Treatment of Tobacco Dependence

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Case: Nancy D.

• 55 year old woman with right breast cancer, s/p chemoradiation and mastectomy with history of HTN, AUD in early remission, and underlying depression.
• Smokes about a ½ pack of cigarettes per day.
• Expresses interest in stopping when asked but reluctant as ‘nothing has ever worked.’
• Has tried nicotine patch, nicotine lozenges, and trial of bupropion.
• Tells you she has heard about varenicline but her other providers was concerned about her depression and potential side effects.
• She does not feel confident that she can stop.
Smoking: Scope of the Problem

- Leading preventable cause of death worldwide
- In the U.S., affects 45 million adults (18%)
- Overall decrease in smoking rates over time, and patterns are changing (lower consumption, combinations of products)
- Higher prevalence of smoking in pts with a MH or SUD diagnosis

Trends in cigarette smoking among adults, 1955-2013

- Male
- Female


Current smokers– VA system

Smoking: Scope of the Problem

- Smoking rates vary by race/ethnicity and poverty status
- Prevalence is higher in those with lower educational attainment

CDC (2011) MMWR 60: 1207.
### Annual U.S. Deaths Attributable to Smoking, 2005 - 2009

<table>
<thead>
<tr>
<th>Category</th>
<th>Deaths</th>
<th>Percent of all smoking-attributable deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular &amp; metabolic diseases</td>
<td>160,600</td>
<td>33%</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>130,659</td>
<td>27%</td>
</tr>
<tr>
<td>Pulmonary diseases</td>
<td>113,100</td>
<td>23%</td>
</tr>
<tr>
<td>Second-hand smoke</td>
<td>41,280</td>
<td>9%</td>
</tr>
<tr>
<td>Cancers other than lung</td>
<td>36,000</td>
<td>7%</td>
</tr>
<tr>
<td>Other</td>
<td>1,633</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

**TOLL:** >480,000 deaths annually, $130 billion/yr in added medical costs

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69% of smokers want to quit
53% of smokers have tried in the past year
Only 6% attain abstinence at one year, and 50% relapse within 1 week
Success of quitting lower with concurrent SUD or psychiatric disorder

**HOWEVER:**
- Cessation benefits all smokers—regardless of length of smoking, level of illness, comorbidity, or age

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**Slowing the decline of pulmonary function**


- Never smoked or not susceptible to smoke
- Stopped smoking at 45 (mild COPD)
- Stopped smoking at 65 (severe COPD)

COPD = chronic obstructive pulmonary disease
Smoking Cessation: Benefits

Reduction in cumulative risk of death from lung cancer in men


50-year follow-up of 34,000 British male physicians

Nicotine Pharmacology

• Readily absorbed through intact skin
• Well absorbed in the small intestine but has low bioavailability (20-45%) due to first-pass hepatic metabolism
• Carried in tar droplets and rapidly absorbed across respiratory epithelium
  – Significant proportion lipophilic at pH 7.4
  – Large alveolar surface area
  – Extensive capillary system in lung
Nicotine Pharmacology

Nicotine reaches the brain within 10–20 seconds.

Nicotine binds to receptors in the brain and other sites in the body.

Other:
- Neuromuscular junction
- Sensory receptors
- Other organs

Central nervous system
Exocrine glands
Adrenal medulla
Peripheral nervous system

Nicotine has predominantly stimulatory effects.
Nicotine Pharmacology

Central nervous system
– Pleasure
– Arousal, enhanced vigilance
– Improved task performance
– Anxiety relief

Other
– Appetite suppression
– Increased metabolic rate
– Skeletal muscle relaxation

Cardiovascular system
– ↑ Heart rate
– ↑ Cardiac output
– ↑ Blood pressure
– Coronary vasoconstriction
– Cutaneous vasoconstriction
Nicotine enters brain

Stimulation of nicotine receptors

Dopamine release

Prefrontal cortex

Nucleus accumbens

Ventral tegmental area

Nicotine enters brain

Stimulation of nicotine receptors

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Nicotine enters brain
Effects of Drugs on Dopamine Release

**AMPHEMATINE**

Much greater Activity than any Other drug of abuse -causes neurotoxicity

**COCAIN**

**NICOTINE**

**ETHANOL**

Source: Di Chiara and Imperato
Nicotine Withdrawal

- Irritability/frustration/anger
- Anxiety
- Difficulty concentrating
- Restlessness/impatience
- Depressed mood/depression
- Insomnia
- Impaired performance
- Increased appetite/weight gain
- Cravings

Most symptoms manifest within the first 1–2 days, peak within the first week, and subside within 2–4 weeks.

Cycle of Nicotine Dependence

Factors Affecting Nicotine Use

Individual
- Sociodemographics
- Genetic predisposition
- Coexisting medical conditions

Pharmacology
- Alleviation of withdrawal symptoms
- Weight control
- Pleasure, mood modulation

Environment
- Tobacco advertising
- Conditioned stimuli
- Social interactions
Proven Smoking Cessation Therapies

Though expensive, hiring a professional actor dressed as death to stalk his every move finally broke Ted of his smoking addiction.
Proven Smoking Cessation Therapies

Two modalities with a strong evidence base

**Behavioral Support**
- CBT / motivational enhancement
- Brief counseling by clinicians
- Phone-based counseling—e.g., the system of state-based quit lines (1-800-QUIT-NOW)
- Text and internet-based counseling methods

NOT (yet) well supported:
- Hypnosis
- Acupuncture
- Contingency management

**Pharmacotherapy**
- Nicotine replacement
- Bupropion
- Varenicline

NOT (yet) as well supported:
- SSRI s
- Anxiolytics
- E-cigarettes (1st, 2nd, 3rd generation)
- Nicotine vaccine
Proven Smoking Cessation Therapies

Summary of treatment efficacy for behavioral and pharmacologic methods


<table>
<thead>
<tr>
<th>Method</th>
<th>Nonpharmacologic Methods vs Minimal or Usual Care, Risk Ratio (95% CI)</th>
<th>No. of Trials in Meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonpharmacologic methods</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking cessation counseling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Individual</td>
<td>1.39 (1.24-1.57)</td>
<td>22</td>
</tr>
<tr>
<td>Group</td>
<td>1.98 (1.60-2.46)</td>
<td>13</td>
</tr>
<tr>
<td>Telephone quit line</td>
<td>1.37 (1.26-1.50)</td>
<td>9</td>
</tr>
<tr>
<td>Physician intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brief advice to quit vs no advice or usual care</td>
<td>1.66 (1.42-1.94)</td>
<td>17</td>
</tr>
<tr>
<td>Brief counseling vs No advice or usual care</td>
<td>1.84 (1.60-2.13)</td>
<td>11</td>
</tr>
<tr>
<td>Brief advice</td>
<td>1.37 (1.20-1.56)</td>
<td></td>
</tr>
<tr>
<td><strong>Pharmacologic Methods vs Placebo or No Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-line drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion SR</td>
<td>1.69 (1.53-1.85)</td>
<td>36</td>
</tr>
<tr>
<td>Varenicline</td>
<td>2.27 (2.02-2.55)</td>
<td>14</td>
</tr>
<tr>
<td>Nicotine replacement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patch</td>
<td>1.66 (1.53-1.81)</td>
<td>41</td>
</tr>
<tr>
<td>Gum</td>
<td>1.43 (1.33-1.53)</td>
<td>53</td>
</tr>
<tr>
<td>Lozenge</td>
<td>2.00 (1.63-2.45)</td>
<td>6</td>
</tr>
<tr>
<td>Inhaler</td>
<td>1.90 (1.36-2.67)</td>
<td>4</td>
</tr>
<tr>
<td>Nasal spray</td>
<td>2.02 (1.49-3.73)</td>
<td>4</td>
</tr>
<tr>
<td>Second-line drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>2.03 (1.48-2.78)</td>
<td>6</td>
</tr>
<tr>
<td>Clonidine</td>
<td>1.63 (1.22-2.18)</td>
<td>6</td>
</tr>
</tbody>
</table>
Effect of Provider Interventions

Compared to patients who receive no assistance from a clinician, patients who receive assistance are 1.7–2.2 times as likely to quit successfully for 5 or more months.

$n = 29$ studies

A Frame for Intervention: The 5 A’s

- ASK
- ADVISE
- ASSESS
- ASSIST
- ARRANGE
A Frame for Intervention: The 5 A’s

ASK about tobacco use

- “Do you ever smoke or use other types of tobacco or nicotine, such as e-cigarettes?”

- “Condition X often is caused or worsened by smoking. Do you, or does someone in your household smoke?”

- “Medication X often is used for conditions linked with or caused by smoking. Do you, or does someone in your household smoke?”
A Frame for Intervention: The 5 A’s

**ADVISE** tobacco users to quit (clear, strong, personalized)

- “It’s important that you quit as soon as possible, and I can help you.”
- “Cutting down while you are ill is not enough.”
- “Occasional or light smoking is still harmful.”
- “I realize that quitting is difficult. It is the most important thing you can do to protect your health now and in the future. I have training to help my patients quit, and when you are ready, I will work with you to design a specialized treatment plan.”
A Frame for Intervention: The 5 A’s

**ASSESS** readiness to change

**ASSIST** with the quit attempt

- Set a quit date (abrupt vs gradual cessation)
- Address barriers (withdrawal, triggers, drug SEs)
- Discuss pharmacologic / nonpharmacologic options
- If not ready for change → take an MI approach
A Frame for Intervention: The 5 A’s

ARRANGE follow-up— (starting within 1 week of quit date)

<table>
<thead>
<tr>
<th>Number of sessions</th>
<th>Estimated quit rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 1</td>
<td>12.4%</td>
</tr>
<tr>
<td>2 to 3</td>
<td>16.3%</td>
</tr>
<tr>
<td>4 to 8</td>
<td>20.9%</td>
</tr>
<tr>
<td>More than 8</td>
<td>24.7%</td>
</tr>
</tbody>
</table>

* 5 months (or more) postcessation

Provide assistance throughout the quit attempt.
A More Brief Team-Based Approach: Ask, Advise, Refer

**ASK**
- about tobacco use

**ADVISE**
- tobacco users to quit

**REFER**
- to other resources

Patient receives assistance from other resources, with follow-up counseling arranged

**ASSESS**

**ASSIST**

**ARRANGE**
Nicotine Replacement Therapy

- Three OTC options: patch, gum, lozenge.
- Two Rx-only options: oral inhaler, nasal spray
- Range for rate of onset is variable amongst them
Nicotine Replacement Therapy

Nicotine Replacement Therapy

- Long-acting, slow onset
  - Skin patch
    - Steady nicotine level
    - Simple with good compliance
    - No user control
- Short-acting, faster onset
  - Oral: gum, lozenge, inhaler
    - Nasal: spray
  - User controls the dose
  - Greater fluctuations

- Newer ways to use old meds
  - Combine short and long-acting NRT
  - Treat longer to minimize relapse
  - Start NRT before quit talk
  - NRT or varenicline to decrease use in those not ready for full cessation
    - ‘Reduce to quit’
Bupropion

- Atypical antidepressant that increases dopamine and norepinephrine levels in mesolimbic pathways.
- Improvement in cessation rates independent of antidepressant effects
- Usage: begin 1-2 weeks prior to quit date
- Side-effects: nausea, vivid / abnormal dreams, dry mouth
- Lowers seizure threshold (0.1% risk of seizure in smokers)
- May temporarily blunt cessation-related weight gain
- May be more effective in combination with NRT or varenicline
Varenicline

- Partial agonist at the α4β2 nicotinic acetylcholine receptor subtype (most important for nicotine dependence)
- Long-term efficacy superior to bupropion and NRT
- Usage: begin 1 week prior to quitting
- Side-effects: nausea, insomnia, vivid / abnormal dreams
- Post-marketing case reports of behavioral changes / suicidality, leading to a black box warning by the FDA
- However— a large 2016 trial (Anthenelli et al. (2016) *Lancet*) including patients with psychiatric comorbidity that showed no such negative effects
  - Black box warning removed in December of 2016
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Positives</th>
<th>Negatives</th>
</tr>
</thead>
</table>
| Nicotine patch     | • 1 new patch daily  
                   • 21 mg for > 10 cigs/d  
                   • 14 mg for < 10 cigs/d  
                   • Taper after 4-6 wks | • Steady Nicotine level  
                   • Ease of use                                                   | • Nicotine released slowly, cannot be adjusted  
                   • Skin irritation, insomnia                                        |
| Nicotine gum       | • 1 piece per hour  
                   • 2 mg for < 25 cigs/d  
                   • 4 mg for > 25 cigs/d  
                   • < 24 pieces/d | • User controlled Nicotine level  
                   • Oral substitute for cigs                                | • Requires proper chewing technique (chew, pocket)  
                   • Can affect dental work  
                   • Can’t mix with food/drink  
                   • Mouth irritation, jaw sx                                           |
| Nicotine lozenge   | • 1 piece every 1-2 hours  
                   • 2 mg for non-AM smokers  
                   • 4 mg for AM smokers | • User controlled  
                   • No effect on dentition | • Can’t mix with food/drink  
                   • Hiccups, heartburn                                                |
| Nicotine inhaler   | • Inhale as needed  
                   • 6-10 cartridges/d | • User controlled  
                   • Oral substitute                                                  | • Device visible during use  
                   • Mouth / throat irritation                                           |
| (10 mg cartridge)  |                                                                        |                                                |                                                            |
| Nicotine nasal     | • One puff in each nostril every 1-2 hours  
                   • < 40 applications/d | • User controlled  
                   • Most rapid Nicotine delivery                          | • Nasal irritation, sneezing, cough, eye tearing                 |
| inhaler            |                                                                        |                                                |                                                            |
## Pharmacologic Options: Summary

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Positives</th>
<th>Negatives</th>
</tr>
</thead>
</table>
| Bupropion SR | • 150 mg/d for 3 days, then 150 mg BID  
• Start 1 wk before quit date  
• Continue for 3-6 months | • Blunts cessation-related weight gain  
• Orally bioavailable | • Increased seizure risk  
• Concern re: psychiatric side-effects (boxed warning)  
• Insomnia, vivid dreams, dry mouth |
| Varenicline  | • 0.5 mg/d for 3 days, then 0.5 mg BID for 4 days, then 1 mg BID  
• Start 1 wk before quit date  
• Continue for 3-6 months | • Dual action— both relieves withdrawal and blocks Nicotine-related reward  
• Orally bioavailable | • Concern re: psychiatric side-effects (boxed warning 2009, removed 2016)  
• FDA communication re: potential CV risk  
• Needs adjustment for renal dysfunction  
• Nausea, insomnia, vivid dreams |

Pharmacologic Options: Summary

Long-term (> 6 month) quit rates for available therapies

Adapted from Cahill et al. (2012), Cochrane Database Syst Rev; Stead et al. (2012), Cochrane Database syst Rev; Hughes et al. (2014), Cochrane Database Syst Rev
Pharmacologic Options: Summary

Combinations are likely more effective than monotherapy

Pharmacologic Options: Summary

Adding Bupropion or NRT to varenicline

Pharmacologic Options: Summary

Triple Therapy?

• Methods:
  • 12-week, observational study exploring tolerability, via adverse events (AEs) elicited at each of nine phone assessments. Secondary outcomes included satisfaction rates, medication changes and self-reported quit rates at week 12.
  • Patient received varenicline 0.5 mg once daily for 3 days, followed by 0.5 mg twice daily for 4 days, followed by 1 mg twice daily for 11 weeks, nicotine 21 mg for 8 weeks (starting on the TQD), followed by transdermal nicotine 14 mg for 2 weeks; followed by transdermal nicotine 7 mg for 2 weeks; nicotine mini lozenges (2 mg) used as needed for relief of withdrawal and craving, for 12 weeks (starting on the TQD), participants were urged to use at least four mini lozenges per day, but no more than 20 per day.

• Results:
  • Thirty five of thirty six participants reported at least one AE. Insomnia (75%), abnormal dreams (72%) and nausea (64%) were most common. Most were mild to moderate. No deaths, hospitalisations, cardiovascular events or suicidality were reported. Six participants (17%) decreased the dose of at least one medication, 5 (14%) decreased the dose then discontinued at least one medication and 13 (36%) discontinued at least one medication without trying a lesser dose. Participants were highly satisfied with their medications, and 58% reported quitting at 12 weeks, with 38% reporting prolonged abstinence.

Smoking treatment in SUD patients

Meta-analysis of smoking treatment in 5700 pts with SUD

- Pharmacotherapy
- Pharmacotherapy + counseling
- In SUD treatment
- In SUD recovery
- Alcohol dependence
- Other drug dependence

RR (cessation)

Appolonio et al. (2016) Cochrane Database of Systematic Reviews 11: CD010274.
Returning to our case...

• 55 year old woman with right breast cancer, s/p chemoradiation and mastectomy, with history of HTN, AUD in early remission, and underlying depression.
  - Has history of breast cancer and HTN which can be leads into tobacco cessation discussion and also carries two diagnoses (depression, AUD) with higher smoking rates

• Smokes 10-15 cigarettes per day.
  - Fits the trend toward lower total daily dosage (affects perceived risk)
Returning to our case...

• Expresses interest but that nothing has worked in the past
• Used a nicotine patch and lozenges for about 7 days, but discontinued when she smoked a cigarette
• While trying bupropion, she decreased cigarette intake however never stopped completely

- Has only tried two FDA-approved therapies (one for only 1 week)
- Has not tried combination therapies
- Important to persist w/ NRT despite lapses
- Did not set a clear quit date w/ use of NRT or bupropion
Returning to our case...

- Tells you she’s heard that varenicline could be dangerous for him
  - No evidence that varenicline is dangerous in stable depression

- Says she does not feel confident in stopping
  - Good efficacy of treatment in patients in early or later recovery
Summary

• Cigarette smoking is the leading preventable cause of death worldwide, causing almost half a million deaths annually in the U.S.

• Quitting smoking causes improvements in health and survival regardless of when it occurs in the life / disease cycle

• Nicotine is rapidly absorbed into the body and quickly crosses the blood-brain barrier, where it readily activates the brain’s addiction circuitry

• Treatment should accomplish the following:
  – Utilize both behavioral and pharmacologic treatments together
  – Combine different pharmacologic modalities when appropriate
  – Start BEFORE the quit date and continue despite setbacks
  – Proceed without hesitation for patients with psychiatric and substance use disorders