Pharmacotherapy for Smokeless Tobacco Use

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Disclosures

- Research has been supported by:
  - National Cancer Institute
  - Mayo Clinic College of Medicine
  - Pfizer
    - Varenicline supplied for drug trial

- Opinions expressed do not necessarily reflect the official views of the funding institutions

- **Off-Label Use:** Varenicline, bupropion, NRT not approved for the treatment of ST use
Goals & Objectives

• Provide a brief overview of smokeless tobacco (ST)

• Review what we know about the pharmacologic treatment of ST use
  • Nicotine replacement therapy (NRT)
    • Patch/Gum/Lozenge
  • Bupropion SR
  • Varenicline
Smokeless Tobacco: United States

- **Chewing tobacco**
  - Loose leaf (i.e., Redman)
  - Plugs
  - Twists

- **Snuff**
  - Moist (Copenhagen, Skoal)
  - Dry (Honest, Honey bee, Navy, Square)
Scandinavian Snus
Pan Masala (Betel quid)

Handmade

Manufactured
A street vendor in Mumbai makes paan, a South Asian chewing tobacco product made from the leaf of the Betel tree packed with a lime paste and spices, decorated with coconut shavings and cherries on top. McT
Toombak

Toombak wholesale advertisement
RJ Reynolds's
Phillip Morris (Altria)
Tobacco-less Nicotine Product - Altria

“VERVE discs are a new kind of tobacco product designed to appeal to adult smokers interested in innovative types of spit-free tobacco product alternatives to cigarettes. Adult tobacco product consumers put the product in their mouth, chew on it and should properly dispose of it when they are done.”

Package of 16 discs, each containing about 1.5 milligrams of nicotine = $3

Virginia test market
Tobacco-Related Oral Disease
## Health Effects: Cancers - U.S. Data

<table>
<thead>
<tr>
<th>Location</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer, Mouth and Gum</td>
<td>11.2 (4.1-30.7)A</td>
</tr>
<tr>
<td>Gum &amp; Buccal Mucosa</td>
<td>4.2 (2.6-6.7)B</td>
</tr>
<tr>
<td>Larynx</td>
<td>7.3 (2.9-18.3)A</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>5.3 (1.2-23.4)A</td>
</tr>
<tr>
<td>Kidney cancer</td>
<td>4.0 (1.2-12.9)C</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>3.5 (1.1-11)D</td>
</tr>
</tbody>
</table>

ST Health Effects: CV Disease

• CPS-II

  • *Current ST use vs. never associated with death from:

    • **All causes**: HR 1.18 (95% CI: 1.08-1.29)
    
    • **CHD**: HR 1.26 (95% CI: 1.08-1.47)
    
    • **Cerebrovascular dz**: HR 1.40 (95% CI: 1.10-1.79)
    
  • No difference between snuff and chewing tobacco

  *Multivariate-adjusted

What do we know about ST treatment?
USPHS Guideline Recommendations

- **First-Line**
  - Nicotine Replacement Therapy
    - Gum
    - Patch
    - Inhaler
    - Nasal Spray
    - Lozenge
  - Non-NRT
    - Bupropion SR
    - Varenicline
USPHS Guideline Recommendations

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Nicotine Gum (2 mg)

- 210 ST users
  - Group Tx + 2 mg gum
  - Group Tx + placebo
  - Min. contact + 2 mg gum
  - Min. contact + placebo
- 2 mg gum: 8 weeks

- Groups involving group therapy or placebo were equally effective and superior to minimal contact + 2 mg group
- Withdrawal symptoms were reduced

Nicotine Patch

- 402 ST users
  - Active Patch + Mint Snuff
  - Active Patch + Ø Snuff
  - Placebo Patch + Mint Snuff
  - Placebo Patch + Ø Snuff

- Patch: 21 mg x 6 weeks; 14 mg x 2 weeks; 7 mg x 2 weeks

- Nicotine patch increased continuous abstinence rates compared to placebo at 10 weeks but not at 23 weeks

- Nicotine patch decreased craving and withdrawal
  - But so did the mint snuff

Bupropion SR for ST Users Study

- NCI R01 9088

- Randomized 225 ST users to:
  - Bupropion SR (N = 113)
    - 150 mg twice daily x 12 weeks
  - Placebo (N = 112)

7-Day Point Prevalence Abstinence


![Graph showing 7-Day Point Prevalence Abstinence with two lines representing Bupropion (yellow dots) and Placebo (red squares). The graph includes a legend indicating the distinction between the two treatments and a timeline indicating the start and end of medication (TQD) and weeks.]
Desire (Craving) to Use Tobacco


*P ≤ 0.05 comparing groups
Weight Change During Medication Phase


![Graph showing weight change during medication phase](image)

- Bupropion
- Placebo

*P ≤ 0.05 bupropion compared to placebo
Nicotine Lozenge for ST Users

- NCI RO1 CA121165
- 270 ST users
- Randomized to:
  - Placebo
  - 4-mg nicotine lozenge
Self-reported 7-day point prevalence abstinence with 4-mg nicotine lozenges

<table>
<thead>
<tr>
<th></th>
<th>4 mg nicotine lozenge (N=136)</th>
<th>Placebo (N=134)</th>
<th>Logistic Regression Results†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstinence Definition*</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>OR</td>
</tr>
<tr>
<td><strong>Week 12 (end-of-medication)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Point Prevalence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smokeless tobacco abstinence</td>
<td>69   50.7</td>
<td>46  34.3</td>
<td>2.0</td>
</tr>
<tr>
<td>All tobacco abstinence</td>
<td>60   44.1</td>
<td>39  29.1</td>
<td>1.9</td>
</tr>
<tr>
<td>Prolonged</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smokeless tobacco abstinence</td>
<td>65   47.8</td>
<td>41  30.6</td>
<td>2.1</td>
</tr>
<tr>
<td><strong>Week 24</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Point Prevalence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smokeless tobacco abstinence</td>
<td>43   31.6</td>
<td>35  26.1</td>
<td>1.3</td>
</tr>
<tr>
<td>All tobacco abstinence</td>
<td>36   26.5</td>
<td>29  21.6</td>
<td>1.3</td>
</tr>
<tr>
<td>Prolonged</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smokeless tobacco abstinence</td>
<td>41   30.2</td>
<td>31  23.1</td>
<td>1.4</td>
</tr>
</tbody>
</table>

*Abstinence is based upon self-reported 7-day point prevalence defined as no use within the past 7 days. In all cases, subjects that missed a visit were assumed to be using tobacco.
† In addition to treatment (nicotine vs. placebo) the logistic regression analysis included a covariate for study site. Odds ratios > 1.0 indicate an increased likelihood of abstinence for active nicotine lozenge compared to placebo.
Mean Composite Withdrawal

4-mg nicotine lozenge vs. placebo (treatment effect = -0.213, SE=0.071; p=0.003).
Mean Craving

4-mg nicotine lozenge vs. placebo (treatment effect = -0.452, SE=0.164; p=0.006)
Pharmacotherapy may decrease craving & withdrawal among ST users trying to achieve ST abstinence

but....

What’s the overall effect of pharmacotherapy on long-term (≥ 6 months) abstinence rates?
Long-term (abstinence (>= 6 months) for ST Users
Bupropion: Effect at ≥ 6 months

NRT: Effect at ≥ 6 months

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Nicotine replacement</th>
<th>Placebo</th>
<th>Odds Ratio</th>
<th>Weight</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Nicotine Patch</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ebbert 2007</td>
<td>2/10</td>
<td>2/11</td>
<td></td>
<td>1.0 %</td>
<td>1.13 [0.13, 9.94]</td>
</tr>
<tr>
<td>Hatsukami 2000</td>
<td>62/201</td>
<td>49/201</td>
<td></td>
<td>23.0 %</td>
<td>1.38 [0.89, 2.15]</td>
</tr>
<tr>
<td>Howard-Pitney 1999</td>
<td>78/206</td>
<td>69/204</td>
<td></td>
<td>29.3 %</td>
<td>1.19 [0.80, 1.79]</td>
</tr>
<tr>
<td>Stotts 2003</td>
<td>6/98</td>
<td>13/100</td>
<td></td>
<td>8.2 %</td>
<td>0.44 [0.16, 1.20]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>515</strong></td>
<td><strong>516</strong></td>
<td></td>
<td><strong>61.5 %</strong></td>
<td><strong>1.16 [0.88, 1.54]</strong></td>
</tr>
</tbody>
</table>

Total events: 148 (Nicotine replacement), 133 (Placebo)
Heterogeneity: Chi² = 4.23, df = 3 (P = 0.24); I² = 29%
Test for overall effect: Z = 1.05 (P = 0.29)

2 Nicotine Gum
Boyle 1992             | 13/50                | 13/50   |            | 6.5 %  | 1.00 [0.41, 2.44] |

NRT: Effect at $\geq 6$ months

Why is NRT Not Effective?

- Under-replacement of nicotine with standard NRT dosing
- Similarities between ST and certain nicotine replacement products (i.e., nicotine gum)
- Treatment-naïve ST users
- High control condition abstinence rates in clinical trials of ST users
Why is NRT Not Effective?

• Under-replacement of nicotine with standard NRT dosing
• Similarities between ST and certain nicotine replacement products (i.e., nicotine gum)
• Treatment-naïve ST users
• High control condition abstinence rates in clinical trials of ST users
Nicotine Patch for ST Users

- NCI RO1 96881
- 42 ST users
- Randomized to:
  - Placebo
  - 21 mg/day
  - 42 mg/day
  - 63 mg/day

All subjects (n=42)

Ad lib ST use

8:00 16:00
Day 1

Serum samples

8:00 16:00
Day 2

8:00 16:00
Day 3

Abstinent from all tobacco

63 mg (21 mg, 21 mg, 21 mg) (n=10)

42 mg (21 mg, 21 mg, placebo) (n=11)

21 mg (21 mg, placebo, placebo) (n=10)

Placebo (placebo, placebo, placebo) (n=11)

Attention Disturbance

Decreased Arousal

Negative Affect

Week 1

Placebo 21 mg 42 mg 63 mg

P=0.050

Week 2

P=0.154

Restlessness

Median Serum Nicotine Concentration

High Dose Patch Therapy: Adverse Events

- No difference in overall adverse events

- 63 mg/day
  - 1 subject with nausea/vomiting
    - Completed study on 2 patches
  - 1 subject with nausea
    - Completed study on 2 patches

- 42 mg/day
  - Vomiting – possibly unrelated
    - Completed study on 3 patches
Nicotine Patch for ST Users

- NCI R21 CA140125
- 52 ST users
- Randomized to:
  - Placebo
  - 42 mg/day
- 8 weeks of therapy

### Abstinence Rates: Self-Reported

<table>
<thead>
<tr>
<th></th>
<th>42 mg Nicotine Patch N=25</th>
<th>Placebo Patch N=27</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End of treatment (week 8)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Point prevalence abstinence</td>
<td>13 (52%)</td>
<td>8 (30%)</td>
<td>0.050</td>
</tr>
<tr>
<td>Prolonged abstinence</td>
<td>13 (52%)</td>
<td>7 (26%)</td>
<td>0.027</td>
</tr>
<tr>
<td><strong>6-months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Point prevalence abstinence</td>
<td>13 (52%)</td>
<td>8 (30%)</td>
<td>0.050</td>
</tr>
<tr>
<td>Prolonged abstinence</td>
<td>10 (40%)</td>
<td>7 (26%)</td>
<td>0.140</td>
</tr>
</tbody>
</table>

* Subjects met criteria for point-prevalence all tobacco abstinence if they reported not using any tobacco in the last 7 days. To meet criteria for prolonged abstinence, subjects had to meet criteria for 7-day point prevalence abstinence and also report not using tobacco for 7 consecutive days or at least once each week on 2 consecutive weeks, since 2 weeks following their target quit date. In all cases, subjects with missing information were assumed to be using tobacco.

† One-tailed, Chi-square test.
Summary of NRT Studies for ST Users

- NRT increases short-term (3 month) ST abstinence
- Decreases craving & withdrawal
- Does not increase long-term (≥ 6 month) abstinence
Scandinavian Snus

32% of men aged 16-35 use snus daily

19% adult snus use prevalence
Varenicline for Snus Users

- Norway (7 sites) & Sweden (9 sites)
- Male/female daily ST users
  - Use at least 8 times/day
- Randomized to:
  - Varenicline for 12 weeks
  - Placebo
- Biochemical confirmation of abstinence
  - Salivary cotinine > 15 ng/mL

Evidence

Constraints

Patient/Physician Preferences

Decision

Evidence
Recommended ST Treatment Approach

- Bupropion SR
  - Weight gain prevention
  - Craving reduction
- Tailored nicotine patch therapy
  - Craving reduction
  - Short-term (end-of-treatment) abstinence
- Nicotine lozenge (short-term abstinence)
- Nicotine gum (craving reduction)
- Varenicline
### Nicotine Patch Dosing Algorithm for ST Users

<table>
<thead>
<tr>
<th></th>
<th>Peak serum nicotine concentrations (ng/mL)</th>
<th>Cans or pouches per week</th>
<th>Patch dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0-10</td>
<td>&lt; 2</td>
<td>14 mg/d</td>
</tr>
<tr>
<td>Intermediate</td>
<td>11-20</td>
<td>2-3</td>
<td>21 mg/d</td>
</tr>
<tr>
<td>High</td>
<td>&gt; 20</td>
<td>&gt; 3</td>
<td>42 mg/d</td>
</tr>
</tbody>
</table>

Question #1:

Which medication has been shown to increase ST abstinence rates at 6 months?

1. Nicotine patch
2. Nicotine lozenge
3. Bupropion
4. Varenicline
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Which medication has been shown to increase ST abstinence rates at 6 months?

1. Nicotine patch
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Question #2:

If a ST user uses 4 cans/week, what dose of nicotine patch should they be placed on?

1. 7 mg
2. 14 mg
3. 21 mg
4. 42 mg
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If a ST user uses 4 cans/week, what dose of nicotine patch should they be placed on?

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2. 14 mg
3. 21 mg
4. 42 mg
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