Educational Objectives:
1. Review key features in obtaining a medical history pertinent to nicotine/tobacco use.
2. Review relevant discussion points regarding e-cigarette use in pulmonology practice.
3. Review concepts to apply when counseling treatments to patients with nicotine/tobacco use disorders.
4. Review the relevance of psychiatric comorbidities in nicotine/tobacco use.

Scenario:
Mrs. Smith is a 34-year-old woman with a history of mild intermittent asthma, opioid use disorder, and depression who comes to your outpatient pulmonology office for an initial visit. She was diagnosed with asthma as a teenager with mild reversible obstruction noted on spirometry (FEV1 79% predicted), reporting one exacerbation over the last year requiring outpatient prednisone. She takes albuterol as-needed albuterol and was previously on inhaled fluticasone several years ago.

Question 1: You want to gather information regarding Mr. Smith’s nicotine/tobacco use. What information is important to collect and why?

Nicotine/tobacco dependence is a deadly disease process and is the leading cause of preventable death in the United States. Over 70% of individuals who smoke will visit a provider throughout the year and will have an opportunity to receive one of several evidence-based treatment methods, including counseling, nicotine replacement therapy (NRT), and other pharmacotherapies. Pulmonologists are uniquely positioned to engage with patients who may use nicotine/tobacco given the close relationship between these substances and their impact on a patient’s pulmonary disease(s), comorbid disease(s), quality of life, and other considerations, including implications for oxygen therapy and lung cancer screening.

The “5 As” framework outlines an approach to incorporate brief office-based interventions to counsel patients on nicotine/tobacco use (Table 1). The first step in the 5As includes asking about nicotine/tobacco use systematically and approachable to identify every patient who presents with nicotine/tobacco use. It is also important to collect a patient’s pack-year history (pack year history = cigarettes/day x duration of years smoked) to identify the relative exposure of nicotine/tobacco use to approximate the risk of certain diseases (i.e., COPD, lung cancer) and the intensity of nicotine addiction.
Additionally, anyone who smokes should be evaluated for eligibility for lung cancer screening with annual low-dose CT scans. This should be considered in patients that are a) age 50-80 who have at least a 20-pack year history and b) either currently smoke or have quit smoking within the last 15 years.

<table>
<thead>
<tr>
<th>Ask</th>
<th>Systematically identify all tobacco users at every visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advise</td>
<td>Strongly urge all tobacco users to quit</td>
</tr>
<tr>
<td>Assess</td>
<td>Determine willingness to make a quit attempt</td>
</tr>
<tr>
<td>Assist</td>
<td>Aid the person in quitting (provide counseling and medication)</td>
</tr>
<tr>
<td>Arrange</td>
<td>Ensure follow-up contact</td>
</tr>
</tbody>
</table>

Table 1. The “5 As” model for treating tobacco use and dependence. Adapted from A Clinical Practice Guideline for Treating Tobacco Use and Dependence: 2008 Update.

Additionally, several questionnaires have been developed to better understand the severity of nicotine addiction. This information collected can potentially inform the prescribed intensity and duration of treatment for nicotine/tobacco dependence. Table 2 outlines the scoring scheme for the Fagerström Test for Nicotine Dependence (FTND). A more simplified approach has been described by simply using the patient’s time to the first cigarette of the day to stratify as the intensity of addiction: time ≤30 minutes is associated with higher intensity addiction, and thereby may require higher intensity therapy compared to the time to first cigarette >30 minutes from awakening.

For those patients who are not ready to quit smoking, it is useful to inquire further about their motivations and thoughts. The 5 R’s (Relevance, Risks, Rewards, Roadblocks, Repetition) is a motivational interview model that can be useful in navigating this conversation.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answers</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>How many cigarettes do you smoke per day?</td>
<td>≤10</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>11-20</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>20-30</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&gt;30</td>
<td>3</td>
</tr>
<tr>
<td>How soon after waking do you smoke?</td>
<td>≤5 min</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>6-30 min</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>31-60 min</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;60 min</td>
<td>0</td>
</tr>
<tr>
<td>Which cigarette would be the most difficult to give up?</td>
<td>First in AM</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Any other</td>
<td>0</td>
</tr>
<tr>
<td>Is it hard to refrain from smoking where it is forbidden?</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Do you smoke even though you are sick in bed all day?</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Do you smoke more often in the first few hours of the day, compared to the rest of the day?</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2. The Fagerström test for nicotine dependence. Scores correlating to 8+ (highly dependent), 5-7 (moderately dependent), 3-4 (low-moderately dependent), 1-2 (minimally dependent). Adapted from Heatherton et al.
**Scenario continued:** Ms. Smith states that she smokes cigarettes every day. She started smoking at age 15 and smokes about 1 pack per day (i.e., 19 pack-years). She feels compelled to smoke within 15 minutes of awakening with her morning coffee and has noticed smoking much more during emotional stress. Ms. Smith acknowledges that it may not be the healthiest habit for her, but she feels that it has now become a significant part of her life. She has been contemplating cutting back and asking you what you think about e-cigarettes, as she has heard they are mostly water vapor and, therefore, healthier than regular cigarettes.

**Question 2: How do you approach her question regarding using e-cigarettes for nicotine/tobacco use treatment?**

The basic anatomy of an electronic cigarette (i.e., e-cigarettes, e-cigs, vapes, vape pens, dab pens, dab rigs, tanks, mods, pod-mods, electronic nicotine delivery systems (ENDS), JUUL) consists of a power source utilized to heat a coil that aerosolizes an e-liquid to be delivered to the user (Figure 1). Various generations of products are commonly used today. While e-cigarette liquid contains water, other compounds are included in varying concentrations, including nicotine, flavors (menthol, sweeteners), bases (propylene glycol, vegetable glycerin), with changes in composition resulting after combustion. Additionally, devices can be modified or “hacked” to allow varied product and potential toxin administration, including volatile organic compounds, heavy metals, and other particles.

![Figure 1. Overview of electronic cigarette products. Adapted from E-cigarette, or vaping, products visual dictionary. Centers for Disease Control and Prevention CDC. https://stacks.cdc.gov/view/cdc/103783/cdc_103783_DS1.pdf.](https://stacks.cdc.gov/view/cdc/103783/cdc_103783_DS1.pdf)
E-cigarettes have been associated with pulmonary diseases. In July 2019, the United States experienced an outbreak of E-cigarette or vaping product use-associated acute lung injury (EVALI), responsible for at least 2,600 cases and 68 deaths. Tetrahydrocannabinol (THC)-containing products accounted for most cases, strongly associated with the constituent vitamin E acetate. Before this outbreak, several other reports documented various lung injury patterns associated with e-cigarette use. Given the potential for lung disease and nicotine addiction, providers' history should include e-cigarette habits, including frequency, device(s) used, e-liquid(s) used, and specific modifications made to the device.

Although some have proposed e-cigarettes for nicotine/tobacco use treatment, e-cigarette products have only recently been introduced to the market, and there is limited information regarding their safety and efficacy. Additionally, there is no strong supporting evidence for e-cigarette use over currently approved safe and effective pharmacotherapies. In this context, it is wise to share this uncertainty regarding e-cigarettes with patients and encourage using established and approved methods for nicotine/tobacco use treatment (i.e., counseling, NRT, and other pharmacotherapies). Table 3 identifies the estimated nicotine content in various nicotine-containing products.

<table>
<thead>
<tr>
<th>Product</th>
<th>Nicotine content in mainstream smoke</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cigarette</strong></td>
<td>0.5-1.6 mg per cigarette</td>
</tr>
<tr>
<td><strong>Roll-your-own cigarette</strong></td>
<td>1.5-1.8 mg per cigarette</td>
</tr>
<tr>
<td><strong>Cigar</strong></td>
<td>-</td>
</tr>
<tr>
<td>Little cigar</td>
<td>1.5 mg per cigar</td>
</tr>
<tr>
<td>Large cigar</td>
<td>1.4 mg per cigar</td>
</tr>
<tr>
<td><strong>Premium cigar</strong></td>
<td>3.4 mg per cigar</td>
</tr>
<tr>
<td><strong>Bidis (hand-rolled Indian cigarettes)</strong></td>
<td>2.7 mg per bidi</td>
</tr>
<tr>
<td><strong>Chutta (hand-made Indian cigars)</strong></td>
<td>6.98 mg per chutta</td>
</tr>
<tr>
<td><strong>Clove cigarettes</strong></td>
<td>2 mg per cigarette</td>
</tr>
<tr>
<td><strong>Waterpipe tobacco (i.e., hookah)</strong></td>
<td>2.25-2.94 mg per smoking session (i.e., 10 g, 100 puffs, 1 puff/second, 30 seconds between puffs)</td>
</tr>
<tr>
<td><strong>E-cigarette</strong></td>
<td>-</td>
</tr>
<tr>
<td>Disposable</td>
<td>0.74 mg per 15 puffs in standard machine conditions</td>
</tr>
<tr>
<td>Prefilled</td>
<td>1.06 mg per 15 puffs in standard machine conditions</td>
</tr>
<tr>
<td>Tank</td>
<td>1.39 mg per 15 puffs in standard machine conditions</td>
</tr>
<tr>
<td><strong>example: JUUL</strong></td>
<td>5.0% JUULpod contains 40 mg (59 mg/mL)</td>
</tr>
<tr>
<td></td>
<td>3.0% JUULpod contains 23 mg (35 mg/mL)</td>
</tr>
</tbody>
</table>

Table 3. Approximate nicotine content in various nicotine products within mainstream smoke as determined by standard conditions with a smoke machine. Note that smoke machine conditions may not estimate actual nicotine exposure, as many individuals may significantly vary their behavior including puffing patterns, intervals, blocking filter holes, and smoking to a certain butt length. Adapted from Djordjevic et al.
**Scenario continued:** Mrs. Smith decides against vaping, and asks you what options exist to help her cut back on her cigarette smoking.

**Question 3: What are currently available treatment options for nicotine/use treatment?**

The backbone of established treatment methods for nicotine/tobacco use includes counseling and pharmacotherapy. Counseling in the forms of individual counseling, group counseling, and telephone counseling has been described as successful. Additionally, supplemental therapy can include Internet, mobile phone texting, and app-based services. The 1-800-QUIT-NOW Quitline is a patient resource that often includes free telephone-based counseling and support in obtaining pharmacotherapy. Other potential resources for behavioral intervention include phone-based apps, such as QuitGuide, quitSTART, and Stay Quit Coach.

The 2020 ATS Clinical Practice Guidelines recommend the following approach to pharmacologic therapy:

1. Varenicline as a first line agent over nicotine replacement therapy or bupropion alone
2. Varenicline plus nicotine patch as a preferred agent over varenicline alone
3. In patients who continue to use tobacco, it is recommended to start varenicline rather than wait until patients are ready to stop smoking

While most of the high-quality evidence centers around pharmacologic options or behavioral interventions for smoking cessation, other interventions can be considered in some patients. There is some evidence that acupuncture or hypnotherapy could help selected patients, though the results of numerous studies have mixed conclusions.

The combination of the counseling and pharmacotherapy modalities has the best-associated outcomes. A Cochrane Review in 2013 compared major pharmacotherapies compared to placebo on smoking abstinence and revealed efficacy for NRT (OR 1.84; 95% CI 1.71-1.99), bupropion (OR 1.82; 95% CI 1.60-2.06), and varenicline (OR 2.88; 95% CI 2.40-3.47). Overall, varenicline was superior to single NRT and bupropion. Notably, there was no difference between combined NRT and varenicline. Table 4 reviews practical information regarding prescribing select pharmacotherapies, and Figure 2 reviews an example of a scheme for prescribing combined NRT.
<table>
<thead>
<tr>
<th>Nicotine replacement</th>
<th>Formulations*</th>
<th>Dosing</th>
<th>Adverse effects</th>
</tr>
</thead>
</table>
| Nicotine replacement | 2 mg 4 mg | Week 1-6: 1 piece q 1-2 hours  
Week 7-9: 1 piece q 2-4 hours  
Week 10-12: 1 piece q 4-8 hours  
Duration: ≤12 weeks  
Maximum: 24 pieces/day | Mouth/jaw soreness  
Hiccups  
Dyspepsia  
Hypersalivation  
Lightheadedness  
Nausea/vomiting  
Throat and mouth irritation |
| Lozenge | 2 mg 4 mg | Week 1-6: 1 piece q 1-2 hours  
Week 7-9: 1 piece q 2-4 hours  
Week 10-12: 1 piece q 4-8 hours  
Duration: ≤12 weeks  
Maximum: 24 pieces/day | Nausea  
Hiccups  
Cough  
Heartburn  
Headache  
Flatulence  
Insomnia |
| Transdermal patch | 7 mg 14 mg 21 mg | >10 cigarettes/day:  
4-6 weeks: 21 mg/day  
2 weeks: 14 mg/day  
2 weeks: 7 mg/day  
Duration: 8-10 weeks  
≤10 cigarettes/day:  
6 weeks: 14 mg/day  
2 weeks: 7 mg/day | Local skin reactions  
Headache  
Sleep disturbances |
| Nasal spray | 10mg/mL solution | 1-2 doses/hour (1 dose=2 sprays)  
Duration: 3-6 months  
Maximum: 5 doses/hour or 40 doses/day | Nasal and/or throat irritation  
Rhinitis  
Tearing  
Sneezing  
Cough  
Headache |
| Oral inhaler | 10 mg cartridge delivers 4-mg inhaled vapor | 6-16 cartridges/day  
1 cartridge q1-2 hours  
Duration: 3-6 months | Mouth and/or throat irritation  
Cough  
Headache  
Rhinitis  
Dyspepsia  
Hiccups |
| Bupropion SR | 150 mg tablet | 150 mg p.o. every morning  
3 days 150 mg p.o. b.i.d.  
Duration: 7-12 weeks, up to 6 months  
Maximum: 300 mg qd | Insomnia  
Dry mouth  
Nervousness/ difficulty concentrating  
Nausea  
Dizziness  
Constipation  
Rash  
Seizures (risk is 0.1%, but exercise caution in patients with prior history of seizures)  
Neuropsychiatric symptoms (rare) |
| Varenicline | 0.5 mg 1 mg | Day 1-3: 0.5 mg  
Day 4-7: 0.5 mg b.i.d.  
Week 2-12: 1 mg b.i.d.  
Duration: 12 weeks; consider an additional 12 weeks in selected patients | Nausea  
Sleep disturbances  
Constipation  
Flatulence  
Vomiting  
Neuropsychiatric symptoms (rare) |

**Table 4. FDA-approved medications for smoking cessation. *4 mg for 1st cigarette ≤30 minutes after waking, 2 mg for 1st cigarette >30 minutes after waking, 21 mg/day for >10 cigarettes per day, 14 mg/day for ≤10 cigarettes per day. Adapted from Smoking Cessation: A Report of The Surgeon General.**
Scenario continued:
After discussing some of the initial treatment options with Ms. Smith, she informs you that she is hoping to have another child and wonders how a pregnancy might impact the approach to smoking cessation pharmacotherapy. She also asks about any implications of her history of depression, as she has heard that some of the available medications might affect mood.

Question 4: Are there special considerations for pharmacotherapy for patients of child-bearing age or those that are breastfeeding?

For many reasons, pregnant patients should receive special attention with regard to provider-initiated interventions. Potential perinatal implications of continuing to smoke include a higher risk of orofacial clefts, fetal growth restriction, placenta previa, abruptio placentae, preterm labor and rupture of membranes, low birth weight, increased perinatal mortality, ectopic pregnancy, decreased maternal thyroid function. Additionally, a 2017 meta-analysis showed that smoking cessation had been associated with decreased incidence of low fetal birth weight (odds ratio 0.65, 95% CI 0.42-0.88).

The general approach to counseling and non-pharmacologic treatment remains the same for pregnant patients. Counseling should be started early on in a patient’s pregnancy. Regarding pharmacotherapy in pregnant patients, the USPSTF concluded there was insufficient data on the risks versus benefits of pharmacotherapy in pregnant women (I statement) as recently as 2021. While the efficacy of NRT in pregnant patients has not been well studied, the SNAP trial in 2014 did show less infant impairment at the 2-year mark when mothers used NRT vs. placebo (odds ratio [OR] 1.40, 95% CI 1.05-1.86, p=0.023).

Bupropion has been shown in small observational studies to improve smoking cessation compared to control, and there is no evidence of increased risk of overall fetal anomalies or...
adverse pregnancy events with its use. Bupropion does cross the placenta, and there has been inconsistent data on cardiovascular malformations. Bupropion also accumulates in breast milk at doses of 300 mg or higher, but this is unlikely to correlate with clinically significant drug levels in breast milk. At the same time, infant seizure events have been potentially linked with bupropion exposure through breast milk.

Varenicline also has limited data in pregnant patients. Survey data from a 2016 study showed no increase in congenital malformations. However, this study limited varenicline use to the first trimester, and several participants had early discontinuation of the medication.

It is important to carefully discuss the potential risks and benefits of using these medications in pregnant or breastfeeding patients.

**Question 5: Is varenicline safe to prescribe to those with neuropsychiatric history?**

Individuals with mental health illnesses often have an elevated risk of comorbid conditions and benefit from introducing nicotine/tobacco use pharmacotherapy. However, varenicline previously had an FDA black box warning on its label initially in 2009, alerting patients about the risk of serious neuropsychiatric adverse events, including suicide and depression. Additionally, concerns were raised about neuropsychiatric adverse events in patients prescribed bupropion SR. However, the EAGLES study was published in 2016, which randomized 8,144 patients who were active smokers with and without psychiatric disease to interventions, including varenicline, bupropion, NRT, and placebo. The study demonstrated an overall low rate of serious adverse events, and there was no statistically significant difference in overall or serious neuropsychiatric events in all patients, in patients with psychiatric disorders, or in patients without psychiatric disorders.

Subsequently, the FDA black box warning was removed in 2016. Additionally, the 2020 ATS Clinical Practice Guideline on initiating pharmacologic treatment in tobacco-dependent adults recommends that “for tobacco-dependent adults with comorbid psychiatric conditions, including substance use disorder, depression, anxiety, schizophrenia, and/or bipolar disorder, for whom treatment is being initiated, we recommend varenicline over a nicotine patch (strong recommendation, moderate certainty in the estimated effects).”

Regarding patients with concurrent substance use disorder, a 2017 prospective study showed continued smoking was associated with substance use (OR=1.56, 95% CI=1.10-2.20) and SUD relapse (OR=2.02, 95% CI=1.65-2.47).

**Scenario continued:**

After an informed discussion, Ms. Smith wishes to start varenicline. You provide her with instructions, potential side effects, and a scheduled follow-up phone call in about 4 weeks. You congratulate her on her motivation and effort to improve her health.
Questions:

1. Which of the following is true regarding smoking cessation outcomes:
   a. Combination of counseling and pharmacotherapy has shown to have the best outcomes.
   b. The use of E-cigarettes is recommended to help patients quit smoking
   c. Use of nicotine-replacement therapy has higher smoking cessation rates compared to use of varenicline.
   d. Bupropion is an ineffective therapy for smoking cessation

2. Which pharmacotherapy regimen would be the preferred option, based on the 2020 ATS Clinical Practice Guideline on smoking cessation, for 65-year-old patient with a 35-pack-year history of smoking as well as underlying epilepsy:
   a. Bupropion combined with nicotine transdermal patch
   b. Varenicline combined with nicotine transdermal patch
   c. Varenicline combined with bupropion
   d. Nicotine transdermal patch combined with nicotine nasal spray

References:


