Time to Butt Out

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Objectives

After this presentation, participants should be able to:

1. Describe the benefits of smoking cessation
2. List the withdrawal symptoms of quitting smoking
3. List the main treatment options to help people quit smoking and their likelihood of producing abstinence at 6-12 months
4. Describe the advantages and drawbacks of various pharmacological smoking cessation treatment options
5. List the appropriate dosages and duration of treatment of smoking cessation medications
6. Describe the monitoring parameters you would use when initiating a specific smoking cessation treatment

Smoking Cessation

“The single most important step that smokers can take to enhance the length and quality of their lives.”


Potential Lifetime Health Benefits of Quitting Smoking

Cardiovascular heart disease (CHD) risk is similar to never smokers
Lung CA risk is 30-50% that of continuing smokers
Stroke risk returns to the level of people who have never smoked at 5-15 years post-cessation
CHD risk is ↓ by 50% -

Lung function starts to improve with ↓ cough, sinus congestion, fatigue and shortness of breath

Created
1 year
3 months
10 years
5 years
15 years


Smoking Cessation

“Stopping smoking…may have a greater effect on reducing the risk of mortality among patients with CHD who smoke than the effect of any other intervention or treatment.”

Critchley JA, Capewell S. JAMA. 2003;290:86-97

Nides, M. Am J Med 2008;121;S20-31

Did you know?

- ~40% of smokers attempt quitting each year
- Most attempts are unaided
- 6 mo abstinence rates (unaided) = 3-5%
  - Most relapse in the first week
  - Most smokers have several triggers
- Nicotine’s half life is <2 hrs
- Withdrawal symptoms peak at 1 week and can last months

Benowitz NL. Prog Cardiovasc Dis 2003;46:91-111


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If you had a patient (with your age and medical history) who smoked 1ppd x 4 yrs – what method would you use to quit?

Going “smoke free”

- Ask, Assess and Assist
- Nonpharmacological approaches
- Nicotine Replacement Therapy (NRT)
  - The ‘patch’
  - Chewing gum, lozenges
  - Nasal spray
  - Nicotine Inhaler
- Delayed onset options
  - Bupropion (antidepressant)
  - Varenicline
  - Nortriptyline (antidepressant) 2nd line [OR = 2.14 (1.49-3.06)]
  - Clonidine (antihypertensive) 2nd line [OR = 1.89 (1.30-2.74)]

Ask, Assess and Assist

**Ask:** “Are you willing to try quitting?”

**YES:**
- Set a quit date
- Tell family & friends
- Anticipate challenges
- Remove tobacco items
- Tobacco replacements?

**NO:**
Here to help if you change your mind.

Choose a stop smoking medication?

<table>
<thead>
<tr>
<th>Description</th>
<th>Indications</th>
<th>Cost</th>
<th>Possible Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine Patch</td>
<td>Easier to use than the ‘nicotine gum’, especially if you have a nicotine addiction</td>
<td>High</td>
<td>Nicotine rash, skin irritation</td>
</tr>
<tr>
<td>Nicotine Gum</td>
<td>A patch that provides nicotine in a controlled manner</td>
<td>Low</td>
<td>Nicotine rash, skin irritation</td>
</tr>
<tr>
<td>Nicotine Transdermal System</td>
<td>Provides nicotine through the skin</td>
<td>Medium</td>
<td>Nicotine rash, skin irritation</td>
</tr>
<tr>
<td>Nicotine Inhaler</td>
<td>Provides nicotine in a mist form</td>
<td>Low</td>
<td>Nicotine rash, skin irritation</td>
</tr>
<tr>
<td>Nicotine Lozenge</td>
<td>Provides nicotine in a chewable form</td>
<td>Low</td>
<td>Nicotine rash, skin irritation</td>
</tr>
</tbody>
</table>

Nicotine Replacement Therapy (NRT)

- Delivers nicotine that binds to the nicotinic acetylcholine receptor (nAChR) receptors
- Does not counter the additional satisfaction from smoking
- NRTs does not deliver nicotine to the circulation as fast as smoking

Need a Comprehensive Strategy

- Smoking addiction has two main components:
  - Psychological (behavioural factors)
  - Physiological (pharmacological treatment)
- Advice and behavioural support increase the chances of successfully quitting!
- The biggest predictor of success is the number of quit attempts.

**References**

1. American Heart Association website
Nicotine Plasma Levels by Cigarettes vs. NRT Products

NRT: Nicotine Gum
- Nicotine polacrilex
  - (e.g., Nicorette®: Thrive gum®)
- Method of delivery:
  - Nicotine released from gum upon chewing
  - Bite the gum then, chew, chew until tingle, then park for 30-60 sec, repeat for 30 min
  - Start with about 10-12 pieces/day
  - Chew regularly for 4 - 12 wks, then PRN cravings for up to 6 months
- Avoid acidic beverages (coffee, alcohol, pop, citrus fruit juice) within 15 min (↓ absorption)

NRT: Nicotine Lozenge
- Dehydrated Nicotine bitartrate
  - (e.g., Thrive Lozenge®)
  - Nicotine released by sucking on lozenge, then park lozenge (when taste is strong); repeat x 30 min
- Dosage:
  - ≥ 20 cigarettes / day = 2 mg
  - < 20 cigarettes / day = 1 mg
  - 5-15 lozenges/day for 1-3 months, then PRN cravings

NRT: Nicotine Inhaler
- Nicotine is absorbed through oral mucosa
- Dose:
  - 1 cartridge (4 mg)
  - 4-12 cartridges/d X 3 mo, then taper
  - 20 min/cartridge
  - Expires within 24 hours if not used
- Side effects
  - Cough
  - Mouth and throat irritation
    - Changing the technique might help in these cases (small puffs less irritating than long puffs)
  - Rhinitis, pharyngitis

NRT: Nicotine Patches
- E.g., Habitrol®, Nicoderm®
  - New patch (7, 14, 21 mg) applied every 24 hrs, taper dose q 3-4 wks
  - 3 months therapy
- Advantages:
  - Eliminate variability of GI absorption
  - Reduce nicotine first-pass metabolism
  - Enhance patient compliance
- Disadvantages:
  - Local skin irritation
  - Insomnia
  - Wears off in 20-24 hrs

NRT: Nicotine Gum or Lozenge: Common Adverse Events

Local
- Jaw pain, tooth disorders
- Gum sticking to dentures
- Throat irritation (5%)
- Stomatitis (4%)
- Gingivitis (1%)
- Taste perversion

GI
- Hiccups (10%)
- Dyspepsia (9%)
- Nausea (9%)

CNS symptoms
- Headache (11%)
- Dizziness (4%)
- Insomnia (2%)
Efficacy of NRT vs. Placebo (@ 6 or longer)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Trials (n)</th>
<th>Participants (n)</th>
<th>Pooled OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gum</td>
<td>52</td>
<td>17,783</td>
<td>1.66 (1.52–1.81)</td>
</tr>
<tr>
<td>Patch</td>
<td>37</td>
<td>16,691</td>
<td>1.81 (1.63–2.02)</td>
</tr>
<tr>
<td>Nasal spray</td>
<td>4</td>
<td>887</td>
<td>2.35 (1.63–3.38)</td>
</tr>
<tr>
<td>Inhaler</td>
<td>4</td>
<td>976</td>
<td>2.14 (1.44–3.18)</td>
</tr>
<tr>
<td>Tablets/lozenges</td>
<td>4</td>
<td>2739</td>
<td>2.05 (1.62–2.59)</td>
</tr>
<tr>
<td>Combination vs. single type</td>
<td>7</td>
<td>3202</td>
<td>1.42 (1.14–1.76)</td>
</tr>
<tr>
<td>Any NRT vs. control</td>
<td>103</td>
<td>39,503</td>
<td>1.77 (1.66–1.88)</td>
</tr>
</tbody>
</table>


Is it withdrawal or too much NRT?

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Withdrawal</th>
<th>Overdose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety, irritability</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Headache, dizziness</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Nausea, vomiting, abdominal pain</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>sweating, diarrhea</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Salivation</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td>√</td>
<td></td>
</tr>
</tbody>
</table>

NRT Contraindications

- Unstable cardiac condition
- 2 weeks following heart attack
- Unstable angina
- Any unstable cardiac condition
- Pregnancy and breastfeeding ???
- Patients under 18 years old ???

Safety of NRT

- NRT delivers nicotine without the toxins associated with smoking¹
  - Toxins, not nicotine, cause most tobacco-related health concerns¹
  - Tobacco smoke contains >4000 chemicals; at least 50 are carcinogenic²
- In more than 100 clinical trials, including long-term (>5-yr) data,³ NRT has not been associated with increased risk of cancer¹


NRT: Key Messages

- Safe and effective for smoking cessation (esp. in conjunction with a behavioural program).
- Delivers nicotine (more slowly and at lower levels vs. smoking) to nAChR receptors
- NNT vs placebo ~11-19
- Acidic beverages affect absorption
- NO Carbon monoxide, oxidants or >4000 other chemicals and mutagens!
- The use of NRT is not associated with any increase in risk of MI, stroke, cancer or death.

Hubbard R et al. Tobacco Control 2005;14:436-21

Which of the following statements regarding bupropion is/are TRUE?

A. Bupropion’s efficacy at 6 months is equivalent or slightly better than NRT
B. Bupropion’s efficacy at 6 months is less effective than NRT
C. Bupropion’s efficacy at 6 months is superior to nortriptyline
D. Bupropion’s efficacy at 6 months is equivalent to varenicline

Bupropion SR (Zyban®, Wellbutrin®)
- Non-nicotine SR tablet
- Blocks reuptake of dopamine and noradrenaline\(^1,2\)
- Non-competitive inhibition of brain nicotine receptors
- Started 1-2 wks before quit date
  - 150mg once daily x 3 days, then bid for 7 - 12 wks
- Contraindications
  - History of head injury, CNS tumour, seizures
  - Anorexia, bulimia, heavy alcohol use

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Most Frequent Adverse Events With Bupropion

<table>
<thead>
<tr>
<th>Event</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>20-40%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>10%</td>
</tr>
<tr>
<td>Disturbed concentration</td>
<td>9%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9%</td>
</tr>
<tr>
<td>Nausea</td>
<td>9%</td>
</tr>
<tr>
<td>Constipation</td>
<td>8%</td>
</tr>
<tr>
<td>Discontinuations</td>
<td>8%</td>
</tr>
</tbody>
</table>

Nortriptyline
- Tricyclic antidepressant
- Blocks the reuptake of NA and SHT
- Start 1-3 wks before quit date
- 25mg daily and titrate up to 100 mg
- Treat for 12 wks
- As effective as bupropion
- Side effects:
  - Dry mouth, blurred vision, constipation, sedation, confusion, urinary retention

Most Frequent Adverse Events With Nortriptyline

<table>
<thead>
<tr>
<th>Event</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>10%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9%</td>
</tr>
<tr>
<td>Nausea</td>
<td>9%</td>
</tr>
<tr>
<td>Constipation</td>
<td>8%</td>
</tr>
<tr>
<td>Discontinuations</td>
<td>8%</td>
</tr>
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Varenicline (Champix®)
- Partial agonist and antagonist at \(\alpha_4\beta_2\) nAChR
- Health Canada NoC: January 24, 2007
- Start before quit date
- 0.5mg – 1mg bid x 12 weeks
- Though not studied, given the mode of action, there may be limited additional benefit of combo with NRT
- May be more effective than NRT or bupropion?

\(\alpha_4\beta_2\) nAChR Partial Agonists
- \(\alpha_4\beta_2\) nAChR Agonist
- \(\alpha_4\beta_2\) nAChR Partial Agonist
- \(\alpha_4\beta_2\) nAChR Antagonist

Response
- 100%
- 90%
- 80%

Dual action of a partial agonist

4. Cahill et al. Cochrane Database of Systematic Reviews, 2007
Extensive Meta-analysis of RCTs
- 69 trials; n=32,908 pts
- Included studies reporting 6-12 mo abstinence rates for 7 pharmacological therapies

Objectives:
- Summarize the efficacy of approved therapies
- Compare varenicline vs. bupropion
- Indirect comparison of all 7 approved therapies

Nicotine Gum/Patch Efficacy
- With Nicotine Gum or Patch, the odds of abstinence at 6 months or longer is 1.71 or 1.95

Bupropion Efficacy
- Bupropion doubles your odds of abstinence at 6 months or longer

Varenicline Efficacy
- Varenicline more than doubles your odds of abstinence at 6 months or longer

Varenicline vs. Bupropion at 26 wks +
- Though quite rates are small, Varenicline increases the odds of abstinence at 6 months over bupropion

Efficacy of treatments
Adverse Effects

<table>
<thead>
<tr>
<th>Common side effects</th>
<th>Nicotine gum</th>
<th>Nicotine patch</th>
<th>Nicotine inhaler</th>
<th>Bupropion</th>
<th>Varenicline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysgeusia (9%)</td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Nausea (9%)</td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Headache (10%)</td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Jaw pain</td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Dental issues</td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Headache (5%)</td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Site rash</td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Throat irritation (5%)</td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serious side effects</th>
<th>Nicotine gum</th>
<th>Nicotine patch</th>
<th>Nicotine inhaler</th>
<th>Bupropion</th>
<th>Varenicline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures</td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Angioedema</td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Severe allergic</td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>reactions</td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td>+</td>
</tr>
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</table>

Cost/ 3 months
- Nicotine gum: $250 - 400
- Nicotine patch: $280 - 345
- Nicotine inhaler: $500 (6x/d)
- Bupropion: $180 (Nortriptyline = $75)
- Varenicline: $330

Limitations of Current data
- Many patients lost to follow up (high drop out rates 30-45%) at 52 wks
- No head-to-head trials of varenicline vs. NRT
- Limited data for some treatment options
- Need to look at a similar time frame
- Abstinence data >12 months is sparse
- Patient characteristics differ
- Publication bias?
  - No negative studies published
  - 2 studies dominate varenicline data (published multiple times?)

Questions?