up to date evidence/research on a subject.
  2. Also understand what the research does not or has not yet determined.

- Practice involves the following:
  1. Your patient: preferences, health history, past attempts, finances.
  2. Your experience.
  3. The evidence.

THERE IS NO HARD AND FAST ALGORITHM!
KEYPOINTS:

• Again as in the discussion re evidence-based medicine, there is a foundation on which to begin when developing a particular treatment strategy for clients.

• Latest guidelines where published in 2008.

• Keep in mind, research continues and there are many good studies to consider that have been published since this.
Evidence-Based Pharmacotherapy for Tobacco Treatment

What evidence from RCTs provides and doesn’t provide:

- A rationale for following explicit guidelines when the evidence is strong
- Flexibility to make choices when appropriate
- An opening for informed clinical judgments when the evidence is limited

KEYPOINTS:

- RCTs or randomized controlled trials are considered the gold standard of a research study.
- An RCT includes strict and defined criteria re: patient population.
- For example, many studies exclude those with mental health diagnosis.
- Another example was deciding on a minimum # of cigs/day that the participant needed to smoke to be included in the study. This may be more or less than your patient. Intensive counseling is often provided.
- Finally, patients are often self-selected and may be compensated, meaning they could have more motivation.
- Therefore, conclusions of a particular study can only be drawn on the population included.
- Role of TTS (if not a prescriber)
  - Educate client about all medications
  - Make recommendations regarding use of OTC meds
  - Coordinate with prescribing clinician for Rx meds
Selecting Pharmacotherapy: The Science and the Art

The Science:

- Studies to date suggest nearly equivalent effectiveness of all first line medications
- Studies needed to directly compare effectiveness

The Art:

- Using detailed knowledge of basic pharmacology, clinical studies, and patient factors to choose the optimum medication

KEYPOINTS:

- Remember, different studies often have different study populations.
- Therefore, some of the apparent differences in effectiveness can be due to the different populations.
- Unless a study directly compares one agent against another can you really define the differences in effectiveness of various agents.
- Examine recent studies comparing agents.

REFERENCES: Mills, 2012; Aubin, 2008
Factors in the Selection of Pharmacotherapy

- Medication factors
- Patient factors
- Medical issues

KEYPOINTS:

- Considering each of these factors will help you make a recommendation of pharmacotherapy.

- We will review each of these factor and how they contribute to decision making with respect to pharmacotherapy.
Factors in the Selection of Pharmacotherapy

**Medication factors**

- Patient factors
- Medical issues

**AGENT FACTORS**

Factors related directly to the medication itself
# Agent Factors in Choosing Pharmacotherapy

- Effectiveness
- Side Effects
- Ease of Use/Convenience
- Cost

**KEYPOINTS:**

Each of these factors will be reviewed separately
Effectiveness of First Line Medications

Results from meta-analyses comparing to placebo (6 month F/U)

<table>
<thead>
<tr>
<th>Medication</th>
<th>No. Studies</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nic. Patch (6-14 wks)</td>
<td>32</td>
<td>1.9</td>
<td>1.7-2.2</td>
</tr>
<tr>
<td>Nic. Gum (6-14 wks)</td>
<td>15</td>
<td>1.5</td>
<td>1.2-1.7</td>
</tr>
<tr>
<td>Nic. Inhaler</td>
<td>6</td>
<td>2.1</td>
<td>1.5-2.9</td>
</tr>
<tr>
<td>Nic. Spray</td>
<td>4</td>
<td>2.3</td>
<td>1.7-3.0</td>
</tr>
<tr>
<td>Bupropion</td>
<td>26</td>
<td>2.0</td>
<td>1.8-2.2</td>
</tr>
<tr>
<td>Varenicline (2mg/day)</td>
<td>5</td>
<td>3.1</td>
<td>2.5-3.8</td>
</tr>
</tbody>
</table>

PHS Clinical Practice Guideline 2008 Update

KEYPOINTS:

This table summarizes the results of the meta-analyses conducted for the PHS Guideline. There are several factors to consider when interpreting these results.

- A meta-analysis combines the results of similar studies, using very specific criteria.
- OR refers to Odd Ratio – a statistical term that describes the effect size. So OR of 1.9 for the patch indicates that it is almost 2 times as effective as placebo.
- CI refers to the Confidence Interval – the range of effect size that can be expected. The smaller the range the stronger the result. We can see that the analyses with the smallest number of studies have the widest CI – which indicates a need for additional studies.
- Generally the larger the number of studies the more confidence we have in the results. Given that there are different number of studies for each one, it is hard to compare head to head, but this gives us a good idea.

REFERENCE: USPHS, 2008
Effectiveness of First Line Medications

- Recent study showed no difference in 26 or 52 week abstinence rates amongst NRT patch, varenicline nor combination NRT

- Meta-analysis of 12 studies in 2014
  - All agents better than placebo
  - No difference between varenicline and combination NRT
  - Varenicline was better than single NRT

- Newer studies indicate that the difference in efficacy may not be as much as previously thought.
- The take away is that it is not necessarily important what is the best in studies, but more so what is the best for your patient. In practice, I usually say most are about equal, so let’s focus on what fits your situation.
- Interestingly, NRT gum performed slightly better than other NRTs

REFERENCES: Baker JAMA 2016; Cahill Cochrane Review 2014
This studies shows that actual results from the study, not the OR. It is important to take these quit rates with a grain of salt as the populations included may be self-selected and have increased likelihood on quitting since they are in a study. It is important to look at this as well as the OR, and pay attention to the difference between the active ingredient and the placebo.

REFERENCE: Silagy, 2004; Hughes, 2005; Gonzales, 2006; Jorenby, 2006
Effectiveness of Mono-therapy Compared to Nicotine Patch

<table>
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<tr>
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<td>32</td>
<td>1.0</td>
<td>Reference Group</td>
</tr>
<tr>
<td>Nic. Gum (6-14 wks)</td>
<td>15</td>
<td>0.8</td>
<td>0.6-1.0</td>
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PHS Clinical Practice Guideline 2008 Update

KEYPOINTS:

• These analyses use the nicotine patch as the comparison or reference group.

• Except for varenicline we see very little difference when comparing to the nicotine patch.

• Note however that there are far fewer studies of Varenicline than the patch – this likely contributes to the wider confidence interval.

• This is also from a meta-analysis in 2008, and there have been studies done since then, so newer meta-analyses may have slightly different results.

REFERENCE: USPHS, 2008
Combining Medications

NRT Combinations

Why? *Ad libitum (as needed)* use for acute craving
Long acting patch + short acting product
   - Gum, lozenge, spray or inhaler
1st line in PHS Clinical Practice Guideline 2008 Update
NRT + Bupropion
NRT + Varenicline
   - *Controversial*
   - *Limit to smokers with high addiction levels*

KEYPOINTS:

- The patch: administered transdermally. Slow, steady distribution of nicotine, i.e., The Foundation, to mitigate craving and withdrawal symptoms.
- Short-acting NRT can be used for breakthrough cravings that occur with various triggers, i.e., upon waking, break time at work, leaving work, stress.
- The combination gives a more complete coverage for the smoker.
- Allows treatment “in the moment”.
- Very low potential for nicotine toxicity, very rare. Similar, to fingertip control, smokers can control their nicotine levels through the as needed use of the gum/lozenge.
- Bupropion combines nicely with NRT, see references below to allow a 2 pronged approach as well.
- Varenicline use with NRT is controversial due to the mechanism of each. NRT works by providing nicotine for the NAC receptors to decrease craving and withdrawal symptoms. Similarly, varenicline acts as a partial agonist/antagonist on the NAC receptors. So if used together, they would be trying to occupy the same receptors. It may work with smokers who have high addiction levels (some studies showed benefit in smokers who use > 3ppd) due to the up-regulation of nicotine receptors.

REFERENCES: Killen, 2004; Mills, 2014; Schneider, 2008; Shiffman, 2005; USPHS, 2008
KEY POINTS:

- This table from USPHS Guidelines compares 2 combinations against the patch alone.
- These are the 2 types of combination therapy approved by FDA at this time.
- Combining different forms of NRT provides a stable baseline nicotine level (i.e. the patch) with the opportunity for intermittent increases in the nicotine level from immediate-release NRT (gum, lozenges, inhaler, spray) in response to withdrawal symptoms.
- Combining 2 different drugs (i.e. bupropion plus patch) provides the opportunity to gain therapeutic synergism by using medications with distinct mechanisms of action.
- Since these Guidelines have been published research continues on various combinations. Steinberg and colleagues (below reference) added short acting NRT to patch and bupropion in medically ill patients with good results.
- Research is ongoing on combining varenicline and bupropion.

High Dose Patch (28-42mg)

- High dose NRT for heavy smokers >1ppd has been clearly shown to induce initial abstinence
- More complete nicotine replacement
- Consider lengthening treatment duration for heavily dependent smokers
- Cochrane reviewers suggest possible small benefit from high dose; PHS update reports no added benefit beyond standard dose & duration

KEYPOINTS:

- For long term efficacy. We know that the 21mg patch delivers approx. 50-60% of what a 1ppd smoker takes in. Some facilities recommend 2 patches (42 mg) for smokers using >1 ppd, but this is not recommended by the guidelines. It also states on the patch box to not use more than 1, so this would be a opportunity for education.

- For those smoking >1ppd, it might make sense to “increase the foundation level” of their nicotine replacement and then add your short acting to that.

- The goal is not to full replace nicotine levels, but to mitigate withdrawal symptoms.

- Those with hx of mental illness have been shown to be heavily dependent and often need more aggressive treatment

- Study in 2014 summarizing 11 articles using high dose nicotine patch shows that there is a dose response relationship with adverse effects, but no safety concerns. The same study showed no benefit

REFERENCES: Mills et al, 2012; Stead, Perera et al 2012; USPHS 2008; Brokowski 2014
KEYPOINTS:

PRETREATMENT-
• Various studies have demonstrated that pre-treatment (using patch prior to quit date and then adding more on quit date) doubled the odds of quitting successfully over and above the more standard regimen for nicotine patches (beginning patch on quit date)

WHY? POSSIBLE MECHANISMS:
• Often there is a spontaneous reduction in # of cigs smoked and/or the intake of nicotine from each cig. (even though in most studies not instructed to do so)
• Smoking on top of ongoing, steady nicotine infusion from the patch may help break some of the learned associations that help maintain smoking
• This may give the smoker the confidence or self-efficacy to believe that becoming smoke free is possible
• Having substantial blood levels of nicotine may blunt the effect (or reinforcement) of additional smoking- less satisfaction

(REMEMBER BOTH BUPROPION AND VARENICLINE USE PRE-CESSATION TREATMENT- RAISING THE POSSIBILITY THAT DIMINISHING SMOKING REINFORCEMENT THROUGH PRE-CESSATION TREATMENT MAY BE A COMMON MECHANISM DESPITE THE DIFFERENCES OF PHARMACOLOGY OF THESE DRUGS)

REDUCE TO QUIT-
• We know from 7 studies on those not willing to make a quit attempt, that using NRT (patch, gum inhaler) for 6 months or more increased quit rates. New study just published using varenicline on those not ready to quit which showed increased abstinence.
• We find we are using this concept more and more. This is less daunting to those with little confidence, less pressure, more doable.

SLIPS DURING NRT-
• Smokers should be encouraged to continue wearing patch even if they have a slip- recent study (below) indicates greater likelihood they will go on to successfully quit. *NRT LABELS CHANGED 12/2013 TO REFLECT THIS

REFERENCES: Ferguson, 2012; Shiffman, 2008
Ebbert 2/17/2015
Long Term Bupropion for Maintenance

- Conflicting evidence
- Bupropion 300 mg/day for up to 12 months for successful quitters
  - Effective at 12 months
  - No effect at 24 months
- Bupropion for 6 months for successful quitters who had used patch
  - Bupropion: 28% abstinent at 6 months
  - Placebo: 25% abstinent

KEYPOINTS:

- Anyone who has worked with smokers trying to quit, knows how preventing relapse is “the name of the game”.
- As Mark Twain is to have said “Quitting smoking is easy….I’ve done it hundreds of times”.
- Prevention of relapse is the next major challenge for pharmacotherapy.
- Bupropion has been looked at as a potential tool. But as you can see, evidence is not completely convincing. At 6mths – 12 mths an effect, not so at 24mths.

E-Cigarettes/Vaping/Juuling/E-Hookah

- Electronic nicotine delivery system (ENDS)
- Limited government oversight/regulation
  - Lack of quality assurance
  - Ingredient lists
- Brief FDA Regulation Timeline
  - 2016: Deeming rule extends FDA authority to ENDS and prohibits sale of ENDs products that were not commercially marketed as of 8/8/16
  - 2022: Grace period for products already on the market as of deeming rule ends

Key Points:
- E-cigarettes are officially known by the FDA as electronic nicotine delivery systems
- Unlike, NRT and tobacco products (cigarettes, cigars, dip, etc.), electronic cigarettes are not regulated by the FDA, and investigations have shown that there is a lack of standard of manufacturing practices and labelling reflecting ingredients.
- By 2022, all products that were not marketed on 8/8/2016 need to have an application filed and approved by the FDA. Similar to tobacco products.

REFERENCES: FDA Website:
https://www.fda.gov/tobacco/products/labeling/rulesregulationsguuidance/ucm394909.htm
E-Cigarettes/Vaping/Juuling/E-Hookah

Systematic reviews
- Quality of evidence considered ‘low’ to ‘very low’
- Highly variable methods and products amongst studies
- Some evidence that ENDS better than placebo, and equal to nicotine replacement
- Need for stronger studies, some underway

Considerations
- Appealing to smokers
- Not FDA approved nor USPTF recommended
- Pending regulation by FDA

Key Points:
- Use of e-cigarettes as a cessation tool is not evidence-based. Evidence regarding using e-cigarettes for cessation is very limited. There is evidence from two trials that e-cigarettes with nicotine helped smokers to quit or reduce smoking compared to placebo e-cigarettes, but the authors of the meta-analysis noted the need for further randomized controlled trials with adequate power and applicability to real-life settings.
- Additionally, the safety has not been established and there is high variability between the inert ingredients and nicotine contents of ENDS devices.
- Possible discussion: how to help the smoker already using ENDS with the goal of quitting
- It can be seen as transferring the addiction from one nicotine delivery system to another without addressing the behavioral portion.

Background
- McRobbie et al reported:
  2 RCTs compared EC to placebo: % quit at 6 mos: 9% EC vs 4% placebo (RR 2.29, 95% CI 1.05 to 4.96)
  1 RCT compared EC to nicotine patch: No difference in quit rates (RR 1.26, 95% CI: 0.68 to 2.34)
Note the wide confidence intervals indicating potential low confidence in the stability of the results

FDA regulation will not necessarily indicate safety as the ENDS would be regulated in the same way as tobacco. It would, however, provide more clarity about the ingredients and manufacturing processes. Source: McRobbie et al, 2014; Malas et al, 2016
### Potential Side Effects

<table>
<thead>
<tr>
<th>Item</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patch</strong></td>
<td>Skin redness is common (50%), abnormal dreams</td>
</tr>
<tr>
<td><strong>Gum</strong></td>
<td>Mouth or jaw soreness, stomach upset. Dependence: 15-20% will use for &gt; 1 year</td>
</tr>
<tr>
<td><strong>Lozenge</strong></td>
<td>Irritation of mouth, nausea, heartburn</td>
</tr>
<tr>
<td><strong>Inhaler</strong></td>
<td>Irritation of mouth and throat, cough, rhinitis</td>
</tr>
<tr>
<td><strong>Nasal Spray</strong></td>
<td>Irritation of nose and throat, cough, rhinitis, sneezing</td>
</tr>
<tr>
<td><strong>Bupropion</strong></td>
<td>Dry mouth, difficulty sleeping, shakiness, agitation, sedation, increased blood pressure</td>
</tr>
<tr>
<td><strong>Varenicline</strong></td>
<td>Nausea, insomnia, headaches, abnormal dreams, irritability, depression</td>
</tr>
</tbody>
</table>

**KEYPOINTS:**

- Side effects can impact compliance.
- Education and proper instruction is critical to minimize and/or manage any side effects.
- **PATCH:** Most common – localized skin irritation. Rotate sites – hips up, non hairy area. Use OTC hydrocortisone cream on area.
- Many report vivid dreams. May take off last thing before bed. Apply new one next AM.
- **GUM:** Proper technique – chew, park. Emphasize that nicotine is absorbed in mouth, not in stomach.
- **LOZENGE:** Make sure to park, do not bite, chew, swallow.
- **INHALER:** A “Puffer” not actually inhaled – can cause coughing fit.
- **BUPROPION:** If sleep disturbance, try taking 2nd dose in afternoon, early evening – not close to bedtime.
- **VARENICLINE:** Take with 10oz of H2O and food. Particularly in AM.

[Note: Adverse effects occur at the following frequencies: Headache (12% to 19%), insomnia (9% to 19%), abnormal dreams (8% to 13%), irritability (11%), suicidal ideation (11%), depression (4% to 11%)]
Cost of Pharmacotherapy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Cost (package size)</th>
<th>Cost (per unit)</th>
<th>Cost (per month)</th>
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</thead>
<tbody>
<tr>
<td>NRT Patch</td>
<td>$25.98 (box of 14)</td>
<td>$1.86/patch</td>
<td>$55.80</td>
</tr>
<tr>
<td>NRT Gum</td>
<td>$25.98 (100ct)</td>
<td>$0.26/piece</td>
<td>$124.80 - 187.20</td>
</tr>
<tr>
<td>NRT Lozenge</td>
<td>$32.98 (108 ct)</td>
<td>$0.30/piece</td>
<td>$144 - 180</td>
</tr>
<tr>
<td>NRT Inhaler</td>
<td>$443.39/device</td>
<td>$2.64/cartridge</td>
<td>$475-1267 (6-16 cartridges per day)</td>
</tr>
<tr>
<td>NRT Nasal Spray</td>
<td>$465.14 (40mL)</td>
<td>$1.16/ 1 dose (2 sprays)</td>
<td>$279-1395 (8-40 doses per day)</td>
</tr>
<tr>
<td>Zyban (bupropion)</td>
<td>$267 (60 ct) ~$25-110 (60 ct)</td>
<td>$4.45/tab (~$41-1.83/tab)</td>
<td>$267 ~$25-110</td>
</tr>
<tr>
<td>Chantix</td>
<td>~$117-150 (30 ct)</td>
<td>~ $3.9- 5/tab</td>
<td>~$234-300/month</td>
</tr>
</tbody>
</table>

KEYPOINTS:
1 month = 30 days

Patch is reflective of 21 mg patch/1 patch per day

Gum and lozenge is reflective of 4 mg gum/lozenge x 20 or 24 per day (max dose- 8 hours to sleep) – use less lozenges per day

Zyban- brand and top line and bupropion (generic) bottom line

Chantix is listed, but not generic because it is only available brand at this time.

Nasal spray monthly cost based on minimum and maximum daily recommended doses
- Generics will be cheaper.
- Coverage by insurance plans vary considerably. Have clients look into their coverage.
- Some insurers (such as MassHealth, MA's Medicaid program) will cover with script including those that are OTC.
- Practical suggestion is to have each individual do the math on their weekly, monthly, and yearly costs to smoking.

REFERENCES: Generic Walmart brand /drugs.com
KEYPOINTS:

- This graph depicts the plasma venous nicotine concentration achieved with the various delivery systems.

- The concentration time curves in this slide depict levels achieved after administration of a single dose of nicotine following a period of overnight abstinence (Cigarette smoked- 5", Snuff placed in cheek-30", Inhaler was puffed over 20", Gum chewed – 30", Lozenge in cheek - 30").

- “I’m sure you may notice by this graph…what is our best drug delivery system? The CIGARETTE, OF COURSE!!. Which uses the lungs and rapidly reaches the reward pathway in the brain.

- Nasal Spray is most rapid – however, uncomfortable side effects of rhinitis and it is expensive. Not used often.

- You can see by this slide that NRT delivers nicotine more slowly and at lower levels – they are far less likely to be associated with dependence when compared to cigarettes.

- ALSO POINT OUT Nicotine Content Handout in their manual for comparison of nicotine delivered by the different products.

REFERENCES: Choi, 2003; Fant , 1999; Schneider, 2001
Adherence and Convenience

Factors:
- Frequency of dosing
- Mode of administration
- Side effects
- Cost

Among NRT products patch has highest adherence

KEYPOINTS:
- Compliance and convenience can often trump all other considerations when deciding on pharmacotherapy.
- The Patch often becomes a “go-to” or a starting point because it is relatively easy to use, once a day, few side effects.
- Using monotherapy with any of the short-acting NRTs requires a real vigilance and discipline by an individual to keep ahead of cravings.
- (Of course the combo of these can work well for many).
- If the smoker does not have coverage of varenicline, it is very expensive, as is the nasal spray
- The inhaler is also expensive if not covered.
- YOU NEED TO GET TO KNOW YOUR SMOKER, THEIR FINANCIAL RESOURCES, THEIR ABILITY AND DESIRE TO PROACTIVELY USE MEDS OR MORE “PASSIVELY” WITH THE PATCH FOR INSTANCE.
Now we will consider patient factors.
Patient Factors in Selecting Pharmacotherapy

- Level of nicotine dependence
- Prior experiences with medications
- Access to medications
- Preference/Confidence
- Beliefs/Cultural considerations

KEYPOINTS:

- GET TO KNOW YOUR CLIENT!!

- The more you understand about them, their life, their resources, their environment the more you will be able to guide them to a plan of pharmacotherapy that makes sense to them.

- What have they used before? What was that experience like? How long were they abstinent? What happened when they relapsed? “The patch didn’t work for me”... Why not? Maybe it simply wasn’t enough… they needed a higher dose or patch and/or short acting. EXPLORE!!

- Do they have a preference? E.g., Uncle Joe quit with varenicline and that’s what they want to use.

- Honor their beliefs/cultural considerations…“I don’t want any meds I can stay addicted to”…“I don’t want any more meds”…Express your understanding while asking if they would like to have more information on what helps many other smoker quit successfully.
Level of Dependence: Smoking

- Fagerstrom Test for Nicotine Dependence (FTND – see handouts)
  - >6 may indicate high dependence
- Time to first cigarette: < 30” = high dependence
- Expired carbon monoxide (CO) levels
  - >21 = 20 cigarettes per day
- Patient reports of withdrawal or strong cravings

KEYPOINTS:

- All 4 of the above are good tools in helping to determine an individual’s dependence.

- Due to the changing landscape of tobacco use in recent years, such as increased taxes, increased costs and restrictions in smoking public places, many smokers smoke differently. Many restrict their smoking to certain places, certain times of day, and many re-light. This is important when getting a sense of the level of dependence. If we only take into consideration how MANY cigarettes per day they smoke we may miss how heavily dependent they are.

- Remember relighting each cigarette twice and smoking of a total of 5 CPD IS NOT EQUAL to smoking 5CPD without the relights. The first inhalations on a cigarette are deeper and more complete than those towards the end of the cigarette.

- Time to first use is being used more often to determine dependence.

- Also, night smoking is a marker for a heavily addicted smoker.

- When using bupropion or varenicline the doses are consistent no matter the dependence level.

REFERENCES: Baker, 2007
**Level of Dependence: Smokeless Tobacco**

- PHS Guideline reports insufficient evidence for pharmacotherapy recommendations
- Consider Mayo Clinic protocol*
  - Bupropion:
    - 150 mg by mouth twice a day
    - Continue for 3-6 months.
  - Tailored nicotine replacement therapy:
    - <2 can/pouch/week: 14 mg patch
    - 2-3 cans/pouches/week: 21 mg patch
    - >3 cans/pouches/week: 42 mg patch
    - Consider adding gum/or lozenge for self-titration
  - 4 mg lozenge alone may decrease craving

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**KEYPOINTS:**

- We don’t have specific evidence regarding what might be most successful with smokeless tobacco users. MAYO has developed this protocol, which Mass General Hospital also uses.

- Because smokeless tobacco can be used more discreetly (say in the work environment) as well as concurrently with smoking cigarettes, the users are often heavily addicted.

- Both MAYO and MGH among others have found aggressive NRT (Patch, often more than one plus short acting) to be the first approach. Again, there is little evidence from trials to go off of when making recommendations.

- The gum and lozenge can be dose by time to first use (> or < 30 min after waking) or by >/= or < 2 cans per week.

- Due to the similar mode of administration, many patients like the lozenge, particularly those who “pack a lip”

REFERENCES: Ebbert, 2009; Ebbert, 2011; Mayo Clinic, 2013
Prior Experience with Medications

- What products were used?
- How were they used?
  - Check for proper administration and duration of use
- What side effects, withdrawal symptoms were experienced during use?

KEYPOINTS:

ASK A LOT OF QUESTIONS!

- What was their experience? Tell me how you used it? How often? How long? Many, many times people have *not used enough* and/or for *not long enough*.
- And not used properly…particularly with lozenges and gum.
- What have you heard about this med? Do you know anyone else who has used it? Why do you think that “cold turkey is the only real way to quit?”
- Also ask about the patient mindset during that quit attempt and any other life stressors?

GET TO KNOW THIS PERSON!
Access and Preferences

Consider insurance coverage, cost of products, availability of any free products, proximity to pharmacies etc.

Unless there are clear contraindications using the client’s preferred product may increase compliance and confidence

KEYPOINTS:

• Remember: all meds have approx. the same efficacy.

• The most important factor in deciding on a plan of pharmacotherapy for an individual is:

• Their preference!!

• However .....you want to make sure they have basic info about pros and cons of all meds and ways to use them, so that they can make an informed decision.
Beliefs/Cultural Factors

1. Consider any religious health beliefs
2. Provide written materials at appropriate reading level
3. Explore and respect any cultural beliefs regarding medications while providing accurate information

KEYPOINTS:

- Research over decades has demonstrated that specific populations experience health disparities and are at greater risk for chronic disease and premature mortality simply due to racial/ethnic/economic group.

- Individuals with an income <$15,000 smoke at nearly 3x the rate of those with incomes >$50,000.

- Ask questions and empower people to make a choice to quit. Avoid making assumptions about someone’s culture and barriers to quitting.

- Avoid making assumptions about those with psych disorders and/or substance abuse.

REFERENCES: Centers for Disease Control and Prevention, 2012
Factors in the Selection of Pharmacotherapy

- Agent factors
- Patient factors
- Medical issues

There are in fact very few medical issues that will impact the choice of pharmacotherapy. We will review the precautions for each product and briefly discuss some medical issues where there might be concerns.
KEYPOINTS:

• **Please note the word precautions.** This does not read contraindication.

• It is important to understand that these medical conditions require more caution and consideration. In many cases would need the collaboration of prescribing clinician.

• In the case of acute coronary events (i.e., recent heart attack and/or arrhythmia or unstable angina) the guidelines did not support pharmacotherapy due to lack of research in these groups. However: (refer to references below) We know from observational analyses of patients in these categories who received NRT while hospitalized that there were no associations with increased risk of another cardiac event or death and appeared to be safe. Of note: in most medical centers now, patients in CCU’s are routinely given the patch. From a risk mitigation standpoint, if the patient is going to be exposed to nicotine either way (tobacco product use or NRT), it is probably safer to be from NRT.

REFERENCES: Hubbard, 2005; Meine, 2005; Rigotti, 2013
**Precautions: Bupropion SR**

- History of seizure or condition that lowers seizure threshold
  - History of anorexia or bulimia
  - Excessive or binge drinking
  - Medications associated with increased seizure risk
- MAO inhibitor use within 14 days
- History of mania
- Concomitant use of Wellbutrin/bupropion for another indication
- Liver disease and/or renal insufficiency
  - Consider reduced dose

**KEYPOINTS:**

- The risk of seizure is associated with the use of bupropion (approx. 1 in 1,000) therefore is not used in those with a definite history of seizures.

- Likewise with a history of anorexia/bulimia or heavy drinking, which are known to lower the seizure threshold, specifically alcohol withdrawal and electrolyte abnormalities associated with eating disorders are what increase seizure risk.

- As there is with many meds, precaution is taken with anyone with liver or renal disease but still used but at a reduced dose.

- There is a risk of increasing blood pressure. In the case of someone with significant uncontrolled hypertension, bupropion would be avoided.

- Any medication, including bupropion, varenicline and NRT should be avoided if patient has a history of allergy to that specific agent.
Precautions: Varenicline (Chantix)

- Post-marketing case reports indicate potential neuropsychiatric risks**
  - Behavior changes
  - Agitation, aggression
  - Depressed mood
  - Suicidal ideation

**However, at this time, there is no objective data to justify that there is such a risk

- End stage renal disease
  - Dose reduction recommended

KEYPOINTS

- There have been concerns in the past regarding increase in suicide and depression with varenicline use, but this has not been supported in objective studies. We will discuss more about these warnings in the next slide.

- For patients with a strong psychiatric history, who have active disease or poor control, try combination NRT first. Also confer with their behavioral health prescriber to assess the control of their disease. If they are stable and have a support system at home, varenicline is a reasonable option. Always tell the patient of the risks, and let them make an informed decision.

REFERENCES: Gibbons, 2013; Stapleton, 2007; Anthenelli 2016 (EAGLES trial)
In 2009, at the request of FDA due to the post marketing reports, the Chantix full prescribing information included information in the WARNINGS and PRECAUTIONS sections about the possibility of serious neuropsychiatric symptoms (changes in behavior, agitation, depressed mood, and suicidal ideation and behavior) in patients taking Chantix. Recommendations and Considerations for Healthcare Professionals

However, since that Black Box warning there has not been any research to back this up. In fact, in 5/2013 An article in the American Journal of Psychiatry by Gibbons and Mann concluded that their analysis revealed no evidence of increase in these events. The authors reanalyzed data from 17 placebo-controlled randomized (considered the gold standard in research) trials to look at this as well as data from a large Dept. of Defense observational study. These trials included both those with mental illness and those without it. There was no evidence (n=8000+) of adverse neuropsychiatric events.

In 2016 the FDA removed the black box warning based on the outcome of the EAGLES study. The EAGLES study showed that there were no significantly increased neuropsychiatric safety risk vs. placebo, in smokers with or without a history of psychiatric disorders: It also found significantly higher continuous abstinence rates vs. bupropion, NRT patch and placebo at weeks 9-12 and 9-24 in both cohorts.

REFERENCES: Anthenelli, R et al, 2016; Gibbons, 2013
Medical Conditions

- Cardiovascular Disease (CVD)
- Chronic Obstructive Pulmonary Disease (COPD)
- Diabetes Mellitus (DM)
- Pregnancy
- Psychiatric comorbidity and substance abuse

**KEYPOINTS:**

- Encourage participants to review the module on health effects of smoking in the basic skills course to gain a better understanding of these conditions.

- The first 3 conditions here are extremely common in smokers. Smoking is a critical risk factor in all of them. In fact, you often see a combination of all three of these conditions.

- Pregnancy is not a medical condition or disease but does require some special considerations regarding the use of pharmacotherapy.

- Smokers are over-represented in psychiatric populations.

- Psychiatric patients are 2-3 times more likely to smoke:
  - 40-50% of pts. with depression and anxiety disorders smoke.
  - 70-90% of pts. with schizophrenia smoke.
  - 75-100% of substance abusers smoke.

- 44% of all cigarettes smoked in U.S. are by individuals with psychiatric or substance abuse disorders.
Cardio-vascular Disease (CVD) - NRT

- Nicotine patch – proven safe in stable CVD patients
  - Lower absolute levels, steady state, tolerance
  - NRT can be used safely by majority of people with STABLE cardiovascular disease, even with concomitant smoking
  - Nicotine patch therapy – likely to be safe in acute coronary syndrome (ACS) also
- Nicotine gum, lozenge, inhaler – likely to be safe in stable CVD patients
  - Lower nicotine levels than active smoking

*All data has supported use of NRT in CVD patients.*

*Carbon monoxide and 4000+ chemicals/toxins are the real threat to cardiovascular health!*

Keypoints:

Cardiovascular disease includes: Coronary artery disease, cerebrovascular accidents (stroke) and peripheral artery disease (plaque build up in legs)

- **SMOKING IS THE #1 RISK FACTOR IN CVD:**

  - Emphasize that the patch provides a slow, steady, and lower level of nicotine than that of a cigarette which uses your best drug delivery system, i.e., your lungs.

  - Key educational point to patients with CVD is that nicotine is not the problem….It is the carbon monoxide (robbing them of O2) and the 4000+ chemicals that act as an irritant to the lining of the vessels. This irritation is the cornerstone of the development of plaque in the vessels.

  - Recommend to them to read the references below:

    • Hubbard, 2005
    • Meine, 2005
    • Rigotti, 2013
CVD - Bupropion

- Small risk of hypertension in otherwise healthy smokers
- In CVD patients – excellent tolerance and no increase in adverse events
- May be of benefit in post heart attack patients in which depression is often associated

KEYPOINTS:

- In the studies done in this area, bupropion has been shown to be safe in CVD. No increase in cardiovascular events
- An small increase in BP has been shown in some studies but not in others.
- It may be particularly good in this population as depression is associated with the development of CAD.

REFERENCES: Settle, 1998; Kiev, 1994; Mills, 2014
CVD - Varenicline

- July 2011 FDA updated label to include new info
- CVD-latest evidence showed varenicline doubled the chance that patients remain abstinent at 1 yr
- Also, varenicline may be associated with a very small, increased risk of CVD adverse events (although considered not statistically significant)
- Conclusion: The absolute risk of CVD adverse events with varenicline, in relation to its efficacy, is small.
- *Smoking is an independent and major risk factor for CVD, smoking cessation is of particular importance in this population*

KEYPOINTS:

- There was a meta analysis published by Canadian Medical Association Journal re: varenicline and CAD. This is the study that prompted the label change. This raised a lot of controversy. Concerns were raised about the methodology of the analysis (types of events included, self-report of events, higher drop out rate in placebo group) and how the risk was reported.

- This was addressed in another article you have in your bibliography by Hays in the same journal.

- The major conclusion was that there appears to be a slight increase in the risk of major cardio events with the use of varenicline – although this is not statistically significant!

- The FDA then again released other updates the most recent being in 2012. Again emphasizing that the risk of continued smoking must be weighed against the risk of an event. “The agency continues to believe that the drug’s benefits outweigh the risks”

REFERENCES: Singh, 2011; Hays, 2011; Rigotti, 2010
Pharmacotherapy for Patients with COPD

Nicotine gum therapy has been proven safe in COPD patients. Reduction in tobacco consumption along with nicotine gum appears to slow progression of COPD.

Bupropion has been shown to be safe and effective in patients with mild to moderate COPD.

Varenicline has also been shown to be safe and effective in patients with mild-moderate COPD.

GOLD Guidelines for COPD recommend any of the above with counseling for smoking cessation.

KEYPOINTS:

- COPD refers to 2 diseases, chronic bronchitis and emphysema.
  - 3rd leading cause of death in US.
  - Smoking is the primary risk factor.
  - 90% of all COPD patients were or are smokers.
- It is firmly established that quitting smoking will slow the progression of this disease.
- In many cases, a patient who has smoked long enough to have developed and diagnosed with COPD and is still smoking tend to need aggressive, long term pharmacotherapy.
- Bupropion, as well as varenicline, has proven to be both safe and effective in those with mild-moderate COPD.
- “Harm reduction” as shown by Jimenez study might be a course of action for those not willing to quit. Using NRT and reducing cigarette intake has been shown to help lung function.
- New labeling states that recent evidence shows varenicline was effective in this population, with no increase in adverse events demonstrated and no new safety concerns.

REFERENCES: National Lung Study; Tashkin, 2001; Jiménez-Ruiz, 2002; Wagena, 2003; GOLD 2019
Diabetes – NRT, Bupropion, Varenicline

**Nicotine patch**
- Increased glucose levels (but less than with smoking)

**Bupropion**
- Increased insulin levels in mice - no information in humans with diabetes

**Varenicline**
- Same effectiveness and safety compared to those without diabetes

**All options should be considered**

KEYPOINTS:

- Smoking increases the risk of the development of diabetes.
- We know that nicotine, itself, impairs the cells response to insulin. Another way of saying this is that it increases insulin resistance. So this is technically the case with NRT. Keep in mind, the levels of nicotine in NRT are most often much less than what the smoker had previously taken in.
- Bupropion has been studied in mice which demonstrated an increase in insulin level. This, *in theory*, could lead to hypoglycemia (low blood sugar)
- A recent review of pooled studies found that the effectiveness and safety of varenicline was the same for those with and without diabetes
- Be wary of the sugar content of the lozenges (some are sugar free, such as Nicorette) in patients with diabetes who are taking lozenges every 1 -2 hours. This is not a reason not to use, but something to be aware of.

Women who smoke during pregnancy risk the following:

- Ectopic pregnancy
- Miscarriage
- Low birth-weight baby
- Stillbirth
- Complications of the placenta
- Premature birth
- Certain fetal malformations

Cessation of smoking during pregnancy is important for both maternal and fetal health

REFERENCES: (for all slides on pregnancy)
Benowitz, 2000; Lambers, 1996; Oncken, 1997; Slotkin, 1995; Wright, 1997; Coleman, 2012
Smoking During Pregnancy

Increases the risk of:
- Spontaneous abortion
- Prematurity
- Low birthweight
- Congenital malformations
- Sudden Infant Death Syndrome

KEYPOINTS:
Up to 45% of women who smoke before pregnancy stop before their first prenatal visit. Women who quit spontaneously are more likely to have higher social status, no smoking partner, a lower degree of nicotine dependence, and less concern about weight gain.
Most mothers who quit smoking during pregnancy resume smoking within 6 months of delivery and about 70% relapse by 12 months.

Nicotine readily gains access to the fetal compartment via placental blood flow.

In fact, nicotine blood levels are higher in the fetus than in the mother.

Although precise mechanisms that underlie the various effects of smoking on pregnancy are not completely understood, several major processes have been implicated:

1. Nicotine induces vasoconstriction, restricts blood flow and reduces the supply of nutrients and oxygen to the fetus
2. Carbon monoxide in tobacco smoke inhaled by the mother displaces oxygen in the circulation further reducing the amount available to the fetus
3. It affects the placenta, as smoking disrupts the growth and proliferation of blood vessels in it
Pharmacotherapy

2008: PHS Guideline update:
- Recommended behavioral counseling as FIRST line treatment

2015: Cochrane Review 2015
- Low adherence in many studies included
- Moderate evidence of effectiveness AND safety
- Support for ethical rationale to study the use of higher doses

2016: Berard, Ahao & Sheehy
- Both bupropion and NRT associated with higher rates of abstinence during pregnancy
- Effect maintained after pregnancy
- Both associated with a decreased risk of prematurity

2017 ACOG guidelines
- NRT studies have been inconclusive, but is a potential option
- Varenicline has limited data, and is not recommended
- Bupropion has insufficient evidence and limited data available

Key Points:

- Cochrane review looked at 6 randomized control trials with 1745 subjects.
- The success of higher dosing should be discussed as possible reason for moderate success and low adherence in earlier trials
- American College of Obstetricians and Gynecologists (ACOG)- studies on NRT were stopped early due to adverse drug reactions or lack of effectiveness. Discuss risks with patients and use with goal of getting off NRT rather than using throughout pregnancy.
- Small studies in varenicline have not shown teratogenicity, but it is not recommended by ACOG at this time.
- Bupropion has limited data. There is conflicting data regarding malformations. There have been non-congenital malformations, but the jury is still out on cardiovascular. From a mental health care standpoint, benefits may outweigh risks, but there is a different risk benefit analysis that would need to occur to start a new med during pregnancy rather than continue an existing one.
- Try non-pharmacologic first.

- Quitting before 15 weeks is of most benefit to the fetus (ACOG 2017). If non-pharmacological intervention is unsuccessful, it may be best to try NRT to achieve a quit prior to this time rather than persisting with behavioral interventions alone. Successful quit prior to the third trimester can help reduce the risk of low birthweight due to maternal smoking.

- If that does not work, exposure to nicotine in NRT is likely safer than exposure to nicotine from other tobacco products.
Lactation - Recommendations

- NRT is preferred but has not been studied directly in lactating women
  - Negligible absorption of nicotine from breast milk
  - Short-acting forms could be used right after breast feeding
- Bupropion
  - Safety of bupropion in infants or children has not been established
  - Bupropion accumulates in human breast milk
  - Daily dose of bupropion and metabolites that would be delivered to an infant of a woman taking a therapeutic dose of bupropion is small
  - Not enough information to make recommendations
- Varenicline not recommended

KEYPOINTS:

- Mothers who smoke are less likely to breastfeed
- Those who do breastfeed do so for a shorter time
- We know that in breastfeeding mothers who smoke produce poorer quality milk
- The effect of smoking on breastfeeding may be mediated by nicotine regulation of the hormone prolactin. Prolactin is essential for the initiation and maintenance of milk production. Breastfeeding mothers who smoke have lower levels of prolactin than those who do not smoke. This results in poorer milk supply

Again, in terms of pharmacotherapy the same applies.

- varenicline avoided because safety of varenicline in infants and children has not been studied

- May try lozenges/gum first

REFERENCES: ACOG 2017
KEY POINTS

Smokers are over represented in psychiatric populations
• Psychiatric patients are 2-3 times more likely to smoke
• 40-50% of pts. with depression and anxiety disorders smoke.
• 70-90% of pts. with schizophrenia smoke.
• 75-100% of substance abusers smoke.
• 44% of all cigarettes smoked in US are by individuals with psychiatric or substance abuse disorders

• We also know that smokers in this population have even worse risks than others.

• Among treated narcotic addicts, smokers’ death rates were 4X that of nonsmokers.

• Among treated alcoholics who died, 51% of mortality attributed to smoking-related illness.
• It appears there is a synergistic effect between smoking and other substances.

REFERENCES: Hurt, 1996; Grant, 2004
Mood Disorders

• Bupropion or nortriptyline started prior to quitting (along with NRT) may help with cravings, depressive symptoms in highly dependent
• Bupropion may be most useful for those with past history of depression
• Psychosocial mood management important component of treatment

KEY POINTS:

• It is important to emphasize that a common myth/misconception is that quitting smoking worsens psychiatric symptoms.
• Coordination of pharmacotherapy with prescriber of psychiatric medications is critical.
• People with mental health disorders can quit successfully and at rates similar to the general population.
• A new meta-analysis published 2014 in BMJ that contrary to common perception, smoking cessation is associated with reduced depression, anxiety, and stress and improved positive mood and quality of life compared with those continuing to smoke. The effect size is equal and even larger than that seen with antidepressant treatment.

REFERENCE: Taylor, 2014; Wilhelm, 2004; Lerman, 2004; Cook, 2004; van der Meer et al, 2013
Anxiety Disorders

- Less data is available
- Stable NRT blood levels throughout the day reduce fluctuations in nicotine which may feel like anxiety
- Use caution if considering bupropion
- If needed, consult with therapist/psychiatrist regarding medication management

KEY POINT
- Remember to keep NRT doses stable over the course of the day to reduce fluctuations in nicotine which may feel like anxiety.
- In some individuals bupropion can increase anxiety. However, there is no determining beforehand who that might be.
Schizophrenia

RCTs have found varenicline to be more effective than placebo

Bupropion associated with stable symptoms, increased quit rates but high relapse rates after treatment discontinuation in this population

Combination bupropion plus NRT may be superior

This group is usually highly dependent

  NRT may need higher doses and for longer duration.

KEY POINTS:

• We have seen what a high percentage of this population smokes
• Data also shows that people with mental illness are at greater risk of dying early from smoking than of dying from their mental health conditions
• The most effective cessation strategies for the general public, a combination of medication and counseling also apply to people with mental health conditions.
• None of the meds are contraindicated in this group. As always in those with active mental health diagnosis the psychiatrist should be consulted and worked with closely.
• This population often need greater intensity and duration of services. Many in the field believe that some will need indefinite duration of treatment- maybe even lifetime.


These authors reanalyzed data from 17 studies previously conducted by Pfizer (n= >8000) plus a large DOD data set to look at any neuropsychiatric symptoms from varenicline or NRT (n= >35,000). The analysis revealed no evidence that varenicline is associated with these adverse events in either individuals with and without a recent history of a psychiatric disorder.
Some Common Drugs That May Require Dose Reduction During Smoking Cessation

- Methadone
- Many psychoactive drugs:
  - Benzodiazepines (Valium, Ativan, etc.)
  - Clozapine
  - Haloperidol (Haldol)
  - Imipramine (Tofranil)
  - Fluvoxamine (Luvox)
- Insulin (absorption increase)
- Propranolol (Inderal)
- Warfarin (Coumadin)
- Caffeine

KEY POINTS:

- Smoking affects enzymes involved in the metabolism of many drugs
- Smoke has polycyclic aromatic hydrocarbons that induce these enzymes. When one quits smoking, this enzyme activity goes down and it could result in higher levels of certain drugs (since they aren’t being metabolized as well). There are drugs that may need to be adjusted.
- Many of the psychoactive drugs, And even caffeine.
- Also both Coumadin and insulin can be affected by smoking cessation. Anyone on Coumadin already should have a schedule of blood draws to test their levels. Likewise with insulin, close blood sugar monitoring should be done by the patient.

REFERENCES: Murray, 2010; Clair, 2013; Wahawisan, 2011
Drug Interactions– Bupropion

- Levadopa
- MAO inhibitors
- Tricyclic antidepressants
- SSRIs (fluoxetine, paroxetine)
- Cimetidine (Tagamet)
- Ritonavir (HIV med)

**KEY POINTS:**

- Bupropion can interact with these meds.

- A patient’s physician would be part of the decision in prescribing bupropion.
Weight Gain and Smoking Cessation

Nicotine gum and nicotine lozenge may delay weight gain
Long term bupropion may reduce weight gain
Consider continuing pharmacotherapy after cessation until patient has developed an effective weight maintenance regimen of diet and exercise

KEYPOINTS:

• Many smokers (particularly women) are concerned about their weight and fear that quitting will produce weight gain.

• Evidence does show that the majority of smokers who quit smoking do gain weight. Most will gain fewer than 10lbs. But it can vary quite a bit, with some gaining as much as 30lbs.

• As a clinician, we should not deny that weight gain may happen nor should we minimize the significance to that individual

• Of course, we also have to inform the smoker, that smoking presents a far greater health risk than even a significant weight gain

• Both nicotine gum/lozenge as well as bupropion have shown a delay in weight gain and this may prove to be helpful to some. It could provide time in which they could increase their exercise and change eating habits.

• Please emphasize new study below.
  • Smoking cessation was associated with a lower risk of CVD events among both diabetics and non diabetics even in the presence of significant weight gain.

REFERENCES: Clair, 2013
**NRT and Adolescents: PHS Recommendations**

- NRT should be considered only when there is clear evidence of nicotine dependence and a clear desire to quit.
- Factors such as degree of dependence and body weight should be considered when selecting NRT dosage.
- Meta-analysis showed varying benefit with patch, gum or lozenge.

**KEYPOINTS:**

- The evidence thus far shows NRT is safe to use in adolescents with varying efficacy.
- Meta-analysis of 8 trials in 13-19 year olds smoking > 1 to 20 cigarettes per day using NRT gum patch or lozenge for 4-12 weeks. Quit rate ranged from 7-47%. Most were self-reported.
- It is approved for use in children in the UK.
- You would want to engage the adolescent's pediatrician. With vaping there is a renewed call for studies of NRT in adolescents.

Reference: King 2016
Case Study Examples
Case Study: Tim

Tim is a 35 year old male; construction worker. Started smoking at age 14 and smokes 1½ppd. He currently lives with 2 other people that smoke. About 60% of his co-workers who are also his friends are smokers. At work, they are no longer able to smoke on the site. Recently he has begun using chewing tobacco during the day in addition to his smoking before and after work and on weekends. He now has decided to stop smoking after the recent death of his uncle from lung cancer. He has never tried to quit. He wonders if he should start chewing more tobacco to help himself quit.

Let's begin to apply some of this to real life type of cases. We'll start with a rather uncomplicated case.

Read the case study or ask participant to read aloud.

Invite the class ask more questions about Tim that pertain to Agent, Patient or Medical factors in decision making. As the instructor, you will pretend you are Tim and can answer any way you like. If there is time after providing more information have class discuss in small groups and provide a recommendation.

• For Tim typical answers might be: “Yes, we smoke in the house. I smoke my first cig when within 10mins”, “I smoke more on the weekends…sometimes over a pack. During the week, I smoke less but I chew tobacco in between”
• There are no real wrong answers here but hopefully their thinking will be to go with NRT first. Less complicated and OTC. Hopefully with his concurrent chewing they will come to combo NRT……
• Having said that, it is perfectly acceptable if they considered any of the meds.
• Just get them thinking about Tim!
• Try to keep this discussion on the shorter side since there are no significant issues to consider.

Goal time: 10 minutes
Case Study: Sam

Sam is a 56 year old male who experienced his first heart attack 6 months ago. His risk factors for coronary artery disease include smoking one pack per day for 40 years, an elevated cholesterol, and mild hypertension. His blood pressure is now under excellent control with an adjustment of his anti-hypertensive medications. The addition of a new medication (simvastatin) has brought his cholesterol down below 180.

He has made several attempts to quit smoking, but has been successful for only a day or two at a time. He would like to try the nicotine patch but is not certain he could completely abstain from smoking while on the patch and thus is very worried that he might have another heart attack.

Read the case study or ask participant to read aloud.

Invite the class ask more questions about Sam that pertain to Agent, Patient or Medical factors in decision making. As the instructor, you will pretend you are Sam and can answer any way you like. If there is time after providing more information have class discuss in small groups and provide a recommendation.

- In Sam’s case, since he has stated he is interested in the patch it probably makes since to start there. Adding a short acting would also make sense.
- Elicit from the group a discussion re risk for another heart attack if he smokes on the patch. You want them to mention how important education is around this and that it needs to be imparted to Sam. That there is no increase in risk if he smokes on the patch, however, the goal is to become smoke free and the importance of having a plan in place for a “safety net” should he experience breakthrough cravings on patch….e.g., have lozenge, gum, or inhaler with him at all times.
- Remind group that there is data to support continuing to wear patch even after a lapse.

Goal time: 10 minutes

REFERENCES: Ferguson, 2012; Hubbard, 2005
Case Study: Irene

Irene is a 67 year old female. She is a semi-retired registered nurse and had worked in ICU at a local hospital. She lives alone. Has smoked since the age of 15 and smokes about 1 ppd.

She was diagnosed with COPD a year ago. She also has osteoporosis, GERD and hypothyroidism. She is taking medication for all her medical conditions and they are all under control.

She is a former binge drinker who has been sober for 6 months and continues to attend AA meetings. She has continued to experience hot flashes with profuse sweating daily since menopause.

She has tried to quit before using hypnosis and acupuncture each time she relapsed at about two weeks mainly due to cravings, trouble sleeping and coworkers who smoked around her.

Irene would like to try Chantix because her friends have used it and they have been successful in quitting.

Read the case study or ask participant to read aloud.

Invite the class ask more questions about Irene that pertain to Agent, Patient or Medical factors in decision making. As the instructor, you will pretend you are Irene and can answer any way you like. If there is time after providing more information have class discuss in small groups and provide a recommendation.

• Given this case, it would make sense to have her begin varenicline given her preference. Education re how to use, i.e., take with water and food, don’t take too late at night, stop med and tell MD if experiencing any changes in behavior or thoughts, etc.”
• May encourage class to consider also selecting a short acting NRT to have available after quit date.
• If time, you may also throw out question. "Is there any med you would not recommend and why?”
• Some thoughts, but not necessarily conclusions, include…She does have a history of GERD, maybe avoid gum as could upset her stomach. She has a history of binge drinking which, in theory, could put her at risk for seizures and therefore would avoid bupropion. However, she is sober x 6mths and has support. Not all patients who binge drink are at risk of seizures, it is important to keep in mind. Note that varenicline can increase sensitivity to alcohol.

• And of course, no reason she couldn’t use NRT other than her preference is varenicline.

Goal time: 10 minutes
CASE STUDY: Natalie

Natalie is a 41 yr old single mother of 2 teenagers. She has a history of depression since her divorce 10 yrs ago. She has been on Prozac since that time. She initially had psychotherapy after the divorce which she found helpful. Once her therapist moved out of state many years ago, she did not continue. She smokes approx. 1 1/2ppd since age 16. She had one previous quit attempt using the 21mg patch in which she was smoke free for 21 days but relapsed due to severe cravings and feeling “sad and alone”. She wonders if e-cigarettes would help; her teens talk about them.

Let’s discuss a couple of cases to look at this area of mental health and substance abuse.

Read the case study or ask participant to read aloud.

Invite the class ask more questions about Natalie that pertain to Agent, Patient or Medical factors in decision making. As the instructor, you will pretend you are Natalie and can answer any way you like. If there is time after providing more information have class discuss in small groups and provide a recommendation.

• Again, there are no right or wrong recommendations
• Discuss lack of knowledge of content of ENDS devices and variability between devices as well as lack of evidence supporting efficacy for cessation.
• Hopefully, the discussion will include some of these concepts:
  • She needed more NRT….If she is to use that, she needs at least 21mg patch plus prn short acting. An alternative would be wearing more than 1 patch (21 plus 14 mg).
  • If her mental health becomes more stable or if her provider concurs, varenicline may be an option
  • Perhaps bupropion plus NRT. Of course her md would need to be involved. There is an interaction between fluoxetine and bupropion; fluoxetine blood concentrations may be increased.
  • Encourage re-engaging in therapy, and other support systems- groups, quitlines, etc.

Time goal of 2 cases= 15"
Read the case study or ask participant to read aloud.

Invite the class ask more questions about George that pertain to medication, Patient or Medical factors in decision making. As the instructor, you will pretend you are George and can answer any way you like. If there is time after providing more information have class discuss in small groups and provide a recommendation.

- Discuss how wanting to be “substance free” may affect his view of medications
- Bupropion would not be an initial choice due to elevated liver enzymes and recent history of alcohol abuse and relapse. Patient is at risk for seizures, too.
- Encourage combo NRT
- Consider varenicline (excreted through the kidney, not the liver). Note that varenicline can increases sensitivity to alcohol.
CASE STUDY: Ann

Ann is a 30 year old Army veteran who uses 1-5 cans of dip per day. She is looking to quit to better her health. She uses dip as a distraction, tending to use more on days when she is home with nothing else to do. She is not working at this time due to disability. She is not on any other medications, and she has a history of PTSD. She is interested in varenicline to help her quit.

Read the case study or ask participant to read aloud.

Invite the class ask more questions about Ann that pertain to medication, Patient or Medical factors in decision making. As the instructor, you will pretend you are Ann and can answer any way you like. If there is time after providing more information have class discuss in small groups and provide a recommendation.

• Discuss varying nicotine exposure given variation in dip use.
• PTSD presents in a variety of ways, so it would be good to investigate further.
• Consider varenicline as this is patient preference and has been shown as effective.
• High dose patch per Mayo clinic recommendations; zyban is also an option
• Lozenge high dose would be useful as well, given administration mode.
FDA has approved 7 first line medications to use in smoking cessation
Use of combination therapy is increasing
  Combo NRT use may be more effective for highly addicted patients
  Those with psych history first try combination NRT

KEYPOINTS:

• Meds more than double one’s chance for success

• Combination therapy is quickly becoming a standard for many. Although some data has shown it to have the same efficacy as Chantix or monotherapy. It may be best to use for patients with high levels of addiction or report high levels of cravings.
Summary

- Other pharmacotherapy at least doubles success and should be recommended for nearly all smokers
- Counseling and pharmacotherapy have additive effects
- Evidence-based medicine integrates clinical expertise and research findings

KEYPOINTS:

- Meds more than double one’s chance for success
- The gold standard = counseling + meds. Consistently across studies the use of both pharm and non-pharm therapy have been proven to be better than either alone. This makes since given the biopsychosocial model of tobacco addiction.
Summary

- Consider medication, patient and medical factors when recommending pharmacologic therapy.
- Be aware of any past or present MH/sub abuse history.
  - Understand the relationship between MH sx, tobacco use and quitting.
- Safety and efficacy can be enhanced through careful monitoring.
- Recognize need to individualize decisions.

KEYPOINTS:

- Consider several factors with each individual.
- Choice of therapy may vary according to the underlying medical conditions. Some medical conditions may exclude some of the meds.
- Those with mental health/substance abuse history may need more aggressive therapy and for longer duration.
- Let the individual be “the captain”. Their preference (after education about meds) most often will drive the recommendation.