Allan Prochazka, M.D., M.Sc.
Asst. Chief, Research
Ambulatory Care
Denver VAMC
Professor of Medicine
University of Colorado School of Medicine

PREOPERATIVE SMOKING CESSATION---TOO RISKY TO QUIT NOW?
Outline

- Case
- Smoking and Postoperative pulmonary complications (POPC)
- Effect of Cessation on POPC’s
- Approaches to enhancing cessation in the preop setting
Typical Case

- 62 yo man, referred for preoperative evaluation prior to partial colectomy next week for localized colon cancer found on screening colonoscopy, CT didn’t reveal mets
- PMH: HTN, mild COPD (FEV1 1.9 L), DJD, Gout
- Social Hx: smokes 20-25 cigs per day, Marlboro, several short quit attempts in the past, relapsed due to ‘stress’, tried OTC nicotine patch for a few days. Last year took varenicline from a friend for two days and it made cigarettes taste bad
- BP 138/76 R 16 O2 Sat 91% RA
- Lungs? Sl hyperresonance at bases
- Cor JVP 4 cm, s1 s2 nl, possible s4, no murmur
- Abd nl bs nontender no h/s megaly no mass palpable
- Ext no c, c, e

- ECG NSR, Axis 30, Intervals nl, borderline voltage for LVH

- In addition to one’s usual preop evaluation, should one recommend that he quit smoking?
Smoking and POPC’s

- Overall, smokers have an elevated rate of POPC (OR 1.26, 95% CI 1.01-1.56)¹
- For abdominal surgery, such as colectomy, the rates of any pulmonary complication are about 20%²
- Rates of serious POPC are relatively low in this age group (e.g. 1.2% for respiratory failure)³
- Smoking within the past year raises the risk of postop pneumonia (OR 1.28, 95% CI 1.17-1.42)⁴

Why Would Smoking Affect POPC Rates?

- Two general categories: short term effects on function and chronic lung disease
- **Short Term Effects** \(^1,^2\)
  - Bronchial inflammation leading to sputum production and retained secretions is common in smokers
  - Ciliary function is impaired by nicotine and other inhaled tobacco products\(^3\)
  - Airway reactivity is increased in many
  - Immune function (alveolar macrophages) is impaired

### Long Term Effects of Smoking

- COPD and ROAD develop in many smokers
- Associated with higher rates of POPC (OR 1.79, 95% CI 1.44-2.22)\(^1\)

### Having surgery itself is associated with higher rates of quitting

- Health and Retirement Survey (n=5498)
  - Had major surgery  20.6/100 py quit
  - Outpatient surgery  10.2/100 py quit
  - Totals about 8% of all successful quits in US

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1. Quaseem, ibid.
2. Shi Y, Warner DO. Anesthesiology 2010;112:102-107
What happens after un-aided cessation?

- Non-respiratory
  - Withdrawal symptoms typically peak in 3-5 days, last at least 2 weeks
  - CO is at baseline in 2-3 days
  - Nicotine metabolized out in 1-2 days

- Respiratory
  - Ciliary function recovers in a few days
  - Sputum production may increase for several weeks post cessation, but then goes away in most by a month \(^1\)
  - Small airways function improves over a period of weeks
  - Large airways function in those who are impaired may improve in younger individuals, stabilizes in those who are older\(^2\)

Since Smoking is so Bad, Why Would Anyone Hesitate to Recommend Preop Quitting?

- Observational studies have raised the concern that there may be an increased rate of POPC in those who quit within a few weeks of elective surgery

- CABG (n=500), 1979-1980, Mayo Clinic, (%POPC)¹
  
<table>
<thead>
<tr>
<th>-duration of quit</th>
<th>POPC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never Quit</td>
<td>47%</td>
</tr>
<tr>
<td>Quit &lt; 2 wks</td>
<td>56%</td>
</tr>
<tr>
<td>Quit 2-4 wks</td>
<td>62%</td>
</tr>
<tr>
<td>Quit 4-8 wks</td>
<td>46%</td>
</tr>
<tr>
<td>Quit &gt; 8 wks</td>
<td>17%</td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>12%</td>
</tr>
</tbody>
</table>

- **CABG pts, N=200, Mayo Clinic, 1986-87, (% POPC)**
  - Current: 33%
  - Quit < 8 wks: 57%
  - Quit > 8 wks: 12%
  - Never Smoked: 12%

- **Non-Cardiac Surgery (n=410), Syracuse VA, 1990-92 (OR of POPC)**
  - Non-smoker: 1.0
  - Reduced < 1 month: 14.2
  - Reduced 2-4 wks: 4.0
  - Reduced 1-2 wks: 4.7
  - Reduced < 1 wk: 10.6

- 288 Pulmonary Surgery pts, 1997-98, (% POPC)¹
  - Current 43%
  - Ex (2-4 wks) 54%
  - Ex (> 4 wks) 35%
  - Never 24%

- 7900 Pulmonary Resections, 1999-2007, (% POPC)²
  - Current 6.9%
  - 14-30 Days 6.2%
  - 30 D-12 Mo 6.4%
  - > 12 Mo 5.8%
  - Never Smoker 2.6%

Bottom Line from Observational Studies

- There appears to be an increase in POPC in those who have quit within a few weeks of surgery
- Quitting 2 months prior seems to result in the lowest rates of POPC
- Caveats:
  - Reports of cessation not validated
  - Definitions of POPC varied (e.g. for the pulmonary surgery cases it included tube drainage for more than 7 days)
  - If a smoker who quits always has more cough and sputum for a few weeks, then is it really a POPC if he/she happened to have surgery in the interim?
What do RCT’s Tell Us?

- Cochrane Systematic Review pulled all the relevant studies¹
  - RCT’s only (n=8)
  - Elective surgery
  - Preop interventions (started at least 48 hr prior) only
  - Smoking cessation outcomes
  - Complication outcomes

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¹ Thomsen T, Villebro N, Moller AM. Interventions for preoperative smoking cessation. Cochrane Database of Systematic Reviews 2010. Issue 7. Art No CD002294
Study Characteristics

- 102 surgical pts, UK¹
  - Intervention: booklet, letter, contact info for cessation program, nurse advice (4 wks prior)
- 117 hernia/lap chole/THA or TKA, Sweden²
  - Intervention: 4 weekly sessions (face to face or phone) plus NRT
- 120 elective THA or TKA, Denmark³
  - Intervention: Weekly meetings 6-8 wks prior with nurse or counselor, NRT
- 210 general surgery pts, Australia
  - Intervention: 1-2 wks prior, computer session, 1 phone call, NRT

- 237 pts, all surgery types, Canada\textsuperscript{1}
  - Intervention: 15 min counseling session 1-3 wks prior, nicotine gum, quit kit, quitline number
- 60 colorectal surgery pts, Denmark\textsuperscript{2}
  - Intervention: 2 wks prior nurse visit, one phone call, one support session, hot line, NRT available
- 244 hernia pts, Denmark\textsuperscript{3}
  - Intervention: advice from nurse, reminder, NRT
- 130 breast cancer patients, Denmark\textsuperscript{4}
  - Intervention: MI based counseling (1 hr visit), NRT

## Cessation at time of Surgery

### 1.1.1 Intensive intervention

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Intervention</th>
<th>Control</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindström 2008</td>
<td>19 Events</td>
<td>54 Total</td>
<td>18.5%</td>
</tr>
<tr>
<td>Moller 2002</td>
<td>36 Events</td>
<td>52 Total</td>
<td>81.5%</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>104</strong> Events</td>
<td><strong>106</strong> Total</td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

- Total events: 55
- Heterogeneity: $\chi^2 = 0.73, df = 1 (P = 0.39); I^2 = 0$
- Test for overall effect: $Z = 5.41 (P < 0.00001)$

### 1.1.2 Brief intervention

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Intervention</th>
<th>Control</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrews 2006</td>
<td>18 Events</td>
<td>51 Total</td>
<td>5.5%</td>
</tr>
<tr>
<td>Ratner 2004</td>
<td>81 Events</td>
<td>120 Total</td>
<td>42.2%</td>
</tr>
<tr>
<td>Sorensen 2007</td>
<td>23 Events</td>
<td>48 Total</td>
<td>5.6%</td>
</tr>
<tr>
<td>Thomsen 2009</td>
<td>16 Events</td>
<td>62 Total</td>
<td>4.7%</td>
</tr>
<tr>
<td>Wolfenden 2005</td>
<td>92 Events</td>
<td>79 Total</td>
<td>42.1%</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>445</strong> Events</td>
<td><strong>360</strong> Total</td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

- Total events: 230
- Heterogeneity: $\chi^2 = 6.51, df = 4 (P = 0.16); I^2 = 39$
- Test for overall effect: $Z = 4.89 (P < 0.00001)$
12 Month Cessation Rates

### 1.2.1 Intensive intervention

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Intervention</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moller 2002</td>
<td>13</td>
<td>56</td>
<td>5.5%</td>
<td>6.04 [1.43, 25.48] 2002</td>
</tr>
<tr>
<td>Lindström 2008</td>
<td>18</td>
<td>48</td>
<td>22.6%</td>
<td>2.21 [1.10, 4.44] 2008</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>104</td>
<td>105</td>
<td>28.0%</td>
<td>2.96 [1.57, 5.55]</td>
</tr>
</tbody>
</table>

Total events: 31 vs. 11
Heterogeneity: Chi² = 1.61, df = 1 (P = 0.20); I² = 38%
Test for overall effect: Z = 3.37 (P = 0.0008)

### 1.2.2 Brief intervention

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Intervention</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratier 2004</td>
<td>22</td>
<td>111</td>
<td>59.1%</td>
<td>1.01 [0.60, 1.70] 2004</td>
</tr>
<tr>
<td>Thomsen 2009</td>
<td>7</td>
<td>58</td>
<td>12.9%</td>
<td>1.47 [0.50, 4.38] 2009</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>169</td>
<td>178</td>
<td>72.0%</td>
<td>1.09 [0.68, 1.75]</td>
</tr>
</tbody>
</table>

Total events: 29 vs. 26
Heterogeneity: Chi² = 0.38, df = 1 (P = 0.54); I² = 0%
Test for overall effect: Z = 0.36 (P = 0.72)

Total (95% CI): 273 vs. 283
100.0%      | 1.61 [1.12, 2.33] |

Total events: 60 vs. 39
Heterogeneity: Chi² = 7.13, df = 3 (P = 0.07); I² = 58%
Test for overall effect: Z = 2.55 (P = 0.01)
## Rate of Any Post Op Complication

### 2.1.1 Intensive intervention

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Total Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Møller 2002</td>
<td>10</td>
<td>56</td>
<td>27</td>
<td>52</td>
<td>27.2%</td>
<td>0.34 [0.19, 0.64]</td>
<td>2002</td>
</tr>
<tr>
<td>Lindström 2008</td>
<td>10</td>
<td>48</td>
<td>22</td>
<td>54</td>
<td>20.1%</td>
<td>0.51 [0.27, 0.97]</td>
<td>2008</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>104</strong></td>
<td><strong>106</strong></td>
<td></td>
<td></td>
<td>47.4%</td>
<td><strong>0.42 [0.27, 0.65]</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Total events**

- Treatment: 20
- Control: 49

Heterogeneity:
- $\chi^2 = 0.76$, df = 1 (P = 0.38); $I^2 = 0$

Test for overall effect: $Z = 3.89$ (P < 0.0001)

### 2.1.2 Brief intervention

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Total Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorensen 2003</td>
<td>11</td>
<td>27</td>
<td>13</td>
<td>30</td>
<td>12.0%</td>
<td>0.94 [0.51, 1.73]</td>
<td>2003</td>
</tr>
<tr>
<td>Sorensen 2007</td>
<td>6</td>
<td>101</td>
<td>4</td>
<td>48</td>
<td>5.3%</td>
<td>0.71 [0.21, 2.41]</td>
<td>2007</td>
</tr>
<tr>
<td>Thomsen 2009</td>
<td>35</td>
<td>57</td>
<td>38</td>
<td>62</td>
<td>35.4%</td>
<td>1.00 [0.75, 1.33]</td>
<td>2009</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>185</strong></td>
<td><strong>140</strong></td>
<td></td>
<td></td>
<td>52.6%</td>
<td><strong>0.96 [0.74, 1.25]</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Total events**

- Treatment: 52
- Control: 55

Heterogeneity:
- $\chi^2 = 0.32$, df = 2 (P = 0.85); $I^2 = 0$

Test for overall effect: $Z = 0.31$ (P = 0.75)

**Total (95% CI)**

<table>
<thead>
<tr>
<th>Treatment Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>289</td>
<td>246</td>
<td>100.0%</td>
<td>0.70 [0.56, 0.88]</td>
</tr>
</tbody>
</table>

**Total events**

- Treatment: 72
- Control: 104

Heterogeneity:
- $\chi^2 = 12.90$, df = 4 (P = 0.01); $I^2 = 69$

Test for overall effect: $Z = 3.05$ (P = 0.002)
## Wound Complications

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Treatment Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Year</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2.2.1 Intensive intervention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moller 2002</td>
<td>3</td>
<td>56</td>
<td>16</td>
<td>52</td>
<td>23.8%</td>
<td>0.17 [0.05, 0.56]</td>
<td>2002</td>
<td></td>
</tr>
<tr>
<td>Lindström 2008</td>
<td>6</td>
<td>48</td>
<td>14</td>
<td>54</td>
<td>18.9%</td>
<td>0.48 [0.20, 1.16]</td>
<td>2008</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>9</td>
<td>104</td>
<td>14</td>
<td>106</td>
<td>42.8%</td>
<td>0.31 [0.16, 0.62]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>9</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 1.91, df = 1 (P = 0.17); I² = 48%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Test for overall effect: Z = 3.34 (P = 0.0009)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**2.2.2 Brief intervention**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Treatment Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Year</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorensen 2003</td>
<td>9</td>
<td>27</td>
<td>8</td>
<td>30</td>
<td>10.9%</td>
<td>1.25 [0.56, 2.78]</td>
<td>2003</td>
<td></td>
</tr>
<tr>
<td>Sorensen 2007</td>
<td>6</td>
<td>101</td>
<td>4</td>
<td>48</td>
<td>7.8%</td>
<td>0.71 [0.21, 2.41]</td>
<td>2007</td>
<td></td>
</tr>
<tr>
<td>Thomsen 2009</td>
<td>25</td>
<td>57</td>
<td>28</td>
<td>62</td>
<td>38.5%</td>
<td>0.97 [0.65, 1.45]</td>
<td>2009</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>185</td>
<td>140</td>
<td>78</td>
<td>140</td>
<td>57.2%</td>
<td>0.99 [0.70, 1.40]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>40</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.62, df = 2 (P = 0.73); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Test for overall effect: Z = 0.06 (P = 0.95)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**

<table>
<thead>
<tr>
<th>Treatment Events</th>
<th>Treatment Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Year</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>289</td>
<td>246</td>
<td>100.0%</td>
<td></td>
<td></td>
<td>0.70 [0.51, 0.95]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>49</td>
<td>70</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 10.69, df = 4 (P = 0.03); I² = 63%
Test for overall effect: Z = 2.29 (P = 0.02)
## Pulmonary Complications

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moller</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Sorensen 2003</td>
<td>11%</td>
<td>16%</td>
</tr>
<tr>
<td>Lindstrom</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Thomsen</td>
<td>30%</td>
<td>34%</td>
</tr>
</tbody>
</table>

N.B. No serious pulmonary complications were seen in any study.
Conclusions from RCT’s

- No study showed any difference in pulmonary complications (albeit small samples)
- Low intensity interventions don’t have a lot of impact on quitting or on complications
- Higher intensity interventions lead to significant quit rates both short and long term
- Effective cessation is associated with reduction in overall postop complication rates and in fewer wound complications
So, I’ve decided to Encourage Cessation, now what?

A’s approach is quite applicable in this setting:

- **Ask**: make sure that one always asks about smoking status
- **Advise**: take advantage of the teachable moment (i.e. upcoming surgery) to provide personalized advice

  - ‘You’re going to have colon surgery next week. You won’t be able to smoke in the hospital. Since you’re going to have to ‘fast’ from smoking anyway, you should think about taking advantage of this to work on quitting for the long run. Your chance of wound complications is a lot less if you can quit now. We have a lot of ways we can help you to quit and to help control any withdrawal symptoms’

2. Shi Y, Waner DO. Anesthesiology 2010;112:102-107
Assess
- Has the person thought about long term quitting? If yes, this is a great time to do it. If no, remind about potential benefits

Assist
- Behavioral
- Pharmacological

Arrange
- Behavioral support (e.g. quitline)
- Postop f/u reinforcement at the surgical f/u
- Postop f/u by PCP or if available cessation team
Behavioral Interventions

- Key element is time with patient and empathic counselor
- More time, more benefit
- Key question is whether one can duplicate the intensive interventions in one’s setting

- Practical Actions
  - Set a quit date, at a minimum ‘fasting’ for 12 hours prior to surgery
  - Tell family, friends, coworkers
  - Make the home smoke free, start acting like a non-smoker
  - Identify barriers to cessation
  - Remove tobacco products from environment

- Ideally the entire team should reinforce cessation at every contact
  - Outpatient physician
  - Anesthesia staff
  - Surgical nurses
  - Surgeon
Simple Behavioral Interventions

- Review prior quit attempts, learn from them
- Anticipate triggers and challenges
- Encourage others in the home to quit
- Provide a supportive clinical environment (e.g. ‘We can help you if you are having problems’)
- Provide options
  - Referral—not always available
  - Quitlines are proven to increase success rates, available in most states
- Self-help materials


Lichtenstein E, et al. Amer Psychol 2010;65:252-261
I want to quit, but....

- Identify the barriers
  - Fear of weight gain
    - Less of a problem in the short run in surgical pts
  - Worry about urges
    - Reinforce that meds can help
  - Too much stress, etc.

- Give tailored information about benefits of quitting, risks of smoking, availability of treatment
  - E.g. ‘We can use medication to take the edge off urges during the weeks after quitting’.
Nicotine Replacement Therapy

- Gum
- Patch
- Lozenge
- Inhaler
- Nasal Nicotine

Has been used in several of the randomized trials of preop cessation, and although the numbers are small no indication of increased complications, either wound or cardiovascular

However a recent APACHE matched obs study of CABG pt’s (n=134) found that 4.5% in NRT died vs 0% in no NRT

NRT

- Overall success rate comparable among the products
  - Odds ratios for quitting: Patch 1.66; Gum 1.43; Lozenge 2.00; Inhaler 1.90; Nasal Spray 2.02
- Doubles the quit rate
  - (e.g. 5-8% to 10-15%) compared to advice
  - (e.g. 10% to 17%) compared to placebo, overall odds ratio 1.58 (based on 40,000 patients studied, 132 trials)
    - L Stead et al, NRT for Smoking Cessation, Cochrane Review, 2008
- Selection based on side effects, patient preference, insurance coverage
- PDR duration of therapy 8-12 weeks
- Selected patients need longer therapy or higher doses
Nicotine Gum

- 2 forms (2 mg and 4 mg), 4 mg best for most smokers
- Available OTC and in generic forms and in various flavors
- Absorption is buccal, so park and chew
- Regular dosing better than ad lib
- Typical patient will use 5-8 pieces per day
- Retail cost $35-50 for 108 pieces
- Side Effects
  - Dental trauma, jaw pain, nausea, upset stomach
- Duration of Use
  - 8-12 weeks
  - 2-5% have trouble quitting gum
  - Long term use combined with behavioral therapy (up to 5 years) safe and effective, 25% validated quit rate in Lung Health Study
Transdermal Nicotine

- 3 strengths (21, 14, 7 mg/24 hr)
- Some patients require higher doses (e.g. very heavy smokers), but for typical pack a day smoker 21mg is the starting dose
- 4-6 weeks on 21 mg, 2-4 weeks on 14 mg, then 2-4 weeks on 7 mg
- Costs $35-50 per 14 day supply

Side Effects
- Skin irritation (30%)
- Skin allergy (1-4%)
- Poor sleep/nightmares (10%)
- Arm pain (2-4%)
Nicotine Lozenge

- Available OTC, 2 mg and 4 mg
- Allow lozenge to slowly dissolve, no chewing or swallowing of the lozenge—need to be careful not to develop too much saliva
- 20-30 minutes per lozenge
- Dose 20 max per day
- Side effects: hiccups, nausea, stomach upset, palpitations
- Cost $30-40.00 for box of 72 lozenges
Nasal Nicotine Spray

- Very rapid absorption of nicotine
- Dosing 0.5 mg per spray, one spray in each nostril is one dose (about the amount of nicotine in one cigarette)
- Typical patient uses 3-6 doses per day
- Side Effects: mostly irritation, face pain, perhaps more likely to result in difficulty stopping use due to fast absorption
- Costs $46.99 per 10 ml vial (100 doses)
Nicotine Inhaler

- Each cartridge 10 mg nicotine, 4 mg released, 2 mg absorbed
- Best with continuous puffing (80 deep inhalations over 20 minutes give 2 mg nicotine, about the same as one cigarette)
- Dosage 6-16 cartridges per day
- Side Effects: mouth/nose irritation
- Costs up to $160 per 168 cartridges (about 2-4 weeks’ supply)
High Dose NRT

- Not FDA approved, but has been tested in many trials (however, not in the perioperative setting)
- Higher dose patches—not better when given as a routine for all smokers, best to titrate by intake/level of dependence
  - Useful for the very heavy smoker
  - Safety in trials and practice has been good
- Nicotine patch+nicotine gum or lozenge
  - Higher quit rate than either alone
  - Allows for steady level with ad lib gum
- Cochrane review (6 trials of high dose or combo therapy) odds ratio for quitting 1.21 (95% CI 1.03-1.42) compared to monotherapy
- Primary care trial found that cessation rate with patch/lozenge was 27% at 6 months compared to 18% with patch alone
- Main limitation is the cost of the therapy
- In the pt who has cut down recently, should generally dose based on their long term use level
How to handle NRT in the Postop Setting

- Ad lib meds with frequent dosing (e.g. gum, lozenge, inhaler, nasal spray) don’t work well in a hospital environment
- Nicotine patch is the simplest from a dosing/nursing perspective
- When person goes home, can switch to the mode of delivery that fits best for the patient

Allan’s Opinion, Virtually no data
Antidepressants

- Bupropion (Zyban)
- Antidepressant, works in normal, non-depressed smokers
- Relatively slow onset of action (7-10 days)
- Dosage: 150 mg a day for 3 days, then 150 mg bid, but not much difference in effectiveness between 150 and 300 mg /day
- Duration: 3 months, but longer term therapy is safe and effective
- Minimal cardiovascular effects when given alone
$70/month for generic long acting bupropion

Side Effects
- Common
  - Shaky, tremor
  - Headache
  - Dry mouth
- Rare but serious
  - Seizures
- Avoid in those with epilepsy, active drug use, concomitant psychiatric medications, bulimia, MAOI use
- Rare, not a large problem
  - Worsened HTN when combined with NRT
  - Allergic reactions (hives, angioedema)
Bupropion Efficacy

- Overall odds ratio for cessation 1.94 (95% CI 1.72 to 2.19) based on 19 trials
  - Hughes JR et al, Cochrane Review 2007
- Combination Therapy (patch+oral inhaler+bupropion) can work well with quit rates at 26 weeks 35% compared to 19% with patch alone and acceptable side effects
- Combined with lozenge, 30% 6 month quit rate
- Less weight gain than with patch
- Only 1 trial in periop setting, 47 pts randomized to bupropion or placebo, 20 followed to surgery¹
  - Some reduction in CO
  - Very few quit
  - No difference in complications

Bupropion Summary

- **Very useful**
  - Healthy populations (e.g. worksite)
  - Active cardiac disease
- **Harder to use**
  - Psychiatric comorbidity
  - Substance Abuse
- **Probably ok in the periop setting, but need to start it several days in advance**
- **Bottom Line:** very useful agent overall, limited info on use perioperatively, main issue is caution with regard to seizure risk
Varenicline

- First designer drug for tobacco dependence\(^1\)
- A derivative of cytisine, derived from the golden rain tree
- Hasn’t really been a clinical reason to know about central nicotine receptors before this, but interactions with the $\alpha_4\beta_2$ receptor are the main mechanism of action
- Acts as a partial agonist causing dopamine release, also is an antagonist and blocks the binding of exogenous nicotine

Varenicline Cessation Efficacy at 24 Wks

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Treatment Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonzales 2006</td>
<td>77</td>
<td>352</td>
<td>29</td>
<td>344</td>
<td>2.59 [1.74, 3.87]</td>
<td></td>
</tr>
<tr>
<td>Jorenby 2006</td>
<td>73</td>
<td>344</td>
<td>35</td>
<td>341</td>
<td>2.24 [1.55, 3.24]</td>
<td></td>
</tr>
<tr>
<td>Nakamura 2007</td>
<td>56</td>
<td>155</td>
<td>35</td>
<td>154</td>
<td>1.59 [1.11, 2.28]</td>
<td></td>
</tr>
<tr>
<td>Nides 2006</td>
<td>13</td>
<td>127</td>
<td>6</td>
<td>127</td>
<td>3.00 [1.23, 7.31]</td>
<td></td>
</tr>
<tr>
<td>Oncken 2006</td>
<td>58</td>
<td>259</td>
<td>5</td>
<td>129</td>
<td>5.78 [2.38, 14.05]</td>
<td></td>
</tr>
<tr>
<td>Tsai 2007</td>
<td>53</td>
<td>126</td>
<td>27</td>
<td>124</td>
<td>2.15 [1.47, 3.15]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 1363 | 1219 | 100.0% | 2.33 [1.95, 2.80]

Total events 347 | 137

Heterogeneity: Chi² = 9.21, df = 5 (P = 0.10); I² = 48%

Test for overall effect: Z = 9.12 (P < 0.00001)

<table>
<thead>
<tr>
<th>Table 4. Treatment-Emergent Adverse Events (Including Those Not Necessarily Related to Study Drug)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. (%)</strong></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Dry mouth</td>
</tr>
<tr>
<td>Flatulence</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
</tr>
<tr>
<td>Insomnia</td>
</tr>
<tr>
<td>Abnormal dreams†</td>
</tr>
<tr>
<td>Irritability</td>
</tr>
<tr>
<td>Sleep disorder</td>
</tr>
<tr>
<td>Neurological disorders</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
</tr>
<tr>
<td><strong>Study Drug Treatment Discontinuations Due to Adverse Events‡</strong></td>
</tr>
<tr>
<td>All causes</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
</tbody>
</table>

Abbreviation: bupropion SR, sustained-release bupropion.

* Treatment-emergent adverse events were defined as adverse events that began or increased in severity during study drug treatment or up to 7 days after the last dose. Reported events occurred at ≥5% or more for varenicline and at a higher frequency than reported for placebo.

†Self-described as any change in dreaming, such as vivid dreams or increased frequency of dreaming.

‡Includes participants who discontinued study drug treatment but remained in the study, as well as those who discontinued the overall study.

Varenicline in CVD Pts

- 714 smokers, stable CVD (hx MI, Revasc, Angina, PVD, Cerebrovascular)
- Excluded recent procedure or unstable CAD, uncontrolled HTN, severe CHF, severe COPD, liver, GI, Diabetes (A1c >9), psych or recent psych tx, drug use

Rigotti, N. A. et al. Circulation 2010;121:221-229
<table>
<thead>
<tr>
<th>Event</th>
<th>Varenicline (n=353), n (%)</th>
<th>Placebo (n=350), n (%)</th>
<th>Difference Between Groups, %</th>
<th>95% CI for Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adjudicated cardiovascular event†</td>
<td>25 (7.1)</td>
<td>20 (5.7)</td>
<td>1.4</td>
<td>-2.3–5.0</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>7 (2.0)</td>
<td>3 (0.9)</td>
<td>1.1</td>
<td>-0.6–2.9</td>
</tr>
<tr>
<td>Need for coronary revascularization</td>
<td>8 (2.3)</td>
<td>3 (0.9)</td>
<td>1.4</td>
<td>-0.4–3.2</td>
</tr>
<tr>
<td>Hospitalization for angina pectoris</td>
<td>8 (2.3)</td>
<td>8 (2.3)</td>
<td>-0.02</td>
<td>-2.2–2.2</td>
</tr>
<tr>
<td>Hospitalization for congestive heart failure</td>
<td>0 (0.0)</td>
<td>2 (0.6)</td>
<td>-0.6</td>
<td>-1.5–0.3</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>2 (0.6)</td>
<td>1 (0.3)</td>
<td>0.3</td>
<td>-0.7–1.2</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>-0.0</td>
<td>-0.8–0.8</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New diagnosis or admission for a procedure to treat peripheral vascular disease</td>
<td>5 (1.4)</td>
<td>3 (0.9)</td>
<td>0.6</td>
<td>-1.0–2.1</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All causes</td>
<td>2 (0.6)</td>
<td>5 (1.4)</td>
<td>-0.8</td>
<td>-2.3–0.6</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>1 (0.3)</td>
<td>2 (0.6)</td>
<td>-0.3</td>
<td>-1.3–0.7</td>
</tr>
<tr>
<td>Noncardiovascular death</td>
<td>1 (0.3)</td>
<td>3 (0.9)</td>
<td>-0.6</td>
<td>-1.7–0.5</td>
</tr>
<tr>
<td>Event</td>
<td>Varenicline (n=353, n (%)</td>
<td>Placebo (n=350, n (%))</td>
<td>Difference Between Groups, %</td>
<td>95% CI for Difference</td>
</tr>
<tr>
<td>-----------------------------------------------------------------------</td>
<td>---------------------------</td>
<td>------------------------</td>
<td>------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Total AEs†</td>
<td>949</td>
<td>656</td>
<td>16.7</td>
<td>10.3–23.2</td>
</tr>
<tr>
<td>Participants with ≥1 AE</td>
<td>288 (81.6)</td>
<td>227 (64.9)</td>
<td>16.7</td>
<td>10.3–23.2</td>
</tr>
<tr>
<td>Participants who stopped drug because of AE</td>
<td>34 (9.6)</td>
<td>15 (4.3)</td>
<td>5.3</td>
<td>1.6–9.1</td>
</tr>
<tr>
<td>Participants with ≥1 serious AE</td>
<td>23 (6.5)</td>
<td>21 (6.0)</td>
<td>0.5</td>
<td>−3.1–4.1</td>
</tr>
<tr>
<td>Deaths (all causes)</td>
<td>2 (0.6)</td>
<td>5 (1.4)</td>
<td>−0.8</td>
<td>−2.3–0.6</td>
</tr>
<tr>
<td>Most common AEs‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>104 (29.5)</td>
<td>30 (8.6)</td>
<td>20.9</td>
<td>15.3–26.5</td>
</tr>
<tr>
<td>Headache</td>
<td>45 (12.7)</td>
<td>39 (11.1)</td>
<td>1.6</td>
<td>−3.2–6.4</td>
</tr>
<tr>
<td>Insomnia</td>
<td>42 (11.9)</td>
<td>23 (6.6)</td>
<td>5.3</td>
<td>1.1–9.6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>29 (8.2)</td>
<td>4 (1.1)</td>
<td>7.1</td>
<td>4.0–10.1</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>26 (7.9)</td>
<td>6 (1.7)</td>
<td>6.2</td>
<td>3.1–9.4</td>
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<tr>
<td>Fatigue</td>
<td>25 (7.1)</td>
<td>14 (4.0)</td>
<td>3.1</td>
<td>−0.3–6.5</td>
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<tr>
<td>Nasopharyngitis</td>
<td>23 (6.5)</td>
<td>30 (8.6)</td>
<td>−2.1</td>
<td>−6.0–1.8</td>
</tr>
<tr>
<td>Constipation</td>
<td>23 (6.5)</td>
<td>7 (2.0)</td>
<td>4.5</td>
<td>1.6–7.5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22 (6.2)</td>
<td>18 (5.1)</td>
<td>1.1</td>
<td>−2.3–4.5</td>
</tr>
<tr>
<td>Dizziness</td>
<td>22 (6.2)</td>
<td>16 (4.6)</td>
<td>1.7</td>
<td>−1.7–5.0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>19 (5.4)</td>
<td>12 (3.4)</td>
<td>2.0</td>
<td>−1.1–5.0</td>
</tr>
<tr>
<td>Psychiatric AEs†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep disorders or disturbances (abnormal dreams, insomnia, nightmare, sleep disorder)</td>
<td>78 (22.1)</td>
<td>34 (9.7)</td>
<td>12.4</td>
<td>7.1–17.7</td>
</tr>
<tr>
<td>Anxiety disorders or symptoms (anxiety, generalized anxiety disorder, neurosis, phobia, stress)</td>
<td>12 (3.4)</td>
<td>16 (4.6)</td>
<td>−1.2</td>
<td>−4.1–1.7</td>
</tr>
<tr>
<td>Depressed mood disorders or disturbances (depression, depressed mood, depressive symptom, dysthymia)</td>
<td>11 (3.1)</td>
<td>8 (2.3)</td>
<td>0.8</td>
<td>−1.6–3.2</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>1 (0.3)</td>
<td>0 (0)</td>
<td>0.3</td>
<td>−0.4–1.0</td>
</tr>
<tr>
<td>Other mood disorders or disturbances (apathy, listlessness, dysphoria, mood alteration, mood swings, emotional disorder)</td>
<td>9 (2.5)</td>
<td>3 (0.9)</td>
<td>1.7</td>
<td>−0.2–3.6</td>
</tr>
</tbody>
</table>

(Continued)
Varenicline

- Varenicline effective compared to placebo with at least a doubling of the quit rate OR 2.33 (95% CI 1.95-2.88)
  - Cahill C. Cochrane Review, 2008
- Moderately (OR 1.52, 95% CI 1.22-1.88) better quit rate than bupropion SA
- Perhaps better than NRT (OR 1.33 (1.01-1.71), but few trials
- Nausea was the most predominant side effect
- Rate of drug discontinuation was relatively low
- Probably safe in CVD pts
Psychiatric Morbidity with Varenicline

- In approval RCT’s 2 cases of psychosis
- Numerous case reports since approval
  - Worsening of schizophrenia 5 days after starting varenicline in patient who was stable on low dose neuroleptic
  - Mania requiring hospitalization 1 week after starting varenicline in a bipolar patient who was stable on valproate
    - Am J Psych 2007;164:1269-1270
- UK 2682 pts in general practice
  - 2 cases of attempted suicide
  - Mood change/depression 1.7%
  - Anxiety 1.2%
- VA PBM July 2009, 149 cases of suicidal behaviors out of approximately 100,000 patients treated
  - VA Bulletin, July 2, 2009
### UK Surveillance

#### Varenicline Bupropion

<table>
<thead>
<tr>
<th></th>
<th>Varenicline</th>
<th>Bupropion#</th>
<th>Nicotine</th>
<th>Control*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Market Share</td>
<td>13%</td>
<td>7%</td>
<td>77%</td>
<td>n/a</td>
</tr>
<tr>
<td>Suicides</td>
<td>22</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Attempts</td>
<td>46</td>
<td>6</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ideation</td>
<td>377</td>
<td>104</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Agression</td>
<td>172</td>
<td>131</td>
<td>8</td>
<td>22</td>
</tr>
</tbody>
</table>


# all indications

* Amoxicillin
FDA Black Box on Bupropion and Varenicline

- July 2009
  - Watch for changes in behavior, hostility, agitation, depressed mood, suicidal thinking and behavior
  - Stop the meds if above occur and monitor until resolved
  - Rates of suicide and depression are low (less than 1/1000), but warrants caution with both drugs in patients with psychiatric disorders and also means that both should be prescribed only with adequate followup
Varenicline’s Place in Therapy

- Expensive ($370 for 168 1 mg tabs, enough for 12 weeks)
- No data on use in perioperative setting
- Probably best to save for those who have failed first line therapies
- VA Guidelines
  - Second line agent
  - Avoid in patients with psychiatric disorders unless working collaboratively with mental health provider
  - Monitor after starting therapy on regular basis
Back to the Case

- Do I want to/can I take advantage of the ‘teachable moment’?
- Can I implement a preop cessation plan in my setting or should I focus on the postop followup?
- Is the patient willing to do more than a ‘fast’?
Back to the Case

- Advise to quit with a goal of long term quitting, at a minimum a ‘fast’, provide contact info for quitline
  - If available, reinforce with additional counseling by ancillary staff

- Assist: Provide NRT
  - Prior to surgery patch plus lozenge works well in most
  - Hold lozenge/patch the night before
  - Resume patch in hospital when stable
  - Restart patch/lozenge after d/c

- Arrange:
  - Ask surgeon to reinforce quitting at post op visit
  - If possible, have a followup call or visit after d/c from hospital
  - Continue ongoing NRT with an appropriate duration (8-12 weeks)