Combination Pharmacotherapy for Smoking Cessation

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Megan E. Piper, Ph.D.
Center for Tobacco Research & Intervention
UW School of Medicine and Public Health
Smoking in the U.S.

- 18.9% of adult Americans smoke (2011)
- 1 out of every 5 deaths in America is directly caused by smoking
- Kills more than 440,000 Americans each year
  - ⅓ to ½ of all tobacco users in this country will die prematurely from tobacco dependence
  - Smokers lose an average of 14 years of life
Tobacco directly causes:

- ~ 30% of all cancers, including 90% of all lung cancers
- ~ 30% of all cardiovascular diseases
- ~ 90% of all COPD
- ~ 10% of all healthcare costs
  - ~ $100 billion/year
Tobacco in the Clinic

- Tobacco dependence – chronic, relapsing disease
- Most smokers want to quit
  - About 40% try each year
- 70% visit a primary care physician each year
  - At most, about 25% of patients receive cessation treatment from their primary care physician
- Effective treatments exist
The FDA will allow changes to the labeling for over-the-counter nicotine replacement products. "The agency heard from several public health groups that the labeling for OTC NRT products may stop consumers who are trying to quit smoking from using them. FDA hopes the recommended changes will allow more people to use these products effectively for smoking cessation and that tobacco dependence will decline in this country."

- FDA Commissioner Margaret A. Hamburg, M.D.
FDA Changes

- “There are no significant safety concerns associated with using more than one OTC NRT at the same time, or using an OTC NRT at the same time as another nicotine-containing product—including a cigarette. If you are using an OTC NRT while trying to quit smoking but slip up and have a cigarette, you should not stop using the NRT. You should keep using the OTC NRT and keep trying to quit.”

- “NRT users should still pick a day to quit smoking, and begin using the OTC NRT product on their "quit" day, even if they aren't immediately able to stop smoking.”
FDA Changes

“Users of NRT products should still use the product for the length of time indicated in the label—for example, 8, 10 or 12 weeks. However, if they feel they need to continue using the product for longer in order to quit, it is safe to do so in most cases. Consumers are advised to consult their health care professional if they feel the need to use an OTC NRT for longer than the time period recommended in the label.”
FDA Changes

The labeling for OTC NRTs may not change immediately, so consumers should:

- Make sure to read the packaging and labeling of any NRT product you purchase;
- Talk to your health care professional if you are thinking about quitting smoking and have questions or concerns about NRT. Your health care professional is also the expert to consult with questions about an NRT you are currently using.
- Report side effects involving an OTC NRT to the FDA MedWatch Reporting Program
<table>
<thead>
<tr>
<th>Current Drug Facts Labeling</th>
<th>Proposed Drug Facts Labeling</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Warnings:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Do not use</strong></td>
<td>None. The &quot;Do not use&quot; statement would be deleted.</td>
</tr>
<tr>
<td>• if you continue to smoke, chew tobacco, use snuff, or use [a different NRT product] or other nicotine containing products</td>
<td></td>
</tr>
<tr>
<td><strong>Directions:</strong></td>
<td></td>
</tr>
<tr>
<td>• stop smoking completely when you begin using [the NRT product]</td>
<td>• begin using [the NRT product] on your quit day</td>
</tr>
<tr>
<td>• it is important to complete treatment. Stop using [the NRT product] at the end of [a specified number of] weeks. If you still feel the need to use [the NRT product], talk to your doctor</td>
<td>• it is important to complete treatment. If you feel you need to use [the NRT product] for a longer period to keep from smoking, talk to your health care provider</td>
</tr>
</tbody>
</table>
Summary of FDA Changes

- OK to use NRT while smoking
- OK to use more than one NRT (Combo NRT)
- OK to use NRT for more than 3 months
Evidence for Combination NRT
## Selected Medication Options: Monotherapy and Combination Therapy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Number of arms</th>
<th>Estimated odds ratio (95% C.I.)</th>
<th>Estimated abstinence rate (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine Patch</td>
<td>32</td>
<td>1.9 (1.7 - 2.2)</td>
<td>23.4% (21.3 – 25.8)</td>
</tr>
<tr>
<td>Bupropion SR</td>
<td>26</td>
<td>2.0 (1.8 – 2.2)</td>
<td>24.2% (22.2 – 26.4)</td>
</tr>
<tr>
<td>Varenicline</td>
<td>5</td>
<td>3.1 (2.5 – 3.8)</td>
<td>33.2% (28.9 - 37.8)</td>
</tr>
<tr>
<td>Patch (&gt;14 wks) + NRT (gum or spray)</td>
<td>3</td>
<td>3.6 (2.5 – 5.2)</td>
<td>36.5% (28.6 – 45.3)</td>
</tr>
<tr>
<td>Patch + Bupropion SR</td>
<td>3</td>
<td>2.5 (1.9 – 3.4)</td>
<td>28.9% (23.5 – 35.1)</td>
</tr>
</tbody>
</table>
## Relative Efficacy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Number of arms</th>
<th>Estimated odds ratio (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine Patch (reference group)</td>
<td>32</td>
<td>1.0</td>
</tr>
<tr>
<td>Varenicline (2 mg/day)</td>
<td>5</td>
<td>1.6 (1.3, 2.0)</td>
</tr>
<tr>
<td>Patch (&gt;14 weeks) + NRT (gum or spray)</td>
<td>3</td>
<td>1.9 (1.3, 2.7)</td>
</tr>
<tr>
<td>Patch + Bupropion SR</td>
<td>3</td>
<td>1.3 (1.0, 1.8)</td>
</tr>
</tbody>
</table>
Guideline Recommendation: FDA-Approved Cessation Medications

- Clinicians should encourage medication for all patients attempting to quit smoking
  - EXCEPT when medically contraindicated
  - EXCEPT when there is insufficient evidence of effectiveness (i.e., pregnant women, smokeless tobacco users, light smokers and adolescents)

- The combination of counseling and medication is more effective for smoking cessation than either medication or counseling alone. Therefore, whenever feasible and appropriate, both counseling and medication should be provided to patients trying to quit smoking.
Guideline Recommendation: FDA-Approved Cessation Medications

- Seven first-line medications (5 nicotine and 2 non-nicotine) reliably increase long-term smoking abstinence rates
  - Bupropion SR
  - Nicotine gum*
  - Nicotine lozenge*
  - Nicotine nasal spray
  - Nicotine inhaler
  - Nicotine patch*
  - Varenicline

- Clinicians should also consider the use of certain combinations of medications identified as effective in this Guideline
  - Long-term (> 14 weeks) nicotine patch + other NRT (gum and spray)
  - Nicotine patch + the nicotine inhaler
  - Nicotine patch + bupropion SR.

*Available without a prescription
Combining a nicotine patch with a rapid delivery form of NRT was more effective than a single type of NRT

- 9 trials
- RR 1.34 (95% CI = 1.18 - 1.51)
Effectiveness Study: Cessation Rates

![Bar chart showing percent abstinent over different time periods and treatments.]

- **Bupropion**
- **Lozenge**
- **Patch**
- **Bupropion+Lozenge**
- **Patch+Lozenge**

**Post-Quit Study Endpoints**

- **Week 1**
- **Week 8**
- **Six Months**
Efficacy Study: Latency to Relapse
What Does Combination NRT Do?
Reduce Craving

- Compared to monotherapy, combination NRT has a stronger effect on:
  - Post-quit craving
  - Post-quit withdrawal
  - Post-quit smoking expectancies
Ameliorates Gender Differences

![Graph showing gender differences in percent abstinent at 6 months across different treatment conditions.](image)
Ameliorates Education Differences
Smoking While Using NRT

- Pre-quit use
- Post-quit use
Pre-quit NRT Use

- Blunts the pharmacologic and rewarding effects of smoking before cessation
  - Explicit unpairing of smoking and reward which may affect smoking expectations
- Reduces of smoking rate
- Mixed evidence that it improves cessation
- No sign of increased adverse events
Continued NRT Use After Lapse

- High-dose nicotine patch (35 mg) vs. placebo patch
  - Explicitly told to continue patch independent of whether they lapsed
  - Biggest therapeutic effect of nicotine patch was prevention of relapse following a lapse (not initial cessation or lapse prevention)
  - Among those who lapsed, 23% of those who continued nicotine patch during a lapse episode progressed to relapse (7 consecutive days of smoking) by the end of 6 weeks vs. 77% of those who continued placebo (OR= 7.1)

- Replicated in two other clinical trials with smaller effect sizes (OR = 1.9-2.5, depending on study, outcome and time of lapse)
Conclusions

● Using Combination NRT is no longer an off-label use of NRT

● Combination NRT (patch + ad lib) represents one of the 2 most effective smoking cessation medications
  - It does a better job of ameliorating cravings than a single NRT
  - It is especially effective for women and those with low education

● Patients should be encouraged to use the full course of NRT, even if they lapse
  - It could prevent a full relapse or allow them to re-establish abstinence if they have relapsed