Treatment of Nicotine Dependence: a brief review

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Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.
Case: Thomas F.

- 50 yo M truck driver with a h/o HTN, depression treated with Citalopram, and alcohol use disorder in remission.
- Smokes 15-20 cigarettes per day.
- Expresses interest in quitting but says, “I’ve tried everything, and nothing works!”
- Used a Nicotine patch for 7 days, but discontinued when he smoked a cigarette.
- While trying Bupropion, he decreased cigarette intake to 5 cigarettes/day but never stopped completely.
- Tells you he’s heard that Varenicline could be dangerous for him.
- Says he knows he can’t quit because he has an “addictive personality”
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


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

## Smoking: Scope of the Problem

### Annual U.S. Deaths Attributable to Smoking, 2005 - 2009

<table>
<thead>
<tr>
<th>Cause</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, $96 billion/yr in added medical costs

Smoking Cessation: benefits

- 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

**Slowing the decline of pulmonary function**


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

*Nicotiana tabacum*

Natural liquid alkaloid
Non-ionized form is lipophilic, readily crosses membranes
31% non-ionized at physiologic pH
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 reaches the brain within 10–20 seconds. 

Nicotine pharmacology

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

Central nervous system
Exocrine glands
Adrenal medulla
Peripheral nervous system
Cardiovascular system
Gastrointestinal system

Other:
- Neuromuscular junction
- Sensory receptors
- Other organs

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 neurobiology

Nicotine enters brain

Stimulation of nicotine receptors

Dopamine release

Prefrontal cortex

Nucleus accumbens

Ventral tegmental area

Nicotine enters brain
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

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

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NOT (yet) as well supported:
- SSRIs
- 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><strong>Physician intervention</strong></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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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><strong>First-line drugs</strong></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><strong>Second-line drugs</strong></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>

*Table 1. Efficacy of Methods Used to Treat Tobacco Dependence: Meta-analyses From the Cochrane Database of Systematic Reviews*
Effect of interventions by providers

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.

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 (Nicotine wdwl, 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 wk 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 briefer, 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 of rate of onset (5-10 min for nasal spray → 1-2 hrs for patch); all with less rapid absorption than smoked Nicotine
- Usage: may be most effective when used in combination (patch + shorter-acting agent)
- Consider starting 2 wks before quit date
- Continue therapy throughout setbacks
- Side-effects: skin irritation; mucosal irritation; heartburn
Nicotine replacement therapy

Sources:
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
Varenicline

- Partial agonist at the α4β2 nicotinic acetylcholine receptor subtype (most important for nicotine dependence)
- Long-term efficacy superior to Bupropion and Nicotine
- Usage: begin 1 wk prior to quitting, w/ gradual increase in dose
- 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) enriched in patients with psychiatric comorbidity showed no such negative effects
- Association with increased cardiovascular events suggested by a 2011 meta-analysis, contradicted by a later meta-analysis
# Pharmacologic options: Summary

<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

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<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

- Nicotine gum: 16.3%
- Nicotine patch: 15.9%
- Nicotine lozenge: 18.9%
- Nicotine nasal spray: 18.9%
- Nicotine inhaler: 17.1%
- Bupropion: 19.7%
- Varenicline: 28.0%

Source: 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

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)

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

• 50 yo M truck driver with a h/o HTN, depression treated with Citalopram, and alcohol use disorder in remission.
  - Has HTN— a comorbidity that could be a “hook” for discussing smoking.
  - Carries two diagnoses (depression, AUD) with higher smoking rates

• Smokes 15-20 cigarettes per day.
  - Fits the trend toward lower total daily dosage (affects perceived risk)
Returning to our case...

• Expresses interest in quitting but says, “I’ve tried everything, and nothing works!”
• Used a Nicotine patch for 7 days, but discontinued when he smoked a cigarette
• While trying Bupropion, he decreased cigarette intake to 5 cigarettes/day but never stopped completely
  - Has only tried two FDA-approved therapies (one for only 1 wk)
  - Has not tried combination therapies
  - Important to persist w/ NRT despite lapses
  - Did not set a clear quit date w/ use of Bupropion
Returning to our case...

• Tells you he’s heard that Varenicline could be dangerous for him
  - No evidence that Varenicline is dangerous in stable depression

• Says he knows he can’t quit because he has an “addictive personality”
  - 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
  – Precede the quit date and continue despite setbacks
  – Proceed without hesitation for patients with psychiatric and substance use disorders